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INVESTIGATION OF IBUPROFEN RELEASE FROM ETHYLCELLULOSE MATRIX COMPACTS

by

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Being a thesis submitted for

the degree of

Doctor of Philosophy in Pharmaceutics

at

University of Dublin, Trinity College

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April 2004

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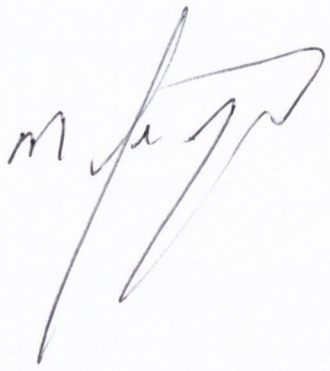
Signed: 

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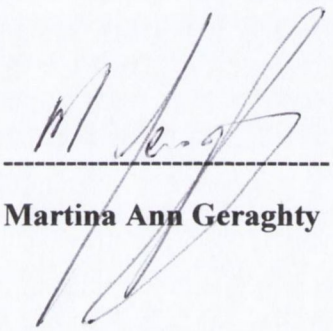

Martina Ann Geraghty

To my wonderful parents

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Poster Presentations

"Investigation of the release of ibuprofen from ethylcellulose matrices" in *17th Pharmaceutical Technology Conference*, Dublin, March (1998) Volume 1, 218-232. [M.A. Geraghty and A.M. Healy]

"A study of factors affecting the release of a model drug from ethylcellulose matrices" in *22nd Joint Research Seminar*, Queen's University of Belfast, March (1998) 28-49. [M.A. Geraghty and A.M. Healy]

ABBREVIATIONS AND SYMBOLS

μ	conductivity exponent
>>	much greater than
ϖ	(effective) diffusion boundary layer
~	approximately
η	intrinsic viscosity
γ	surface tension
δ	thickness of thin polymer film
ε_0	initial porosity
η_{app}	apparent viscosity
ε_d	porosity due to drug/acid excipient
~	approximately
<	less than
>	greater than
±	plus or minus
≤	less than or equal to
2θ	diffraction angle
A	concentration of drug in matrix
AA	adipic acid
Abs.	absorbance
AE	acid excipient
A_s	area
C or c	concentration
CoD	coefficient of determination
cP	viscosity grade
C_s	saturated solubility
d	diameter
D	diffusion coefficient
D[v,0.1]	the diameter at the 10% point of the particle size distribution
D[v,0.5]	the diameter at the 50% point of the particle size distribution

D[v,0.9]	the diameter at the 90% point of the particle size distribution
D_o	apparent diffusion coefficient
D_p	pore diameter
DS	degree of substitution
D_s	surface fractal dimension
DSC	differential scanning calorimetry
D_v	volume fractal dimension
EC	ethylcellulose
ED 50	drug's median effective dose
E-Z	$\times 10^{-Z}$ where Z is a number
f	correction factor
F_c	face curvature
FP	finely milled form of ethylcellulose
f_t	fraction of drug released
g	acceleration due to gravity
G	dissolution rate per unit surface area
G_1	Cobby shape factor
G_2	Cobby shape factor
G_3	Cobby shape factor
H	compact height
h	diffusion layer thickness
h_1	height of cylindrical portion of biconvex compact
h_2	maximum biconvex height
h_d	droplet height
HD_o	initial height of one of the spherical segments of the biconvex tablet
h_o	half the initial tablet height
IB	ibuprofen
J	diffusional flux
K	converts A to its corresponding volume fraction
k	release rate constant
k'	release rate constant
k_1	release rate constant

k_2	release rate constant
k_3	release rate constant
k_4	release rate constant
K_b	boundary retreat constant.
k_q	dissolution rate constant
k_r	effective interfacial transport rate constant
K_R	release rate constant
L	evaluation length
l	sampling length
L_c	depth of pore
l_t	lag time
min	minute
mmHg	millimetres of mercury
MS	molar substitution
MSC	Model Selection Criterion
M_w	Molecular weight
N	diffusional exponent
OS_{abs}	corrected surface tension
OS_{ruk}	uncorrected surface tension
P	applied pressure
p	percolation probability
p.s.i.a.	pounds per square inch absolute
p_{c1}	lower percolation threshold
p_{c2}	upper percolation threshold
pH	-log10(hydrogen ion concentration)
pK_a	-log10(dissociation constant)
P_o	saturation vapour pressure
P_s	hardness
Q	percentage drug release
Q(t)	the amount of drug released time per unit surface area
R_a	roughness parameter (as defined in text)
r_o	initial tablet radius
R_o	Radius of curvature
rpm	revolutions per minute

R_{tm}	roughness parameter (as defined in text)
SA	succinic acid
t	time
TA	L-(+)-tartaric acid
TD 50	drug's median toxic dose
TI	therapeutic index
t_r	retention time
V	volume
V_{HG}	volume of mercury
V_i	incremental volume
V_p	pore volume
V_t	true volume
V_{tot}	apparent volume
W	weight
z	the coordination number
γ_{HG}	surface tension of mercury
ε	porosity
ε_{cb}	critical porosity on a Bethe lattice
ε_{cd}	critical porosity on a 3-D lattice
θ	contact angle
λmax	maximum absorbance wavelength
ρ	true density
ρ_{sa}	skeletal density
ρ_{se}	bulk density
σ_f	tensile strength of compact
τ	tortuosity

SUMMARY

A comprehensive study of ethylcellulose powder and ethylcellulose compacts (of different ethylcellulose viscosity grades) was undertaken. Studies showed that the lower viscosity grade ethylcellulose (4 cP) was more compressible than the higher ethylcellulose viscosity grades, resulting in compacts of higher tensile strength and lower compact porosity. These differences, in addition to differences such as surface roughness, water uptake and contact angle (with phosphate buffer) affected the release of ibuprofen from ethylcellulose:ibuprofen compacts prepared with different ethylcellulose viscosity grades.

The effect of ethylcellulose viscosity grade and polymer-to-drug weight ratio on ibuprofen release from ethylcellulose:ibuprofen compacts was investigated. Results showed that the higher the ethylcellulose viscosity grade used during formulation the greater the percentage drug release. Experiments also found that as the level of drug concentration in the ethylcellulose:ibuprofen matrix formulation increased, the drug release rate also increased. It was thought that the increase in drug concentration resulted in an increase in compact porosity and a concomitant decrease in the tortuosity of the matrix. Percolation theory was also used to explain the change in dissolution kinetics of the matrix controlled release system over the range of drug loadings examined.

The effect of the ethylcellulose particle size fraction on percentage ibuprofen release from ethylcellulose:ibuprofen compacts (50:50 weight ratio) was also investigated. Ibuprofen release was greater from compacts prepared with the larger ethylcellulose particle size fraction than the smaller ethylcellulose particle size fraction, for compacts formulated with either ethylcellulose 4 cP or 100 cP viscosity grade. The greater release rate from compacts prepared with larger ethylcellulose particle size fractions was due to the greater porosity of these compacts and the concomitant decrease in the tortuosity. Based on percolation theory, the use of smaller ethylcellulose particle size fractions resulted in the formation of a more consistent insoluble infinite cluster, which determined a slower release rate of ibuprofen than the release from compacts prepared with larger ethylcellulose particle size fractions. Changing the disc compaction pressure did not affect the drug release rates of ethylcellulose:ibuprofen compacts.

By freeing the time diffusional exponent in model 2 i.e. $Q=kt^N+c$ (where Q is percentage drug release, k is a release rate constant, t is time, c is a constant and N is the diffusional exponent) a better fit of dissolution data was achieved than when the

square root of time model was fitted to the data. The diffusional exponent was higher for model fits of release profiles from formulations prepared with higher ethylcellulose viscosity grades than ethylcellulose 4 cP viscosity grade. In addition, the diffusional exponent increased when the drug loading of the formulation increased, or when a larger ethylcellulose particle size fraction was used in the formulation. This implies a gradual change in drug release from Fickian diffusion to zero-order kinetics. Model 3 i.e. $Q=k_1t^{1/2}+k_2t$ (where Q is percentage drug release, k_1 and k_2 are release rate constants and t is time) proved a better fit to the release profiles from ethylcellulose:ibuprofen compacts prepared with higher drug loads than model 2. It also proved a better fit (than model 2) when fitting release profiles from ethylcellulose:ibuprofen compacts (50% w/w drug loading) prepared with different ethylcellulose particle size fractions (except the release profile from ethylcellulose 4 cP compacts prepared with the ethylcellulose 40–63 μm particle size fraction). This indicates that under these formulation conditions polymer relaxation or swelling becomes a mechanism of drug release to consider.

The inclusion of acid excipients in ethylcellulose:ibuprofen formulations caused Higuchi drug release to be altered so that it resembled a zero-order release profile. For each formulation examined, ibuprofen release from ethylcellulose 100 cP compacts was a step nearer constant drug release than release from ethylcellulose 4 cP compacts.

Ibuprofen dissolution profiles from biconvex compacts showed less profile curvature than plane-faced compacts. This was because the reducing surface area of the biconvex compact reduced the upward curvature of the ibuprofen dissolution profile. As compared to their similar plane-faced formulation, biconvex compacts prepared with adipic acid showed the greatest reduction in ibuprofen profile curvature, while compacts prepared with L-(+)-tartaric acid showed the least. This was because of the differing solubilities between the acid excipient:ibuprofen systems.

To conclude, the lower viscosity grades ethylcellulose are more compressible than the higher ethylcellulose viscosity grades, resulting in harder tablets and slower drug release rates. Both the drug release rate and mechanism can be altered by modifying the parameters considered in this thesis.

INTRODUCTION

ORIGIN AND SCOPE OF THE THESIS

The concept of controlled release systems is to deliver a constant supply of the active ingredient, usually at zero order rate, by continuously releasing for a certain period of time, an amount of drug equivalent to that eliminated by the body (Abdou, 1989). The kinetics of the drug release will be dependent on the specific prolonged action mechanism utilised in manufacturing the controlled release system.

In matrix tablets the drug is suspended in an inert nondissolving polymer matrix, mixed with appropriate agents and compressed into tablets. Drug release from matrix tablets becomes progressively slower with time (Higuchi, 1963). This is in contrast to the ideal situation in which the drug is released from the tablet at the same slow rate throughout the release period. The primary reason for the continuously decreasing drug release rate in matrix type formulations is the increasing distance that must be traversed by the dissolution medium and drug molecules into, and out of, the tablet respectively. Therefore, any mechanism that lessens the time dependent increase in the diffusion path length would reduce the attenuation of the dissolution rate.

Ethylcellulose is non-toxic, stable compressible, inert hydrophobic polymer that has been used widely to prepare pharmaceutical dosage forms, including matrix tablets (Lin and Lin, 1996, Upadrashta *et al.*, 1993, Narisawa *et al.*, 1994).

Work undertaken by Healy (1995) showed that ibuprofen dissolution profiles from mixed ibuprofen:acid excipient compressed discs had a positive curvature, the extent of which depended on the acid excipient used and the acid excipient:ibuprofen weight fraction ratio in the disc.

The primary objectives were:

(1) to use ethylcellulose as a matrix-forming material to deliver the sparingly soluble drug ibuprofen;

(2) to examine the effects of physiochemical properties of ethylcellulose (ethylcellulose viscosity grade and particle size), and processing variables (polymer-to-drug weight ratio, disc compaction pressure) on ibuprofen release from ethylcellulose:ibuprofen compacts;

(3) to apply "classical theories" and percolation theory to ibuprofen release data from ethylcellulose:ibuprofen compacts;

(4) to explore the mechanism of drug release from ethylcellulose:ibuprofen systems by fitting the release data to various models based on the basic model of Ritger and Peppas (1987);

(5) to investigate the effect of including an acid excipient in the ethylcellulose:ibuprofen matrix compact. It was hoped that by matching the positive curvature of ibuprofen dissolution profiles as observed from single surface acid excipient:ibuprofen compressed discs (Healy, 1995), to the downward curvature of ibuprofen dissolution profiles from ethylcellulose:ibuprofen matrix compacts, zero-order drug release could be approached;

(6) to investigate the effect of matching the positive curvature of ibuprofen dissolution profiles from acid excipient:ibuprofen compressed compacts to a reducing biconvex surface area, in an attempt to achieve zero-order drug release.

CHAPTER 1
THEORY OF DISSOLUTION

1.1. INTRODUCTION

The dissolution of a solid into a liquid may be regarded as an important phase in drug release from pharmaceutical formulations. It involves an interfacial reaction, which results in the liberation of solute molecules from the solid phase (solvation) and the transport of these molecules from the interface into the bulk of the liquid phase (Grijseels et al., 1981). The dissolution rate can be defined as the quantity of drug that goes into solution per unit time under standardised conditions of liquid/solid interface, temperature and solvent composition.

1.2. DISSOLUTION OF SINGLE COMPONENT SOLIDS

The dissolution of the solute can be classified according to three general categories (Wurster and Taylor, 1965):

(1) Diffusion controlled

This occurs where the solvent-solute step occurs much faster than the transport of solute into the bulk solution. The overall dissolution rate is controlled by the transport process.

(2) Interfacially controlled

The rate of reaction at the interface is much slower than the transport processes and hence determines the rate. The actual process of liberation and solvation of molecules at the interface determines the overall dissolution rate.

(3) Interfacial/Diffusion controlled

The rate constants of the interfacial reaction, and the transport of solute into the bulk solution are approximately the same. As a result, the dissolution rate is a function of both the rate of the reaction at the interface as well as the transport process.

1.2.1. Diffusion controlled dissolution

In most cases of dissolution of solids in liquids, dissolution is diffusion controlled (Carstensen, 1972). The overall rate of mass transfer into the bulk solution can be evaluated by assuming the existence at the surface of a film which offers the same resistance to mass transfer as the combined laminar flow region, transition region and turbulent region.

The *Diffusion layer model* of dissolution assumes a static liquid film exists adjacent to the solid surface and is the classical model used to describe dissolution processes. In 1897, Noyes and Whitney studied dissolution of rotating cylinders of benzoic acid and lead chloride in water. Based on their theories and those of Nernst and Brunner (1904), it is assumed that transport through the thin film (of thickness h) at the surface is a diffusion process occurring due to a concentration gradient that is constant over the whole layer. It is also assumed that this concentration gradient imparts a concentration C at the boundary between the film and the bulk solution and that the concentration at the surface is the saturation concentration, C_s (see figure 1.1.).

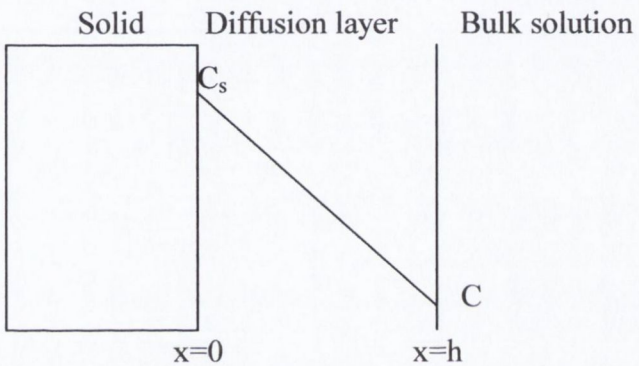


Figure 1.1. The Nernst-Brunner model for the dissolution of a single component solid in a pure solvent.

Assuming steady state kinetics, Fick's first law of diffusion can be applied to describe the dissolution process. Fick's first law of diffusion states:

$$J = -D\frac{\delta C}{\delta x} \qquad \text{Eqn. 1.1.}$$

where J (the diffusional flux) is the amount of material flowing perpendicularly through a unit surface area of a barrier in unit time, $\delta C/\delta x$ is the concentration gradient and D is the diffusion coefficient.

For a mass of substance dissolved in a given volume V, of dissolution medium with a surface area A_s, of dissolving particles, equation 1.1. can be rewritten as:

$$\frac{V}{A_s}\frac{dC}{dt} = \frac{-D\,(C_s - C)}{h} \qquad \text{Eqn. 1.2.}$$

The weight of the solid dissolved, W with time can be written as:

$$\frac{dW}{dt} = \frac{DA_s(C_s - C)}{h} \qquad \text{Eqn. 1.3.}$$

or

$$\frac{dW}{dt} = k_q A_s (C_s - C) \qquad \text{Eqn. 1.4.}$$

where k_q is the dissolution rate constant. This does not account for the boundary conditions.

When sink conditions exist i.e. $C_s >> C$ (typically less than 10%), then equation 1.4. can be rewritten as:

$$\frac{dW}{dt} = \frac{DA_s C_s}{h} \qquad \text{Eqn. 1.5.}$$

or

$$G = \frac{dW}{dt} \Big/ A_s = \frac{D\,C_s}{h} \qquad \text{Eqn. 1.6.}$$

where G is the dissolution rate per unit surface area or the *intrinsic dissolution rate* (Wells, 1988).

The limitation of this model is it does not describe the actual situation since in reality no stagnant layer exists. In reality, convection rather than diffusion controls the transport process (Grijseels *et al.*, 1981). It is only in the immediate vicinity of the surface where liquid motion is almost absent that a region exists where molecular diffusion must be accounted for. This zone is called the *(effective) diffusion boundary layer (ϖ)* (Levich, 1962). The thickness of ϖ can be calculated from hydrodynamic theory independently of dissolution rate data, and can be expressed in terms of viscosity, diffusion coefficient and distance from the leading edge of the dissolving surface. Within the diffusion boundary layer, the concentration of the solution shows a rapid change. As a first approximation, a linear concentration gradient may be assumed and the expression for the diffusional flux is approximated by:

$$J = \frac{D(C_s - C_b)}{\varpi} \qquad \text{Eqn. 1.7.}$$

This resembles the equation derived for the stagnant layer model and represents the *convective diffusion theory,* based on hydrodynamics.

1.2.2. Surface reaction controlled dissolution

Deviations from the Nernst-Brunner model will occur if the interfacial reaction is not instantaneous. For solutes having a high energy of activation for the interfacial reaction, the rate of release of the solute molecules at the interface may be much lower than the transport rate across the film. As a result, the solvation process becomes the rate-limiting step. Unlike in the Nernst-Brunner model, one can no longer assume that the concentration of solute at the surface is in equilibrium with the solvent (Higuchi, 1967). The overall dissolution rate per unit area is written as:

$$G=k_r(C_s-C) \qquad \text{Eqn. 1.8.}$$

where k_r is the effective interfacial transport rate constant. Under sink conditions, this may be written as:

$$G=k_r(C_s) \qquad \text{Eqn. 1.9.}$$

A diagrammatic representation of the interfacial barrier model is shown in figure 1.2. below.

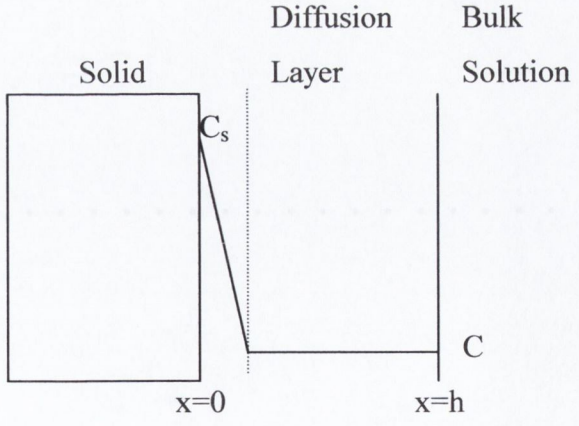


Figure 1.2. The interfacial barrier model for the dissolution of a solid solute.

When the interfacial barrier model is combined with the diffusion layer model, it is known as a *double barrier model* and is diagrammatically represented in figure 1.3. below. The dissolution rate is given by:

$$G = \frac{D(C_s - C)}{h\left[1 + \frac{D}{hk_r}\right]} \qquad \text{Eqn. 1.10.}$$

This equation breaks down to equation 1.6. and equation 1.8. when $k_r >> D/h$ and $k_r << D/h$, respectively.

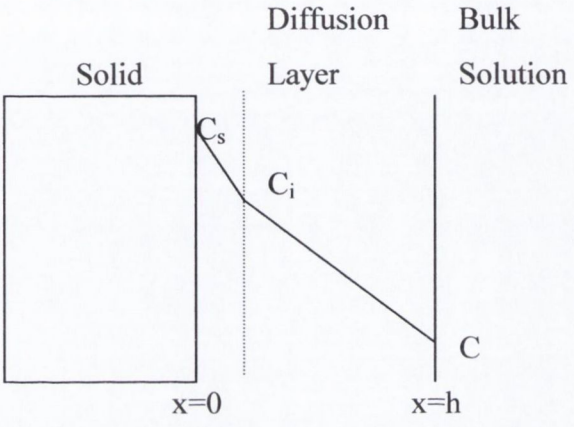


Figure 1.3. The double barrier model for the dissolution of a solid solute.

1.3. DISSOLUTION OF TWO-COMPONENT SOLIDS (NON-INTERACTING MODEL)

Higuchi *et al.* (1965) examined two-phase mixtures where there are two components, A and B, which do not interact in any way with each other. Upon exposure to the bulk medium, both species of the system should initially begin to dissolve at rates proportional to their solubilities and their diffusion coefficients. Generally, one of the components will become depleted at the solid liquid interface. This happens because N_A/N_B may not equal D_AC_A/D_BC_B, where N_A and N_B are the original amounts of A and B in the mixture, D_A and D_B are the respective diffusion coefficients and C_A and C_B are the respective solubilities. As a result one of the species will be present in a higher concentration at the solid liquid interface than the other depleted species. Therefore, a porous surface layer is formed composed of only one of the phases. The two phases will coexist at the surface only at the critical mixture ratio (cmr) given by:

$$N_A/N_B=(D_AC_A/D_BC_B) \qquad \text{Eqn. 1.11.}$$

The three different cases which could be found after a finite time of dissolution are shown in figure 1.4.:

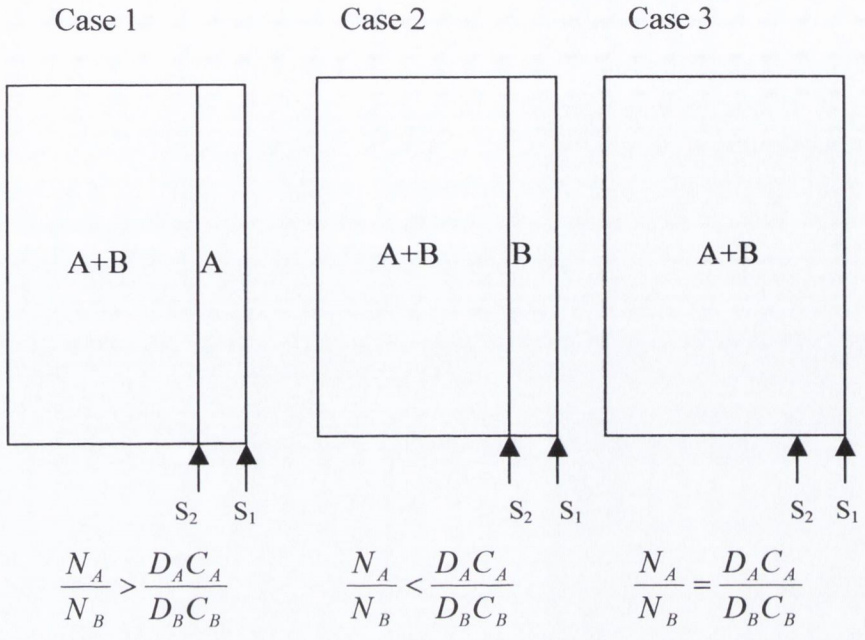


Figure 1.4. Dissolution behaviour of mixtures of A and B. Case 1: phase B dissolves fast enough to leave a layer of pure A at the surface. Case 2: phase A dissolves fast enough to leave a layer of pure B at the surface. Case 3: the two phases always coexist at the solid liquid interface.

In case 3, both components of the mix are always present at the surface. Under sink conditions the dissolution rate for each component is based on the model employed by Nernst-Brunner i.e.:

$$G_A = \frac{D_A C_A}{h} \qquad \text{Eqn. 1.12.}$$

and

$$G_B = \frac{D_B C_B}{h} \qquad \text{Eqn. 1.13.}$$

where G_A and G_B are the dissolution rates of components A and B, respectively and h is the effective diffusion layer thickness. Assuming that case 1 above exists, since component A is always at the surface, its dissolution rate is given by equation 1.12. The molecules of component B however must diffuse through the liquid diffusion layer and through the porous layer of component A at the surface.

Two boundaries may be defined, namely the bulk mixture (A+B)-phase A boundary, designated as S_2 and the phase A-diffusion layer boundary designated as S_1.

The diffusion coefficient of B (D_B) is influenced by the tortuosity τ of the A layer. Molecules of B must diffuse not only through the liquid diffusion layer, but also through the A phase layer of thickness, S_2-S_1. The diffusion coefficient of B may be taken to be $D_B/(\tau/\varepsilon)$ where ε is the porosity of the surface porous layer (Higuchi *et al.*, 1965).

From the Nersnt-Brunner equation, the overall dissolution rate of compound B is given by:

$$G_B = \left[\frac{D_B C_B}{(S_2 - S_1)(\tau/\varepsilon) + h} \right] \qquad \text{Eqn.1.14.}$$

One can also express the relevant dissolution rates under steady state diffusion condition as:

$$G_A = A_A (dS_1 / dt) \qquad \text{Eqn. 1.15.}$$

and

$$G_B = A_B (dS_2 / dt) \qquad \text{Eqn. 1.16.}$$

where A_A and A_B are the amounts per unit volume of A and B in the mixture.
Combining equation 1.12. with equation 1.15., and integrating results in equation 1.17.:

$$S_1 = (D_A C_A / A_A h)t \qquad \text{Eqn. 1.17.}$$

Therefore, substituting equation 1.17. into equation 1.14. and integrating, Higuchi *et al.* (1965) deduced that:

$$A_B \frac{dS_2}{dt} = \frac{D_B C_B}{h + (\tau/\varepsilon)[S_2 - (D_A C_A / A_A h)t]} \qquad \text{Eqn. 1.18.}$$

The resulting solution to equation 1.18. when $S_1=S_2=0$, at $t=0$ is:

$$t = K_1\left\{\left[S_2 - \frac{\varepsilon}{\tau}\left(\frac{K_1}{K_2} - h\right)\right]\left[1 - \exp\left(\frac{K_1\tau}{K_2\varepsilon}S_2\right)\right]\right\} \qquad \text{Eqn. 1.19.}$$

where

$$K_1 = A_A h / D_A C_A \qquad \text{Eqn. 1.20.}$$

and

$$K_2 = A_B h / D_B C_B \qquad \text{Eqn. 1.21.}$$

Therefore, when $S_2>>\varepsilon K_1/\tau K_2$, equation 1.19. may be written as:

$$t \approx K_1\left[S_2 - \frac{\varepsilon}{\tau}\left(\frac{K_1}{K_2} - h\right)\right] \qquad \text{Eqn. 1.22.}$$

Since in the steady state, $G_B=A_B(dS_2/dt)$ (equation 1.16) the dissolution rate of B in the steady state is constant i.e.:

$$G_B = \left[\frac{A_B D_A C_A}{A_A h}\right] = \frac{N_B}{N_A} G_A \qquad \text{Eqn. 1.23.}$$

One of the limitations of this model is it is quantitatively applicable in the steady state only. As a result C_A and C_B values must be similar and not differ greatly. If one of the components has a solubility significantly different from that of the other component, then the more soluble component can be envisaged as dissolving through the more insoluble component, which acts as an inert matrix. In this way, one of the components acts as a carrier for the other component. As a result, the range of weight fractions over which the carrier controls dissolution is very limited and occurs only at the higher carrier weight fractions.

Higuchi *et al.* (1965) investigated the dissolution behavior of benzoic acid:salicylic acid tablet mixtures dissolving in HCl. This is an unreactive medium in which ionisation of both acids will be suppressed. Discs were prepared from both mechanical mixtures and melts of the mixtures. The steady-state rates predicted by the model were in good agreement with observed dissolution rates. Some deviations of theory from the data were observed near the critical mixture ratio, where predicted dissolution rates were higher than were experimentally determined. This was

accounted for by local variations in composition. The data obtained with the melt matrices agreed better with theory. This was attributed to the more intimate mixing of the phases in the melt preparation and a resulting better definition of the boundaries, S_1 and S_2.

Shah and Parrott (1976) applied this theory to compressed sphere mixtures of salicylic acid:aspirin and aspirin:phenacetin dissolving in water. Some deviations existed between the observed and predicted dissolution rates at compositions near the critical mixture ratio. This was attributed to the small local variations in compositions since the mixtures were not prepared by a melt method.

1.4. EFFECT OF IONISABLE EXCIPIENTS ON THE DISSOLUTION OF IONISABLE DRUGS

Work undertaken by Nelson (1958) revealed the enhancement of the dissolution rate of poorly soluble weak acids (benzoic acid, theophylline, theobromine and phenobarbital) following the addition of tribasic sodium phosphate. This was attributed to the ability of the base to create an environment near the dissolving solid in which the solubility of the acid was higher than that in the bulk dissolution medium.

Ramtoola (1988) investigated the dissolution from mixtures of two weak acids in phosphate buffer solution. The limiting rates were found to deviate from the predicted rates for the two component non-interacting model. This was explained in terms of the pH changes occurring in the microenvironment at the solid-liquid interface. The two-component model was modified to account for pH changes at the interface and the resulting change in solubility and dissolution rate of the surface component. The rates predicted by the model agreed well with the observed limiting rates from benzoic acid:salicylic acid discs. The model predicted dissolution profiles with positive curvature for acids with very different dissociation constants and/or intrinsic solubility values. Ramtoola (1988) also studied the dissolution behaviour of indomethacin:citric acid (monohydrate) 1:1 mixtures. Indomethacin dissolution rates from the mixed disc were 5-10 times lower than those of pure indomethacin in the stirring speed range 180-60 rpm, respectively. The dissolution profile of indomethacin showed positive curvature at low stirring speed while at high stirring

speed, the dissolution profiles became linear. These positive curvatures were explained in terms of pH changes occurring at the solid liquid interface, i.e. as the citric acid dissolves, it recedes from the disc surface and the interfacial pH rises leading to an increased indomethacin dissolution rate.

Dissolution from discs containing mixtures of an acidic drug and a basic excipient was investigated by McGloughlin (1989). Two new models were proposed to account for deviations from the two-component non-interacting model.

- The two component (linear solubility) model incorporated an expression relating the solubility of the dissolving acid in the diffusion layer and the concentration of the base. The model predicted a plateau in the dissolution rate when the diffusion layer was mutually saturated with the acid and the base, determined the solubility of the salt form. Results obtained from mixtures of benzoic acid and tris(hydroxymethyl)aminomethane (TRIS) in phosphate buffer were consistent with results predicted from the model.
- The two component (salt formation) model assumed that the salt formation reaction between the acid and the base went to completion. Therefore, at the acid:base 1:1 molar ratio, the system was thought to consist entirely of the salt form. For 0 to 0.5 mole fraction of the base, the acid was present in excess and the two component non-interacting model was applied to the acid:salt system. For higher mole fractions of base, the two component non-interacting model was applied to the base:salt system. This model also predicted a plateau in the dissolution rate in some situations, depending on the relative solubilities of the acid, the base and the salt. The dissolution rates determined for naproxen:procaine systems were in good agreement with rates calculated from the model.

The experimental dissolution rates determined for naproxen:TRIS and phenylbutazone:TRIS systems were intermediate between the rates predicted by the two models.

Healy (1995) measured the solubility of ibuprofen and acid excipients in phosphate buffer (table 1.1.). The dissolution rates of ibuprofen:acidic excipient compressed mixtures in phosphate buffer was also measured. The acid excipients used were

adipic, succinic, adipic, L-(+)-tartaric and citric acids. The acid excipient dissolution profiles showed a downward curvature, consistent with the two component non-interacting model. Ibuprofen dissolution profiles showed a positive curvature, which was attributed to the recession of the acid excipient from the disc surface, leading to a rise in microenvironmental pH. The two component non-interacting model was modified to include the effect of changing acid excipient concentration on ibuprofen solubility and hence, dissolution rate. The best agreement between predicted and observed limiting dissolution rates was found for systems prepared with the acid excipient of lower solubility, adipic acid and succinic acid. The experimental limiting rates for the systems prepared with the more soluble acid excipient were lower than predicted for ibuprofen and higher than predicted for the excipient. These deviations were attributed to the fact that steady-state concentrations had not been reached prior to depletion of the acid excipient from the disc. Prediction of non-steady-state dissolution rates and dissolution profiles were based on the determination of surface concentrations of the acid excipient. Having determined the concentration of excipient at the solid-liquid interface, the solubility of ibuprofen at the interface and its dissolution rate were determined. Discrepancies were observed between predicted and observed dissolution rates. Initial dissolution rates tended to be higher than predicted.

Healy (1995) with a view to accounting for the differences between experimental and predicted dissolution, investigated the effect of changing acid excipient particle size on dissolution of ibuprofen from two-component discs. In general, the smaller the particle size of acid excipient used, the lower was the dissolution rate of ibuprofen from a compressed disc. This pattern was observed for 50:50 mixtures of each of three different systems containing acid excipient of very different solubilities (adipic acid, succinic acid and L-(+)-tartaric acid).

Table 1.1

The pK_a values and saturated solubilities of acids

Acid	pK_{a1} [a]	pK_{a2} [a]	Solubility[b] (mg/ml)
Adipic acid	4.418	5.412	49.4
Succinic acid	4.207	5.635	134.6
L(+)-tartaric acid	2.930	4.230	875.3
Ibuprofen	4.39	-	6.3

[a] Acid excipients measured in water at 25°C (Dean, 1985: Merck Index, 1989), ibuprofen measured in buffered and unbuffered media of different pH values, at 37°C (Healy, 1995), [b] Measured in phosphate buffer pH 7.35 in excess ibuprofen (Healy, 1995)

Several authors have investigated the use organic acids as pH adjusters in the formulation of sustained release dosage forms for salts of weakly basic drugs. Ventouras *et al.* (1977) reported that succinic acid enhanced the release rate of vincamine hydrochloride hemihydrate from hydrophilic matrices and that the enhancement was independent of the pH of the dissolution medium. Enhancements were in the region of 5 to 9 fold. The effect was seen to increase with increasing acid excipient content. The pH of the microenvironment of the matrix was measured using microelectrodes. The enhancement in release rates could be attributed to a decrease in the microenvironmental pH relative to the pH of the bulk medium.

Studies on the effect of acid excipients on the release of salts of the weakly basic drugs, ketanserin tartrate and mianserin hydrochloride, from programmed release megaloporous systems in both acidic and neutral media have been published (van der Veen *et al.*, 1991a and 1991b). An acid excipient (citric, succinic, tartaric acid) was incorporated into formulations with a view to enhancing the release of weakly basic drugs in neutral media, thus counteracting the occurrence of decreasing release rates with increasing pH in the gastrointestinal tract. Dramatic increases in release rates in neutral media (pH 6.8) were observed from the dosage forms containing acidic excipients. This effect was attributed to a localised pH change in the pores of the megaloporous dosage forms, resulting in a retardation of the conversion of the soluble drug to the insoluble base. Incorporation of succinic acid in the formulation resulted in a lowering of release rates in neutral media relative to the systems employing citric

or tartaric acid. These authors attributed these lower release rates to the lower solubility and lower acidity of succinic acid compared to the other two acids.

Gabr (1992) reported an increase in the release of papaverine hydrochloride from tablet matrices in buffer (pH 7.4) by the incorporation of organic acids in the formulation. The study was carried out using the same acids as those employed by van der Veen *et al.* (1991a and 1991b). Contrary to findings on megaloporous systems (van der Veen *et al.*, 1991a and 1991b), the matrix tablets containing succinic acid demonstrated the highest release rates compared to those containing citric or tartaric acid. These findings were supported by Thoma and Zimmer (1990) who proposed that the very soluble acids diffused rapidly through the matrix tablet, while the moderately soluble succinic acid diffused at a relatively slow rate, thus maintaining an acidic pH inside the tablets for a longer time.

Work undertaken by Streubel et *al.* (2000) investigated pH-independent release of verapamil hydrochloride from tablets composed of ethylcellulose or hydroxypropyl methylcellulose and an organic acid. The addition of fumaric, sorbic or adipic acid to the matrix former lowered pH values during drug release in phosphate buffer (pH 6.8 and 7.4). The more pronounced enhancements in drug release rates were observed following the inclusion of fumaric acid in the formulation. This was attributed to the lower pK_a values of fumaric acid, relative to those of sorbic acid or adipic acid.

1.5. CONCLUSION

Each type of dosage form requires careful study of the physical and chemical properties of drug substances to achieve a stable and efficacious product. These properties include a clear understanding of the dissolution properties of the drug and excipients included in the formulation.

CHAPTER 2

CONTROLLED RELEASE DOSAGE FORMS: HYDROPHOBIC MATRICES

2.1. INTRODUCTION

Conventional drug therapy involves the periodic dosing of a therapeutic agent that has been formulated to ensure its stability, activity and bioavailability. For most drugs, conventional methods of formulation are quite effective. However, some drugs warrant continuous administration, in the form of a controlled release device. Controlled release dosage forms cover a wide range of prolonged action preparations, which provide a continued release of their active agent at a predetermined rate and for a specific period of time (Abdou, 1989). It usually applies to preparations where the mechanism of prolonged action is inherent and determined totally by the drug delivery system (Abdou, 1989). It has also become associated with oral formulations, where the mechanism of prolonged action is dependent, and invariably sensitive to environmental factors in the gastrointestinal tract such as pH, a specific enzyme or gastric motility (Abdou, 1989). The use of hydrophobic or inert controlled drug delivery systems using ethylcellulose polymers has been investigated (Neau *et al.*, 1999, Crowley *et al.*, 2004).

This chapter summarises the advantages and disadvantages of controlled release technology. It also examines the factors that the formulator must consider when developing this type of formulation. In addition, the various matrix systems are classified using the characteristics that differentiate them from other controlled release dosage forms. This chapter will also focus on hydrophobic/inert matrix systems as controlled release systems. In particular, the modelling of drug release from inert matrix systems will be discussed, and percolation theory will be used to explain drug release from matrix systems.

2.2. ADVANTAGES OF ORAL CONTROLLED-RELEASE DOSAGE FORMS

The main goal of controlled-release dosage forms is the improvement of drug therapy. Advantages include:

- A steady concentration of drug release into the body, without the frequently seen "peaks" and "valleys" in the drug blood level, thereby improving efficiency in drug treatment. For example, aminophylline has a very narrow therapeutic blood level range and many daily dosages must be given in order that the correct

therapeutic blood level can be maintained. Therefore, conventional tablets must be administered at exact time intervals. Instead, if one formulates aminophylline as a sustained release tablet a 12 hourly dosage regimen can be achieved. This reduces the incidence of toxicity associated with "peaking" (Rubinstein, 1988).

- A reduction in the accumulation of drug in body tissues with chronic dosing (Salsa *et al.*, 1997).
- A reduction in local and systemic side effects. Aspirin for example has been shown to produce less gastric bleeding when formulated as a sustained release formulation than conventional aspirin preparations (Rubinstein, 1988).
- Improvement in patient compliance and therefore condition. The frequency with which the patient has to take their medication is reduced. In addition, it is possible that the drug's activity can be extended to take effect throughout the night, permitting morning dosing (Rubinstein, 1988).
- There are also good commercial reasons for the strong trend towards controlled release systems. Drug patents on the majority of today's drugs are expiring. Formulation of these drugs in controlled release systems is one means to extend the proprietary protection against generic products (Abdou, 1989).

2.3. DISADVANTAGES OF ORAL CONTROLLED-RELEASE DOSAGE FORMS

The main disadvantages include:

- Release rate is dependent on pharmaceutical dosage form integrity. Controlled release tablets can fail because of poor formulation. This can result in the entire dose being released at once (Rubinstein, 1988).
- Sometimes the controlled release dosage form can be larger than the ideal. This can present problems with patient compliance. In isolated cases, large sustained release formulations have been known to lodge in the gastrointestinal tract. For example, potassium chloride tablets have been known to cause ulceration due to delayed gastrointestinal transit time (Rubinstein, 1988).
- Greater cost than conventional dosage forms. The cost of controlled release tablets is more per unit dose than conventional dosage forms.

- Reproducibility of drug release can be affected by gastric emptying and intestinal motility (Abdou, 1989). In general, the presence of food in the stomach reduces the gastric emptying rate and thus can delay the absorption of drugs that are normally absorbed from the small intestine. In addition, the residence time in the small intestine, as determined by intestinal motility, may be an important factor with respect to drug bioavailability. The longer a drug is in contact with the absorption site(s) the greater the amount of drug absorbed. This will be important for controlled release dosage forms as they pass along the entire length of the gastrointestinal tract.
- If poisoning or intolerance develops it is almost impossible to stop the pharmacological action of the drug. The slow release of the drug into the gastrointestinal tract and its extended absorption often results in slow clearance of drug from the body (Rubinstein, 1988).

2.4. FACTORS TO BE CONSIDERED DURING THE FORMULATION OF CONTROLLED RELEASE PREPARATIONS

The preparation of controlled release dosage forms is subject to a number of variables. While the oral administration route is the most popular route for administering drug formulations, a number of problems exist. These include the possibility of chemical degradation under various pH conditions in the gastrointestinal tract, the influence of gastric emptying, and its dependence on food.

Both physiochemical and biological properties of the drug are important including:

- Dose

The amount of drug in oral controlled-release dosage forms is approximately two to three times greater than the amount of oral conventional dosage forms. The drug should ideally be effective in a relatively small dose or else the large dose will make the preparation hazardous to swallow (Abdou, 1989).

- Partition coefficient and pK_a

The more effectively a drug crosses a mucosal membrane the greater its activity. This degree of effectiveness is determined by the drug's partition coefficient and pK_a. Membranes of absorbing mucosa are more permeable to unionised forms of drugs than to ionised species. This is because of the greater lipid solubility of the unionised

forms and the highly charged nature of the cell membrane. Hence the absorption of drugs (either weak acids or bases) is influenced by the pH at the site of absorption and the lipid solubility of the unionised species. Drugs with a partition coefficient that is extremely high or low are poorer candidates for formulating into controlled-release dosage forms (Salsa *et al.*, 1997).

- Molecular weight

The ability of a drug to diffuse through polymeric membranes is a function of its diffusion coefficient. Drugs with a greater molecular weight have low diffusion coefficients, and therefore are unsuitable for controlled release formulations (Salsa *et al.*, 1997).

- Surface area

The surface area exposed to the dissolution media affects the dissolution rate of a drug. According to the Noyes-Whitney equation, an increase in the total effective surface area of drug in contact with the dissolution media will cause an increase in dissolution rate (Noyes and Whitney, 1897). If the fluid intimately wets each particle of drug, the effective surface area exhibited by the drug will be directly proportional to the particle size of the drug. Therefore, when the particle size of the drug is reduced the greater is the effective surface area and the higher the drug dissolution rate. For example, when the particle size of the antifungal drug griseofulvin is reduced from 10 μm to 2.7 μm the amount absorbed in humans is almost doubled (Proudfoot, 1988).

- Biological half-life

This is a major limitation. Drugs with short half-lives, such as levodopa and frusemide require relatively large doses to be incorporated into the controlled release systems. This can present problems with swallowing of large dosage forms, while drugs with long half-lives inherently are sustained release, and therefore there is no need to formulate them in a sustained release form (Abdou, 1989). Generally, drugs with half-lives between 2 and 6 hours are used.

- Therapeutic Index

The median effective dose of a drug is that amount which will produce the desired intensity of effect in 50% of the individuals tested. The median toxic dose is that amount which will produce a defined toxic effect in 50% of the individuals tested. The relationship between the desired and undesired effects of a drug is commonly

expressed as the therapeutic index (*TI*) and is defined as the ratio between a drug's median toxic dose (*TD* 50) and its median effective dose (*ED* 50):

$$TI = TD\ 50/ED\ 50 \qquad \text{Eqn. 2.1.}$$

Thus a drug with a therapeutic index of 15 would be expected to have a greater margin of safety in its use than a drug with a therapeutic index of 5 (Ansel *et al.*, 1999). Very potent drugs generally have a small margin of safety and, therefore present serious safety problems if the system fails (Abdou, 1989).

- Direct correlation between blood concentration and the duration of its pharmacological effect.

Ideally, for a drug to be useful in a controlled release system, there should be direct correlation between blood concentration and the duration of its pharmacological effect. For example, a drug such as reserpine has a biological half-life of 15 minutes, but its effect lasts for almost 48 hours. Consequently, formulating reserpine as a long acting form is needless (Abdou, 1989).

2.5. CLASSIFICATION OF MATRIX SYSTEMS

The matrix system is a release system for delay and control of the release of a drug that is dissolved or dispersed in a disintegration resistant support (Salsa *et al.*, 1997). Matrix devices are relatively easy to formulate by direct compression (Upadrashta *et al.*, 1993), give higher initial release rates than other controlled release systems, and can be made to release at a near constant release rate.

There are a number of differences, which differentiate matrix controlled release systems from other controlled release dosage forms (Salsa *et al.*, 1997). Therefore the following must be considered:

- The chemical nature of the support

In matrix systems the drug is embedded in an inert plastic material, by compression. In other controlled release formulations such as mixed release granules, part of the granules in the formulation are uncoated to give immediate release of the drug, while the rest are coated with a dissolving waxy or polymeric substance to give sustained release.

- Physical state of the drug

In matrix type systems the physical state of the drug can be dispersed in a molecular or particulate form, or both. In other controlled release preparation such as in ion exchange based controlled release systems, the drug is bound chemically to a solid carrier such as a resin or a polymer from which it is released slowly by the digestive fluids.

- The route of administration

Matrix type controlled release systems are usually oral. Other routes such as ocular controlled release systems use a drug core reservoir, surrounded by two copolymer membranes.

- The release kinetics

In accordance with Higuchi's equation, matrix systems are considered to have a linear release as a function of the square root of time (Higuchi, 1963). Non-matrix based controlled release systems exhibit different drug release kinetics from root time release kinetics. For example, in osmotically controlled oral preparations, the mechanism of drug release is based on the principle of osmotic pressure as opposed to a solution–diffusion mechanism. The rate of osmotic water influx, and therefore drug release stays constant as long as a constant thermodynamic activity gradient exists across the membrane.

There are different types of controlled release matrix systems depending on a number of criteria. These include the matrix structure, release kinetics, controlled release properties, chemical nature and properties of polymeric materials. Table 2.1. shows the different classifications of some matrix systems, using the latter criterion (Salsa *et al.*, 1997).

Table 2.1.

Classification of matrix systems[*]

Mineral Matrices	Hydrophilic Matrices	Inert Matrices	Lipidic Matrices
Drug retained in the support	Swelling is unlimited, delivery by diffusion	Controlled delivery by diffusion	Delivery by diffusion
Drug adsorbed on the support	Swelling is limited, controlled-delivery through swelling		Delivery by surface erosion

[*] Salsa *et al.* (1997)

2.6. HYDROPHOBIC (INERT) MATRIX SYSTEMS

In these preparations, the drug is dispersed in an inert nondissolving polymer matrix, mixed with appropriate excipients and compressed into tablets (Abdou, 1989). The limiting factor in the release of the drug is the rate at which the drug escapes by diffusion through the polymer and into the surrounding medium. The drug delivery rate is independent of pH, gastric intestinal motility or enzymatic action, but is largely affected by the type of polymer, drug:polymer weight ratio, tablet compaction pressure (which may affect tablet porosity), and tablet geometry (Abdou, 1989). Examples of polymers used in the formulation of inert matrix tablets include ethylcellulose and hydrogenated castor oil (Leuenberger *et al.*, 1995).

Higuchi was the first to propose a model for the mechanism of drug release from inert matrix systems (Higuchi, 1963). He determined that to develop mathematical relations for drug release from inert matrix systems of planar geometry, two systems have to be considered including release from a homogenous matrix and release from a granular matrix. Following this, Cobby *et al.* (1974a) derived a kinetic expression for the rate of drug release from slow release tablets, which related release rate to tablet shape. In 1983, Korsmeyer formulated a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices, including inert matrices (Korsmeyer *et al.*, 1983). In 1987, Leuenberger proposed percolation theory as an alternative method of explaining drug release from matrices (Leuenberger *et al.*, 1987).

2.7. RELEASE EQUATIONS AND MODELS RELEVANT TO HYDROPHOBIC INERT MATRICES

2.7.1. Higuchi Release: Release from a homogenous matrix of planar geometry

Release from a homogenous matrix involves the extraction of the medicament by a simple diffusional process and from an enveloping homogenous matrix. The drug is presumed to go into the uniform matrix and out into the medium (Higuchi, 1963).

Higuchi initially derived an equation to examine drug release from an ointment base containing finely dispersed drugs, which was equally applicable to release from a sustained-action homogenous matrix (Higuchi, 1961, Higuchi, 1963). He determined that the amount of total drug released from a planar system into a dissolution medium acting essentially as a perfect sink would be determined by the relationship:

$$Q(t) = \sqrt{Dt(2A - C_s)C_s} \qquad \text{Eqn. 2.2.}$$

where $Q(t)$ is the amount of drug released after time t per unit exposed area, D is the diffusitivity of the drug in the liquid medium, A is the total amount of drug present in the matrix per unit volume and C_s is the maximum solubility of the drug in the matrix substance.

2.7.2. Higuchi Release: Release from a granular matrix of planar geometry

The release from a granular matrix involves leaching of the medicament by the surrounding medium. The medium enters the drug-matrix through pores, cracks, and intergranular spaces. The drug is assumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and channels filled with the dissolution medium. It is assumed that minimal intragranular diffusion occurs (Higuchi, 1963).

For the leaching type release mechanism occurring through diffusion movement and utilising intergranular openings, the previous equation 2.2 must be modified for the effective volume where diffusion can occur and the effective diffusional path. Therefore,

$$Q(t) = \sqrt{DC_s \frac{\varepsilon}{\tau}(2A - \varepsilon C_s)t} \qquad \text{Eqn. 2.3.}$$

where D is the diffusitivity of the drug in the permeating fluid, C_s is the maximum solubility of the drug in the permeating fluid, ε is the total porosity of the matrix and τ is the tortuosity factor of the capillary system. The latter two parameters are dimensionless. This equation is similar to equation 2.2. except for the fact that in the case of a granular matrix, the cross sectional area of the diffusional path and the apparent solubility of the drug in the total system per unit volume, must be reduced by the porosity factor.

In equation 2.3. the tortuosity factor (τ) accounts for an increase in the drug path length of diffusion, due to the branching and bending of pores (Higuchi, 1963). This can lead to a reduction in the amount of drug released and as a result it appears as a denominator in equation 2.3. The most direct route for the drug to escape from the matrix system is given a tortuosity value of one, while the more difficult a drug diffusional pathway becomes the higher will be the tortuosity.

Additionally, equation 2.3. is subject to the factor of porosity. Porosity refers to the volume fraction that is permeated by the solvent and available for diffusion in the already leached portion of the matrix (Desai *et al.*, 1966a). This is equal to the initial porosity ε_0 due to pores or channels within the matrix before dissolution, and the porosity created after leaching of the drug ε_d i.e.:

$$\varepsilon = \varepsilon_d + \varepsilon_0 \qquad \text{Eqn. 2.4.}$$

The initial porosity before leaching is calculated from the apparent volume V_{tot} and the true volume V_t of the tablet constituents (Desai *et al.*, 1966b). V_{tot} is calculated from the tablet dimensions, while V_t is calculated knowing the weight and true density of the tablet components:

$$\varepsilon_0 = \frac{V_{tot} - V_t}{V_{tot}} \qquad \text{Eqn. 2.5.}$$

ε_d is the porosity corresponding to the volume occupied by the drug substance in the matrix and is calculated as follows (Desai *et al.*, 1966b):

$$\varepsilon_d = \frac{m_d}{\rho . V_{tot}} \qquad \text{Eqn. 2.6.}$$

with m_d equal to the total amount of drug present in the tablet and ρ is equal to the true density of the drug. Alternatively, equation 2.4. can be written as:

$$\varepsilon = \varepsilon_0 + AK \qquad \text{Eqn. 2.7.}$$

where K is introduced to convert A to its corresponding volume fraction (Higuchi, 1963). K is equal to the specific volume of the drug or 1/ (density of the drug) if A is expressed in terms of grams of drug per millilitre i.e. equation 2.8.:

$$\varepsilon = \varepsilon_0 + A(1/\rho) \qquad \text{Eqn. 2.8.}$$

If the initial porosity of a tablet is small relative to the porosity after leaching, the porosity is commonly determined by disregarding the initial porosity factor i.e.:

$$\varepsilon \cong AK \qquad \text{Eqn. 2.9.}$$

Equation 2.3. now becomes:

$$Q(t) = A\sqrt{\frac{DKC_s}{\tau}(2 - KC_s)t} \qquad \text{Eqn. 2.10.}$$

It would appear from this equation that the amount of drug released at any time is independent of the total amount of drug in the matrix (Higuchi, 1963).

For equation 2.2. and equation 2.3., the derivation is based on the existence of a pseudo steady state condition during the release process. It also assumes that the drug particles are relatively small compared to the diffusional length, and are evenly dispersed in the matrix system. As a result, the equations are essentially valid for matrix systems in which A is greater than C_s, or A is greater than εC_s by a factor of 3-4 (Higuchi, 1963).

2.7.3. Cobby model

Cobby *et al.* (1974a) developed a model to describe the dissolution kinetics of a drug from a slow-release matrix tablet and to relate drug release to tablet shape. He proposed that the fraction of drug released f_t to time t, could be written as:

$$f_t = G_1 K_R t^{1/2} - G_2\left(K_R t^{1/2}\right)^2 + G_3\left(K_R t^{1/2}\right)^3 \qquad \text{Eqn. 2.11.}$$

where K_R is the release rate constant having the dimension of the reciprocal of the square root of time, and G_1-G_3 are shape factors. The values of G_1-G_3 are dependent on the shape of the tablet under study i.e. spherical, cylindrical or biconvex and are shown in table 2.2. For spherical and cylindrical shaped tablets, the shape factors are constants obtained from measurements of the initial dimensions of the tablet. For biconvex tablets the value of the shape factors vary with time and may be obtained partially from the initial dimensions of the tablet and partially in the course of the kinetic considerations of the release process.

Table 2.2.

Values of shape factors in release expressions derived for three shapes of slow release tablets

Shape factor	Tablet shape		
	Spherical	Cylindrical	Biconvex
G_1	3	q+2	$\frac{3p}{C_3}\left\{C_4 + C_6\left(\frac{Z_t}{K_r}\right)\right\}$
G_2	3	2q+1	$\frac{3p^2}{C_3}\left\{C_5 + C_7\left(\frac{Z_t}{K_r}\right) + q\left(\frac{Z_t^2}{K_r^2}\right)\right\}$
G_3	1	q	$\frac{p^3 q}{C_3}\left\{4 + 3\left(\frac{Z_t^2}{K_r^2}\right) - \left(\frac{Z_t^3}{K_r^3}\right)\right\}$

Measurable parameters: r_o=initial tablet radius, h_o=half the initial tablet height, R_o=radius of curvature and HD_o=initial height of one of the spherical segments of the tablet. Ratio constants: $\Phi = R_o/r_o$, $q_o = r_o/h_o$, and $p_o = r_o/HD_o$. Simplifying factor (time dependent): $Z_t = 1/t^{1/2}[(C_1)^{1/2} - (C_1 - K_R t^{1/2} C_2)^{1/2}]$. Simplifying constants: $C_1 = \Phi^2 - 1$, $C_2 = 2(\Phi - 1)$, $C_3 = 6p_o^3 - 3p_o^2 q_o + q_o$, $C_4 = 4p_o^2 + p_o^2 q_o - 2p_o q_o + q_o$, $C_5 = 2p_o(1 + q_o)$, $C_6 = q_o(p_o^2 - 1)$, and $C_7 = 2q_o(p_o - 1)$.

The value of the release rate constant K_R varies inversely with the initial tablet radius r_o as shown in equation 2.12.:

$$K_R = \frac{K_b}{r_0} \qquad \text{Eqn. 2.12.}$$

where K_b is a proportionality constant, termed the boundary retreat constant. The boundary retreat constant is a measure of the rate at which the dissolution fluid can penetrate into the insoluble matrix to effect dissolution and release. It has the dimensions of length per unit square root of time. The value of the boundary retreat rate constant depends only on the physiochemical properties of the tablet constituents and the degree of compression. It is independent of both the initial tablet radius, which partly rules the size of a tablet, and the tablet shape (Cobby *et al.*, 1974b). While the value of the release rate constant (like that of the boundary retreat rate constant), is independent of tablet shape but not of initial tablet radius. Therefore, if a pair of tablets of different shape of the same formulation, and of equal overall weight and compressed to the same degree are considered, the release rate constants K_R should not differ under identical test conditions and where the initial radii are equal (Cobby *et al.*, 1974b).

2.7.4. Korsmeyer model and other derivations

Several other physical models of drug release from matrices are worth considering. Korsmeyer *et al.* (1983) proposed a simple semi-empirical equation, which could be used to analyse data of controlled release of drugs under perfect sink conditions. The general form of this equation is:

$$\frac{M_t}{M_\infty} = kt^N \qquad \text{Eqn. 2.13.}$$

where M_t / M_∞ is the fractional release of the drug, t is the release time, k is a constant incorporating structural and geometric characteristics of the controlled release device and N is the release exponent, indicating the mechanism of release.

This equation was developed from the well-known Fickian model for drug release from thin polymer films (Ritger and Peppas, 1987). Fickian diffusion of a drug from a thin polymer film device of thickness δ may be expressed by equation 2.13. where one assumes that the diffusion coefficient of the drug D, is concentration independent, with one-dimensional diffusion in the x direction (Crank, 1975):

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad \text{Eqn. 2.14.}$$

If the release experiment is undertaken under perfect sink conditions, the initial and boundary conditions can be written as:

$$t=0 \quad -\delta/2<x<\delta/2 \quad c=c_o \qquad \text{Eqn. 2.15.}$$

$$t>0 \quad x=\pm\delta/2 \quad c=c_1 \qquad \text{Eqn. 2.16.}$$

where c_o is the initial concentration of drug loading in the slab, and c_1 is the constant external concentration at the polymer/water interface, which can also be zero.

Crank (1975) proposed a solution to equation. 2.13. such that the fractional release of drug may be expressed as:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{1/2}\left\{\pi^{-1/2} + 2\sum_{N=1}^{\infty}(-1)^n \, ierfc\frac{N\delta}{2\sqrt{Dt}}\right\} \qquad \text{Eqn. 2.17.}$$

where *ierfc x* represents the integrated complementary error function of x under the conditions of equations 2.15. and 2.16. This is the exact solution of equation 2.13. and as such should be used to determine fractional drug release. However, a sufficiently accurate expression can be obtained by recognising that the second term in the brackets of equation 2.17. reduces to nothing under short time conditions (i.e. for the first 60% of the total drug released). Therefore, equation 2.17. becomes equation 2.18.:

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2} = kt^{1/2} \qquad \text{Eqn. 2.18.}$$

As indicated by the above equation, Fickian diffusional release is characterised by an initial $t^{1/2}$ time dependence of the drug released.

Therefore, a simple semi-empirical equation is introduced to express general drug release behavior from polymers. For Fickian diffusion in a thin film, the above equation indicated that the first 60% of the fractional release at any time could be characterised by some constant multiplied by the square root of time. A second limiting step is one where the drug release rate is independent of time i.e. zero-order kinetics. Such a situation is described by a general equation of the form (Ritger and Peppas, 1987):

$$\frac{M_t}{M_\infty} = k't \qquad \text{Eqn. 2.19.}$$

Many situations of release processes represent a coupling of a Fickian and non-Fickian mechanism of drug release (Ritger and Peppas, 1987). So, a simple expression of this observation can be achieved by combining both equations 2.18. and 2.19. to give:

$$\frac{M_t}{M_\infty} = k_1\sqrt{t} + k_2 t \qquad \text{Eqn. 2.20.}$$

This can also be written as:

$$\frac{M_t}{M_\infty} = kt^N \qquad \text{Eqn. 2.13.}$$

The drug release rate per unit area $dMt/A_s.dt$ can be readily calculated from the previous equation as:

$$\frac{dM_t}{A_s dt} = Nc_o kt^{N-1} \qquad \text{Eqn. 2.21.}$$

Therefore, the constant k incorporates characteristics of the macromolecular network system and the drug, and N is the diffusional exponent, which is indicative of the transport mechanism. Fickian diffusion is defined by N equal to 0.50 and anomalous (non-Fickian) transport by N greater than 0.50 but less than 1.0 (table 2.3.). The latter scenario indicates that there is a mechanism other than diffusion that contributes to drug release, for example polymer relaxation. The exponent N=1 defines zero-order (time dependent) drug release. For slabs the mechanism that creates zero-order release is known among polymer scientists as Case-II transport (Peppas, 1985). Equation 2.13. is valid for the first 60% of the fractional drug release.

Ritger and Peppas (1987) claimed that this equation, in addition to describing release from films, could adequately describe the release from cylinders, spheres and discs (tablets), regardless of the release mechanism. They also proposed that the value of N could give an indication of the release mechanism dependent on the controlled release system (table 2.3.). A value of N=1, however, means that the drug release is independent of time, regardless of the geometry. Thus, zero-order release can exist for any geometry.

Table 2.3.

*Diffusional exponent and mechanism of diffusional release of drug from various non–swellable controlled release systems**

Diffusional exponent *N*			
Thin film	**Cylindrical sample**	**Spherical sample**	**Release Mechanism**
0.50	0.45	0.43	Fickian Diffusion
0.50<n<1.00	0.45<n<1.00	0.43<n<1.00	non-Fickian transport (Anomalous)
1.0	1.0	1.0	Zero-order release

* Ritger and Peppas (1987)

Frequently equation 2.13. is simplified to (Ford *et al.*, 1991):

$$Q = kt^N \qquad \text{Eqn. 2.22.}$$

or

$$Q = kt^N + c \qquad \text{Eqn. 2.23.}$$

where Q is the percentage of drug released at time t and c is a constant. Equation 2.22. can be further modified to account for a lag period (l_t) prior to drug release (Ford *et al.*, 1991) giving equation 2.24.:

$$Q = k(t - l_t)^N \qquad \text{Eqn. 2.24.}$$

Ford *et al.* (1991) also developed a simple Higuchi-type equation:

$$Q = kt^{0.5} + c \qquad \text{Eqn. 2.25.}$$

They determined that drug release data dependent on the square root of time, would give a straight line release profile, with k represented as a root time dissolution rate constant and c as a constant.

Peppas and Sahlin (1989) noted that contributions to drug release should be considered additive, and this allowed the development of several other models for drug release from matrix tablets. Cattellani *et al.* (1988) and Harland *et al.* (1988) used equation 2.26. to describe release from matrices when both diffusion and polymer relaxation contribute to the mechanism of transport:

$$\frac{M_t}{M_\infty} = k_1 t^{0.5} + k_2 t \qquad \text{Eqn. 2.26.}$$

Catellani *et al.* (1988) proposed that the right side of the equation contained the two limiting cases involved in release from matrices i.e., Fickian diffusion by which the first 60% relates to the square root of time, and polymer relaxation transport which, if solvent uptake is linearly related to time and is slower than drug diffusion, will lead to zero-order drug release. Therefore, k_1 and k_2 in equation 2.26. represent the relative contributions of Fickian and relaxation mechanisms. Ford *et al.* (1991) modified this equation to:

$$Q = k_1 t^{0.5} + k_2 t \qquad \text{Eqn. 2.27.}$$

where Q is the percentage release.

Peppas and Sahlin (1989) determined that the fraction of drug released (f_t) due to Fickian diffusion is calculated from equation 2.28.:

$$f_t = \frac{1}{1 + \frac{k_2}{k_1} t^{\frac{1}{2}}} \qquad \text{Eqn. 2.28.}$$

Peppas and Sahlin (1989) also changed the exponent term in equation 2.26 to represent Case-II transport:

$$\frac{M_t}{M_\infty} = k_1 t^N + k_2 t^{2N} \qquad \text{Eqn. 2.29.}$$

The constants k_1 and k_2 in equation 2.29. represent (in a manner analogous to equation 2.26.) the relative contributions of Fickian diffusion and Case-II relaxation mechanisms to release, respectively. Regardless of the geometric device used, the value of the exponent for Case-II mechanism of release is twice that of the Fickian diffusion mechanism of release. This equation was modified to equation 2.30 by Ford *et al.* (1991):

$$Q = k_1 t^N + k_2 t^{2N} \qquad \text{Eqn. 2.30.}$$

where Q is the percentage release.

Additionally, Upadrashta *et al.* (1993) developed the diffusion-relaxation-erosion (DRE) model, to model drug release from matrices (equation 2.31.):

$$Q=k_1t^{1/2}+k_2t+k_3t^2+k_4t^3 \qquad \text{Eqn. 2.31.}$$

The DRE model takes into account all the processes that are likely to have a major influence on the rate of drug release (diffusion, relaxation or swelling of the polymer and erosion) from polymer matrices. The diffusional component is again represented in the first term on the right hand side, with polymer relaxation and erosion contributing to the second term. k_3 and k_4 terms are associated with the erosional component of release in equation 2.31.

Equation 2.32. is the drug release model based on erosion as the single drug release mechanism and developed by Bidah and Vergnaud (1990):

$$f_t = 1-(1-k_1t)^3 \qquad \text{Eqn. 2.32.}$$

2.8. PERCOLATION THEORY

2.8.1. General

The concepts of percolation theory have a wide application in many disciplines of science. In pharmaceutical technology, they are mainly used to explain mechanical properties of compacts and the mechanisms of the formation of the tablet (Blattner *et al.*, 1990, Leuenberger and Leu, 1992 and Leu and Leuenberger, 1993, Leuenberger *et al.*, 1992). Percolation theory based on the formation of clusters and on the existence of site or bond percolation phenomena was proposed by Leuenberger *et al.* (1987, 1990) and Bonny and Leuenberger (1991), to explain the dissolution kinetics from a matrix controlled release system over the range of drug loadings, and derive a model for readily estimating the values of the percolation thresholds for the diffusion behaviour. Percolation theory proposes a new interpretation over the concepts of "classical theories" such as that of Higuchi (1963). In addition, it provides a reasonable explanation for understanding the drug release behaviour from matrix systems.

2.8.2. Theory

Generally, percolation theory deals with the number and properties of clusters (Stauffer and Aharony, 1992). A percolation system is considered to consist of sites in an infinitely large real or virtual lattice. Applying the principles of random-site percolation to a particulate system, a cluster may be considered as a single particle or a group of similar particles, which occupy bordering sites in the particulate system. In the case of bond percolation, a group of particles is considered to belong to the same cluster only when bonds are formed between neighbouring particles.

Site percolation is an important model of a binary mixture consisting of two different materials. In the three dimensional case, two percolation thresholds will exist: a lower percolation threshold p_{c1} where one of the components just begins to percolate the system, and a second upper percolation threshold, p_{c2}, where the other component ceases to have an infinite cluster. Between the two percolation thresholds, the two components form two interpenetrating percolation networks. Below p_{c1} and above p_{c2}, the clusters of the corresponding component are finite and isolated. Therefore, in site percolation of a binary powder mixture, p_c corresponds to a critical concentration ratio of the two components.

Table 2.4. shows the critical volume-to-volume ratios for well-defined geometrical packing of monosized spherical particles (Stauffer and Aharony, 1992). The critical volume-to-volume ratios depend on the type of percolation and the type of lattice. Therefore, in the case of real binary powder systems, the geometrical packing is a function of the particle size, particle size distribution and the shape of the particles. Table 2.4. also shows the coordination numbers of isometric spherical particles of different packing structures (Leuenberger *et al.*, 1992). The coordination number is the number of nearest neighbours to each site or the maximum number of bonds that may emanate from a site. In this way, it reflects the richness of potential connections between lattice sites.

Table 2.4.

Selected percolation thresholds and coordination numbers of isometric spherical particles of different packing structures for 3-D lattices.

Lattice type	Site	Bond	Coordination number	Porosity
Diamond	0.428	0.388	4	0.66
Simple cubic	0.312	0.249	6	0.48
Body-centered cubic	0.254	0.179	8	0.32
Face-centered cubic	0.198	0.119	12	0.26

In the case of a Bethe Lattice approximation, the percolation threshold is identical to:

$$p_c = \frac{1}{z-1} \qquad \text{Eqn. 2.33.}$$

where z is the coordination number (Stauffer and Aharony, 1992). In a Bethe lattice, each bond ends in another site from which again z bonds emanate. One of these z bonds is the connection with the origin or the central point, the other $(z-1)$ bonds lead to new sites. This branching process is continued again and again. Therefore, if one reaches one site in the interior of a Bethe lattice one can go in $(z-1)$ other directions, in addition to the direction from which one came. (There is only one bond connecting the surface site to the interior at the surface of the lattice, where the branching has stopped.) There are no closed loops in this structure, which means one can always reach new sites (apart from the direction where one came from).

At a percolation threshold, some property of a system may change abruptly or may suddenly become evident (Leuenberger *et al.*, 1992). Such an effect starts to occur close to p_c and is usually called a "critical phenomenon" (Stauffer and Aharony, 1992).

One can relate this to dissolution kinetics from pharmaceutical tablets if one imagines that a drug enclosed in a matrix system can be compared to an "ant in a labyrinth" trying to escape from an ordered or disordered network (Stauffer and Aharony, 1992). For low drug concentrations i.e. low porosity matrices, the matrix will encapsulate most of the drug and drug release will be incomplete. At the lower percolation threshold p_{c1}, the drug particles begin to form a connective network within the matrix and diffusion will be anomalous at this point. At the upper percolation threshold p_{c2}, the particles forming the matrix structure become isolated within the drug particles, so

the tablet begins to disintegrate.

2.8.3. Dissolution kinetics from a matrix tablet

The concentration of the drug particles within the matrix can be expressed as site percolation probability (Leuenberger *et al.*, 1992) or site occupation probability p (Stauffer and Aharony, 1992). The amount of drug $Q(t)$ released from one tablet surface after the time t is proportional to t^N and the exponent N depends on the percolation probability p:

Case 1: $p<p_{c1}$ only the particles connected to the tablet surface can be dissolved and $Q(t)$ reaches a constant value.

Case 2: $p \approx p_{c1}$ Anomalous diffusion with $N \approx 0.2$ in three dimensions, valid for p within the range $p_{c1} \pm 0.1\ p_{c1}$ approximately.

Case 3: $p_{c1}<p<p_{c2}$ Normal matrix-controlled diffusion with $N = 0.5$

Case 4: $p_{c2}<p$ Zero order kinetics with $N = 1.0$

Between the two-percolation thresholds when the drug substance is percolating the matrix substance, the drug release kinetics follows the square-root-of-time law of Higuchi for porous matrices (Higuchi, 1963):

$$Q(t)=b\sqrt{t} \qquad \text{Eqn. 2.34.}$$

with

$$b = \sqrt{D_o C_S (2A - \varepsilon C_s)} \qquad \text{Eqn. 2.35.}$$

which leads to

$$D_o = \frac{b^2}{C_s(2A - \varepsilon C_s)} \qquad \text{Eqn. 2.36.}$$

and

$$D_o = D\ \frac{\varepsilon}{\tau} \qquad \text{Eqn. 2.37.}$$

where $Q(t)$ is the amount of drug released per unit surface area,

b is the slope of plot $Q(t)$ versus $\sqrt{t}$

D is the diffusion coefficient of the drug in the permeating medium

D_o is the apparent or observed diffusion coefficient

ε is the total porosity of the matrix (carcass)

τ is the tortuosity of the pore system of the matrix

C_s is the solubility of the drug in the permeating liquid

A is the concentration of dispersed drug in the tablet.

Close to the percolation threshold ε_c the apparent diffusion coefficient D_o obeys the following scaling law (Stauffer and Aharony, 1992):

$$D_o \, \alpha \, (p\text{-}p_{cl})^{\mu} \qquad \text{Eqn. 2.38.}$$

with

p = site percolation/occupation probability or concentration of drug particle in the matrix

p_{cl} = critical percolation probability (lower percolation threshold)

μ = conductivity exponent which is 2.0 for a three-dimensional and 3.0 for a Bethe lattice, respectively (Stauffer and Aharony, 1992).

In the case of a porous matrix, p can be expressed by the total porosity ε of the matrix and p_{cl} corresponds to a critical porosity ε_c, where the pore network begins to span the whole system. This equation can be written as:

$$D_o \, \alpha \, (\varepsilon\text{-}\varepsilon_{cl})^{\mu} \qquad \text{Eqn. 2.39.}$$

or

$$D_o = xD\,(\varepsilon - \varepsilon_{C1})^{\mu} \qquad \text{Eqn. 2.40}$$

with xD as the scaling factor.

Combining equations 2.36. to equation 2.40. the tablet property β can be calculated as a function of the drug load ε (Leuenberger *et al.*, 1992,1995).

For μ=2.0:

$$\beta = \frac{b}{\sqrt{2A - \varepsilon C_s}} = \sqrt{x_d DC_s}\,(\varepsilon - \varepsilon_{cd}) \qquad \text{Eqn. 2.41.}$$

For μ=3.0:

$$\beta^{2/3} = \sqrt[3]{x_b DC_s}\,(\varepsilon - \varepsilon_{cb}) \qquad \text{Eqn. 2.42.}$$

Therefore, the percolation thresholds ε_{cd} and ε_{cb} for a three-dimensional and Bethe lattice (respectively) can be calculated using a nonlinear or even linear regression analysis giving a slope of c and an intercept $-c\varepsilon_c$.

2.9 FRACTAL DIMENSIONS OF POROUS SOLID DOSAGE FORMS

2.9.1 General

Mercury porosimetry is widely used to determine the pore size distribution of porous materials and the void size distribution of tablets and compacts. In addition it can be used to determine the apparent density and the specific surface area of porous solids. The pressure intrusion data of mercury porosimetry analysis has also been used to determine the fractal dimension of a porous body, such as a tablet (Leuenberger *et al.*, 1990, Usteri *et al.*, 1990, Bonny and Leuenberger, 1993).

A fractal dimension (Mandelbrot, 1982) is a very suitable concept to describe a complex structure, i.e. an internal surface of a pore system, the roughness of a particle. Fractal geometry is related to the principle of self-similarity, i.e. the geometrical shape is kept identical independent of the scale, magnification or power of resolution (Mandelbrot, 1982). In practice the range of self-similarity may only be limited to a physical range of one or two orders of magnitude.

The first model, which allowed the calculation of a fractal dimension from mercury intrusion porosimetry data, was presented by Pfeifer and Avnir (1983). Porous tablet systems were characterised by fractal dimensions by Usteri *et al.*, 1990 and Bonny and Leuenberger (1993). The porous systems can be considered as an ideal fractal when the geometry i.e. the pore size distribution is similar for all magnifications. In this instance, the internal surface of the pores tends to infinity, whereas the volume of the material is finite.

2.9.2. Volume Fractal Theory

The volume fractal concept is based on the principle that as the function of the resolution power to detect a pore volume or pore size is increased the void volume is increased. Usteri *et al.* (1990) based this relationship between the accessible void space (sum of pore volumes) and the power of resolution of the pore size on a mathematical self-similar model of pores, i.e. a Menger sponge. The construction of a

Menger sponge is outlined by Pfeifer and Avnir (1983). The Menger sponge represents an idealized three-dimensional network of a pore system with the fractal dimension D of 2.727 (figure 2.1.) (Pfeifer and Avnir, 1983). A unit cube is considered from which seven cubes of side length 3^{-1} are removed in the first iteration resulting in a system of eight corner cubes being connected with twelve bridging cubes. In the second iteration seven cubes of side length 3^{-2} are removed from each of the remaining twenty cubes of the first iteration. This process of cutting out an increasing number of smaller and smaller cubes produces a sponge like structure. With increasing power of resolution the internal surface tends to infinity, whereas the volume of the solid vanishes.

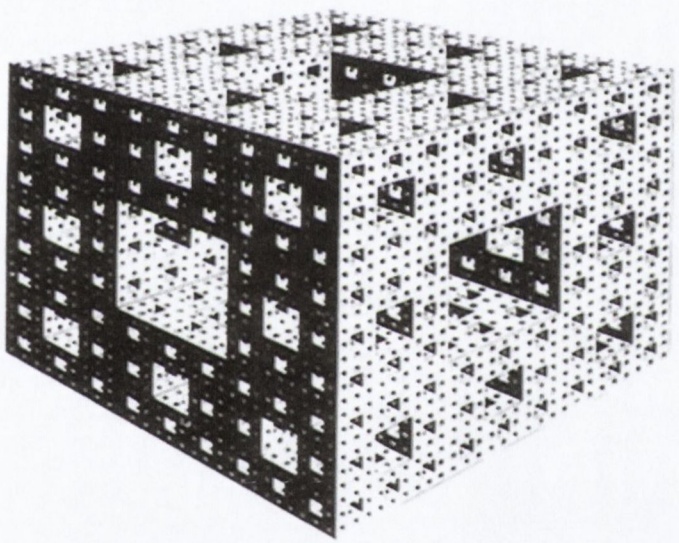


Figure. 2.1. Menger sponge with fractal dimension of 2.727 (idealised three-dimensional network of a pore system.

In figure 2.1. the removal of cubes has been finished after four iterations. Usteri *et al.* (1990) considered that the true density of the solid material forming the Menger sponge is always 1. However, the solid fraction or the ratio of the solid volume to the total volume depends on the number of iterations or the removal of cubes. The solid fraction or relative density, $V_s(j)$ can be defined as follows:

$$V_s(j) = \frac{V_{tot} - V_p(j)}{V_{tot}} \qquad \text{Eqn. 2.43.}$$

where $V_p(j)$ is equal to the pore volume at the resolution j and V_{tot} or apparent volume corresponds to the measured volume i.e. from the height and diameter of the tablet. The volume fractal dimension D_v of the Menger sponge is calculated as:

$$log(V_s[j])=(3-log20/log3)\cdot log(d[j]) \qquad \text{Eqn. 2.45.}$$

where $d(j)$ is the side length of the cube and $log20/log3$ is equal to the volume fractal dimension D_v of 2.727. The general form of this equation for any sponge like system including a tablet/compact is:

$$log(V_s[j])=(3-D_v)\cdot logd[j]+c \qquad \text{Eqn. 2.46.}$$

where c is a constant.

The pore system of any "real" porous body is finite and the internal surface reaches an upper limit. In "real" systems, no sharp transition of an ideal fractal to a non-fractal region exists. Instead, one has a continuous change of the fractal behaviour (Usteri *et al.*, 1990).

As the resolution power increases the solid fraction of a compact/tablet approaches a finite value. Therefore, it is possible to determine by mercury porosimetry the volume fractal dimension of a sponge-like system such as a slow release dosage form after elution of an appreciable amount of drug (Usteri *et al.*, 1990). Papers characterising matrix types systems have elucidated that the fractal dimension can only be determined in a narrow range of resolution (Leuenberger *et al.*, 1990, Usteri *et al.*, 1990, Bonny and Leuenberger, 1993).

2.9.3 Surface Fractal Theory

In the case of the surface area $A(j)$ of the Menger sponge a similar equation can be obtained:

$$log(A[j])=(2-log20/log3)\cdot log(d[j]) \qquad \text{Eqn. 2.47.}$$

It is a unique property of the Menger sponge that the volume fractal D_v is equal to the surface fractal D_s=log20/log3. The above equation can be generalised as follows:

$$log(A[j])=(2-D_s)\cdot logd[j]+c \qquad \text{Eqn. 2.48.}$$

It is possible to calculate D_s on the basis of this equation and applying mercury porosimetry intrusion data (Bonny and Leuenberger, 1993). The specific surface area is plotted on a log-log plot as a function of the yardstick length or power of resolution (pore diameter). The slope of the resulting straight line is equal to $2\text{-}D_s$. Since the slope is negative, i.e. the surface is higher at a higher resolution power the value for D_s is between 2 and 3. Therefore, the surface fractal D_s can describe the roughness of a surface and includes the prerequisite of a self-similar shape independent of the scale. This has implications for powder technology i.e. if the roughness measurement shows at least within a certain range an approximate self-similarity it might be possible to describe the surface by indicating a value for the specific surface area and a value for the surface fractal D_s.

2.9.4. Fractal Geometry and Percolation Theory

Percolation theory and the concept of fractal dimensions are related since close to percolation thresholds critical phenomena may occur (Stauffer and Aharony, 1992). As a consequence of percolation theory not all of the pores are accessible (to mercury intrusion) in the same way and some pores are not accessible at all i.e. larger pores hidden behind pores of smaller sizes or closed pores. This is evident in the hysteresis loop between filling-up and draining-off the mercury from the void space within the tablet. Below the first percolation threshold only those finite clusters of drug particles are dissolved directly connected to the surface of the tablet. Above the first percolation threshold the drug particles forming the infinite network, as well as the surface connected isolated clusters are dissolved. In both instances, the isolated clusters of drug within the tablet will not be released if the structure remains unchanged. If the content of the drug is raised to a higher amount exceeding usually 60% w/w of drug, the excipient does not encapsulate anymore the drug, but the drug particles start to encapsulate the excipient (Leuenberger *et al.*, 1990). These reservations have to be taken into account when the fractal dimensions of a porous network are determined.

2.10. CONCLUSION

Controlled release dosage forms cover a wide range of prolonged action formulations, including hydrophobic matrix systems. "Classical theories" such as Higuchi have an

important role in the understanding of release kinetics from inert matrices. In addition, models based on the physical model proposed by Korsemeyer *et al.* (1983) have an integral role in differentiating the drug release mechanism from matrix systems. Besides, the concepts of percolation theory can be used to explain the dissolution kinetics of matrix type controlled release systems. By using these concepts, a more rational basis for design of dosage forms may be achieved.

CHAPTER 3

ETHYLCELLULOSE: A REVIEW

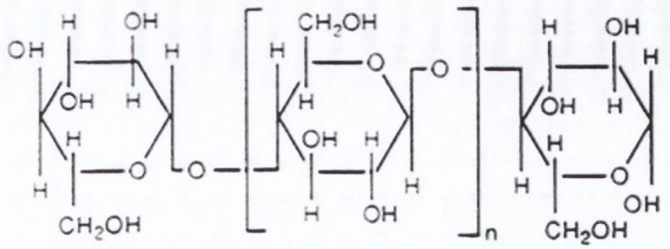
3.1. INTRODUCTION

Ethylcellulose ethers are a family of organosoluble thermoplastics, which are widely used in pharmaceuticals since their commercial introduction in the mid-1930's (Pollock and Sheskey, 1996). They are among a very small number of water insoluble excipient polymers that are approved and accepted globally for pharmaceutical applications (Pollock and Sheskey, 1996). In addition, environmental issues are having an impact on the extent of ethylcellulose usage in the pharmaceutical industry. Processes such as solid dispersion techniques and microsphere formation are seen as less tolerable and more expensive, since they involve several unit operations and use organic solvents (Upadrashta *et al.*, 1993). Other methods of drug delivery including direct compression technique, which avoid these pitfalls are considered as suitable alternatives. Past research has shown that ethylcellulose satisfies all the criteria as a direct compression matrix (Upadrashta *et al.*, 1993). Additionally, ethylcellulose is both an inert and hydrophobic polymer (Upadrashta *et al.*, 1993). The powder is essentially tasteless, odourless, colourless and very inert physiologically.

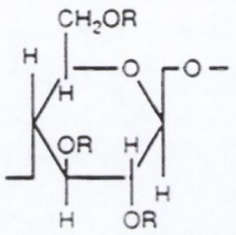
3.2. STRUCTURE

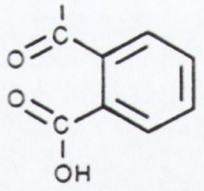
Ethylcellulose belongs to a group of polymers called the cellulose ethers (Savage, 1965). Cellulose ethers comprise a class of cellulose derivatives, soluble in water or organic solvents. All cellulose ethers are derived from and hence posses the polymeric backbone of cellulose, containing a basic repeating structure of β-anhydroglucose (glucopyranose) units bound through acetal (glycosidic) linkages. The repeat unit is the disaccharide 4-*O*-β-D-glucopyranosyl-d-glucopyranose (cellobiose). The anhydroglucose moiety contains three reactive hydroxyl functions: one primary at the C-6 position, and two secondary at the C-2 and C-3 positions (figure. 3.1.). The chemical difference between the various cellulose ethers is the difference in the hydroxyl group substituent, for example ethylcellulose has an ethyl hydroxyl group substituent, methylcellulose has a methyl hydroxyl group substituent (figure 3.1.).

The number of substituent groups of these hydroxyls can be designated either by a weight percentage or by the number of points where the groups are attached, commonly know as the degree of substitution (DS). In the case where the three available positions on each anhydroglucose units are substituted, the DS is 3, i.e. the group cannot be further alkylated. Additionally, a term 'molar substitution' (MS) is given to describe the total number of moles of a group attached to the cellulose backbone, or to the side chain. A cellulose derivative can have a MS of 4 but a DS of 1, but in no case can its DS exceed 3. In this instance, the length of the pendant chain will be the ratio of MS to DS (Savage, 1965).



Cellulose n - 1000 approx



Polymer	Substituent Groups [R]
Methylcellulose	· H · CH_3
Hydroxypropyl methylcellulose	· H · CH_3 · CH_2 · CH(OH) · CH_3
Hydroxypropylcellulose	· H · CH_2 · CH(OH) · CH_3
Ethylcellulose	· H · CH_2CH_3
Cellulose Acetete Phthalate	· H · C(=O) · CH_3 
Hydroxypropylmethylcellulose Phthalate	· H · CH_3 · CH_2 · CH(OH) · CH_3

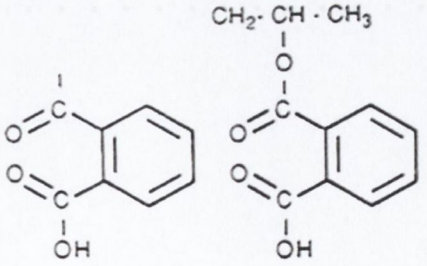


Figure 3.1. The molecular structure of cellulose and the cellulose derivatives, including ethylcellulose.

3.3. MANUFACTURE OF ETHYLCELLULOSE

3.3.1. Raw materials

Cellulose is abundant in nature, and suitable forms for manufacturing cellulose ethers including ethylcellulose can be obtained from a variety of sources, such as seed fibres (cotton) and wood fibres (hardwoods and soft woods), bast fibres (flax, hemp, jute), grasses (bamboo), algae (*Valonia ventricosa*) and bacteria (*Acetobacter xylinium*). Cottonseed fibre and wood fibre are the main sources for production of cellulose ethers (Savage, 1965).

Cotton cellulose is produced from the cotton ball. This is composed of long and short fibre hairs attached to a seed. The longer cotton fibres or lint fibres are used to produce textile fibres, while the shorter fibres (also known as linters) are the raw material for chemical modification. After ginning to remove the staple fibre, the linters are removed by passing the cottonseed through a delinting machine. The cellulose content at this stage varies between 65-80% w/w cellulose, the remainder composing primarily of fats, waxes, and pectins coating the fibres. Other foreign debris may also be present including, particles of dirt, bits of seed hulls and metal shavings. Before use in the manufacture of cellulose ether, the raw linters are mechanically cleaned to remove all foreign debris; digested under pressure in dilute caustic to remove fats, waxes, pectins, seed hulls etc, bleached, washed, formed into sheets and dried. The final product called chemical cotton may contain up to 99.5% pure cellulose.

Wood fibre is the other major source of cellulose. However it only contains 35-45% w/w cellulose (Savage, 1965). The remainder composes mainly of alkali-soluble hemicelluloses. Purification yields varying grades of cellulose, known as dissolving wood pulps. High purity wood pulps can be obtained from sulfite or prehydrolyzed kraft processes.

Dissolving wood pulp is less expensive than cotton cellulose but lower purity and yields may offset this advantage. In addition wood cellulose yields lower molecular weight cellulose substrates than cotton cellulose. This molecular weight difference between the purified form of cotton and wood cellulose is exploited by manufacturers of cellulose ethers to control solution viscosities of products. High viscosity grades

may be made from cotton cellulose while lower viscosity grades may be made from wood cellulose (Savage, 1965).

3.3.2. Processes and purification

The reaction used to synthesise cellulose ethers including ethylcellulose is based on the nucleophilic reaction of cellulose under alkaline conditions, with one or more alkylating reagents such as an alkyl halide (Savage, 1965). Alkylation processes are homogenous or heterogeneous; the latter having achieved greater commercial importance. The heterogeneous process means that the cellulose and the cellulose ether remain in a fibrous or particulate state throughout the reaction. The problem with cellulose is its crystalline–amorphous nature, which establishes a gradient of reactivity under heterogeneous conditions (Savage, 1965).

To overcome this problem and to promote a uniform reaction, an activated cellulose substrate is formed, generally in situ, before reaction with the alkylating reagent. Activated cellulose substrates are formed by the addition of reagents that can disrupt the crystalline regions without dissolution. Aqueous solutions of sodium hydroxide > 18% (above 20°C) are most commonly used to give a uniform reaction; the resulting mixture is termed alkali cellulose. In addition to promoting decrystallisation of the cellulose, sodium hydroxide also acts as a catalyst for the etherification. The alkali treatment also causes swelling and decrystallisation of cellulose, and consequently increases the number of accessible regions in the cellulose. The preparation of alkali cellulose is the first step performed in the manufacture of cellulose ethers, including ethylcellulose.

Ethyl chloride is added to the alkali cellulose at 90-150°C, 828 to 965 Kp for 6-12 hours in a nickel-clad reactor to form ethylcellulose as outlined in equation 3.1.:

$$C_6H_{10}O_5.NaOH + C_2H_5Cl \rightarrow C_6H_90_5C_2H_5 + NaCl + H_2O \quad \text{Eqn. 3.1.}$$

Alkali cellulose + Ethyl chloride → Ethylcellulose

Diluents such as benzene or toluene can be used. The resulting sodium chloride is rinsed away with water. Purification may also involve the brightening of the cellulose ether with a reagent such as sodium bisulphite. The product is then spin-dried to a water content of 55-60%, homogenized and compacted in a screw extender (Greminger, 1978).

The ethylcellulose powder produced may be white to light tan in appearance and granular in nature (Rowe *et al.*, 2003). The variations in physical properties of the ethylcellulose powders are a result largely of the variation in the degree of etherification. The ethoxyl substitution values of commercial products range from a DS of 2.20 to 2.60 ethoxyl groups per anhydro-glucose units, which corresponds to an ethoxyl content of 44.5% to 49% (Greminger, 1978).

Solution viscosity and concentration significantly influence the utility of cellulose ethers, including ethylcellulose in industrial applications. To meet these needs, manufacturers usually supply ethylcellulose in various viscosity grades, such as 4 cP, 10 cP, 22 cP and 100 cP. These different viscosity grades are obtained by controlling the molecular weight during processing. This is achieved by heterolytic or homolytic cleavage of the glycosidic acetal linkages under a variety of conditions (Savage, 1965).

Ethylcellulose is commercially available from Hercules Inc. and Dow Chemical Co (trade name Ethocel®) in different types of ethoxyl substitution. It is also available in aqueous colloidal dispersion forms under the trade names Aquacoat® and Surelease®. The Aquacoat® dispersion has a 28%-32% solid content consisting of 24.5-29.5% ethylcellulose, 0.9-1.7% of sodium lauryl sulphate and 1.7-3.3% of cetyl alcohol. Surelease® is marketed as a 25% solid (ethylcellulose, oleic acid and fumed silica) dispersion in an ammonical water (Kumar and Banker, 1993).

3.4. GENERAL PROPERTIES

3.4.1. Viscosity and Molecular weight

The suitability of polymers (including ethylcellulose) used in film coating is determined by means of an apparent viscosity (η_{app}). The apparent viscosity of a polymer is the viscosity of a specified concentration of a polymer, dissolved in a specified solvent at a specified temperature (table 3.1.) (Rowe, 1984). Since viscosity control is achieved by controlling the chain length during the production process, the η_{app} can be regarded as an indirect measure of the molecular weight of the polymer, as clearly shown by the equation 3.2.:

$$M_w = k_y (\eta_{app})^{\Omega} \qquad \text{Eqn. 3.2.}$$

where M_w is the molecular weight, k_y and Ω are constants for each polymer determined by regression analysis. k_y and Ω values are influenced by the method used to determine the molecular weight of the polymer, which can include osmotic pressure, light scattering or gel permeation chromatography.

Table 3.1.

Apparent viscosity specifications for cellulose ether polymers[a]

Polymer	Solvent	% w/w	Temp. °C	Specification
Methylcellulose	Water	2	20	±20% of nominal
Ethylcellulose				
(<46.5%w/w ethoxyl)	Toulene:EtOH			
	(60:40)	5	25	3.0-5.5%[1]
(>46.5%w/w ethoxyl)	(80:20)	5	25	6.0-8.0%[2]
				±10% of nominal
HPMC	Water	2	20	±20% of nominal

[a] Rowe, 1984, [1] (for nominal 4), [2] (for nominal 7)

Generally high concentrations of polymers are needed when determining the apparent viscosity. This can lead to significant molecular interaction. In order to provide more basic information on the molecular weight-viscosity relationship, viscosity measurements are performed in more dilute solutions using fractionated samples of the polymer. The intrinsic viscosity can then be obtained from the Mark-Houwink equation:

$$[\eta] = k_t M_w^{\alpha} \qquad \text{Eqn 2.3.}$$

where [η] is the intrinsic viscosity of the polymer, and k_t and α are constants, which depend on the solvent and solution temperature. The constant α is an indicator of the polymer-solvent interaction or the general form of the polymer molecule in solution. If the polymer molecule is coiled tightly as a spheroid than α should have a value of zero. When the polymer molecule is fully extended (as in the presence of a good solvent) the value is one. Values of k_t and α for some of the cellulose ethers

(including ethylcellulose) used in film coating are outlined in table 3.2. below (Rowe, 1984).

Table 3.2.

Constants for Mark-Houwink equation for cellulose ether polymers

Polymer	Solvent	Temperature (^{0}C)	k_t (x10 $^{-5}$ dl g^{-1})	α
Methylcellulose	Water	25	316.0	0.55
Ethylcellulose	Chloroform	25	11.8	0.89
	Benzene	25	29.2	0.81
Hydroxypropylcellulose	Ethanol	25	2.6	0.92

3.4.2. Effect of Molecular Weight on Mechanical Properties of Ethylcellulose Films

Mechanical properties of cellulose ethers including flexibility, elongation and tensile strength, depend on the degree of polymerisation or polymer molecular weight rather than group substitution. Flexibility increases linearly with viscosity and has no measurable maximum. In addition, the elongation and tensile strength of films increases with the viscosity of the solution, until some critical molecular weight when there is no further increase. Theoretical predictions for this point of inflection correspond to a molecular weight of 4-5 x 10^4, or DP of 200-25 for the cellulose ethers. However, under experimental conditions the molecular weight value determined was higher 7-8 x 10^4 (Rekhi and Jambhekar, 1995). This discrepancy in theoretical and experimental values is accounted for by the presence of low molecular weight components (less than 5 x 10^3) within the molecular weight distribution (Rekhi Jambhekar, 1995). These low molecular weight components have a detrimental effect on the mechanical properties of film coating polymers.

3.4.3. Solubility

Ethylcellulose shows greatest solubility in solvents that have almost the same solubility parameter as the material itself. The solubility of ethylcellulose is determined in three types of solvents, namely, poor, moderate and strongly hydrogen bonding solvents, by mixing a known weight of the polymer in a selected solvent and observing the resultant mixture (table 3.3.) (Burrell, 1975).

In addition, the solubility parameter range may vary with DS. The lower substitution types (DS 2.3) are soluble in few solvents e.g. methylene chloride and ethanol. Solubility in all classes of organic solvents improves with increased ethoxyl substitution up to a maximum composition of DS 2.4-2.6. Further ethoxylation has the effect of limiting the solubility to non-polar aromatic hydrocarbons. Ethylcellulose when completely ethoxylated (DS 3.0) displays low strength, flexibility and thermoplasticity, in addition to extremely limited solubilities and compatibilities (Savage, 1965).

Table 3.3.

Solubility parameter range for ethylcellulose in poorly, moderately and strongly hydrogen bonded solvents

Degree of substitution	**Ethoxyl Content**	**Solubility Parameter ($MPa^{1/2}$) Poor***	**Solubility Parameter ($MPa^{1/2}$) Moderate***	**Solubility Parameter ($MPa^{1/2}$) Strong***
2.28-2.38	45.5-46.8	0	17.4-22.1	19.4-23.3
2.42-2.53	47-49.0	16.6-22.7	15.1-22.1	19.4-29.7
>2.53	>50	17.4-19.4	16.0-20.1	19.4-23.3

*hydrogen bonded solvents

3.4.4. Stability to water and pH

Ethylcellulose is the most unreactive of the cellulose ether polymers. Ethylcellulose absorbs very little moisture from the atmosphere and this evaporates easily leaving the ethylcellulose polymer unchanged (Rekhi and Jambhekar, 1995). However although it does not react with water, when ethylcellulose is maintained under sufficient humidity it can absorb water in large amounts (Dubernet *et al.*, 1990)

3.4.5. Stability to heat and light

In the dry state ethylcellulose and the films produced are stable up to the temperatures used during stability testing i.e. below 50°C (Rowe, 1984). In fact, ethylcellulose shows stability up to temperatures as high as its softening temperature (Rekhi and Jambhekar, 1995). Light, visible or ultra violet light has no discoloring action on ethylcellulose. However, formulations prepared with ethylcellulose should still be

stabilised to prevent oxidative degradation in the presence of sunlight or ultraviolet light and at elevated temperatures (Rekhi and Jambhekar, 1995). This may be prevented using an antioxidant and a compound with light absorption properties between 230-340 nm (Rowe *et al.*, 2003).

3.4.6. Biological stability

In the dry state or as films all the cellulose ether polymers including ethylcellulose show good resistance to degradation by moulds and bacteria (Rowe, 1984).

3.4.7. Health and Safety Factors

Ethylcellulose showed no evidence of toxicity in animal studies undertaken by Dubernet *et al.* (1990). It is neither a skin irritant nor a sensitising agent (Dow Chemical Company, 1997). It is cleared for many applications in food and cosmetic products (Rowe *et al.*, 2003). Since, ethylcellulose is not metabolised it is not recommended for use in parenteral products (Rowe *et al.*, 2003).

Some powders may be considered nuisance dusts; and fine dusts may reach explosive levels in an enclosed atmosphere (Dow Chemical Company, 1997).

3.5. ANALYSIS AND SPECIFICATIONS

Analytical methods for cellulose ethers including ethylcellulose include the determination of (Rowe, 1984):

- the degree of substitution (DS), usually expressed as a weight percentage
- the apparent viscosity
- the moisture content or loss on drying
- the ash content or residue on ignition
- IR absorption spectra

3.6. APPLICATIONS IN PHARMACEUTICAL FORMULATIONS

3.6.1. Matrix Agents

Ethylcellulose has been used as a carrier for the preparation of prolonged release solid dispersions of drugs (Shaikh *et al.*, 1987). In addition, ethylcellulose has been used in

the preparation of matrix tablets by direct compression (Upadrashta *et al.*, 1993, Lin and Lin, 1996).

3.6.2. Binder in tablets

In tablet formulation, ethylcellulose may be employed as a binder. The ethylcellulose is blended dry, or wet granulated with a solvent such as ethanol (95%) (Rowe *et al.*, 2003).

3.6.3. Coating material for stabilisation and taste masking

When ethylcellulose is dissolved in propan-2-ol, it is used as a coating for ascorbic acid granules. This prevents oxidation of the ascorbic acid and also hides the unpleasant taste on administration (Rowe *et al.*, 2003).

3.6.4. Thickening agent in topical formulations

When used with an appropriate solvent, ethylcellulose can be used as a thickening agent in creams, lotions or gels (Rekhi and Jambhekar, 1995).

3.6.5. Coating for drug microcapsules and beads

Ethylcellulose has been used to coat particles to form microcapsules and beads. The release of the drug is a function of the microcapsule wall thickness (Deasy *et al.*, 1980). Generally, high ethylcellulose viscosity grades are used (Rowe *et al.*, 2003).

3.6.6. Coating material for controlled release

Ethylcellulose is available as an aqueous polymer dispersion for use in controlled release (Aquacoat® and Surelease®). This facilitates high solid contents with relatively low viscosity (Kumar and Banker, 1993).

3.6.7. Film forming agent

Caffeine and salicylic acid incorporated into ethylcellulose films have been shown to exhibit diffusion-controlled release (Rekhi and Jambhekar, 1995).

3.7. APPLICATIONS IN NON-PHARMACEUTICAL APPLICATIONS

Properties of ethylcellulose such as its toughness and high temperature stability mean that it has extensive applications outside the pharmaceutical industry (Savage, 1965). These are outlined in table 3.4.

Table 3.4.

Application and Products of Ethylcellulose

Application	Functions
lacquer	Paper, linoleum, surgical tape, cellophane
inks	Screen-process, gravure and flexographic
varnishes	Shorten drying time, increase toughness, decrease surface tack
film and foil	Wrapping material, electrical insulation
adhesives	Low temperature flexibility, strength, increased melting point
plastics	Scrap reuse; adaptable to extrusion and injection processes

3.8. CONCLUSION

Ethylcellulose is an inert hydrophobic polymer and its properties such as its lack of toxicity, stability during storage and good compressibility make it suitable as a pharmaceutical vehicle in a number of dosage forms.

EXPERIMENTAL

CHAPTER 4

MATERIALS AND METHODS

4.1. MATERIALS USED IN EXPERIMENTS

Materials	Supplier/Manufacture
Ethylcellulose 4 cP	Aldrich Chemical Company
Ethylcellulose 10 cP	Aldrich Chemical Company
Ethylcellulose 22 cP	Aldrich Chemical Company
Ethylcellulose 100 cP	Aldrich Chemical Company
Ethylcellulose 100 cP FP	Dow Chemicals
di-Sodium hydrogen phosphate-12-hydrate	Riedel-de Haën
Sodium dihydrogen phosphate-2-hydrate	Riedel-de Haën
Sodium chloride	Riedel-de Haën
Adipic acid	SIGMA chemicals Ltd.
Succinic acid	SIGMA chemicals Ltd.
L-(+)-tartaric acid	SIGMA chemicals Ltd.
Ibuprofen	Elan Corporation plc.
Amaranth dye	BDH Chemicals Ltd.
Paraffin wax, pastillated	BDH Chemicals Ltd.
ortho-Phosphoric acid 85%	BDH Chemicals Ltd.
Standard buffer solution pH 4.00	Riedel-de Haën
Standard buffer solution pH 7.00	Riedel-de Haën
Reference material for Gemini 2370:	
Kaolinite (P/N 004-16819-00)	Micromeritics Instrument Corporation
Triple distilled mercury (GPR^{TM})	BDH Chemicals Ltd.
Nitrogen Gas	Air Products
Helium Gas	Air Products
Apiezon-H^{tm} vacum grease	Gec Alsthom (M&I) Ltd.
Dow Corning high vacuum grease	Dow Corning
High pressure fluid	Micromeritics Instrument Corporation
Circular microscope glass cover slips	Chance Proper Ltd.
Supor-450^{tm} (0.45 μm) membrane filters	Gelman Sciences Inc.
Syringe filter holders, plastic, 13 mm	Gelman Sciences Inc.
Omnifix 5 ml syringe	B. Braun
Magnetic stirrer bars (3.5 cm)	Fisons

Mettler ME-27331 Aluminium crucibles 40µl	Mettler

4.2. INSTRUMENTS (AND ACCESSORIES) USED IN EXPERIMENTS

Instrument	**Manufacture**
Mettler analytical balance AE240	Mettler
Mettler PE160 balance	Mettler
Twin shaft RZR1 stirrer motors	Heidolph
Thermostat pumping motor	Heto
Digital IONALYSER pH meter	Orion Research
Manesty E2 tablet machine	BWI Manesty
IR hydraulic press	Perkin-Elmer UK Ltd.
13 mm punch and die set	Graseby Specac Ltd.
Agate Mortar and Pestle	FSA Apparatus
Vacuum dessicator	FSA Apparatus
Vacuum Oven	FSA Apparatus
Sliding calliper	Inox helios
HP8452A UV/visible spectrophotometer (and associated software)	Hewlett Packard
Spherisorb C8, 5um 250 x 4.6 mm HPLC	Jones Chromatography
Shimadzu C-R3A chromatopac	Shimadzu
Shimadzu SPD-6A UV spectrophotometeric detector	Shimadzu
Mettler Toledo DSC 821^{e} (and associated software)	Mettler, Switzerland
Mettler Toledo MT5 microbalance	Mettler, Switzerland
X-Ray Diffraction Machine (D500)	Siemens
MM2 Mixer Mill	Retsch
MM2 Mixer Mill accessories:	
Stainless steel jars of 25ml volume x 2	*Retsch*
Stainless steel grinding balls (12 mm) x 4	*Retsch*
Hand Held sieves (BS 410) aperture size	Endecotts

63, 90, 125, 250, 355 and 500 µm	
Alpine Air Jet sieve	Alpine
Alpine air jet sieve accessories:	
40 µm aperture sieve	*Haver & Boecker*
Fines collection filter	*Alpine*
Vacuum cleaner	*Nilfisk*
Malvern 2600c laser diffraction particle sizer analyser and software	Malvern
Malvern 2600c accessories:	
100 mm and 300 mm lens	*Malvern*
Dry powder feeder attachment	*Malvern*
Jun-Air compressor	*Jun-Air*
Vacuum cleaner	*Nilfisk*
Malvern Mastersizer 2000	Malvern
Scirocco dry powder feeder attachment	*Malvern*
Poresizer 9320 (Mercury porosimeters) (and associated software)	Micromeritics Instrument Corporation
Poresizer 9320 accessories:	
Penetrometer ($3cm^3$) for solids	*Micromeritics Instrument Corporation*
TD3 double stage vacuum pump	*Leybold-Heraeus GMBH*
Air compressor	*Charles Austen Pumps Ltd.*
Gemini 2370 Surface Area Analyser	Micromeritics Instrument Corporation
Gemini 2370 accessories:	
Large bulb sample tubes	*Micromeritics Instrument Corporation*
Long filler rods	*Micromeritics Instrument Corporation*
Sample tube stoppers	*Micromeritics Instrument Corporation*
Glass Beads 3 mm	*Micromeritics Instrument Corporation*
Liquid Nitrogen dewar 600ml	*Micromeritics Instrument Corporation*
Welch DirecTorr V vacuum Pump	*Welch*
Flow Prep 060 Degasser	*Micromeritics Instrument Corporation*
UBM profilometer with microfocus sensor (and associated software)	Advanced Products & Technologies Ltd.
Optical micrometer	Graticules Ltd.
Contact Anglometer Model 1501	Micromeritics Instrument Corporation

Lauda Tensiometer TD 1E	Lauda
Lauda Tensiometer accessories:	
Sample beaker	*Lauda*
Displacer	*Lauda*
500 mg calibration weight	*Lauda*
19.1 mm diameter ring	*Lauda*
Reichert hot stage	Mettler
Meopta microscope	Mettler

4.3. COMPUTER SOFTWARE*

Software	**Supplier**
Scientist, version 1.0	Micromath Scientific Software
Microsoft Excel for Windows, version 2000	Microsoft

*excluding the software mentioned with particular instrumentation

4.4. DISSOLUTION STUDIES

4.4.1 Preparation of compressed discs

4.4.1.1. Preparation of two-component 13 mm discs of different polymer-to-drug weight ratio and viscosity grade

Discs were prepared by compressing 250 mg powder in a Perkin-Elmer hydraulic press, for 10 minutes under 7000 kg pressure, using a 13 mm flat faced punch and die set. The long dwell time ensured consistent deformation of the viscoelastic ethylcellulose, since compact porosity is an important aspect of dissolution control (Potter *et al.*, 1992). Each powder component was sieved less than 180 μm and mixed together in an agate mortar and pestle for ten minutes before compression. Composition was on a weight for weight basis. The ethylcellulose 4 cP:ibuprofen weight ratio was varied in the following polymer-to-drug weight ratios; 72:25, 65:35, 60:40, 55:45, 50:50, 45:55, 40:60 and 25:75. Similarly, for compacts prepared with ethylcellulose 100 cP. The polymer-to-drug weight ratios 75:25, 50:50 and 25:75 were varied for compacts prepared with ethylcellulose 10 cP and 22 cP. Compacts were also prepared with ethylcellulose 100 cP FP in a 50:50 polymer to drug weight.

In addition, ethylcellulose 4 cP:ibuprofen compacts and ethylcellulose 100 cP:ibuprofen compacts (50:50 weight ratio) were compacted at different compaction pressures for ten minutes. Compaction pressures used were within the range of 2000 kg, and 14000 kg. All compacts were prepared at least twenty-four hours before release studies were performed.

4.4.1.2. Preparation of two-component 13 mm discs of different ethylcellulose particle size and of different ethylcellulose viscosity grade

Powder mixtures were prepared by mixing one of four different ethylcellulose particle size fractions, of either ethylcellulose 4 cP or 100 cP viscosity grade, and one ibuprofen particle size fraction (sieved less than 180 μm) in an agate mortar and pestle for ten minutes. A drug-to-polymer weight ratio of 50:50 was used for each of these formulations. The four different ethylcellulose particle size fractions included 40-63 μm, 90-125 μm, 180-250 μm and 355-500 μm. Each mixture was compacted at 7000 kg compaction pressure in a Perkin-Elmer hydraulic press (for ten minutes) to produce discs of approximately 250 mg in weight. All compacts were prepared at least twenty-four hours before any release studies were performed.

4.4.1.3. Preparation of three-component 13 mm discs

Ibuprofen powder and one of three different acid excipients (adipic acid, succinic acid or L-(+)-tartaric acid) were used in the disc formulation in a polymer:acid excipient:drug weight ratio of 50:25:25. Each acid excipient was ground in an agate mortar and pestle for ten minutes and then sieved less than 180 μm (by hand) before being mixed together with the other components in an agate mortar. The ethylcellulose powder (either ethylcellulose 4 cP or 100 cP viscosity grade) and ibuprofen were also sieved less than 180 μm before mixing with the other disc components. Each physical mixture was then compressed at 7000 kg for 10 minutes. Target disc weight was 250 mg. The succinic acid:ibuprofen weight ratio was also varied to include weight ratios of 30:20, 35:15 and 40:10. The effect of using a further reduced acid excipient particle size (sieved less than 40 μm) during formulations was also investigated. Before sieving, the acid excipient was ground in a Retsch MM2 Mixer Mill to facilitate particle size reduction. All compacts were prepared at least twenty-four hours before any release studies were performed.

4.4.1.4. Preparation of two-component 8.5 mm discs

Compressed discs were made from ibuprofen and one of three different acid excipients (adipic acid, succinic acid or L-(+)-tartaric acid) in a 50:50 weight ratio. This weight ratio was chosen because sufficient number of compacts could be produced for experimental evaluation. Problems with discs breaking were encountered at other weight ratios. Both powder components were sieved less than 180 μm before being mixed in an agate mortar for 10 minutes. The powder mixture was then compressed on a Manesty E2 single-punch tabletting machine using either a 8.5 mm diameter flat-faced punch set or 8.5 mm diameter concave punch set. Compacts were compacted at one of two different compaction pressures, designated high and low compaction pressure. Target disc weight was 200 mg. After ejection the discs were stored for 24 hours in amber glass jars before any further evaluation was undertaken.

4.4.2. Dissolution medium

Dissolution studies were performed in 0.0668 M phosphate buffer pH 7.40, maintained at 37°C. Phosphate salts frequently contribute to the buffering capacity of physiological fluids (Martin, 1993). The dissolution medium was prepared using deionised water. The composition of phosphate buffer is outlined in table 4.1.

Table 4.1.

The composition of phosphate buffer used in dissolution medium

pH	$Na_2HPO_4.12H_20$ (g/L)	$NaH_2PO_4.2H_2O$ (g/L)	NaCl (g/L)
7.40	19.1	2.1	4.476

4.4.3. U.S.P paddle method and U.S.P basket method

Dissolution studies were undertaken on two component and three component compacts 13 mm in diameter, using the United States Pharmacopoeia (U.S.P. 22) paddle apparatus (Vankel dissolution apparatus VK6000). Compacts 8.5 mm in diameter underwent dissolution using the United States Pharmacopoeia (U.S.P. 22) basket apparatus.

The stirring speed of the paddles or baskets was set to 60 rpm. The volume of dissolution medium was 500 ml, in 1 L dissolution vessels. At intervals, 3 ml of

sample was removed from a zone midway between the base of the vessel and the surface of the dissolution medium, approximately 2 cm from the vessel wall. Samples were filtered through a 0.45 μm membrane filter. The sample volume was then replaced with an equal volume of fresh medium at 37°C. All runs were performed in triplicate so all results are the average of at least three dissolution runs.
Samples were analysed by UV spectroscopy or HPLC.

4.4.4. UV analysis

A Hewlett Packard HP8452A UV/visible spectrophotometer was used for UV analysis.

When measuring the ibuprofen concentration a λmax of 222 nm was used. Internal referencing was used for quantitation purposes. A reference wavelength of 400 nm was selected. Internal referencing measures the absorbance at a reference wavelength. This absorbance is subtracted from the absorbance measured at the analytical wavelength. The resulting absorbance is used for quantitation. The reference wavelength is selected at a point along the baseline beyond the analytical wavelength (Owen, 1988). This method of internal referencing improves the accuracy of the absorbance used in quantitation, by reducing the effects of any changes in the baseline absorbance.

Absorbance values at the λmax wavelength of ibuprofen solutions were converted to drug concentrations using a calibration curve. Calibration curves were determined from absorbance values of a series of dilutions of three freshly prepared standard solutions in phosphate buffer pH 7.4 (appendix 1).

4.4.5. High performance liquid chromatography (HPLC) analysis

4.4.5.1. HPLC ibuprofen analysis

HPLC analysis of ibuprofen sample solutions was undertaken using a Spherisorb C8 5μm, 250 x 4.6 mm column. The other components of the HPLC system included a Shimadzu C-R3A chromatopac and a Shimadzu SPD-6A UV spectrophotometeric detector and pump. Experiments were run at ambient temperature at a flow rate of 0.8 ml/min and an absorbance wavelength of 220 nm. The mobile phase used to detect ibuprofen was methanol:1% phosphoric acid, 70:30 in all cases. Under these conditions, the ibuprofen retention time (t_r) was 10 minutes (table 4.2.). The method

of analysing ibuprofen was adapted from methods outlined by Schwarzenbach (1982) and Lalande *et al.* (1986).

Peak area was used for quantitation. A calibration curve was constructed using at least four solutions of known concentration. A new calibration curve was obtained each day the HPLC was run. Examples of the type of calibration curve obtained are shown in appendix 1.

Table 4.2.

HPLC conditions for ibuprofen and acid excipient analysis

Compound	**Mobile phase**	**Retention time (t_r) (minutes)**	**Flow rate (ml/min)**	**Absorbance detection (nm)**
Ibuprofen	Methanol:1% phosphoric acid (70:30)	10	0.8	220
Adipic acid	Methanol:1% phosphoric acid (50:50)	4	0.8	210
Succinic acid	0.025 M phosphoric acid	7	0.8	210
L-(+)-tartaric acid	0.025 M phosphoric acid	3	0.8	210

4.4.5.2. HPLC acid excipient analysis

HPLC analysis of acid excipients was undertaken using a Spherisorb C8 5µm, 250 x 4.6 mm column. The other components of the HPLC system included a Shimadzu C-R3A chromatopac and a Shimadzu SPD-6A UV spectrophotometeric detector and pump. The various mobile phases, retention times, flow rates and analysis wavelengths for the detection of different acid excipient sample solutions are outlined in table 4.2. All experiments were carried out at ambient temperature.

The mobile phase 0.025 M phosphoric acid was used to detect all acid excipients except adipic acid. In this case the mobile phase methanol:1% phosphoric acid (50:50) was used. Under these conditions, the adipic acid had a retention time of 4 minutes. As ibuprofen elutes with this mobile phase and has a retention time of approximately 70 minutes, adipic acid injections were only injected when the ibuprofen began to elute. Consequently, another sample was not injected until 80 minutes after the ibuprofen had eluted, while continuously running mobile phase through the system at a flow rate of 0.8 ml/min.

Peak area was used for quantitation of each of the acid excipients. A calibration curve was constructed each day the HPLC was run using at least four solutions of known acid excipient concentration. Examples of the different types of calibration curves for each acid excipient are outlined in appendix 1.

4.5. DIFFERENTIAL SCANNING CALORIMETRY

Differential scanning calorimetry (DSC) was carried out on powdered samples approximately 10 mg in weight, using a Mettler Toledo DSC 821^e. Ethylcellulose powder of 4 cP or 100 cp viscosity grades was sieved less than 180 μm before being analysed at a heating rate of 5.0°C/min between -30°C and 300°C or between 25°C and 250°C. Ibuprofen samples and acid excipient samples were also sieved less than 180 μm, prior to DSC analysis. (Acid excipients were ground in an agate mortar and pestle for ten minutes before sieving). These samples i.e. ibuprofen, acid excipients and their mixtures were analysed at a heating rate of 5.0°C/min between 25°C and 250°C (table 4.3.). During measurement nitrogen gas flowed over two aluminium crucibles, one of which contained the sample and the other an empty reference crucible. The crucibles were hermetically sealed, with vent holes. Values for onset, peak melting point and enthalpy of endothermic events were determined using Mettler Toledo Star^e system software. DSC temperature calibration was performed using an indium standard.

Table 4.3.

Sample analysed using differential scanning calorimety

Sample	Weight ratio % w/w
EC4	100
EC100	100
Ibuprofen	100
EC4:IB	75:25
EC4:IB	60:40
EC4:IB	50:50
EC4:IB	40:60
EC4:IB	25:75
EC100:IB	75:25
EC100:IB	60:40
EC100:IB	50:50
EC100:IB	40:60
EC100:IB	25:75
Adipic acid	100
AA:IB	50:50
EC4:AA	50:50
EC4:AA:IB	33:33:33
EC100:AA:IB	33:33:33
Succinic acid	100
SA:IB	50:50
EC4:SA	50:50
EC4:SA:IB	33:33:33
EC100:SA:IB	33:33:33
L-(+)-tartaric acid	100
TA:IB	50:50
EC4:TA	50:50
EC4:TA:IB	33:33:33
EC100:TA:IB	33:33:33

IB: ibuprofen, EC4: ethylcellulose 4 cP,
EC100: ethylcellulose 100 cP,
AA: adipic acid, SA: succinic acid,
TA: L-(+)-tartaric acid

4.6. XRD

X-ray diffraction (XRD) pattern were obtained using a Siemens D500 x-ray powder diffractometer. Powdered samples were examined by placing a thin layer of a powder on a glass slide. The various samples were scanned in all cases from 5 to 35 ^{o} 2θ. The aperture diaphragms used (position i, ii and iii) were 3 ^{o}, the detector diaphragm used (position iv) was 0.15 ^{o}.

4.7. GRINDING

Grinding was undertaken using either an agate mortar and pestle or a Retsch MM2 Mixer Mill. When grinding with the mill was performed, stainless steel grinding jars having a volume of 25 ml were used with two stainless steel grinding balls (12 mm in diameter). Particle size reduction (less than 40 μm) of the acid excipient was achieved using the Retsch Mixer Mill. Each of the three different acid excipients (adipic acid, succinic acid and L-(+)-tartaric acid) were ground for 15 minutes in the mixer mill at 85% maximum vibration.

4.8. SIEVING

Sieving was performed using Endecotts (BS 410) sieves (aperture sizes 63 μm, 90 μm, 125 μm, 180μm, 250 μm, 355 μm and 500 μm) and a mechanical shaker. Ethylcellulose powder size fractions collected for formulation included: 40-63 μm, 90-125 μm, 180-250 μm and 355-500 μm. A mechanical shaker was used with the sieves to ensure more accurate and dependable results. The sieves were arranged so the openings had a ratio of 1/(square root of 2) with the preceding sieve opening i.e. every second sieve had an opening in the ratio of 1/2. In addition, an Alpine Air Jet sieve with fines collecting filter (Haver & Boecker sieve of aperture size 40 μm) was used to obtain the finer particle size fraction of 40 μm to 63 μm and less than 40 μm.

4.9. PARTICLE SIZING

Particle sizing was undertaken on powders using a Malvern 2600c laser diffraction particle size analyser with a dry powder feeder attachment, or a Malvern Mastersizer 2000 with a Scirocco dry powder feeder attachment. A 300 and/or a 100 mm lens was used with the Malvern 2600. Results quoted are the average of three measurements. Results are expressed as percentage undersize.

4.10. MERCURY POROSIMETRY

4.10.1. General

Mercury porosimetry is widely used for the characterisation of pore size distribution of porous samples and the void size distribution of tablets and compacts. Mercury does not wet most substances and will not penetrate pores by capillary action. Entry into pore spaces requires applying pressure in inverse proportion to opening size. When mercury is in contact with a pore opening of circular cross section, the surface tension of the mercury acts along the circle of contact for a length equal to the perimeter of the circle. Thus, the force with which the mercury resists entering the pore is equal to $-\pi D_p \gamma_{HG} \cos\theta$, where D_p is the pore diameter, γ_{HG} is the surface tension of mercury, θ is the contact angle between the mercury and the perimeter of the pore (Webb and Orr, 1997). The force due to an externally applied pressure acts over the area of the circle of contact and is expressed by $\pi D_p^2 P/4$, where P is the applied pressure (Webb and Orr, 1997). At equilibrium, the opposing forces are equal. The equation used to relate the diameter D_p and applied pressure P is called the Washburn equation (equation 4.1.):

$$D_p = \frac{-4\gamma_{HG}\cos\theta}{P} \qquad \text{Eqn. 4.1.}$$

According to this relationship, if a known pressure is applied to a container of mercury which surrounds a porous sample, mercury will be forced to enter pores only of a certain size or larger. The volume of mercury forced to enter the intruded pores at a specific pressure is equal to the total volume of pores of a certain size. This not only applies to pores, but also to the filling of voids and interstitial space (space

between particles). As a result, the bulk and apparent density of a porous solid material can be determined from the mercury intrusion data.

4.10.2. Obtaining basic measurements

A PoreSizer 9320 (Mercury Porosimeter) from Micromeritics Instrument Corporation was used to undertake mercury porosimetry analysis on various solid samples. All porosimeters consist of three parts, including the container of the sample or the penetrometer, the source of the pressure, and the equipment and software for monitoring the progress of mercury into the sample measured. The glass penetrometer used in the PoreSizer 9320 consists of a sample bowl attached to a stem containing a precision capillary bore, which is open at both ends, one end of the capillary bore being terminated within the bowl. The outside sleeve of the glass stem of the penetrometer is also covered with a metal sleeve. The solid sample is placed within the bowl, and the bowl is sealed. A vacuum is then applied to evacuate both the bowl and capillary bore. This has the effect of removing adsorbed species from the sample and removing air from the penetrometer. Subsequent to evacuation, mercury is moved through the bore into the bowl, until both are filled with mercury. The mercury source is removed. Pressure (either low or high) is applied depending on the pressure range. During our study intrusion pressures between 0.5 and 30,000 p.s.i.a. were used, corresponding to pore diameters between 360 μm and 0.006 μm. The low-pressure analysis range was between 0.5 and approximately 20 p.s.i.a. and was undertaken semi automatically. The high-pressure analysis range was automatically measured between approximately 20 and 30,000 p.s.i.a. (appendix 2). The metal sleeve and the mercury within the penetrometer are separated by glass. This system acts as a cylindrical capacitor, where the metal sleeve and mercury acts as conductors and the glass acts as a dielectric. As the pressure is applied the capacitance changes as mercury moves out of the capillary into the sample. The measured change in capacitance is proportional to the change in the amount of mercury in the capillary.

4.10.3. Interpretation of analytical data

Standard porosimetry reports give precision intrusion volumes for each equilibrium pressure. Using the sample mass, appropriate parameters and the Washburn equation,

these data are converted to pore diameter (μm), and specific intrusion volumes (ml/g), respectively. Graphs from the data allow one to see important pore characteristics and pore size distribution. These are illustrated in high-resolution plots. They include:

Cumulative intrusion volume versus diameter: The most basic plot from a mercury intrusion analysis is pore diameter on a logarithmic scale versus the corresponding specific cumulative intrusion volume. This curve helps define pore shape and shows how the sample takes up mercury during the intrusion branch, and how much mercury is trapped during the extrusion branch.

Incremental intrusion volume versus diameter: Incremental volume is calculated by subtracting the cumulative volume V_i measured at pressure P_i from the cumulative volume V_{i+n} measured at a higher pressure P_{i+n}. Because of this, the y-axis values are dependent upon point spacing. This provides a convenient method by which to see at what diameter (D_i) pore volume is concentrated and to see distribution characteristics.

Incremental pore area versus diameter: The underlying theory of mercury porosimetry as expressed by Washburn's equation is based on a cylindrical pore model. The wall area of a cylinder is $\pi D_p L_c$, where L_c is the depth of the pore. The volume of a cylindrical pore is $\pi D_p^2 L_c/4$. Thus, for a cylinder, the relation between volume and wall area is $A_s=4V/D_p$. The instrument directly monitors and logs cumulative volume as a function of pressure. These volume data are converted to specific volume by dividing by the sample mass. Incremental specific volume is calculated from changes in cumulative volumes over each pressure increment. Specific surface area is calculated simply by multiplying specific volume by 4 and dividing by the mean diameter (D_m), over which the volume increment was determined, that is $D_{mi}=(D_{i-1}+D_i)/2$. Incremental specific pore area therefore is:

$$A_i = \frac{4V_1}{D_{mii}} \qquad \text{Eqn. 4.2.}$$

Cumulative pore (surface) area versus diameter: This curve pinpoints the location of pore activity at various diameters. This allows one calculate total pore surface area and is the surface area within the pores determined as a function of the pressure range and based on the assumption of cylindrical geometry.

Other data information points include:

Total intrusion volume: This is the maximum volume of mercury intruded into the sample at the highest pressure attained during analysis.

Total pore (surface) area: This is the surface area within pores determined as a function of the pressure range and based on the assumption of cylindrical geometry.

Median pore diameter: The median pore diameter is the 50% (percentile) value obtained from either the area or volume distribution curve.

Average pore diameter: The average pore diameter is the pore volume (multiplied by four) and divided by the area assuming that all pores are cylinders.

Bulk Density: Bulk density (ρ_{se}) is a measurement that occurs at the intial mercury filling pressure. It takes the sample volume, which includes all open and closed pores and divides it by sample weight.

Apparent (or skeletal) density: Apparent density (ρ_{sa}) is a measurement of the sample's solid phase i.e. the sample volume minus all open pores as measured by the total intrusion at the highest pressure, which is then divided by the sample weight. If there are no hidden or closed pores, the apparent density equals the true density of the material.

Porosity: the percent porosity (P_{pc}) of a sample is:

$$P_{pc} = \left(1 - \frac{\rho_{se}}{\rho_{sa}}\right)100 \qquad \text{Eqn. 4.3.}$$

4.10.4. Limitations of the mercury porosimetry method

Contact angle: The use of an incorrect contact angle does not matter when porous materials of the same type are being compared. However, if an exact measure of the pore opening is needed it is necessary to either measure the contact angle directly or look at the pores under a microscope to establish the relationship between the actual pore size opening to that measured by mercury intrusion. A value of 130° is

recommended in the absence of specific information to the contrary and the use of triple distilled mercury is recommended for optimum performance (Allen, 1990).

Surface tension: Another variable factor arises from assuming a constant value for the surface tension of mercury. The best of the published values is 485 dynes cm^{-1} at 25°C. The differences in surface tension values of mercury are generally attributed to contaminated mercury (Allen, 1990).

"Network effects" and "ink bottle pores": The presence of "network effects" and "ink bottle pores" can lend to erroneous results. The "network effect" is evident as voids between particles, and pores within them which are interconnecting and narrow inlets leading to wide voids. "Ink bottle pores" are pores with narrow necks and wide bodies. The experimental data overweighs the narrower pores (Allen, 1990).

Compressibility of the material under test conditions: This is a problem of importance for materials with pores that do not connect with the surface e.g. cork.

Assumption of a cylindrical pore model: Pores are rarely cylindrical; hence, the Washburn equation constitutes a special model. Such a model may not represent pores in actual materials, but its use is generally accepted as a practical means for treating what, otherwise would be a complex problem.

Insufficient degassing of solid samples with fine pore structure: Some samples, particularly those of high surface area, may require pre-treatment by heat and vacuum to drive off vapours. These are typically water vapours that occupy small pores and prevent the entry of mercury. If the sample is heat sensitive, then drying in a dessicator is needed.

Degradation of solid under high pressure: Many materials, particularly those containing closed pores cannot sustain high pressure undamaged.

4.10.5. Method

Mercury porosimetry analysis was performed on compacts of ethylcellulose:ibuprofen 50:50 weight ratio. Compacts were prepared (as for dissolution studies) with either ethylcellulose 4 cP or 100 cP viscosity grade and were 13 mm in diameter. Compacts were examined before and after a dissolution period of seven hours. Discs that had been in phosphate buffer medium were removed from the buffer solution, placed on filter paper for approximately one hour and then placed in a vacuum oven at 30°C until constant weight was achieved. All samples were left in a silica containing

dessicator and removed just prior to analysis. Four compacts were used for each measurement in a 3 cm^3 solid sample penetrometer.

Penetrometers were calibrated (by filling with mercury under pressure) prior to use, in order to obtain an accurate measurement of penetrometer volume.

The advancing and receding contact angle for the mercury was taken to be 130° and the surface tension was taken as 485.0 dyn/cm. Mercury density was dependent on room temperature (Micromeritics PoreSizer Operator's Manual V2.02, 1992). Other variables (e.g. penetrometer stem volume and maximum head pressure) were a function of the penetrometer used (Micromeritics PoreSizer Operator's Manual V2.02, 1992). The equilibrium mode of analysis was used with an equilibration time of 10 seconds.

4.11. BET SURFACE AREA ANALYSIS

Surface area analysis was performed using a Micromeritics Gemini 2370 Surface Area Analyser with nitrogen as the absorptive gas. The Gemini system is a balanced adsorption system that uses a technique called SMART (a sorption method using adaptive rate technology), i.e. adsorbate gas is supplied to the sample at the same rate that it is adsorbed (Camp and Stanley, 1991).

Moisture was removed from the powder samples by placing them in a silica containing vacuum dessicator for a minimum of three days at a temperature of 30°C. Subsequently, the samples were degassed in a Micromeritics FlowPrep 060 Degasser, where helium was passed over the samples maintained at a constant temperature. As a result any remaining moisture or contaminants attached to the sample were removed.

Samples of ethylcellulose 4 cP and ethylcellulose 100 cP powder sieved less than 180 μm (~3 g), were degassed at 80°C for a minimum of 24 hours.

The Gemini Analyser consists of two large sample bulb tubes of matched internal volume. The sample being analysed was placed in the sample tube containing a filler rod. Powdered samples were added to within 1/8 inch of the top of the bulb in the sample tube. The other bulb tube contains an equal volume of 3 mm glass beads of negligible surface area. A long filler rod was worked into each tube through the

material (powder or glass bead) until it was resting on the bottom of the tube. Approximate equal volume content between the two tubes was confirmed by a ΔFree Space value in the range of -0.5 to +0.5 cm^3 in all cases. This serves to reduce the pressure "noise" caused by the boiling of the liquid nitrogen. As a result, the random pressure fluctuations caused by slight temperature variations at or near the liquid nitrogen surface are reduced. By displacing most of the gas from this gradient region, the filler rods leave less gas to expand and contract in response to temperature fluctuations (Healy, 1995). Therefore, the Gemini system can achieve a more precise gas uptake measurement.

Helium gas was used for free space measurement, while nitrogen was used as the adsorptive gas.

The saturation pressure (P_o) was measured each day. BET multipoint surface areas were determined. The volume of nitrogen adsorbed at six relative pressures between 0.05 and 0.3 was measured. The linearity of the BET plot is usually restricted to this range. The BET multipoint area was calculated using either five or six of the measured points, depending on the best correlation coefficient. Analyses were performed at least in duplicate.

4.12. CONTACT ANGLE MEASUREMENT

4.12.1. General

The wettability of powders is a preliminary step in several pharmaceutical processes, and in the subsequent disintegration and dissolution of the product *in vivo* (Fell and Efentakis, 1978). Wetting occurs if the mutual attraction between the atoms or ions of the solid and the molecules of the liquid is stronger than the attraction among the molecules of the liquid. Whether a solid is wetted by a liquid or not depends on the system considered, but also on the type of wetting. (Water, for example wets a great many solids while mercury wets very few). One can theoretically distinguish between wetting by adhesion, by immersion and by spreading. Criteria for wetting, according to these processes were given by Kossen and Heertjes (1965), who used the contact angle θ to measure wetting. This angle is the angle between the tangent to the air-liquid interface at the point of contact with the solid and the solid surface itself, measured so that the liquid is included within the angle.

4.12.2. General description of technique

The contact angle may be measured by the method of Kossen and Heertjes (1965) as used by Lerk *et al.* (1976) for pharmaceutical powders. The method consists essentially of measuring the maximum height of a drop of liquid on a presaturated compact of the powdered solid under test and is commonly called the *(h-ε)* method.

The anglometer permits measurement of the maximum height a drop or a small pool of liquid can attain on a horizontal surface. When the solid is in powder form a compressed cake of powder is produced and the maximum height of liquid attained on its horizontal surface is measured. A precision micrometer indicates the height. The distance to the surface is first determined and then as liquid is added onto the surface in increments (with a needle and syringe), the distance to the upper liquid surface is determined. The first small drop of test liquid will not project as far above the surface as will the liquid after several additions. However, continuous additions of the test liquid will produce spreading and no further increase in the liquid height. This ultimate height is the measure needed and is incorporated into one of the two following equations (Schubert, 1968) to obtain the contact angle θ. When $\theta < 90^0$ i.e. when the liquid wets and spreads the equation used is:

$$\cos\theta = 1 - \sqrt{\frac{Bh_d^{\,2}}{3(1-\varepsilon)(1-Bh_d^{\,2}/2)}} \qquad \text{Eqn. 4.4.}$$

When $\theta > 90^0$ i.e. when the liquid does not wet but "balls up" the equation used is:

$$\cos\theta = -1 + \sqrt{\frac{4-2h_d^{\,2}B}{3(1-\varepsilon)Bh_d^{\,2}}} \qquad \text{Eqn. 4.5.}$$

In these equations, $B=\rho g/2\gamma$, where ρ is the liquid density (g/cm^3), g the acceleration due to gravity (approx. 980 cm/sec^2), and γ the surface tension (mN/m) of the liquid; h_d is the maximum measured droplet height (cm); and ε is the porosity of the surface. A porosity strictly applicable to a surface formed of uniform spheres was defined in deriving the above equation (Hansford *et al.*, 1980). The definition is not rigorously applicable to either a solid surface or a compressed powder composed of various particle sizes. For practical purposes, the porosity of a solid may be taken as zero; and for a compressed powder it can be employed as the volume of the pore spaces

divided by the overall volume of the compressed cake. Specifically, porosity is given by:

$$\varepsilon = \frac{vol_{tot} - vol_t}{vol_{tot}} = \frac{\left(d^2 \pi t_c\right)/4 - \left(W/\rho\right)}{\left(d^2 \pi t_c\right)/4} \qquad \text{Eqn. 4.6.}$$

where ε is the compact porosity/surface porosity, vol_t is the true volume, vol_{tot} is the apparent volume, d is the cake diameter (in this study 5.080 cm), t_c is the cake thickness, W is the weight of powder composing the cake, and ρ is the absolute density of the powder.

4.12.3. The apparatus

The Contact Anglometer Model 1501 consists of a micrometer mounted on a transparent cover. The cover screws onto a base plate, which supports the cake of a compressed powder. A guide that also screws onto the base plate and a plunger that fits into the guide facilitates the formation of a compressed powder. The base plate, guide, levelling plate and plunger are made of stainless steel. The plunger is indented with a ring configuration on its face.

4.12.4. Test procedure

The plunger guide was screwed onto the base plate and powder was poured into the resulting container. The amount of powder was added such that after compaction, the cake was approximately level with the upper rim of the bottom plate and a smooth, firm surface was created. The most accurate results are achieved when the cake has a minimum porosity. The anglometer was then located in a rigid vibration-free support. The micrometer was run down until its plunger lightly contacted the compressed powder. The micrometer reading was set to zero. The micrometer was raised and the test liquid was added through the hole in the transparent body with the syringe. A drop or pool of test fluid roughly ¼ inch in diameter and directly beneath the micrometer constituted good initial conditions. The micrometer was turned down until the plunger contacted the droplet. This was easily established if the plunger descent was carefully followed. Upon contact, a small quiver ran across the test liquid surface. The height measurement was indicated by the micrometer but was not likely to be the maximum value. The micrometer plunger was carefully wiped dry by

inserting a pipe cleaner through the hole in the transparent cover. Additional liquid was added with the syringe. This addition was undertaken slowly with the tip of the needle under the level of the liquid on the compressed powder. After each additional increment of liquid, the micrometer was again lowered into contact and the indicated liquid height recorded. This procedure was repeated until further additions of liquid resulted in no increase in the height of the droplet. This height minus the initial reading for the surface only height was the height to be employed in the calculation of the contact angle. Analyses were performed in triplicate (at least).

In this study, the powder examined included ibuprofen, ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP. Each powder was sieved less than 180 μm before being compacted (using the plunger and die) on a Perkin Elmer press at 7000 kg for 10 minutes. The test liquid used was phosphate buffer pH 7.4 at 25°C or ibuprofen saturated phosphate buffer at 25°C. The saturated solution was prepared by allowing excess solid to equilibrate with phosphate buffer at 25°C. The compact was pre-saturated with the test liquid by spraying a film of the test solution onto the compact using an atomizer. This means the liquid will not be sucked into the cake and a well-shaped drop will be formed.

4.13. SURFACE TENSION MEASUREMENTS

Determination of the surface tension of phosphate buffer pH 7.4 at 25°C and ibuprofen-saturated phosphate buffer at 25°C was undertaken using a Lauda tensiometer TD 1E. This consists of measuring the vertical force which the surface or interface of the liquid exerts on the test body. Force measurement without any displacement is achieved by electromagnetic compensation of the force transmitted by the test body to a measuring beam. The current required to do this is directly proportional to the force. The value obtained by current/voltage conversion is shown on the digital display after analogue processing so that it corresponds to the actual force.

The surface tension of phosphate buffer pH 7.4 at 25°C and ibuprofen-saturated phosphate buffer at 25°C was determined using the ring attachment. The 19.1 mm diameter ring is attached to the hook of the Lauda tensiometer TD 1E and the

calibration value for the ring calculated. After calibration the sample stage is returned to the lowest possible position and the test liquid placed in the temperature controlled glass vessel. The stage with vessel and liquid is moved up slowly until the ring is at least 2-3 mm below the liquid surface. The stage is then gradually moved down slowly so that the ring draws a lamella out of the solution. This gives rise to a force, which reaches its maximum before the lamella collapses. This maximum value represents the uncorrected surface tension i.e. the value determined from the lamella drawn up with the ring includes a weight in addition to the surface tension. To eliminate this weight force, the measured value is multiplied by a factor (*f*) depending on the density, the ring diameter, the gravitational constant and the wire diameter. The correction factor (*f*) for the ring is calculated using equation 4.7. (Lauda Tensiometer TD1 manual):

$$f = 0.8759 + \frac{(0.0009188)(OS_{ruk})}{\rho} \qquad \text{Eqn. 4.7.}$$

OS_{ruk}: uncorrected surface tension (mN/m)

ρ: density of the test liquid (g/cm^3)

Using this correction factor the absolute surface tension is calculated according to equation 4.8. (Lauda Tensiometer TD1 manual):

$$OS_{abs} = f \, x \, OS_{ruk} \qquad \text{Eqn. 4.8.}$$

OS_{abs}: corrected surface tension (mN/m)

4.14. LIQUID DENSITY MEASUREMENTS

The Lauda tensiometer TD 1E is also used to determine the density of liquids. In this instance, the ring is replaced with a displacer (similar to a glass weight) and the test mode switch is set to the symbol for density measurement. The stage is turned down as far as possible and the test glass filled with pure water is placed on it. Using the tare potentiometer the reading on the display is set to zero. The system is then calibrated with the displacer. Performing a measurement on a liquid of known density i.e. pure water does this. The displacer is fully immersed in the water and the density set according to density values in table 4.4. The test glass with water is then removed

from the TD 1E and the displacer is thoroughly dried. The test glass is then emptied and filled with the test solution. The density of phosphate buffer at a temperature of 25°C and ibuprofen-saturated phosphate buffer at a temperature of 25°C were measured. The sample stage with the test liquid is slowly moved up until the displacer is fully immersed. The value when the displacer is fully immersed in the liquid is measured. In order to allow for the density of air the reading is increased by "1", giving the density of the test liquid in g/dm^3.

Table 4.4.

*Density values of pure water for different temperatures**

Temperature (°C)	Density (g/dm^3)
15	998
16-22	997
23-26	996
27-29	995
30-33	994
33-35	993

*Lauda Tensiometer TD1 Handbook

4.15. HOT STAGE MICROSCOPY

Hot stage microscopy was carried out on a Reichert hot stage mounted on Meopta microscope without crossed polarising filters. Samples were mounted in air or in silicone oil (to detect desolvation). Samples analysed included ibuprofen (sieved less than 180 μm), ethylcellulose 4 cP (sieved less than 180 μm), ethylcellulose 100 cP (sieved less than 180 μm) and their 50:50 mixtures.

4.16. PROFILOMETRY

4.16.1. General

Non-contact laser profilometry is traditionally used in engineering and material sciences to examine the surface texture of materials. In pharmaceutics, the profilometer can be used to examine the surface roughness of solid dosage forms before and after dissolution (Healy, 1995).

4.16.2. Instrumentation

The profilometer was a UBM Microfocus Measurement System that uses an infrared light from a semiconductor laser focused on the surface by an objective lens. The light reflected by the object surface is directed by a beam splitter, through a prism, and is imaged as a pair of spots onto an arrangement of photodiodes. This is done in such a way that when the objective lens is exactly at its focal distance from the surface both diodes are illuminated equally. If the distance between the object surface and the objective is then changed, the imaged focus point is shifted and the illumination of the photodiode becomes unequal. The unequal illumination of the photodiodes generates a focus error signal by means of a differential amplifier. A control circuit (UBM Microfocus Measurement System) that monitors the focus error signal also controls the position of a moveable lens suspended within the sensor. The focal spot of the beam therefore remains coincident with the measurement surface. This lens movement is accomplished by a coil and magnet arrangement. The sensor therefore operates such that it is always set to the zero crossing of its characteristic. The changing illumination of the photodiode can then be translated to a measurement of the surface roughness.

4.16.3. Surface Texture Analysis By Profilometry

4.16.3.1. Measuring lengths

Figure 4.1. illustrates the sampling, assessment (evaluation) and traverse lengths for surface measurements.

(1) Sampling length: This is the length of surface over which a single assessment of a parameter is made (Dagnall, 1980)

(2) Assessment Length: This is the length of surface over which a measurement is made. It generally includes five sampling lengths. Therefore, the measurement is an average (Dagnall, 1980).

(3) Traverse Length: This is the total length of surface traversed by the laser light spot when making a measurement. Generally, this is greater than the evaluation length because of the need with contact profilometer to allow a short over travel at either end of the evaluation length. This has the effect of excluding mechanical and electrical transients from the measurement (Dagnall, 1980).

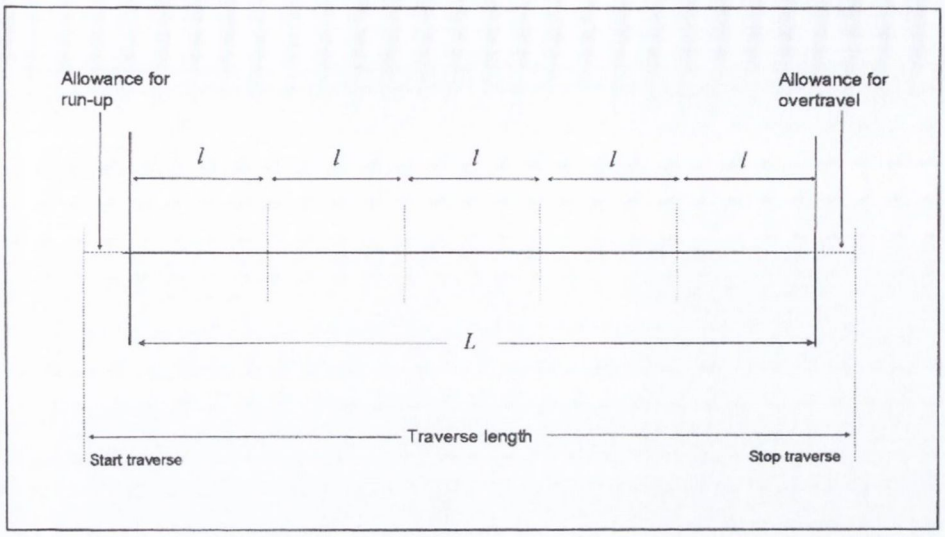


Figure 4.1. Sampling length (l), evaluation (or assessment) length (L) and traverse length.

4.16.3.2. Roughness parameters

In surface texture analysis, deviations from an ideal shape or perfectly flat shape are examined. This ideal shape (or approximation) is used as the "reference line". For practical reasons, the reference adopted for most parameters is the centreline of the profile (Dagnall, 1980). It is located such that, within the sampling length, the sum of areas enclosed by the profile above the centre line equals the sum of those below it. Therefore, it is drawn parallel to the general shape of the surface. This line forms the basis for a number of surface texture parameters including R_a and R_{tm}.

(1) Roughness Average

The R_a (roughness average) value is universally recognised and the most widely used international parameter of surface roughness. For line scans, the R_a is the arithmetic mean of the departure of the profile from the centre line throughout the assessment length (Dagnall, 1980) figure 4.2. The UBSOFT software calculates the R_a value as the arithmetic average of the absolute values of all point of the profiles (Healy, 1995). Therefore, for a line scan:

$$R_a = \frac{1}{n}\sum_{i=1}^{n}|z_i| \qquad \text{Eqn. 4.9.}$$

where n is the number of measurements and z_i is the i^{th} point.

When an area scan is performed, by obtaining a series of lines scans, one obtains a 3D picture of the surface, i.e. an X-Y-Z representation rather than an X-Y representation i.e. 2-D that one obtains for line scans. R_a is therefore the arithmetic average of the absolute values of all profiles values (Healy, 1995):

$$R_a = \frac{1}{nm}\sum_{i,j=1,1}^{nm}|z_{ij}| \qquad \text{Eqn. 4.10.}$$

where n is the number of measurement points, z_{ij} is the i^{th} point in the j^{th} row where the number of rows is m.

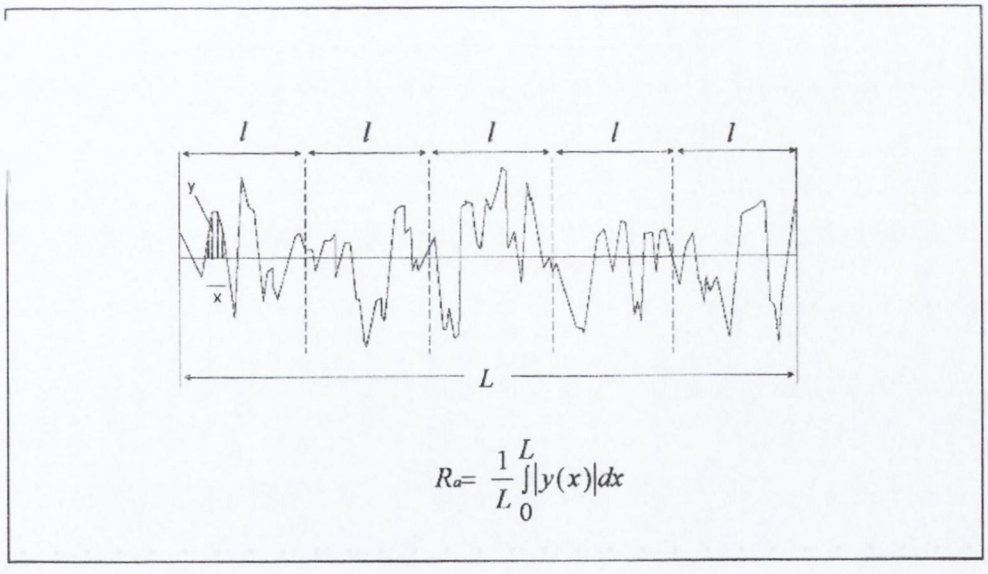


Figure 4.2. Derivation of the roughness average, R_a, from a line scan of the surface

(2) R_{tm} parameters

For line scans of the surface, the R_{tm} parameter is the arithmetic average of all the R_{ti} values obtained during the assessment length, where R_{ti} is the maximum peak to valley height of the profile in one sampling length. The UBSOFT software associated with the system calculates the R_{tm} value according to the following equation:

$$R_{tm} = \frac{1}{5}\sum_{i=1}^{5} R_{ti} \qquad \text{Eqn. 4.11.}$$

The R_{tm} value for an area scans is an average of the maximum peak-to-valley height R_{tm} in each of 25 rectangles that result from splitting the sample surface into a 5x5 grid (Healy, 1995).

4.16.4. Test procedure

Ibuprofen, ethylcellulose 4 cP powder and ethylcellulose 100 cP powder were sieved less then 180 μm using a hand held Endecotts sieve. Discs where ibuprofen or ethylcellulose (of either viscosity grade) were the only component were prepared by compressing 250 mg powder in a Perkin-Elmer hydraulic press, for 10 minutes under 7000 kg pressure, using a 13 mm flat faced punch and die set. The target disc weight was 250 mg.

In addition physical mixtures of ethylcellulose 4 cP and ibuprofen, or ethylcellulose 100 cP and ibuprofen were prepared in a 25:75, 50:50 and 75:25 weight ratio. The ethylcellulose and ibuprofen were mixed in an agate mortar and pestle for 10 minutes, and compressed in a Perkin-Elmer hydraulic press for 10 minutes at 7,000 kg pressure, using a 13 mm flat faced punch and die set. The target disc weight was 250 mg.

Area scans of the discs surfaces were made. The traverse lengths were 4.00 mm in the X direction and 4.00 mm in the Y direction, with 400 resolution points per mm in the X direction and 20 resolution points per mm in the Y direction. Scans were levelled using third order polynomial in both directions. The roughness parameters, R_a and R_{tm} were determined after levelling. Values quoted are the average of determinations made for at least two discs. The UBM profilometer in use had a light spot diameter of 1 μm and a measurement range of +/- 500 μm.

4.17. SURFACE DENSITY MEASUREMENTS

Controlled release matrix tablets which normally contain larger amounts of drug than conventional tablets, should remain indivisible in the gastro-intestinal tract. It is apparent that these matrices must be mechanically strong. Since ethylcellulose is the major component of the matrix delivery system under study, it is important to characterise the response of the polymer under compression. The effect of ethylcellulose viscosity grade and ethylcellulose particle size on the surface density of compacts was evaluated. The method outlined by Fassihi (1988) was employed. In this method, the white ethylcellulose compacts are coloured using amaranth dye and the intensity of surface colour was used as an indicator of surface densification.

Each powder component (ethylcellulose 4 cP powder or ethylcellulose 100 cP powder) was sieved less than 180 μm. Amaranth dye (1% w/w) was added to each powder fraction and mixed for one minute. Ethylcellulose discs (with amaranth) were then prepared by compressing 250 mg powder in a Perkin-Elmer hydraulic press, for 10 minutes under 7000 kg pressure, using a 13 mm punch and die set.

In addition, physical mixtures of ethylcellulose 4 cP and ibuprofen, or ethylcellulose 100 cP and ibuprofen were prepared in a 50:50 weight ratio. Two different ethylcellulose particle size fractions were used, namely ethylcellulose powder sieved less than 180 μm and the 180-250 μm powder fraction. (The ibuprofen powder was sieved less than 180 μm). Each physical mixture was mixed for 9 minutes. Amaranth dye 1% w/w was then added. This mixture was then mixed for a further 1 minute. Discs were prepared by compressing 250 mg powder in a Perkin-Elmer hydraulic press, for 10 minutes under 7000 kg pressure, using a 13 mm punch and die set.

The flat side of the compact facing the lower punch and nearest the source of compression was termed the bottom side. The other flat side facing the upper punch was termed the topside.

The color intensity of the prepared compact surface was then examined by visual inspection. Photographs of discs were taken.

4.18. CHARACTERISATION OF COMPACTS

4.18.1. Area

The dimensions of the compacts were measured using a Inox helios sliding calliper. The smallest division that could be measured was +/- 0.05 cm. The surface area (A_s) of the plane-faced discs is given by equation 4.12. where r_o is the radius of the compact, and H is the compact height:

$$A_s = 2\pi r_o^2 + 2\pi r_o H \qquad \text{Eqn. 4.12.}$$

The surface area (A_s) of the convex–shaped compacts is given by equation 4.13. where h_1 is the height of the wall of the compact or the cylindrical portion of the compact (cylinder length), and h_2 is the maximum compact thickness at the centre of the convex disc (Ford *et al.* 1987) (figure 4.3.):

$$A_s = 2\pi r_o h_1 + 2\pi\left(r_o^2 + \left(\frac{h_2 - h_1}{2}\right)^2\right) \qquad \text{Eqn. 4.13.}$$

The radius of curvature R_o of the biconvex compact face was 0.595 cm, and the diameter of the biconvex compact was 0.85 cm (figure 4.3.). The face curvature F_c is calculated from equation 4.14.:

$$F_c = d/R_o \qquad \text{Eqn. 4.14.}$$

where d is the compact diameter (Pitt *et al.*, 1990). The face curvature of the biconvex compacts under study was 1.43. Pitt. (1986) established that only the central cylindrical portion of the biconvex compact changed in dimension when either the weight or formation pressure changed. Hence measurement of the overall thickness of the biconvex compact reflects a change in the value of h_1. The total height of the spherical portion (h_2-h_1) of the biconvex tablets under study was 0.357 cm.

4.18.2. Volume and porosity

The volume of plane-faced compacts is given by equation 4.15:

$$V = \pi r_o^2 H \qquad \text{Eqn. 4.15.}$$

The volume of the convex–shaped compacts is given by equation 4.16. (Cobby *et al.* 1974a):

$$V = \pi \left[\frac{\left[\frac{h_2 - h_1}{2} \right]^3}{3} + r_o^2 \left(h_1 + \left(\frac{h_2 - h_1}{2} \right) \right) \right] \qquad \text{Eqn. 4.16.}$$

The total porosity of plane faced or biconvex-faced compacts is equal to:

$$\varepsilon = \varepsilon_d + \varepsilon_0 \qquad \text{Eqn. 2.4.}$$

where ε_d is the porosity corresponding to the volume occupied by the drug substance in the compact and ε_o is the initial porosity or interparticulate porosity. The porosity due to drug content is calculated as follows (Desai *et al.*, 1966b):

$$\varepsilon_d = \frac{m_d}{\rho . V_{tot}} \qquad \text{Eqn. 2.6.}$$

with m_d equal to the total amount of drug present in the tablet and ρ is equal to the true density of the drug. The initial porosity is calculated from the apparent volume V_{tot} and the true volume V_t of the tablet constituents (Desai *et al.*, 1966b):

$$\varepsilon_0 = \frac{V_{tot} - V_t}{V_{tot}} \qquad \text{Eqn. 2.5.}$$

4.18.3. Hardness

The hardness of discs was measured using a Schleuniger Hardness Tester and the tensile strength calculated. The average hardness of seven compacts was used. Compacts were prepared 24 hours before hardness measurement was undertaken. This allowed for any stress relaxation of the compact to occur. Calculation of the tensile strength allows a valid comparison to be made between the different shaped compacts (Pitt *et al.*, 1989a). The material tensile strength σ_f of the plane-faced discs was calculated from equation 4.17. (Fell and Newton, 1970):

$$\sigma_f = \frac{2P_s}{\pi d H} \qquad \text{Eqn. 4.17.}$$

where σ_f expresses the material tensile strength of the tablet, P_s is the fracture load, d is the disc diameter, and H is the overall thickness. This equation can be derived theoretically (Den Hartog, 1952). .

A theoretical solution for the tensile strength of convex tablets is not available. Instead, Pitt *et al.* 1989b established an empirical solution that has been confirmed using homogenous brittle specimens formed from gypsum (Pitt *et al.* 1988). Pitt et *al.* (1990) also used this equation to determine the effect of compaction variables on the tensile strength of convex-faced aspirin tablets of different face-curvature, and different cylinder length (h_1). The equation expresses the material tensile strength of the tablet specimen in terms of the fracture load P_s, disc diameter, d and overall height h_2 and cylinder length, h_1:

$$\sigma_f = \frac{10P_s}{\pi d^2}\left(2.84\frac{h_2}{d} - 0.126\frac{h_2}{h_1} + 3.15\frac{h_1}{d} + 0.01\right)^{-1} \quad \text{Eqn. 4.18.}$$

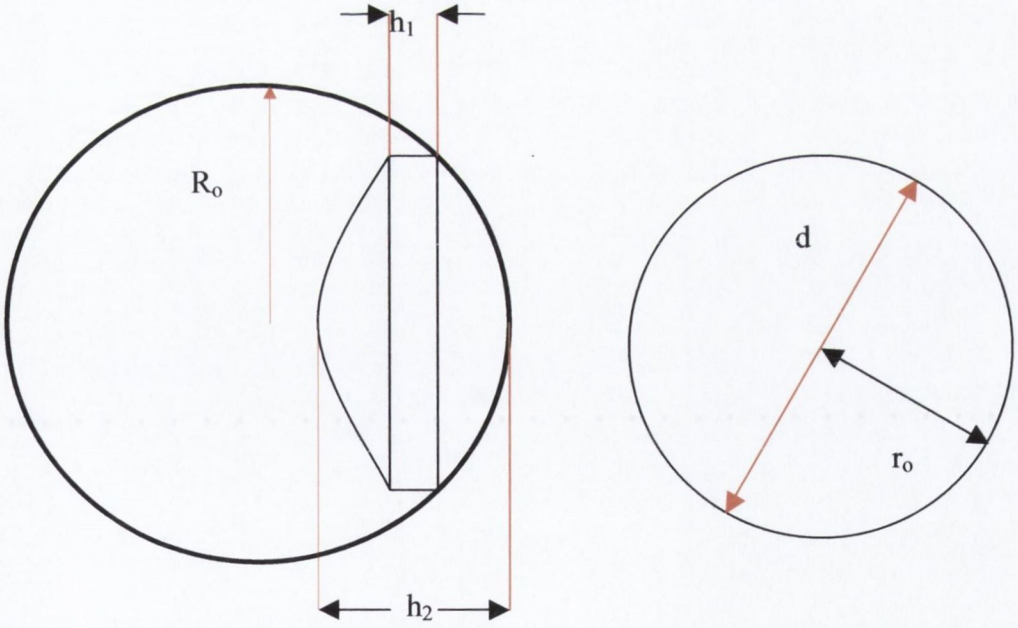


Figure 4.3. *Side and front elevation of biconvex compact showing radius of curvature* R_o

4.19. COMPACT SWELLING STUDIES/ WATER UPTAKE STUDIES

The method outlined by Humphreys (1986) was used to examine the phenomenon of disc swelling. Deasy *et al.* (1980) also used this method to examine swelling in discs prepared with ethylcellulose based microcapsules. Discs were submerged in the test fluid and any increase in disc thickness was measured over a period of time.

Discs were prepared by compressing 250 mg of ethylcellulose powder on a Perkin-Elmer hydraulic press for 10 minutes under 7000 kg pressure, using a 13 mm flat faced punch and die set. Powders were sieved less than 180 μm beforehand. Four different ethylcellulose viscosity grade powders were used, namely ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP. Discs were stored in tightly sealed amber jars for 48 hours prior to study.

The device used to determine increase in thickness in discs consisted of a specially designed holder in a petri dish (figure 4.4.) (Humphreys, 1986). The petri dish was positioned at the stage of an optical micrometer and contained the test fluid i.e. phosphate buffer pH 7.40 at 37°C. Each disc was mounted on a holder in the petri dish using melted paraffin wax. When fixing the disc on a holder the surface of the back of the disc was coated with wax. This prevented access of fluid to the back of the disc. Prior to immersion in phosphate buffer, the optical micrometer was used to measure the initial thickness. This was taken to be the thickness at time zero. After immersion in the buffer, any increase in disc thickness was measured at variable periods over a seven-hour period. Swelling was indicated as a percentage of increase in thickness over the original thickness. Results shown are the average of three determinations.

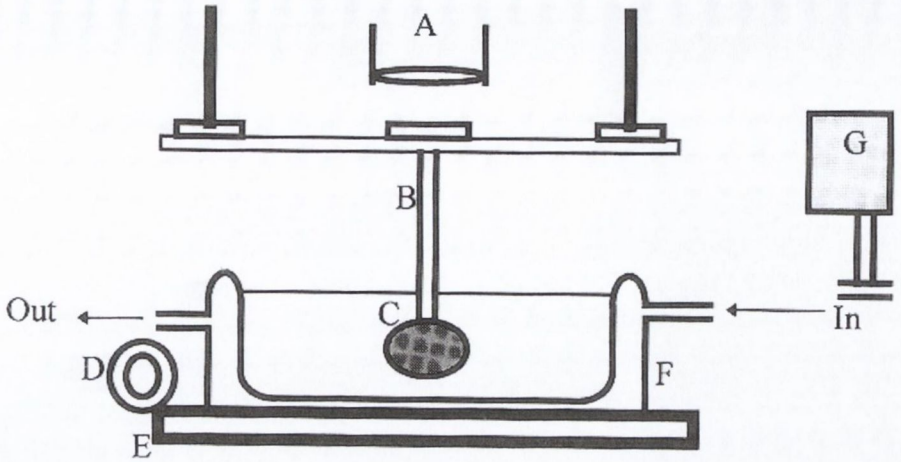


Figure 4.4. Swelling apparatus

A: eye piece of microscope, B: sample holder, C: mounted disc, D: micrometer, E: adjustable illuminated stage, F: glass water bath, G: heating unit with pump

4.20. SCANNING ELECTRON MICROGRAPHS

Scanning electron micrographs were taken of ethylcellulose 4 cP powders and ethylcellulose 100 cP powders. Both powders were sieved less than 180 μm before examination. Magnification levels of x 50 and x 1000 were used.

4.21. COMPUTER MODELLING/ CURVE FITTING

A non-linear curve-fitting program (Scientist, version 1.0) was used to produce goodness-of-fit statistics for various models. The statistical outputs used to evaluate goodness-of-fit were the coefficient of determination and the model selection criterion (MSC).

The coefficient of determination is a measure of the fraction of the total variance accounted for by the model and is defined by the formula:

$$\frac{\sum_{i=1}^{n_i} w_i^2 \left(Y_{obs_i} - \overline{Y}_{obs}\right)^2 - \sum_{i=1}^{n_i} w_i^2 \left(Y_{obs_i} - \overline{Y}_{cal\,i}\right)^2}{\sum_{i=1}^{n_i} w_i^2 \left(Y_{obs_i} - \overline{Y}_{obs}\right)^2} \qquad \text{Eqn. 4.19.}$$

Where n_i is the number of points, w_i are the weights applied to each point, and $\overline{Y}_{obs}$ is the weighted mean of the observed data. A value of +1 for the coefficient of variation indicates a perfect fit.

The model selection criterion represents the "information content" of a given set of parameters by relating the coefficient of determination to the number of parameters (or equivalently the number of degrees of freedom) that were required to obtain the fit. When comparing two models with different numbers of parameters, this criterion places a burden on the model with more parameters to have a better coefficient of determination. This also quantifies how much better it must be for the model to be deemed more appropriate. The most appropriate model is that with the highest MSC. The MSC is defined by the formula:

$$MSC = \ln\left(\frac{\sum_{i=1}^{n_i} w_i\left(Y_{obs_i} - \overline{Y}_{obs}\right)^2}{\sum_{i=1}^{n_i} w\left(Y_{obs_i} - Y_{cal_i}\right)^2_i}\right) - \frac{2p}{n_i} \qquad \text{Eqn. 4.20.}$$

where p is the number of parameters.

4.22. STATISTICAL TECHINQUES

Statistical analysis was performed using Microsoft Excel 6.0 for Windows on the PC. Statistical significance was tested for using two sample t-test, assuming equal variance. In addition a statistical method which compares entire dissolution profiles was used. According to FDA guidelines on scale up and postapproval changes (SUPAC) for immediate release solid dosage forms, dissolution profiles can be compared using the following equation that defines a similarity factor f_2:

$$f_2 = 50\log\left\{\left[1 + \frac{1}{n_i}\sum_{t=1}^{n_i}\left(R_t - T_t\right)^2\right]^{-0.5} .100\right\} \qquad \text{Eqn. 4.21.}$$

Where R_t and T_t are the percentage drug dissolved at each time point t for the reference (R) and test formulations (T) respectively, for n_i number of time points (O'Hara *et al.*, 1997). An f_2 value between 50-100 suggests that the dissolution profiles are similar i.e. they are assumed to differ by no more than 15% at any of the

time points used. The similarity factor has also been used to compare dissolution profiles from extended release formulations (Sievert and Siewart, 1998).

RESULTS AND DISCUSSION

CHAPTER 5

CHARACTERISATION OF ETHYLCELLULOSE POWDERS AND COMPACTS OF DIFFERENT VISCOSITY GRADES

5.1. INTRODUCTION

Pharmaceutically acceptable polymer powders are nowadays widely used in prolonged release compressed tablets as matrix systems. It is important to clarify the characteristics of these polymers, since several properties related either to the material or to the particle might influence the compressibility and the compactibility of the polymer in powder form (Rime *et al.*, 1997). Therefore the following properties of ethylcellulose powders of different viscosity grades were examined: thermal behaviour, crystallinity, particle shape, particle size distribution and particle surface area. In addition, basic compact characteristics were examined including; height, porosity, tensile strength, surface density, surface roughness, swelling factor and contact angle (in contact with phosphate buffer).

5.2. THERMAL BEHAVIOUR

5.2.1. Glass Transition temperature

The glass transition temperature (T_g) of a polymer represents a change in the polymer from a brittle to a less brittle, rubbery state. It is considered a reversible process and heating the polymer through its T_g will convert the polymer from a glassy state to a liquid state. Various T_g values were obtained by different authors depending on the ethylcellulose grade being measured, as well as the experimental technique undertaken (Sakellariou *et al.*, 1985 and Entwistle and Rowe, 1979 and Rekhi and Jambhekar, 1995). Values ranged between 129°C and 140°C.

The glass transition temperature of ethylcellulose 4 cP or 100 cP viscosity grade could not be detected when samples were measured at a heating rate of 5 °C per minute from a temperature of 25°C to 250°C. A successful measurement was undertaken when samples were measured at a heating rate of 5 °C per minute from a temperature of –30°C to 300°C (figure 5.1.). Values are tabulated in table 5.1. The glass transition temperature was recorded as a slight change in the baseline. No indication of any crystallinity was recorded in the DSC (differential scanning calorimetry) thermograms. The polymers were therefore considered amorphous.

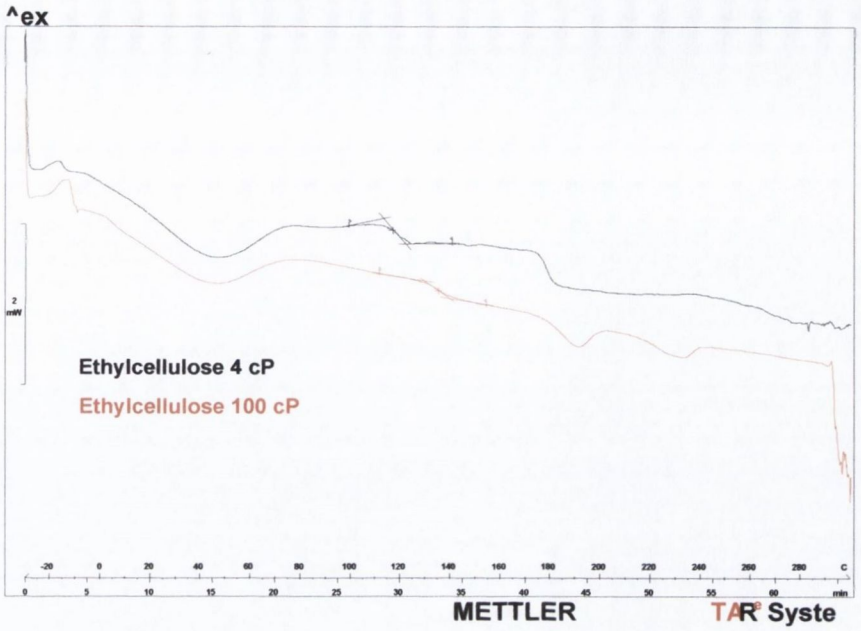


Figure 5.1. DSC thermograms of ethylcellulose 4 cP powder and ethylcellulose 100 cP powder undertaken at a heating rate of 5°C per minute, from –30°C to 300°C.

Table 5.1. *Glass transition temperature of ethylcellulose 4 cP and ethylcellulose 100 cP viscosity grade powder*

Ethylcellulose viscosity grade	Onset temperature °C	Peak Temperature °C
Ethylcellulose 4 cP	113.24	116.98
Ethylcellulose 100 cP	130.30	135.03

5.2.2. Differential scanning calorimetry

Ibuprofen and ethylcellulose are relatively inactive compounds, which have a patented use together as a sustained release matrix tablet (Radebaugh *et al.*, 1988).

The DSC thermograms of ibuprofen and ethylcellulose (4 cP or 100 cP viscosity grade) and their mixtures showed that both the peak and onset melting point of ibuprofen was lowered in the presence of ethylcellulose powder (appendix 3). This suggests the possibility of some interaction or complexation between ethylcellulose and ibuprofen at the melting temperature of ibuprofen powder. The onset, peak and normalised energy values of melting, of ibuprofen are tabulated in appendix 3.

Ethylcellulose 4 cP powder affected the melting point of ibuprofen more than ethylcellulose 100 cP powder. This may be because the lower molecular weight

ethylcellulose 4 cP viscosity grade has shorter polymer chains, which facilitate greater chain mobility than the higher molecular weight 100 cP viscosity grade. Upadrashta *et al.* (1994) determined that higher molecular weight grades were inherently more ordered than the lower molecular weight grades.

5.3. HOT STAGE MICROSCOPY

Hot stage microscopy (HSM) is also referred to as thermal microscopy. It can be an extremely valuable tool for the characterisation of solid state forms (Brittain, 1999). The technique involves heating and/or cooling a few milligrams of a substance on a microscope slide and observing the sample. Thermal microscopy can be used to determine melting points or phase transition temperatures. During phase transformations, the optical properties of the crystals will undergo changes (Newman and Brittain, 1995). In addition, the loss of solvent molecules from a solvate can be detected by immersing the sample in oil. The evolution of gases is evident in the generation of gaseous bubbles from the sample (Newman and Brittain, 1995).

Ibuprofen samples were analysed by thermal microscopy between the temperatures of 25°C and 180 °C. Prior to heating the ibuprofen sample was present as crystals. The crystals began to melt at 75°C and were completely melted at 77°C. After melting a clear liquid remained.

Ethylcellulose 4 cP and ethylcellulose 100 cP powder samples were analysed by thermal microscopy between the temperatures of 25°C and 180°C. At 25°C both ethylcellulose 4 cP and 100 cP powder samples appeared granular and white in appearance. Up to 120°C the morphological characteristics of the ethylcellulose samples were unchanged. Between 120°C and 130°C the ethylcellulose granules appeared to acquire a clear/transparent appearance. At 140°C the samples appeared as clear liquid globules.

Mixtures of ethylcellulose:ibuprofen: In the presence of ethylcellulose 4 cP powder, the ibuprofen began to melt at 67°C and had completely melted at 73°C. In the presence of ethylcellulose 100 cP powder, the ibuprofen began to melt at 73°C and had completely melted at 76°C. At 120°C the ethylcellulose granules (in the presence of melted ibuprofen) appeared glassy in appearance. At 140°C the mixture appeared

as clear liquid globules. At 170°C the globules begin to coalesce and spread leading to a fluid.

5.4. X-RAY DIFFRACTOMETRY

The low crystallinity of ethylcellulose 4 cP powders and ethylcellulose 100 cP powders was qualitatively confirmed by powder X-ray diffractometry (figure 5.2.). Both viscosity grades were amorphous and no significant differences were found between the grades.

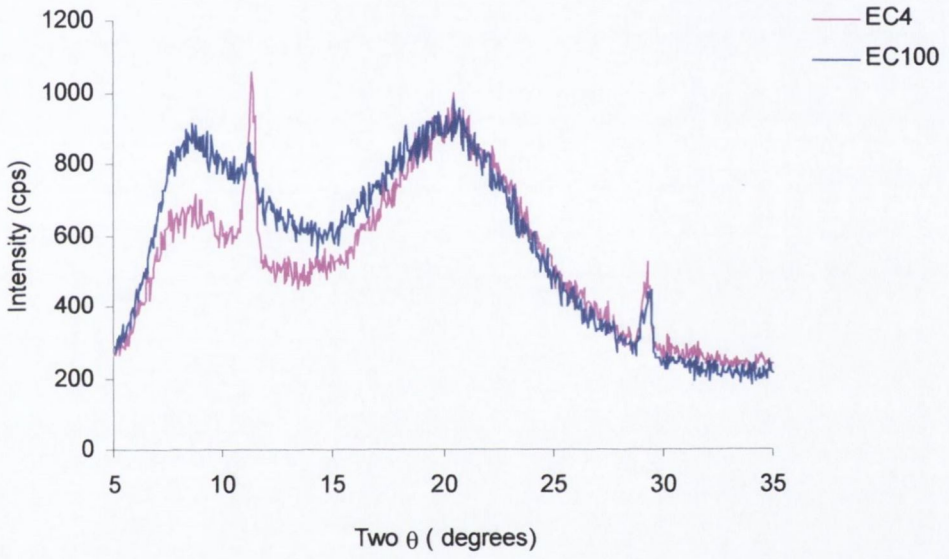


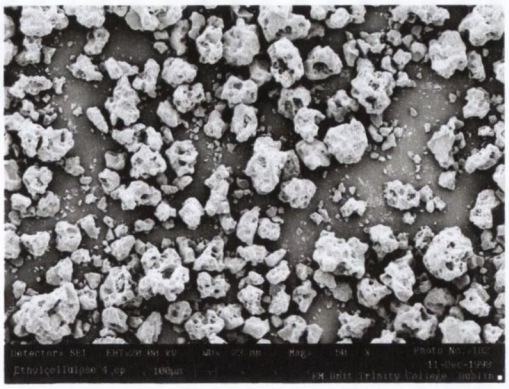
Figure 5.2. X-ray diffraction patterns of ethylcellulose 4 cP (EC4) and ethylcellulose 100 cP (EC100) powder.

5.5. PARTICLE SHAPE

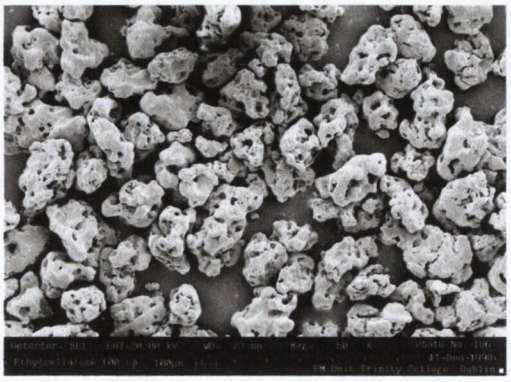
Katikaneni et *al.* (1995a) confirmed that to undertake a comprehensive study of compaction characteristics of powders (including tabletting) one needed to consider the effect of particle shape and size on packing density. Therefore, SEM photographs of ethylcellulose 4 cP powder and ethylcellulose 100 cP powder (each fraction sieved less than 180 μm) were taken at different magnification levels and the particle size and shape observed. The relevant photographs are shown in figures 5.3 and 5.4.

At a magnification of x 50, the particle size distribution of ethylcellulose 4 cP powders appeared different to ethylcellulose 100 cP powders (figure 5.3.). There were clearly a greater number of finer particles present in the ethylcellulose 4 cP powder sample than in the ethylcellulose 100 cP powder sample. Particles of ethylcellulose 100 cp viscosity grade powder also appeared more uniform in shape than particles of ethylcellulose 4 cP viscosity grade powder. At a higher magnification of x 1000, it was easier to examine the difference in surfaces of different ethylcellulose viscosity grade particles (figure 5.4.). The surface of ethylcellulose 4 cP powder particles appeared more ruptured and rougher than ethylcellulose 100 cP powder particles. The surface of ethylcellulose 100 cP particles appeared smoother and more uniform than those of ethylcellulose 4 cP particles.

The differences in particle morphology and size of ethylcellulose powders of different viscosity grades may have a number of implications. Wong and Pilpel (1990) showed that the mixing of powders was influenced by particle shape, while York (1978) showed that the degree of particle slippage and rearrangement taking place during compression increased as the particle size of the powder decreased, and was more extensive for powders composed of non-spherical particles. Rime *et al.* (1997) also found that differences in mechanical strength of polyvinyl chloride powders could be assigned to the particle morphology of the powder. He found that a direct relationship existed between the compact strength and the specific surface area of the particle. Therefore, differences in viscosity grade powder morphology and particle size distribution characteristics may manifest themselves in different tabletting characteristics.

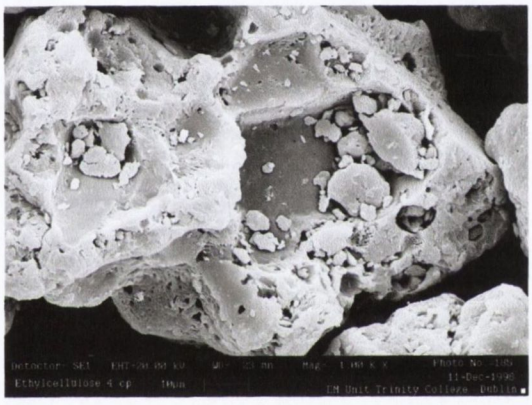


(A)

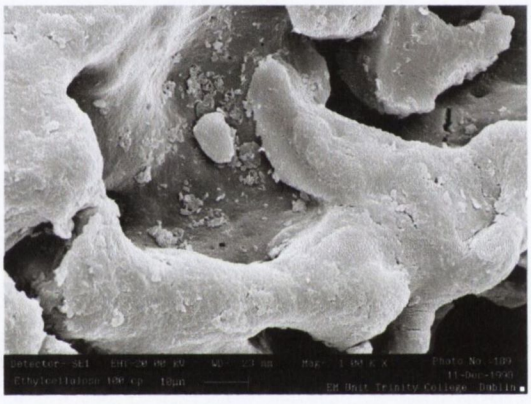


(B)

Figure 5.3. Scanning electron micrograph of ethylcellulose 4 cP (A) and ethylcellulose 100 cP powder (B), at a magnification of x 50.



(A)



(B)

Figure 5.4. Scanning electron micrograph of ethylcellulose 4 cP (A) and ethylcellulose 100 cP powder (B), at a magnification of x 1000.

5.6. POWDER PARTICLE SIZE DISTRIBUTION AND SURFACE AREA ANALYSIS

Rhines (1947) established that the packing density of a powder was influenced by the particle size distribution. Generally smaller particles allowed a greater packing density after the particle rearrangement phase of consolidation and a greater number of contact points for interparticulate bonding.

The particle size characteristics of ethylcellulose powders of different viscosity grades and of ibuprofen powder are outlined in table 5.2. All particle size data quoted is an average of at least three determinations. The distribution is depicted as percentage undersize. The (D[v,0.5]) is the median diameter of the volume distribution, the

(D[v,0.1]) is the diameter at the 10% point in the distribution, while the (D[v,0.9]) is the diameter at the 90% point in the distribution. Before particle size analysis, each powder fraction was sieved less than 180 μm. The median particle size (D[v,0.5]) of ethylcellulose 4 cP powder was less than the median particle size of ethylcellulose 100 cP powder. In addition, the particle size distribution of ethylcellulose 4 cP powder at D[v,0.1] and D[v,0.9] volume fractions were less than those determined for ethylcellulose 100 cP powder.

Ethylcellulose 100 cP FP had a smaller D[v,0.5], D[v,0.1] and D[v,0.9] than either ethylcellulose 4 cP powder or ethylcellulose 100 cP premium grade powder.

Table 5.2.

Particle size distribution of ethylcellulose powder of different viscosity grades and ibuprofen, and surface area analysis of ethylcellulose powder

Powder	D[v,0.1] (μm)	D[v,0.5] (μm)	D[v,0.9] (μm)	Surface area sq.m/g
Ibuprofen[(a)]	6.50	18.19	41.16	-
Ethylcellulose 4 cP[(a)]	29.90	88.66	167.88	0.6894 ± 0.0914
Ethylcellulose 10 cP[(b)]	28.93	97.26	195.84	-
Ethylcellulose 22 cP[(b)]	29.88	99.61	197.88	-
Ethylcellulose 100 cP[(a)]	40.71	109.51	196.92	0.3350 ± 0.0280
Ethylcellulose 100 cP FP[(a)]	11.95	32.76	65.65	-

[(a)] determined using a Malvern 2600c laser diffraction particle size analyser

[(a)] determined using a Malvern Mastersizer 2000 with a Scirocco dry powder feeder

5.7. CHARACTERISATION OF COMPACTS (HEIGHT, POROSITY AND TENSILE STRENGTH)

Compacts were prepared using different ethylcellulose:ibuprofen weight ratios, namely 25:75, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35 and 75:25, using one of two different ethylcellulose viscosity grade powders i.e. 4 cP or 100 cP. In addition, compacts were prepared of ibuprofen powder 100% w/w, ethylcellulose 4 cP powder 100 % w/w and ethylcellulose 100 cP powder 100% w/w. Compacts were also prepared with the finely milled form of ethylcellulose 100 cP i.e. ethylcellulose 100 cP FP in an ethylcellulose:ibuprofen weight ratio of 50:50. Further compacts were prepared of ethylcellulose 10 cP:ibuprofen or ethylcellulose 22 cP:ibuprofen in the

following ethylcellulose:ibuprofen weight ratios, 25:75, 50:50, 75:25 and 100:0. All powders were sieved less than 180 μm beforehand, and all compacts were compacted at 7000 kg for ten minutes.

5.7.1. Height

The height of compacts was measured using a sliding calliper. Results are outlined in tables 5.3, 5.4., 5.5. and 5.6. and illustrated in figure 5.5. The height of compacts prepared with ethylcellulose 4 cP 100% w/w was not significantly different from the height of compacts prepared with ibuprofen 100% w/w. Indeed, the height of ethylcellulose 4 cP compacts was not affected by altering the ethylcellulose:ibuprofen weight ratio. Compacts prepared with higher ethylcellulose viscosity grades behaved differently. The height of compacts prepared with ethylcellulose 100 cP 100% w/w was greater than the height of compacts prepared with ibuprofen 100% w/w. In addition, the height of compacts prepared with ethylcellulose 100 cP and a drug load of 25% w/w was less than the height of compacts prepared with 100% w/w ethylcellulose 100 cP. Increasing the ibuprofen content further to 35% w/w caused a further reduction in ethylcellulose 100 cP compact height, but beyond this drug load i.e. 40% w/w, 45% w/w, 50% w/w, 55% w/w, 60% w/w and up to 75% w/w there was no further reduction in compact height. A similar trend was evident for compacts prepared with either ethylcellulose 10 cP or 22 cP viscosity grade i.e. the height of compacts prepared with ethylcellulose 10 cP or 22 cP (100% w/w) was greater than the height of compacts prepared with 25% w/w drug load of the same ethylcellulose viscosity grades. However at higher drug loadings, the height of compacts prepared with 10 cP or 22 cP viscosity grade was unaffected by an increase in drug load. It is possible that this effect was not evident in compacts prepared with ethylcellulose 4 cP because compacts of ibuprofen (100% w/w) and ethylcellulose 4 cp (100% w/w) had similar heights originally.

Overall, the height of ethylcellulose 4 cP compacts was less than the height of compacts prepared with ethylcellulose 10 cP, 22 cP or 100 cP for each polymer-to-drug weight ratio examined, while the height of compacts prepared with ethylcellulose 100 cP was greater than the height of compacts prepared with ethylcellulose 10 cP or 22 cP viscosity grade at zero and 25% w/w drug loading. At drug loads of 50% w/w and 75% w/w the height of compacts prepared with the higher ethylcellulose viscosity grades (10 cP, 22 cP and 100 cP) were equal. Vromans and

Lerk (1988) used tablet thickness as an indicator of tablet consolidation i.e. increased consolidation was demonstrated by lower tablet thickness. This would suggest that compacts prepared with higher ethylcellulose viscosity grades (10 cP, 22 cP and 100 cP) were not as consolidated as compacts prepared with the lower ethylcellulose viscosity grade.

The height of compacts prepared with ethylcellulose 100 cP FP did not differ from the height of compacts prepared with ethylcellulose 100 cP granular form. One may have expected the height of compacts prepared with ethylcellulose 100 cP FP to be smaller than the height of compacts prepared with ethylcellulose 100 cP, because of the smaller median particle size of the ethylcellulose 100 cP FP particle size fraction (section 5.6). However, this was not observed. The sliding callipers may not have been accurate enough to detect any reduction in compact height when preparing compacts with ethylcellulose 100 cP FP (as opposed to ethylcellulose 100 cP granular form). The height of compacts prepared with ethylcellulose 100 cP FP was greater than the height of compacts prepared with ethylcellulose 4 cP. This may be explained by the greater compressibility and compactibility of the lower ethylcellulose viscosity grade versus the higher ethylcellulose viscosity grade (Upadrashta *et al.*, 1994).

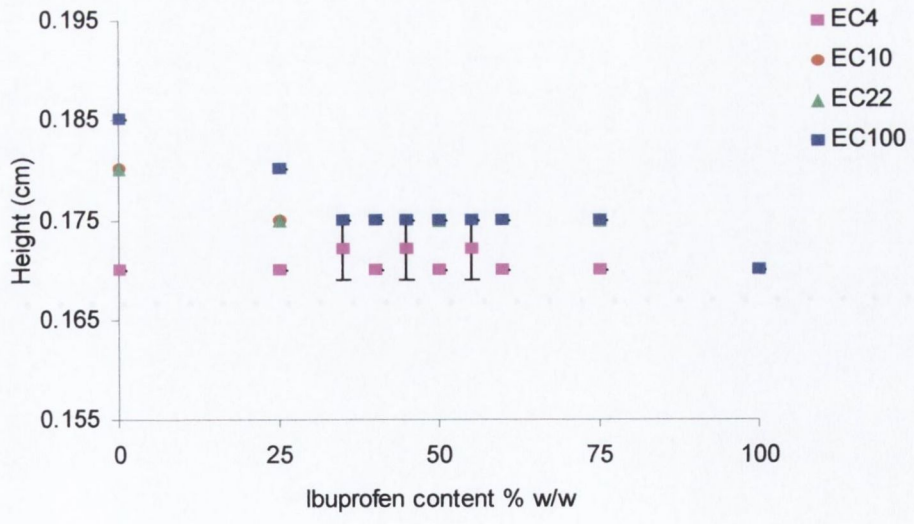


Figure 5.5. The height of compacts prepared with ethylcellulose of different viscosity grades. EC is ethylcellulose and the number following it is the viscosity grade (cP).

Table 5.3.

Characterisation of ethylcellulose 4 cP compacts prepared with different ethylcellulose:ibuprofen weight ratios

Ibuprofen content % w/w	Height (cm)	Initial porosity	Porosity drug	Total porosity	Hardness (kg)	Tensile strength (kg/cm^2)
0	0.170 ± 0.000	0.0346	0.0000	0.0346	18.63 ± 2.13	53.68 ± 6.15
25	0.170 ± 0.000	0.0270	0.2489	0.2760	14.90 ± 0.20	42.93 ± 0.56
35	0.172 ± 0.003	0.0313	0.3452	0.3765	13.29 ± 0.46	37.87 ± 1.83
40	0.170 ± 0.000	0.0225	0.3983	0.4208	13.48 ± 0.57	38.82 ± 1.65
45	0.172 ± 0.003	0.0302	0.4438	0.4741	13.10 ± 0.27	37.73 ± 0.78
50	0.170 ± 0.000	0.0194	0.4979	0.5173	11.64 ± 0.65	33.53 ± 1.87
55	0.172 ± 0.003	0.0272	0.5425	0.5697	9.52 ± 0.28	27.11 ± 0.66
60	0.170 ± 0.000	0.0164	0.5975	0.6139	9.50 ± 0.54	27.37 ± 1.70
75	0.170 ± 0.000	0.0119	0.7468	0.7587	8.32 ± 0.35	23.96 ± 1.01
100	0.170 ± 0.000	0.0044	0.9966	1.0000	5.87 ± 0.45	16.91 ± 1.31

Table 5.4.

Characterisation of ethylcellulose 100 cP compacts prepared with different ethylcellulose:ibuprofen weight ratios

Ibuprofen content % w/w	Height (cm)	Initial porosity	Porosity drug	Total porosity	Hardness (kg)	Tensile strength (kg/cm^2)
0	0.185 ± 0.000	0.1100	0.0000	0.1110	11.90 ± 0.36	31.41 ± 0.95
25	0.180 ± 0.000	0.0796	0.2258	0.3054	11.00 ± 0.19	29.95 ± 0.52
35	0.175 ± 0.000	0.0486	0.3386	0.3872	9.56 ± 0.20	26.76 ± 0.55
40	0.175 ± 0.000	0.0491	0.3870	0.4361	9.40 ± 0.41	26.30 ± 1.15
45	0.175 ± 0.000	0.0477	0.4354	0.4831	9.13 ± 0.34	25.56 ± 0.96
50	0.175 ± 0.000	0.0463	0.4837	0.5300	8.69 ± 0.51	24.30 ± 1.42
50 FP	0.175 ± 0.000	0.0480	0.4837	0.5317	10.10 ± 0.53	28.35 ± 1.48
55	0.175 ± 0.000	0.0449	0.5321	0.5770	8.54 ± 0.34	23.9 ± 0.95
60	0.175 ± 0.000	0.0436	0.5803	0.6240	8.36 ± 0.52	23.39 ± 1.47
75	0.175 ± 0.000	0.0394	0.7256	0.7650	6.87 ± 0.15	19.23 ± 0.43
100	0.170 ± 0.000	0.0043	0.9966	1.0000	5.87 ± 0.45	16.91 ± 1.31

Table 5.5.

Characterisation of ethylcellulose 10 cP compacts prepared with different ethylcellulose:ibuprofen weight ratios

Ibuprofen content % w/w	Height (cm)	Initial porosity	Porosity drug	Total porosity
0	0.180	0.0756	0.0000	0.0756
25	0.175	0.0451	0.2419	0.2870
50	0.175	0.0409	0.4837	0.5247
75	0.175	0.0367	0.7260	0.7623
100	0.170	0.0043	0.9966	1.0000

Table 5.6.

Characterisation of ethylcellulose 22 cP compacts prepared with different ethylcellulose:ibuprofen weight ratios

Ibuprofen content % w/w	Height (cm)	Initial porosity	Porosity drug	Total porosity
0	0.180	0.0764	0.0000	0.0764
25	0.175	0.0457	0.2421	0.2879
50	0.175	0.0412	0.4889	0.5301
75	0.175	0.0369	0.7259	0.7628
100	0.170	0.0043	0.9966	1.0000

5.7.2. Porosity

The total porosity referred to in tables 5.3., 5.4., 5.5. and 5.6. refers to the porosity of the leached portion of the tablet and is equal to the porosity due to air (initial porosity) and porosity due to drug content. The porosity due to air or initial porosity is calculated from the difference in apparent and true volume. The true volume is calculated knowing the true density of each powder component. The true density of ethylcellulose 4 cP was 1.1474 g/ml (Litchfield, 1999), ethylcellulose 100 cP was 1.145 g/ml (Pollock and Sheskey, 1997), ethylcellulose 100 cP FP was 1.149 g/ml (Pollock and Sheskey, 1997), ethylcellulose 10 cP was 1.132 g/ml (Pollock and Sheskey, 1997), ethylcellulose 22 cP 1.133 g/ml was (Litchfield, 1999) and ibuprofen was 1.1124 g/ml (Healy, 1995). Porosity due to drug content corresponds directly to the volume of free space previously occupied by the extracted drug. In this manner matrix total porosity includes the available and inaccessible pores. Low porosities were achieved for compacts prepared with ethylcellulose 4 cP, 10 cP, 22 cP and

ethylcellulose 100 cP. This is usually the case for plastically deforming materials (Rime *et al.*, 1997). Examination of figure 5.6. shows that a linear relationship exists between the total porosity of the matrix and the drug loading. This was evident for compacts prepared with any of the four different ethylcellulose viscosity grades. Statistical parameters are outlined in table 5.7.

Results also showed that the initial porosity of compacts prepared with ethylcellulose had a tendency to decrease with increasing ibuprofen content. This was evident for compacts prepared with any of the different ethylcellulose viscosity grades.

At the same drug loading, compacts prepared with ethylcellulose 4 cP had lower porosity values than compacts prepared with any of the other ethylcellulose viscosity grades. The greatest total porosity difference was between ethylcellulose 4 cP compacts 100% w/w and ethylcellulose 100 cP compacts 100% w/w. Closer examination of porosity values showed that the initial porosity of compacts prepared with ethylcellulose 4 cP was less than the initial porosity of compacts prepared with ethylcellulose 10 cP, 22 cP or 100 cp, for each ethylcellulose:ibuprofen weight ratio. This work was consistent with findings by Shlieout and Zessin (1996). They showed that tablets prepared with different ethylcellulose viscosity grades and a consistent compression force displayed an increase in porosity with an increase in the viscosity grade. This was accounted for by the higher compressibility and compactibility of the lower ethylcellulose viscosity grades. Katikaneni *et al.* (1995a) stated that the packing density of a powder is influenced by the particle size distribution, particle shape and interparticulate forces and electrostatic interactions. Generally, smaller particles allow a greater packing density after the particle rearrangement phase of consolidation and a greater number of contact points for interparticulate bonding (Rhines, 1947). Katikaneni *et al.* (1995a) stated that with ductile materials, the difference in packing density will be retained throughout the compression process, and tablet strength and porosity will be dependent on initial particle size distribution. Katikaneni *et al.* (1995a) also showed that the porosity in the ethylcellulose tablet structure is dependent on the initial porosity of the powder bed and that plastic deformation is the primary consolidation mechanism. Therefore, the differences in particle morphology, size and area of ethylcellulose 4 cP powders and ethylcellulose 100 cP powders (previously confirmed by SEM scans, particle size measurement and powder surface area analysis) may have also contributed to the porosity difference between compacts of different ethylcellulose viscosity grades.

In addition, the calculated porosity of compacts prepared with ethylcellulose 100 cP FP did not differ greatly from the calculated porosity of compacts prepared with ethylcellulose 100 cP granular form. Earlier work in section 5.7.1. showed no difference in the height (and therefore apparent volume) of compacts prepared with either ethylcellulose 100 cP granular form and the finely milled form of ethylcellulose 100 cP. Because porosity was determined using the apparent volume measurement, no difference in the porosity of compacts prepared with either ethylcellulose 100 cP form was calculated. However, the porosity of compacts prepared with ethylcellulose 4 cP was less than the porosity of compacts prepared with ethylcellulose 100 cP FP. This was consistent with the findings of Shlieout and Zessin (1996), that tablets displayed an increase in porosity with an increase in viscosity grade.

Table 5.7.

Statistical parameters of linear trend line fitted to plots of total porosity versus ibuprofen content in compacts of different ethylcellulose viscosity grades

Viscosity grade	**CoD**	**MSC**
Ethylcellulose 4 cP	0.9999	9.23116
Ethylcellulose 10 cP	0.9995	6.7811
Ethylcellulose 22 cP	0.9996	6.9344
Ethylcellulose 100 cP	0.9977	5.6587

CoD: coefficient of determination, MSC: model selection criterion

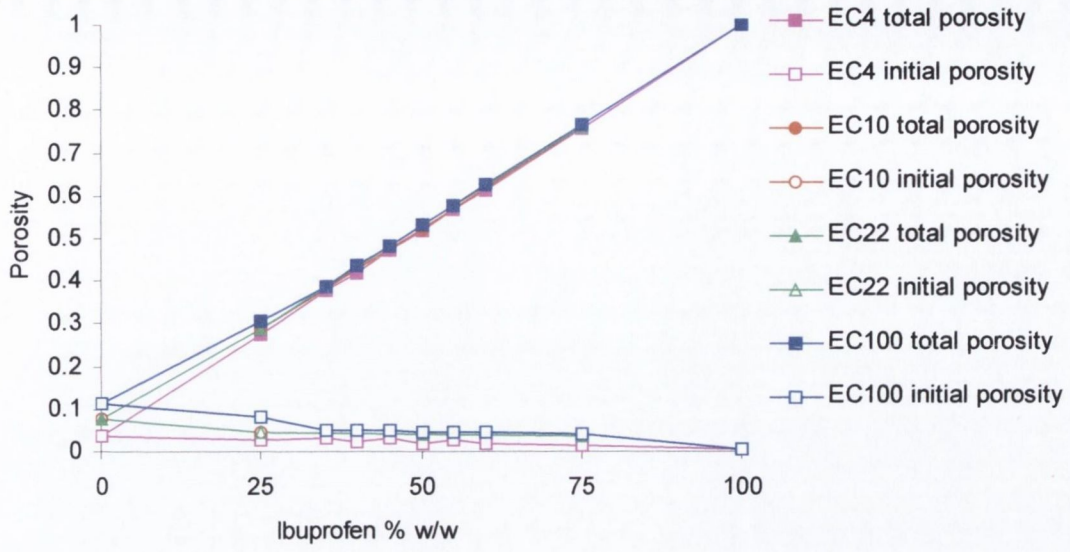


Figure 5.6. Relationship between drug load and porosity in compacts prepared with ethylcellulose of different viscosity grades. EC is ethylcellulose and the number following it is the viscosity grade (cP).

5.7.3. Tensile strength

The hardness of compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade and of different polymer to drug weight ratios was measured using a Schleuniger Hardness tester, and the tensile strength calculated (table 5.3. and 5.4.). Figure 5.7. shows a plot of tensile strength versus drug content of compacts of either ethylcellulose 4 cP or 100 cP viscosity grade.

A two-sample t-test, assuming equal variance was used to determine if the tensile strengths of compacts prepared with different ethylcellulose loadings, and different ethylcellulose viscosity grades were significantly different. It was found that the tensile strength of ethylcellulose 4 cP compacts 100% w/w was significantly greater ($p \leq 0.05$) than the tensile strength of compacts prepared with ibuprofen 100% w/w. In addition, the tensile strength of ethylcellulose 4 cP compacts 100% w/w was significantly greater ($p \leq 0.05$) than the tensile strength of ethylcellulose 4 cP compacts prepared with a drug load of 25% w/w. There was also a significant difference ($p \leq 0.05$) in the tensile strength of ethylcellulose 4 cP compacts of 25% w/w drug load and 35% w/w drug load. However, there was no significant difference ($p \leq 0.05$) in the tensile strength of the following ethylcellulose 4 cP compacts prepared with different

drug loads; 35% w/w and 40% w/w, and 40% w/w and 45% w/w. The tensile strength of ethylcellulose 4 cP compacts prepared with drug loads of 45% w/w and 50% w/w, and 50% w/w and 55% w/w were significantly different ($p \leq 0.05$). However, the tensile strength of ethylcellulose 4 cP compacts prepared with drug loads of 55% w/w and 60% w/w were not significantly different ($p \leq 0.05$). The tensile strength of ethylcellulose 4 cP compacts prepared with 60% w/w and 75% w/w drug load, and 75% w/w and 100 % drug load were significantly different ($p \leq 0.05$).

The tensile strength of compacts prepared with ethylcellulose 100 cP powder and different ethylcellulose:ibuprofen weight ratios was also measured. The tensile strength of ethylcellulose 100 cP compacts 100% w/w was significantly greater ($p \leq 0.05$) than the tensile strength of ibuprofen compacts 100 % w/w. Additionally, the tensile strength of ethylcellulose 100 cP compacts 100% w/w was significantly greater ($p \leq 0.05$) than the tensile strength of ethylcellulose 100 cP compacts of a drug load of 25% w/w. There was also a significant difference ($p \leq 0.05$) in the tensile strength of ethylcellulose 100 cP compacts prepared with 25% w/w drug load and 35% w/w drug load. However, there was no significant difference ($p \leq 0.05$) in the tensile strength of the following ethylcellulose 100 cP compacts prepared with different drug loads, 35% w/w and 40% w/w, 40% w/w and 45% w/w, 45% w/w and 50% w/w, 50% w/w and 55% w/w, 55% w/w and 60% w/w. There was a significant difference ($p \leq 0.05$) in the tensile strength of ethylcellulose 100 cP:ibuprofen compacts prepared with the following drug loads: 60% w/w and 75% w/w, and 75 w/w and 100% w/w.

These findings were supported by work undertaken by Katikaneni *et al.*, 1995b. He found a slight decrease in ethylcellulose tablet hardness with an increase in drug loading. This may be accounted for by a decrease in the compressibility of the matrix resulting from the higher drug concentration (Katikaneni *et al.*, 1995b). Fell (1996) also proposed that in binary mixtures consisting of components A and B, three types of bonds will occur after compaction; A-A, A-B and B-B. The relative magnitude of these bonds may determine the pattern of results obtained. Therefore, in binary mixtures of ibuprofen and ethylcellulose there are three possible types of bonds, ibuprofen-ibuprofen, ethylcellulose-ethylcellulose and ethylcellulose-ibuprofen. Compacts of ethylcellulose 100% w/w (of either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade) showed greater tensile strength then compacts of ibuprofen 100% w/w. This would suggest that ibuprofen-ibuprofen bonds were not as strong as

ethylcellulose-ethylcellulose bonds. In addition, the initial reduction in tensile strength of compacts on increasing ibuprofen content suggests that the strengths of bonds between ibuprofen and ethylcellulose particles were less than the strength of bonds between ethylcellulose particles. As stated by Blattner *et al.* (1990) as soon as the component with the lower (or higher) mechanical strength percolates the powder system, tablet hardness is completely controlled by this component.

Results also showed that compacts prepared with ethylcellulose 4 cP powder had a significantly greater ($p \leq 0.05$) tensile strength than compacts prepared with ethylcellulose 100 cP, for all ethylcellulose:ibuprofen weight ratios. This is clearly illustrated in figure 5.7. This is in agreement with work undertaken by Upadrashta *et al.* (1994). The dependence of the compressibility and compactibility on molecular weight and viscosity grade was expected to be due to the increase in polymer order as a result of increased molecular weight. The higher molecular weight grades i.e. higher viscosity grades are inherently more ordered than the lower molecular weight grades because of their longer polymer chains.

Previous work in this section showed that a linear relationship existed between total porosity and ibuprofen content (section 5.7.2.). Therefore, the tensile strength of compacts prepared with different ethylcellulose viscosity grades versus total porosity was plotted (figure 5.8.). It was clear that for compacts of either ethylcellulose viscosity grade, as the total porosity decreased the tensile strength had a tendency to increase. In addition, even at similar total porosity values the tensile strength of ethylcellulose 4 cP compacts appeared to be higher than the tensile strength of ethylcellulose 100 cP compacts.

Shlieout *et al.* (1999) found similar results. They investigated the consolidation behaviour of different ethylcellulose viscosity grades, and compressed each powder to the same porosity value. A distinctive or a developed irreversible deformation of the ethylcellulose with low molecular weight was measured using the parameters outlined. Electron microscope pictures examined the surfaces of the ethylcellulose tablets of different viscosity grade (but of the same porosity) and found a developed fragmentation process in the lower ethylcellulose viscosity tablets. This can readily explain the better compressibility and compactibility of ethylcellulose with the lower molecular weight. Katikaneni *et al.* (1995a) showed that smaller particles have a greater number of contact points for interparticulate bonding. Hence, the smaller particle size distribution of the ethylcellulose 4 cP particle size fraction (as opposed to

ethylcellulose 100 cP particle size fraction) may contribute to the increased tensile strength of compacts prepared with ethylcellulose 4 cP. Rime *et al.* (1997) also showed that strong compacts were also the result of increased interparticulate contact area. He observed a parallel between the specific surface area of poly(vinyl chloride) powders and the strength of compacts. The compact hardness was thus only dependent on the inter- and the intraparticulate contact area, which in turn was dictated by the particle morphology of the different polyvinyl chloride powders. Therefore, the differences in surface area, morphology and particle size of the ethylcellulose powders of different viscosity grades may have also contributed to the differences in tensile strength of compacts prepared with different ethylcellulose viscosity grades.

The tensile strength of compacts prepared with the finely milled form of ethylcellulose 100 cP (FP) was greater than the tensile strength of the granular form of ethylcellulose 100 cP. A characteristic of the finely milled form of ethylcellulose 100 cP was the much smaller particle size distribution as compared to the granular form of ethylcellulose 100 cP. This results in a strengthening of intraparticle cohesive forces in the compact due to the increased surface area of the micronized particles. Results also showed that the tensile strength of compacts prepared with ethylcellulose 100 cP FP was less than the tensile strength of compacts prepared with ethylcellulose 4 cP. This may be because of the lower compressibility and compactibility of the higher ethylcellulose viscosity grade (Upadrashta *et al.*, 1994).

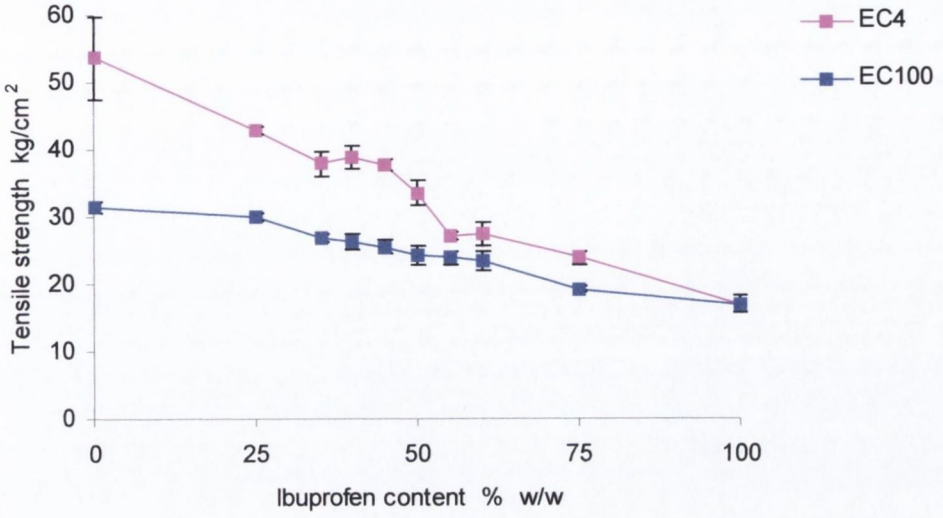


Figure 5.7. Relationship between drug load and tensile strength in compacts prepared with ethylcellulose of different viscosity grades. EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cP viscosity grade.

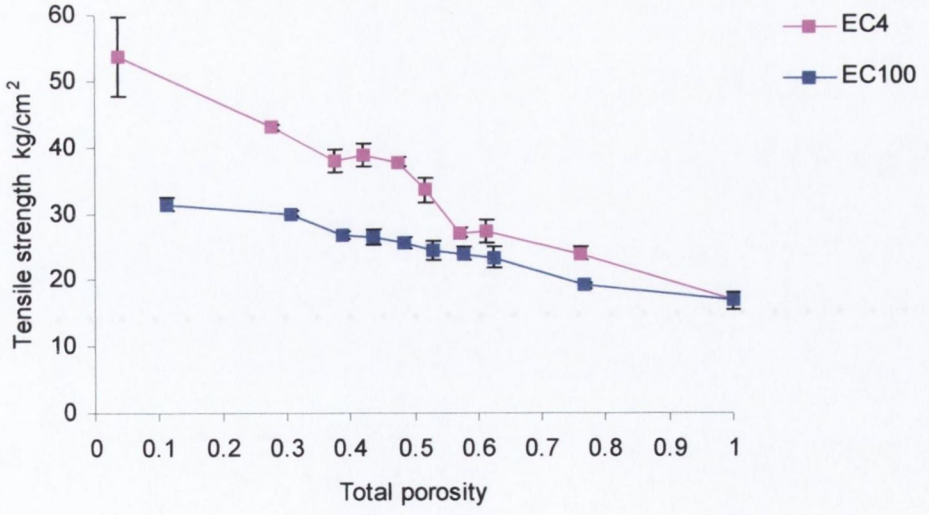


Figure 5.8. Relationship between compact porosity and tensile strength in compacts prepared with ethylcellulose of different viscosity grades. EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cP viscosity grade.

5.8. PROFILOMETRY STUDIES

Surface roughness of pharmaceutical systems, such as tablets have been previously measured using stylus instruments (Rowe, 1978). However, there were limitations to the stylus instrument method of roughness determination. The stylus instrument measured by contact and as a result there was a risk that the surface being examined could be altered by contact with the stylus. In addition, the radius of the stylus was between 2.5-5 μm which limited the resolution of the instrument (Healy, 1995). This limited the variety of systems that could be successfully examined. Also, with stylus instruments surface roughness parameters were determined from line scans since it was not possible to undertake area scans and three-dimensional surface profiles. In contrast, the UBM non-contacting laser profilometer does not have any damaging contact with the system being examined. Systems could therefore be used after surface roughness examination. In addition, the profilometer has a vastly superior resolution power using a 1 μm light spot diameter and a measurement range of +/-500 μm. It also has the ability to perform line scans and area scans of the sample surface, enabling a three-dimensional surface profile to be constructed.

The objective of this section was to examine the surface roughness of compacts prior to dissolution. Surface roughness measurements were successfully undertaken of ibuprofen compacts (100% w/w), ethylcellulose compacts (of 4 cP or 100 cP viscosity grades) 100% w/w and of ethylcellulose:ibuprofen compacts of either ethylcellulose 4 cP or 100 cP viscosity grade (50:50 weight ratio). The three-dimensional surface profiles obtained for compressed discs are shown in figures 5.9. to 5.13. Two roughness parameters were used to quantify the surface roughness. These were the roughness average R_a and the roughness parameter R_{tm}. The derivation and meaning of these parameters is outlined in Chapter 4. Results are given in Table 5.8.

The roughness parameters R_a and R_{tm} of ethylcellulose:ibuprofen compacts were less than those parameters determined for compacts prepared with ethylcellulose alone. This was evident for compacts prepared with either ethylcellulose viscosity grade. The roughness parameters of compacts prepared with ibuprofen 100% w/w were less than those of compacts prepared with ethylcellulose 100 cP:ibuprofen, but not of those compacts prepared with ethylcellulose 4 cP:ibuprofen. In addition, the

roughness parameters R_a and R_{tm} of ibuprofen 100% w/w were less than those values determined for ethylcellulose 100% w/w compacts, of either ethylcellulose viscosity grade. This suggests that the addition of ibuprofen can cause a reduction in the surface roughness of compacts prepared with either ethylcellulose viscosity grade, at certain ethylcellulose:ibuprofen weight ratios. A possible explanation for this phenomenon is that the median particle size (D[v,0.5]) of the ibuprofen powder was less than the median particle size of ethylcellulose powder of either 4 cP or 100 cP viscosity grade (section 5.6.). As a result, the ibuprofen powder may consolidate better than powders of ethylcellulose or their ethylcellulose:ibuprofen mixtures. This was supported by earlier findings, which showed that the initial porosity of compacts prepared with increasing ibuprofen content showed a tendency to decrease for compacts of either ethylcellulose viscosity grade. In fact, the initial porosity of compacts prepared with ibuprofen 100% w/w was less than the initial porosity of compacts prepared with ethylcellulose 100% w/w (of 4 cP or 100 cP viscosity grade) (section 5.7.2.).

One-component compacts prepared with ethylcellulose 100 cP viscosity grade had greater roughness parameter (R_a, R_{tm}) than one-component compacts prepared with ethylcellulose 4 cP viscosity grade (table 5.8.). In addition, the roughness parameters for two-component compacts prepared with ethylcellulose 100 cP viscosity grade and ibuprofen were greater then the roughness parameters for two-component compacts prepared with ethylcellulose 4 cP viscosity grade and ibuprofen. This may be explained on the basis of the larger particle size and morphology of ethylcellulose 100 cP particle size fraction as opposed to the ethylcellulose 4 cP particle size fraction.

These differences in roughness parameters between compacts of either ethylcellulose viscosity grade may persist after dissolution. Healy (1995) showed that succinic acid:ibuprofen compacts of very large and very small acid excipient particle size fractions had different roughness parameters (R_a and R_{tm}) before dissolution. Measurement of roughness parameters of the relevant discs after dissolution showed that the relative differences in R_a remained approximately the same, although the actual difference increased. The R_{tm} parameters showed a reduction in magnitude although the actual difference increased.

The difference in roughness parameters between compacts of either ethylcellulose 4 cP or 100 cP may have implications for drug dissolution. Grijseels *et al.* (1984) showed that the nature of the solid surface would influence the flow characteristics of

the dissolution medium adjacent to that surface. He postulated that the presence of pores in a surface could change the laminar character of the boundary layer flow to turbulent and induce locally an increased dissolution flux in the wake of the pores. Therefore, turbulent flow at the disc surface will be increased the greater the surface roughness. Consequently, it is to be expected that the initial dissolution flux would be greater from the rougher surface i.e. from compacts prepared with ethylcellulose 100 cP as opposed to compacts prepared with ethylcellulose 4 cP.

The R_{tm} value gives an indication of pore depth. The value of this parameter was almost one and a half times greater for compacts prepared with ethylcellulose 100 cP:ibuprofen (50:50 weight ratio) than for compacts prepared with ethylcellulose 4cP:ibuprofen (50:50 weight ratio), and was almost twice as great for compacts of ethylcellulose 100 cP (100% w/w) than for compacts of ethylcellulose 4 cP (100% w/w). These values confirm that prior to dissolution, compacts prepared with ethylcellulose 100 cP had greater pore depth and rougher surfaces than compacts prepared with ethylcellulose 4 cP.

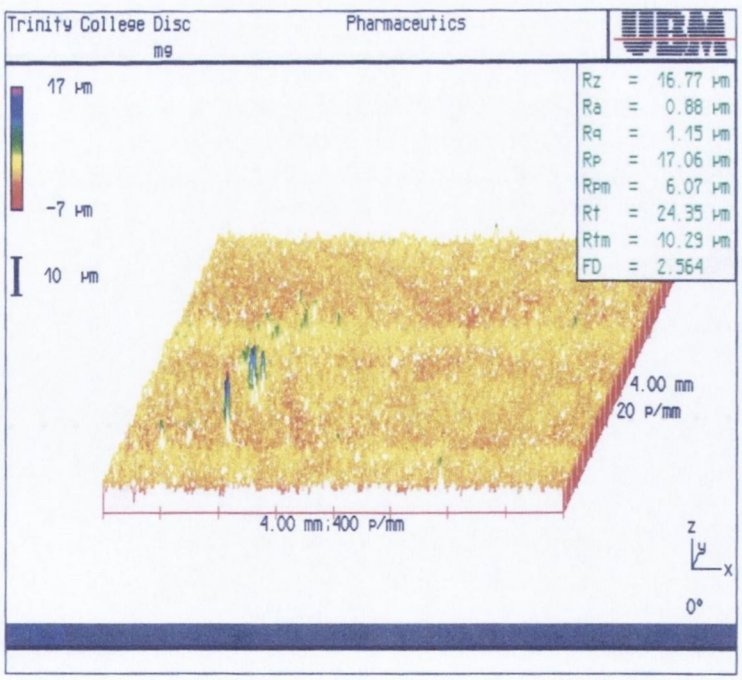


Figure 5.9. Surface profile of ibuprofen compact (100% w/w).

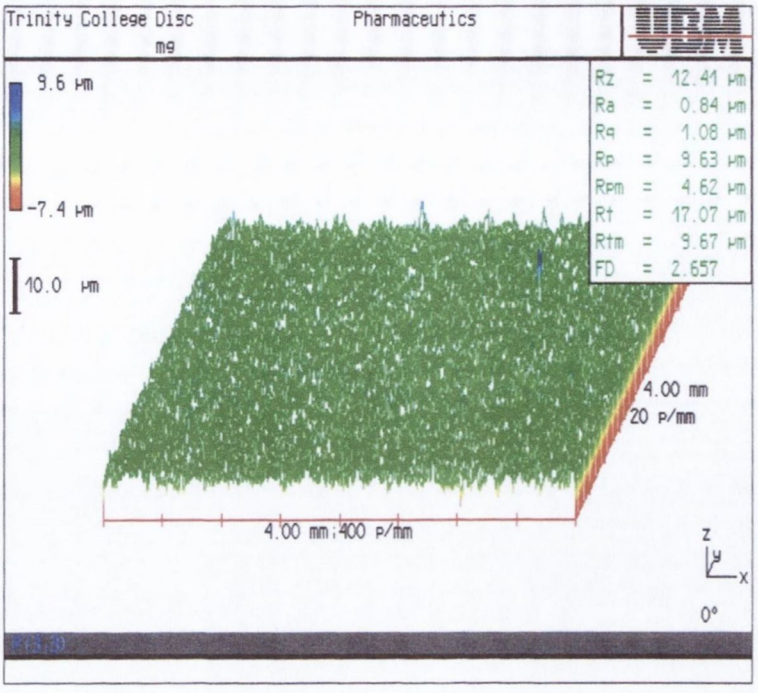


Figure 5.10. Surface profile of ethylcellulose 4 cP:ibuprofen compact (50:50) weight ratio.

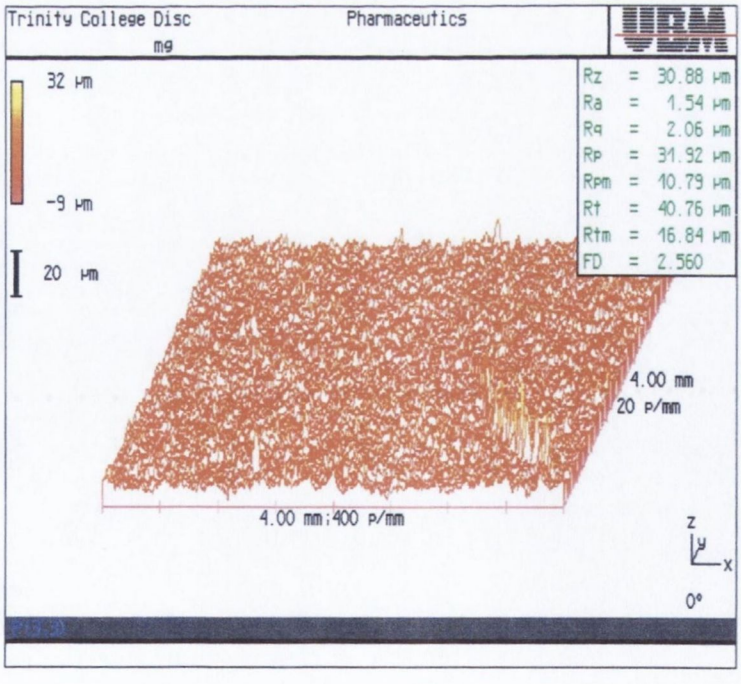


Figure 5.11. Surface profile of ethylcellulose 100 cP:ibuprofen compact (50:50) weight ratio.

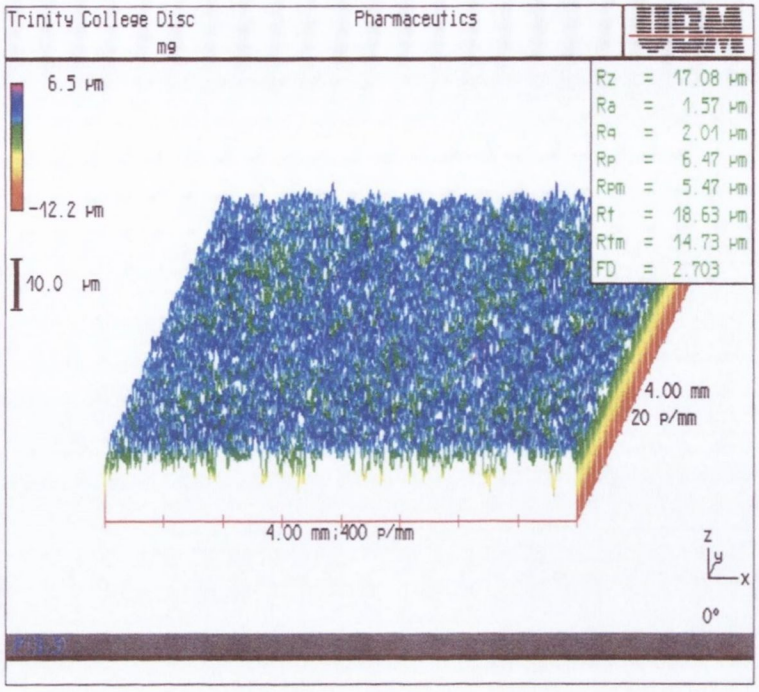


Figure 5.12. Surface profile of ethylcellulose 4 cP compact (100% w/w).

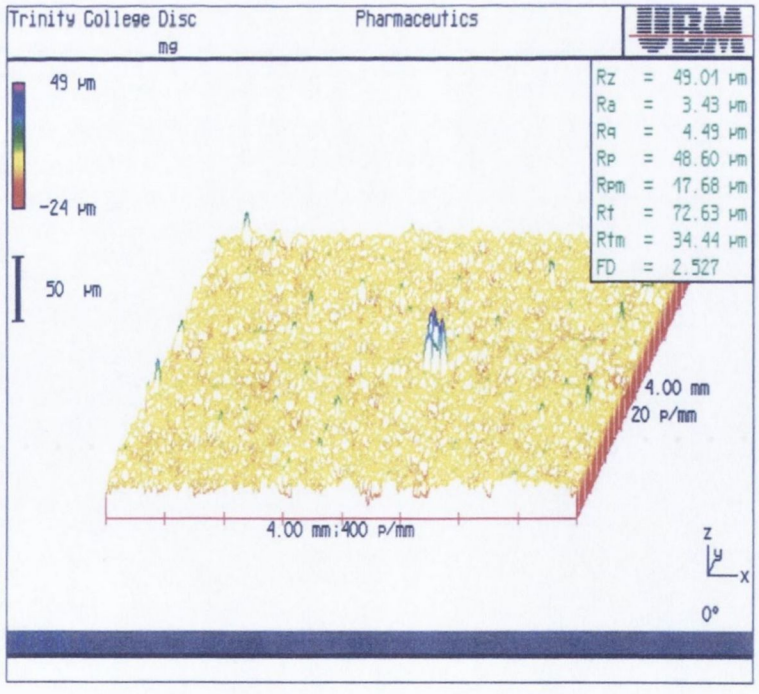


Figure 5.13. Surface profile of ethylcellulose 100 cP compact (100% w/w).

Table 5.8.

Surface roughness parameters of compacts

Compact	R_a (μm)	R_{tm} (μm)
Ibuprofen (100% w/w)	0.88 ± 0.01	11.11 ± 1.15
Ethylcellulose 4 cp:ibuprofen (50:50 weight ratio)	0.82 ± 0.03	9.22 ± 0.64
Ethylcellulose 100 cp:ibuprofen (50:50 weight ratio)	1.53 ± 0.02	15.48 ± 1.93
Ethylcellulose 4 cP (100% w/w)	1.61 ± 0.05	15.34 ± 0.86
Ethylcellulose 100 cP (100% w/w)	3.28 ± 0.22	31.71 ± 3.87

5.9. SURFACE DENSITY STUDIES

The major factors influencing drug distribution in a matrix type delivery system, and drug release from the matrix core include particle size, drug solubility, core composition and core hardness (Fassihi, 1988). Previous work by Barra *et al.* (2000) related the colour of binary powder blends to the tensile strength of the tablets made from the binary mixes. Work undertaken by Fassihi (1988) examined changes in surface density or colour intensity of polymeric matrices with increasing compression pressure i.e. the greater the compression pressure the greater the surface density, reflected in greater colour intensity. The purpose of this section was to characterise the surface density of ethylcellulose compacts after compaction at 7000 kg for ten minutes. The effect of ethylcellulose viscosity grade and ethylcellulose particle size fraction on surface density properties of compacts was evaluated.

5.9.1. Surface density of ethylcellulose compacts

Compacts were prepared using either ethylcellulose 4 cP or ethylcellulose 100 cP powder (white in appearance) and amaranth 1% w/w (a deep purple colour). All powders were sieved less than 180 μm before being mixed and compacted at 7000 kg for ten minutes. (Particle size analysis of each of the major powder components is outlined in section 5.6.) The resulting compacts were a deep purple colour in appearance (figure 5.14A.). However the colour intensity was not uniformly distributed throughout the compact. The greatest colour intensity was observed at the edges of the compact nearest the lower punch. This was identified as the side facing the punch next to the source of force of compression i.e. bottom side. This was more evident when viewing compacts from the side. The least colour intensity was

observed towards the central part of the tablet. This suggests the existence of different surface densities across the different regions of the compact (top, bottom and edges).

These findings were supported by Train (1956). He extensively studied the distribution of pressure and densities within a compact. He found that the density of a tablet produced on an alternative press is not homogenous, because the force transmission in a powder under pressure is not uniform (Train, 1956). He showed that in a tablet, there are regions of low density and regions of high density. He found that regions of high density and pressure correlate with the edge of the upper punch, where the pressure is applied (Train, 1956). In addition, Fassihi (1986) showed that when isotropic homogenous powders were compressed on a rotary machine, regions of greatest density were produced in a peripheral ring parallel with and near to the points of greatest pressure. Fassihi (1988) also confirmed that that a lower degree of consolidation occurred in the central part of the tablet. This would appear to agree with our work.

In addition, the colour intensity of compacts prepared with ethylcellulose 4 cP powder was greater (for all areas of the compact) than the colour intensity of compacts prepared with ethylcellulose 100 cP powder i.e. ethylcellulose 4 cP compacts have a greater surface density than ethylcellulose 100 cP compacts. This would suggest that the force transmission in powders of ethylcellulose 4 cP and 100 cP under pressure were not the same. Shlieout and Zessin (1996) showed that ethylcellulose powders of low viscosity grades were more compressible and compactible than ethylcellulose powders of higher ethylcellulose viscosity grades.

5.9.2. Surface density of ethylcellulose:ibuprofen compacts

Physical mixtures of ethylcellulose:ibuprofen (50:50 weight ratio) were prepared. For each physical mixture a different ethylcellulose viscosity grade (4 cP or 100 cP) was used. In addition, one of two different ethylcellulose particle size fractions were used, namely ethylcellulose sieved less than 180 μm and ethylcellulose 180-250 μm particle size fraction. Amaranth powder was added to each physical mixture at a concentration of 1% w/w. Mixtures were then compacted at 7000 kg for ten minutes. Photographs of compacts are shown in figure 5.14B. and 5.14C.

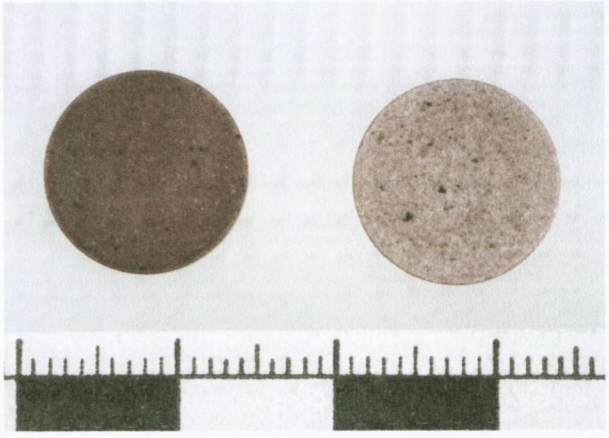
Compacts prepared using a mix of ethylcellulose and ibuprofen showed less colour intensity then compacts prepared with ethylcellulose alone. This was evident for

compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade. In addition, the colour was visibly uniform in appearance across the surface of the compact. There was no evidence of increased colour intensity at the edge of the compacts prepared with ethylcellulose and ibuprofen, which was evident when compacts were prepared with ethylcellulose alone. This was apparent for both ethylcellulose viscosity grades. This suggests that the addition of a second component, ibuprofen to ethylcellulose powder in a 50:50 weight ratio reduces the densification of the ethylcellulose powder.

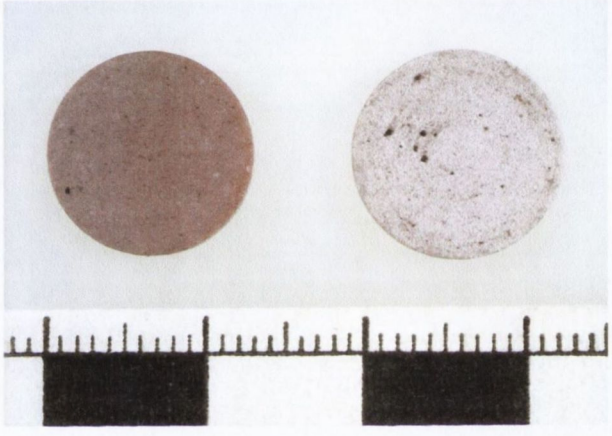
Compacts prepared with ethylcellulose:ibuprofen, using ethylcellulose sieved less than 180 μm showed greater colour intensity than compacts prepared with ethylcellulose 180-250 μm particle size fraction. This was evident for compacts prepared with either ethylcellulose viscosity grade. This would imply that compacts prepared with the smaller ethylcellulose particle size fraction had greater overall surface density properties then compacts prepared with the larger ethylcellulose particle size fraction.

Rhines (1947) stated that the packing density of a powder is influenced by the particle size distribution, particle shape and interparticulate forces as in frictional and electrostatic interactions. Generally, the smaller particle size fractions will allow a greater degree of packing density after the particle rearrangement phase of consolidation and a greater number of contact points for interparticulate bonding. Therefore, it would appear that on compaction the ethylcellulose powder sieved less than 180 μm underwent a greater degree of packing density and bonding than compacts prepared with the larger ethylcellulose particle size fractions. Fasshi (1988) also showed that the formation of high-density zones was related to pressure exerted on particles directly in contact with the punch surfaces. This results in very high pressure at small individual points of contact and formation of high density zones. Compacts prepared with the smaller ethylcellulose particle size fraction have a greater number of smaller individual particles in contact with the punch surface and therefore experience the effects of pressure (including densification) to a greater extent.

The colour intensity of compacts prepared with ethylcellulose 4 cP viscosity grade powder was visibly greater than the colour intensity of compacts prepared with ethylcellulose 100 cP powder, for each particle size fraction. This was in agreement with previous findings (section 5.9.1) which found that ethylcellulose 4 cP compacts showed greater surface densification than compacts of ethylcellulose 100 cP.



(A)



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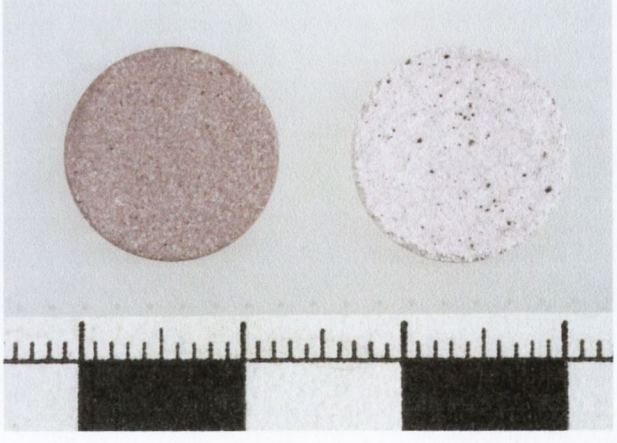

(C)

Figure 5.14. Photographs of compacts prepared with ethylcellulose 4 cP (left) or ethylcellulose 100 cP (right) and amaranth powder. A. ethylcellulose 100% w/w and sieved less than 180 μm. B. Ethylcellulose:ibuprofen 50:50 weight ratio using ethylcellulose sieved less than 180 μm. C. Ethylcellulose:ibuprofen 50:50 weight ratio using ethylcellulose 180-250 μm particle size fraction. One black ruler marking indicates one millimetre.

5.10. COMPACT SWELLING STUDIES/ WATER UPTAKE STUDIES

In swelling systems such as hydroxypropylmethylcellulose, or sodium carboxymethlycelluose, the release of a solute is controlled by one or more of the following processes: the transport of solvent into the polymer matrix, swelling of the associated polymer, diffusion of the solute through the swollen polymer and erosion of the swollen polymer (Bouwstra and Junginger, 1993). Ethylcellulose is an inert hydrophobic polymer and cannot swell in the manner similar to the above polymers. Nevertheless, Neau *et al.* (1999) when discussing drug release mechanisms from ethylcellulose matrix tablets referred specifically to ethylcellulose compacts undergoing the process of swelling during the dissolution process. Huang and Schwartz (1995) also referred to the mechanism of polymer relaxation as swelling.

Release of drug from dosage forms is a mass transport phenomenon involving three main processes: solvent penetration into the dosage form, dissolving the drug and diffusion of drug molecules into the surrounding environment. There is little doubt that liquid absorption must be the first step in the process of dissolution. This would suggest that the rate of drug dissolution from dosage forms can be controlled by the extent and rate of liquid absorption by the tablet system, and any factors that influence this uptake will ultimately influence the dissolution rate. Washburn and Footitt (1921) found that the uptake rate of liquid into a tablet depended on the porosity and pore size distribution in the tablet and the wettability of the constituent excipients of the tablet.

Studies have shown that ethylcellulose powder absorbs very little water from humid air or during immersion and that this small amount evaporates readily (Soriano *et al.*, 1998). Dabbagh *et al.* (1996) showed that there was no significant difference between the enthalpies of pure water and the enthalpies of discs containing ethylcellulose after 1 minute of contact with water. This implies a weak ability of ethylcellulose to absorb water. However, ethylcellulose does have the ability to bind to water. There were significant differences between the percentage of bound water to discs containing ethylcellulose at 1, 5 and 15 minutes of contact with water. However, no significant increase in bound water was observed after 15 minutes indicating the saturation of ethylcellulose. This ability to bind water may facilitate the hydration of ethylcellulose and consequently the process of swelling. Neau *et al.* (1999) noticed this phenomenon, finding at low drug loadings, more soluble drugs encouraged water

penetration into the core of the tablet allowing the ethylcellulose to hydrate and swell. This in turn provided a less tortuous pathway by which the drug could exit the tablet.

Previous work by Lin and Lin (1996) measured water uptake/water absorption of ethylcellulose tablets of different viscosity grades (of different particle size). They found that the larger the particle size of the ethylcellulose powder used, the higher the water uptake in drug free ethylcellulose compacts. It was proposed that this might be due to the higher tensile strength and better compactibility of compacts made of the smaller particle size of ethylcellulose powder, leading to less porosity of compacts i.e. the actual porosity of the compact was the major factor influencing water uptake.

The purpose of this section was to examine the water uptake of ethylcellulose compacts of different viscosity grades. Compacts of ethylcellulose 4 cP, 10 cP, 22 cP or 100 cP were submerged in phosphate buffer over a period of seven hours and the percentage increase in disc thickness or swelling was measured (figure 5.15.). It was thought that any increase in disc thickness was linked to relative water uptake in the disc.

Prior to immersion in phosphate buffer, compacts prepared with ethylcellulose 100 cP powder, 22 cP powder or 10 cP powder showed greater compact heights than compacts prepared with ethylcellulose 4 cP (Table 5.9.). In addition, the initial porosity of compacts prepared with ethylcellulose 4 cP powder was less than that of ethylcellulose 10 cp, 22 cP or 100 cP (Table 5.9.). Results also showed that the median particle of ethylcellulose 4 cP powder was less than that of ethylcellulose 10 cP, 22 cP or 100 cP powder, even though the particle size of each ethylcellulose viscosity grade powder was controlled (by hand sieving less than 180 um) (Table 5.2.). After immersion in phosphate buffer for seven hours compacts prepared with ethylcellulose 100 cP viscosity grade showed the greatest increase in disc thickness (6.35% ± 2.02%), followed by compacts prepared with ethylcellulose 22 cP (4.10% ± 2.23%) and ethylcellulose 10 cP (2.4% ± 1.5%). Compacts prepared with ethylcellulose 4 cP powder showed no increase in disc thickness. For compacts prepared with ethylcellulose 100 cP, 22 cP or 10 cP powder it would appear that the maximum increase in thickness occurs in the first 3 hours after which the rate of increasing thickness begins to level off.

Compacts prepared with ethylcellulose 100 cP showed the greatest initial porosity. This may be responsible for the fastest water uptake, as is evident in the increase in disc thickness. Ethylcellulose compacts of 22 cP and 10 cP viscosity grade had lower

initial porosity values than compacts of ethylcellulose 100 cP, and also showed less increase in disc thickness than compacts prepared with ethylcellulose 100 cP. With an increase in immersion time, the porosity of compacts was gradually filled with the test fluid, and resulted in a slow absorption behaviour reaching equilibrium i.e. no further swelling. However, the tight structure (and low porosity) of the ethylcellulose 4 cP compact markedly retarded the water penetration, leading to no evident increase in thickness or water uptake. This is in agreement with previous findings by Lin and Lin (1996). In addition, Deasy *et al.* (1980) using the same method, found that discs prepared with ethylcellulose microcapsules showed marked increase in disc thickness or swelling.

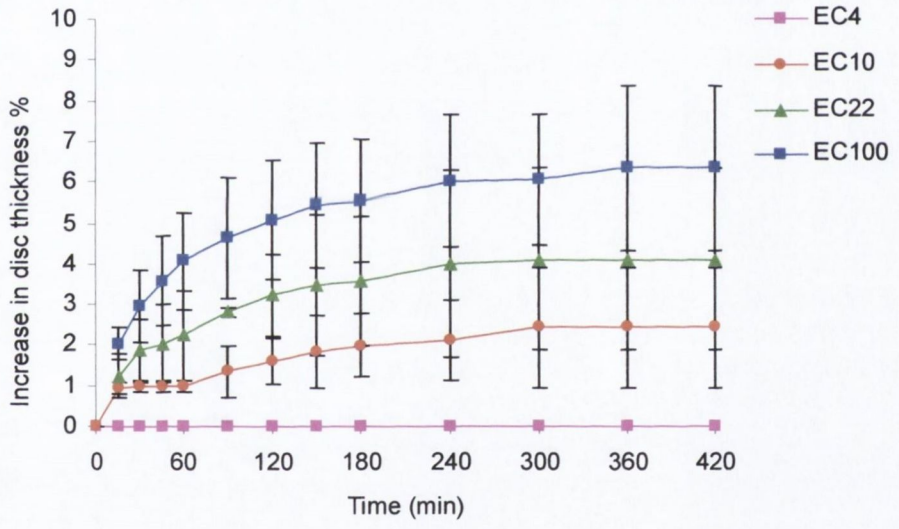

Figure 5.15. Swelling studies of ethylcellulose compacts of different viscosity grades. EC is ethylcellulose and the number following it is the viscosity grade (cP).

Table 5.9.

Swelling studies of ethylcellulose compacts of different viscosity grade immersed in phosphate buffer over a seven-hour period

	Ethylcellulose 4cP	**Ethylcellulose 10 cP**	**Ethylcellulose 22 cP**	**Ethylcellulose 100 cP**
Initial porosity	0.0341	0.0756	0.0764	0.1110
Initial height (cm)	0.170 ± 0.000	0.180 ± 0.000	0.180 ± 0.000	0.185 ± 0.000
Increase in height	0.0% ± 0.0%	2.4% ± 1.5%	4.10% ± 2.24%	6.35% ± 2.02%

5.11. CONTACT ANGLE MEASUREMENT

The wetting of solid dosage forms is an important initial step in the process of drug dissolution both *in vitro* and *in vivo* (Lerk *et al.*, 1977). Lerk *et al.* (1976) determined that the contact angle is one parameter controlling the penetration of liquid into capillaries in capsules and tablets. Determination of contact angles of solids gives a measure of their wettability, but problems arise when the solid is a finely divided powder. The particles in powders are so small that direct measurement of the wettability as indicated by the contact angle (e.g. by direct observation of a drop of liquid on the particle) is not possible, and thus the method outlined by Kossen and Heertjes (1965) is adopted instead to measure the angle.

The contact angle of phosphate buffer in contact with compacts of different ethylcellulose viscosity grades and ibuprofen was determined. In addition, the contact angle of ibuprofen saturated phosphate buffer in contact with ibuprofen was also measured.

Before determination of contact angles was undertaken, it was necessary to measure the liquid density and surface tension of phosphate buffer at 25^0C. Results are outlined in table 5.10.

Table 5.10.

Liquid density and surface tension measurements of phosphate buffer at 25^0C

Test solution	**Liquid density g/cm^3 (ρ)**	**OS_{ruk} mN/m* (γ)**	**f***	**OS_{abs} mN/m (γ)***
Phosphate buffer	1.014	63.53 ± 0.10	0.93	59.30 ± 0.095
Ibuprofen saturated phosphate buffer	1.014	44.57 ± 0.06	0.92	40.84 ± 0.06

* OS_{ruk}: uncorrected surface tension, *f*: correction factor, OS_{abs}: corrected surface tension. See section 4.13. for further explanation

Table 5.11. shows the contact angles of phosphate buffer pH 7.4 (at 25^0C) in contact with compacted cakes of ibuprofen, and ethylcellulose of different viscosity grades (4 cP, 10 cP, 22 cP and 100 cP). It also shows the contact angle of ibuprofen in contact with an ibuprofen saturated phosphate buffer. Using a two-sample t-test assuming equal variance, the contact angle of the buffer in contact with ethylcellulose of each

viscosity grade was found to be significantly greater ($p \leq 0.05$) than the contact angle of phosphate buffer in contact with ibuprofen. This means that the ibuprofen compact was more easily wetted by the phosphate buffer than compacts of ethylcellulose. This was evident visually. When the phosphate buffer was added to the ibuprofen compact the drop tended to spread, but when the phosphate buffer was added to the ethylcellulose compact the drop tended to remain spherical or "ball" up. These results are not surprising since previously Upadrashta *et al.* (1994) stated that ethylcellulose is a hydrophobic polymer, which has characteristically high contact angles (Lerk *et al.*, 1977). The difference in wettability between ibuprofen and ethylcellulose compacts may have implications for the wettability of (and for drug release rates from) compacts of varying ethylcellulose:ibuprofen weight ratios.

The contact angle of ibuprofen-saturated buffer in contact with ibuprofen was also measured. Practically, the contact angle of a solid against its saturated solution may be the more valuable measurement, because when a solid dissolves it forms a saturated layer and it is this layer which will be in contact with the solid (Fell and Efentakis, 1978). Using a two-sample t-test, assuming equal variance the contact angle of ibuprofen saturated phosphate buffer in contact with an ibuprofen cake was found to be significantly less ($p \leq 0.05$) than the contact angle of phosphate buffer in contact with an ibuprofen cake.

Results showed that the contact angle of phosphate buffer in contact with ethylcellulose 4 cP compact was significantly greater ($p \leq 0.05$) than the contact angle of phosphate buffer in contact with other ethylcellulose viscosity grades (10 cP, 22 cP and 100 cP). This was confirmed using a two-sample t-test of equal variance. A similar test also showed that there was no significant difference ($p \leq 0.05$) between the contact angles of ethylcellulose 10 cP, 22 cP or 100 cP compacts.

The differences in contact angle of buffer in contact with ethylcellulose 4 cP compacts and other higher viscosity grades compacts established that a difference existed in the surface properties of the compacts prepared with ethylcellulose 4 cP viscosity grade and other higher viscosity grades. The differing contact angles between compacts prepared with different ethylcellulose viscosity grades may have implications for the subsequent dissolution of a drug from their solid dosage form.

Hansford *et al.* (1980) stated that surface roughness was one of the properties that affected contact angle. It is claimed that an effect due to roughness will be observed

with discontinuities of heights greater than 0.1 μm (Hansford *et al.*, 1980). Previous work in this section established that compacts of ethylcellulose 100 cP viscosity grade had greater surface roughness parameters than ethylcellulose 4 cP compacts. Therefore, this may account for the different contact angles measured for ethylcellulose 4 cP and 100 cP compacts. In addition, during the measurement of the contact angle it was assumed that that the powder particles were spherical and had equal size, thereby eliminating the effect of surface porosity (Hansford *et al.*, 1980). However, work previously undertaken in this section has shown the particles of ethylcellulose powder of different viscosity grade were not entirely spherical or of equal particle size distribution. As a result, the effect of surface porosity on the contact angle was not entirely eliminated. Therefore, the difference in contact angles may be explained by differences in surface characteristics and particle morphology of the powders. Results demonstrate that the contact angle provides a sensitive measure of the surface characteristics of the different materials investigated.

Table 5.11.

Contact angle determination of phosphate buffer in contact with different compacted powders

	EC4	**EC10**	**EC22**	**EC100**	**IB**	**IB[a]**
Thickness of compact (cm)	0.510	0.523	0.523	0.509	0.545	0.545
Weight (g)	9.90	9.70	9.70	9.68	11.04	11.04
Porosity	0.1653	0.1916	0.1924	0.1805	0.1016	0.1016
B*	8.3790	8.3790	8.3790	8.3790	8.3790	12.1673
Droplet height (cm)	0.39	0.385	0.384	0.381	0.154	0.106
Contact Angle ^{O}	109.98	106.99	106.50	106.12	44.45	39.94
	±1.68	±0.61	±1.18	±1.43	±0.3	±0.64

* see section 4.12.2. for explanation, [a] with ibuprofen saturated phosphate buffer, EC: ethylcellulose and the number following it is the viscosity grade (cP), IB: ibuprofen

5.12. CONCLUSION

The results of the present investigation demonstrated that ethylcellulose (of any viscosity grade) was a good direct compression excipient. The lower viscosity grades of ethylcellulose were more compressible than the higher ethylcellulose viscosity grades, resulting in compacts of higher tensile strength and lower compact porosity.

These differences, in addition to differences in surface roughness, surface density and contact angle (with phosphate buffer) may have implications for the release of drug from compacts prepared with different ethylcellulose viscosity grades.

CHAPTER 6

EFFECT OF POLYMER-TO-DRUG WEIGHT RATIO AND ETHYLCELLULOSE VISCOSITY GRADE ON IBUPROFEN RELEASE FROM MATRIX COMPACTS

6.1. INTRODUCTION

One of the purposes of this chapter was to investigate the applications of ethylcellulose as a potential carrier for the preparation of prolonged release formulations, using ibuprofen as a model drug. The effects of polymer-to-drug weight ratio, and ethylcellulose viscosity grade on ibuprofen release from matrix compacts were investigated.

Katikaneni *et al.* (1995b) found that the mechanism of release of a water soluble drug from an inert ethylcellulose matrix follows the Higuchi square root of time law (Higuchi, 1963) i.e. drug release was predominantly diffusion based. Therefore, the relevant drug release data was fitted to the Higuchi "classical theory" for drug release from a granular matrix.

6.2. EFFECT OF POLYMER-TO-DRUG WEIGHT RATIO AND ETHYLCELLULOSE VISCOSITY GRADE ON IBUPROFEN RELEASE

6.2.1. Effect of polymer-to-drug weight ratio on ibuprofen release from ethylcellulose 4 cP matrix compacts

Ethylcellulose 4 cP viscosity grade powder was used to prepare matrix compacts of ethylcellulose:ibuprofen in varying polymer-to-drug weight ratios i.e. between 25% w/w and 75% w/w drug loads. Figure 6.1. shows the effect of polymer-to-drug weight ratio on percentage release of ibuprofen. It was observed that as the drug fraction in the formulation increased the percentage release of the model drug increased. These results were supported by Dabbagh *et al.* (1996) and Katikaneni *et al.* (1995b) and were attributed to an increase in porosity with an increase in drug concentration, and a concomitant decrease in tortuosity of the matrix (Desai *et al.*, 1966a and Foster and Parrott, 1990a). Conversely, the drug release decreased with increasing ethylcellulose content. When the insoluble excipient has plastic behaviour such as ethylcellulose, it is expected to surround the drug particles and to reduce the number and size of the pores that are present in the compact before dissolution of the drug (initial porosity). Therefore, a decrease in the drug release was expected, due to a decrease in the effective diffusion coefficient (Soriano *et al.*, 1998) with increasing ethylcellulose content.

Table 6.1. contains the initial and limiting ibuprofen release rates from ethylcellulose 4 cP matrix compacts prepared with different polymer-to-drug weight ratios. The initial release rate was taken as the average release rate of drug at 15 minutes and 30 minutes while the limiting release rate was taken to be the ibuprofen release rate at the end of the dissolution run i.e. 720 minutes (or 420 minutes where indicated). It was clear that both the initial and limiting drug release rates increased with increasing ibuprofen content. In addition, for each formulation the ibuprofen initial release rate was greater than the ibuprofen limiting release rate. This can be readily explained. When a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablets superficial layers and consequently the release rate is relatively fast. As time passes the external layers of the tablet become depleted of the drug and the solution molecules must travel long capillaries to reach the external dissolution medium. Therefore, the primary reason for the continuously decreasing rate of drug release is the increasing distance that must be traversed by the solution and drug molecules into and out of the tablet, respectively (Pather *et al.*, 1998).

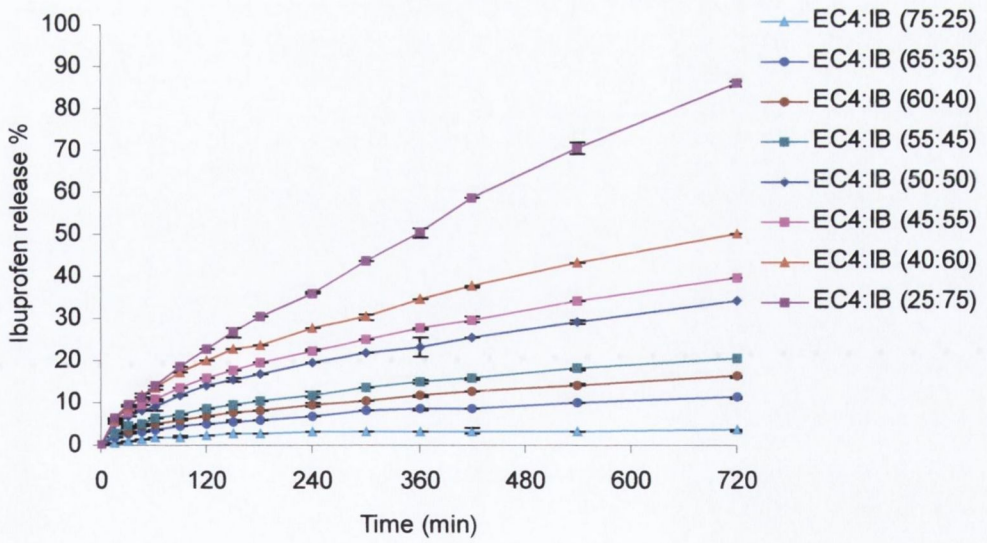

Figure 6.1. The effect of polymer-to-drug weight ratio on ibuprofen release from ethylcellulose 4 cP compacts. EC4 is ethylcellulose 4 cp viscosity grade, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

Table 6.1.

Ibuprofen initial and limiting release rates from compacts prepared with ethylcellulose 4 cP:ibuprofen of different polymer-to-drug weight ratios

Ibuprofen drug load % w/w	Ethylcellulose 4 cP Initial release rate (I) (mg/min/cm^2)	Limiting release rate (L) (mg/min/cm^2)	I:L
25	0.0067	0.0009	7.5537
35	0.0263	0.0041	6.4454
40	0.0417	0.0067	6.1770
45	0.0568	0.0095	5.9676
50	0.1024	0.0176	5.8099
55	0.1263	0.0226	5.5947
60	0.1603	0.0312	5.1369
75	0.2092	0.0666	3.1393

6.2.2. Effect of ethylcellulose viscosity grade on ibuprofen release from ethylcellulose matrix compacts of different ethylcellulose viscosity grades

Figures 6.2., 6.3. and 6.4. show ibuprofen release profiles from matrix compacts of different ethylcellulose viscosity grades (10 cP, 22 cP or 100 cP) in different polymer-to-drug weight ratios. Similar to ibuprofen release studies from compacts prepared with ethylcellulose 4 cP, it was observed that as the polymer fraction of ethylcellulose 10 cP, 22 cP or 100 cP increased in the compact the percentage release of the drug decreased. The greatest ibuprofen release was measured from compacts prepared with ethylcellulose 100 cP viscosity grade, while the lowest release was measured from compacts prepared with ethylcellulose 4 cP, for each polymer-to-drug weight ratio examined (figures 6.5., 6.6. and 6.7.). Ibuprofen release profiles from compacts prepared with ethylcellulose 10 cP and 22 cP were very similar, for each polymer-to-drug weight ratio examined. In addition, ibuprofen release from compacts prepared with ethylcellulose 10 cP or 22 cP was greater than ibuprofen release from compacts prepared with ethylcellulose 4 cP, but less than the release from compacts prepared with ethylcellulose 100 cP, for each polymer-to-drug weight ratio examined. Upadrashta *et al.* (1993) found that tablets prepared using different ethylcellulose viscosity grades and a consistent compression force displayed an increase in hardness with a decrease in viscosity grade. Harder tablets were then associated with lower drug dissolution rates. This was also supported by Katikaneni *et al.* (1995b).

Tables 6.2., 6.3. and 6.4. show the various initial and limiting ibuprofen release rates for compacts prepared with ethylcellulose of higher viscosity grade (10 cP, 22 cP and 100 cP). Similar to matrix compacts prepared with ethylcellulose 4 cP, the ibuprofen initial release rate from compacts prepared with ethylcellulose of higher viscosity grade was faster than the limiting release rate. It was thought that (similar to compacts prepared with ethylcellulose 4 cP) the primary reason for this continuously decreasing rate of drug release was the increasing distance that must be traversed by water and drug molecules into and out of the tablet, respectively (Pather *et al.*, 1998). The initial and limiting ibuprofen release rates from matrix discs prepared with ethylcellulose 4 cP were lower than initial and limiting ibuprofen release rates from matrix compacts prepared with other ethylcellulose viscosity grades. This was evident for formulations of each different polymer-to-drug weight ratio examined. The initial and limiting ibuprofen release rates from matrix discs prepared with ethylcellulose 100 cP were greater than initial and limiting ibuprofen release rates from matrix compacts prepared with other ethylcellulose viscosity grades.

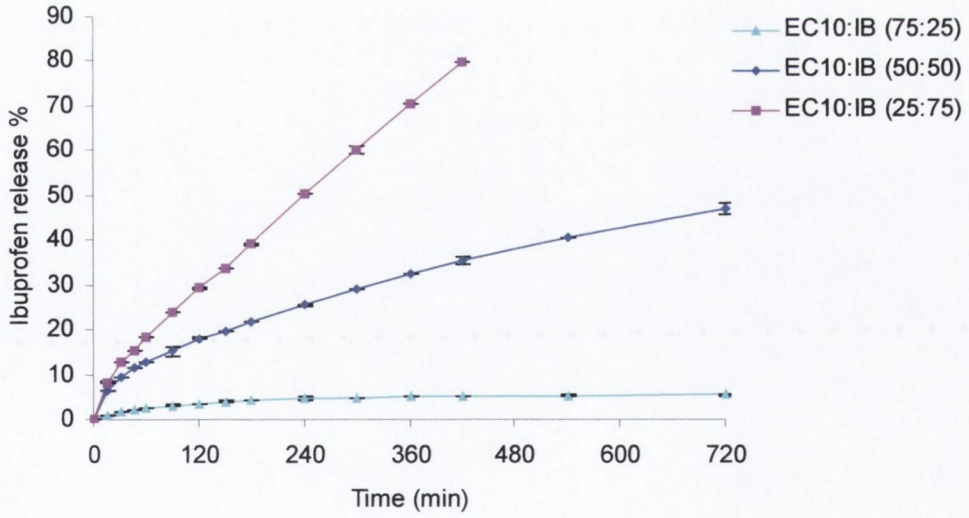

Figure 6.2. The effect of polymer-to-drug weight ratio on ibuprofen release from ethylcellulose 10 cP compacts. EC10 is ethylcellulose 10 cp viscosity grade, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

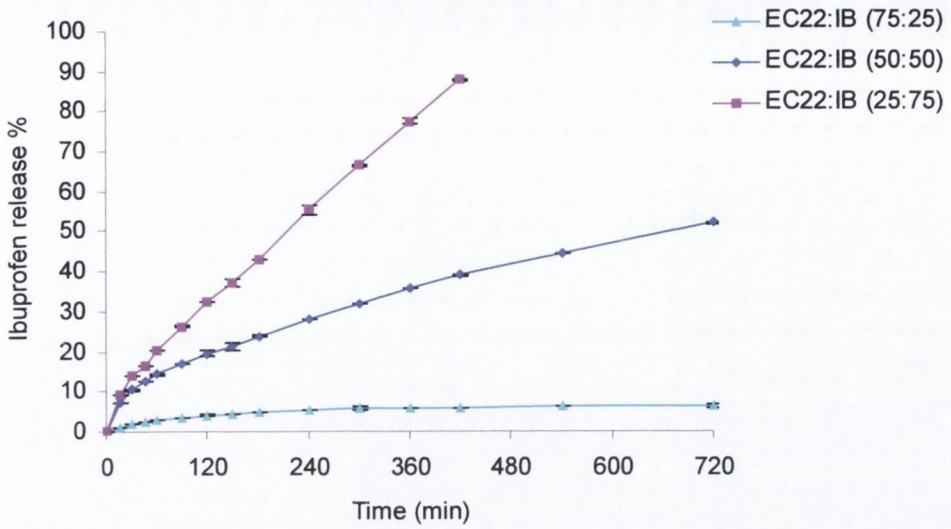

Figure 6.3. The effect of polymer-to-drug weight ratio on ibuprofen release from ethylcellulose 22 cP compacts. EC22 is ethylcellulose 22 cp viscosity grade, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

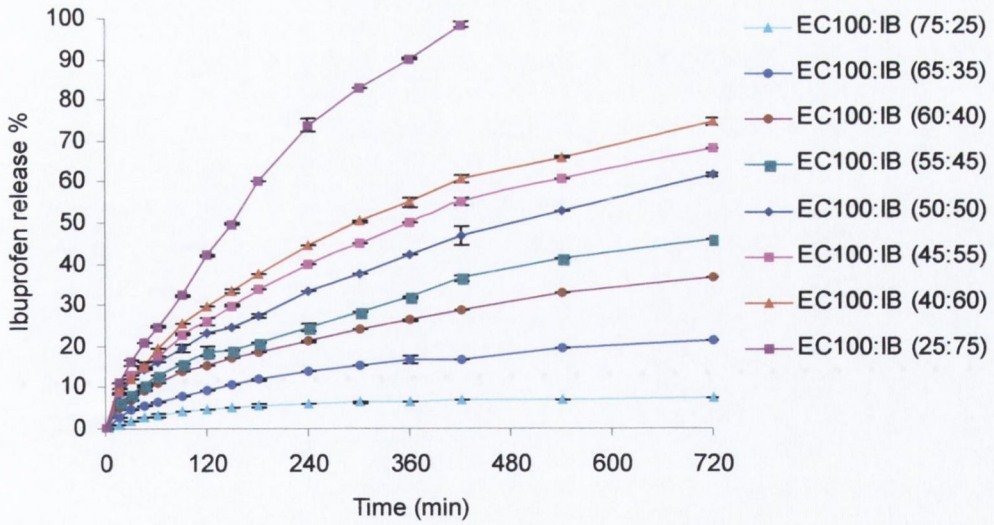

Figure 6.4. The effect of polymer-to-drug weight ratio on ibuprofen release from ethylcellulose 100 cP compacts. EC100 is ethylcellulose 100 cp viscosity grade, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

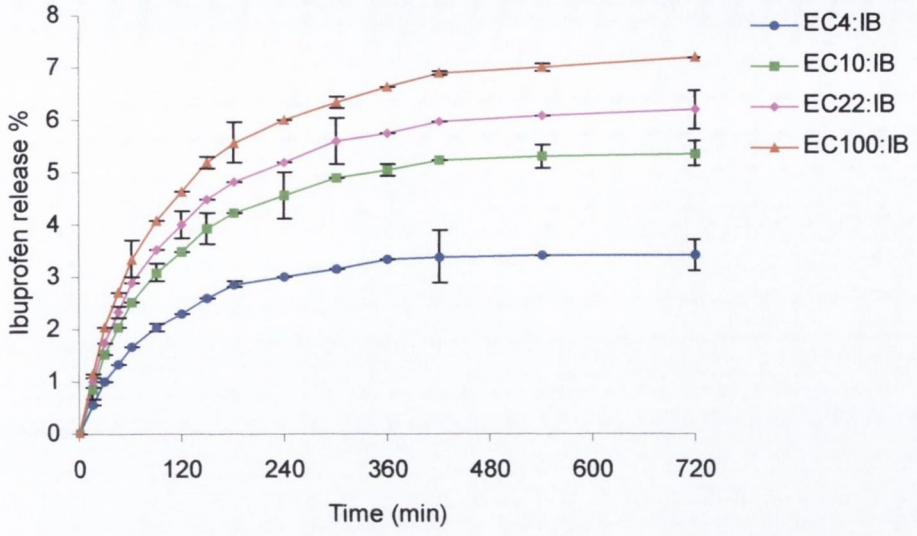

Figure 6.5. The effect of ethylcellulose viscosity grade on ibuprofen release from compacts prepared with a 25% w/w drug loading. EC is ethylcellulose and the number following it is the viscosity grade (cP), IB is ibuprofen.

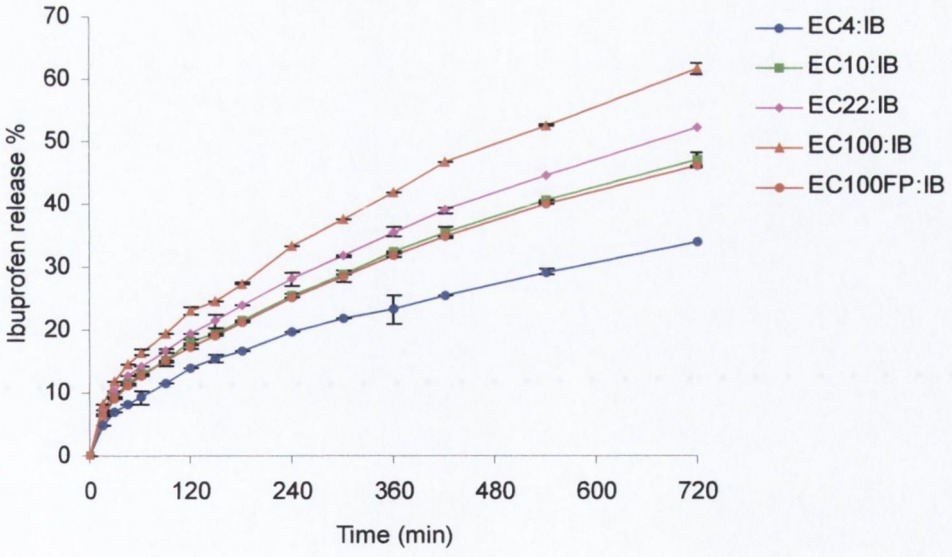

Figure 6.6. The effect of ethylcellulose viscosity grade on ibuprofen release from compacts prepared with a 50% w/w drug loading. EC is ethylcellulose and the number following it is the viscosity grade (cP), IB is ibuprofen.

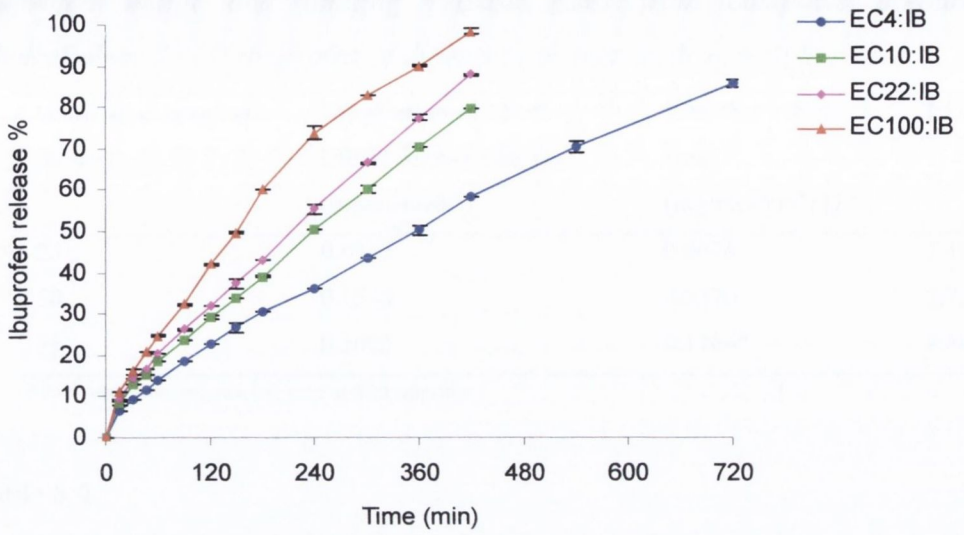

Figure 6.7. The effect of ethylcellulose viscosity grade on ibuprofen release from compacts prepared with a 75% w/w drug loading. EC is ethylcellulose and the number following it is the viscosity grade (cP), IB is ibuprofen.

Table 6.2.

Ibuprofen initial and limiting release rates from compacts prepared with ethylcellulose 10 cP:ibuprofen of different polymer-to drug weights ratios

Ibuprofen drug load % w/w	**Ethylcellulose 10 cP Initial release rate (I) (mg/min/cm^2)**	**Limiting release rate (mg/min/cm^2) (L)**	**I:L**
25	0.0101	0.0014	7.3075
50	0.1396	0.0242	5.7623
75	0.2731	0.1057*	2.5839

* indicates limiting release rate at 420 minutes

Table 6.3.

Ibuprofen initial and limiting release rates from compacts prepared with ethylcellulose 22 cP:ibuprofen of different polymer-to-drug weight ratios

Ibuprofen drug load % w/w	**Ethylcellulose 22 cP Initial release rate (I) (mg/min/cm^2)**	**Limiting release rate (mg/min/cm^2) (L)**	**I:L**
25	0.0115	0.0016	7.1964
50	0.1548	0.0270	5.7293
75	0.3005	0.1164*	2.5824

* indicates limiting release rate at 420 minutes

Table 6.4.

Ibuprofen initial and limiting release rates from compacts prepared with ethylcellulose 100 cP:ibuprofen

Ibuprofen drug load % w/w	**Ethylcellulose 100 cP Initial release rate (I) (mg/min/cm^2)**	**Limiting release rate (L) (mg/min/cm^2)**	**I:L**
25	0.0132	0.0018	7.1771
35	0.0448	0.0077	5.801
40	0.084	0.0151	5.5565
45	0.1182	0.0212	5.5684
50	0.1766	0.0318	5.5612
50 ethylcellulose 100cp FP	0.1342	0.0237	5.6725
55	0.2045	0.0385	5.3096
60	0.2325	0.0461	5.0491
75	0.3317	0.1303*	2.5457

* indicates limiting release rate at 420 minutes

A measure of the attenuation of the ibuprofen dissolution rate as dissolution proceeded was given by the ratio of initial release rate to limiting release rate (in the fourth column of tables 6.1., 6.2., 6.3. and 6.4.). This ratio appeared to decrease with increasing ibuprofen content in formulations of different ethylcellulose viscosity grade. This suggests that the attenuation of the ibuprofen dissolution rate was reduced with increasing ibuprofen content in the formulation. This was to be expected since with increasing drug concentration there is a concomitant increase in compact porosity and a resulting decrease in the distance that must be traveled by the solution

and drug molecules into and out of the tablet. Results also showed that the initial to limiting ibuprofen release rate ratio was greater for compacts prepared with ethylcellulose 4 cP than for compacts prepared with ethylcellulose 10 cP, 22 cP or 100 cP. That is to say, that the attenuation of the release rate was greater for compacts prepared with ethylcellulose 4 cP than for compacts prepared with other ethylcellulose viscosity grades (10 cP, 22 cP or 100 cP), for each weight ratio examined. This may be accounted for by the increased distances that must be traversed by the solution and drug molecules into and out of the ethylcellulose 4 cP compacts as opposed to compacts prepared with higher ethylcellulose viscosity grades. Previous work in chapter 5 demonstrated that compacts prepared with ethylcellulose 4 cP viscosity grade were more consolidated than compacts prepared with higher ethylcellulose viscosity grades.

6.2.3. Effect of ethylcellulose 100 cP FP on drug release from matrix compacts as compared to granular ethylcellulose viscosity grades

Traditionally premium ethylcellulose polymers were differentiated only by viscosity grade. However, a finely milled form or micronised form of ethylcellulose powder was introduced to the market in the mid. 1990s i.e. ethylcellulose FP. The finely milled forms of ethylcellulose viscosity grade powders have a smaller particle size distribution than their granular counterparts, but are chemically equivalent to the existing standard ethoxyl grade of premium ethylcellulose (Pollock and Sheskey, 1997). It has been well established that the particle size of a dry excipient can have a dramatic effect on the characteristics of the final product. Therefore, the purpose of this work was to evaluate the release of ibuprofen from compacts prepared with the finely milled form of ethylcellulose 100 cP and to compare this release behaviour with ibuprofen release from compacts prepared with granular ethylcellulose.

Figure 6.6. shows the ibuprofen release profile from matrix compacts prepared with the granular form of ethylcellulose viscosity grades and the finely milled form of ethylcellulose 100 cP, of identical polymer-to-drug weight ratio. It was evident that the percentage ibuprofen release from matrix compacts of ethylcellulose 100 cP FP was less than the percentage ibuprofen release from compacts of the granular ethylcellulose 100 cP, but greater than the percentage release from compacts of granular ethylcellulose 4 cP. Examination of the ibuprofen initial and limiting release rates showed that both the ibuprofen initial and limiting release rate for compacts

prepared with the micronized ethylcellulose 100 cP were less than those from compacts prepared with the granular ethylcellulose 100 cP (table 6.4.), but greater than those from ethylcellulose 4 cP matrix compacts (table 6.1.). It is also noteworthy that the ratio of initial to limiting ibuprofen release rate of the ethylcellulose 100 cP FP system was higher than the ratio determined for formulations prepared with granular ethylcellulose 100 cP, but less than the ratio determined for the ethylcellulose 4 cP system.

This difference in drug release performance (between granular and finely milled ethylcellulose 100 cP) may be explained due to the different relative sizes of the drug and the finely milled or granular ethylcellulose polymer. The particle size distribution of each of the different viscosity grade powder fractions was previously outlined in chapter 5. Results showed that the median particle size of the finely milled form of ethylcellulose 100 cP was closer to the median particle size of ibuprofen powder, than the granular ethylcellulose 100 cP powder. This difference may affect the packing component of the compacts and consequently the drug-to-polymer distribution within the compact (Pollock and Sheskey, 1997). Ibuprofen release from compacts prepared with ethylcellulose 100 cP FP matrix compacts was greater than ibuprofen release from matrix compacts prepared with ethylcellulose 4 cP. Previous studies in chapter 5 established that the porosity of compacts prepared with ethylcellulose 4 cP was lower than the porosity of compacts prepared with ethylcellulose 100 cP FP. Results also showed that tablets prepared with ethylcellulose 4 cP had greater tensile strength than compacts prepared with ethylcellulose 100 cP FP. Ethylcellulose tablets of lower porosity values and higher hardness values have been previously associated with lower drug release rates (Upadrashta *et al.*, 1993).

6.3. f_2 SIMILARITY FACTOR

Ibuprofen release data was statistically analysed using the similarity factor (f_2) defined in FDA SUPAC guidelines (O'Hara *et al.*, 1997). The release data examined included ibuprofen release profiles from matrix compacts of different ethylcellulose viscosity grades, namely ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP at 25% w/w, 50% w/w and 75% w/w drug loads. Ibuprofen release profile from matrix compacts of granular ethylcellulose viscosity grades and finely milled forms of ethylcellulose 100 cP were also compared. The f_2 values for each of these products are given in tables 6.5., 6.6.

and 6.7.). An f_2 value between 50-100 suggests that the two dissolution profiles are similar.

It was found that ibuprofen release profiles from compacts prepared with the lowest ethylcellulose viscosity grade i.e. 4 cP were statistically dissimilar from ibuprofen release profiles from compacts of ethylcellulose 100 cP viscosity grade at drug loads of 50% w/w and 75% w/w, but not at 25% w/w. In addition, ibuprofen release profiles from ethylcellulose 4 cP matrix compacts were dissimilar from ibuprofen release profiles from ethylcellulose 10 cP matrix compacts of a 75% w/w drug load, but not of a 25% w/w and 50% w/w drug load. Results also showed that ibuprofen release profiles from ethylcellulose 4 cP matrix compacts and ethylcellulose 22 cP matrix compacts were statistically dissimilar at all drug loads, excepts at 25% w/w.

The f_2 similarity factor determined for ibuprofen release profiles from ethylcellulose 100 cP compacts and ethylcellulose 10 cP or 22 cP compacts at 25% w/w or 50 % w/w drug load indicated that all ibuprofen release profiles were similar at the same drug load (table 6.6.). However, the similarity factor determined for ibuprofen release profiles from ethylcellulose 10 cP or 22 cP compacts and ethylcellulose 100 cP compacts at a 75% drug load showed dissimilarity. As indicated by the f_2 factor, ibuprofen release profiles from ethylcellulose 10 cP and ethylcellulose 22 cP matrix compacts were similar for all formulation drug loads examined.

The similarity factor determined for ibuprofen release profiles from compacts of ethylcellulose 100 cP FP and ethylcellulose 100 cP indicated similarity (table 6.7.). (However, the product value was at the lower range of similarity.) Indeed, the similarity factor indicated no statistical difference between the release profiles from compacts prepared with ethylcellulose 4 cP, 10 cP or 22 cP of drug load 50% w/w and the release profiles from compacts prepared with the finely milled form of ethylcellulose 100 cP.

Table 6.5.

In vitro Dissolution Similarity Factors (f_2) of ibuprofen release profiles from ethylcellulose matrix compacts of ethylcellulose 4 cP (reference profile) and from matrix compacts of other viscosity grades.

Reference profile	**Test profile**	**Weight ratio % w/w**	**f_2**	**Similar/ Dissimilar**
Ec 4 cP:Ib	Ec 10 cP:Ib	75:25	88.87	Similar
Ec 4 cP:Ib	Ec 22 cP:Ib	75:25	83.44	Similar
Ec 4 cP:Ib	Ec 100 cP:Ib	75:25	77.97	Similar
Ec 4 cP:Ib	Ec 10 cP:Ib	50:50	58.57	Similar
Ec 4 cP:Ib	Ec 22 cP:Ib	50:50	49.90	Dissimilar
Ec 4 cP:Ib	Ec 100 cP:Ib	50:50	42.41	Dissimilar
Ec 4 cP:Ib	Ec 10 cP:Ib	25:75	47.82	Dissimilar
Ec 4 cP:Ib	Ec 22 cP:Ib	25:75	40.86	Dissimilar
Ec 4 cP:Ib	Ec 100 cP:Ib	25:75	29.81	Dissimilar

Table 6.6.

In vitro Dissolution Similarity Factors (f_2) of ibuprofen release from ethylcellulose matrix compacts of ethylcellulose 100 cP (reference profile) and from compacts of other viscosity grades.

Reference profile	**Test profile**	**Weight ratio % w/w**	**f_2**	**Similar/ Dissimilar**
Ec 100 cP:Ib	Ec 10 cP:Ib	75:25	89.95	Similar
Ec 100 cP:Ib	Ec 22 cP:Ib	75:25	95.93	Similar
Ec 100 cP:Ib	Ec 10 cP:Ib	50:50	56.07	Similar
Ec 100 cP:Ib	Ec 22 cP:Ib	50:50	64.85	Similar
Ec 100 cP:Ib	Ec 10 cP:Ib	25:75	41.62	Dissimilar
Ec 100 cP:Ib	Ec 22 cP:Ib	25:75	48.43	Dissimilar
Ec 10 cP:Ib	Ec 22 cP:Ib	75:25	97.04	Similar
Ec 10 cP:Ib	Ec 22 cP:Ib	50:50	78.11	Similar
Ec 10 cP:Ib	Ec 22 cP:Ib	25:75	68.22	Similar

Table 6.7.

In vitro Dissolution Similarity Factors (f_2) of ibuprofen release from ethylcellulose matrix compacts of ethylcellulose 100 cP FP (reference profile) and other viscosity grades.

Reference profile	Test profile	Weight ratio % w/w	f_2	Similar/ Dissimilar
Ec100 cP FP:Ib	Ec 4 cP:Ib	50:50	60.19	Similar
Ec100 cP FP:Ib	Ec 10 cP:Ib	50:50	97.58	Similar
Ec100 cP FP:Ib	Ec 22 cP:Ib	50:50	74.80	Similar
Ec100 cP FP:Ib	Ec100 cP:Ib	50:50	54.77	Similar

6.4. APPLICATION OF "CLASSICAL THEORIES"

6.4.1. Higuchi Theory

The drug release data obtained from discs prepared with different polymer-to-drug weight ratios and of different ethylcellulose viscosity grades was fitted to the Higuchi "classical theory", using Scientist software. Higuchi (1963) stated that the amount of total drug released from a planar system having a heterogeneous matrix would be determined by the following relationship:

$$Q(t) = \sqrt{\frac{D\varepsilon C_s}{\tau}(2A - \varepsilon C_s)t} \qquad \text{Eqn. 6.1.}$$

or

$$Q(t) = bt^{1/2} \qquad \text{Eqn. 2.34.}$$

where $Q(t)$ is the amount of drug released after time t per unit area; D is the diffusitivity of the drug; ε is the total porosity in the matrix; τ is the tortuosity factor; A is the total amount of drug present in the matrix; C_s is the solubility of the drug present in the matrix, t is the time and b is the release rate constant or the slope of $Q(t)$ versus $t^{1/2}$. According to the equation, the cumulative amount of drug released is a linear function of the square root of time. The drug is presumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent.

The values for D (4.595×10^{-4} cm^2/min) and C_s (6.3114 mg/ml) were previously determined by Healy (1995).

Two statistical parameters were used to determine the quality of fit. These were the co-efficient of determination and the model selection criteria (MSC) (tables 6.8., 6.9.,

6.10. and 6.11.). Both these statistical parameters were relatively high when the Higuchi model was fitted to ibuprofen release profiles from ethylcellulose matrix compacts of all drug loads, except 25% w/w and 75% w/w drug loads. This was evident for release studies from compacts of different ethylcellulose viscosity grades. Appendix 4 includes samples of Higuchi model fits to ibuprofen release data.

Table 6.8.

Results of ibuprofen release data from ethylcellulose 4 cP matrix compacts fitted to Higuchi theory model

Ibuprofen drug load % w/w	**A (mg/cm^3)**	**Tortuosity**	**CoD**	**MSC**	**Release rate constant (b) ($mg.cm^{-2}.min^{-1/2}$)**
25	276.92	24.26 ± 0.48	0.8322	1.6514	0.0259 ± 0.0026
35	383.94	18.89 ± 0.25	0.9937	4.9398	0.1103 ± 0.0293
40	443.07	16.18 ± 0.20	0.9988	6.5886	0.1808 ± 0.0015
45	493.64	13.91 ± 0.18	0.9988	6.6189	0.2583 ± 0.0023
50	553.83	7.57 ± 0.06	0.9992	7.0529	0.4709 ± 0.0034
55	603.33	5.58 ± 0.03	0.9996	7.6403	0.6040 ± 0.0024
60	664.60	3.53 ± 0.05	0.9976	5.9097	0.8385 ± 0.0091
75	830.75	1.97 ± 0.15	0.9441	2.7302	1.5972 ± 0.0828

CoD: coefficient of determination, MSC: model selection criterion

Table 6.9.

Results of ibuprofen release data from ethylcellulose 10 cP matrix compacts fitted to Higuchi theory model

Ibuprofen drug load % w/w	**A (mg/cm^3)**	**Tortuosity**	**CoD**	**MSC**	**Release rate constant (b) ($mg.cm^{-2}.min^{-1/2}$)**
25	269.05	18.87 ± 0.36	0.8586	1.8232	0.0402 ± 0.0037
50	538.10	4.10 ± 0.07	0.9965	5.5082	0.6463 ± 0.0095
75	807.15	1.30 ± 0.11	0.9416	2.6578	1.9191 ± 0.1210

CoD: coefficient of determination, MSC: model selection criterion

Table 6.10.

Results of ibuprofen release data from ethylcellulose 22 cP matrix compacts fitted to Higuchi theory model

Ibuprofen drug load % w/w	A (mg/cm^3)	Tortuosity	CoD	MSC	Release rate constant (b) (mg.cm^{-2}.min$^{-1/2}$)
25	261.34	17.50 ± 0.39	0.8657	1.8741	0.0463 ± 0.0041
50	543.84	3.40 ± 0.06	0.9959	5.3706	0.7189 ± 0.0127
75	807.43	1.07 ± 0.09	0.9397	2.6272	2.1203 ± 0.1364

CoD: coefficient of determination, MSC: model selection criterion

Table 6.11.

Results of ibuprofen release data from ethylcellulose 100 cP matrix compacts fitted to Higuchi theory model

Ibuprofen drug load % w/w	A (mg/cm^3)	Tortuosity	CoD	MSC	Release rate constant (b) (mg.cm^{-2}.min$^{-1/2}$)
25	251.15	15.2 ± 0.38	0.8678	1.8904	0.0530 ± 0.0047
35	376.67	9.63±0.10	0.9924	4.7370	0.2167± 0.0052
40	430.48	6.40 ± 0.65	0.9986	6.4157	0.4132 ± 0.0043
45	484.29	4.26 ± 0.10	0.9927	4.7853	0.5832 ± 0.0124
50	538.10	2.52 ± 0.05	0.9939	4.9617	0.8351 ± 0.0169
50 EC 100 cP FP	538.10	4.31 ± 0.07	0.9965	5.5175	0.6353 ± 0.0091
55	591.91	1.82 ± 0.05	0.9903	4.4790	1.1101 ± 0.0232
60	645.72	1.51 ± 0.05	0.9875	4.2189	1.3369 ± 0.0330
75	807.15	0.79 ± 0.08	0.9379	2.5572	2.4553 ± 0.1911

CoD: coefficient of determination, MSC: model selection criterion

According to Higuchi (1963) in the matrix type delivery system, the degree of tortuosity in the capillaries and porosity influence drug release rate. He also stated that the amount of drug per unit of matrix volume decreased with time as dissolution occurred. The tortuosity value corrects for the lengthened diffusional pathway caused by necessary lateral excursions of the drug. Generally, a straight channel will have a tortuosity value of 1, whereas a spherical glass bead column will have a tortuosity value of about 2 to 3 (Desai *et al.*, 1966a). Previous work has shown that porosity and drug load are linearly related. Figure 6.8. shows a plot of tortuosity values versus the total porosity of compacts prepared with different ethylcellulose viscosity grades. It was evident that as the porosity in the matrix compact increased the tortuosity value decreased for compacts prepared with the different ethylcellulose viscosity grade.

This suggests that with increasing compact porosity the drug diffusional path length becomes less arduous. This was reflected in the drug release rate; results showed that with increasing drug load (and increasing porosity) the drug release rate increased for all formulations of different ethylcellulose viscosity grade. Desai *et al.* (1966a) and Foster and Parrott (1990a,b) showed that an increase in release rate generally follows an increase in porosity and a concomitant decrease in the tortuosity of the matrix.

In addition, the tortuosity values for release studies from compacts prepared with ethylcellulose 4 cP were greater than those values determined for release studies from compacts prepared with ethylcellulose of higher viscosity grade, at each different formulation drug load. The tortuosity values obtained for formulations prepared with ethylcellulose 4 cP and drug loadings of 25-75% w/w were within the range of 24.26 to 1.97. While the tortuosity values obtained for formulations prepared with ethylcellulose 100 cP of the same drug loading range were within the range of 15.2 and 0.79. Indeed, as the ethylcellulose viscosity grade used in the formulation decreased (100 cP, 22 cP, 10 cP to 4 cP) the tortuosity value also tended to increase, for each drug load examined. This implies that the drug follows a more lengthened diffusional pathway from compacts of lower ethylcellulose viscosity grade than from compacts prepared with higher ethylcellulose viscosity grades, and is reflected in the lower drug release rates from ethylcellulose 4 cP compacts, as opposed to higher ethylcellulose viscosity grade compacts. A possible reason for this is that compacts prepared with lower ethylcellulose viscosity grades such as 4 cP have a lower porosity than compacts prepared with higher ethylcellulose viscosity grades. It was also evident from figure 6.8. that even at the same total porosity, the tortuosity values determined for release studies from compacts prepared with ethylcellulose 4 cP was higher than the values determined for release studies from compacts prepared with other ethylcellulose viscosity grades.

In addition, the tortuosity values determined for release studies from ethylcellulose 100 cP FP matrix formulations was greater than those value determined for release studies from formulations of granular ethylcellulose 100 cP. Each of these formulations had the same polymer-to-drug weight ratio and similar total porosity values (chapter 5, section 7.2.). Due to the limitations in measuring capability of the sliding caliper any reduction in height (and therefore apparent volume or porosity) was not detected when using the finely milled ethylcellulose. Other factors may have contributed to the difference in drug release from the finely milled ethylcellulose

matrix formulation as opposed to the granular ethylcellulose matrix formulation. It is thought that the finely milled form of ethylcellulose affected the packing component within the matrix compact (Pollock and Sheskey, 1997). This results in an increase in the necessary lateral excursions for the drug to escape during drug dissolution. The tortuosity value determined for release studies from ethylcellulose 4 cP matrix formulations was greater than the tortuosity value determined for release studies from ethylcellulose 100 cP FP matrix formulations. This confirms that drug release from compacts prepared with ethylcellulose 4 cP follows a more lengthened diffusional pathway than drug release from compacts prepared with ethylcellulose 100 cP FP. This may be attributed to the lower porosity of the ethylcellulose 4 cP compact as compared to the compacts prepared with ethylcellulose 100 cP FP.

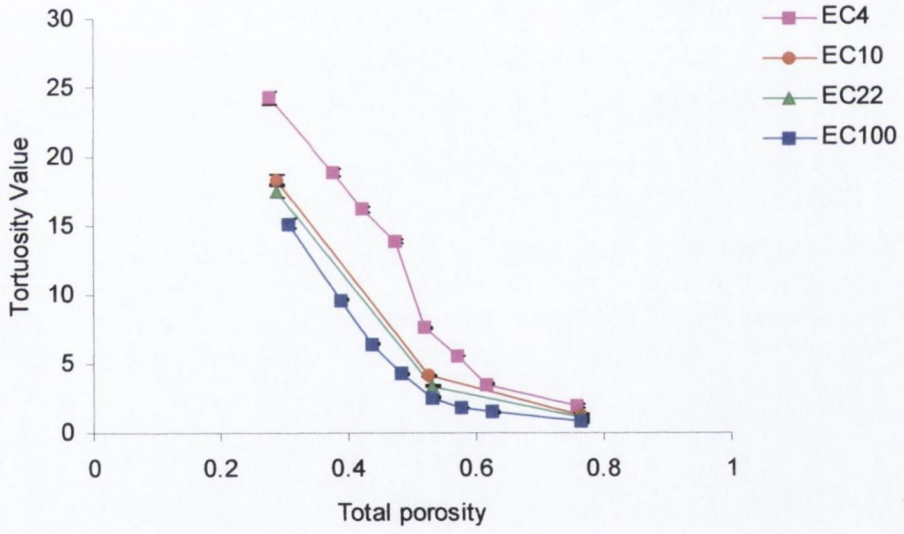

Figure 6.8. Plot of tortuosity value versus total porosity of ethylcellulose:ibuprofen compacts. EC is ethylcellulose and the number following it is the viscosity grade (cP).

At first glance, the Higuchi theory rate equation may seem to indicate that the slope of the release curve should be proportional to the square root of the amount of drug in the tablet (*A*), as it appears raised to the first power under the square root sign. However, closer examination by Higuchi revealed a direct relationship as shown in equation 2.10 (Higuchi, 1963). To investigate this relationship the ibuprofen release

rate constant (*b*) from formulations of ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP viscosity grade were plotted as a function of drug concentration in the matrix (*A*) (figure 6.9.). Table 6.12. shows the statistical parameters determined for a linear fit equation of plots of drug release rate constants from ethylcellulose compacts (4 cP or 100 cP) versus (*A*) between 35% w/w and 60% w/w drug loads. Results suggested a linear relationship existed between ibuprofen release rate and drug concentration (between 35% w/w and 60% w/w drug loads) in ethylcellulose 4 cP formulations or ethylcellulose 100 cP formulations. This indicated that between these drug loadings drug release was primarily matrix-controlled diffusion. Below 35% w/w and above 60% w/w drug-loading (for formulations of either ethylcellulose viscosity grade) deviation from the linear relationship was observed. This implies that other mechanisms of release were present other than square root of time release.

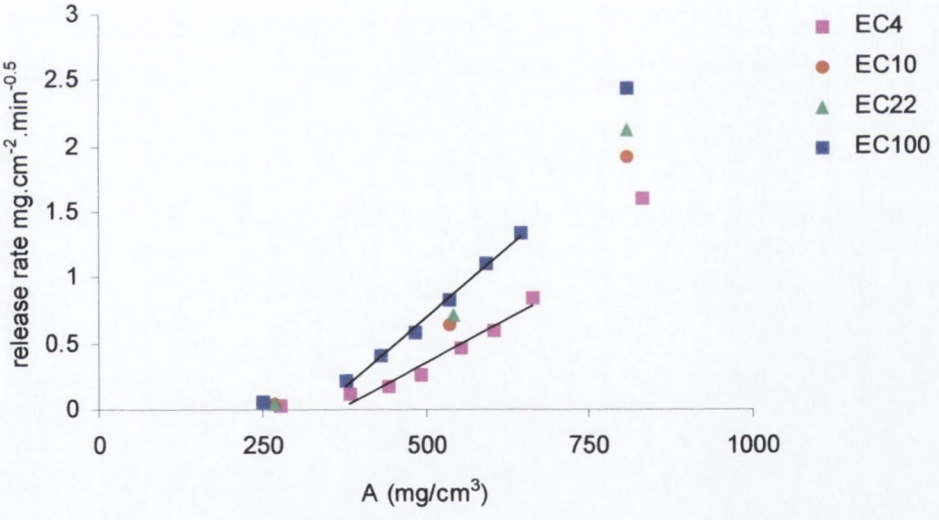

Figure 6.9. Plot of ibuprofen release rate constant (*b*) versus drug concentration (*A*) from ethylcellulose:ibuprofen compacts. EC is ethylcellulose and the number following it is the viscosity grade (cP).

Table 6.12.

Statistical parameters of a linear fit equation to plots of release rate constant (b) versus A (mg/cm^3)

Ethylcellulose Viscosity grade	Drug Load Range	CoD	MSC
4 cP	35-60% w/w	0.9739	3.1653
100 cP	35-60% w/w	0.9938	4.4230

CoD: coefficient of determination, MSC: model selection criterion

6.4.2. Cobby theory

Data was also fitted to the model of diffusion controlled drug release from matrices having a cylindrical shape, as described by Cobby *et al.* (1974a):

$$f_t = G_1 K_R t^{1/2} - G_2\left(K_R t^{1/2}\right)^2 + G_3\left(K_R t^{1/2}\right)^3 \qquad \text{Eqn. 2.11.}$$

where f_t is the fraction of drug released at time t, K_R is the release rate constant having the dimension of the reciprocal of the square root of time, and G_1-G_3 are shape factors. Two statistical parameters were used to determine the quality of fit. These were the co-efficient of determination and the model selection criteria (MSC) (tables 6.13., 6.14., 6.15. and 6.16.). Both these statistical parameters were high when the Cobby model was fitted to ibuprofen release profiles from ethylcellulose matrix compacts of all drug loads, except 25% w/w and 75% w/w drug load. This was evident for release studies from compacts of different ethylcellulose viscosity grades. Appendix 4 includes samples of Cobby model fits to ibuprofen release data.

Results showed that the release rate constant (K_R) of compacts prepared with different ethylcellulose viscosity grades increased as the drug load used during formulation increased. Results also showed that the constant K_R increased as the ethylcellulose viscosity grade used during compact formulation increased i.e. compacts prepared with ethylcellulose 4 cP showed the lowest release rate constant K_R, while compacts prepared with ethylcellulose 100 cP showed the greatest (for each drug loading). The release rate constant K_R is directly proportional to the boundary retreat constant K_b in the relationship outlined in equation 2.12 i.e. a low K_R constant equals a low K_b constant. The boundary retreat constant is a measure of the rate at which the dissolution fluid can penetrate into the insoluble matrix to effect dissolution and release (Cobby *et al.* 1974a). Therefore, the dissolution medium could not penetrate matrices of low drug loading as easily as it penetrated matrices of a high drug loading,

and could not penetrate matrices of ethylcellulose 4 cP as easily as matrices of higher ethylcellulose viscosity grades, for each drug loading examined.

Table 6.13.

Results of ibuprofen release data from ethylcellulose 4 cP matrix compacts fitted to Cobby model

Ibuprofen drug load % w/w	**K_R**	**Std Dev of K_R**	**CoD**	**MSC**
25	0.00041	8.35E-6	0.8321	1.6510
35	0.00062	4.28E-6	0.9937	4.9397
40	0.00080	2.59E-6	0.9987	6.5880
45	0.00091	3.07E-6	0.9987	6.6090
50	0.00136	8.61E-6	0.9980	6.0562
55	0.00161	1.18E-5	0.9973	5.7959
60	0.00202	2.44E-5	0.9932	4.8514
75	0.00270	0.00013	0.9264	2.4549

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-Z} where Z is a number

Table 6.14.

Results of ibuprofen release data from ethylcellulose 10 cP matrix compacts fitted to Cobby model

Ibuprofen drug load % w/w	**K_R**	**Std Dev of K_R**	**CoD**	**MSC**
25	0.00056	1.21E-5	0.8581	1.8138
50	0.00190	2.60E-5	0.9913	4.6137
75	0.00340	0.00020	0.9224	2.3747

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-Z} where Z is a number

Table 6.15.

Results of ibuprofen release data from ethylcellulose 22 cP matrix compacts fitted to Cobby model

Ibuprofen drug load % w/w	K_R	Std Dev of K_R	CoD	MSC
25	0.00062	1.35E-5	0.8609	1.8610
50	0.00213	3.18E-5	0.9896	4.4365
75	0.00375	0.00021	0.9180	2.3193

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-Z} where Z is a number

Table 6.16.

Results of ibuprofen release data from ethylcellulose 100 cP matrix compacts fitted to Cobby model

Ibuprofen drug load % w/w	K_R	Std Dev of K_R	CoD	MSC
25	0.00071	1.58E-6	0.8610	1.8800
35	0.00111	9.86E-6	0.9923	4.7000
40	0.00155	1.03E-5	0.9978	5.9705
45	0.00190	3.17E-5	0.9872	4.2258
50	0.00249	4.27E-5	0.9869	4.1927
50 EC 100 cP FP	0.00188	2.52E-5	0.9973	4.6365
55	0.00290	6.55E-5	0.9803	3.7732
60	0.00320	8.11E-5	0.9771	3.6105
75	0.00440	0.0003	0.9199	2.2910

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-Z} where Z is a number

6.5. MODELLING OF IBUPROFEN RELEASE DATA

6.5.1. Introduction

Matrix compacts were prepared using different ethylcellulose viscosity grades (4 cP, 10 cP, 22 cP or 100 cP) and a range of polymer to drug weight ratios. The release data from these ethylcellulose matrix compacts was analysed to determine which model release equation provided the best fit to the data, and to observe the effect of ethylcellulose viscosity grade and polymer-to-drug weight ratio on the various model parameters and exponents.

The suitability of several equations that are reported to define different release mechanisms were tested with respect to the release data. The mechanisms of drug release considered include: drug diffusion, polymer relaxation (also referred to as swelling) and tablet erosion. Parameters were generated and statistical analysis (MSC and coefficient of determination values) used to ascertain the best-fit equation. In addition, the model that best fitted the data was chosen by examination of the validity of the final parameter estimates (including magnitude and confidence intervals).

The following models were considered. In each case Q refers to the percentage drug released at time t. Time in each case was measured in minutes. Data corresponding to 0-60% release from an average of three dissolution runs was used when model fitting.

Model 1 is based on drug diffusion through the matrix and is a simplification of the Higuchi square root of time model for drug release (Ford *et al.,* 1991):

$$Q = kt^{0.5} + c \qquad \text{Model 1}$$

Model 2 is similar to model 1 except that the exponent N is not fixed at 0.50 (Ford et al., 1991):

$$Q = kt^{N} + c \qquad \text{Model 2}$$

In model 3, Fickian diffusion is represented by the square root of time term, with the polymer relaxation or swelling contribution represented in the linear second part of the equation (Ford *et al.,* 1991):

$$Q = k_1 t^{0.5} + k_2 t \qquad \text{Model 3}$$

Model 4 is based on model 3 without any exponents fixed at N=0.50 (Ford *et al.*, 1991):

$$Q = k_1 t^{N} + k_2 t^{2N} \qquad \text{Model 4}$$

Model 5 (DRE model) includes diffusion, polymer relaxation, and tablet erosion contributions to drug release (Upadrashta *et al.*, 1993):

$$Q = k_1 t^{1/2} + k_2 t + k_3 t^2 + k_4 t^3 \qquad \text{Model 5}$$

Bidah and Vergnaud (1990) developed model 6 to describe drug release from a tablet due to erosion alone:

$$f_t = 1 - (1 - k_1 t)^3 \qquad \text{Model 6}$$

where f_t is the fraction of drug released.

These models are discussed in greater detail in the introductory chapter 2. Appendix 4 includes samples of model fits to ibuprofen release data.

6.5.2. Model 1

Ibuprofen release profiles from matrix compacts prepared with different ethylcellulose viscosity grades (4 cP, 10 cP, 22 cP and 100 cP) and of different ibuprofen loadings were fitted to model 1. It was expected that model 1 would provide a good overall fit to the data because it is based on the assumption that drug diffusion is the primary release mechanism from inert matrix compacts. The model adequately described ibuprofen dissolution data from ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP compacts of all drug loadings, except at 25% w/w and 75% w/w drug loads (table 6.17. to 6.20.). These profiles displayed the poorest fit above all other drug loadings of ethylcellulose matrix compacts. This was indicated by the relatively low coefficient of determination and MSC values. This was evident for model fits to release profiles from compacts prepared with different ethylcellulose viscosity grades. Similar results were found by Bonny and Leuenberger (1991). He found that at high drug loadings the caffeine release from ethylcellulose matrix tablets was no longer in good agreement with the square root of time law. This may be accounted for by the inability of the model to account for the increasing porosity of the matrix with increasing dissolution time, and subsequent increase in dissolution rate. At low drug loadings, the model may tend to over predict drug release towards the later stages of dissolution, due to its inability to account for the amount of drug trapped in the matrix (Bonny and Leuenberger, 1991).

Comparing the root time dissolution rate constants (k) of the various dissolution curves it can be observed that as the ethylcellulose polymer fraction (of 4 cP, 10 cP, 22 cP or 100 cP viscosity grade) increased the release rate constant of the drug decreased. In addition, the release rate constant from formulations prepared with

ethylcellulose 10 cP, 22 cP or 100 cP was greater than the release rate constant from formulations prepared with ethylcellulose 4 cP, for each weight ratio examined.

Table 6.17.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	**k ($\%min^{-0.50}$)**	**Std Dev of k**	**c**	**Std Dev of c**	**CoD**	**MSC**
25	0.1389	0.0140	0.4909	0.2073	0.8827	1.8769
35	0.4229	0.0076	0.2846	0.1124	0.9958	5.2074
40	0.6054	0.0052	0.1455	0.0760	0.9991	6.6900
45	0.7704	0.0069	0.1252	0.1022	0.9990	6.5948
50	1.2616	0.0092	-0.1442	0.1364	0.9993	6.9000
55	1.4742	0.0059	-0.3179	0.0870	0.9998	8.2139
60	1.872	0.0203	-0.8084	0.2991	0.9985	6.2222
75	2.8528	0.1479	-5.9280	1.8388	0.9713	3.2428

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.18.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	**k ($\%min^{-0.50}$)**	**Std Dev of k**	**c**	**Std Dev of c**	**CoD**	**MSC**
25	0.2167	0.0199	0.6692	0.2945	0.9008	2.0441
50	1.7420	0.0257	-0.6915	0.3798	0.9972	5.6020
75	3.4486	0.2175	-5.7360	2.3001	0.9654	3.0013

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.19.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	**k ($\%min^{-0.50}$)**	**Std Dev of k**	**c**	**Std Dev c**	**CoD**	**MSC**
25	0.2493	0.0222	0.7764	0.3289	0.9060	2.0975
50	1.9223	0.0301	-0.8456	0.4450	0.9968	5.4822
75	3.8081	0.2450	-6.4011	2.5903	0.9641	2.9633

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.20.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k ($\%min^{-0.50}$)	Std Dev of k	c	Std Dev c	CoD	MSC
25	0.2875	0.0254	0.8944	0.3744	0.9081	2.1209
35	0.8345	0.0201	0.1826	0.2961	0.9925	4.6325
40	1.3920	0.0145	-0.0849	0.2146	0.9986	6.1740
45	1.7466	0.0370	-1.0053	0.5462	0.9942	4.8836
50	2.2509	0.0453	-1.0670	0.6117	0.9952	5.0448
55	2.7201	0.0568	-2.3850	0.7066	0.9952	5.0362
60	3.0030	0.0740	-2.7786	0.8516	0.9940	4.7772
75	4.4122	0.3434	-5.7687	3.0071	0.9593	2.7574

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

6.5.3. Model 2

Model 2 provided a better fit (than model 1) to the ibuprofen release data from ethylcellulose compacts of different viscosity grades over a range of drug loadings (tables 6.21. to 6.24.). This was indicated by the higher coefficient of determination and MSC values returned for model 2 fits as compared to model 1 fits. This was to be expected since the diffusional exponent N in model 2 is not fixed at 0.50 as it is in model 1. The poorest of modelling fits was to ibuprofen release profiles from ethylcellulose matrix compacts with a 25% w/w drug load, for each ethylcellulose viscosity grade.

The diffusional exponent N is frequently used an indicator of the drug release mechanism from inert polymer based formulations (Bonny and Leuenberger, 1991, Neau *et al.*, 1999, Ford *et al.*, 1991). Ritger and Peppas (1987) determined that N should be in the range of 0.425-0.500 for disk shaped matrices when diffusion is the release mechanism, and between 0.500 and 1.00 for non-Fickian transport. The use of flat-faced punches produced discs in this study. Matrix compacts prepared with ethylcellulose 4 cP and 25-75% w/w ibuprofen content had a diffusional exponent N range between 0.281-0.769. Between drug loads of 35-60% w/w the exponent N had a range of 0.449-0.525. The higher exponent N=0.769 for the model 2 fit to the release profile of 75% w/w ibuprofen loaded ethylcellulose 4 cP compacts confirmed

a change in release kinetics from diffusion controlled release to zero-order controlled release.

Formulations prepared with ethylcellulose 100 cP viscosity grade and 25-75% w/w drug load, had a diffusional exponent *N* range between 0.304-0.799. The estimates of *N* for 35-60% w/w ibuprofen content ranged between 0.459 and 0.582. The higher exponent *N*=0.799 for the model fit to the release profile of 75% w/w ibuprofen loaded compacts confirmed a change in release kinetics from the square root of time law. Compacts prepared with ethylcellulose 10 cP, and 22 cP viscosity grades and between 25% w/w–75% w/w drug load, had a diffusional exponent range between 0.301-0.773, and 0.304-0.780, respectively.

It is note worthy that the exponent *N* tended to be higher for compacts prepared with ethylcellulose of higher viscosity grades (ethylcellulose 10 cP, 22 cP and 100 cP) than for compacts prepared with ethylcellulose 4 cP, for each ibuprofen loading. Similar results were found by Dabbagh *et al.* (1996) i.e. the diffusional exponent was higher for compacts prepared with ethylcellulose 10 cP viscosity grade than 7 cP viscosity grade. In addition, it was observed that as the ibuprofen loading increased in the formulation the exponent *N* appeared to increase, implying a gradual change in drug release from Fickian diffusion to zero-order release kinetics. This was evident for formulations prepared with each of the different ethylcellulose viscosity grades.

Table 6.21.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	**k (%min^{-N})**	**Std Dev of k**	**N**	**Std Dev of N**	**c**	**Std Dev of c**	**CoD**	**MSC**
25	0.5348	0.1917	0.2810	0.0165	-0.2015	0.2962	0.9377	2.3750
35	0.6032	0.0553	0.4486	0.0044	-0.1348	0.1413	0.9981	5.8531
40	0.6578	0.0436	0.4879	0.0032	0.0138	0.1299	0.9991	6.6910
45	0.8711	0.0559	0.4821	0.0031	-0.1249	0.1628	0.9992	6.7274
50	1.1933	0.0737	0.5074	0.0030	0.0180	0.2377	0.9993	6.9250
55	1.3407	0.0283	0.5139	0.0001	0.03417	0.0935	0.9999	9.0935
60	1.5817	0.1311	0.5247	0.0040	-0.0274	0.4533	0.9989	6.4007
75	0.5690	0.1007	0.7688	0.0095	1.1767	0.7506	0.9978	5.6534

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.22.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k (%min^{-N})	Std Dev of k	N	Std Dev of N	c	Std Dev of c	CoD	MSC
25	0.7736	0.260	0.3012	0.0155	-0.3029	0.4159	0.9482	2.5607
50	1.25333	0.1231	0.5483	0.0048	0.6807	0.4691	0.9986	6.1556
75	0.7015	0.1559	0.7725	0.0126	1.5078	1.0224	0.9966	5.1478

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.23.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k (%min^{-N})	Std Dev of k	N	Std Dev of N	c	Std Dev of c	CoD	MSC
25	0.8722	0.2860	0.3039	0.0151	0.2860	0.3430	0.9514	2.6249
50	1.3315	0.1343	0.5539	0.0057	0.1343	0.8295	0.9985	6.1299
75	0.7427	0.1731	0.7798	0.0132	0.1731	1.7533	0.9964	5.0737

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.24.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k (%min^{-N})	Std Dev of k	N	Std Dev of N	c	Std Dev of c	CoD	MSC
25	1.0019	0.3229	0.3040	0.0148	-0.3906	0.5221	0.9532	2.6613
35	1.1116	0.1841	0.4585	0.0079	-0.4749	0.4884	0.9941	4.7248
40	1.4488	0.1257	0.4942	0.0042	-0.2289	0.3843	0.9986	6.1789
45	1.2533	0.2152	0.5487	0.0083	0.3800	0.8218	0.9957	5.0419
50	1.4919	0.2052	0.5627	0.0070	0.8998	0.7543	0.9974	5.5287
55	1.5977	0.1102	0.5841	0.0036	0.3579	0.4063	0.9994	6.9678
60	1.812	0.2033	0.5822	0.006	-0.1005	0.6986	0.9975	5.7400
75	0.9464	0.2708	0.7989	0.0177	1.2405	1.4335	0.9952	4.6648

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

6.5.4. Model 3

The coefficient of determination values determined when the dissolution data was fitted to model 3 (table 6.25. to table 6.28.), were equal to or greater than those values determined for model 2 (table 6.21. to table 6.24.). All MSC values determined for dissolution data fitted to model 3 were greater than those values determined for model 2. However, the k_2 constants determined for model 3 fits to ibuprofen release data from ethylcellulose 4 cP compacts of a 45% w/w drug load or less, were negative in nature. Similarly, the k_2 constants returned for model 3 fits to ibuprofen dissolution data from ethylcellulose 100 cP compacts of 40% w/w drug load or less, and for ethylcellulose 10 cP or 22 cP compacts of a 25% w/w drug load, displayed a negative sign. In model 3, the square root of time term (k_1) is representative of Fickian diffusion and the linear second part of the equation (k_2) is representative of polymer relaxation contribution. Peppas and Sahlin (1989) noted that contributions to drug release should be considered additive. As a result the negative value calculated for k_2 is considered to imply a zero contribution by polymer relaxation to drug release from compacts at these drug loads. Therefore, by ruling out the contribution of relaxation/swelling at these drug loads, model 3 confirms the previously selected best-fit model, i.e. model 2 to describe drug release from compacts at these drug loads.
At higher drug loadings the k_2 constant was positive and confirms the existence of non-Fickian mechanisms of drug release. Therefore, at low drug loadings model 2 provided a better fit than model 3 to dissolution data, but at higher drug loads polymer relaxation (or non-Fickian release) became a mechanism of drug release to consider and model 3 became the more suitable model.

Non-Fickian behaviour represents a step towards achieving the constant release of active agent, since the relaxation component of the release is characterised by zero-order kinetics (Catellani *et al.*, 1988). Figures 6.10., 6.11., 6.12. and 6.13. show the contribution of Fickian diffusion to the release of active agent from ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP viscosity grade compacts over a range of drug loads and time. It was evident that by increasing the drug load beyond 50% w/w for compacts prepared with ethylcellulose 4 cP, 10 cP or 22 cP viscosity grade and beyond 45% w/w for ethylcellulose 100 cP systems, the contribution of diffusion to drug release was reduced. Conversely, the contribution of polymer relaxation to drug release was increased. In addition, it was clear that with increasing time drug release from these

compacts became progressively controlled by non-Fickian behaviour. These results were not surprising since, with increasing drug load and increasing time the dissolution medium was more likely to penetrate into the core of the tablet. With time therefore it was possible that the ethylcellulose could hydrate and swell, and this in turn provided a less tortuous pathway by which the drug could exit the tablet.

In addition, at higher drug loads the contribution of Fickian diffusion to drug release decreased as the ethylcellulose viscosity grade used in the formulation increased. Conversely, the contribution of polymer relaxation to drug release increased as the ethylcellulose viscosity grade used in the formulation increased. This trend is illustrated in appendix 5.

Therefore, ibuprofen release from formulations prepared with higher drug loads and of higher ethylcellulose viscosity grades are closer to achieving the constant release of active agent, than formulations of low drug load and of lower ethylcellulose viscosity grade.

Table 6.25.

Parameters and statistical estimates of model 3 fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 ($\%min^{-0.50}$)	Std Dev of k_1	k_2 (%min)	Std Dev of k_2	CoD	MSC
25	0.2622	0.0103	-0.0049	0.0005	0.9791	3.6028
35	0.4901	0.0070	-0.0026	0.0003	0.9988	6.4924
40	0.6327	0.0086	-0.0010	0.0004	0.9991	6.7895
45	0.8052	0.0100	-0.0014	0.0005	0.9993	6.9769
50	1.2315	0.0155	0.0011	0.0008	0.9994	7.0698
55	1.4086	0.0054	0.0024	0.0003	0.9999	9.5076
60	1.7126	0.0299	0.0058	0.0015	0.9989	6.5540
75	1.2280	0.0555	0.0763	0.0034	0.9989	6.4244

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.26.

Parameters and statistical estimates of model 3 fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	Std Dev of k_1	k_2 (%min)	Std Dev of k_2	CoD	MSC
25	0.3914	0.0146	-0.0069	0.0007	0.9824	3.7719
50	1.5591	0.0286	0.0073	0.0014	0.9988	6.4957
75	1.4857	0.0911	0.1118	0.0066	0.9982	5.9585

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.27.

Parameters and statistical estimates of model 3 fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	Std Dev of k_1	k_2 (%min)	Std Dev of k_2	CoD	MSC
25	0.4448	0.0164	-0.0077	0.0008	0.9832	3.8210
50	1.6999	0.0315	0.0089	0.0016	0.9989	6.5011
75	1.5440	0.1062	0.1253	0.0074	0.9980	5.8505

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.28.

Parameters and statistical estimates of model 3 fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	Std Dev of k_1	k_2 (%min)	Std Dev of k_2	CoD	MSC
25	0.5116	0.0185	-0.0088	0.0009	0.9839	3.8610
35	0.9143	0.0292	-0.0036	0.0014	0.9948	4.9876
40	1.3931	0.0254	-0.0003	0.0013	0.9986	6.2870
45	1.5256	0.0551	0.0083	0.0027	0.9959	5.1963
50	1.9338	0.0536	0.0143	0.0030	0.9979	5.8895
55	2.0839	0.0318	0.0296	0.0019	0.9996	7.4168
60	2.2538	0.0835	0.0368	0.0055	0.9977	5.8800
75	1.7259	0.1898	0.1957	0.0172	0.9968	5.3068

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

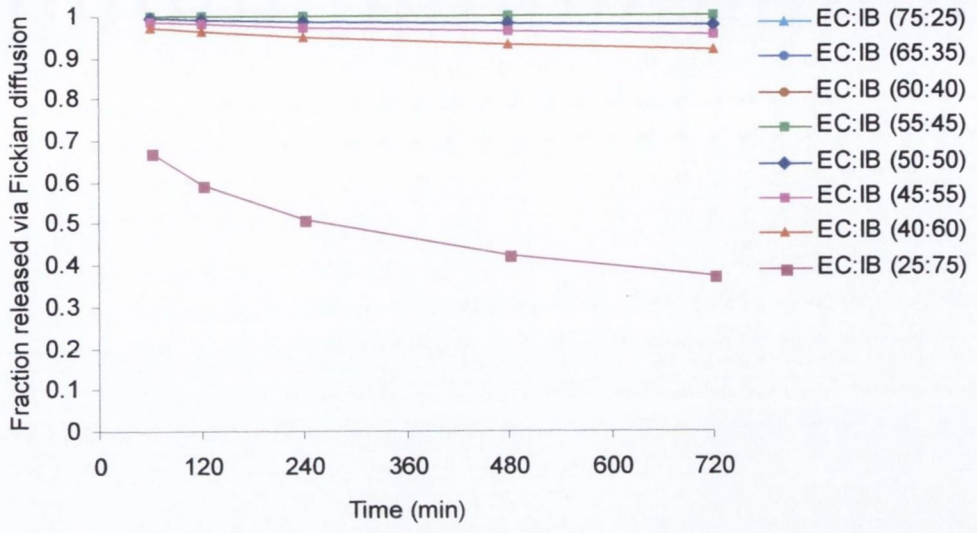

Figure 6.10. The contribution of Fickian diffusion to drug release from compacts prepared with ethylcellulose 4 cP, over a range of drug loadings. EC is ethylcellulose, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

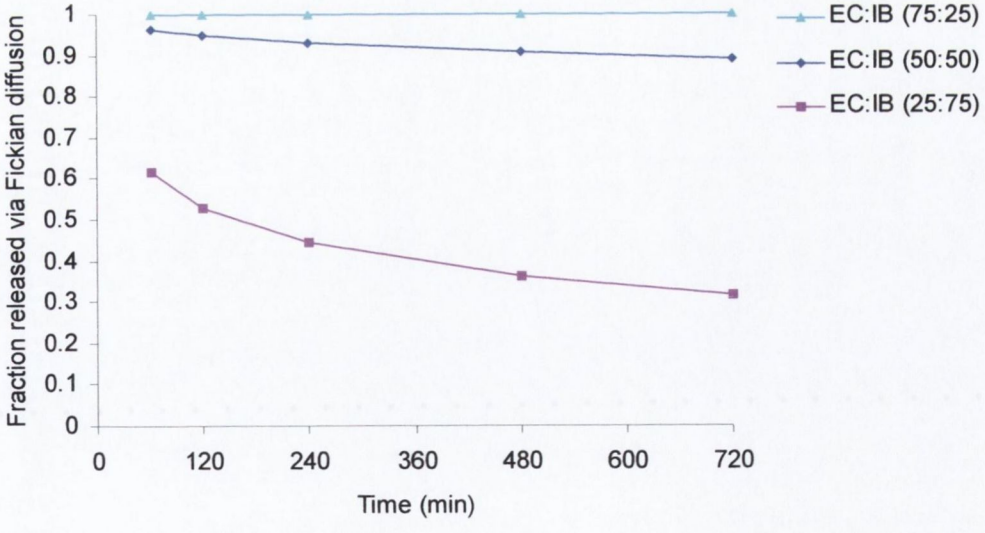

Figure 6.11. The contribution of Fickian diffusion to drug release from compacts prepared with ethylcellulose 10 cP, over a range of drug loadings. EC is ethylcellulose, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

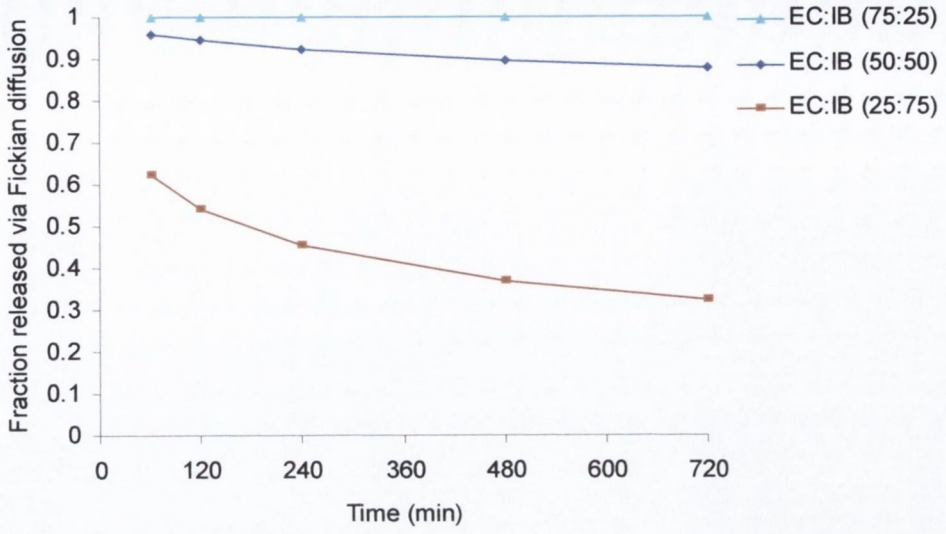

Figure 6.12. The contribution of Fickian diffusion to drug release from compacts prepared with ethylcellulose 22 cP, over a range of drug loadings. EC is ethylcellulose, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

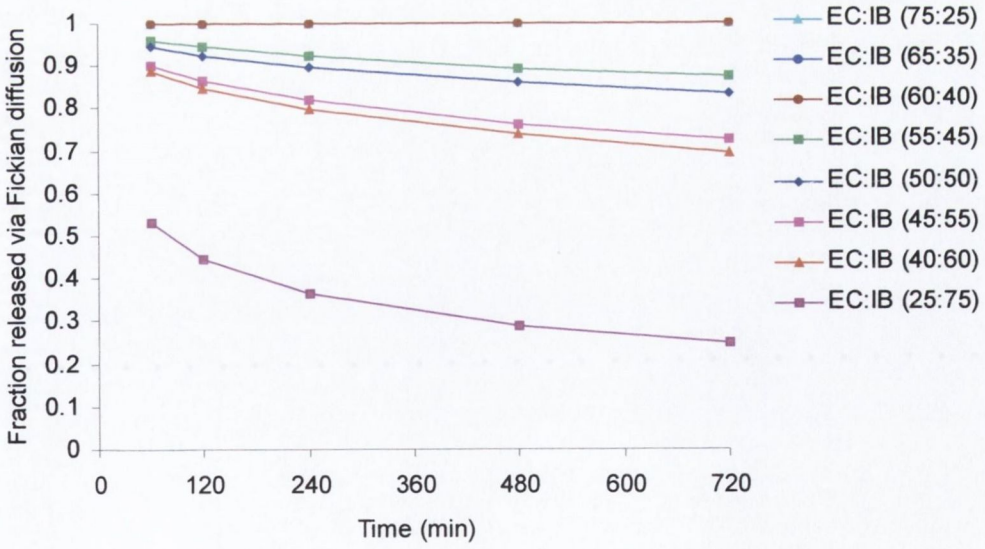

Figure 6.13. The contribution of Fickian diffusion to drug release from compacts prepared with ethylcellulose 100 cP, over a range of drug loadings. EC is ethylcellulose, IB is ibuprofen. The ethylcellulose:ibuprofen weight ratio is indicated in brackets.

6.5.5. Model 4

Ibuprofen dissolution profiles from compacts prepared with 25% w/w drug load could not be successfully fitted to model 4. Ibuprofen dissolution profiles from compacts prepared with ethylcellulose 4 cP and 45% w/w drug load or less (excluding 25% w/w drug load) were fitted to model 4 (table 6.29.). These model fits had coefficient of determination values equal to or greater than the previous best-fit model i.e. model 2. In addition for each of these model fits, the MSC value was higher for model 4 fits than for model 2 fits. Similarly, model 4 fits of ibuprofen release data from ethylcellulose 100 cP matrix compacts of 40% w/w drug load or less (except for 25% w/w drug load) had higher coefficient of determination values and MSC values than the previous best fit model (table 6.32.). Model 4 fits of release data from compacts (of ethylcellulose 4 cP, 10 cP, 22 cP or 100 cP), prepared with larger drug loads had coefficients of determination less than or equal to the previous best-fit model, and MSC values less than the previous best-fit model (tables 6.29. to table 6.32.).

Neau *et al.* (1999) showed that k parameters which converged to zero, or fell within the 95% confidence interval provided no confidence in that particular model. For each of the profiles fitted to model 4, k_2 displayed a negative nature, or converged with zero within its standard deviation. Therefore, this provided no confidence in model 4 for any of the profiles fitted, confirming the previous best-fit model (model 2 or 3) as being the more suitable to describe drug release.

Table 6.29.

Parameters and statistical estimates of model 4 fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min^{-N})	Std Dev of k_1	k_2 (%min^{-2N})	Std Dev of k_2	N	Std Dev of N	CoD	MSC
25								
35	1.7427	0.4576	-1.7073	0.6313	0.1709	0.0045	0.9990	6.5160
40	0.6085	0.2380	0.0832	0.3701	0.2480	0.0070	0.9992	6.6941
45	1.5089	0.3680	-1.0410	0.5561	0.2126	0.0043	0.9994	7.0068
50	1.1239	0.3829	0.1292	0.6144	0.2571	0.0061	0.9993	6.9280
55	1.1897	0.1348	0.2602	0.2185	0.2633	0.0020	0.9999	9.1841
60	1.5212	0.6563	0.0889	0.0889	0.2645	0.0079	0.9989	6.4009
75	1.1991	0.5910	0.0402	0.2963	0.5373	0.1384	0.9989	6.3041

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.30.

Parameters and statistical estimates of model 4 fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min^{-N})	Std Dev of k_1	k_2 (%min^{-2N})	Std Dev of k_2	N	Std Dev of N	CoD	MSC
25								
50	1.9064	0.2945	0.1613	0.5981	0.3803	0.0608	0.9988	6.4900
75	1.4703	0.7963	0.0620	0.7501	0.5361	0.2380	0.9982	5.8190

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.31.

Parameters and statistical estimates of model 4 fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min^{-N})	Std Dev of k_1	k_2 (%min^{-2N})	Std Dev of k_2	N	Std Dev of N	CoD	MSC
25								
50	2.0711	0.2563	0.1621	0.6798	0.3853	0.0690	0.9989	6.4071
75	1.5925	0.9562	0.0652	0.8245	0.5401	0.2487	0.9980	5.7190

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.32.

Parameters and statistical estimates of model 4 fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min^{-N})	Std Dev of k_1	k_2 (%min^{-2N})	Std Dev of k_2	N	Std Dev of N	CoD	MSC
25								
35	5.3292	2.1560	-6.2390	2.8660	0.1504	0.0067	0.9968	5.3334
40	2.4549	0.8497	-1.6846	1.3101	0.2196	0.0062	0.9988	6.3113
45	1.3011	1.2522	0.5664	0.7852	0.3166	0.0249	0.9959	5.0882
50	2.2810	0.3700	0.1650	1.6566	0.3984	0.1669	0.9979	5.8890
55	1.7249	0.5862	0.6441	0.6776	0.3443	0.0113	0.9996	7.3493
60	2.4552	1.3886	-1.1150	2.919	0.2731	0.0114	0.9977	5.8700
75	1.7468	1.5285	0.0794	1.7965	0.5597	0.4735	0.9968	5.1497

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

6.5.6. Model 5

This model introduced erosion as an additional drug release mechanism. According to Upadrashta *et al.* (1993), the last two terms in model 5 represent contributions solely from erosion while the second term represents a partial contribution from erosion. Previous authors (Pather *et al.*, 1998) have noticed that matrix compacts of ethylcellulose experienced erosion due to the separation of surface particles. Therefore, it was decide to investigate if this model fitted the data under discussion.

This model provided an excellent fit to the ibuprofen release data of ethylcellulose 4 cP, 10 cP, 22 cP or 100 cP viscosity grade formulations (for all drug loadings), as judged by the very high coefficient of determination and MSC values (table 6.33. to table 6.36.). However, it was ruled out because in each case two or more of the model parameters (k_2, k_3 or k_4) converged to zero when its standard deviation was considered, and/or displayed a negative value. Model fitting indicated that only the first term, k_1 could be reliably predicted in the DRE model. This represented the contribution from Fickian diffusion. This indicated that erosion was not a component of drug release mechanism from ethylcellulose compacts of 4 cP, 10 cP, 22 cP and 100 cP viscosity grade, over the range of drug loadings examined.

It is noteworthy that examination of compacts during dissolution showed that all compacts remained intact over the dissolution period examined, except those

compacts prepared with a 75% w/w drug load. These compacts showed diminished dimensions at the end of the dissolution period.

Table 6.33.

Parameters and statistical estimates of model 5 fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	k_2 (%min)	k_3 (%min^{-2})	k_4 (%min^{-3})	CoD	MSC
25	0.1567 ± 0.0160	-0.0075 ± 0.0019	-2.42E-5 ± 4.28E-6	-1.69E-8 ± 3.50E-9	0.9963	5.0753
35	0.4386 ± 0.0199	0.0036 ± 0.0037	-1.24E-5 ± 5.31E-6	-9.01E-9 ± 4.34E-9	0.9993	6.7488
40	0.6667 ± 0.0297	-0.0053 ± 0.0038	-9.96E-6 ± 7.95E-6	-7.95E-9 ± 6.51E-9	0.9993	6.7199
45	0.7844 ± 0.0333	0.0003 ± 0.0040	-5.33E-7 ± 8.89E-6	-1.45E-9 ± 7.28E-9	0.9994	6.9153
50	1.8170 ± 0.0512	0.0084 ± 0.0086	-2.00E-5 ± 1.36E-5	-1.78E-8 ± 1.12E-8	0.9995	7.0799
55	1.3812 ± 0.0104	-0.0066 ± 0.0012	-1.20E-5 ± 2.77E-6	-1.09E-8 ± 2.27E-9	0.9999	10.5444
60	1.6929 ± 0.1089	0.0092 ± 0.0130	-1.12E-5 ± 2.91E-5	1.07E-8 ± 2.39E-8	0.9989	6.5560
75	1.1861 ± 0.1321	0.0944 ± 0.0990	-0.0002 ± 7.21E-5	-2.47E-7 ± 9.94E-8	0.9997	7.1875

CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-z} where Z is a number

Table 6.34.

Parameters and statistical estimates of model 5 fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	k_2 (%min)	k_3 (%min^{-2})	k_4 (%min^{-3})	CoD	MSC
25	0.2437 ± 0.0231	-0.0103 ± 0.0028	-3.31E-5 ± 6.17E-6	-2.29E-8 ± 5.05E--8	0.9968	5.2140
50	1.8496 ± 0.0507	-0.0293 ± 0.0060	8.09E-5 ± 8.36E-5	-6.31E-8 ± 1.11E-8	0.9997	7.067
75	2.2105 ± 0.1718	-0.0027 ± 0.0304	0.0004 ± 0.0002	-5.47E-7 ± 2.90E-7	0.9997	7.3747

CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-z} where Z is a number

Table 6.35.

Parameters and statistical estimates of model 5 fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	k_2 (%min)	k_3 (%min^{-2})	k_4 (%min^{-3})	CoD	MSC
25	0.2764 ± 0.0258	-0.0121 ± 0.0031	-3.90E-5 ± 6.91E-6	-2.76E-8 ± 5.66E-9	0.9970	5.2609
50	2.0254 ± 0.0539	-0.0317 ± 0.0064	8.83E-5 ± 1.44E-5	-6.79E-8 ± 1.18E-8	0.9998	7.7810
75	2.3964 ± 0.1793	0.0047 ± 0.0317	0.0004 ± 0.0005	-4.69E-7 ± 3.63E-7	0.9997	7.4889

CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-z} where Z is a number

Table 6.36.

Parameters and statistical estimates of model 5 fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts, over a range of drug loadings

Drug load % w/w	k_1 (%min$^{-0.50}$)	k_2 (%min)	k_3 (%min^{-2})	k_4 (%min^{-3})	CoD	MSC
25	0.3247 ± 0.0321	-0.0133 ± 0.0038	-4.38E-5 ± 8.57E-6	-3.12E-8 ± 7.015E-9	0.9965	5.1129
35	0.7032 ± 0.0689	-0.0194 ± 0.0082	-3.78E-5 ± 1.84E-5	-2.21E-8 ± 1.50E-8	0.9980	5.6242
40	1.3973 ± 0.0689	-0.0029 ± 0.0104	1.30E-5 ± 2.32E-5	-1.44E-8 ± 1.90E-8	0.9988	6.1790
45	1.8688 ± 0.1317	-0.0402 ± 0.0157	-0.0001 ± 3.52E-5	-1.09E-7 ± 2.88E-8	0.9982	5.8034
50	2.4734 ± 0.1025	-0.0600 ± 0.0137	-0.0002 ± 3.92E-5	-1.98E-7 ± 4.18E-8	0.9995	6.9944
55	2.0900 ± 0.1242	0.0263 ± 0.0286	2.57E-5 ± 6.78E-5	-4.75E-8 ± 9.34E-8	0.9996	7.4260
60	1.9513 ± 0.2498	0.0721 ± 0.0734	-3.58E-5 ± 0.0002	-7.21E-8 ± 2.74E-7	0.9989	6.1166
75	2.5868 ± 0.4116	0.0566 ± 0.0895	0.0003 ± 0.0007	-7.65E-7 ± 2.09E-6	0.9995	6.7652

CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-z} where Z is a number

6.5.7. Model 6

This model provided an estimation of the contribution (if any) of erosion to the release of active agent from ethylcellulose matrix compacts. However, as indicated

by the poor coefficient of determination and MSC statistical parameters a very poor quality of model fit was achieved for all dissolution profiles of ethylcellulose 4 cp, 10 cP, 22 cP or 100 cP viscosity grade (tables 6.37. to tables 6.40.). Therefore, erosion was not the sole contributing drug release mechanism. This was not surprising since drug diffusion was confirmed earlier as one of the main contributing mechanisms for release from these compacts.

Table 6.37.

Parameters and statistical estimates of model 6 fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts, over a range of drug loadings

Drug load	k_1	Std Dev	CoD	MSC
25	2.55E-5	3.38E-6	0.0416	-0.1741
35	7.17E-5	6.39E-6	0.5879	0.7532
40	0.00010	8.36E-6	0.6771	0.9972
45	0.00013	1.72E-5	0.7603	1.0330
50	0.00023	1.08E-5	0.6885	1.2948
55	0.00027	2.00E-5	0.7852	1.4049
60	0.00036	2.51E-5	0.8283	1.6288
75	0.00060	1.86E-5	0.9775	3.6380

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.38.

Parameters and statistical estimates of model 6 fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts, over a range of drug loadings

Drug load	k_1	Std Dev	CoD	MSC
25	3.97E-5	5.08E-6	0.0401	-0.0924
50	0.00033	2.54E-5	0.8293	1.6347
75	0.00089	2.96E-5	0.9772	3.5976

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.39.

Parameters and statistical estimates of model 6 fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts, over a range of drug loadings

Drug load	k_1	Std Dev	CoD	MSC
25	4.57E-5	5.80E-6	0.0628	-0.0684
50	0.00037	2.49E-5	0.8446	1.7284
75	0.00101	3.30E-5	0.9794	3.7002

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.40.

Parameters and statistical estimates of model 6 fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts, over a range of drug loadings

Drug load	k_1	Std Dev	CoD	MSC
25	5.30E-5	6.70E-6	0.0712	-0.0595
35	0.00015	1.24E-5	0.6598	0.9448
40	0.00030	1.97E-5	0.7565	1.2792
45	0.00030	2.20E-5	0.8378	1.6858
50	0.00049	3.13E-5	0.8632	1.8466
55	0.00064	3.61E-5	0.9080	2.2319
60	0.00077	4.33E-5	0.9161	2.3109
75	0.00140	4.62E-5	0.9821	3.7984

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

6.6. PERCOLATION THEORY

6.6.1. Introduction

The increased use of drug delivery formulations based on porous or "channeled" polymeric materials has led to the reevaluation of such "classical theories" as the square root of time law of Higuchi and an increase in the use of percolation theory (Salomon and Doelker, 1980). "Classical theories" explain the effect of initial drug loading on drug release, as a reflection of the increase in porosity which will occur as the drug is dissolved (Potter *et al.*, 1992), while percolation theory proposes the existence of three percolation clusters (pores, drug and excipient). Initial drug and excipient clusters can be either finite or span the whole matrix tablet (indefinite cluster). The effect of increasing the drug load of the compact will be reflected in the

formation of a more extensive drug cluster and in a less extensive excipient network. This is used to explain the change in dissolution kinetics of a matrix controlled release system over a range of drug loadings.

The percolation threshold is the probability at which a cluster just percolates a system (a compact in this instance) (Stauffer and Aharony, 1992). In a three-dimensional lattice, it is known that there are two site percolation thresholds, which define a volume-to- volume range of drug to matrix material where both percolate i.e. form an interpenetrating network. For low drug concentrations i.e. below the lower percolation threshold (pc_1) the plastic matrix will encapsulate most of the drug and the drug release will be incomplete. At the lower percolation threshold, the drug particles begin to form a connective network within the matrix and the diffusion will be anomalous just at the threshold. At the upper percolation threshold (pc_2), the plastic particles forming the matrix structure become isolated within the drug particles and the compact begins to disintegrate.

An aim of this chapter was to apply percolation theory to dissolution data from compacts of different ethylcellulose viscosity grades (namely ethylcellulose 4 cP and ethylcellulose 100 cP) and then to examine if this theory explained the release kinetics over a range of drug loadings. This involved determining the lower and upper percolation thresholds (based on a three dimensional lattice or a Bethe lattice) of matrix compacts prepared with either ethylcellulose 4 cP viscosity grade or ethylcellulose 100 cP viscosity grade.

6.6.2. Calculation of percolation threshold based on 3-D system

Ibuprofen release profiles from the matrix systems prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade are plotted in figure 6.1. and 6.4. The release data was evaluated using the square root of time-release model i.e. model 1 (table 6.17. and 6.20.) and model 2 (table 6.21. and 6.24.). The latter model allowed the diffusion mechanism to be clarified.

As discussed previously, both ethylcellulose 4 cP matrix systems and ethylcellulose 100 cP matrix systems prepared with a drug load of 25% w/w or 75% w/w showed a reduced compliance to the square root of time law. That is to say that release profiles

from compacts prepared with an ibuprofen load at or below 25 % w/w, or at or above 75% w/w were no longer in agreement with the square root of time law.

Matrix compacts prepared with ethylcellulose 4 cP viscosity grade or 100 cP viscosity grade and 35-60% w/w ibuprofen content had a diffusional exponent N value between 0.449-0.525, and 0.459-0.582, respectively. This was in good agreement with the square root of time kinetics with N=0.500 i.e. a bicoherent system. The higher exponents N=0.769 and N=0.799 achieved when model 2 was fitted to ibuprofen release profiles from 75% w/w ibuprofen loaded matrix systems of ethylcellulose 4 cP and 100 cP respectively, confirmed a change in release kinetics from the square root of time law. This confirmed that the upper percolation threshold pc_2 lies at approximately 75% w/w ibuprofen loading. By simply subtracting the compact porosity at 75% w/w drug load from the porosity of a 100% w/w ibuprofen compact i.e. 1 the critical volume fraction of matrix substance that was required to ensure the integrity of the matrix during drug release can be determined. This corresponds to a volume fraction smaller than 0.2413 of ethylcellulose 4 cP matrix material or 0.2350 of ethylcellulose 100 cP matrix material.

For the quantitative determination of the lower percolation threshold pc_1 or the critical porosity ε_{cd} (based on a 3-D system), the compact properties β and D_o were determined (see chapter 2, section 8.3 for further explanation of these properties). The values obtained for the β property and D_o of ethylcellulose 4 cP and ethylcellulose 100 cP matrix systems are outlined in table 6.41. and table 6.42., respectively. According to the method of Bonny and Leuenberger (1991) when the property β of the compacts containing a bicoherent system is plotted versus the corresponding total porosity ε, the intercept with the abscissa gives an estimation of the drug percolation pc_1 or ε_{cd}. In our study, data between 35% w/w and 60% w/w ibuprofen loading of ethylcellulose 4 cP or 100 cP matrix systems were used, because this represented the best agreement with the normal diffusion law.

In order to estimate the confidence interval corresponding to the lower percolation threshold, it was necessary to introduce a slight modification in the treatment of the data (Soriano *et al.*, 1998). Therefore, the critical porosity ε_{cd} was obtained from a linear regression of the total porosity ε versus the β property (figure 6.14.). In this way, it was possible to calculate a confidence interval for the critical porosity ε_{cd}. The statistical data of the regression analysis for the estimation of the percolation

thresholds are shown in table 6.43 and table 6.44. for matrix systems of ethylcellulose 4 cP and ethylcellulose 100 cP, respectively. Linear regression analysis yields critical porosity values of 0.349 +/- 0.0240 for matrix systems prepared with ethylcellulose 4 cP, and 0.327 +/- 0.009 for matrix systems prepared with ethylcellulose 100 cP. Both percolation threshold values were determined with a 95% confidence interval.

When one compared the found percolation thresholds to the theoretical percolation thresholds, it was found that good agreement existed with the simple cubic lattice that has a site percolation threshold of 0.312 and a coordination number (z) of 6 (Stauffer and Aharony, 1992). In the compact, a brittle substance (ibuprofen) and a plastic substance (ethylcellulose 4 cP or 100 cP viscosity grade) were compacted together so that the postulated lattice type of isometric spheres was only a rough estimate but it indicated that the magnitude of the found ε_{cd} was reasonable. As a rough model, it can be assumed that the particles of ibuprofen as well as those of ethylcellulose were sites on the same cubic lattice model. In the model of the "ant in the labyrinth" on which Bonny and Leuenberger (1991) based his approach, the ibuprofen particle would represent the "occupied sites" i.e. accessible sites on the lattice that have to form a continuous network to enable a satisfactory drug release, while the remaining sites containing ethylcellulose would be termed "unoccupied" (by drug) i.e. inaccessible, because diffusing drug particles cannot move into the matrix substance. Approaching the critical mixing ratio termed the upper percolation threshold, the matrix substance was the component reaching a critical volume ratio below which no more coherent network was formed.

The obtained confidence intervals showed no significant difference between the drug percolation thresholds of matrix systems of different ethylcellulose viscosity grades. The ethylcellulose 4 cP was more compressible than ethylcellulose 100 cP viscosity grade, as well as having a greater number of smaller particles present. Percolation theory predicts therefore, that fewer clusters of soluble drug substance will be present in the ethylcellulose 4 cP compact, compared to the ethylcellulose 100 cP compact. The presence of finite drug cluster (encapsulated drug particles) was also more statistically plausible. Because of the lower initial porosities of the ethylcellulose 4 cP matrix systems the value of ε_{cd} corresponds to a higher ibuprofen loading than in the case of ethylcellulose 100 cP matrix systems. In fact, the lower percolation threshold for compacts prepared with ethylcellulose 4 cP corresponds to an ibuprofen

loading of approximately 33% w/w and for ethylcellulose 100 cP to an ibuprofen loading of approximately 27% w/w (see chapter 5 section 7.2).

Table 6.41.

Calculation of D_o and the tablet property β for matrix systems prepared with ethylcellulose 4 cP viscosity grade

Drug load % w/w	ε	A (mg/cm^3)	b	D_o	β, 3-D	$\beta^{2/3}$, Bethe
25	0.2760	276.92	0.0259	1.9251 E-07	0.0011	0.0107
35	0.3765	383.94	0.1103	2.5181 E-06	0.0040	0.0251
40	0.4208	443.07	0.1808	5.8624 E-06	0.0061	0.0333
45	0.4741	493.64	0.2583	1.0740 E-05	0.0082	0.0408
50	0.5173	553.83	0.4709	3.1809 E-05	0.0142	0.0586
55	0.5697	603.33	0.6040	4.8046 E-05	0.0174	0.0672
60	0.6139	664.6	0.8385	8.4054 E-05	0.0230	0.0809
75	0.7587	830.75	1.5972	0.00025	0.0392	0.1155

Drug content in % w/w, ε = total porosity of matrix, A= concentration of dispersed drug in compacts mg/cm^3, b= slope mg.cm^{-2}.min$^{-1/2}$, D_o= apparent diffusion coefficient cm^2/min, β=tablet property mg$^{1/2}$.cm$^{-1/2}$.min$^{-1/2}$, $\beta^{2/3}$=tablet property (mg$^{1/2}$.cm$^{-1/2}$.min$^{-1/2}$)$^{2/3}$, E-Z = x 10^{-z} where Z is a number

Table 6.42.

Calculation of D_o and the tablet property β for matrix systems prepared with ethylcellulose 100 cP viscosity grade

Drug load % w/w	ε	A (mg/cm^3)	b	D_o	β 3-D	$\beta^{2/3}$ Bethe
25	0.3054	251.15	0.0530	8.9957 E-07	0.0024	0.0178
35	0.3872	376.67	0.2167	9.9086 E-06	0.0079	0.0397
40	0.4361	430.48	0.4132	3.1521 E-05	0.0141	0.0584
45	0.4831	484.29	0.5832	5.5814 E-05	0.0188	0.0706
50	0.5300	538.10	0.8351	0.00010	0.0255	0.0866
55	0.5770	591.91	1.1101	0.00017	0.0323	0.1014
60	0.6240	645.72	1.3369	0.00022	0.0373	0.1115
75	0.7650	807.15	2.4553	0.00059	0.0612	0.1553

Drug content in % w/w, ε = total porosity of matrix, A= concentration of dispersed drug in compacts mg/cm^3, b= slope mg.cm^{-2}.min$^{-1/2}$, D_o= apparent diffusion coefficient cm^2/min, β=tablet property mg$^{1/2}$.cm$^{-1/2}$.min$^{-1/2}$, $\beta^{2/3}$=tablet property (mg$^{1/2}$.cm$^{-1/2}$.min$^{-1/2}$)$^{2/3}$, E-Z = x 10^{-z} where Z is a number

Table 6.43.

Percolation threshold of ethylcellulose 4 cP systems and relevant statistical parameters determined from linear regression analysis of the total porosity versus the tablet property β

	Percolation Threshold	Std Dev	CoD	MSC	Range Used
3-D	0.3487	0.0240	0.9529	2.3894	35-60% w/w
Bethe	0.2731	0.0230	0.9587	2.5190	35-60% w/w

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

Table 6.44.

Percolation threshold of ethylcellulose 100 cP systems and relevant statistical parameters determined from linear regression analysis of the total porosity versus the tablet property β

	Percolation Threshold	Std Dev	CoD	MSC	Range Used
3-D	0.3268	0.0092	0.9972	5.2231	35-60% w/w
Bethe	0.2418	0.0136	0.9950	4.6368	35-60% w/w

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

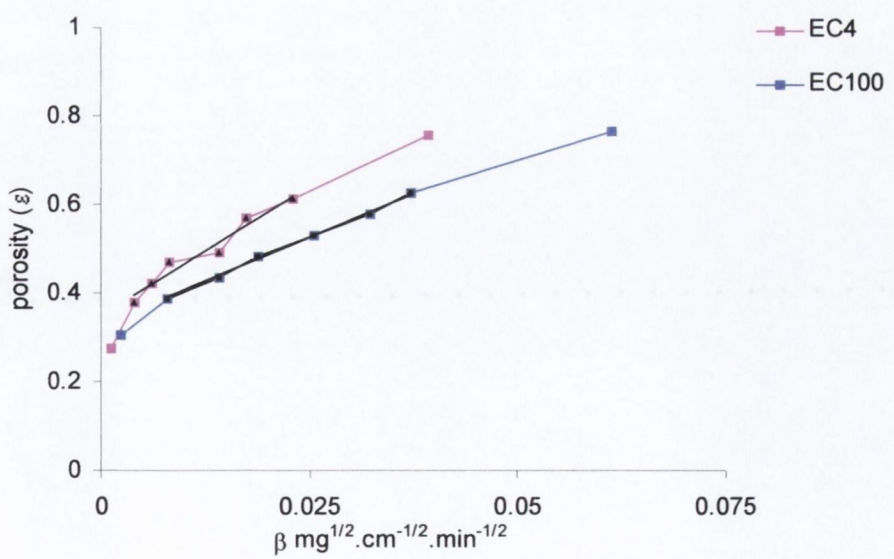

Figure 6.14. Plot of the tablet property β versus the total porosity of ethylcellulose:ibuprofen compacts. EC4 is ethylcellulose 4 cP viscosity grade and EC 100 is ethylcellulose 100 cP viscosity grade. The black line represents the regression lines of the evaluated ranges.

6.6.3. Calculation of percolation threshold based on the Bethe lattice

According to the method of Leuenberger *et al.* (1995) when the property $\beta^{2/3}$ of compacts containing a bicoherent system is plotted versus the total porosity, the intercept with the abscissa gives an estimation of the drug percolation pc_1 or the critical porosity ε_{cb} based on the Bethe lattice. A further modification of this method is to plot total porosity versus the tablet property $\beta^{2/3}$ (figure 6.15.). This has the benefit of obtaining a confidence interval for the percolation threshold value ε_{cb}. The values obtained for the $\beta^{2/3}$ property are outlined in tables 6.41. and 6.42.. The statistical data of the linear regression analysis for the estimation of the percolation thresholds based on a Bethe lattice are shown in table 6.43. and table 6.44. (for ethylcellulose 4 cP matrix systems and ethylcellulose 100 cP matrix systems, respectively). Critical porosity ε_{cb} values of 0.273+/-0.023 and 0.242+/-0.014 for ethylcellulose 4 cP matrix systems and ethylcellulose 100 cP matrix systems were determined, respectively. Both values were determined with a 95% confidence interval. The ε_{cb} value determined for ethylcellulose 100 cP systems falls between two percolation thresholds on a Bethe lattice i.e. between the theoretical percolation threshold of 0.200 on a Bethe lattice with a coordination number of 6, or 0.250 on a Bethe lattice with a coordination number of 5. The first theoretical percolation threshold i.e. 0.200 has the same coordination number as for the percolation threshold for a 3-D system. The ε_{cb} value determined for ethylcellulose 4 cP matrix systems was slightly higher, and was nearer the theoretical percolation threshold of 0.250 on Bethe lattice with a coordination number of 5. The ε_{cb} value determined for compacts prepared with ethylcellulose 4 cP corresponds to an ibuprofen loading of approximately 25% w/w and for ethylcellulose 100 cP to an ibuprofen loading of approximately 18% w/w (see chapter 5 section 7.2).

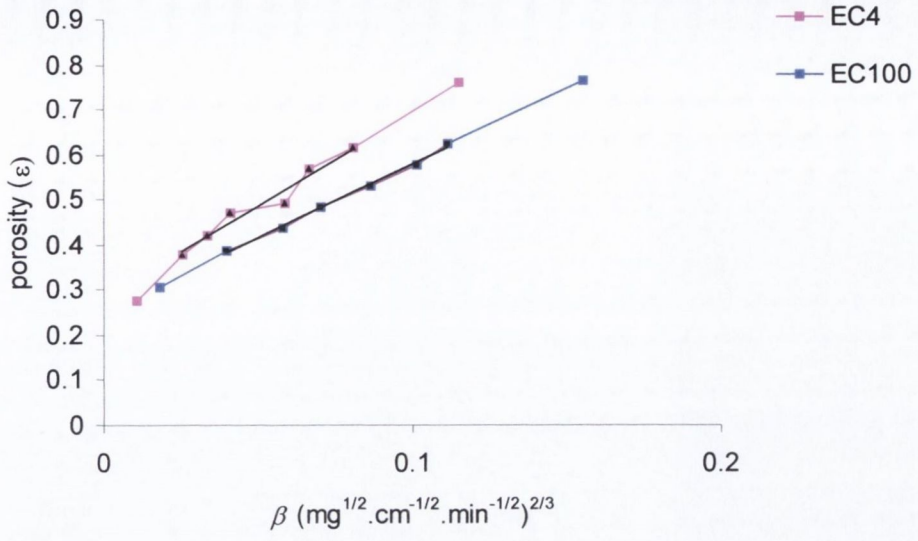

Figure 6.15. Plot of the tablet property $\beta^{2/3}$ versus the total porosity ε of ethylcellulose:ibuprofen compacts. EC4 is ethylcellulose 4 cP viscosity grade and EC 100 is ethylcellulose 100 cP viscosity grade. The black line represents the regression lines of the evaluated ranges.

6.7. MERCURY POROSIMETRY AND FRACTAL DIMENSIONS

6.7.1. Mercury porosimetry

Mercury porosimetry was used to determine the changing porosity and pore size distribution of ethylcellulose:ibuprofen compacts, prepared with ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade, in a 50:50 weight ratio. These disc compositions were chosen because they were far from the lower and upper percolation thresholds. Discs were examined before and after a dissolution time of 420 minutes.

The manner by which the porosity characteristics of the disc change when using either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade (before and after dissolution) are illustrated in plots of cumulative pore volume intruded by mercury versus the pore diameter (calculated from the pressure applied), or plots of incremental intrusion volume versus pore diameter. Such plots are illustrated in figures 6.16. to figures 6.19. Table 6.45. details the porosity data relevant to these plots in terms of total intrusion volume, median diameter (by volume), average

diameter (calculated by multiplying the pore volume by four and dividing by the area) and percentage porosity.

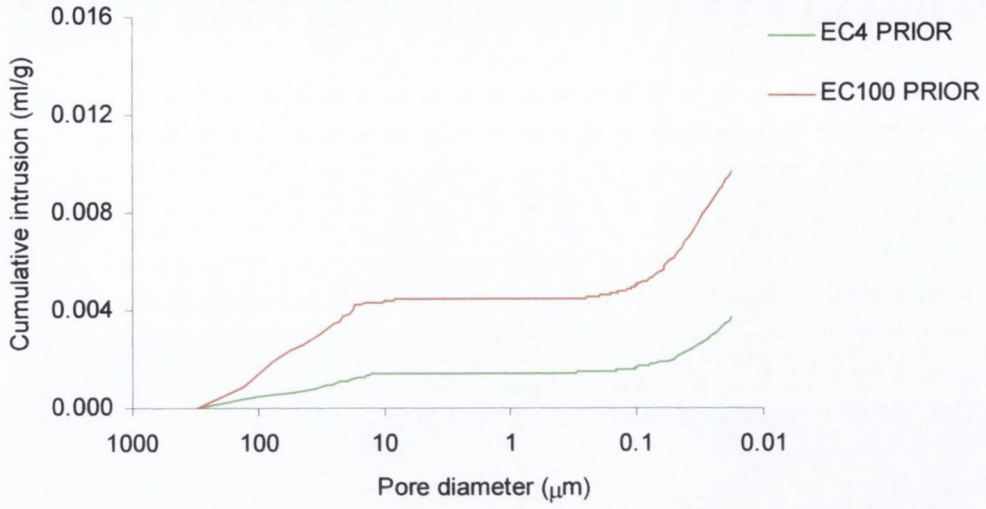

Figure 6.16. Cumulative mercury intrusion curve for ethylcellulose:ibuprofen (50:50 weight ratio) compressed discs, of ethylcellulose 4 cP viscosity grade (EC4) or 100 cP viscosity grade (EC100) prior to dissolution.

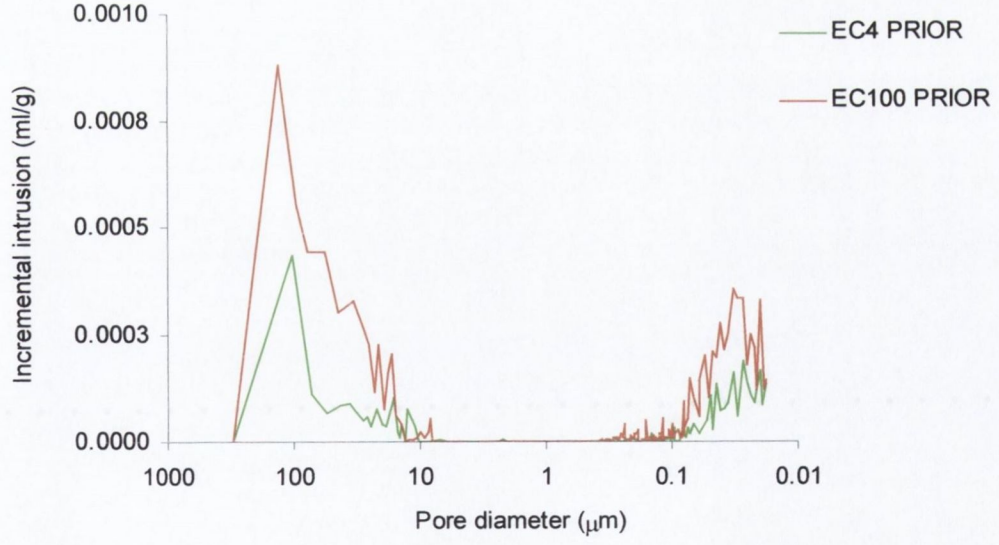

Figure 6.17. Incremental mercury intrusion plot for ethylcellulose:ibuprofen (50:50 weight ratio) compressed discs, of ethylcellulose 4 cP viscosity grade (EC4) or 100 cP viscosity grade (EC100) prior to dissolution.

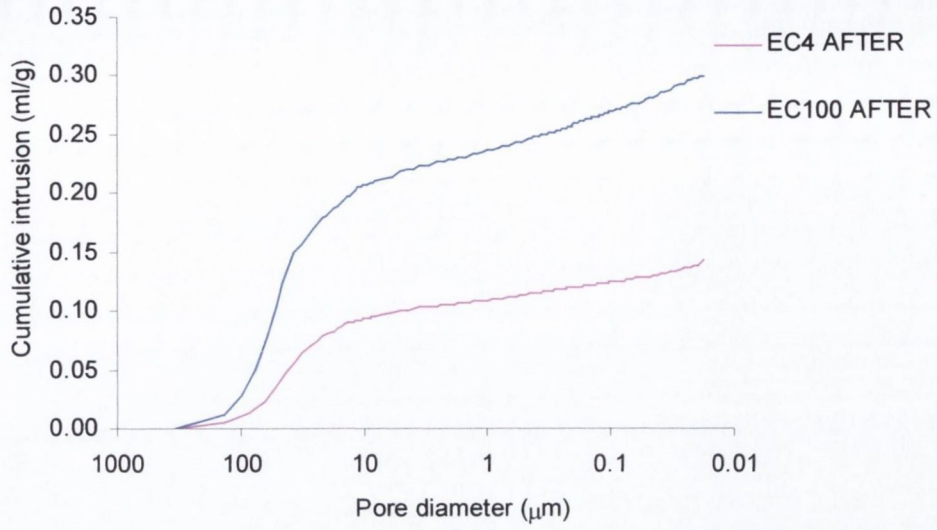

Figure 6.18. Cumulative mercury intrusion curve for ethylcellulose:ibuprofen (50:50 weight ratio) compressed discs, of ethylcellulose 4 cP viscosity grade (EC4) or 100 cP viscosity grade (EC100) after dissolution.

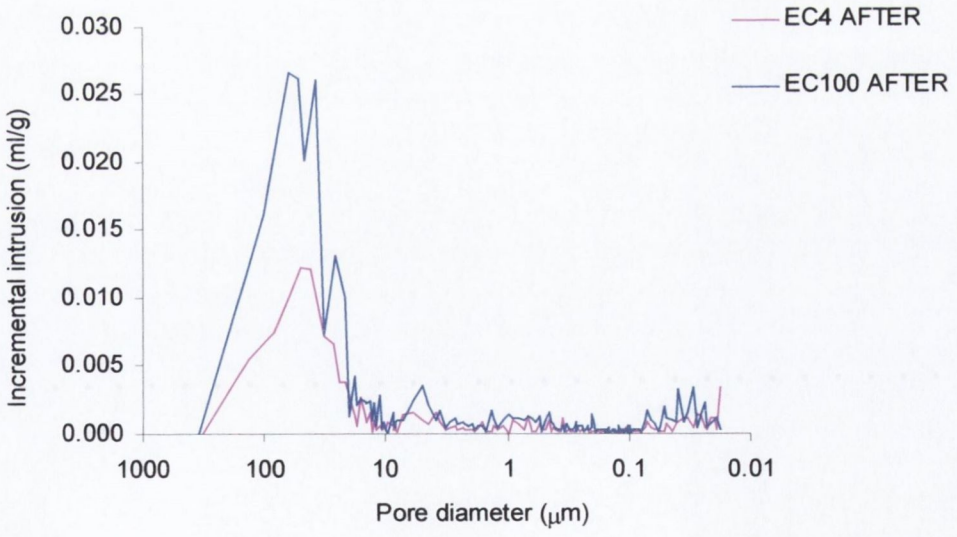

Figure 6.19. Incremental mercury intrusion plot for ethylcellulose:ibuprofen (50:50 weight ratio) compressed discs, of ethylcellulose 4 cP viscosity grade (EC4) or 100 cP viscosity grade (EC100) after dissolution.

Table 6.45.

Pore size distribution and porosity data as determined by mercury porosimetry for ethylcellulose:ibuprofen compacts (50:50 weight ratio), prior to and after dissolution

	EC4 Prior	**EC100 Prior**	**EC4 After**	**EC100 After**
Total intrusion volume (ml/g)	0.0037	0.0096	0.1424	0.2991
Median pore diameter (μm)	0.0671	0.1248	26.52	47.46
Average pore diameter (μm)	0.0547	0.0689	0.2135	0.3165
Porosity %	0.42	1.50	13.48	25.01

EC4: ethylcellulose 4 cP, EC 100: ethylcellulose 100 cP

Prior to dissolution, the total intrusion volume, percentage porosity, median pore diameter and average pore diameter were greater for compacts prepared with ethylcellulose 100 cP than compacts prepared with ethylcellulose 4 cP. This indicates that the inherent porosity and pore size distribution characteristics of compacts can be altered depending on the ethylcellulose viscosity grade. The lower porosity of ethylcellulose 4 cP:ibuprofen compressed systems indicates the formation of a more consolidated disc than compacts prepared with ethylcellulose 100 cP viscosity grade. This is in agreement with earlier findings in chapter 5.7.2 and 5.7.3. The pores contributing most to the overall porous volume could be seen from the incremental intrusion plot to be between 300 μm and 10 μm.

The porosity determined by mercury porosimetry for compacts prepared with ethylcellulose of either viscosity grade was less than the porosity determined in chapter 5.7.2. The closed pores accounted for when calculating the total porosity in chapter 5.7.2., cannot be detected by liquid displacement methods such as mercury porosimetry. Thus, the pore volume or the difference between the apparent volume and true volume is underestimated. Work undertaken by Usteri *et al.* (1990) revealed that the appearance of closed pores, using both plastic and brittle materials depended on the pressure applied at compaction. At high pressure, closed pores could be produced that were not filled with mercury. Thus the porosity might have been under estimated. It might be expected that most of the closed pores were situated between the brittle ibuprofen particles and only a few pores exist in the polymer matrix and at the interface of the drug and the polymer.

The shape of the cumulative intrusion versus pore diameter curve was typically sigmoidal for all samples examined after dissolution. After dissolution, all of the parameters mentioned in the above paragraph increased from their initial values. Leuenberger *et al.* (1990) observed similar behaviour i.e. both the porosity and median pore size of ethylcellulose tablets increased after dissolution. Following dissolution, the increase in median diameter pore size, average pore size and porosity was due to ibuprofen release from the matrix compact. As ibuprofen particles on the outer surface of the compacts are released, a less tortuous pore network was created and porous pathways were formed which extended in towards the centre of the disc. Because it is likely that most of the closed pores existed between the brittle ibuprofen particles and only a few pores existed in the polymer matrix and at the interface of the drug and polymer, the amount of closed pores was reduced as the drug release proceeded and the underestimation of the total pore volume (due to closed pores) could be neglected.

It was also noteworthy that the pore size diameters and porosity were lower for compacts prepared with ethylcellulose 4 cP than compacts prepared with ethylcellulose 100 cP, after dissolution. Based on percolation theory, when a matrix is composed of a soluble drug and a water insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network (Leuenberger *et al.*, 1987). As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse. The ethylcellulose 4 cP was more compressible than ethylcellulose 100 cP viscosity grade, as well as having a greater number of smaller particles present (chapter 5, section 5.6. and 5.7.). Percolation theory predicts therefore, that fewer clusters of soluble drug substance will be present in the ethylcellulose 4 cP compact, compared to the ethylcellulose 100 cP compact. The presence of finite drug cluster (encapsulated drug particles) is also more statistically plausible (Crowley *et al.*, 2004). After 420 minutes of dissolution, 26% w/w of ibuprofen was released from compacts prepared with ethylcellulose 4 cP, while 47% w/w of ibuprofen was released from compacts prepared with ethylcellulose 100 cP (section 6.2.). The resulting pore network in compacts of ethylcellulose 4 cP was more tortuous, and is reflected in the lower median and average pore diameter, as well as the compact porosity.

6.7.2. Fractal dimension determination

Usteri *et al.* (1990) characterised the pore system of ethylcellulose tablets using the volume fractal dimension. Further work by Bonny and Leuenberger (1993) characterised the pore system of tablets prepared with ethylcellulose or hydrogenated castor oil using the surface fractal dimension. A possible relationship between the fractal dimension and the tortuosity of the matrix was also examined. The aim of the present work was to determine the fractal dimensions of ethylcellulose:ibuprofen compacts. The influence of ethylcellulose viscosity grade on the fractal dimensions (before and after dissolution) was also investigated. The possibility of a link between the fractal dimensions and tortuosity values of ethylcellulose:ibuprofen compacts will also be discussed.

6.7.2.1. Volume fractal dimension

In figure 6.20. the solid fraction is plotted versus the pore diameter of compacts on a double logarithmic scale. For clarity, the values were also plotted as logged pore diameter versus logged solid fraction (figure 6.21. and figure 6.22.). The slopes, standard deviation and resulting fractal dimensions are tabulated in table 6.46. The pore diameter range (upper and lower limit) from which the data was calculated is also shown.

The volume fractal dimension D_v of discs before dissolution was examined. The volume fractal dimension of unleached disc was determined in the region 105 μm to 13 μm for ethylcellulose 4 cP systems, and in the region 131 μm to 17 μm for ethylcellulose 100 cP systems. Bonny and Leuenberger (1993) used similar pore diameter ranges when determining the volume fractal of unleached ethylcellulose tablets. The matrix exhibited a D_v value of 3.00 for both ethylcellulose 4 cP systems and ethylcellulose 100 cP systems. Therefore, these systems were considered to be non-fractal. Similar results were found by Bonny and Leuenberger (1993) for unleached ethylcellulose tablets.

The volume fractal dimension of discs after dissolution (of either ethylcellulose viscosity grade) was also determined (figure 6.22.). The volume fractal dimension was measured within a scaling range that included the median diameter. Therefore, the scaling range for the determination of volume fractals of matrices of different ethylcellulose viscosity grades was shifted to smaller pore sizes for ethylcellulose 4 cP matrices as compared to ethylcellulose 100 cP matrices. Bonny and Leuenberger

(1993) observed a similar phenomenon when measuring fractal dimension of tablets prepared with ethylcellulose and hydrogenated castor oil, i.e. the scaling range for the determination of the fractal dimension of tablets was shifted to a lower pore diameter range for the hydrogenated castor oil compacts versus ethylcellulose compacts, as the hydrogenated castor oil systems had a smaller median diameter than ethylcellulose systems. The D_v value determined for ethylcellulose 100 cP systems (2.89) was less than the value determined for ethylcellulose 4 cP systems (2.94). Bonny and Leuenberger (1993) found a possible connection between the volume fractal dimension and the tortuosity of the examined matrices. There existed a tendency that a higher D_v value was related to a higher tortuosity i.e. to a slower drug release from the respective matrix. A similar tendency appears to exist for compacts prepared with ethylcellulose of different viscosity grades. The release rate from matrices of ethylcellulose 4 cP:ibuprofen 50:50 weight ratio was lower than the release rate from ethylcellulose 100 cP:ibuprofen 50:50 weight ratio (chapter 6.2.). Compacts prepared with ethylcellulose 4 cP also had higher tortuosity values than compacts prepared with ethylcellulose 100 cP (chapter 6.4.).

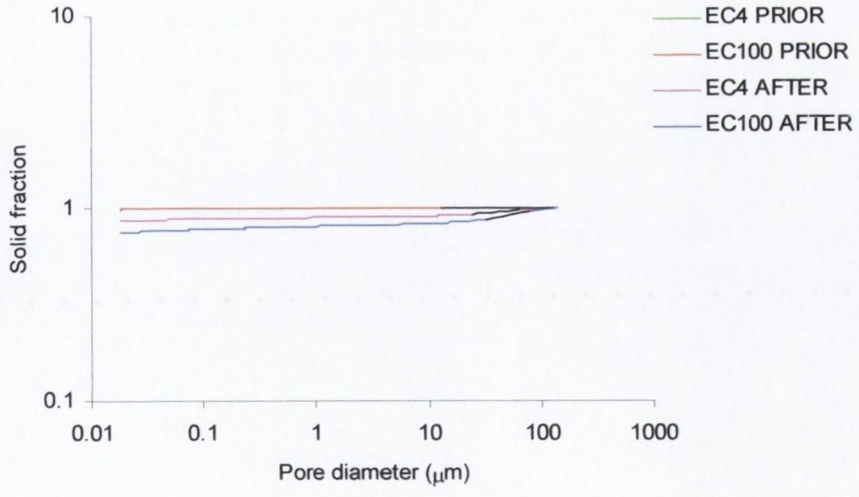

Figure 6.20. Richardson plot of the solid fraction as a function of the pore diameter for ethylcellulose:ibuprofen (50:50 weight ratio) matrix compacts of ethylcellulose 4 cP (EC4) and ethylcellulose 100 cP (EC100) viscosity grade, prior to and after dissolution. The black trend line indicates where regression was performed.

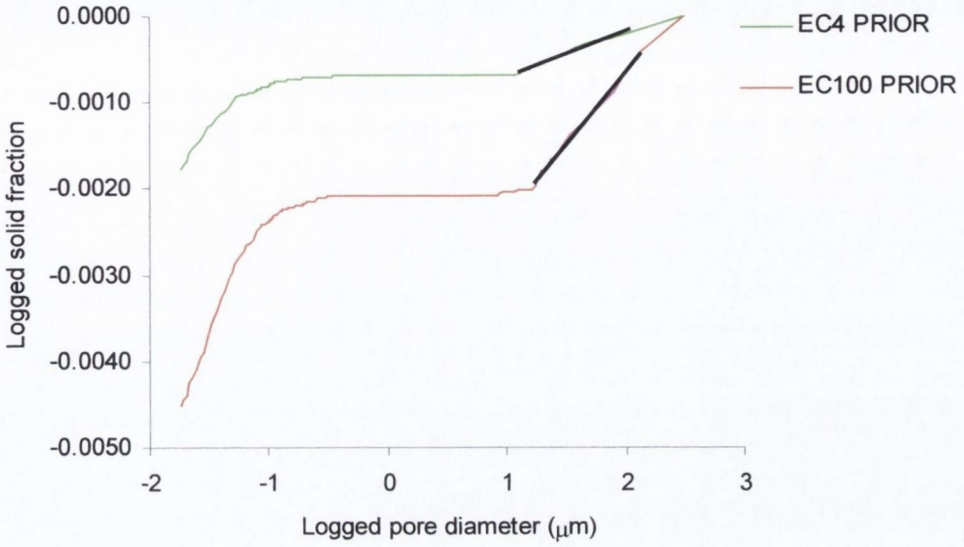

Figure 6.21. Plot of the logged solid fraction as a function of the logged pore diameter for ethylcellulose:ibuprofen (50:50 weight ratio) matrix compacts of ethylcellulose 4 cP (EC4) and ethylcellulose 100 cP (EC100) viscosity grade prior to dissolution. The black trend line indicates the regression line.

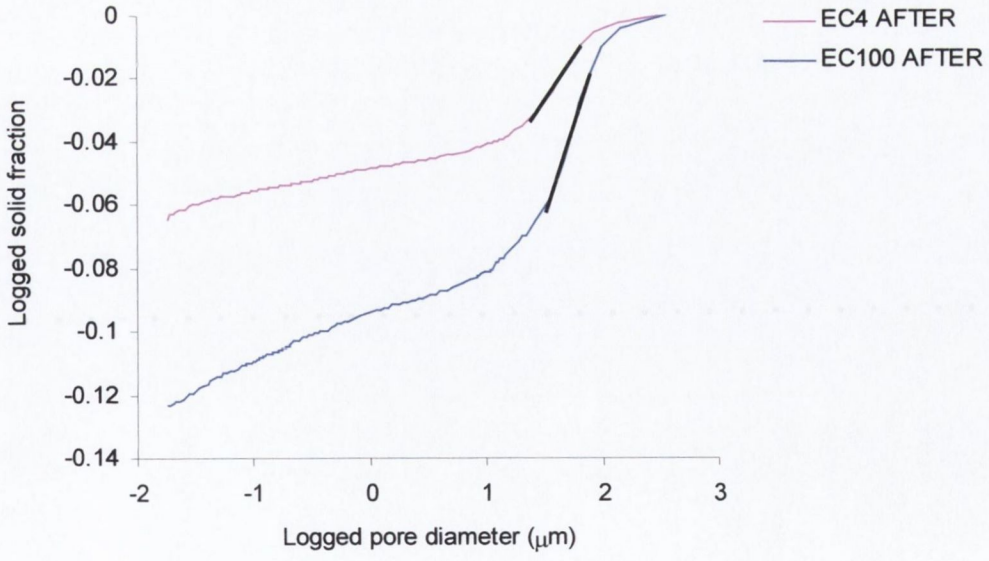

Figure 6.22. Plot of the logged solid fraction as a function of the logged pore diameter for ethylcellulose:ibuprofen (50:50 weight ratio) matrix compacts of ethylcellulose 4 cP (EC4) and ethylcellulose 100 cP (EC100) viscosity grade after dissolution. The black trend line indicates the regression line.

Table 6.46.

Volume fractal dimensions of ethylcellulose:ibuprofen matrix compacts before and after dissolution

Volume fractal	EC4 Prior	EC100 Prior	EC4 After	EC100 After
Pore diameter range* (μm)	13 to 105	17 to 131	25 to 64	33 to 78
No. of points*	18	13	7	6
Slope of trend line	0.0005 ± 1.91E-5	0.0017 ± 3.66E-5	0.0560 ± 0.0021	0.1150 ± 0.0055
Coefficient of determination	0.9792	0.9946	0.9928	0.9909
MSC	3.6529	4.9193	4.3641	4.0301
D_v	2.9995	2.9983	2.9440	2.8850

*Pore diameter range and number of points used when determining the volume fractal dimension, CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-z} where Z is a number, EC4: ethylcellulose 4 cP, EC 100: ethylcellulose 100 cP

6.7.2.2. Surface fractal dimension

In figure 6.23. the surface area was plotted versus the pore diameter of compacts on a double logarithmic scale. The slopes, standard deviation and surface fractal dimension of ethylcellulose:ibuprofen compacts are tabulated in table 6.47. The surface fractal dimension was calculated from pore diameter data in the range 0.37 μm to 11 μm, and for ethylcellulose 100 cP:ibuprofen compacts from pore diameter data in the range 0.40 μm to 14.2 μm. The steep parts of the curves at the beginning of the porosimetry analysis, i.e. for pore diameters between 10 μm to 100 μm (approximately) would lead to a D_s values higher than 3, which are inconsistent with a fractal surface. In addition, Bonny and Leuenberger (1993) determined the surface fractal dimension of an unleached tablet in the pore diameter range beyond that used to determine the volume fractal dimension. The surface fractal dimension of the discs calculated from the pore diameter data in this range was 2.0, as the regression line runs parallel to the abscissa i.e. non-fractal behaviour. Bonny and Leuenberger (1993) determined similar non-fractal behaviour when determining the surface fractal behaviour of an unleached ethylcellulose:caffeine tablet. The ethylcellulose viscosity grade did not appear to influence the surface fractal dimension of compacts before dissolution.

The surface fractal of ethylcellulose 4 cP:ibuprofen compacts (after dissolution) and ethylcellulose 100 cP:ibuprofen compacts (after dissolution) was determined (table

6.47.). The steep parts of the curves at the beginning of the porosimetry analysis, i.e. for pore diameters between 40 μm to 100 μm (approximately) would lead to a D_s values higher than 3, which are inconsistent with a fractal surface. Consistent with work undertaken by Bonny and Leuenberger (1993) the surface fractal was then determined in the scaling range beyond that used to determine the volume fractal dimension. After partial drug release the D_s values were 2.46 for compacts prepared with ethylcellulose 4 cP and 2.45 for compacts prepared with ethylcellulose 100 cP. Using a two-sample t-test, assuming equal variance, there was no significant difference ($p \leq 0.05$) between the surface fractal dimensions for compacts of ethylcellulose 4 cP or 100 cP viscosity grade, after dissolution. Bonny and Leuenberger (1993) stated that the surface fractal tended to be independent of the drug particle size and observed no relationship between the surface fractal dimension and the tortuosity. Further investigative work is needed in this area to establish the utility of the surface fractal dimension. This would include determining the surface fractal of compacts (of 4 cP or 100 cP viscosity grade) leached to the same percentage drug release.

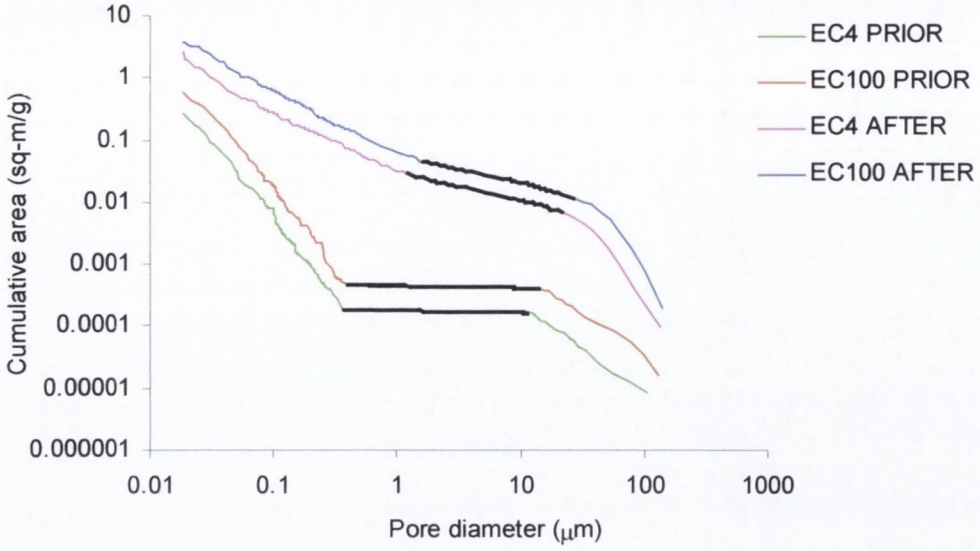

Figure 6.23. Richardson plot of the cumulative pore surface as a function of the pore diameter for ethylcellulose:ibuprofen (50:50 weight ratio) matrix compacts of ethylcellulose 4 cP (EC4) and ethylcellulose 100 cP (EC100) viscosity grade, prior to and after dissolution. The black line indicates where regression was performed.

Table 6.47.

Surface fractal dimensions of ethylcellulose matrices prior to and after dissolution

Surface fractal	**EC4 Prior**	**EC100 Prior**	**EC4 After**	**EC100 After**
Pore diameter range*(μm)	0.37 to 11.30	0.40 to14.20	1.20 to 21.82	1.65 to 26.47
No. of points*	47	46	43	40
Slope of trend line	0.0254 ± 0.0110	0.0260 ± 0.0147	0.4589 ± 0.0044	0.4529 ± 0.0064
Coefficient of determination	0.8432	0.5492	0.9963	0.9925
MSC	4.1345	3.8780	5.5142	4.7875
D_s	2.03	2.03	2.46	2.45

*Pore diameter range and number of points used when determining the surface fractal dimension, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 cP, EC 100: ethylcellulose 100 cP

6.8. CONCLUSION

Results showed that as the level of drug concentration in the ethylcellulose:ibuprofen matrix formulations increased, the drug release rate also increased. It was thought that the increase in drug concentration resulted in an increase in compact porosity and a concomitant decrease in the tortuosity of the matrix. (Desai *et al.*, 1966a, Foster and Parrott, 1990a). This was evident for formulations prepared with any of the four different ethylcellulose viscosity grades and was confirmed when the relevant release data was fitted to the Higuchi "classical theory".

It was thought that any tablet property or mechanism that lessened the time dependent increase in the drug diffusion length would reduce the evident attenuation of the dissolution rate. Results showed that the attenuation of the ibuprofen dissolution rate was reduced when the ibuprofen load was increased in the compact formulation. This was evident for formulations prepared with any of the four different ethylcellulose viscosity grades. Results showed that the greatest ibuprofen release rate was from compacts prepared with ethylcellulose 100 cP, while the lowest was from compacts prepared with ethylcellulose 4 cP, for each different polymer-to-drug weight ratio examined. Results also showed that compacts prepared with higher ethylcellulose viscosity grades showed a lower level of attenuation of the ibuprofen dissolution rate than compacts prepared with ethylcellulose 4 cP. This was reflected in the tortuosity values determined for formulations of different ethylcellulose viscosity grades.

One of the objectives of this chapter was to analyse the drug release data from ethylcellulose matrix tablets over a range of drug loading and to determine which of several release equations provided the best fit to the data. In addition, to observe the effect of ethylcellulose viscosity grade on the drug release mechanism as determined by the best-fit equation.

The square root of time model provided a good fit to the data of ethylcellulose 4 cP, 10 cP, 22 cP and 100 cp formulations because it is based on the assumption that drug diffusion is the primary release mechanism. The poorest fits of this model were at very high (75% w/w) drug loadings or at very low drug loadings (25 %w/w) for all ethylcellulose viscosity grades. These poor fits indicated a change in drug release kinetics from square root of time kinetics.

By freeing the time diffusional exponent from 0.50 in model 2 a better fit of dissolution data was achieved than from the square root of time model. As the compact ibuprofen loading increased, the diffusional exponent appeared to increase, implying a gradual change in drug release from Fickian diffusion to zero-order kinetics. The diffusional exponent was higher for model fits of release profiles of formulations prepared with higher ethylcellulose viscosity grades than ethylcellulose 4 cP viscosity grade, for each drug load examined. Hence, formulations prepared with higher ethylcellulose viscosity grades are closer to achieving the constant release of ibuprofen as characterised by zero order kinetics.

Model 3 allowed a better fit than model 2 to dissolution profiles from ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP at higher drug loadings. However, at lower drug loadings model 3 collapsed confirming the better fit of model 2. This indicated that at low drug loadings of ethylcellulose 4 cP, 10 cP, 22 cP and 100 cP compacts, polymer relaxation was not a relevant mechanism of release, although at higher drug loadings polymer relaxation/swelling became a mechanism of drug release to consider. It was evident that above certain drug loads, polymer swelling contributed more to the release of ibuprofen from ethylcellulose compacts of higher viscosity grades (10cP, 22 cP or 100 cP) than to the release of ibuprofen from compacts of ethylcellulose 4 cP. No confidence was evident in the dissolution data fit to model 4, 5 or 6.

Based on a three-dimensional lattice, the lower percolation thresholds expressed as critical volume-to-volume ratios of the pore system and the matrix substance, respectively were in good agreement with the theoretical site percolation threshold of 0.312 in a simple cubic lattice. Approaching the critical volume-to-volume ratio termed the upper percolation threshold, the ethylcellulose substance was the component reaching a critical volume ratio below which no more coherent network could be found, resulting in the beginning of compact disintegration. Using the concept of two percolation thresholds in the matrix system, the possible range of mixing ratios of drug and matrix substance can be restricted, giving a basis for a more rational design of dosage forms. Additionally, it must be taken into account that the drug content should not be raised completely to the upper percolation threshold in order to ensure the mechanical stability of the matrix. Therefore, only a narrow range of mixing ratios will remain, which will show an almost complete drug release *in vivo* without the danger of an uncontrollable disintegration of the matrix.

Both the volume and surface fractal dimensions of discs prior to dissolution were non-fractal. The ethylcellulose viscosity grade did not affect either fractal dimension. Volume and surface fractal dimensions were measured for ethylcellulose discs (of either 4 cP or 100 cP viscosity grade). After dissolution, the volume fractal dimension was lower for compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP. Therefore, the ethylcellulose viscosity grade has an effect on the geometrical characteristics of the pore system. The volume fractal of ethylcellulose 100 cP system was nearer the value of the Menger sponge (2.73) than the value determined for ethylcellulose 4 cP systems. The surface fractal dimension determined for matrices of ethylcellulose 4 cP was not significantly different from the surface fractal dimension determined for ethylcellulose 100 cP matrices.

CHAPTER 7

EFFECT OF DISC COMPACTION PRESSURE AND ETHYLCELLULOSE PARTICLE SIZE FRACTION ON TABLETTING PROPERTIES AND RELEASE PROPERTIES OF ETHYLCELLULOSE MATRIX COMPACTS

7.1. INTRODUCTION - EFFECT OF DISC COMPACTION PRESSURE

Direct compression is the preferred method of manufacture for producing tablets intended for immediate or sustained release. It is both scientifically and economically appealing, since it entails reduced labour, cost, time, operational space and equipment (Katikaneni *et al.,* 1995b). Pather *et al.* (1998) used ethylcellulose 14 cP to prepare direct compression tablets to control the release of theophylline. In addition, Lin and Lin (1996) used ethylcellulose (of different viscosity grades) to prepare direct compression tablets for retarding sodium diclofenac release. The present study used ethylcellulose as the sole direct compression matrix-forming material to release a sparingly soluble drug, ibuprofen. Previous workers (Dabbagh *et al.*, 1996) found that the tablet compaction pressure could influence the drug release rate from ethylcellulose tablets. Therefore, in a continuing effort to define the characteristics of the ethylcellulose:ibuprofen system, the effect of applied force on compacts of different ethylcellulose viscosity grades was examined.

Also, several model release equations were fitted to the dissolution data in an effort to determine the best model fit. The effect (if any) of compaction pressure and ethylcellulose viscosity grade on the various model parameters was determined.

7.2. CHARACTERISATION OF COMPACTS - EFFECT OF DISC COMPACTION PRESSURE

Physical mixtures were prepared of ibuprofen powder and ethylcellulose 4 cP powder, or ethylcellulose 100 cP powder in a 50:50 weight ratio. These mixtures were then compacted at various compaction pressures between 2000 kg and 14000 kg for 10 minutes.

7.2.1. Height

The height of compacts prepared with ethylcellulose 4 cP or 100 cP viscosity grade and compacted at different compaction pressure is tabulated in table 7.1. and table 7.2., respectively. It was found that the height of compacts (prepared with either ethylcellulose viscosity grade) did not vary with increasing compaction pressure (as measured using a sliding callipers). In addition, the height of compacts prepared with ethylcellulose 4 cP powder was consistently less than the height of compacts prepared

with ethylcellulose 100 cP powder. This is in agreement with earlier findings in chapter 5 section 7.1.

Table 7.1.

Characterisation of ethylcellulose:ibuprofen compacts (50:50 weight ratio) prepared with ethylcellulose 4 cP viscosity grade and compacted at different compaction pressures

Pressure	**Height (cm)**	**Initial porosity**	**Porosity drug**	**Total porosity**	**Hardness (kg)**	**Tensile strength (kg/cm^2)**
2000 kg	0.170 ± 0.000	0.0203	0.4975	0.5177	12.15 ± 0.91	35.00 ± 2.62
4000 kg	0.170 ± 0.000	0.0187	0.4983	0.5169	11.44 ± 0.74	32.95 ± 2.12
5000 kg	0.170 ± 0.000	0.0197	0.4977	0.5174	11.36 ± 0.29	32.71 ± 0.85
6000 kg	0.170 ± 0.000	0.0194	0.4979	0.5173	11.03 ± 0.61	31.77 ± 1.77
7000 kg	0.170 ± 0.000	0.0194	0.4979	0.5173	11.64 ± 0.65	33.53 ± 1.87
8000 kg	0.170 ± 0.000	0.0192	0.4980	0.5172	11.25 ± 0.36	32.42 ± 1.05
9000 kg	0.170 ± 0.000	0.0184	0.4984	0.5168	11.21 ± 0.31	32.30 ± 0.91
10000 kg	0.170 ± 0.000	0.0187	0.4983	0.5169	11.23 ± 0.30	32.36 ± 0.87
11000 kg	0.170 ± 0.000	0.0187	0.4983	0.5169	11.56 ± 0.96	33.30 ± 2.76
12000 kg	0.170 ± 0.000	0.0192	0.4980	0.5172	11.82 ± 0.88	34.06 ± 2.53
13000 kg	0.170 ± 0.000	0.0181	0.4985	0.5167	11.40 ± 0.54	32.83 ± 1.55
14000 kg	0.170 ± 0.000	0.0194	0.4979	0.5173	11.87 ± 1.11	34.18 ± 3.21

Table 7.2.

Characterisation of ethylcellulose:ibuprofen compacts (50:50 weight ratio) prepared with ethylcellulose 100 cP viscosity grade and compacted at different compaction pressures

Pressure	Height (cm)	Initial porosity	Porosity drug	Total porosity	Hardness (kg)	Tensile strength (kg/cm^2)
2000 kg	0.175 ± 0.000	0.0456	0.4841	0.5297	8.60 ± 0.50	24.08 ± 1.41
4000 kg	0.175 ± 0.000	0.0453	0.4842	0.5295	9.07 ± 0.63	25.39 ± 1.76
5000 kg	0.175 ± 0.000	0.0461	0.4839	0.5299	8.79 ± 0.21	24.59 ± 0.58
6000 kg	0.175 ± 0.000	0.0440	0.4849	0.5289	9.01 ± 0.39	25.22 ± 1.08
7000 kg	0.175 ± 0.000	0.0463	0.4837	0.5300	8.69 ± 0.51	24.30 ± 1.42
8000 kg	0.175 ± 0.000	0.0481	0.4828	0.5309	8.93 ± 0.41	24.99 ± 1.15
9000 kg	0.175 ± 0.000	0.0461	0.4839	0.5299	8.89 ± 0.25	24.87 ± 0.71
10000 kg	0.175 ± 0.000	0.4560	0.4841	0.5297	8.76 ± 0.76	24.50 ± 2.13
11000 kg	0.175 ± 0.000	0.0463	0.4837	0.5300	8.42 ± 0.41	23.56 ± 1.13
12000 kg	0.175 ± 0.000	0.0461	0.4839	0.5299	8.93 ± 0.39	24.99 ± 1.10
13000 kg	0.175 ± 0.000	0.0456	0.4841	0.5297	8.97 ± 0.56	25.10 ± 1.58
14000 kg	0.175 ± 0.000	0.0463	0.4837	0.5300	8.48 ± 0.38	23.73 ± 1.07

7.2.2. Porosity

Knowing the physical dimensions of each compact, both the initial and total porosity of each compact was calculated (table 7.1. and 7.2.). Results showed no significant change in the porosity values of compacts prepared at different compaction pressures. This was evident for compacts formulated with either ethylcellulose 4 cp or 100 cP viscosity grade powder. This constancy of ethylcellulose compact porosity with increased compaction pressure was previously reported by Dabbagh *et al.* (1996). Desai *et al.* (1965a) also reported that polyvinyl chloride matrix compacts exhibited constancy of porosity with changes in compression force.

However, both the initial and total porosity were lower for compacts prepared with ethylcellulose 4 cP than for compacts prepared with ethylcellulose 100 cP, at each disc compaction pressure examined. This supports our previous findings in chapter 5, section 7.2.

7.2.3. Tensile strength

The hardness of compacts compacted at different compaction pressure was measured using a Schleuniger Hardness Tester and the relevant tensile strength calculated (table 7.1. and table 7.2.). It was found using a two-sample t-test, assuming equal variance that there was no significant difference ($p \leq 0.05$) in the tensile strength of compacts prepared at different compaction pressure. This was evident for compacts prepared with either ethylcellulose viscosity grade and is illustrated in figure 7.1. This suggests that these compacts have reached their maximal tensile strength. Katikaneni *et al.* (1995b) previously showed that ethylcellulose 10 cP compacts prepared with different ethylcellulose particle size fractions, approached maximum achievable hardness at 12 kN.

There was a significant difference ($p \leq 0.05$) in the tensile strength of compacts prepared with ethylcellulose 4 cP powder and ethylcellulose 100 cP powder, at each different compaction pressure. This supports previous findings in chapter 5 section 7.3.

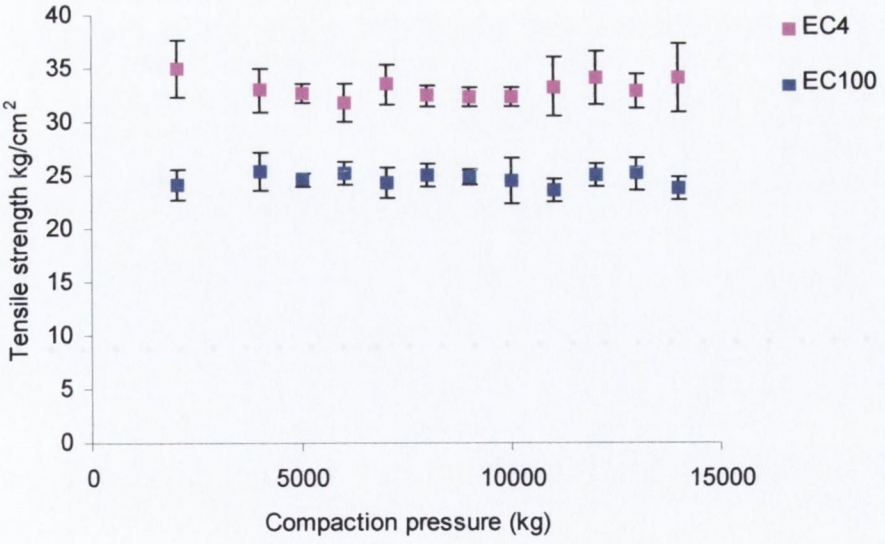

Figure 7.1. The effect of disc compaction pressure on the tensile strength of ethylcellulose:ibuprofen compacts (50:50 weight ratio). EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cP viscosity grade.

7.3. EFFECT OF DISC COMPACTION PRESSURE ON IBUPROFEN RELEASE

The effect of disc compaction pressure on percentage ibuprofen release from compacts compacted at different compaction pressures (2,000 kg, 7,000 kg 11,000 kg and 14,000 kg) was measured over a period of twelve hours and is illustrated in figure 7.2. The initial and limiting ibuprofen release rates of discs prepared with ethylcellulose 4 cP or ethylcellulose 100 cP and compacted at different pressures are outlined in table 7.3. It was clear that the disc compaction pressure did not affect the ibuprofen release rate from compacts prepared with either ethylcellulose 4 cP or 100 cP viscosity grade. Dabbagh *et al.* (1996) examined the effect of disc compaction pressure on the drug release rate. He found that the release rate of propranolol hydrochloride from ethylcellulose 7 cP matrix compacts was affected by compaction pressure up to a certain level. However, increasing the compaction pressure beyond this level did not affect the release rate of the drug. He explained this on the basis that up to a level of compaction pressure, the porosity of the matrix compact was reduced. Beyond this point the porosity was unaffected by increasing the disc compaction pressure. Similarly, Deasi *et al.* (1966a) reported that the release of drug from elastic matrix compacts were independent of the compression force which was attributed to a constancy of porosity within the matrix.

It was also clear that ibuprofen release was greater from compacts prepared with ethylcellulose 100 cP than from compacts prepared with ethylcellulose 4 cP. Upadrashta *et al.* (1993) reported that, when using a range of ethylcellulose viscosity grades, a more controlled release rate of drug was more achievable with the lower viscosity grades of ethylcellulose.

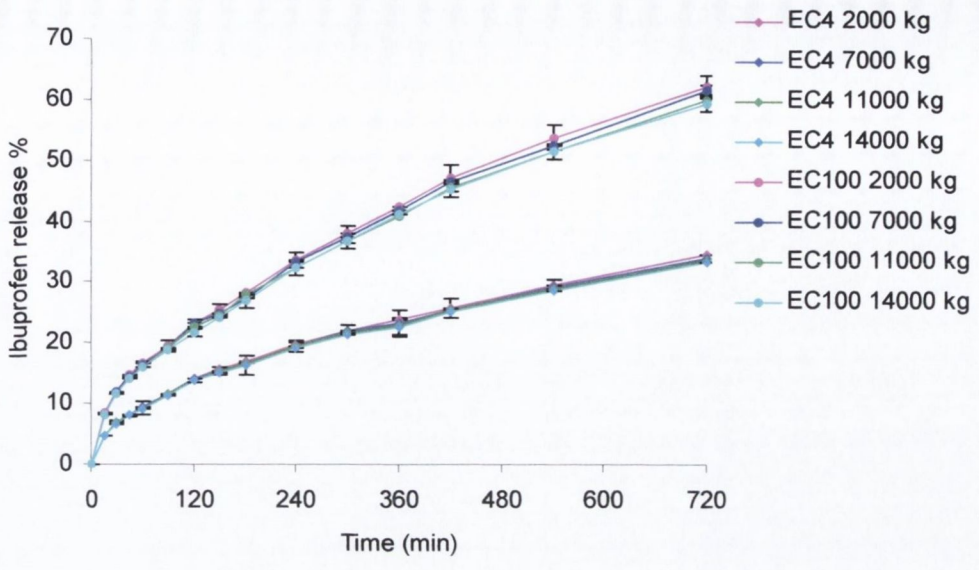

Figure 7.2. The effect of disc compaction pressure (kg) on ibuprofen release from ethylcellulose:ibuprofen compacts (50:50 weight ratio). EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cP viscosity grade.

Table 7.3.

Ibuprofen initial and limiting release rates from compacts prepared with ethylcellulose:ibuprofen (50:50 weight ratio) and compacted at different compaction pressures

Compaction pressure	**Initial release rate**	**Final release rate**	**I:L**
Ethylcellulose 4 cP	**(mg/cm^2/min)**	**(mg/cm^2/min)**	
2000 kg	0.1032	0.0179	5.7741
7000 kg	0.1024	0.0176	5.8099
11000 kg	0.1022	0.0018	5.8494
14000 kg	0.1006	0.0173	5.8241
Ethylcellulose 100 cP			
2000 kg	0.1785	0.0321	5.5563
7000 kg	0.1766	0.0318	5.5612
11000 kg	0.1725	0.0309	5.5759
14000 kg	0.1732	0.0305	5.6773

7.4. APPLICATION OF "CLASSICAL THEORIES" - EFFECT OF DISC COMPACTION PRESSURE

7.4.1. Higuchi Theory

The drug release data obtained from matrix compacts compacted at different compaction pressures was fitted to the Higuchi theory (1963) for drug release. Statistical parameters and constants are outlined in table 7.4. As indicated by the relatively high coefficient of determination and MSC statistical parameters, ibuprofen release profiles from matrix compacts of either ethylcellulose 4 cP or 100 cP viscosity grade, and compacted at different compaction pressures provided a relatively good fit to the Higuchi "classical" model.

Higuchi (1963) showed that in the matrix type of drug delivery system, the porosity and degree of tortuosity in the capillaries are related to each other, and influence the drug release rate. Compacts prepared with either ethylcellulose viscosity grade showed constancy of porosity (section 7.2.2.) and of tortuosity over the different compaction pressures examined. This indicates that the drug diffusional path length is unaffected by the disc compaction pressure and is reflected in the constant drug release rate constant from compact of either ethylcellulose 4 cP or 100 cP.

The calculated tortuosity values obtained for matrix compacts prepared with ethylcellulose 4 cP ranged between 7.42 and 7.88, and for matrix compacts prepared with ethylcellulose 100 cP between 2.44 and 2.60, over a range of different disc compaction pressures. The tortuosity values for ethylcellulose 4 cP compacts were consistently greater then the tortuosity values for compacts prepared with ethylcellulose 100 cP, for each compaction pressure examined.

Table 7.4.

Results of ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) compacted at different compaction pressures and fitted to Higuchi theory model

Compaction pressure	A (mg/cm^3)	Tortuosity	CoD	MSC	Release rate constant (b) mg.cm^{-2}.min$^{-1/2}$
EC4					
2000 kg	553.39	7.42 ± 0.05	0.9994	7.2744	0.4769 ± 0.0030
7000 kg	553.83	7.57 ± 0.06	0.9992	7.0529	0.4709 ± 0.0034
11000 kg	554.28	7.71 ± 0.06	0.9993	7.0549	0.4664 ± 0.0034
14000 kg	553.83	7.88 ± 0.06	0.9993	7.0706	0.4614 ± 0.0035
EC100					
2000 kg	538.53	2.44 ± 0.05	0.9945	5.0598	0.8495 ± 0.0159
7000 kg	538.10	2.52 ± 0.05	0.9939	4.9617	0.8351 ± 0.0169
11000 kg	538.10	2.56 ± 0.05	0.9956	5.2935	0.8294 ± 0.0125
14000 kg	538.10	2.60 ± 0.05	0.9945	5.0727	0.8236 ± 0.0144

CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.4.2. Cobby theory

Data was fitted to the model of diffusion controlled drug release from matrices having a cylindrical shape, as described by Cobby *et al.* (1974a) (table 7.5.). Both the coefficient of determination and model selection criterion were relatively high when the Cobby model for drug release was fitted to the release data.

Our results found that the release rate constant (K_R) of compacts prepared with the different ethylcellulose viscosity grade did not vary for formulations prepared at different compaction pressures. Results also showed that the release rate constant K_R of compacts prepared with ethylcellulose 100 cP viscosity grade was consistently greater than the release rate constant K_R determined for compacts prepared with ethylcellulose 4 cP. The release rate constant K_R is directly proportional to the boundary retreat constant K_b in the relationship outlined in equation 2.12. i.e. a low K_R constant equals a low K_b constant. Therefore, the disc compaction pressure did not affect the rate at which the dissolution medium penetrated the matrix compact. However, in support of previous findings the dissolution medium penetrated matrices

of ethylcellulose 100 cP more easily than matrices of ethylcellulose 4 cP viscosity grade.

Table 7.5.

Results of ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) compacted at different compaction pressures and fitted to Cobby model

Compaction pressure	K_R	Std Dev K_R	CoD	MSC
EC4				
2000 kg	0.00137	8.82E-6	0.9979	6.0372
7000 kg	0.00136	8.61E-6	0.9980	6.0562
11000 kg	0.00134	8.44E-6	0.9980	6.0743
14000 kg	0.00133	8.26E-6	0.9980	6.0950
EC100				
2000 kg	0.00253	4.29E-5	0.9870	4.2180
7000 kg	0.00249	4.27E-5	0.9869	4.1927
11000 kg	0.00248	4.18E-5	0.9874	4.2420
14000 kg	0.00246	4.35E-5	0.9862	4.1501

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.5. MODELLING OF IBUPROFEN RELEASE DATA - EFFECT OF DISC COMPACTION PRESSURE

7.5.1. Introduction

Ibuprofen release data from ethylcellulose matrix compacts (of one of two different viscosity grades) compacted at different compaction pressures, was fitted to different models to determine which model provided the best fit. In addition, the effect of compaction pressure and ethylcellulose viscosity grade on the different model parameters and exponents was investigated.

7.5.2. Model 1

As indicated by the relatively high coefficient of determination and MSC statistical values, the square root of time model provided a good fit to the release data (table 7.6.).

By comparing the root time release rate constant (k) of the various dissolution curves it can be observed that there was no significant difference in the ibuprofen release rate constant from compacts of the same ethylcellulose viscosity grade, compacted at different compaction pressures. However, the ibuprofen release rate constant for compacts prepared with ethylcellulose 100 cP was greater than the release rate constant for compacts prepared with ethylcellulose 4 cP, for each compaction pressure examined.

Table 7.6.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) compacted at different compaction pressures

Compaction pressure	k (%min$^{-0.50}$)	Std Dev of k	c	Std Dev c	CoD	MSC
EC4						
2000 kg	1.2788	0.0080	-0.1933	0.1173	0.9995	7.3307
7000 kg	1.2616	0.0092	-0.1442	0.1364	0.9993	6.9000
11,000 kg	1.2485	0.0092	-0.1312	0.1358	0.9993	6.8999
14,000 kg	1.2363	0.0090	-0.1350	0.1329	0.9993	6.9213
EC100						
2000 kg	2.2881	0.0429	-1.1199	0.5784	0.9958	5.1888
7000 kg	2.2509	0.0453	-1.0670	0.6117	0.9952	5.0448
11,000 kg	2.2356	0.0338	-1.2540	0.4987	0.9970	5.5565
14,000 kg	2.2200	0.0389	-1.2765	0.5741	0.9960	5.2616

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.5.3. Model 2

Both the coefficient of determination and MSC values were higher when model 2 (table 7.7.) was fitted to the ibuprofen release data form compacts prepared at different compaction pressures, than when model 1 (table 7.6.) was fitted to the data.

The exponent N for each formulation exceeded the range defined by Ritger and Peppas (1987). This indicated a mechanism other than diffusion was contributing to drug release in each formulation (Peppas and Sahlin, 1989). For formulations prepared with either ethylcellulose viscosity grade the disc compaction pressure did not appear to affect the diffusional exponent N. Indeed, the exponent N was higher for formulations prepared with ethylcellulose 100 cP viscosity grade than for formulations prepared with ethylcellulose 4 cp viscosity grade.

Table 7.7.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) compacted at different compaction pressures

Compaction pressure	**k ($\%min^{-N}$)**	**Std Dev of k**	**N**	**Std Dev of N**	**c**	**Std Dev of c**	**CoD**	**MSC**
EC4								
2000 kg	1.1959	0.0601	0.5098	0.0024	0.0235	0.1955	0.9996	7.3396
7000 kg	1.1993	0.0737	0.5074	0.0030	0.0180	0.2377	0.9993	6.9250
11,000 kg	1.1857	0.0733	0.5075	0.0030	0.0322	0.2363	0.9993	6.9153
14,000 kg	1.1775	0.0721	0.5071	0.0030	0.0182	0.2320	0.9994	6.9331
EC100								
2000 kg	1.5134	0.1791	0.5631	0.0060	0.8883	0.6591	0.9981	5.8302
7000 kg	1.4919	0.2052	0.5627	0.0070	0.8998	0.7543	0.9974	5.5287
11,000 kg	1.5376	0.1370	0.5549	0.0043	0.7285	0.5372	0.9989	6.3740
14,000 kg	1.4849	0.1721	0.5591	0.0056	0.8263	0.6861	0.9981	5.8653

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.5.4. Model 3

The coefficients of determination values obtained for model 3 fits (table 7.8.) were greater or equal than the values obtained when model 2 (table 7.7.) was fitted to ibuprofen release profiles from ethylcellulose 4 cP or 100 cP formulations. The MSC values were also higher when model 3 was fitted to the release data (as opposed to model 2).

The values of k_1 and k_2 in table 7.8. were used to calculate the relative contribution of Fickian and non-Fickian mechanisms of release to ibuprofen release from the relevant formulation (Peppas and Sahlin 1989). There was no significant difference in the

contribution of Fickian release (and consequently, non-Fickian release) to the release of drug from ethylcellulose 4 cP compacts compacted at different compaction pressures. This trend was also evident for compacts prepared with ethylcellulose 100 cP and compacted at different compaction pressures. In addition for each formulation, polymer relaxation contributed more to the mechanism of release from compacts of ethylcellulose 100 cP, than from compacts of ethylcellulose 4 cP. Conversely, Fickian diffusion contributed less to the mechanism of release from ethylcellulose 100 cP compacts than from ethylcellulose 4 cP compacts.

Table 7.8.

Parameters and statistical estimates of model 3 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) compacted at different compaction pressures

Compaction pressure	**k_1 (%min$^{-0.50}$)**	**Std Dev of k_1**	**k_2 (%min)**	**Std Dev of k_2**	**CoD**	**MSC**
EC4						
2000 kg	1.2389	0.0128	0.0015	0.0006	0.9996	7.4892
7000 kg	1.2315	0.0155	0.0011	0.0008	0.9994	7.0698
11,000 kg	1.2199	0.0154	0.0011	0.0008	0.9993	7.0633
14,000 kg	1.2081	0.0152	0.0010	0.0008	0.9994	7.0767
EC100						
2000 kg	1.9591	0.0443	0.0148	0.0025	0.9986	6.3057
7000 kg	1.9338	0.0536	0.0143	0.0030	0.9979	5.8895
11,000 kg	1.9406	0.0322	0.0114	0.0016	0.9991	6.7600
14,000 kg	1.9162	0.0441	0.0118	0.0022	0.9983	6.1184

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.5.5. Other Models

Model 5, the DRE model, and erosion model did not prove suitable fits to ibuprofen release data from ethylcellulose:ibuprofen compacts prepared with different ethylcellulose viscosity grade and prepared at different compaction pressure.

7.6. INTRODUCTION - EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION

Potter *et al.* (1992) noticed that drug and excipient particle sizes exert a great influence on the drug release behaviour from ethylcellulose matrix tablets. Results found that larger drug particles resulted in slower drug release whilst larger matrix particle sizes resulted in faster drug release. Caraballo *et al.* (1993) used percolation theory to explain this release behaviour. This has led to the re-evaluation of such "classical theories" as the Higuchi model to explain drug release from matrix compacts prepared with different drug or excipient particle size fractions.

The focus of this chapter was to prepare and examine ethylcellulose:ibuprofen compacts of different ethylcellulose particle size fractions, using different ethylcellulose viscosity grades, and to measure ibuprofen release from the different formulations. A further objective was to apply percolation theory in order to determine whether it is useful to explain release profiles from inert matrix compacts of different ethylcellulose particle size fractions, and to compare the proposed interpretations of percolation theory with "classical theories". In addition, we wished to determine which of several model release equations provided the best fit to the data, and to observe the effect (if any) of ethylcellulose particle size fraction and ethylcellulose viscosity grade on the various model parameters.

7.7. PARTICLE SIZE ANALYSIS

The particle size distribution of ethylcellulose powders of different particle size fractions (and of different ethylcellulose viscosity grades) are outlined in table 7.9. The quantity of powder collected of the smallest and largest ethylcellulose 4 cP and 100 cP particle size fractions was so small it was impossible to determine the median particle size using a laser diffraction particle size analyser. In these instances when plotting graphs the median particle size was taken to be the mean of the aperture of the two sieves used.

Table 7.9.

Particle size distribution of ethylcellulose 4 cP/100 cP powder of different particle size fractions as determined using a dry powder method with a laser diffraction particle size analyser[(a)]

Particle size fraction	D[v,0.1] (μm)	D[v,0.5] (μm)	D[v,0.9] (μm)
Ethylcellulose 4 cP			
40-63 μm	*	*	*
90-125 μm	40.79	106.15	152.53
180-250 μm	40.26	185.83	285.81
355-500 μm	*	*	*
Ethylcellulose 100 cP			
40-63 μm	*	*	*
90-125 μm	58.97	117.20	181.93
180-250 μm	142.60	212.70	324.55
355-500 μm	*	*	*

* The weight of fraction recovered after sieving was too small for dry powder particle sizing to be performed. [a]measured using a Malvern 2600c laser diffraction particle size analyser.

7.8. CHARACTERISATIONS OF COMPACTS - EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION

Physical mixtures were prepared by mixing one of four different ethylcellulose particle size fractions, of either ethylcellulose 4 cP or 100 cP viscosity grade, and one ibuprofen particle size fraction. Chapter 5 section 6 contains details of the particle size analysis of ibuprofen powder.

7.8.1. Height

The height of compacts was measured using a sliding callipers (table 7.10.). It was found that the height of compacts prepared with the smallest ethylcellulose particle size fraction was slightly less than the height of compacts prepared with the largest ethylcellulose particle size fraction, for compacts of each ethylcellulose viscosity grade. In addition, studies found that the height of compacts prepared with ethylcellulose 4 cP was less than the height of compacts prepared with ethylcellulose 100 cP, for each ethylcellulose particle size fraction used in each formulation. Therefore, if one uses height as an indicator of consolidation (Vromans and Lerk, 1988), compacts prepared with ethylcellulose 4 cP 40-63 μm or 90-125 μm particle

size fraction showed the greater consolidation, while compacts prepared with ethylcellulose 100 cP 180-250 μm, or 355-500 μm particle size fraction showed the least.

Table 7.10.

Characterisation of ethylcellulose:ibuprofen compacts (50:50 weight ratio) prepared with different ethylcellulose particle size fractions, of either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade

Particle size fraction	**Height (cm)**	ε_0	ε_d	ε	**Hardness (kg)**	**Tensile strength (kg/cm^2)**
EC4						
40-63 μm	0.170 ± 0.000	0.0179	0.4987	0.5165	11.56±0.60	33.30±1.73
90-125 μm	0.170 ± 0.000	0.0187	0.4983	0.5169	11.13±0.13	32.07±0.38
180-250 μm	0.172 ± 0.003	0.0281	0.4935	0.5216	10.58±0.13	30.13±0.67
355-500 μm	0.175 ± 0.000	0.0465	0.4841	0.5307	9.67±0.35	27.10±0.97
EC100						
40-63μm	0.175± 0.000	0.0456	0.4841	0.5297	8.89±0.21	24.87±0.58
90-125 μm	0.175± 0.000	0.0463	0.4837	0.5301	8.60±0.19	24.08±0.52
180-250 μm	0.180± 0.000	0.0727	0.4704	0.5430	8.32±0.12	22.63±0.32
355-500 μm	0.180± 0.000	0.0729	0.4703	0.5431	7.73±0.35	21.02±0.95

ε_0: initial porosity, ε_d: porosity due to drug, ε: total porosity, EC4: ethylcellulose 4 cP, EC100: ethylcellulose 100 cP

7.8.2. Porosity

The total porosity of compacts prepared with the smallest ethylcellulose particle size fraction was less than the total porosity of compacts prepared with the largest ethylcellulose particle size fraction, for compacts of either ethylcellulose viscosity grade (table 7.10.). Closer examination of results showed that as the median ethylcellulose particle size increased the porosity due to air i.e. initial porosity (and consequently total porosity) showed a tendency to increase. This was evident for compacts prepared with either ethylcellulose viscosity grade. Other authors have shown that the total porosity in the tablet structure of ethylcellulose tablets is dependent on the initial porosity of the powder bed and that plastic deformation is the primary consolidation mechanism (Katikaneni *et al.*, 1995a). Katikaneni *et al.* (1995a) found that the initial relative density decreased with decreasing ethylcellulose

particle size, while the changes in relative density, attributed to particle rearrangement, increased significantly. This was then reflected in the calculated pore space of compacts prepared with different ethylcellulose particle size fractions i.e. the porosity of compacts decreased with a decrease in ethylcellulose particle size. Lin and Lin (1996) similarly found that compacts of smaller ethylcellulose particle size had less porosity than compacts prepared with ethylcellulose of larger particle size fraction (of the same ethylcellulose viscosity grade).

Compacts prepared with ethylcellulose 4 cP had a lower total porosity and initial porosity than compacts prepared with ethylcellulose 100 cP, for each particle size fraction examined. Shlieout and Zessin (1996) similarly noted that tablets prepared with different ethylcellulose viscosity grades and a consistent compression force displayed an increase in porosity with an increase in ethylcellulose viscosity grade. They found that the fragmentation rate of ethylcellulose with a low molecular weight is more effective than the rates of those with a higher molecular weight. He proposed this as a possible reason for the better compressibility of lower molecular weight ethylcellulose.

7.8.3. Tensile strength

The hardness of the different compacts was measured using a Schleuniger Hardness tester and the tensile strength calculated (table 7.10.). Two-tailed t-test, assuming equal variance was used to determine if the tensile strengths of the different compacts were significantly different. Results showed that compacts prepared with ethylcellulose 40-63 μm particle size fraction had a significantly greater tensile strength ($p \leq 0.05$) than compacts prepared with the ethylcellulose 355-500 μm particle size fraction, for each ethylcellulose viscosity grade examined. There was no significant difference ($p \leq 0.05$) in the tensile strength of ethylcellulose 4 cP compacts prepared with the 40-63 μm-particle size fraction and 90-125 μm-particle size fraction. However, there was a significant difference in the tensile strength of ethylcellulose 4 cP compacts prepared with the following particle size fractions: 90-125 μm and 180-250 μm, 180-250 μm and 355-500 μm. Similar results were found for compacts prepared with ethylcellulose 100 cP viscosity grade. Figure 7.3. shows a plot of compact tensile strength versus ethylcellulose median particle size of compacts of either ethylcellulose viscosity grade (4 cP or 100 cP), while figure 7.4. shows a plot

of compact tensile strength versus total porosity of compacts prepared with either ethylcellulose 4 cP or 100 cP. It appears that as the ethylcellulose median particle size or total porosity of compacts increased, the tensile strength of compacts showed a tendency to decrease. The increase in tablet hardness with a decrease in particle size is consistent with the theory that smaller particles allow a greater packing density and a greater number of contact points for interparticulate bonding (Katikaneni *et al.*, 1995a). Based on the sensitivity of tablet hardness to the initial particle size it can be concluded that consolidation is via plastic deformation under the tabletting conditions employed. Lin and Lin (1996) also showed that higher tensile strength and better compactibility of compacts composed of smaller particle size of ethylcellulose powders led to less compact porosity.

The tensile strength of compacts prepared with ethylcellulose 4 cP was significantly higher ($p \leq 0.05$) than the tensile strength of compacts prepared with ethylcellulose 100 cP, for each particle size fraction examined. This was confirmed using a two-sample t-test, assuming equal variance. It was also evident in figure 4 that tablets showed an increase in porosity and decreased tensile strength with an increase in viscosity grade. This was explained by Upadrashta *et al.* (1994) on the basis that compacts prepared with lower ethylcellulose viscosity grades were more compressible than higher viscosity grades. It is also noteworthy that the tensile strength of ethylcellulose 4 cP compacts of 355-500 μm particle size fraction was significantly ($p \leq 0.05$) greater than the tensile strength of ethylcellulose 100 cP compacts prepared with 40-63 μm particle size fraction, or 90-125 μm particle size fraction. This was in spite of the porosity of ethylcellulose 4 cP compacts of 355-500 um particle size fraction being (slightly) greater than that of ethylcellulose 100 cP compacts prepared with either 40-63 μm particle size fraction, or 90-125 μm particle fraction. This suggests that other factors (other than porosity) may contribute to the increased tensile strength of compacts prepared with ethylcellulose 4 cP. As discussed earlier Shlieout *et al.* (1999) found that even at the same tablet porosity, ethylcellulose of low viscosity grade showed greater compressibility and compactibility. He accounted for this by the more developed irreversible deformation of the ethylcellulose with low molecular weight. Other factors that may contribute to the difference in tensile strength at the same porosity value include, the smaller particle size distribution and different particle morphology of ethylcellulose 4 cP powders, compared to ethylcellulose 100

cP powders. Previous authors (York (1978) and Rime *et al.* (1997)) have shown that particle morphology can affect the compression process.

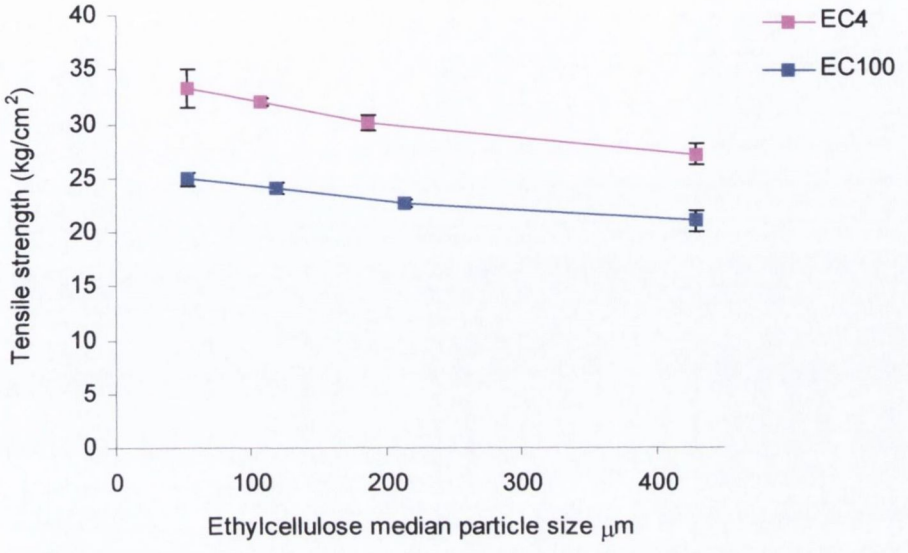

Figure 7.3. Plot of tensile strength of ethylcellulose:ibuprofen compacts (50:50 weight ratio) versus ethylcellulose median particle size. EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cp viscosity grade.

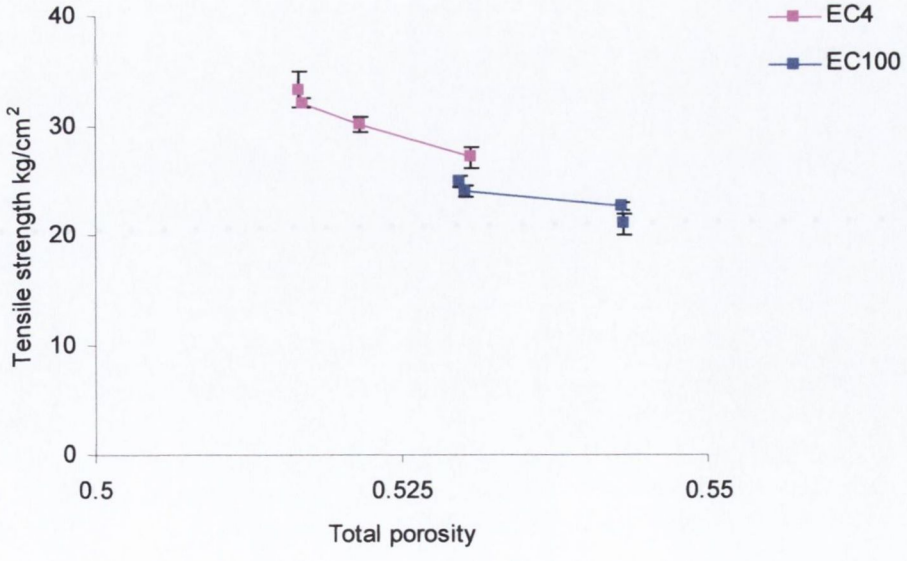

Figure 7.4. Plot of tensile strength of ethylcellulose:ibuprofen compacts (50:50 weight ratio) versus total porosity. EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cp viscosity grade.

7.9. EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION ON IBUPROFEN RELEASE

The effect of ethylcellulose particle size fractions on percentage ibuprofen release from compacts formulated with different ethylcellulose particle size fractions (of either ethylcellulose 4 cP or 100 cP viscosity grade) was measured over a period of twelve hours and is illustrated in figure 7.5.

It was clear that percentage ibuprofen release was greater from compacts prepared with the larger ethylcellulose particle size fraction than the smaller ethylcellulose particle size fraction, for compacts formulated with either ethylcellulose 4 cP or 100 cP. Dabbagh *et al.* (1996) also found that as the particle size of the ethylcellulose increased the drug release increased, indicating that penetration of dissolution medium into the matrices was facilitated when coarser particle size fractions were used. Lin and Lin (1996) showed that the water uptake rate of drug loaded ethylcellulose compacts was directly in proportion to the particle size of the ethylcellulose powder and to the porosity of the compact, in which the porosity increase was also proportional to the drug release rate during dissolution (Usteri *et al.*, 1990).

The initial and limiting ibuprofen release rates were also calculated (table 7.11.). These results also showed that the greater the ethylcellulose particle size fraction used in the formulation, the greater the initial and limiting drug release rates from compacts formulated with either ethylcellulose 4 cP or 100 cP viscosity grade. For each ibuprofen release profile, the initial release rate was greater than the limiting release rate. This was accounted for by the increasing distance that must be traversed by water and drug molecules into and out of the tablet (respectively) during dissolution (Pather *et al.*, 1998). A measure of the attenuation of the dissolution rate was given by the ratio of initial to limiting rates in table 7.11. It was evident that the attenuation of the release rate was reduced when a larger ethylcellulose particle size fraction was used during formulation. This may be because ethylcellulose compacts prepared with the larger ethylcellulose particle size fractions provide a less difficult drug diffusional pathway. This was evident for compacts formulated with either ethylcellulose 4 cP or 100 cP.

Indeed, ibuprofen release was greater from compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP, for each ethylcellulose particle size fraction examined. This was consistent with findings by Katikaneni *et al.* (1995b) who proposed that the

viscosity grade effect on release rates could be accounted for by tablet porosity and hardness effect. Examination of the initial to limiting ratio showed that the attenuation of the release rate was greater for matrix compacts prepared with ethylcellulose 4 cP than for compacts prepared with ethylcellulose 100 cP, for each ethylcellulose particle size fraction examined. This may be accounted for by the less circuitous pathway that ethylcellulose 100 cP compacts provide during drug dissolution, as opposed to compacts prepared with ethylcellulose 4 cP.

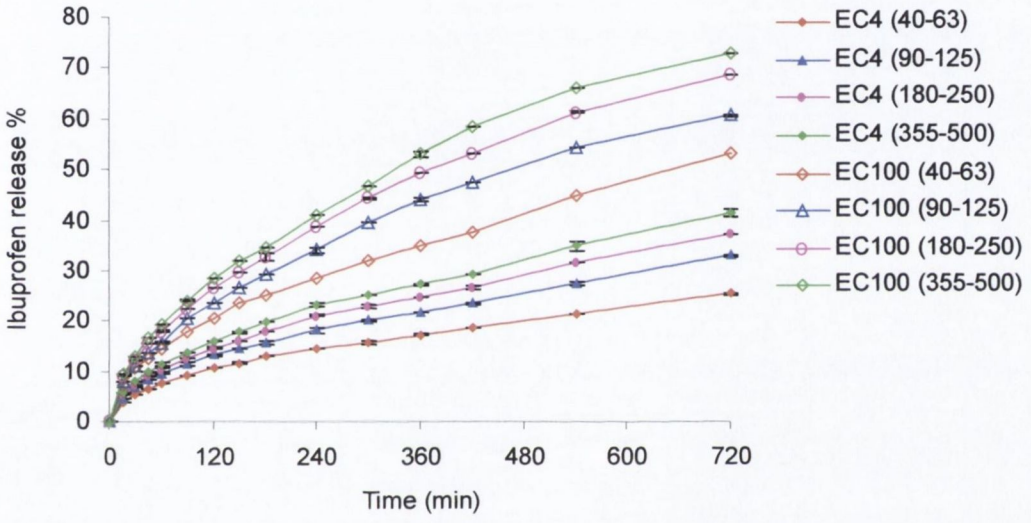

Figure 7.5. The effect of ethylcellulose particle size fraction on ibuprofen release from ethylcellulose:ibuprofen compacts (50:50 weight ratio). EC4 is ethylcellulose 4 cP viscosity grade, and EC 100 is ethylcellulose 100 cP grade. The particle size fraction (μm) is indicated in brackets.

Table 7.11.

Ibuprofen initial and limiting release rates from ethylcellulose:ibuprofen (50:50 weight ratio) compacts prepared with different ethylcellulose 4 cP/100 cP particle size fractions

Particle size fraction	Initial release rate (I) ($mg/cm^2/min$)	Limiting release rate (L) ($mg/cm^2/min$)	I:L
EC4			
40-63 μm	0.0790	0.0131	6.0242
90-125 μm	0.0999	0.0170	5.8669
180-250 μm	0.1099	0.0192	5.7150
355-500 μm	0.1204	0.0214	5.6412
EC100			
40-63 μm	0.1550	0.0273	5.6702
90-125 μm	0.1668	0.0312	5.3427
180-250 μm	0.1863	0.0351	5.3082
355-500 μm	0.1938	0.0372	5.2034

EC4: ethylcellulose 4 cP, EC 100: ethylcellulose 100 cp

7.10. f_2 SIMILARITY FACTOR - EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION

The objective of this study was to compare ibuprofen release profiles from matrix compacts prepared with different ethylcellulose particle size fractions (of either ethylcellulose 4 cP or 100 cP viscosity grade) using the similarity factor defined in FDA SUPAC guidelines (O'Hara *et al.*, 1997). In addition, ibuprofen release from compacts prepared with the same particle size fraction but different ethylcellulose viscosity grades were statistically compared.

The f_2 factors for the profiles statistically compared are given in tables 7.12., 7.13. and 7.14. The f_2 similarity factor of release profiles from ethylcellulose 4 cP matrix compacts of different ethylcellulose particle size fractions showed that there was no statistical difference between release profiles from compacts prepared with the following ethylcellulose particle size fractions: 40-63 μm and 90-125 μm, 90-125 μm and 180-250 μm, 180-250 μm and 355-500 μm, and 40-63 μm and 355-500 μm. However, it was noteworthy that the similarity factor between ibuprofen release profiles from matrix compacts prepared with ethylcellulose 4 cP 40-63 μm particle

size fraction and 355-500 μm particle size fraction were near the limit of dissimilarity (table 7.12.).

The f_2 similarity factor of release profiles from ethylcellulose 100 cP matrix compacts of different ethylcellulose particle size fractions showed that there was no statistical difference between profiles from compacts prepared with the following ethylcellulose particle size fractions: 40-63 μm and 90-125 μm, 90-125 μm and 180-250 μm, and 180-250 μm and 355-500 μm. However, the similarity factor indicated that there was a significant difference between the release profiles of compacts prepared with ethylcellulose 40-63 μm and 355-500 μm (table 7.13.).

It was also found that ibuprofen release profiles from ethylcellulose 4 cP viscosity grade compacts were statistically dissimilar (using the similarity factor) from ibuprofen release profiles from ethylcellulose 100 cP viscosity grade compacts, for each ethylcellulose particle size fraction examined (table 7.14.).

Table 7.12.

In vitro Dissolution Similarity Factors (f_2) of ibuprofen release profiles from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of ethylcellulose 4 cP viscosity grade

Reference profile Ethylcellulose 4 cP	**Test profile Ethylcellulose 4 cP**	**f_2**	**Similar/Dissimilar**
40-63 μm	90-125 μm	70.39	Similar
90-125 μm	180-250 μm	79.66	Similar
180-250 μm	355-500 μm	82.59	Similar
355-500 μm	40-63 μm	54.40	Similar

Table 7.13.

In vitro Dissolution Similarity Factors (f_2) of ibuprofen release profiles from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of ethylcellulose 100 cP viscosity grade

Reference profile Ethylcellulose100 cP	**Test profile Ethylcellulose 100 cP**	**f_2**	**Similar/Dissimilar**
40-63 μm	90-125 μm	62.45	Similar
90-125 μm	180-250 μm	68.39	Similar
180-250 μm	355-500 μm	77.17	Similar
355-500 μm	40-63 μm	45.46	Dissimilar

Table 7.14.

In vitro Dissolution Similarity Factors (f_2) of ibuprofen release profiles from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of ethylcellulose 4 cp viscosity grade (reference profile) and ethylcellulose 100 cP viscosity grade (test profile)

Reference profile Ethylcellulose 4 cP	**Test profile Ethylcellulose 100 cP**	**f_2**	**Similar/Dissimilar**
40-63 μm	40-63 μm	42.16	Dissimilar
90-125 μm	90-125 μm	39.81	Dissimilar
180-250 μm	180-250 μm	37.48	Dissimilar
355-500 μm	355-500 μm	36.68	Dissimilar

7.11. APPLICATION OF "CLASSICAL THEORIES" - EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION

7.11.1 Higuchi Theory

Drug release data obtained from discs prepared with different ethylcellulose particle size fractions (of different ethylcellulose viscosity grades) was fitted to the Higuchi model and the tortuosity value determined (Table 7.15. and appendix 4). As indicated by the relatively high coefficient of determination and MSC values, ibuprofen release profiles from matrix compacts prepared with either ethylcellulose 4 cP or 100 cP, of different ethylcellulose particle size fraction showed good suitability to the Higuchi drug release model. The best fit was achieved for release profiles from matrix compacts prepared with ethylcellulose 4 cP of the smallest particle size fraction, while the poorest fit was achieved for release profiles from ethylcellulose matrix compacts prepared with the largest ethylcellulose 100 cP particle size fraction.

The calculated tortuosity values obtained for matrix compacts prepared with ethylcellulose 4 cP ranged between 5.51 and 10.57, and for ethylcellulose 100 cP systems between 1.68 and 3.34. Figure 7.6. illustrates that with increasing ethylcellulose median particle size the tortuosity value had a tendency to decrease, while figure 7.7. illustrates that as the total porosity of compacts increased the tortuosity value had a tendency to decrease. This was evident for compacts prepared with either ethylcellulose viscosity grade. This suggests that the drug diffusional path length became less tortuous when the median particle size of the ethylcellulose fraction (or compact porosity) was increased. This was reflected in the increased drug release rate constant from formulations of larger ethylcellulose particle size fraction. This was supported by Potter *et al.* (1992) who attributed the increased drug release

rate to an increase in porosity and a possible decrease in tortuosity exhibited by matrix compacts of larger ethylcellulose particle size fractions.

The tortuosity values for ethylcellulose 4 cP compacts were consistently greater than the tortuosity values for compacts prepared with ethylcellulose 100 cP, for each ethylcellulose particle size fraction examined. Since the tortuosity factor corrects for the additional distance a molecule must travel due to its circuitous path within a tablet (Higuchi, 1963), this implies that ibuprofen has greater difficulty escaping from matrix compacts prepared with ethylcellulose 4 cP than from matrix compacts of ethylcellulose 100 cP, for each ethylcellulose particle size fraction examined. This was reflected in the lower drug release rate constant from ethylcellulose 4 cP formulations, as opposed to ethylcellulose 100 cP formulations. A possible reason for this is that compacts prepared with lower ethylcellulose viscosity grades such as 4 cP have a lower porosity than compacts prepared with higher ethylcellulose viscosity grades (chapter 5, section 7.2.). Shlieout and Zessin (1996) found that tablets prepared with different viscosity grades and a consistent compression force displayed an increase in porosity with an increase in viscosity grade. He observed that lower ethylcellulose viscosity grades were more compressible than higher ethylcellulose viscosity grades. It was also clear from figure 7.7. that the tortuosity values of compacts prepared with ethylcellulose 4 cP was greater than the tortuosity values of compacts prepared with ethylcellulose 100 cP, even when compacts of different ethylcellulose viscosity grade had similar total porosity values.

Table 7.15.

Results of ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of different ethylcellulose particle size fractions fitted to Higuchi theory model

Particle size fraction	A (mg/cm^3)	Tortuosity	CoD	MSC	Release rateconstant (b) mg.cm^{-2}.min$^{-1/2}$
EC4					
40-63μm	554.72	10.57 ± 0.91	0.9971	5.7195	0.3391 ± 0.0046
90-125 μm	554.28	8.54 ± 0.12	0.9971	5.7039	0.4387 ± 0.0066
180-250 μm	548.92	6.66 ± 0.09	0.9977	5.9309	0.5041 ± 0.0065
355-500 μm	538.53	5.51 ± 0.09	0.9968	5.5994	0.5558 ± 0.0084
EC100					
40-63μm	538.53	3.34 ± 0.05	0.9969	5.6510	0.7116 ± 0.0106
90-125 μm	538.10	2.36 ± 0.05	0.9940	4.9725	0.8802 ± 0.0136
180-250 μm	523.23	1.92 ± 0.04	0.9941	4.9770	0.9705 ± 0.0162
355-500 μm	523.11	1.68 ± 0.05	0.9975	4.5892	1.0471 ± 0.0222

CoD: Coefficient of determination, MSC: Model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

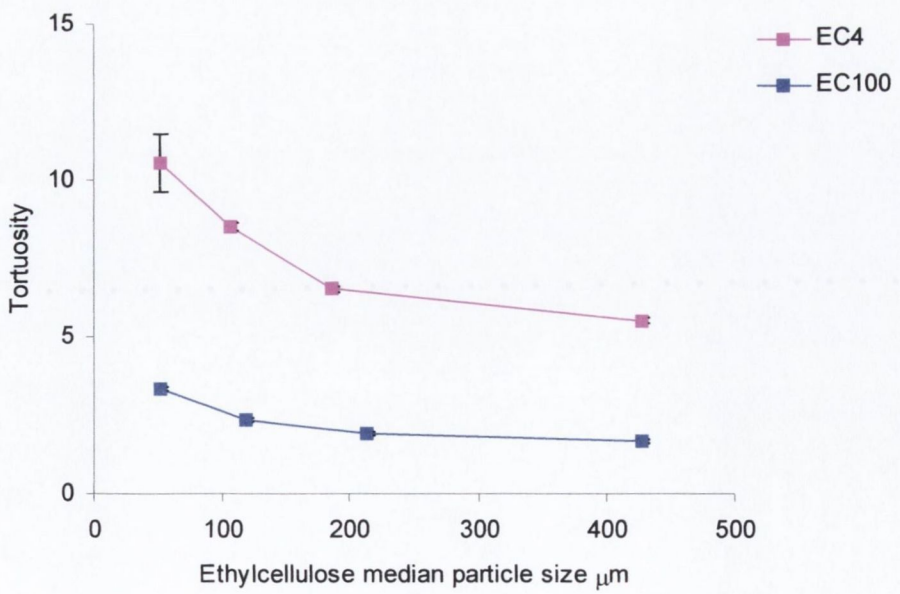

Figure 7.6. Plot of tortuosity of ethylcellulose:ibuprofen compacts (50:50 weight ratio) versus ethylcellulose median particle size. EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cp viscosity grade.

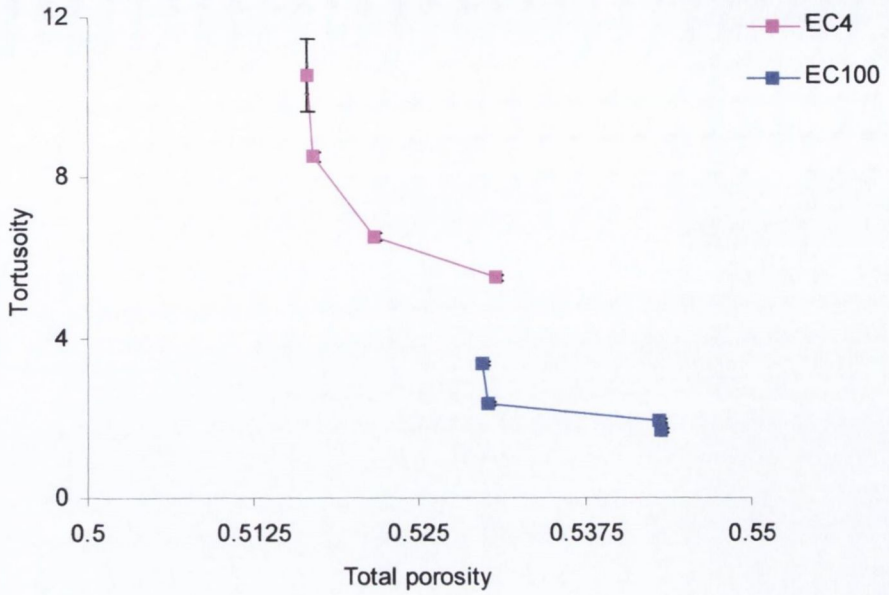

Figure 7.7. Plot of tortuosity of ethylcellulose:ibuprofen compacts (50:50 weight ratio) versus total porosity. EC4 is ethylcellulose 4 cP viscosity grade and EC100 is ethylcellulose 100 cp viscosity grade.

7.11.2. Cobby theory

Drug release data obtained from discs prepared with different ethylcellulose particle size fractions (of different ethylcellulose viscosity grades) was fitted to the model of diffusion controlled drug release from matrices having a cylindrical shape, as described by Cobby *et al.* (1974a) (table 7.16. and appendix 4). As indicated by the relatively high coefficient of determination and MSC values, ibuprofen release profiles from matrix compacts prepared with either ethylcellulose 4 cP or 100 cP, of different ethylcellulose particle size fraction showed good suitability to the Cobby drug release model.

Our results found that the release rate constant (K_R) increased when the larger ethylcellulose particle size fraction was used during formulation. Results also showed that the release rate constant K_R of compacts prepared with ethylcellulose 100 cP viscosity grade was consistently greater than the constant K_R determined for compacts prepared with ethylcellulose 4 cP. Since the release rate constant K_R is directly proportional to the boundary retreat constant K_b, this would suggest that the

dissolution medium penetrated matrices of larger ethylcellulose particle size fraction more easily than matrices prepared with the smaller ethylcellulose particle size fraction. Also, the dissolution medium penetrated matrices of ethylcellulose 100 cP more easily than matrices of ethylcellulose 4 cP viscosity grade.

Table 7.16.

Results of ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of different ethylcellulose particle size fractions fitted to Cobby model

Particle size fraction	K_R	Std Dev K_R	CoD	MSC
Ethylcellulose 4 cP				
40-63 μm	0.00100	6.83E-6	0.9974	5.8099
90-125 μm	0.00128	1.15E-5	0.9958	5.3308
180-250 μm	0.00147	1.45E-5	0.9951	5.1940
355-500 μm	0.00165	1.93E-5	0.9933	4.8770
Ethylcellulose 100 cP				
40-63μm	0.00215	2.77E-5	0.9921	4.710
90-125 μm	0.00258	4.69E-5	0.9859	4.1193
180-250 μm	0.00293	5.51E-5	0.9857	4.0949
355-500 μm	0.00316	6.98E-5	0.9809	3.8019

CoD: Coefficient of determination, MSC: Model selection criterion

7.12. APPLICATION OF PERCOLATION THEORY - EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION

"Classical theories" attribute the increased drug release rate exhibited by matrix compacts prepared with larger ethylcellulose particle size fractions, to an increased compact porosity and a possible decreased tortuosity (Potter *et al.*, 1992). One of the principle drawbacks of these theories was related to the use of the tortuosity parameter i.e. a theoretical parameter that cannot be experimentally determined.

On the other hand, Caraballo *et al.* (1993) used percolation theory to explain the relevant changes in dissolution kinetics from ethylcellulose compacts of varying drug and excipient particle size. The use of smaller particle sizes will result in the easier formation of an infinite cluster of this substance. So the compacts prepared with the insoluble excipient of smaller particle size will contain a more consistent insoluble infinite cluster i.e. its percolation threshold will decrease due to a more effective

distribution. This will determine a slower release rate of the soluble drug than the release rate from compacts prepared with ethylcellulose of larger particle size fraction.

Compacts prepared with the lower ethylcellulose viscosity grade displayed a lower release rate than compacts prepared with higher ethylcellulose viscosity grades, even when the same ethylcellulose particle size fraction was used during formulation. This decrease in release rate may be due to the greater compressibility of ethylcellulose 4 cP compacts resulting in the formation of a more continuous infinite insoluble matrix.

7.13. MODELLING OF IBUPROFEN RELEASE DATA - EFFECT OF ETHYLCELLULOSE PARTICLE SIZE FRACTION

7.13.1. Introduction

Ibuprofen release data from ethylcellulose matrix compacts formulated with one of four different ethylcellulose particle size fractions (of ethylcellulose 4 cP or 100 cP viscosity grade), was fitted to several model release equations. (The relevant models are outlined in chapter 2.) The objective was to analyse the drug release data to determine which of several model release equations provided the best-fit model, and to examine the effect of ethylcellulose particle size fraction and ethylcellulose viscosity grade on the various model exponents and statistical parameters. Drug diffusion, polymer relaxation and compact erosion were the mechanisms of drug release considered. Plots of model fits are shown in appendix 4.

7.13.2. Model 1

Ibuprofen dissolution profiles from compacts formulated with ethylcellulose of different particle size fractions, and of different ethylcellulose viscosity grades were fitted to the square root of time model (table 7.17.). As indicated by the high coefficient of determination and MSC statistical values, model 1 provided a good fit to the release data. This is because the model is based on the assumption that drug diffusion is the primary drug release mechanism. Compacts prepared with the largest ethylcellulose 100 cP particle size fraction (355-500 μm) displayed the poorest quality fit.

By comparing the calculated root time release rate constants (k) of the various dissolution curves it was observed that as the polymer particle size fraction used in the formulation increased the release rate constant of the drug increased. This was evident for formulations prepared with either ethylcellulose viscosity grade. Lin and Lin (1996) showed that porosity, water uptake and drug release rate were related, and that compacts of low porosity (small ethylcellulose particle size fraction) exhibited lower water uptake rates and lower drug release rates than compacts of high porosity (larger ethylcellulose particle size fraction). This may explain the dissolution behaviour from compacts prepared with different ethylcellulose particle size fractions. In addition, the release rate constant from compacts prepared with ethylcellulose 100 cP was greater than the release rate constant from compacts prepared with ethylcellulose 4 cP, for each ethylcellulose particle size fraction examined.

Table 7.17.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ibuprofen:ethylcellulose compacts (50:50 weight ratio) of different ethylcellulose particle size fractions

Particle size fraction	**k ($\%min^{-0.50}$)**	**Std Dev of k**	**c**	**Std Dev of c**	**CoD**	**MSC**
EC4						
40-63 µm	0.9070	0.0122	0.2971	0.1815	0.9976	5.6636
90-125 µm	1.1744	0.0175	0.0864	0.2590	0.9971	5.5790
180-250 µm	1.3524	0.0175	-0.2548	0.2578	0.9978	5.8701
355-500 µm	1.4969	0.0227	-0.3639	0.3345	0.9970	5.5532
EC100						
40-63 µm	1.9167	0.0283	-0.4028	0.4212	0.9971	5.5861
90-125 µm	2.3727	0.0366	-1.8030	0.4936	0.9972	5.5773
180-250 µm	2.6318	0.0439	-1.7546	0.5454	0.9970	5.4863
355-500 µm	2.8403	0.0602	-2.1818	0.7485	0.9951	5.0079

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.13.3. Model 2

Both the coefficient of determination and MSC values were higher when model 2 (table 7.18.) was fitted to the ibuprofen dissolution data in discussion than when model 1 was fitted to the dissolution data (table 7.17.). That is to say that although model 1 described drug release adequately a better model fit can be made on the assumption that the release rates were not dependent on the square root of time. Therefore, when the dependence of time was derived from the data and not given a preconceived value of root of time (N=0.500) better fits of data can be obtained.

When ibuprofen release data from compacts prepared with different ethylcellulose particle size fractions was fitted to model 2, the release exponent N ranged between 0.490-0.546, and 0.534-0.580 for ethylcellulose 4 cP and ethylcellulose 100 cP compacts, respectively. For formulations prepared with either ethylcellulose viscosity grade, as the ethylcellulose median particle size in the formulation decreased the release exponent N decreased correspondingly. This indicated that the value of N was affected by the ethylcellulose particle size fraction and that as the particle size of the ethylcellulose decreased the release became progressively controlled by diffusion. The lowest diffusional exponent was determined for release studies from compacts prepared with ethylcellulose 4 cP 40-63 μm particle size fraction and this was the only formulation that displayed an N value below 0.500. Peppas and Sahlin (1989) stated that if N exceeds 0.50 there is a mechanism other than Fickian diffusion contributing to drug release. This suggests that an additional mechanism of release contributed to ibuprofen release from all formulations, except for those prepared with ethylcellulose 4 cP 40-63 μm particle size fractions.

It was also noteworthy that the exponent N was higher for formulations prepared with ethylcellulose 100 cP than for formulations prepared with ethylcellulose 4 cP, for each ethylcellulose particle size fraction. Similar results were reported by Dabbagh *et al.* (1996)

Table 7.18.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of different ethylcellulose particle size fractions

Particle size fraction	k $\%min^{-N}$	Std Dev of k	N	Std Dev of N	c	Std Dev of c	CoD	MSC
EC4								
40-63 μm	0.9705	0.1078	0.4902	0.0053	0.1370	0.3240	0.9977	5.6903
90-125 μm	1.0493	0.1338	0.5165	0.0062	0.4181	0.4473	0.9973	5.6290
180-250 μm	1.1222	0.1152	0.5273	0.0050	0.3674	0.4027	0.9983	5.9839
355-500 μm	1.1818	0.1415	0.5460	0.0058	0.4996	0.5096	0.9978	5.7067
EC100								
40-63 μm	1.5248	0.1802	0.5335	0.0057	0.6671	0.6460	0.9978	5.7282
90-125 μm	1.5933	0.1027	0.5608	0.0033	0.2084	0.3744	0.9994	7.0356
180-250 μm	1.7432	0.1002	0.5650	0.0030	0.3522	0.3432	0.0996	7.2565
355-500 μm	1.7144	0.1668	0.5798	0.0051	0.5517	0.6045	0.9988	6.2639

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.13.4. Model 3

It was found that when ibuprofen release data from ethylcellulose 4 cP or 100 cP viscosity grade compacts was fitted to model 3 (table 7.19.), the coefficient of determination values were greater or equal to the values determined for model 2 (table 7.18.). In addition, MSC values determined for model 3 were greater than those determined for model 2. However, examination of the relevant model parameters showed that formulations prepared with smallest ethylcellulose 4 cP particle size fraction (40-63 μm) had a negative k_2 constant. This indicated a negative contribution by polymer relaxation to drug release, and confirmed square root of time drug release as the major mechanism of release from this formulation i.e. model 2.

For other formulations prepared with ethylcellulose 4 cP or 100 cP viscosity grade, the values of k_1 and k_2 in table 7.19. can be used to calculate the relative contribution of diffusion release and polymer relaxation to ibuprofen release (Peppas and Sahlin, 1989). In figure 7.8. and figure 7.9. it is evident that for formulations prepared with either ethylcellulose viscosity grade, as the ethylcellulose particle size fraction increased the contribution of Fickian diffusion to ibuprofen release was reduced, while the contribution of polymer relaxation was increased. This became more

evident with time. These results are not surprising since increasing the ethylcellulose particle size fraction in the formulation will allow the dissolution medium to penetrate more easily into the core of the tablet (Lin and Lin, 1996). With time therefore it is possible that the ethylcellulose can hydrate and swell, and provide a less tortuous pathway by which the drug can exit the tablet.

In addition, polymer relaxation contributed more to the mechanism of release from compacts of ethylcellulose 100 cP, than from compacts of ethylcellulose 4 cP for each ethylcellulose particle size fraction. Conversely, Fickian diffusion contributed less to the mechanism of release from ethylcellulose 100 cP compacts than from ethylcellulose 4 cP compacts. This is clearly illustrated in appendix 5.

Table 7.19.

Parameters and statistical estimates of model 3 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of different ethylcellulose particle size fractions

Particle size fraction	**k_1 (%min$^{-0.50}$)**	**Std Dev of k_1**	**k_2 (%min)**	**Std Dev of k_2**	**CoD**	**MSC**
EC4						
40-63 μm	0.9489	0.0224	-0.0013	0.0009	0.9977	5.6991
90-125 μm	1.1540	0.0298	0.0013	0.0011	0.9973	5.6302
180-250 μm	1.2721	0.0252	0.0034	0.0010	0.9990	6.4790
355-500 μm	1.3849	0.0317	0.0047	0.0016	0.9987	6.3163
EC100						
40-63 μm	1.7825	0.0403	0.0057	0.0019	0.9988	6.3240
90-125 μm	1.9523	0.0307	0.0175	0.0017	0.9995	7.1240
180-250 μm	2.1543	0.0224	0.0224	0.0014	0.9998	8.0508
355-500 μm	2.2311	0.0404	0.0288	0.0025	0.9994	7.0251

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

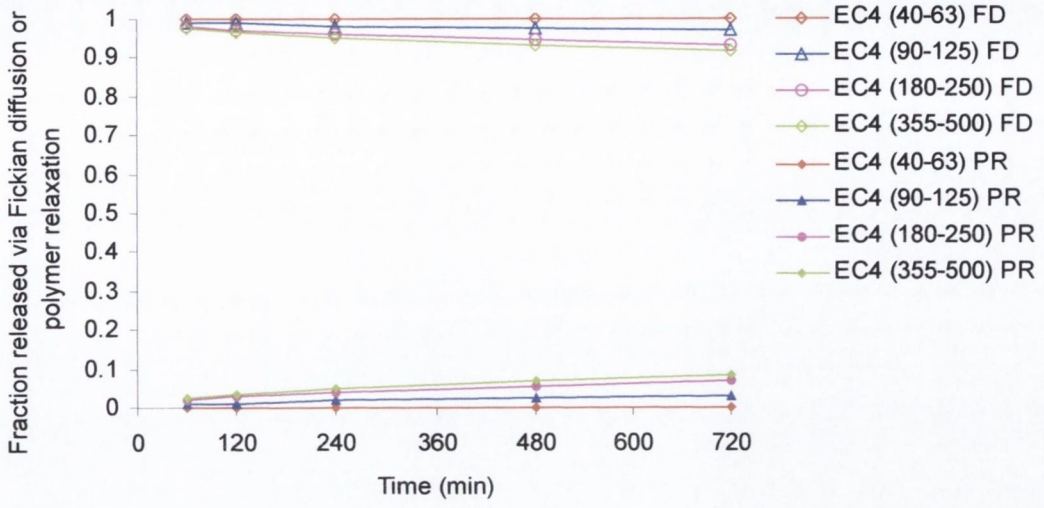

Figure 7.8. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen compacts (50:50 weight ratio). EC4 is ethylcellulose 4 cP viscosity grade. The particle size fraction (μm) is indicated in brackets. .

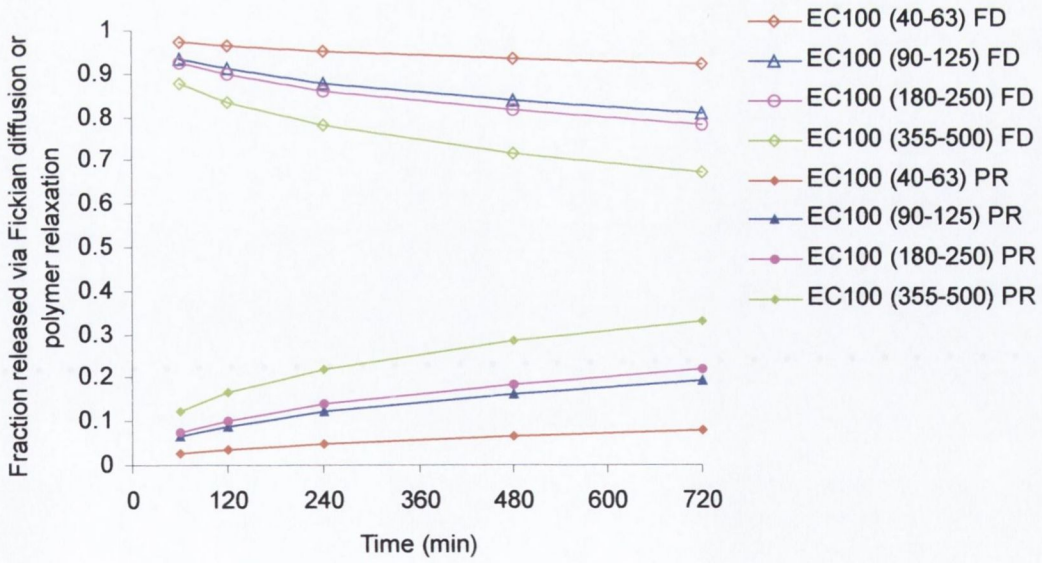

Figure 7.9. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen compacts (50:50 weight ratio). EC100 is ethylcellulose 100 cP viscosity grade. The particle size fraction (μm) is indicated in brackets.

7.13.5. Model 4

Model 4 returned lower MSC values than the previous best-fit model, for all dissolution profiles except the profile from compacts prepared with ethylcellulose 4 cP 40-63 μm particle size fraction (table 7.20.). In addition, the model parameter k_2 converged to zero, or was within the 95% confidence interval. This provided no confidence in the existence of the second term in model 4 and confirmed the previous best-fit model.

Table 7.20.

Parameters and statistical estimates of model 4 fits to ibuprofen release data from ethylcellulose compacts of different ethylcellulose particle size fractions

Particle size fraction	**k_1 ($\%min^{-N}$)**	**Std Dev of k_1**	**k_2 ($\%min^{-2N}$)**	**Std Dev of k_2**	**N**	**Std Dev of N**	**CoD**	**MSC**
EC4								
40-63μm	1.2210	0.1763	0.0287	0.0605	0.4116	0.0260	0.9982	5.9000
90-125μm	1.4972	0.1708	0.0772	0.3529	0.3885	0.0682	0.9973	5.6202
180-250μm	1.5805	0.1999	0.0588	0.1409	0.4112	0.0348	0.9990	6.4782
355-500μm	1.7243	0.2412	0.0782	0.2919	0.4046	0.0562	0.9987	6.2180
EC100								
40-63μm	2.2306	0.2853	0.1052	0.3958	0.4019	0.0057	0.9988	6.3145
90-125μm	2.093	0.4456	0.2262	0.4036	0.3013	0.0077	0.9995	7.1235
180-250μm	2.0155	0.4208	0.2718	0.2948	0.3458	0.0097	0.9998	8.0174
355-500μm	2.4662	0.3005	0.1100	0.3380	0.4407	0.0503	0.9994	7.0250

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.13.6. Model 5

Model 5 provided the best fit to the data, as judged by the very high coefficient of determination and MSC statistical values (table 7.21.). However, it was ruled out because in each case two or more of the model parameters (k_2, k_3 or k_4) converged to zero, and/or displayed a negative sign. Erosion contributed to each of these terms in this model, so the collapse of this model excludes the process of erosion contributing to the release of the active agent from ethylcellulose compacts of different particle size fractions, and of different ethylcellulose viscosity grades.

Table 7.21.

Parameters and statistical estimates of model 5 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of different ethylcellulose particle size fractions

Particle size fraction EC4	k_1 (%min$^{-0.50}$)	k_2 (%min)	k_3 (%min^{-2})	k_4 (%min^{-3})	CoD	MSC
40-63 μm	0.9899 ± 0.0381	-0.0021 ± 0.0046	-1.36E-5 ± 1.03E-5	-1.95E-8 ± 8.45E-9	0.9996	6.9448
90-125 μm	1.2877 ± 0.0350	-0.0095 ± 0.0042	2.63E-6 ± 9.36E-6	-1.03E-8 ± 7.66E-9	0.9997	7.6575
180-250 μm	1.3515 ± 0.0590	-0.0025 ± 0.0071	-2.10E-6 ± 1.58E-5	-1.03E-8 ± 1.30E-8	0.9994	6.8901
355-500 μm	1.4744 ± 0.0620	-0.0008 ± 0.0074	-8.98E-6 ± 1.66E-5	-1.90E-8 ± 1.36E-8	0.9995	6.9999
EC100						
40-63 μm	1.9577 ± 0.0689	-0.0088 ± 0.0082	5.17E-6 ± 1.84E-5	1.14E-8 ± 1.51E-8	0.9996	7.2840
90-125 μm	1.9843 ± 0.0924	0.0088 ± 0.0124	-4.38E-5 ± 3.53E-5	-6.01E-8 ± 3.77E-8	0.9996	7.3050
180-250 μm	2.2830 ± 0.0762	0.0012 ± 0.0114	-8.15E-5 ± 4.16E-5	-1.12E-8 ± 5.73E-8	0.9998	8.1002
355-500 μm	2.2514 ± 0.0889	0.0345 ± 0.0133	-7.53E-5 ± 4.85E-5	1.53E-7 ± 6.68E-7	0.9998	7.9477

CoD: coefficient of determination, MSC: model selection criterion, E-Z = x 10^{-z} where Z is a number, EC4: ethylcellulose 4 Cp, EC100: ethylcellulose 100 cP

7.13.7. Model 6

Model 6 provided an estimation of the contribution of erosion (and no other release mechanisms) to the release of ibuprofen from ethylcellulose matrix compact formulated with different ethylcellulose particle size fractions (table 7.22.). The low values of the coefficient of determination and MSC indicated a poor model fit. This was confirmed by visual inspection since the compacts remained intact during the course of dissolution, making it unlikely that erosion was the sole contributing drug release mechanism.

Table 7.22.

Parameters and statistical estimates of model 6 fits to ibuprofen release data from ethylcellulose:ibuprofen compacts (50:50 weight ratio) of different ethylcellulose particle size fractions

Particle size fraction	k_1	Std Dev	CoD	MSC
Ethylcellulose 4 cP				
40-63μm	0.00016	1.30E-5	0.6938	1.0500
90-125 μm	0.00020	1.62E-5	0.7473	1.2423
180-250 μm	0.00025	1.80E-5	0.7823	1.3913
355-500 μm	0.00028	1.98E-5	0.7977	1.4648
Ethylcellulose 100 cp				
40-63μm	0.00038	2.68E-5	0.8213	1.5888
90-125 μm	0.00051	3.09E-5	0.8849	2.0189
180-250 μm	0.00063	3.79E-5	0.8886	2.0409
355-500 μm	0.00069	3.99E-5	0.9038	2.1872

Std Dev: standard deviation, CoD: coefficient of determination, MSC: model selection criterion

7.14. CONCLUSION

Our studies found that the compaction pressure did not affect either the porosity or tensile strength of compacts prepared at different compaction pressures. This would suggest that the compacts have reached their maximum tensile strength and porosity under these experimental conditions, and is reflected in the constancy of the ibuprofen release rate. Results also showed that compacts prepared with ethylcellulose 100 cP viscosity grade had greater porosity, lower tensile strength and higher release rates than compacts prepared with ethylcellulose 4 cP viscosity grade. This was explained on the basis that compacts of higher viscosity grades were less compressible, and would facilitate quicker drug release.

Using a constant compression force, it was found that increasing the compact ethylcellulose median particle size caused a decrease in tensile strength. Since an increase in ethylcellulose particle size decreases the theoretical number of contact points in the powder, it was reasonable to conclude that the number of interaction points or the bonding surface areas governs the compact tensile strength. Characterisation of compacts prepared using the different particle size of ethylcellulose and consistent compression forces also revealed that the initial and total porosity had a tendency to increase with an increase in ethylcellulose particle size.

This increase in porosity results in a faster drug release and a concomitant decrease in the tortuosity value. In addition it was found that compacts prepared with the lower ethylcellulose viscosity grade were more compressible than compacts prepared with the higher ethylcellulose viscosity grade, resulting in compacts of lower porosity, higher tensile strength and slower drug release rates.

One of the objectives of this chapter was to determine the best model fit to data from ethylcellulose matrix compacts of different ethylcellulose particle size fractions (and of different viscosity grades). The effect of ethylcellulose particle size fraction and ethylcellulose viscosity grade on the different model exponents was also examined.

The square root of time model provided a good model fit to the dissolution data. This was because it is based on the assumption that drug diffusion is the primary release mechanism. It was clear that as the ethylcellulose particle size fraction increased in the formulation, the ibuprofen release rate also increased. This was evident for compacts prepared with either ethylcellulose viscosity grade. The percentage release rate was also greater from compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP, for each particle size fraction examined. Model 2 provided a better fit to release data from compacts prepared with different ethylcellulose particle size fractions (of either ethylcellulose 4 cP or 100 cP viscosity grade) than model 1. As the ethylcellulose particle size fraction increased in formulations the exponent N appeared to increase. This suggests that as the ethylcellulose particle size decreased the release became progressively controlled by diffusion. In addition, the diffusional exponent N was higher for compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP, for each particle size fraction formulation. Model 3 provided a better fit than model 2 to ibuprofen release data, except for the release data from compacts prepared with the smallest ethylcellulose 4 cP particle size fraction (40-63 μm). This model considered an additional mechanism of drug release i.e. polymer relaxation and was confirmed as the best model fit by the collapse of model 5 and the DRE model, and the poor fit of the erosion model.

CHAPTER 8

EFFECT OF ACID EXCIPIENTS ON THE RELEASE OF IBUPROFEN FROM ETHYLCELLULOSE COMPACTS

8.1. INTRODUCTION

Work undertaken by Healy (1995) showed that ibuprofen dissolution profiles from mixed ibuprofen:acid excipient compressed discs had a positive curvature, the extent of which depended on the excipient used and the acid excipient:ibuprofen weight fraction ratio in the disc. It was thought that by matching the positive curvature of the acid drug dissolution profiles as observed from single surface compressed discs to the downward curvature of the acid drug dissolution from ethylcellulose matrix compacts, zero order drug release could be approached.

The dissolution of ibuprofen from compressed ethylcellulose discs containing various acid excipients in phosphate buffer pH 7.4 was examined. One of three different acid excipients was used in each formulation and the acid excipient:ibuprofen weight ratios of one of the acid excipients was varied. Previous work by Healy (1995) showed that the porous layer that develops (during dissolution) at the surface of a two-component acid excipient:ibuprofen compressed disc played an important role in determining ibuprofen dissolution behaviour. The structure of this porous layer was affected by the particle size of the acid excipient. Therefore, the effect of altering the acid excipient particle size on ibuprofen dissolution from ethylcellulose matrix compacts was also investigated.

In addition, the square root of time model (model 1) and model 2 were fitted to the various release studies. Parameters were generated and statistical analysis used to determine the best model fit. In addition, the diffusional exponent in model 2 was used to clarify the drug/acid excipient release mechanism in the formulation.

8.2. DIFFERENTIAL SCANNING CALORIMETRY ANALYSIS

The DSC thermograms of ethylcellulose, ibuprofen, acid excipients (adipic acid, succinic acid and L-(+)-tartaric acid) and their physical mixtures are shown in appendix 3. The melting point onset, peak melting temperature, and normalised energy value of melting of different powders and their mixtures are also tabulated in appendix 3.

The ibuprofen melting point (onset and peak) and normalised energy values of melting were unaffected by the presence of any of the acid excipients in 50:50 physical mixtures. However, the melting point (onset and peak) and normalised

energy values of melting, of adipic acid and succinic acid were affected by the presence of ibuprofen. In mixtures of L-(+)-tartaric acid:ibuprofen, the peak melting point and normalised energy of melting of the L-(+)-tartaric acid component were slightly lowered. (The onset of L-(+)-tartaric acid melting was unaffected by the presence of the ibuprofen.) The lowering of the acid excipient melting point and normalised energy values may be caused by the acid excipient component (in physical mixtures of acid excipient:ibuprofen) melting in the presence of melted ibuprofen, which has a lower melting point than any of the acid excipients examined.

The ethylcellulose did not affect the peak melting point of adipic acid, but it did cause broadening of the peak or lowering of the onset melting temperature of adipic acid. This was reflected in a lowering of the normalised melting energy value. In mixtures of ethylcellulose:succinic acid, the ethylcellulose affected the onset and peak melting point, and normalised energy values of melting of succinic acid powder. In mixtures of ethylcellulose 4 cP:L-(+)-tartaric acid, the ethylcellulose 4 cP caused a lowering of the onset and peak melting point, and normalised melting energy value of L-(+)-tartaric acid. In mixtures of ethylcellulose 100 cP:L-(+)-tartaric acid, the ethylcellulose 100 cP caused a lowering of the peak melting point and normalised energy of melting of the L-(+)-tartaric acid powder. The effect of ethylcellulose on the melting behaviour of acid excipients may be because the acid excipient component was melting in the presence of liquid ethylcellulose. This is because the T_g of ethylcellulose (of either viscosity grade) was lower than the melting temperature of the acid excipient component of the physical mixtures of ethylcellulose:acid excipient.

The melting points (and normalised energy values) of acid excipients in mixtures of ethylcellulose:acid excipient:ibuprofen were lowered.

8.3. PARTICLE SIZE ANALYSIS

The particle size distribution of the various acid excipients are outlined in table 8.1. The particle size distribution of ibuprofen and ethylcellulose 4 cP or 100 cP viscosity grade powder has been previously outlined in chapter 5 section 6.

Table 8.1.

Particle size distribution of acid excipient powders of different particle size fractions as determined using a dry powder method with a laser diffraction particle size analyser

Powder	D[v,0.1] (μm)	D[v,0.5] (μm)	D[v,0.9] (μm)
Adipic acid (<180 μm)[a]	11.19	57.41	151.29
Adipic acid (<40 μm)[b]	5.14	17.61	48.61
Succinic acid (<180 μm) [a]	11.64	75.57	205.24
Succinic acid (<40 μm) [b]	7.22	30.87	93.64
L-(+)-tartaric acid (<180 μm) [b]	12.93	72.09	193.49
L-(+)-tartaric acid (<40 μm) [b]	5.49	18.90	47.72

[a] determined using a Malvern 2600c laser diffraction particle size analyser

[a] determined using a Malvern Mastersizer 2000 with a Scirocco dry powder feeder

8.4. CHARACTERISATION OF ETHYLCELLULOSE:ACID EXCIPIENT:IBUPROFEN COMPACTS

Ethylcellulose powder of either low or high viscosity grade i.e. ethylcellulose 4 cP or 100 cP was used to prepare discs. Work previously undertaken showed that matrix compacts of either ethylcellulose 4 cP or ethylcellulose 100 cP powder and ibuprofen had a bicoherent system between 35-60% w/w ethylcellulose content (chapter 6.6.2.). Outside of these ethylcellulose content levels either one of the two components (ibuprofen or ethylcellulose) was not percolating the system. Therefore, it was decided to prepare formulations with a constant ethylcellulose content of 50% w/w since this represented a percolating system. Ibuprofen powder and one of three different acid excipients (adipic acid, succinic acid or L-(+)-tartaric acid) were used in the disc formulation in a polymer:acid excipient:drug weight ratio of 50:25:25. In addition the succinic acid:ibuprofen weight ratio of the formulation was varied, as well as the acid excipient particle size fraction.

8.4.1. Height

The height of compacts prepared with acid excipient was less than the height of compacts prepared without acid excipient, for compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade (50% w/w) (table 8.2.). If one uses height as an indicator of consolidation (Vromans and Lerk, 1988) this would

suggest that compacts prepared with acid excipient are more consolidated than compacts prepared without acid excipient. Leuenberger and Rohera (1986) established that the mechanism of compaction is largely influenced by the powder properties, including surface characteristics, frictional properties and the particle size of the particles. These factors may account for the apparent reduction in compact height (and implied increased consolidation).

The height of compacts prepared with ethylcellulose 4 cP powder was also less than the height of compacts prepared with ethylcellulose 100 cP powder, for each of the different formulations examined. This was in agreement with previous findings, which found that compacts of ethylcellulose 4 cP had consistently lower height measurements than compacts prepared with ethylcellulose 100 cP (chapter 5.7.1.).

Table 8.2.

Characterisation of ethylcellulose:ibuprofen compacts prepared with and without acid excipient of different ethylcellulose viscosity grades.

EC (50% w/w)	Height (cm)	ε_0	ε_d	ε_{AE}	ε	Hardness (kg)	Tensile strength kg/cm^2
EC4							
AE: IB 0:50	0.170	0.0194	0.4979	NA	0.5173	11.64 ± 0.65	33.53 ± 1.87
SA: IB 25:25	0.155	0.0016	0.2734	0.1950	0.4700	12.84 ± 0.44	40.58 ± 1.40
SA: IB 30:20	0.155	0.0173	0.2187	0.2340	0.4700	12.81 ± 0.21	40.47 ± 0.67
SA: IB 35:15	0.150	0.0017	0.1693	0.2818	0.4528	13.05 ± 0.27	42.60 ± 0.88
SA: IB 40:10	0.150	0.0178	0.1129	0.3221	0.4528	13.39 ± 0.16	43.71 ± 0.51
AA: IB 25:25	0.160	0.0051	0.2645	0.2175	0.4871	12.98 ± 0.39	39.73 ± 1.18
TA: IB 25:25	0.155	0.0231	0.2734	0.1735	0.4700	13.12 ± 0.36	41.44 ± 1.13
SA: IB PS*	0.155	0.0016	0.2734	0.1950	0.4700	13.63 ± 0.06	43.05 ± 0.19
AA: IB PS*	0.160	0.0035	0.2649	0.2178	0.4863	13.66 ± 0.10	41.80 ± 0.32
TA: IB PS*	0.155	0.0223	0.2736	0.1737	0.4695	13.73 ± 0.12	43.37 ± 0.37
EC100							
AE: IB 0:50	0.175	0.0463	0.4837	NA	0.5300	8.69 ± 0.51	24.30 ± 1.42
SA: IB 25:25	0.160	0.0328	0.2645	0.1887	0.4860	10.37 ± 0.33	31.72 ± 1.00
SA: IB 30:20	0.160	0.0479	0.2116	0.2265	0.4860	10.47 ± 0.24	32.03 ± 0.72
SA: IB 35:15	0.155	0.0326	0.1639	0.2728	0.4693	10.74 ± 0.16	33.92 ± 0.49
SA: IB 40:10	0.155	0.0479	0.1093	0.3119	0.4691	10.87 ± 0.21	34.35 ± 0.67
AA: IB 25:25	0.165	0.0341	0.2565	0.2109	0.5015	10.33 ± 0.24	30.66 ± 0.70
TA: IB 25:25	0.160	0.0536	0.2645	0.1679	0.4860	10.43 ± 0.26	31.93 ± 0.79
SA: IB PS*	0.160	0.0312	0.2649	0.1890	0.4852	10.98 ± 0.16	33.59 ± 0.48
AA: IB PS*	0.165	0.0325	0.2570	0.2112	0.5007	11.04 ± 0.06	32.78 ± 0.18
TA: IB PS*	0.160	0.0521	0.2649	0.1682	0.4852	10.92 ± 0.11	33.44 ± 0.33

ε_0: initial porosity, ε_d: porosity due to drug, ε_{AE} : porosity due to acid excipient, ε: total porosity

IB: ibuprofen, EC4: ethylcellulose 4 cP, EC100: ethylcellulose 100 cP, AE: acid excipient, AA: Adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, NA: not applicable, PS: acid excipient sieved less than 40 μm was used during formulation, * ethylcellulose:succinic acid:ibuprofen weight ratio of 50:25:25.

8.4.2. Porosity

Streubel et *al.* (2000) proposed that the addition of organic acids to ethylcellulose tablets prepared with a basic drug, might affect the tablet initial porosity. He suggested that this might subsequently influence the drug release rate.

The total porosity referred to in table 8.2. refers to the porosity of the leached portion of the tablet and is equal to the porosity due to air (initial porosity) and porosity due to

ibuprofen content and acid excipient content. The initial porosity is calculated from the difference in the apparent and true volume. The true volume is calculated knowing the true density of each powder component (chapter 5.7.2. and table 8.3.). Porosity due to drug or acid excipient content corresponds directly to the volume of free space previously occupied by the extracted component. The initial porosity of ethylcellulose compacts prepared with succinic acid:ibuprofen, or adipic acid:ibuprofen of 25:25 weight ratio was less than the initial porosity of compacts prepared with ethylcellulose:ibuprofen 50:50 weight ration, for compacts of either ethylcellulose viscosity grade. However, the initial porosity of compacts prepared with L-(+)-tartaric acid:ibuprofen of 25:25 weight was slightly greater than initial porosity of compacts prepared with ethylcellulose:ibuprofen 50:50 weight ratio. This may be accounted for by the different compressibility and compactibility of the acid excipient powders.

The initial porosity of formulation prepared with ethylcellulose 4 cP was less than the initial porosity of formulation prepared with ethylcellulose 100 cP for each different acid excipient:ibuprofen formulation examined. This was in agreement with previous findings (chapter 5.7.2.).

Table 8.3.

*Density measurements of acid excipients**

Acid Excipient	Density (mg/cm^3)
Adipic acid	1353.1
Succinic acid	1559.3
L-(+)-tartaric acid	1752.5

*Healy (1995)

8.4.3. Tensile strength

Previous work by Streubel *et al.* 2000 proposed that the addition of a third component (hydroxypropyl methylcellulose acetate succinate) to an ethylcellulose:basic drug system might affect the compaction behaviour of ethylcellulose, which might affect the basic drug release rate. Therefore, the hardness of the compacts prepared with and without acid excipient was measured and the tensile strength calculated (table 8.2.). Results showed that the tensile strength of compacts which included acid excipient was significantly greater ($p \leq 0.05$) than the tensile strength of compacts prepared

without acid excipient, at the same ethylcellulose weight fraction i.e. 50% w/w. This was evident for formulations prepared with either ethylcellulose viscosity grade and was confirmed using two sample t-tests, assuming equal variance. Fell (1996) stated that there is an implicit assumption that the strength of a compact is a reflection of the bonding that has occurred during compaction. The relative magnitude of bonds between the different tablet components may determine the pattern of tablet strength results obtained and are influenced by various powder characteristics. Our results suggest that the addition of the acid excipient component to compacts of ethylcellulose:ibuprofen increases the bonding during compaction and subsequently the compact tensile strength.

The tensile strength of ethylcellulose 4 cP compacts prepared with different acid excipients (sieved less than 180 μm) at an acid excipient:ibuprofen weight ratio of 25:25, were not significantly different from each other. Indeed, the tensile strength of compacts prepared with ethylcellulose 4 cP:succinic acid (<180 μm):ibuprofen 50:25:25 weight ratio was not significantly different ($p \leq 0.05$) from the tensile strength of compacts prepared with ethylcellulose 4 cP:succinic acid:ibuprofen 50:30:20, or 50:35:15 weight ratio. However, the tensile strength of ethylcellulose 4 cP:succinic acid (<180 μm):ibuprofen compacts of 50:25:25 weight ratio was significantly less ($p \leq 0.05$) than the tensile strength of ethylcellulose 4 cP:succinic acid:ibuprofen compacts of 50:40:10 weight ratio. The tensile strength of ethylcellulose 4 cP:succinic acid:ibuprofen compacts of 50:30:20 weight ratio was significantly lower ($p \leq 0.05$) than the tensile strength of ethylcellulose 4 cP:succinic acid:ibuprofen compacts of 50:35:15 and 50:40:10 weight ratio. The tensile strength of ethylcellulose:succinic acid:ibuprofen compacts of 50:35:15 weight ratio was not significantly different ($p \leq 0.05$) from the tensile strength of ethylcellulose 4 cP:succinic acid:ibuprofen compacts of 50:40:10 weight ratio. This was confirmed using a two-sample t-test, assuming equal variance. These results indicate that increasing the acid excipient content in ethylcellulose 4 cP formulations resulted in an increase in the compact tensile strength.

Similar results were found for compacts prepared with ethylcellulose 100 cP viscosity grade. The tensile strengths of ethylcellulose 100 cP compacts prepared with different acid excipients (sieved less than 180 μm) at an acid excipient:ibuprofen weight ratio of 25:25, were not significantly different ($p \leq 0.05$) from each other. The tensile strength of compacts prepared with ethylcellulose 100 cP:succinic acid (< 180

μm):ibuprofen 50:25:25 weight ratio was not significantly different ($p \leq 0.05$) from the tensile strength of compacts prepared with ethylcellulose 100 cP:succinic acid:ibuprofen of 50:30:20 weight ratio, but was significantly less ($p \leq 0.05$) than the tensile strength of ethylcellulose 100 cP compacts prepared with a succinic acid:ibuprofen 35:15, and 40:10 weight ratio. The tensile strength of ethylcellulose 100 cP:succinic acid:ibuprofen compacts of 50:30:20 weight ratio was significantly less ($p \leq 0.05$) than the tensile strength of ethylcellulose 100 cP:succinic acid:ibuprofen compacts of 50:35:15 and 50:40:10 weight ratio. However, the tensile strength of ethylcellulose 100 cP:succinic acid:ibuprofen compacts of 50:35:15 weight ratio was not significantly different ($p \leq 0.05$) from the tensile strength of ethylcellulose 100 cP:succinic acid:ibuprofen compacts of 50:40:10 weight ratio. This was confirmed using a two sample t-tests, assuming equal variance. These results confirm earlier findings, which found that increasing the succinic acid content in an ethylcellulose matrix compact resulted in an increased compact tensile strength.

The tensile strength of compacts prepared with the acid excipient sieved less than 40 μm was significantly greater ($p \leq 0.05$) than the tensile strength of compacts prepared with acid excipient sieved less than 180 μm. This was evident for compacts prepared with either ethylcellulose 4 cP or 100 cP viscosity grade and was confirmed using two-sample t-tests, assuming equal variance. This was readily explained. The lower median particle size of the acid excipient sieved less than 40 μm meant there were a greater number of contact points in the compact for interparticulate bonding, which resulted in compacts of higher tensile strength. This was established by Rhine (1947). He showed that smaller particles allow greater packing density and a greater number of contact points for interparticulate bonding. This was reaffirmed by results which showed that the initial porosity of compacts prepared with acid excipient sieved less than 40 μm was less than or equal to the initial porosity of compacts prepared with acid excipient sieved less than 180 μm (table 8.2.).

There was a significant difference ($p \leq 0.05$) in the tensile strength of compacts prepared with ethylcellulose 4 cP powder and ethylcellulose 100 cP powder for each ethylcellulose:acid excipient:ibuprofen formulation examined. This was confirmed using a two-sample t-test, assuming equal variance. Previous work in this thesis has demonstrated that lower viscosity grades of ethylcellulose were more compactible than the higher ethylcellulose viscosity grades, resulting in compacts of higher tensile strength (chapter 5.7.3.).

8.5. RELEASE OF ACID EXCIPIENTS AND IBUPROFEN FROM ETHYLCELLULOSE COMPACTS

8.5.1. Release of different acid excipients and ibuprofen from ethylcellulose:acid excipient:ibuprofen compacts

The effect of different acid excipients on ibuprofen release from ethylcellulose:acid excipient:ibuprofen matrix compacts was examined. The release of acid excipient from ethylcellulose:acid excipient:ibuprofen compacts was also measured. The acid excipients used during formulation were adipic acid, succinic acid and L-(+)-tartaric acid. Compacts were prepared using one of two different ethylcellulose viscosity grades (4 cP or 100 cP). Initially, an ethylcellulose:acid excipient:ibuprofen weight ratio of 50:25:25 was used in the disc formulation.

Figures 8.1. and 8.2. show the percentage acid excipient released from compacts prepared with different acid excipients, and ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade. The greatest percentage acid excipient release was from compacts prepared with the most soluble L-(+)-tartaric acid, while the lowest acid excipient release rate was from compacts prepared with the least soluble adipic acid. (Table 1.1. in chapter one outlines the solubilities and pK_as of the different acid excipients.) This was evident for compacts prepared with either ethylcellulose 4 cP or 100 cP viscosity grade.

Examination of the initial and limiting acid excipient release rates in table 8.4. showed that the initial release rate was greater than the limiting release rate for each of the different formulations examined. (The initial release rate was taken to be the average release rate of excipient at 15 minutes and 30 minutes, while the limiting release rate was the release rate at the end of the dissolution study i.e. 720 minutes or as otherwise indicated). This was evident in the downward release profile of the acid excipient release profile. This can be explained by the initial dissolution of the acid excipient from the superficial layers of the compacts (Pather *et al.*, 1998). As dissolution proceeded the acid excipient traversed increasing distances in the matrix compact to reach the external dissolution medium. Therefore, the decreasing rate of acid excipient was a result of the increasing distance that was travelled by the dissolution medium and acid excipient molecules into and out of the compact, respectively. It was also noteworthy that the I (initial) :L (limiting) acid excipient ratio appeared to

reduce with increasing acid excipient solubility, L-(+)-tartaric acid having the smallest I:L (acid excipient) ratio and adipic acid having the greatest I:L (acid excipient) ratio. This was evident for formulations prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade. Neau *et al.* (1999) showed that the aqueous solubility of a drug could influence the mechanism of drug release from polymer matrix compacts. They showed that at low drug loading of highly soluble drugs, there were additional mechanisms of drug release (in addition to diffusion) and the contribution of additional mechanism of drug release was reduced with decreasing drug solubility. This was explained on the basis that the more soluble drugs would encourage greater water penetration into the core of the ethylcellulose tablet. Therefore, with time ethylcellulose could hydrate and swell, providing a less tortuous pathway by which the drug can exit the tablet. This was reflected in the I:L acid excipient ratio.

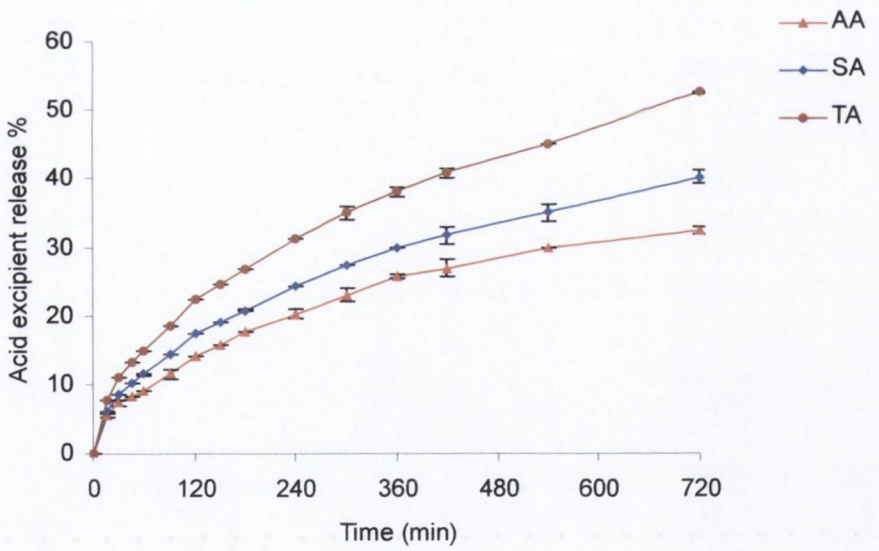

Figure 8.1. Percentage acid excipient release from ethylcellulose 4 cP:acid excipient:ibuprofen (50:25:25 weight ratio) compacts. AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid.

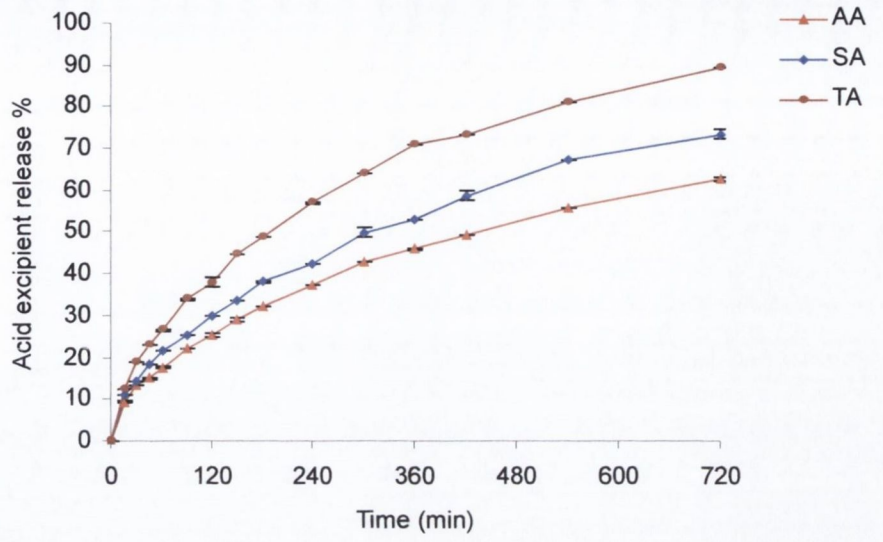

Figure 8.2. Percentage acid excipient release from ethylcellulose 100 cP:acid excipient:ibuprofen (50:25:25 weight ratio) compacts. AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid.

Table 8.4.

Initial and limiting acid excipient dissolution rates from ethylcellulose:acid excipient:ibuprofen compacts of 50:25:25 weight ratio

Dissolution rate ($mg/min/cm^2$) Ethylcellulose 4 cP	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
Initial (I)	0.0575	0.0662	0.0834
Limiting (L)	0.0085	0.0106	0.0138
Ratio (I:L)	6.7773	6.2344	6.0243
Ethylcellulose 100 cP			
Initial (I)	0.1003	0.1136	0.1381
Limiting (L)	0.0164	0.0193	0.0235
Ratio (I:L)	6.1268	5.8892	5.8764

Figures 8.3. and 8.4. show the percentage ibuprofen released from matrix compacts prepared with different acid excipients (ethylcellulose:acid excipient:ibuprofen 50:25:25 weight ratio) and formulated with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade. Figures 8.3. and 8.4. also show ibuprofen release from

compacts prepared with no acid excipient, and an ethylcellulose:ibuprofen 75:25 weight ratio i.e. the same drug load as the three component ethylcellulose:acid excipient:ibuprofen compacts. It was found that the percentage ibuprofen release was greater from compacts prepared with acid excipient than from compacts prepared with an ethylcellulose:ibuprofen 75:25 weight ratio. Although the drug concentration in both types of compacts was constant, the matrix level in the compact containing the acid excipient was decreased and the soluble component of the compact increased. The diffusion of drugs from an inert heterogeneous matrix occurs in the space previously occupied by the soluble component and air (Baker, 1987). Therefore, an increase in the soluble proportion in the ethylcellulose compact (which was accompanied by a decrease in the inert matrix concentration) resulted in an increase in the drug release rate.

Figures 8.3. and 8.4. also show ibuprofen release from compacts with the same ethylcellulose weight fraction as compacts containing acid excipient i.e. ethylcellulose 50% w/w weight ratio. For formulations prepared with either ethylcellulose viscosity grade, the percentage ibuprofen release was lower from compacts prepared with acid excipient than from compacts prepared with an ethylcellulose:ibuprofen 50:50 weight ratio. For compacts prepared with acid excipient, the percentage ibuprofen release was lowest from compacts prepared with L-(+)-tartaric acid and greatest from compacts prepared with adipic acid. This was evident for compacts prepared with either ethylcellulose viscosity grade.

The initial and limiting ibuprofen dissolution rates from compacts prepared with and without acid excipient (for both ethylcellulose viscosity grades) are tabulated in table 8.5. The initial ibuprofen dissolution rate was greater than the limiting ibuprofen dissolution rate in each instance. This can be explained by the initial dissolution of the drug from the superficial layers of the compacts, and the increasing distances that must be travelled by both buffer and drug in and out of the compact as dissolution proceeds (Pather *et al.*, 1998). Compacts prepared with acid excipient had a lower I:L (ibuprofen) ratio than compacts prepared without acid excipient. In fact, compacts prepared with L-(+)-tartaric acid had the lowest I:L (ibuprofen) ratio, followed by compacts prepared with succinic acid and adipic acid. This was evident for matrix compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grades.

Streubel *et al.* (2000) showed that the addition of organic acids (fumaric acid, sorbic acid and adipic acid) to an ethylcellulose matrix system maintained a low pH value within the tablet core during basic drug release in phosphate buffer pH 6.8. Thus, the microenvironmental conditions remained almost constant. It was also observed that during basic drug release in hydrogel matrix systems the tablet core remained acidic due to the presence of organic acids. However, as dissolution proceeded the pH nearing the edges of the tablet increased, due to organic acid dissolution (Streubel *et al.*, 2000). Healy (1995) also showed that as the acid excipient receded from the surface of two component acid excipient:ibuprofen compressed discs, there was a rise in pH at the surface-liquid interface. This in turn led to an increase in both ibuprofen solubility and ibuprofen dissolution rate as dissolution proceeded.

As acid excipient dissolution proceeded in formulations of ethylcellulose:acid excipient:ibuprofen, it was expected that the ibuprofen solubility and resulting dissolution rate would increase. In addition, as the acid excipient dissolved it was expected that the porosity of the ethylcellulose compact would increase, resulting in a (further) increase in the ibuprofen dissolution rate. The proposed increase in the ibuprofen dissolution rate will act to balance the increased distance that must be traversed by the solution and drug molecules into and out of the tablet, respectively. This accounts for the reduction in the I:L ibuprofen ratio between compacts prepared with ethylcellulose:ibuprofen 50:50 weight ratio, and compacts prepared with ethylcellulose:acid excipient:ibuprofen 50:25:25 weight ratio.

In addition, Healy (1995) showed that the greater the solubility of the acid excipient the greater the suppression and curvature of the ibuprofen release profile from two component acid exipient:ibuprofen systems. (The degree of curvature was measured as the difference between the initial and limiting ibuprofen dissolution rate.) This was explained on the basis that the greater the acid excipient solubility the greater the concentration of excipient that will be in solution adjacent to the disc surface, thereby retarding drug dissolution from the surface. Therefore, the greater the solubility of the acid excipient in ethylcellulose:acid excipient:ibuprofen compacts, the greater the concentration of acid excipient that was in solution adjacent to the surface of the compacts thereby retarding ibuprofen dissolution. In addition, it was expected that the greater the solubility of the acid excipient the greater the increase in porosity as the acid excipient dissolved, resulting in an increase in the ibuprofen dissolution rate.

This was reflected in the I:L ibuprofen ratio, which was lowest for compacts prepared with L-(+)-tartaric acid, followed by succinic acid and adipic acid.

For each formulation examined, percentage ibuprofen release and acid excipient release were greater for compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP viscosity grade. In addition there was a greater difference in the initial and limiting ibuprofen release rates for compacts prepared with ethylcellulose 4 cP than for compacts prepared with ethylcellulose 100 cP. This was in agreement with work undertaken in chapter 6.2.2. This showed that the dissolution medium and drug must traverse a more tortuous pathway into and out of ethylcellulose 4 cP compacts, as compared to compacts prepared with ethylcellulose 100 cP.

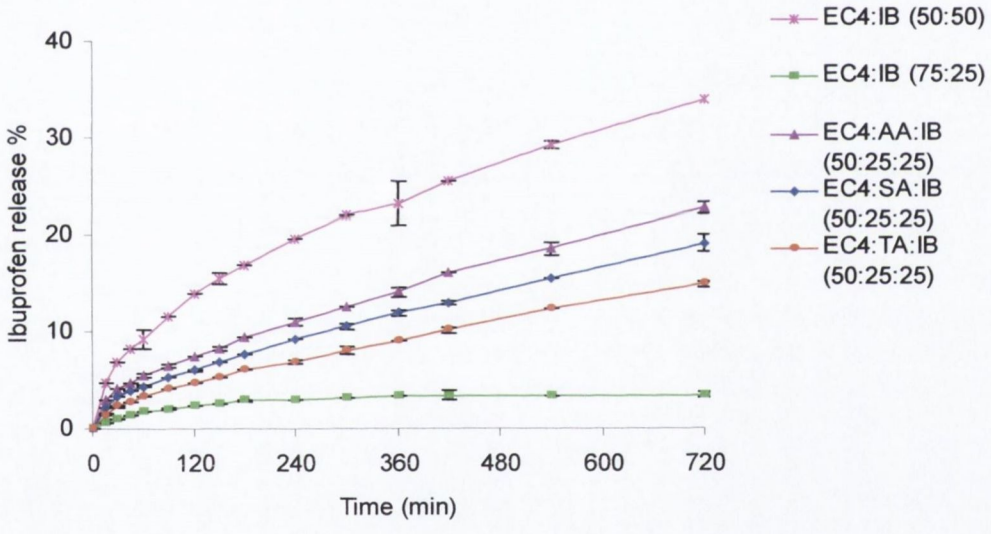

Figure 8.3. Percentage ibuprofen release from ethylcellulose 4 cP compacts prepared with and without acid excipient. Ethylcellulose 4 cP: EC4, AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, IB: ibuprofen. The weight ratio is indicated in brackets.

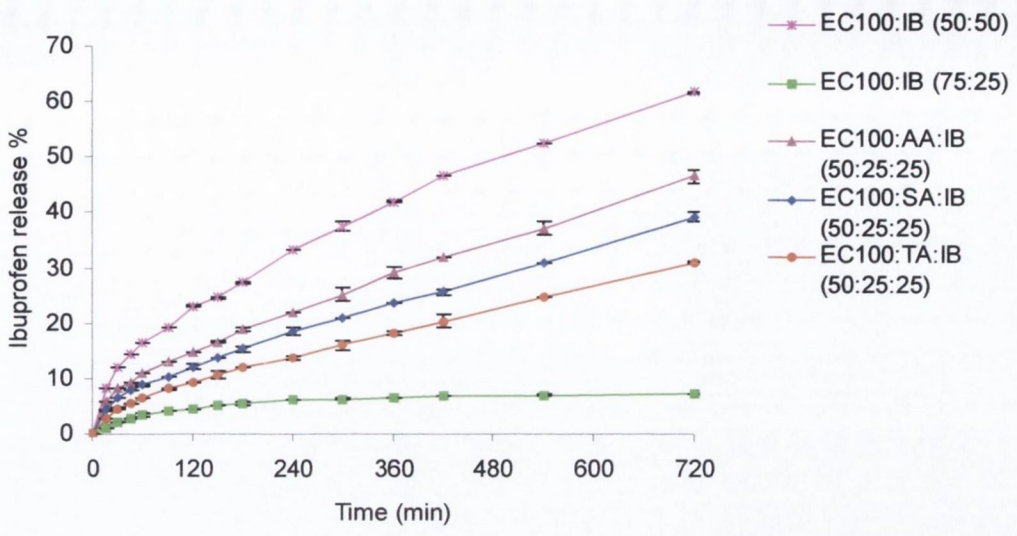

Figure 8.4. Percentage ibuprofen release from ethylcellulose 100 cP compacts prepared with and without acid excipient. Ethylcellulose 100 cP: EC100, AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, IB: ibuprofen. The weight ratio is indicated in brackets.

Table 8.5.

Initial and limiting ibuprofen dissolution rates from ethylcellulose:acid excipient:ibuprofen compacts of 50:25:25 weight ratio, and ethylcellulose:ibuprofen compacts of 50:50 weight ratio and 75:25 weight ratio

Dissolution rate ($mg/min/cm^2$)	**No excipient EC 25% w/w**	**No excipient EC 50% w/w**	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
EC4					
Initial (I)	0.0067	0.1024	0.0317	0.0243	0.0165
Limiting (L)	0.0009	0.0176	0.0060	0.0050	0.0039
Ratio (I:L)	7.5537	5.8099	5.3059	4.8326	4.2212
EC100					
Initial (I)	0.0132	0.1766	0.0631	0.0483	0.0328
Limiting (L)	0.0018	0.0318	0.0121	0.0103	0.0081
Ratio (I:L)	7.1771	5.5612	5.1974	4.6963	4.0289

EC4: ethylcellulose 4 cP, EC100: ethylcellulose 100 cP

8.5.2. Effect of succinic acid:ibuprofen weight ratio on acid excipient and ibuprofen release from ethylcellulose compacts

It was decided to investigate the effect of increasing the acid excipient:ibuprofen weight ratio of the moderately soluble organic acid, succinic acid in ethylcellulose compacts. Previously, when one compared ibuprofen release from matrix compacts containing the different organic acids, it was found that discs containing adipic acid showed the greatest ibuprofen release rate (and the highest I:L ratio) compared with those containing succinic acid or L-(+)-tartaric acid. In addition, it was thought that the very soluble acid L-(+)-tartaric acid might diffuse too rapidly through the matrix compacts at higher acid excipient:drug weight ratios.

Additional compacts were prepared with an ethylcellulose:succinic acid:ibuprofen weight ratio of 50:30:20, 50:35:15 and 50:40:10 and the relevant release studies undertaken. Figure 8.5. and figure 8.6. show the percentage succinic acid release from compacts prepared with ethylcellulose 4 cP or 100 cP viscosity grade, and of varying succinic acid:ibuprofen weight ratio. In each case, the acid excipient dissolution profile showed a downward curvature because the acid excipient initial release rate was greater than the limiting release rate. This has been previously explained. It was clear that for compacts prepared with either ethylcellulose viscosity grade, increasing the formulation succinic acid content resulted in an increase in the percentage succinic acid release.

Table 8.6. shows the relevant acid excipient initial and limiting release rates. It was evident that as the succinic acid content increased the difference between the initial and limiting dissolution rate showed a tendency to decrease. This was evident for formulations prepared with either ethylcellulose viscosity grade. Foster and Parrott (1990a) showed that an increase in the drug release rate was attributed to an increase in drug concentration, resulting in an increase in porosity and a concomitant decrease in tortuosity. This may explain the resulting increase in succinic acid release rate with increasing concentration, and the resulting decrease in I:L acid excipient ratio.

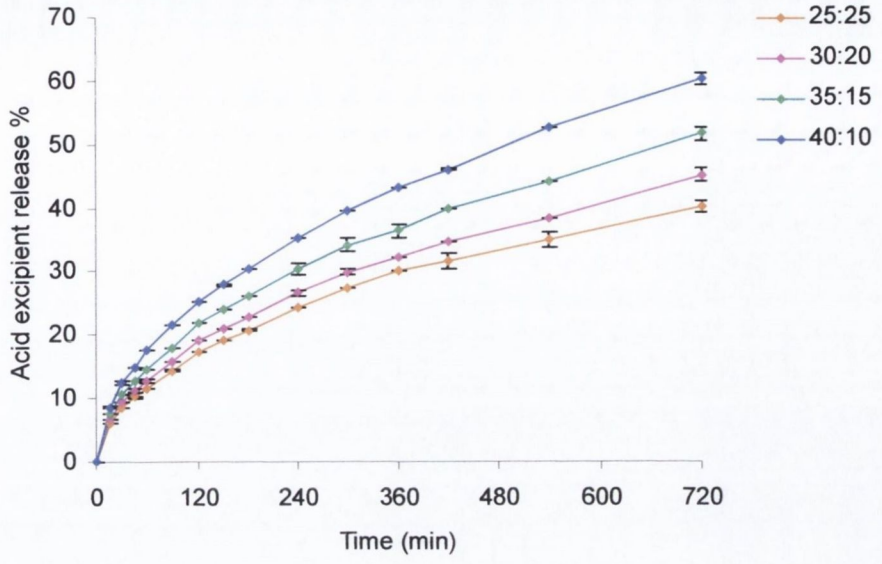

Figure 8.5. Percentage succinic acid release from ethylcellulose 4 cP:succinic acid:ibuprofen compacts prepared with different succinic acid:ibuprofen weight ratios (indicated in legend).

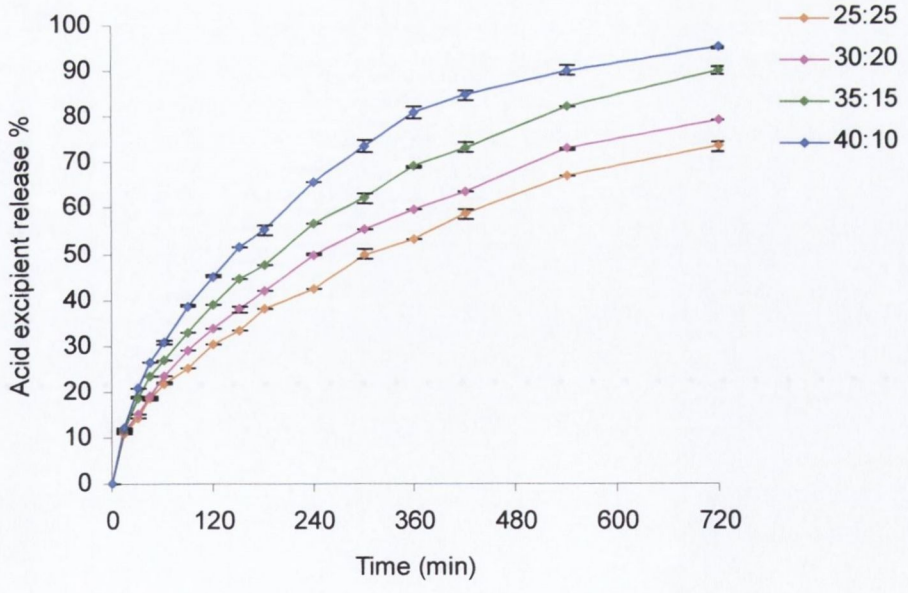

Figure 8.6. Percentage succinic acid release from ethylcellulose 100 cP:succinic acid:ibuprofen compacts prepared with different succinic acid:ibuprofen weight ratios indicated in legend.

Table 8.6.

Initial and limiting succinic acid dissolution rates from ethylcellulose:succinic acid :ibuprofen compacts prepared with different succinic acid:ibuprofen weight ratios

Dissolution rate ($mg/min/cm^2$)	**SA:IB 25:25**	**SA:IB 30:20**	**SA:IB 35:15**	**SA:IB 40:10**
Ethylcellulose 4 cP				
Initial (I)	0.0662	0.0871	0.1157	0.1522
Limiting (L)	0.0106	0.0143	0.0192	0.0256
Ratio (I:L)	6.2344	6.0850	6.0201	5.9407
Ethylcellulose 100 cP				
Initial (I)	0.1136	0.1412	0.1886	0.2271
Limiting (L)	0.0193	0.0249	0.0333	0.0402
Ratio (I:L)	5.8892	5.6619	5.6687	5.6519

Figure 8.7. and figure 8.8. show the percentage ibuprofen release from matrix discs of ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade containing different succinic acid:ibuprofen weight ratios. It was clear that increasing the succinic acid:ibuprofen weight ratio in the compact resulted in a reduction in percentage ibuprofen release. This was evident for formulations of either ethylcellulose viscosity grade.

Table 8.7. shows the relevant initial and limiting ibuprofen release rates. The ibuprofen initial release rate was greater than the ibuprofen limiting release rate for each formulation examined. A measure of the attenuation of the ibuprofen dissolution rate with increasing succinic acid content was given by the ratio of the initial to limiting release rate. Examination of this value showed that when the succinic acid content in the compact was increased, the difference between the ibuprofen initial and limiting release rates was reduced. This suggests that by increasing the succinic acid content in the formulation zero-order ibuprofen release was approached.

Healy (1995) found that the dissolution rate of ibuprofen was decreased in the presence of acid excipients and suppression of ibuprofen dissolution was increased with increasing concentration of acid excipient in the disc. Results showed that the greater the weight fraction ratio of acid excipient in the disc the greater was the amount of excipient dissolved at a particular time. Also, the greater the extent of acid excipient dissolution, the lower was the amount of ibuprofen in solution at any time. Therefore, the matrix compacts containing a higher weight fraction of succinic acid

experienced a greater level of ibuprofen suppression than matrix compacts containing a lower weight fraction of succinic acid content. This will act to balance the fast initial ibuprofen dissolution rate from the superficial layers of the matrix type formulation. As acid excipient dissolution proceeds in the matrix compact the ibuprofen solubility and dissolution rate is increased. In addition, it is expected that as the acid excipient dissolves the porosity of the ethylcellulose compact increases, resulting in an increase in the ibuprofen dissolution rate.

Both succinic acid percentage release and ibuprofen percentage release were lower from ethylcellulose 4 cP formulations than from ethylcellulose 100 cP formulations. It was also noted that the I:L ratios for ibuprofen dissolution from compacts prepared with ethylcellulose 100 cP viscosity grade were less than the I:L ratio for compacts prepared with ethylcellulose 4 cP viscosity grade, for each formulation examined (table 8.7.).

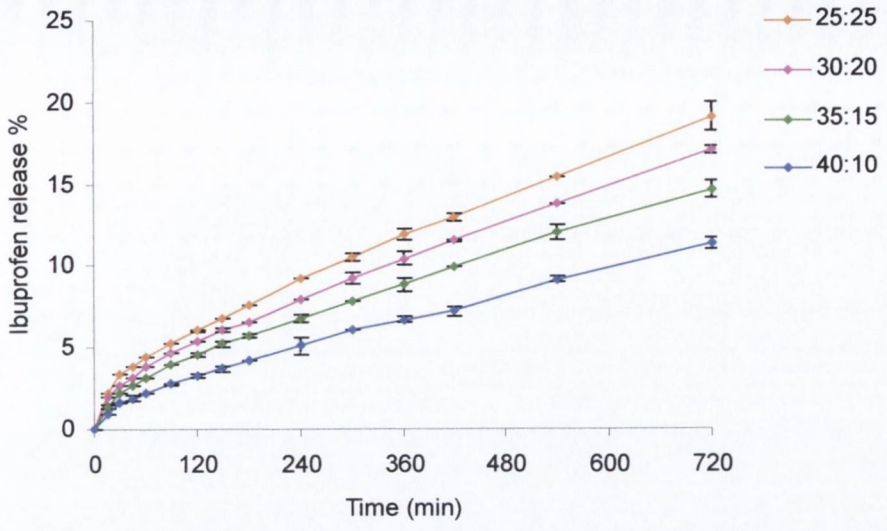

Figure 8.7. Percentage ibuprofen release from ethylcellulose 4 cP:succinic acid:ibuprofen compacts prepared with different succinic acid:ibuprofen weight ratios, as indicated in legend.

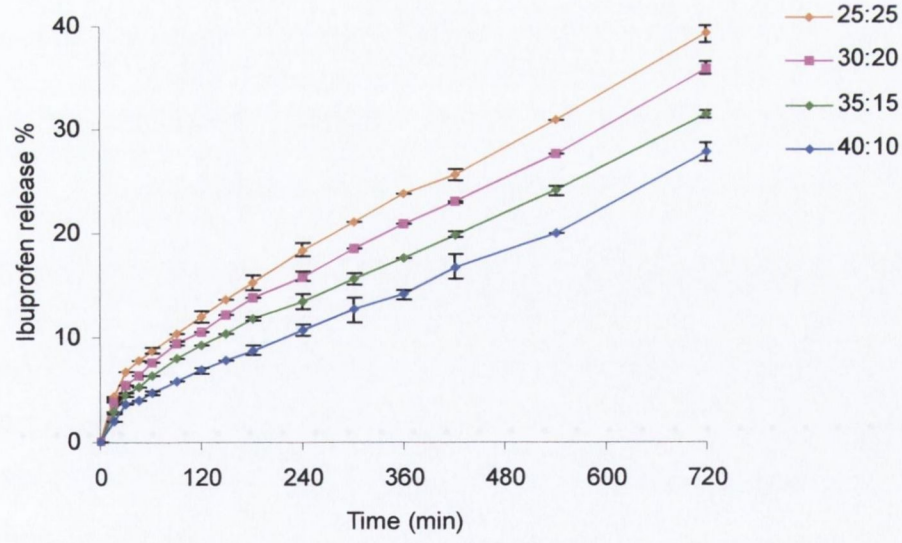

Figure 8.8. Percentage ibuprofen release from ethylcellulose 100 cP:succinic acid:ibuprofen compacts prepared with different succinic acid:ibuprofen weight ratios, as indicated in legend.

Table 8.7.

Initial and limiting ibuprofen dissolution rates from ethylcellulose:succinic acid :ibuprofen compacts prepared with different succinic acid:ibuprofen weight ratios

Dissolution rate ($mg/min/cm^2$)	**SA:IB 25:25**	**SA:IB 30:20**	**SA:IB 35:15**	**SA:IB 40:10**
Ethylcellulose 4 cP				
Initial (I)	0.0243	0.0167	0.0098	0.0045
Limiting (L)	0.0050	0.0036	0.0023	0.0012
Ratio (I:L)	4.8326	4.6245	4.1917	3.7569
Ethylcellulose 100 cP				
Initial (I)	0.0483	0.0331	0.0194	0.0094
Limiting (L)	0.0103	0.0075	0.0050	0.0030
Ratio (I:L)	4.6963	4.3926	3.9006	3.1039*

*measured at 420 minutes as all succinic acid in solution at end of dissolution run

8.5.3. Effect of acid excipient particle size on acid excipient and ibuprofen release from ethylcellulose compacts

Previous work by Healy (1995) showed that acid excipient particle size could have an important effect on ibuprofen dissolution from two component acid excipient:ibuprofen compressed discs.

Compacts were prepared using acid excipient sieved less than 40 μm in an ethylcellulose:acid excipient:ibuprofen 50:25:25 weight ratio.

Figures 8.9. to 8.14. show the percentage acid excipient release from compacts prepared with acid excipient sieved less than 40 μm or less than 180 μm, from compacts prepared with ethylcellulose 4 cP or ethylcellulose 100 cP. It was evident that over the test period examined compacts prepared with the smaller acid excipient particle size fraction (less than 40 μm) showed a greater percentage acid excipient release than compacts prepared with acid excipient sieved less than 180 μm. This was evident for formulations of either ethylcellulose viscosity grade. Two sample t-tests, assuming equal variance showed there was significant difference ($p \leq 0.05$) in the percentage acid excipient released from ethylcellulose 4 cP formulations of different acid excipient particle size fractions, at all sampling time points except at 15 minutes and 30 minutes. In addition, two sample t-tests assuming equal variance showed there was significant difference ($p \leq 0.05$) in the percentage adipic acid release from ethylcellulose 100 cP formulations of different acid excipient particle size fractions, at

all sampling time points except at 15, 30, 45 and 60 minutes. Similar results were found for compacts prepared with succinic acid. Two sample t-tests assuming equal variance also showed there was significant difference ($p \leq 0.05$) in the percentage L-(+)-tartaric acid released from ethylcellulose 100 cP formulations of different acid excipient particle size fractions, at all sampling points except at 15 and 30 minutes. Examination of the initial and limiting acid excipient release rates showed that the initial acid excipient release rate was greater than the limiting release rate, for each acid excipient particle size fraction examined (tables 8.4. and 8.8.). In addition, the I:L (acid excipient) ratio was lower for formulations prepared with acid excipient sieved less than 40 μm than for formulations prepared with acid excipient sieved less than 180 μm (tables 8.4. and 8.8.). This may be because the smaller particle size acid excipient was released quicker, thereby encouraging the dissolution medium to penetrate the centre of the matrix disc. This creates a less tortuous pathway for the acid excipient to escape from the matrix compact (Neau *et al.*, 1999).

Table 8.8.

Initial and limiting acid excipient dissolution rates from ethylcellulose:acid excipient:ibuprofen compacts, formulated with acid excipient sieved less than 40 μm

Dissolution rate ($mg/min/cm^2$)	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
Ethylcellulose 4 cP			
Initial (I)	0.0639	0.0740	0.0893
Limiting (L)	0.0103	0.0125	0.0153
Ratio (I:L)	6.2166	5.9489	5.8379
Ethylcellulose 100 cP			
Initial (I)	0.1053	0.1218	0.1438
Limiting (L)	0.0180	0.0213	0.0260
Ratio (I:L)	5.8504	5.7195	5.5081

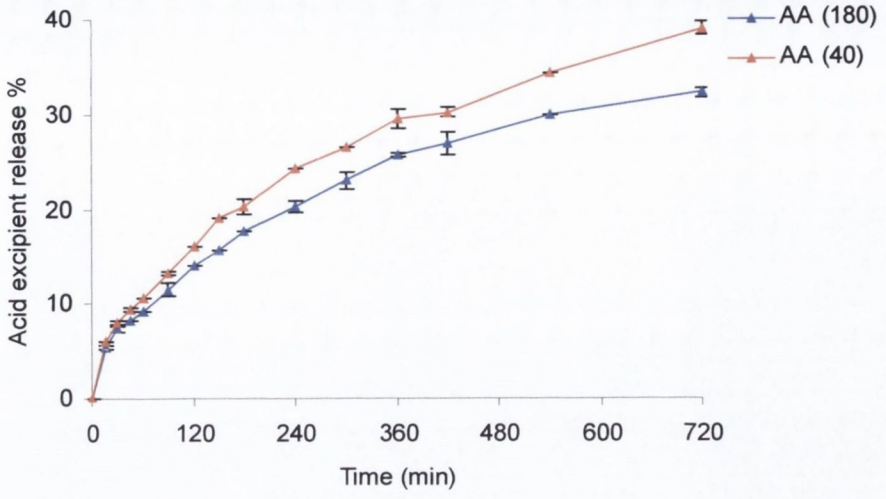

Figure 8.9. Percentage adipic acid release from ethylcellulose 4 cP:adipic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either adipic acid sieved less than 180 μm (180) or less than 40 μm (40). AA: adipic acid.

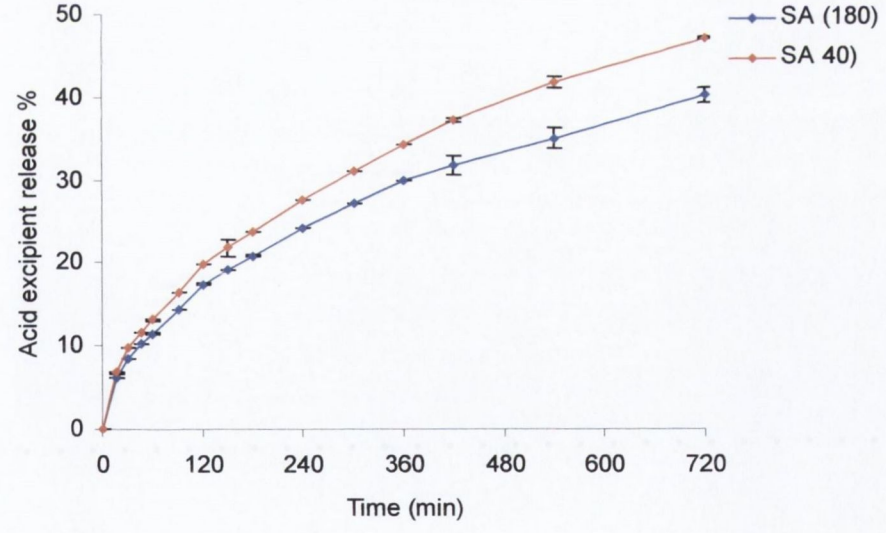

Figure 8.10. Percentage succinic acid release from ethylcellulose 4 cP:succinic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either succinic acid sieved less than 180 μm (180) or less than 40 μm (40). SA: succinic acid.

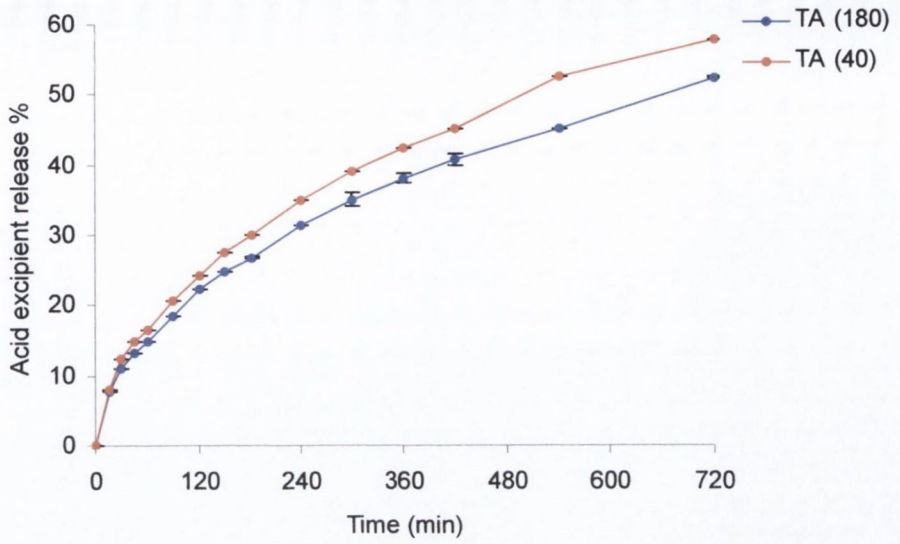

Figure 8.11. Percentage L-(+)-tartaric acid release from ethylcellulose 4 cP:L-(+)-tartaric acid:ibuprofen compacts prepared with either L-(+)-tartaric acid sieved less than 180 μm (180) or less than 40 μm (40). TA: L-(+)-tartaric acid.

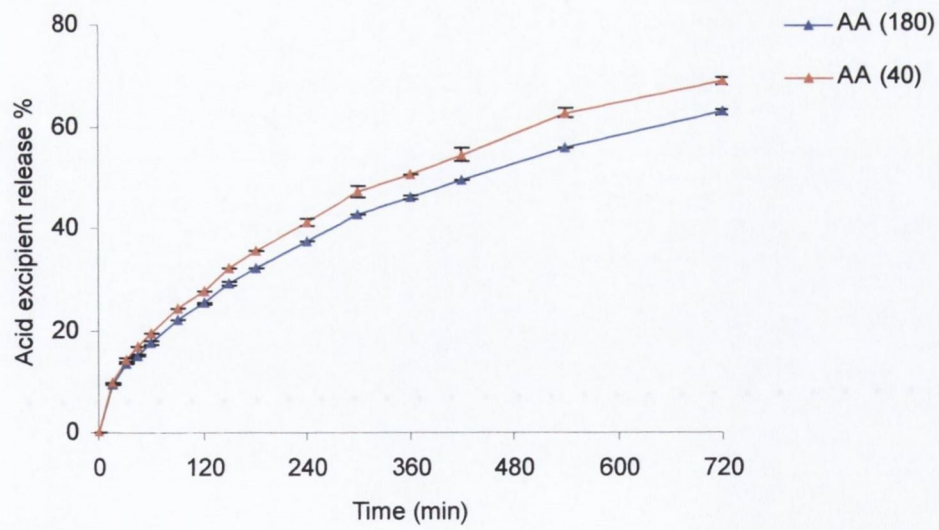

Figure 8.12. Percentage adipic acid release from ethylcellulose 100 cP:adipic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either adipic acid sieved less than 180 μm (180) or less than 40 μm (40). AA: adipic acid.

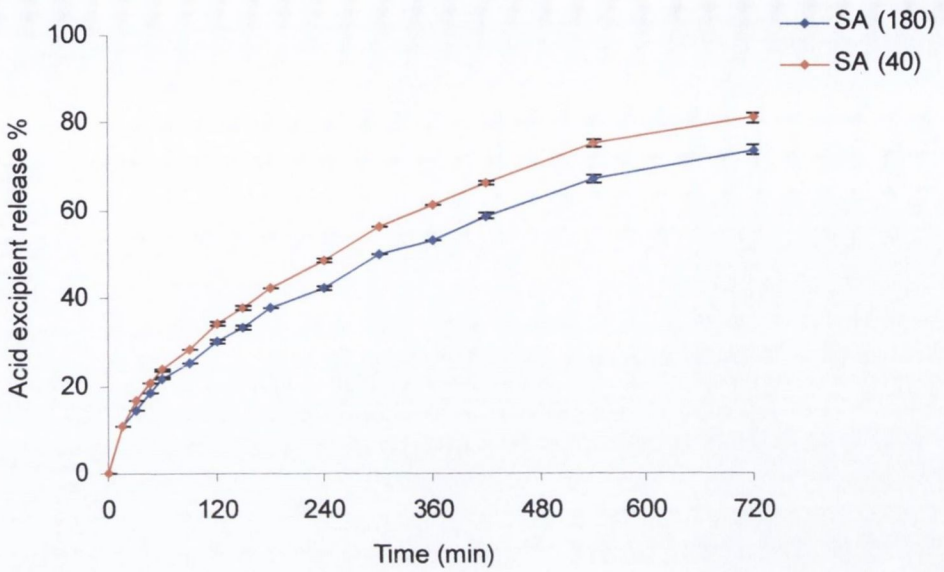

Figure 8.13. Percentage succinic acid release from ethylcellulose 100 cP:succinic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either succinic acid sieved less than 180 μm (180) or less than 40 μm (40). SA: succinic acid.

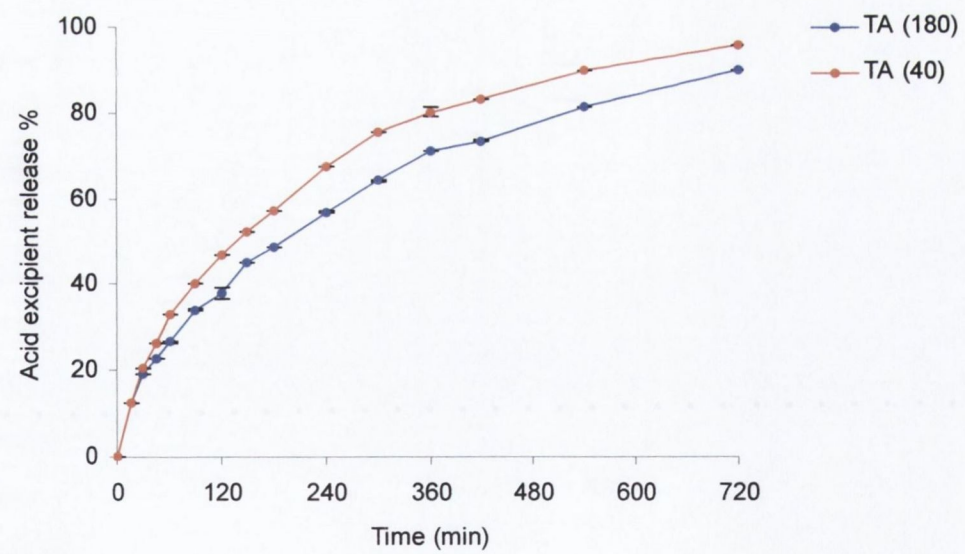

Figure 8.14. Percentage L-(+)-tartaric acid release from ethylcellulose 100 cP:L-(+)-tartaric acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either L-(+)-tartaric acid sieved less than 180 μm (180) or less than 40 μm (40). TA: L-(+)-tartaric acid.

Figures 8.15. to 8.20. show the percentage ibuprofen release from ethylcellulose compacts prepared with acid excipient sieved less than 180 μm or 40 μm, and of ethylcellulose 4 cP or 100 cP viscosity grade, respectively. The percentage ibuprofen release was lower from ethylcellulose compacts prepared with acid excipient sieved less than 40 μm, than from ethylcellulose compacts prepared with acid excipient sieved less than 180 μm. This was evident for compacts prepared with either ethylcellulose viscosity grade. The I:L ratio (ibuprofen) for compacts prepared with acid excipient sieved less than 180 μm was greater than the I:L ratio for compacts prepared with acid excipient sieved less than 40 μm (table 8.5. and table 8.9.). This was evident for compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade.

Healy (1995) found that the dissolution rate of ibuprofen was decreased in the presence of acid excipients and suppression of ibuprofen dissolution was increased with increasing concentration of acid excipient in the disc. Healy (1995) also found that as the particle size of the acid excipient is reduced the dissolution rate of ibuprofen was lowered. Therefore, in matrix formulations the smaller particle size fraction of acid excipient may reduce the ibuprofen dissolution rate more than the greater acid excipient particle size fraction. However, as acid excipient dissolution proceeds the ibuprofen solubility and dissolution rate is gradually increasing in the formulation. This increased ibuprofen solubility will act to balance the suppression of the ibuprofen, and the increasing distance that must be travelled by the solution and drug molecules into and out of the tablet.

Two sample t-tests, assuming equal variance showed there was a significant difference ($p \leq 0.05$) in percentage acid excipient and ibuprofen release from compacts prepared with ethylcellulose 4 cP and ethylcellulose 100 cP and acid excipient sieved less than 40 μm, at each sampling time point. Both ibuprofen release and acid excipient release were greater from compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP viscosity grade, for each formulation examined. Indeed, the I:L ratio for compacts prepared with ethylcellulose 4 cP was greater than the I:L ratio for compacts prepared with ethylcellulose 100 cP, when the acid excipient was sieved less than 40 μm. The difference in dissolution behaviour from compacts of different viscosity grades has been previously accounted for.

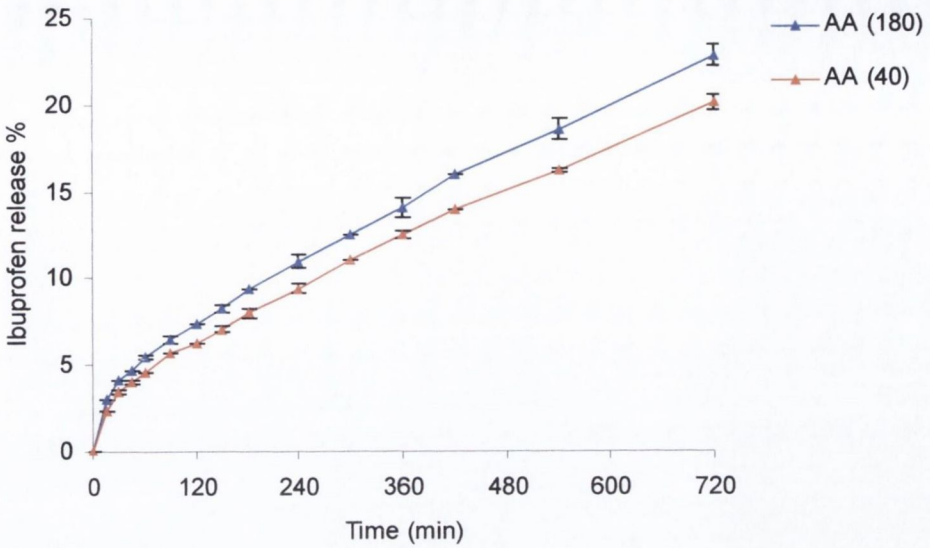

Figure 8.15. Percentage ibuprofen release from ethylcellulose 4 cP:adipic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either adipic acid sieved less than 180 μm (180) or less than 40 μm (40). AA: adipic acid.

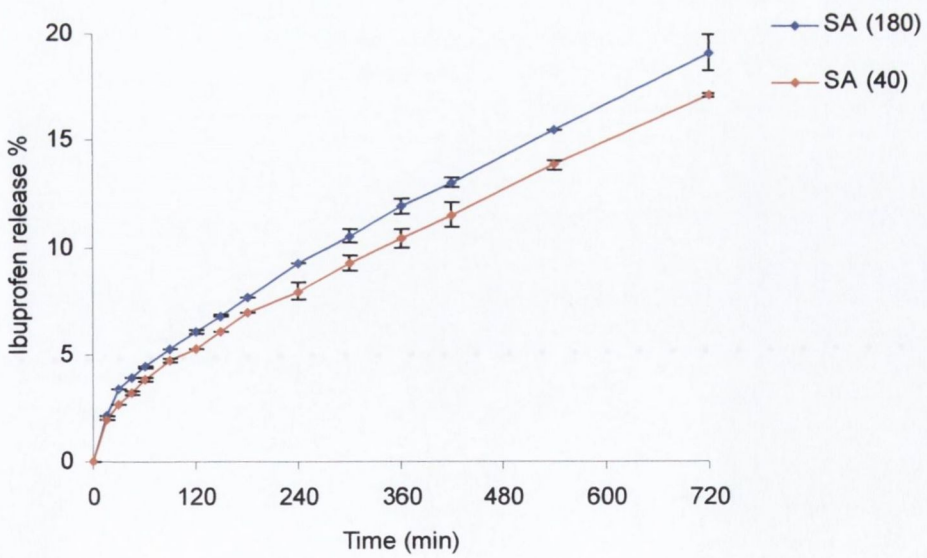

Figure 8.16. Percentage ibuprofen release from ethylcellulose 4 cP: succinic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either succinic acid sieved less than 180 μm (180) or less than 40 μm (40). SA: succinic acid.

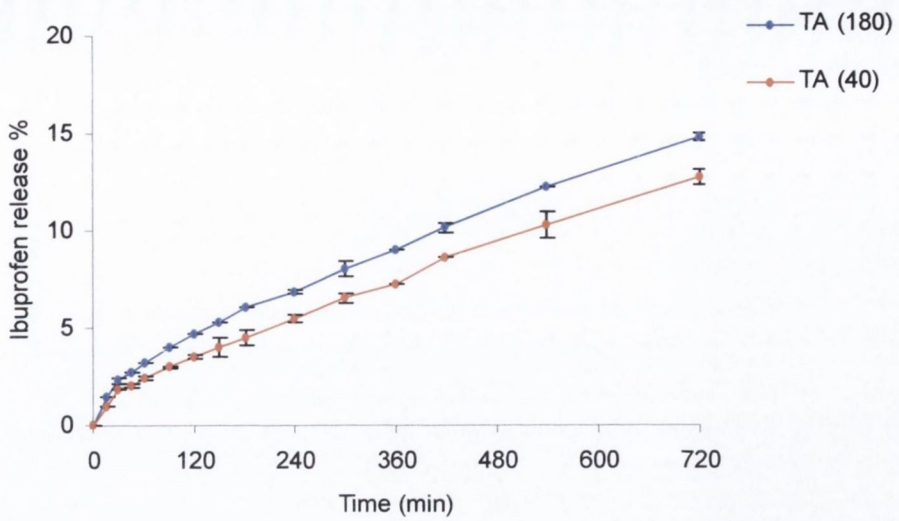

Figure 8.17. Percentage ibuprofen release from ethylcellulose 4 cP:L-(+)-tartaric acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either L-(+)-tartaric acid sieved less than 180 μm (180) or less than 40 μm (40). TA: L-(+)-tartaric acid.

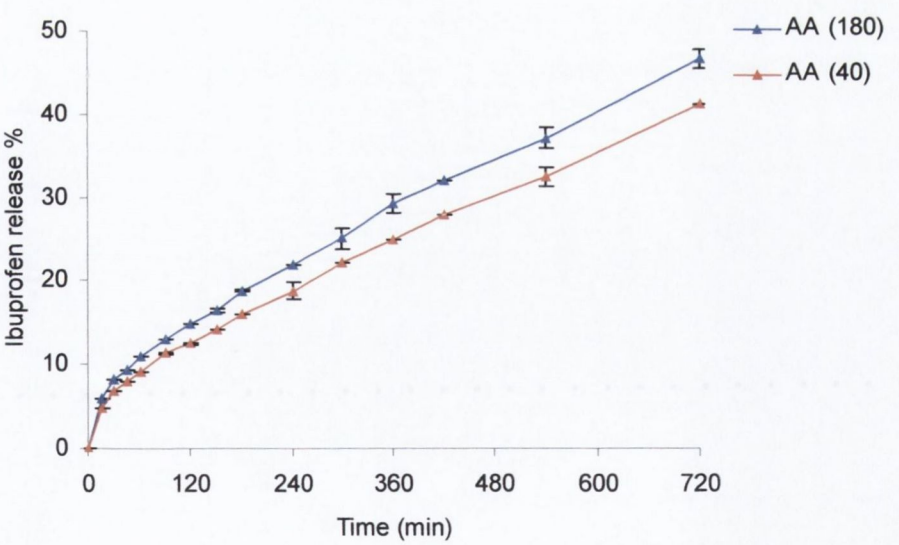

Figure 8.18. Percentage ibuprofen release from ethylcellulose 100 cP:adipic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either adipic acid sieved less than 180 μm (180) or less than 40 μm (40). AA: adipic acid.

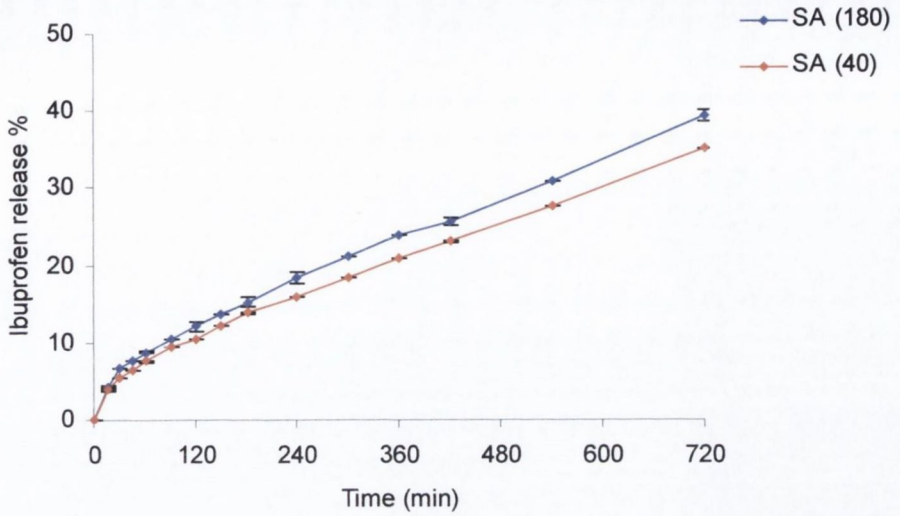

Figure 8.19. Percentage ibuprofen release from ethylcellulose 100 cP: succinic acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either succinic acid sieved less than 180 μm (180) or less than 40 μm (40). SA: succinic acid.

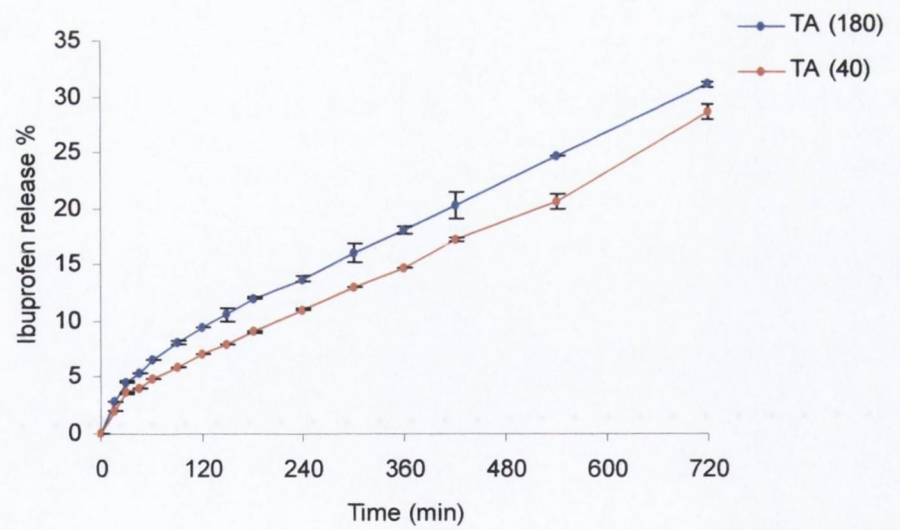

Figure 8.20. Percentage ibuprofen release from ethylcellulose 100 cP:L-(+)-tartaric acid:ibuprofen compacts (50:25:25 weight ratio) prepared with either L-(+)-tartaric acid sieved less than 180 μm (180) or less than 40 μm (40). TA: L-(+)-tartaric acid.

Table 8.9.

Initial and limiting ibuprofen dissolution rates from ethylcellulose:acid excipient:ibuprofen compacts, formulated with acid excipient sieved less than 40 μm

Dissolution rate ($mg/min/cm^2$)	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
Ethylcellulose 4 cP			
Initial (I)	0.0257	0.0208	0.0122
Limiting (L)	0.0053	0.0045	0.0034
Ratio (I:L)	4.8849	4.6245	3.6026
Ethylcellulose 100 cP			
Initial (I)	0.0512	0.0415	0.0241
Limiting (L)	0.0107	0.0092	0.0078*
Ratio (I:L)	4.7739	4.4995	3.1039

*measured at 420 minutes as all L-(+)-tartaric acid in solution at end of dissolution run

One must now explain the difference in dissolution behaviour from compacts containing acid excipient of different acid excipient particle size. "Classical theories" (for particulate solids) attribute the increase in the release rates achieved by using a smaller particle size to the faster dissolution rate of the smaller particles (due to an increased surface area per unit volume). Therefore, it was not surprising that the release of acid excipient from discs containing excipient particles sieved less than 40 μm was greater than the release from discs containing excipient sieved less than 180 μm.

In addition, percolation theory can be used to explain this phenomenon. The surface area of excipient exposed to the medium at any time can be considered to be equal to the sum of all sections corresponding to the pores where the excipient is being dissolved. Initially the acid excipient surface exposed to the medium will be similar. The smaller acid excipient particle size i.e. sieved less than 40 μm will be more likely to form an infinite cluster (of the excipient) than the larger acid excipient particle size fraction i.e. sieved less than 180 μm. Therefore, it is expected that compacts prepared with acid excipient sieved less than 40 μm will contain a more consistent infinite cluster with fewer isolated pockets of these particles. As the excipient dissolves from the surface, uninterrupted connecting porous pathways will extend inwards towards the centre of the compacts. Hence, all the acid excipient (sieved less than 40 μm) present in the disc will be made available for dissolution. In the case of the larger

acid excipient particle size fraction i.e. sieved less than 180 μm, this component has less chance of spanning the whole ethylcellulose:acid excipient:ibuprofen system, and isolated clusters will exist which will not be exposed to the dissolution medium.

What must now be considered is how the dissolution of the acid excipient influences the dissolution profile obtained for ibuprofen. The finer the powder, the higher will be the degree of uniformity that can be achieved (theoretically) by blending. If the uniformity of mix is enhanced, the result will be that no significant area of ibuprofen surface will be left unexposed to the retarding influence of the acid excipient, since each particle of ibuprofen will be adjacent to dissolving acid excipient. If however the particle size of the acid excipient is much larger than that of ibuprofen, there will be fewer particles per unit volume acid excipient in the mix with the result that the uniformity of the mix is reduced. Large areas of ibuprofen may be non-adjacent to dissolving acid excipient and be less affected by the retarding influence of the excipient on solubility and dissolution.

8.6. MODELLING OF RELEASE DATA

Ibuprofen release data from ethylcellulose:acid excipient:ibuprofen compacts was fitted to the square root of time model (model 1) and model 2. Attempts were also made to model acid excipient release from the various formulations of ethylcellulose:acid excipient:ibuprofen.

8.6.1. Model 1 (ibuprofen release data)

Ibuprofen dissolution data from formulations containing acid excipient was fitted to the square root of time model. As indicated by the poor coefficient of determination and MSC values the square root of time model did not fit the dissolution data (table 8.10.). However, both of these parameters were greater than those parameters determined for the model fit to dissolution data from ethylcellulose compacts of a 25% w/w drug load. Both of these parameters were greater when the model was fitted to ibuprofen release data from ethylcellulose:ibuprofen (50:50 weight ratio) compacts than when fitted to release data from compacts prepared with acid excipient. This was evident for model 1 fits to release studies from formulations of either ethylcellulose viscosity grade. This suggests that the ibuprofen release process from compacts

containing acid excipient was not based solely on diffusion as the release mechanism. The poorest of model fits to ibuprofen release data from ethylcellulose:acid excipient:ibuprofen formulations (50:25:25 weight ratio) was to release data from compacts prepared with L-(+)-tartaric acid, while the best fit was to release data from compacts containing adipic acid. This was evident for model fits to release studies from compacts of either ethylcellulose 4 cP or ethylcellulose 100 cP. Indeed, the model 1 fit to ibuprofen release data from ethylcellulose:succinic acid:ibuprofen formulations worsened with increasing succinic acid:ibuprofen weight ratio in the formulation. In addition, ibuprofen release data from ethylcellulose compacts (of 4 cP or 100 cP viscosity grade) prepared with the smaller acid excipient particle size fraction (sieved less than 40 μm) showed an even greater deviation from the square root of time model than release data from similar formulations prepared with acid excipient sieved less than 180 μm.

The ibuprofen release rate constant (k) from ethylcellulose:acid excipient:ibuprofen compacts was greater than the rate constant from ethylcellulose:ibuprofen 75:25 (weight ratio) compacts, but less than the rate constant from ethylcellulose:ibuprofen 50:50 (weight ratio) compacts (table 8.10.). This was evident for model 1 fits to release studies from compacts of either ethylcellulose viscosity grade (4 cP or 100 cP). It was also clear that the ibuprofen release rate constant was lowest for compacts prepared with L-(+)-tartaric acid and greatest for compacts prepared with adipic acid, for compacts prepared with ethylcellulose:acid excipient:ibuprofen 50:25:25 weight ratio (acid excipient sieved less than 180 μm), of either ethylcellulose viscosity grade. Examination of data in table 8.10. also showed that as the level of succinic acid in the formulation increased, the ibuprofen rate constant was reduced for compacts prepared with either ethylcellulose 4 cP or 100 cP viscosity grade. The ibuprofen release rate constant was also reduced for each ethylcellulose:acid excipient:ibuprofen formulation when acid excipient sieved less than 40 μm was used during formulation, as compared to acid excipient sieved less than 180 μm (table 8.10.). For all formulations, the ibuprofen release rate constant was higher for formulations prepared with ethylcellulose 100 cP than for formulations prepared with ethylcellulose 4 cP.

Table 8.10.

Parameters and statistical estimates of model 1 fits to ibuprofen release data from ethylcellulose matrix compacts prepared with and without acid excipient

EC:AE:IB	k ($\%min^{-0.50}$)	Std Dev of k	c	Std Dev of c	CoD	MSC
Ethylcellulose 4 cP						
EC:IB (75:25)	0.1389	0.0140	0.4909	0.2073	0.8827	1.8769
EC:IB (50:50)	1.2616	0.0092	-0.1442	0.1364	0.9993	7.0021
EC:AA:IB (50:25:25)	0.8192	0.0279	-0.9178	0.4116	0.9852	3.9446
EC:TA:IB (50:25:25)	0.5448	0.0191	-0.9141	0.2825	0.9842	3.8815
EC:SA:IB (50:25:25)	0.6891	0.0234	-0.9185	0.3459	0.9852	3.9461
EC:SA:IB (50:30:20)	0.6170	0.0227	-0.9455	0.3344	0.9828	3.7949
EC:SA:IB (50:35:15)	0.5357	0.0199	-0.9253	0.2932	0.9825	3.7764
EC:SA:IB (50:40:10)	0.4130	0.0181	-0.8785	0.2674	0.9756	3.4467
EC:AA:IB PS (50:25:25)	0.7257	0.0259	-1.001	0.3816	0.9838	3.8546
EC:SA:IB PS (50:25:25)	0.6175	0.0221	-0.9415	0.3269	0.9836	3.8416
EC:TA:IB PS (50:25:25)	0.4689	0.0229	-1.1184	0.3376	0.9700	3.2403
Ethylcellulose 100 cP						
EC:IB (75:25)	0.2875	0.0254	0.8944	0.3744	0.9081	2.1209
EC:IB (50:50)	2.2509	0.0453	-1.0670	0.6117	0.9952	5.0448
EC:AA:IB (50:25:25)	1.6630	0.0603	-2.0173	0.8896	0.9832	3.8208
EC:TA:IB (50:25:25)	1.1141	0.0468	-2.0492	0.6915	0.9775	3.5294
EC:SA:IB (50:25:25)	1.3943	0.0546	-2.0017	0.8056	0.9805	3.6697
EC:SA:IB (50:30:20)	1.2664	0.0562	-2.1642	0.8290	0.9751	3.4254
EC:SA:IB (50:35:15)	1.1097	0.0526	-2.1650	0.7772	0.9716	3.2940
EC:SA:IB (50:40:10)	0.9642	0.0638	-2.6533	0.9420	0.9461	2.6548
EC:AA:IB PS (50:25:25)	1.4676	0.0574	-2.1477	0.8471	0.9805	3.6716
EC:SA:IB PS (50:25:25)	1.2516	0.0503	-2.0309	0.7434	0.9794	3.6156
EC:TA:IB PS (50:25:25)	0.9939	0.0648	-2.7308	0.9568	0.9476	2.6826

Std Dev: Standard deviation, CoD: Coefficient of determination, MSC: Model selection criterion, EC: ethylcellulose, AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, IB: ibuprofen, PS: indicates acid excipient sieved less than 40 μm. The ethylcellulose:ibuprofen:acid excipient weight ratio is indicated in brackets.

8.6.2. Model 2 (ibuprofen release data)

The coefficient of determination and MSC values were greater when model 2 was fitted to the ibuprofen dissolution data from compacts prepared with acid excipient than when model 1 was fitted to the release data (table 8.10. and 8.11.).

The diffusional exponent *N* determined for model 2 fits to ibuprofen release data from formulations prepared with acid excipient was greater than the exponent determined for model 2 fits to release data from formulations prepared without acid excipient. This was evident for model 2 fits to ibuprofen release studies from compacts prepared with either ethylcellulose viscosity grade. The increase in the diffusional exponent represented a change in ibuprofen release from (predominately) Fickian controlled diffusion in ethylcellulose:ibuprofen 50:50 compacts to non-Fickian behavior in ethylcellulose:acid excipient:ibuprofen compacts. This latter behaviour represented the effect of the acid excipient on ibuprofen release from matrix compacts.

Examination of individual formulation exponents *N* showed that the diffusional exponent was greater when model 2 was fitted to ibuprofen release data from ethylcellulose:acid excipient:ibuprofen (50:25:25 weight ratio) compacts prepared with L-(+)-tartaric acid (sieved less than 180 μm) than when model 2 was fitted to ibuprofen release data from compacts containing succinic acid (sieved less than 180 μm) or adipic acid (sieved less than 180 μm). This was evident for model 2 fits to ibuprofen release studies from compacts of either ethylcellulose viscosity grade. This implies that ibuprofen release from compacts containing L-(+)-tartaric acid (sieved less than 180 μm) represented a step nearer zero-order kinetics than ibuprofen release from compacts containing succinic acid or adipic acid (of the same particle size fraction). It was also found that the diffusional exponent for ibuprofen release studies from compacts of ethylcellulose:succinic acid:ibuprofen increased as the succinic acid:ibuprofen weight ratio increased in the formulation. This was evident for model 2 fits to release studies from compacts of either ethylcellulose viscosity grade. This implies that compacts prepared with a higher succinic acid:ibuprofen weight ratio were a step nearer constant release of ibuprofen.

The diffusional exponent was greater when model 2 was fitted to ibuprofen release data from compacts prepared with acid excipient, sieved less than 40 μm as opposed to less than 180 μm. This was evident for ibuprofen release data from compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grade.

For each formulation, the exponent N was higher for model fits to release data from compacts prepared with ethylcellulose 100 cP as compared to compacts prepared with ethylcellulose 4 cP viscosity grade. This would suggest that ibuprofen release from matrix compacts prepared with ethylcellulose 100 cP was a step nearer constant release of ibuprofen than release from ethylcellulose 4 cP compacts, for each formulation.

Table 8.11.

Parameters and statistical estimates of model 2 fits to ibuprofen release data from ethylcellulose matrix compacts with and without acid excipient

EC:AE:IB	k ($\%min^{-N}$)	Std Dev of k	N	Std Dev of N	c	Std Dev of c	CoD	MSC
Ethylcellulose 4 cP								
EC:IB 75:25	0.5348	0.1917	0.2810	0.0165	-0.2015	0.2962	0.9377	2.3750
EC:IB 50:50	1.1993	0.0737	0.5074	0.0030	0.0180	0.2377	0.9993	6.9250
EC:AA:IB 50:25:25	0.2900	0.0592	0.6294	0.0101	0.8524	0.3553	0.9957	5.0463
EC:TA:IB 50:25:25	0.1730	0.0283	0.6703	0.0080	0.3582	0.1825	0.9974	5.5356
EC:SA:IB 50:25:25	0.2352	0.0429	0.6494	0.0090	0.6112	0.2640	0.9966	5.2852
EC:SA:IB 50:30:20	0.1841	0.0339	0.6797	0.0091	0.5575	0.2285	0.9967	5.3210
EC:SA:IB 50:35:15	0.1566	0.0272	0.6829	0.0086	0.3965	0.1858	0.9971	5.4465
EC:SA:IB 50:40:10	0.0906	0.0184	0.7263	0.0101	0.3151	0.1528	0.9965	5.2494
EC:AA:IB PS	0.2321	0.0440	0.6492	0.0095	0.6870	0.2863	0.9963	5.2115
EC:SA:IB PS	0.1905	0.0337	0.6747	0.0087	0.5303	0.2217	0.9971	5.3907
EC:TA:IB PS	0.0804	0.0163	0.7438	0.0152	0.3921	0.1613	0.9968	5.3359
Ethylcellulose 100 cP								
EC:IB 75:25	1.0019	0.3299	0.3040	0.0148	-0.3906	0.5221	0.9532	2.6613
EC:IB 50:50	1.4919	0.2052	0.5627	0.0070	0.8998	0.7543	0.9974	5.5287
EC:AA:IB 50:25:25	0.5396	0.1180	0.6571	0.0108	1.8149	0.7510	0.9952	4.9451
EC:TA:IB 50:25:25	0.2702	0.0603	0.7110	0.0111	1.015	0.4683	0.9956	5.0185
EC:SA:IB 50:25:25	0.3989	0.0932	0.6860	0.0174	1.4892	0.6455	0.9948	4.8657
EC:SA:IB 50:30:20	0.2851	0.0745	0.7223	0.0130	1.4571	0.6089	0.9941	4.7328
EC:SA:IB 50:35:15	0.2180	0.0610	0.7430	0.0139	1.2171	0.5485	0.9936	4.6449
EC:SA:IB 50:40:10	0.0699	0.0261	0.7674	0.0168	1.3902	0.4854	0.9916	4.3752
EC:AA:IB PS	0.4104	0.0908	0.6895	0.0110	1.5778	0.6390	0.9954	4.9823
EC:SA:IB PS	0.3285	0.0717	0.7190	0.0108	1.2660	0.5273	0.9956	5.0329
EC:TA:IB PS	0.0754	0.0269	0.7805	0.0180	1.3921	0.4840	0.9922	4.4511

Std Dev: Standard deviation, CoD: Coefficient of determination, MSC: Model selection criterion, EC: ethylcellulose, AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, IB: ibuprofen, PS: indicates acid excipient sieved less than 40 μm, in an ethylcellulose:acid excipient:ibuprofen 50:25:25 compact weight ratio.

8.6.3. Model 1 (acid excipient release data)

Acid excipient dissolution data from all formulations containing ethylcellulose:acid excipient: ibuprofen was fitted to the square root of time model (table 8.12.). The high values of the coefficient of determination and MSC indicated a good model fit. This suggested that diffusion was the main mechanism of acid excipient release from

all matrix compacts. Indeed, all acid excipient dissolution data showed a better quality fit to model 1 than ibuprofen release data from formulations prepared with the same acid excipient:ibuprofen weight ratio.

Comparison of release rate constants k in table 8.10. and 8.12. showed that the acid excipient release rate constant was greater than the ibuprofen release rate constant, from formulations with the same acid excipient:ibuprofen weight ratio. Indeed, of the formulations containing the same acid excipient:ibuprofen weight ratio L-(+)-tartaric acid showed the greatest acid excipient rate constant followed by succinic acid and adipic acid. It was also clear that the succinic acid rate constant increased when the succinic acid:ibuprofen weight ratio was increased in formulations, for compacts prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP.

Table 8.12 also shows the acid excipient release rate constants from formulations containing acid excipient sieved less than 40 μm. The acid excipient release rate constant for formulations containing acid excipient sieved less than 40 μm was greater then the acid excipient release rate constant for formulations containing acid excipient sieved less than 180 μm. This was evident for formulations prepared with either ethylcellulose 4 cP or ethylcellulose 100 cP viscosity grades. Indeed, for each formulation the acid excipient rate constant was greater from compacts prepared with ethylcellulose 100 cP than ethylcellulose 4 cP. This was in agreement with previous findings in previous chapters 6.5.2.

Table 8.12.

Parameters and statistical estimates of model 1 fits to acid excipient release data from ethylcellulose:acid excipient:ibuprofen compacts

AE:IB	k ($\%min^{-0.50}$)	Std Dev of k	c	Std Dev of c	CoD	MSC
Ethylcellulose 4 cP						
EC:AA:IB 25:25	1.2729	0.0293	0.1808	0.4330	0.9932	4.7162
EC:TA:IB 25:25	1.9688	0.0184	0.1988	0.2724	0.9989	6.5100
EC:SA:IB 25:25	1.5220	0.0181	0.2750	0.2673	0.9982	6.0335
EC:SA:IB 30:20	1.6840	0.0144	0.1588	0.2130	0.9990	6.6893
EC:SA:IB 35:15	1.9242	0.0166	0.1704	0.2456	0.9990	6.6707
EC:SA:IB 40:10	2.2574	0.0095	0.1332	0.1404	0.9998	8.1088
EC:AA:IB PS	1.4977	0.0269	-0.0518	0.3980	0.9958	5.2075
EC:SA:IB PS	1.7952	0.0148	-0.1725	0.2179	0.9991	6.7713
EC:TA:IB PS	2.2207	0.0245	-0.0483	0.3619	0.9984	6.1830
Ethylcellulose 100 cP						
EC:AA:IB 25:25	2.4318	0.0247	-0.5165	0.3330	0.9988	6.4116
EC:TA:IB 25:25	3.7114	0.0632	-1.3353	0.6093	0.9977	5.6691
EC:SA:IB 25:25	2.8573	0.0399	-0.7653	0.4968	0.9979	5.8363
EC:SA:IB 30:20	3.2501	0.0430	-1.5551	0.4945	0.9983	6.0183
EC:SA:IB 35:15	3.6868	0.0582	-1.3367	0.5609	0.9980	5.8210
EC:SA:IB 40:10	4.2867	0.1111	-2.1586	0.9736	0.9953	4.9184
EC:AA:IB PS	2.7074	0.0288	-0.9193	0.3586	0.9988	6.3796
EC:SA:IB PS	3.2339	0.0483	-1.0909	0.5103	0.9980	5.8509
EC:TA:IB PS	4.4287	0.1226	-2.3204	1.0730	0.9947	4.7897

Std Dev: Standard deviation, CoD: Coefficient of determination, MSC: Model selection criterion, EC: ethylcellulose, AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, IB: ibuprofen, PS: indicates acid excipient sieved less than 40 μm, in an ethylcellulose:acid excipient:ibuprofen 50:25:25 compact weight ratio.

8.6.4. Model 2 (acid excipient release data)

It was found that when acid excipient release data from ethylcellulose 4 cP or 100 cP viscosity grade compacts was fitted to model 2, the coefficient of determination values were equal to or greater than the values determined for model 1 (table 8.12. and table 8.13.). In addition, in each instance the MSC values determined for model 2 were greater than those determined for model 1.

Ritger and Peppas (1987) determined that N should be in the range of 0.425-0.500 for disk shaped matrices when diffusion is the release mechanism. The diffusional exponent values determined for acid excipient (sieved less than 180 μm) release from

ethylcellulose 4 cP formulations of ethylcellulose:acid excipient:ibuprofen 50:25:25 weight ratio were all within this range i.e. acid excipient release was controlled by Fickian diffusion. However, diffusional exponent values determined for adipic acid, succinic acid or L-(+)-tartaric acid release studies from all ethylcellulose 100 cP formulations exceeded 0.50 i.e. acid excipient release was controlled by a combination of Fickian and non-Fickian mechanisms of release. It was also found that the diffusional exponent determined for acid release studies from formulations prepared with the succinic acid:ibuprofen weight ratio of 40:10 was greater than that value determined for formulations prepared with the succinic acid:ibuprofen weight ratio of 25:25. This was evident for model 2 fits to acid excipient release studies from formulations of either ethylcellulose viscosity grade. Indeed, the exponent N determined for release studies from ethylcellulose 4 cP:succinic acid:ibuprofen 50:40:10 compact was greater than 0.500.

Model 2 when fitted to acid excipient release data from compacts prepared with the acid excipient sieved less than 40 μm had a higher diffusional exponent than the exponent found for acid excipient release data from formulations prepared with the acid excipient sieved less than 180 μm. In fact, the diffusional exponent value for ethylcellulose 4 cP:L-(+)-tartaric acid:ibuprofen formulations prepared with acid excipient sieved less than 40 μm exceeded the Ritger and Peppas (1987) range for Fickian diffusion.

The diffusional exponent determined for model 2 fits to acid excipient release from ethylcellulose 4 cP formulations were less than those values determined for model 2 fits to ibuprofen release from ethylcellulose 100 cP formulations, for each formulation. This suggests that additional mechanisms of release are contributing to acid excipient release from ethylcellulose 100 cP formulations, and represents the coupling of diffusion and polymer relaxation phenomenon.

Table 8.13.

Parameters and statistical estimates of model 2 fits to acid excipient release data from ethylcellulose:acid excipient:ibuprofen compacts

AE:IB	k	Std Dev	N	Std	c	Std	CoD	MSC
Ethylcellulose	**(%min^{-N})**	**of k**		**Dev of**		**Dev of**		
4 cP				**N**		**c**		
EC:AA:IB 25:25	1.5007	0.1344	0.4641	0.0090	-0.3786	0.7641	0.9936	4.7199
EC:TA:IB 25:25	2.1953	0.0769	0.4872	0.0034	-0.3669	0.4515	0.9991	6.5620
EC:SA:IB 25:25	1.7684	0.0759	0.4782	0.0041	-0.3324	0.4353	0.9985	6.1283
EC:SA:IB 30:20	1.8244	0.0611	0.4883	0.0032	-0.1941	0.3650	0.9991	6.6900
EC:SA:IB 35:15	2.0813	0.0707	0.4886	0.0033	-0.2245	0.4224	0.9991	6.6801
EC:SA:IB 40:10	2.3803	0.0375	0.5023	0.0015	-0.1780	0..2284	0.9998	8.1871
EC:AA:IB PS	1.6481	0.1200	0.4841	0.0067	-0.4280	0.7098	0.9960	5.2110
EC:SA:IB PS	1.8202	0.0632	0.4980	0.0033	-0.2364	0.3922	0.9991	6.7719
EC:TA:IB PS	2.4129	0.1062	0.5080	0.0042	-0.5312	0.6328	0.9985	6.1930
Ethylcellulose								
100 cP								
EC:AA:IB 25:25	2.2094	0.089	0.5045	0.0040	0.0133	0.5416	0.9989	6.4120
EC:TA:IB 25:25	2.9258	0.1188	0.5318	0.0047	-0.0054	0.5993	0.9990	6.3336
EC:SA:IB 25:25	2.3919	0.1214	0.5179	0.0053	0.2725	0.7227	0.9984	5.9643
EC:SA:IB 30:20	2.6252	0.0981	0.5349	0.0040	-0.2516	0.5646	0.9991	6.5572
EC:SA:IB 35:15	2.9606	0.1105	0.5385	0.0043	-0.1136	0.5499	0.9992	6.4935
EC:SA:IB 40:10	3.1567	0.2022	0.5567	0.0078	-0.4727	0.9678	0.9978	5.4629
EC:AA:IB PS	2.2940	0.0800	0.5260	0.0036	-0.0007	0.4738	0.9992	6.7018
EC:SA:IB PS	2.5889	0.1030	0.5374	0.0044	0.1360	0.5580	0.9990	6.3953
EC:TA:IB PS	3.2526	0.2348	0.5571	0.0088	-0.5649	1.1257	0.9972	5.2264

Std Dev: Standard deviation, CoD: Coefficient of determination, MSC: Model selection criterion, EC: ethylcellulose, AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid, IB: ibuprofen, PS: indicates acid excipient sieved less than 40 μm, in an ethylcellulose:acid excipient:ibuprofen 50:25:25 compact weight ratio.

8.7. CONCLUSION

The objective of this chapter was to achieve zero order release of a weakly acidic drug from ethylcellulose matrix tablets in phosphate buffer pH 7.40. Organic acid excipients were used to create an acidic micro-environmental pH inside the polymer matrices, which suppressed ibuprofen dissolution. Due to acid excipient dissolution there was a rise in pH at the compact surface liquid interface, resulting in an increase in ibuprofen solubility and dissolution. In addition, the porosity of the matrix

compact increases as the acid excipient is released. This contributes to an increase in the ibuprofen release rate. This balances the increased distance that must be traversed by the ibuprofen molecule out of the matrix compact as dissolution proceeds. As a result the downward curvature of the ibuprofen dissolution profile was reduced and zero order drug release was approached. This was measured using either the initial release rate to limiting release rate ratio, or the diffusional exponent as determined by Ritger and Peppas (1987).

Compacts prepared with L-(+)-tartaric acid (as opposed to succinic acid or adipic acid) were nearest zero-order ibuprofen release. In addition, compacts prepared with higher succinic acid:ibuprofen weight ratios were nearer zero-order ibuprofen release than their lower succinic acid:ibuprofen weight ratio counterparts. Formulating matrix compacts with acid excipient sieved less than 40 μm also resulted in a lowering of the initial to limiting ibuprofen release rate ratio. Therefore, the inclusion of acid excipients in ethylcellulose:ibuprofen formulations caused Higuchi drug release to be altered so that it resembled a zero order profile. For each formulation examined, ibuprofen release from ethylcellulose 100 cP compacts was a step nearer constant drug release than release from ethylcellulose 4 cP compacts. Acid excipient release from all formulations was also examined. This followed a predominately Fickian diffusion controlled mechanism of release.

CHAPTER 9

THE EFFECT OF COMPACT SHAPE AND COMPACTION PRESSURE ON DISSOLUTION FROM TWO-COMPONENT ACID EXCIPIENT:IBUPROFEN COMPACTS

9.1. INTRODUCTION

Previous work has shown that ibuprofen dissolution profiles from mixed ibuprofen:acid excipient compressed discs have a positive curvature, the extent of which depends on the excipient used and the acid excipient:ibuprofen weight ratio in the disc (Healy, 1995). It was thought that by matching the positive curvature of the acid drug dissolution profiles as observed from single surface exposed compressed disc, to a reducing surface area as would be achieved with a sphere, zero-order drug release could be achieved. In this study it was not feasible to prepare spherical compacts of acid excipient:ibuprofen, instead compacts were prepared with a biconvex face.

The dissolution characteristic of ibuprofen in the presence of various acid excipients from compressd discs of different shapes was investigated. Acid excipients of varying solubility and pK_a were incorporated with ibuprofen in mixed discs (50:50 weight ratio) in one of two different tablet shapes plane-face or biconvex, and compacted at one of two different compaction pressures. The dissolution of ibuprofen and acid excipient was then measured.

9.2. CHARACTERISATION OF COMPACTS

9.2.1. Height, area and volume measurements

Compacts prepared with L-(+)-tartaric acid:ibuprofen had lower height, area and volume dimensions than compacts prepared with succinic acid:ibuprofen and adipic acid:ibuprofen at both low and high compaction pressure. This was evident for compacts prepared as plane-faced compacts or biconvex compacts. Adipic acid:ibuprofen compacts had the greatest height, area and volume measurements at low or high compaction pressures, for each of the different compact shapes examined. A similar trend was evident for ethylcellulose:acid excipient:ibuprofen compacts in chapter 8. The height, area and volume of acid excipient:ibuprofen compacts was reduced with increasing compaction pressure. This was evident for compacts prepared as plane-faced or biconvex compacts and suggests increased consolidation exists at higher compaction pressures. Vromans and Lerk (1988) showed that

increased consolidation was demonstrated by a reduced compact thickness. Results also showed that at each compaction pressure, the acid excipient:ibuprofen biconvex compacts had less area and volume than acid excipient:ibuprofen plane-faced compacts (for each of the different acid excipient:ibuprofen systems examined). This was previously shown by Ford *et al.* (1987), who found that biconvex matrix tablets compacted at the same pressure, weight and formula as plane-faced tablets had less area.

A summary of mean results is outlined in tables 9.1. to 9.4.

Table 9.1.

Characterisation of plane-faced acid excipient:ibuprofen compacts compacted at low pressure

Plane-faced compacts	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
Height (cm)	0.300	0.280	0.270
Area (cm^2)	1.936	1.883	1.856
Apparent Volume (cm^3)	0.170	0.159	0.153
Porosity ε_0	0.038	0.031	0.041
Hardness (kg)	6.15 ± 0.06	5.91 ± 0.10	5.64 ± 0.06
Tensile strength (kg/cm^2)	15.35 ± 0.15	15.81 ± 0.27	15.65 ± 0.16

Table 9.2.

Characterisation of plane-faced acid excipient:ibuprofen compacts compacted at high pressure

Plane-faced compacts	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
Height (cm)	0.295	0.275	0.265
Area (cm^2)	1.923	1.869	1.843
Apparent Volume (cm^3)	0.168	0.156	0.150
Porosity ε_0	0.022	0.013	0.023
Hardness (kg)	7.27 ± 0.06	6.90 ± 0.06	6.66 ± 0.06
Tensile strength (kg/cm^2)	18.46 ± 0.15	18.79 ± 0.16	18.82 ± 0.17

Table 9.3.

Characterisation of acid excipient:ibuprofen biconvex compacts compacted at low pressure

Biconvex compacts	**Adipic acid**	**Succinic acid**	**L-(+)-tartaric acid**
Height (h_2)	0.465	0.445	0.435
Area (cm^2)	1.623	1.570	1.543
Apparent Volume (cm^3)	0.169	0.157	0.152
Porosity ε_0	0.029	0.020	0.030
Hardness (kg)	5.74 ± 0.06	4.86 ± 0.06	4.21 ± 0.12
Tensile strength (kg/cm^2)	17.82 ± 0.18	18.09 ± 0.22	17.73 ± 0.50

Table 9.4.

Characterisation of acid excipient:ibuprofen biconvex compacts compacted at high pressure

Biconvex compacts	Adipic acid	Succinic acid	L-(+)-tartaric acid
Height (h_2)	0.460	0.440	0.430
Area (cm^2)	1.610	1.556	1.530
Apparent Volume (cm^3)	0.166	0.154	0.149
Porosity ε_0	0.011	0.008	0.011
Hardness (kg)	7.24 ± 0.10	5.98 ± 0.06	5.23 ± 0.06
Tensile strength (kg/cm^2)	23.38 ± 0.33	23.58 ± 0.23	23.71 ± 0.27

9.2.2. Porosity

In most cases, the interparticulate porosity of compacts formulated with L-(+)-tartaric acid was slightly greater than the interparticulate porosity of compacts formulated with succinic acid or adipic acid. In addition, the interparticulate porosity of acid excipient:ibuprofen compacts compacted at high pressure was less than the interparticulate porosity of acid excipient:ibuprofen compacts compacted at low pressure. Pitt *et al.* (1990) found similar results i.e. increased porosity at reduced compaction pressure. The interparticulate porosity of biconvex tablets was less than the interparticulate porosity of compacts prepared using the flat-faced punch for each of the different acid excipient:ibuprofen systems examined. This was evident at each disc compaction pressure examined.

9.2.3. Tensile strength

There was no significant difference ($p \leq 0.05$) in the tensile strength of succinic acid:ibuprofen compacts and adipic acid:ibuprofen compacts and L-(+)-tartaric acid:ibuprofen compacts compacted under the same conditions i.e. same disc shape and same compaction pressure. This was confirmed using a two-sample t-test, assuming equal variance. The tensile strength of compacts prepared at high pressure was greater than the tensile strength of compacts prepared at low pressure, for each acid excipient:ibuprofen compact shape examined. Examination of tensile strength versus porosity plots in figure 9.1. shows that with reducing porosity (with increased compaction) the material tensile strength of compacts increased, for both biconvex and plane-faced compacts. Similar results were found by Pitt *et al.* (1990).

The tensile strength of acid excipient:ibuprofen biconvex compacts was greater than the tensile strength of acid excipient:ibuprofen plane-faced tablets, for each

compaction pressure. This difference in tensile strength between biconvex and plane-faced compacts is accounted for by differences in compaction behaviour. Pitt *et al.* (1990) proposed that a very complex relationship exists between the movement of powder during compaction, specimen dimensions and material tensile strength. This is because there is more pronounced movement of powder in the concave punch faces than the more shallow (or flat-face) punch set. Leuenberger and Rohera (1986) when examining the fundamentals of powder compression showed that interparticulate slippage leads to closer packing. In addition, there are also likely to be differences between the top and bottom caps as the mechanism of powder filling is different. The lower cap is filled directly by powder settling and the upper one has to be filled by powder movement upwards during the compression cycle. The extent of these differences depends on the different face curvatures and may influence the resulting compact characteristics including, porosity and tensile strength. Pitt *et al.* (1990) showed that tablets of a certain face–curvature range and cylinder length could have a higher tensile strength than plane-faced tablets.

The tensile strength of plane-faced compacts compacted at high pressure was significantly greater than the tensile strength of biconvex tablets compacted at low pressure ($p \leq 0.05$). This was determined using a two-sample t-test, assuming equal variance.

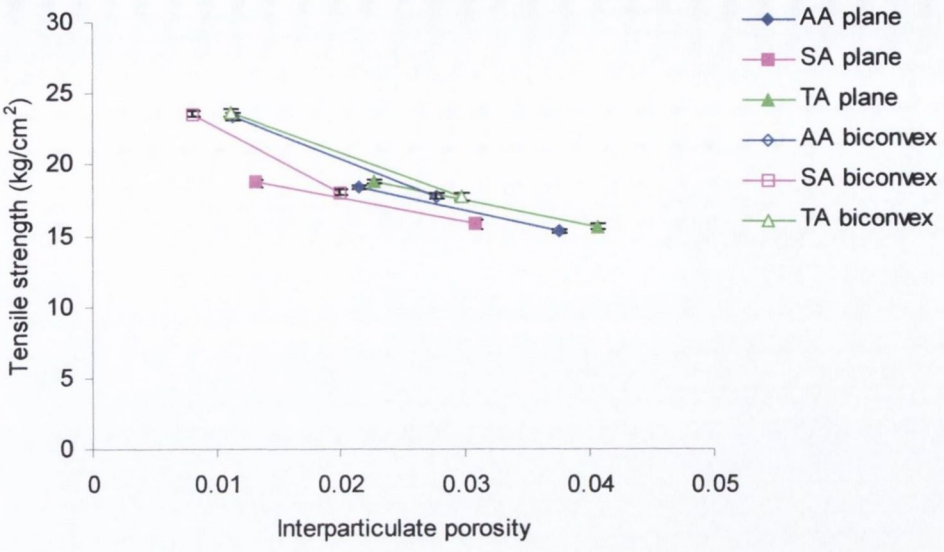

Figure 9.1. Plot of compact tensile strength versus interparticulate porosity of plane-faced or biconvex-faced acid excipient:ibuprofen compacts. AA: adipic acid, SA: succinic acid, TA: L-(+)-tartaric acid.

9.3. RELEASE STUDIES

9.3.1. Effect of acid excipient on ibuprofen dissolution from two-component plane-faced compacts

As can be seen in figures 9.2. and 9.3. the excipient dissolution profiles showed a downward curvature. This was evident for compacts prepared at both high and low compaction pressure. This is because the initial release rate was greater than the final release rate and is illustrated in figures 9.4. and 9.5. This downward curvature is a result of the recession of the acid excipient from the disc surface and the necessity for it to diffuse through a porous layer at the disc surface, the thickness of which increases with time. This was demonstrated by Healy (1995) using X-ray diffraction patterns of the disc surface. The acid excipient with the lowest dissolution rate was adipic acid followed by succinic acid and L-(+)-tartaric acid. This was evident for compacts prepared at both compaction pressures. This was readily explained by the difference in solubility between the various acid excipients (table 1.1. in chapter 1, section 1.4.).

The acid excipient release rate from plane-faced compacts prepared at high compaction pressure was less than the acid excipient release rate from plane-faced compacts prepared at low compaction pressure, for each acid excipient examined. This was determined using a two-sample t-test, assuming equal variance ($p \leq 0.05$) at each sampling time point.

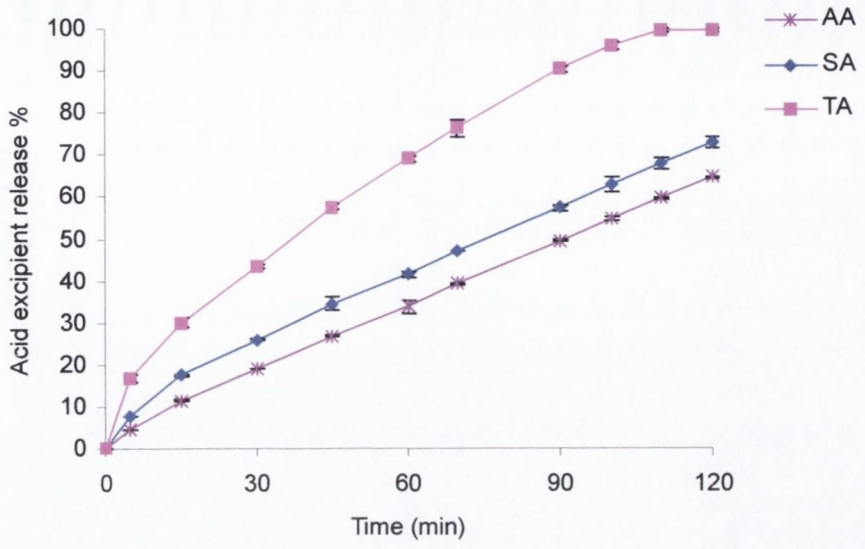

Figure 9.2. Percentage acid excipient release from acid excipient:ibuprofen plane-faced compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

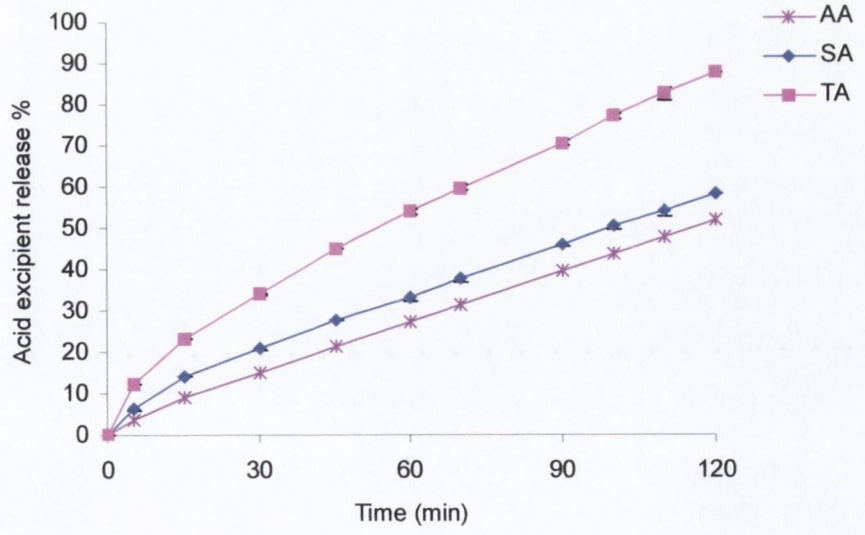

Figure 9.3. Percentage acid excipient release from acid excipient:ibuprofen plane-faced compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

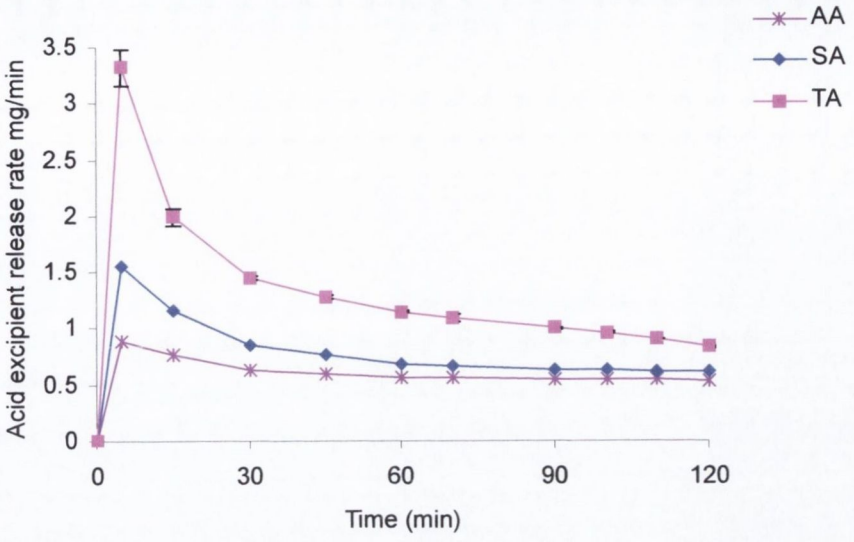

Figure 9.4. Acid excipient release rate from acid excipient:ibuprofen plane-faced compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

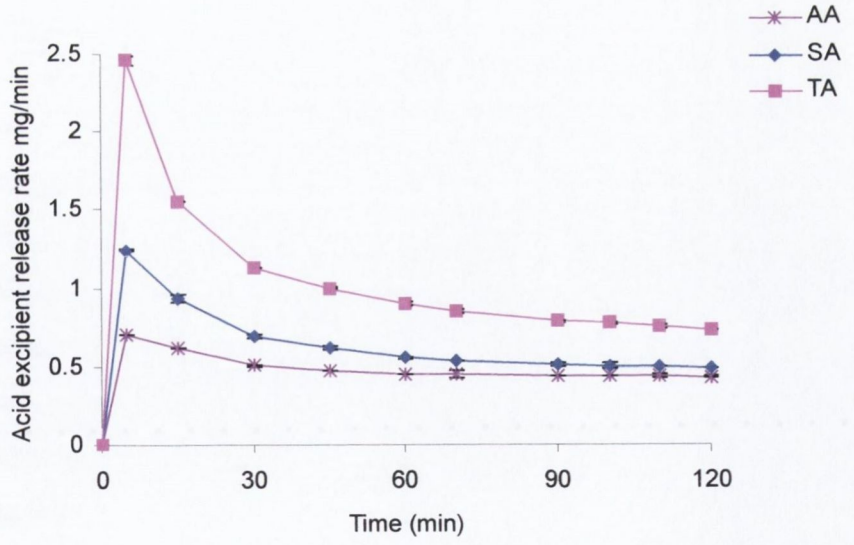

Figure 9.5. Acid excipient release rate from acid excipient:ibuprofen plane-faced compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

Ibuprofen dissolution from acid excipient:ibuprofen plane-faced compacts (compacted at either high or low compaction pressure) was then measured. The profiles rather than being linear, as predicted by the simple non-interacting model for polyphase

mixtures (Higuchi *et al.*, 1965) showed positive–curvature in all cases (figures 9.6. and 9.7.). Healy (1995) showed that the dissolution rate of ibuprofen was decreased in the presence of the various different acid excipients. The positive curvature can be attributed to the recession of the acid excipient from the surface of the disc. As the excipient recedes there is a rise in pH at the surface-liquid interface. This in turn leads to an increase in the ibuprofen solubility and the ibuprofen dissolution rate (figures 9.8. and 9.9.) (Healy, 1995).

Positive curvature of the ibuprofen dissolution profiles shows that the initial dissolution rate is lower than the limiting dissolution rate at the end of the dissolution run.

Limiting ibuprofen dissolution rates were calculated from the mean rates of the last two intervals except in cases where all the acid excipient had dissolved away from the disc before this time (table 9.5 and 9.6). This was evident for flat-faced discs prepared with L-(+)-tartaric acid:ibuprofen and compacted at low compaction pressure. In this instance, the limiting rate was calculated from the mean rates at the last two time points before all of the acid excipient was seen to be in solution. Ibuprofen initial rates were calculated from the mean rates at 5 and 15 minutes (table 9.5. and 9.6.).

For both compaction pressures, the difference between the ibuprofen initial and limiting dissolution rates produced over the sampling time period increased with increasing acid excipient solubility (table 9.5. and 9.6.). In general, the greater the solubility of the acid excipient, the greater the suppression and curvature seen over the sampling time period. This can be explained since, the greater the solubility of the acid excipient the greater the concentration of excipient which will be in solution adjacent to the disc surface. Two sample t-test, assuming equal variance showed a significant difference ($p \leq 0.05$) at all sampling time points between ibuprofen dissolution rates from compacts prepared with either of the three acid excipients. This was evident for acid excipient:ibuprofen systems compacted at either low or high compaction pressure.

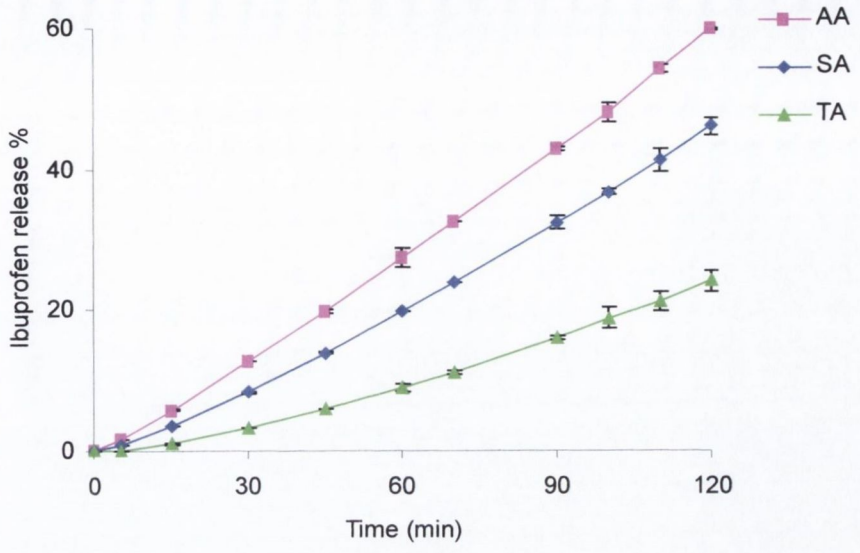

Figure 9.6. Percentage ibuprofen release from acid excipient:ibuprofen plane-faced compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

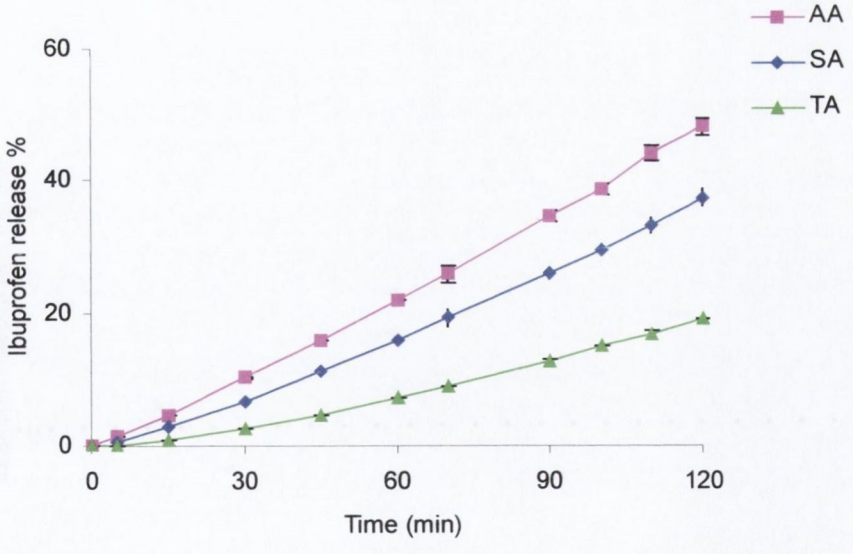

Figure 9.7. Percentage ibuprofen release from acid excipient:ibuprofen plane-faced compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

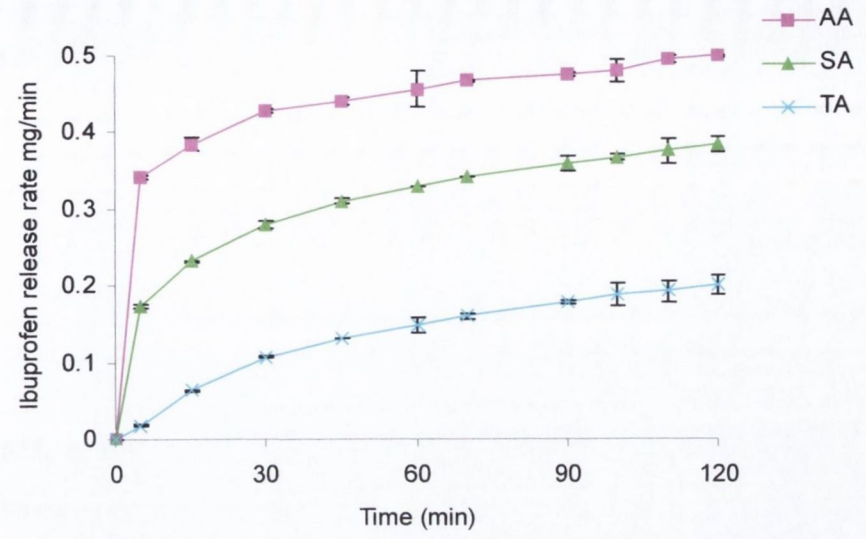

Figure 9.8. Ibuprofen release rate from acid excipient:ibuprofen plane-faced compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

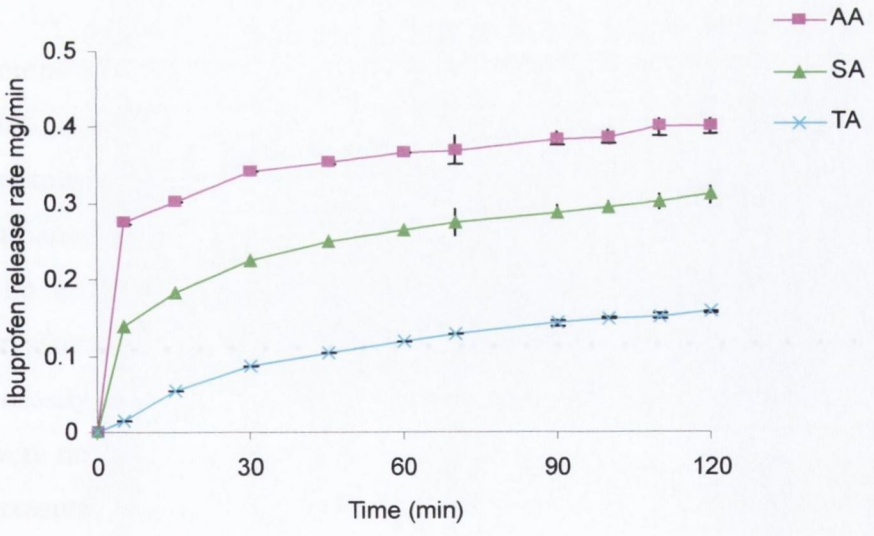

Figure 9.9. Ibuprofen release rate from acid excipient:ibuprofen plane-faced compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

Table 9.5.

Ibuprofen initial and limiting dissolution rates from plane-faced compacts compacted at low pressure

Dissolution rate (mg/min)	Adipic Acid	Succinic acid	L-(+)-tartaric acid
Initial (I)	0.3632	0.2021	0.0411
Limiting (L)	0.4970	0.3795	0.1830*
Ratio (L:I)	1.3684	1.8775	4.4566

*limiting release rate measured at 90 minutes and 100 minutes

Table 9.6.

Ibuprofen initial and limiting dissolution rates from plane-faced compacts compacted at high pressure

Dissolution rate (mg/min)	Adipic Acid	Succinic acid	L-(+)-tartaric acid
Initial (I)	0.2878	0.1607	0.0346
Limiting (L)	0.4003	0.3061	0.1548
Ratio (L:I)	1.3909	1.9049	4.4774

It was also found that the ibuprofen dissolution rate was lower from plane-faced compacts compacted at high compaction pressure than from plane-faced compacts compacted at low compaction pressure, for each of the ibuprofen:acid excipient compacts examined. This was confirmed using a two-sample t-test, assuming equal variance ($p \leq 0.05$) at each sampling time point.

The difference in dissolution rate of compacts prepared at different compaction pressures was attributed to the difference in tensile strength and interparticulate porosity of the relevant compacts. Compacts prepared at the low compaction pressure were not as dense (i.e. higher porosity) as compacts prepared at the higher compaction pressure. It is thought that this facilitated quicker solvent penetration and dissolution of acid excipient and ibuprofen from compacts prepared at low pressure.

A greater degree of suppression of ibuprofen dissolution (as indicated by the higher L:I ratio) was evident for compacts prepared at the high compaction pressure than for compacts prepared at the low pressure, for each acid excipient:ibuprofen plane-faced system. It was thought that the reason for the difference in dissolution properties may

be that on compaction at high pressure, the particle size of the mixed powders is reduced, leading to a more closely packed compact. This compact of finer particles has different dissolution properties. The more intimate contact between ibuprofen and acid excipient may lead to a more uniform suppressing effect of the acid excipient on ibuprofen. To explain, if the uniformity of powder mix is enhanced by compaction, the results will be that no significant area of ibuprofen surface will be left unexposed to the retarding influence of the acid excipient. Therefore, each particle of ibuprofen will be adjacent to dissolving acid excipient or to porous pathways left by the dissolving acid. Hence, the degree of ibuprofen suppression will be more uniform or greater. In the case of compacts prepared at the low compaction pressure, the point of uniformity is not as high. As a result, there is a greater chance in the existence of areas of ibuprofen particles being non adjacent to dissolving acid excipient, and being less affected by the retarding influence of the excipient on solubility and dissolution.

9.3.2. Effect of acid excipient on ibuprofen dissolution from two-component biconvex compacts

Physical mixtures were prepared with ibuprofen and one of three different acid excipients namely adipic acid, succinic acid or L-(+)-tartaric acid in a 50:50 weight ratio. Each powder mixture was compacted into biconvex compacts at one of two different compactions pressures, previously designated high or low compaction pressure. The dissolution profiles of ibuprofen and acid excipient were determined.

As can be seen in figures 9.10. and 9.11. the acid excipient dissolution profiles from biconvex compacts showed a downward curvature (similar to acid excipient dissolution profiles from plane-faced compacts) i.e. the acid excipient initial release rate was greater than the acid excipient limiting release rate. This was evident for compacts at either compaction pressure. Results also found that the acid excipient release rate from biconvex compacts prepared at high pressure was less than those release rates from biconvex compacts compacted at low pressure, for each of the acid excipient:ibuprofen systems examined. This was confirmed statistically by undertaking a two-sample t-test, assuming equal variance ($p \leq 0.05$) on each sampling time point.

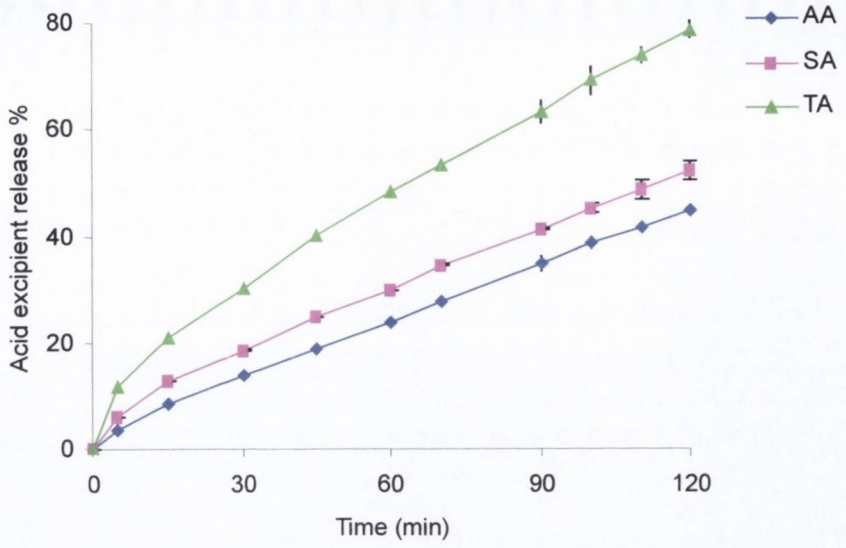

Figure 9.10. Percentage acid excipient release from acid excipient:ibuprofen biconvex compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

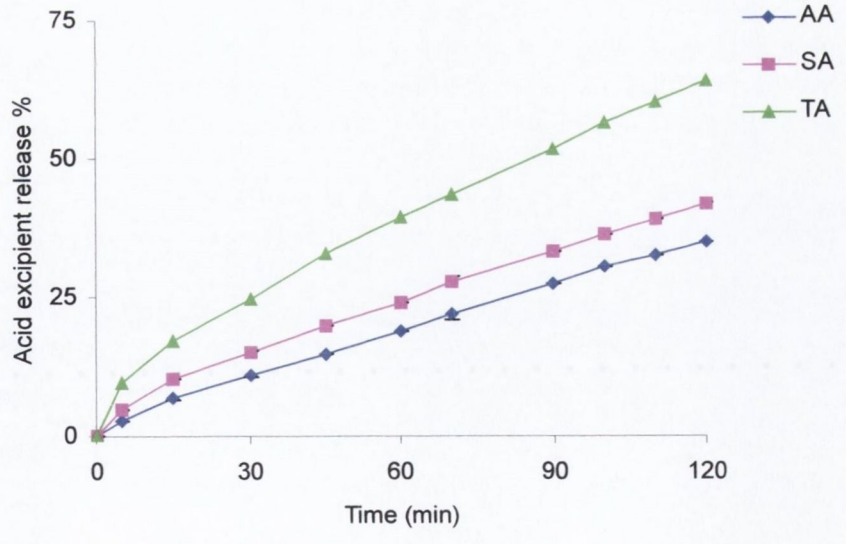

Figure 9.11. Percentage acid excipient release from acid excipient:ibuprofen biconvex compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

Ibuprofen dissolution from the various biconvex systems was then measured. Similar to release studies from plane-faced compacts, the ibuprofen dissolution profile

showed an upward curvature, due to the recession of the acid excipient from the surface of the disc (figures 9.12. and 9.13.). This was evident for compacts prepared at either compaction pressure. Limiting and initial ibuprofen dissolution rates were also calculated and the difference between the two rates measured (table 9.7. and 9.8.). Similar to compacts prepared with a plane-face, the greatest degree of suppression was evident for compacts prepared with L-(+)-tartaric acid, while the least was observed for compacts prepared with adipic acid (figures 9.14. and 9.15.). Two sample t-test assuming equal variance showed there was significant differences ($p \leq 0.05$) at all sampling time points, between ibuprofen dissolution rates from biconvex compacts prepared with either of the three acid excipients. This was evident for compacts prepared at high or low compaction pressure.

The ibuprofen release rate was lower from biconvex compacts compacted at high pressure than from biconvex compacts compacted at low pressure for each of the different acid excipient:ibuprofen biconvex systems examined, except for the L-(+)-tartaric acid:ibuprofen system at the 5 minute sampling point. This was confirmed by performing a two-sample t-test, assuming equal variance on each sampling time point of the dissolution profile. In addition, compacts prepared at high compaction pressure experienced greater ibuprofen suppression than compacts prepared at low compaction pressure. This was evident in the increased L:I ratio for each acid excipient:ibuprofen system prepared at a higher compaction pressure (table 9.7. and 9.8.). The difference in both porosity and hardness of compacts (prepared at different pressures) was thought to be responsible for the difference in dissolution rates at high and low compaction pressure. While the greater suppression of ibuprofen at high compaction pressure is possibly due to the acid excipient and ibuprofen uniformity of mix being improved at higher compaction pressures.

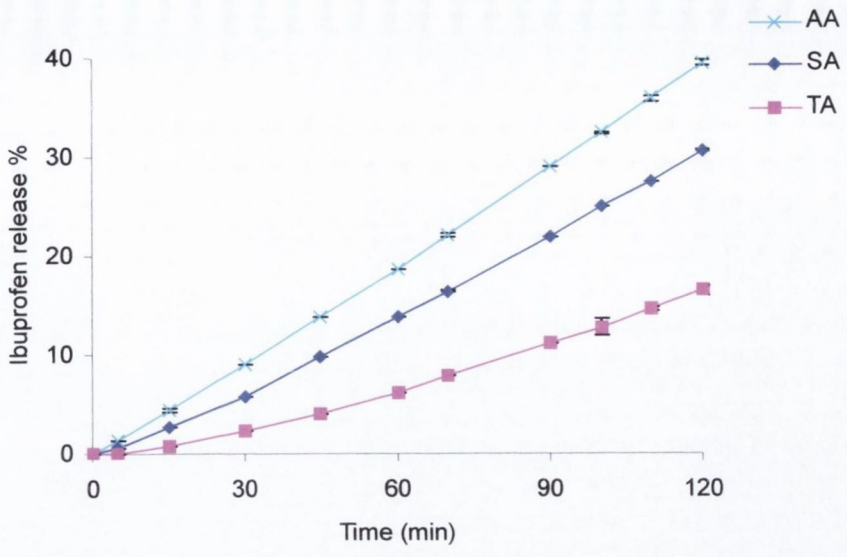

Figure 9.12. Percentage ibuprofen release from acid excipient:ibuprofen biconvex compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

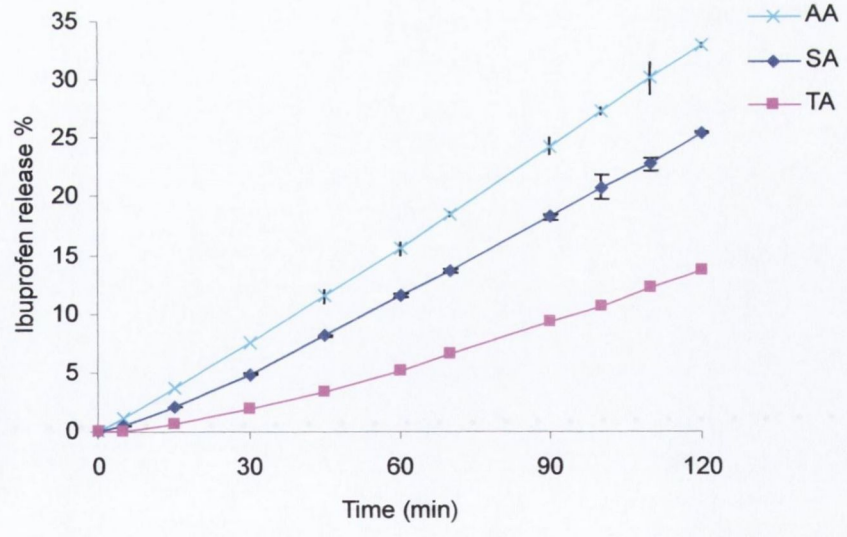

Figure 9.13. Percentage ibuprofen release from acid excipient:ibuprofen biconvex compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

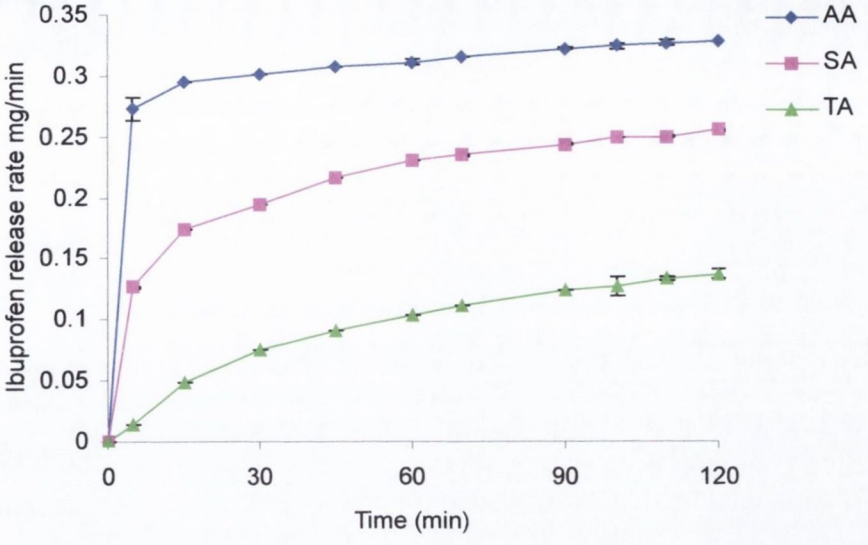

Figure 9.14. Ibuprofen release rate from acid excipient:ibuprofen biconvex compacts compacted at low pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

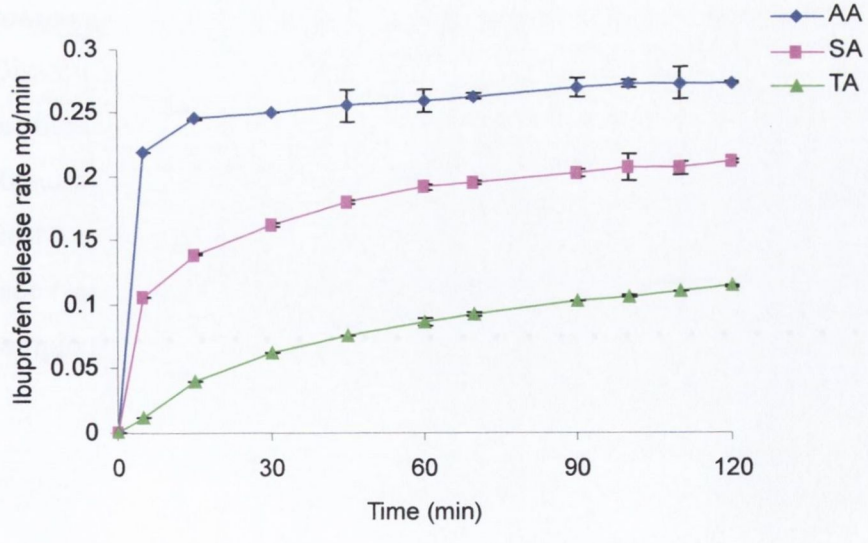

Figure 9.15. Ibuprofen release rate from acid excipient:ibuprofen biconvex compacts compacted at high pressure. AA is adipic acid, SA is succinic acid and TA is L-(+)-tartaric acid.

Table 9.7.

Ibuprofen initial and limiting dissolution rates from biconvex compacts compacted at low pressure

Dissolution rate (mg/min)	Adipic Acid	Succinic acid	L-(+)-tartaric acid
Initial (I)	0.2844	0.1507	0.0314
Limiting (L)	0.3277	0.2527	0.1351
Ratio (L:I)	1.1522	1.6767	4.2990

Table 9.8.

Ibuprofen initial and limiting dissolution rates from biconvex compacts compacted at high pressure

Dissolution rate (mg/min)	Adipic Acid	Succinic acid	L-(+)-tartaric acid
Initial (I)	0.2326	0.1226	0.0261
Limiting (L)	0.2738	0.2094	0.1126
Ratio (L:I)	1.1773	1.7082	4.3190

9.3.3. Effect of compact shape on dissolution from acid excipient:ibuprofen compacts

Dissolution profiles from plane-faced compacts were compared with dissolution profiles from biconvex compacts, for each different compaction pressure investigated. Results showed the acid excipient dissolution rate was significantly lower ($p \leq 0.05$) from compacts prepared with convex face than from compacts prepared with plane-face (for each different compaction pressure) at each sampling time point (using a two sample t-test assuming equal variance) (figure 9.16. to figure 9.21.).

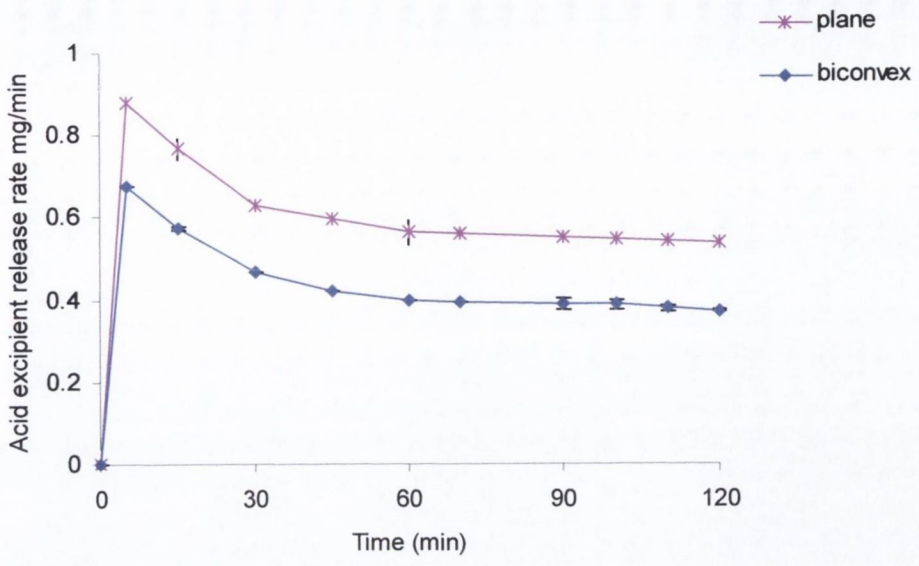

Figure 9.16. Adipic acid release rate from adipic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at low pressure.

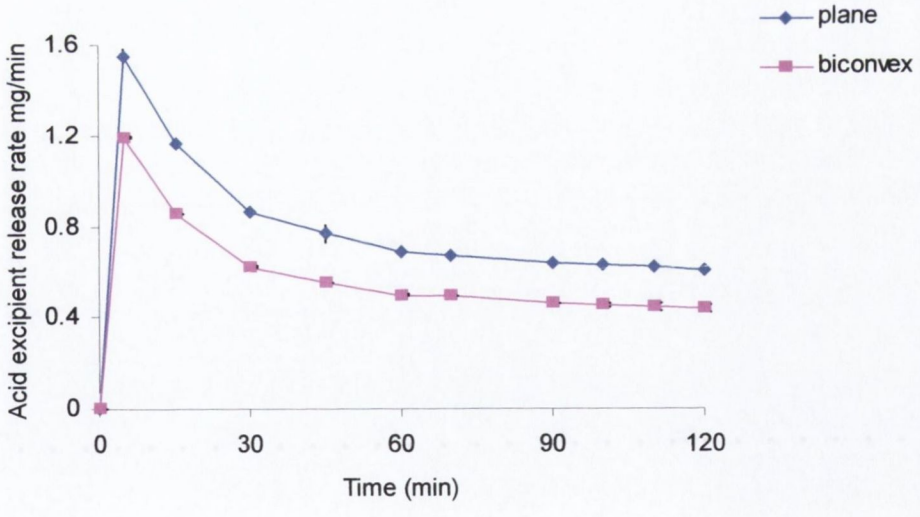

Figure 9.17. Succinic acid release rate from succinic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at low pressure.

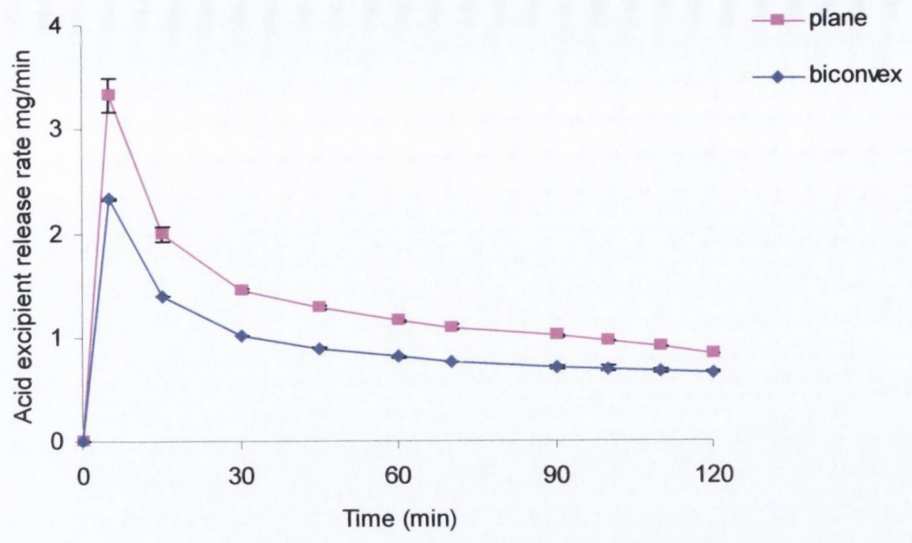

Figure 9.18. L-(+)-tartaric acid release rate from L-(+)-tartaric acid:ibuprofen plane-faced compacts or biconvex compacts compacted at low pressure.

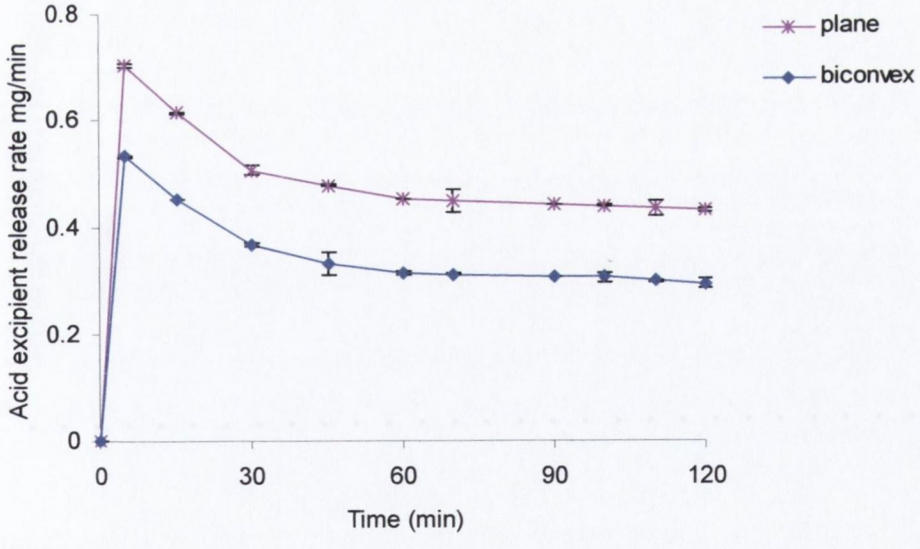

Figure 9.19. Adipic acid release rate from adipic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at high pressure.

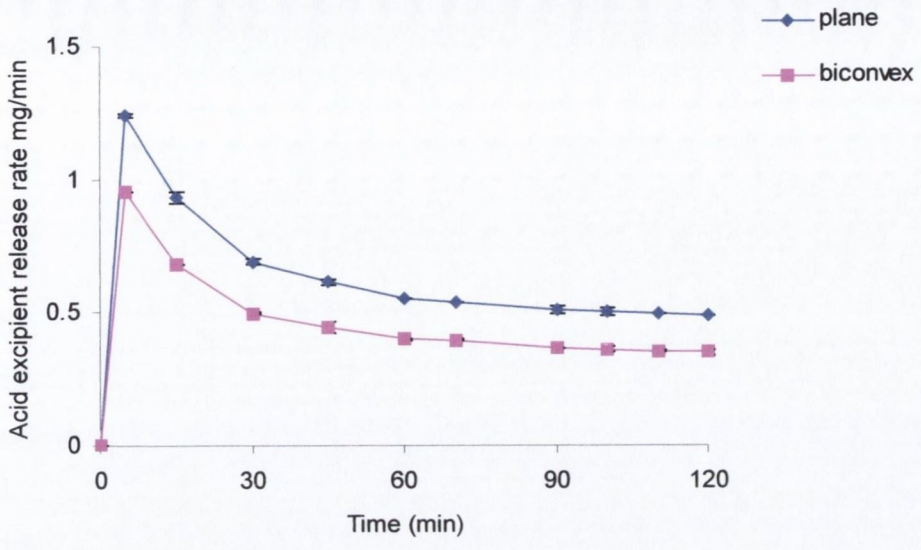

Figure 9.20. Succinic acid release rate from succinic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at high pressure.

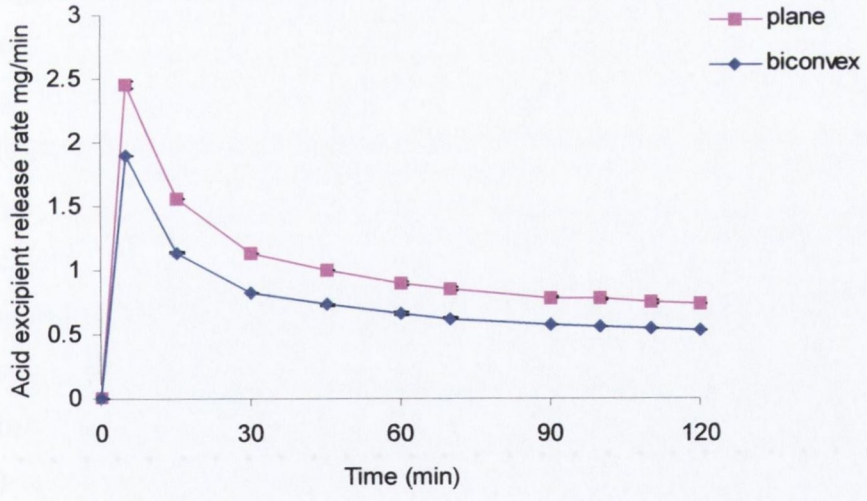

Figure 9.21. L-(+)-tartaric acid release rate from L-(+)-tartaric acid:ibuprofen plane-faced compacts or biconvex compacts compacted at high pressure.

The ibuprofen dissolution rate was significantly lower ($p \leq 0.05$) from biconvex compacts than from plane-faced compacts at each sampling point for each different acid excipient:ibuprofen system examined (except at the 5 minute sampling point for compacts prepared with L-(+)-tartaric acid:ibuprofen). This was evident at each compaction pressure (figures 9.22 to 9.27.).

The higher tensile strength and lower porosity of biconvex compacts (as compared to plane-faced compacts at each compaction pressure), was thought to contribute to the reduction in release rates. Ford *et al.* (1987) also compared drug release rates from biconvex and plane-faced matrix tablets. He found that biconvex tablets had a slower release rate than plane–faced compacts. He showed that a linear relationship existed between release rates and surface area and suggested that tablets should be as near spherical as possible to produce minimum release rates.

There was also an evident reduction in the L:I ratio when compacts were prepared with a biconvex face (as opposed to a plane-face) for each acid excipient:ibuprofen system (for both compaction pressures). In fact biconvex compacts prepared with adipic acid showed the greatest reduction in L:I ratio, while biconvex tablets prepared with L-(+)-tartaric acid showed the least reduction. This was evident at both compaction pressures.

It was thought that the reason for this reduction in L:I ratio (when compacts are prepared with a biconvex face) was due to the reducing surface area of biconvex type compacts i.e. the positive curvature of the acid drug dissolution profile was reduced due to the reducing biconvex surface area. As a consequence, zero-order drug release was approached (evident by the reduction of the L:I ratio). The acid excipient solubility used in the formulation influenced the magnitude of the reduction of the L:I ratio. The solubility of adipic acid was nearer the solubility of ibuprofen, than either succinic acid or L-(+)-tartaric acid and this acid excipient suppressed ibuprofen dissolution the least of all three acid excipients examined. Therefore, in biconvex systems of adipic acid:ibuprofen one had two dissolving components of nearer solubility, as opposed to two dissolving components of very different solubility i.e. L-(+)-tartaric acid:ibuprofen. The reducing biconvex surface area may have had a more pronounced effect on the two similarly dissolving components i.e. adipic acid:ibuprofen as opposed to the two very different dissolving components of L-(+)-tartaric acid:ibuprofen. Healy (1995) showed that with increasing time of dissolution, the porosity of ibuprofen:succinic acid systems and L-(+)-tartaric acid systems increased. The compressed discs using the more soluble acid (L-(+)-tartaric acid) showed a greater porosity at all time points than those which contained the less soluble excipient (succinic acid). This would suggest that the integrity of shape existed longer for the less soluble acid excipient than for the more soluble acid excipient (as was observed).

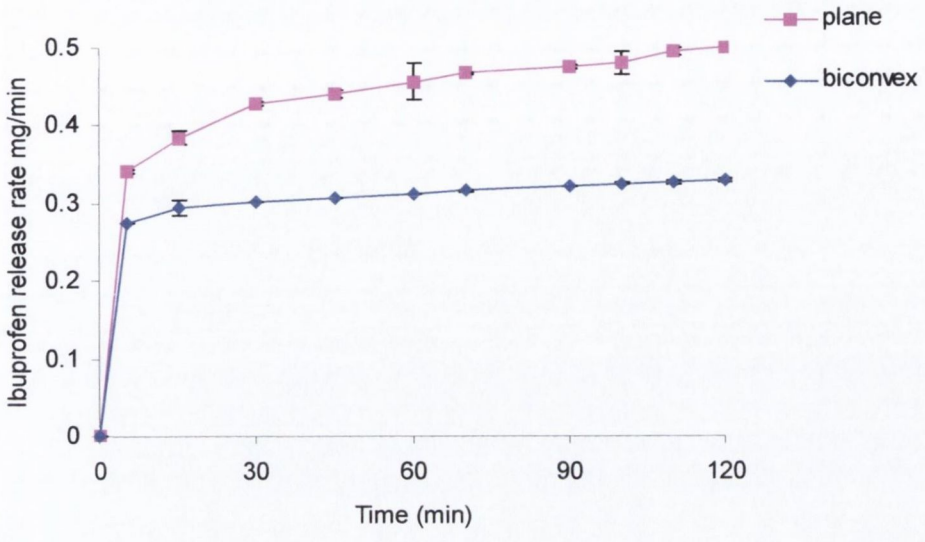

Figure 9.22. Ibuprofen release rate from adipic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at low pressure.

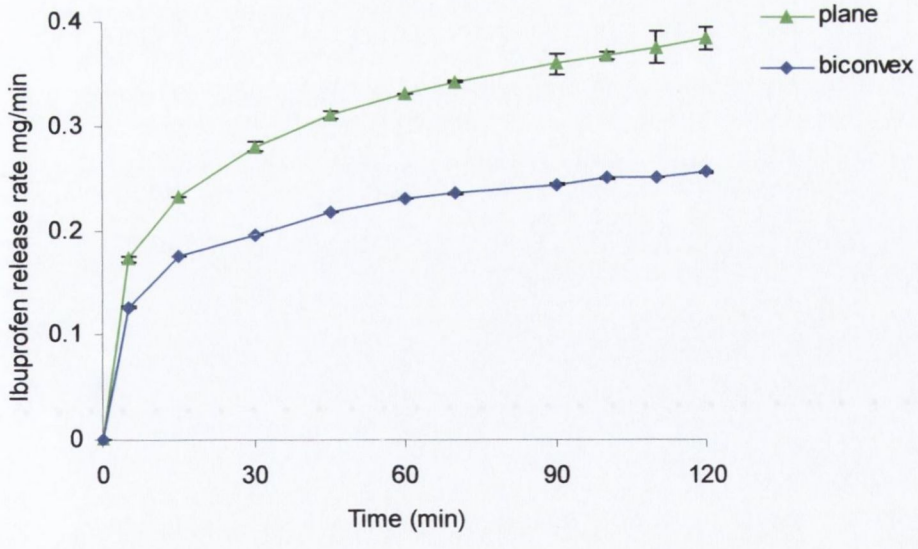

Figure 9.23. Ibuprofen release rate from succinic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at low pressure.

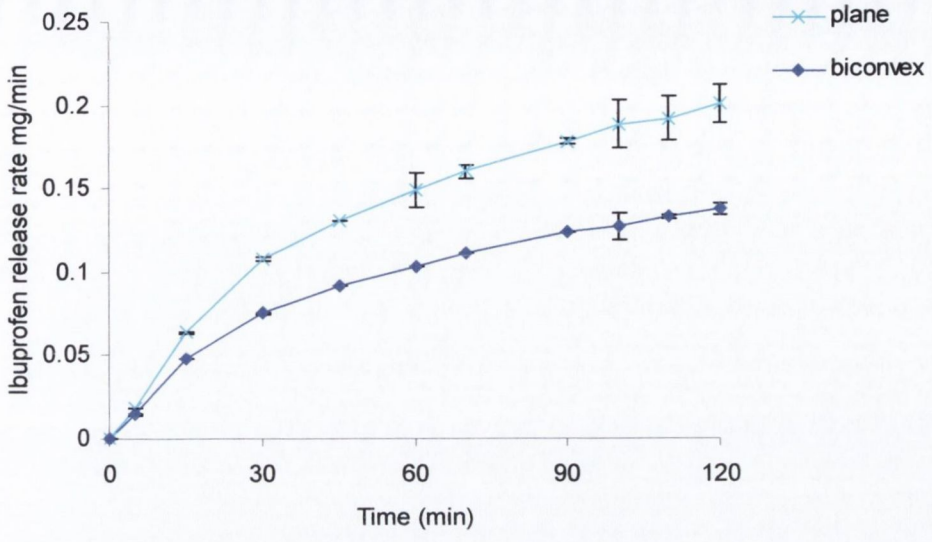

Figure 9.24. Ibuprofen release rate from L-(+)-tartaric acid:ibuprofen plane-faced cylindrical or biconvex compacts compacted at low pressure.

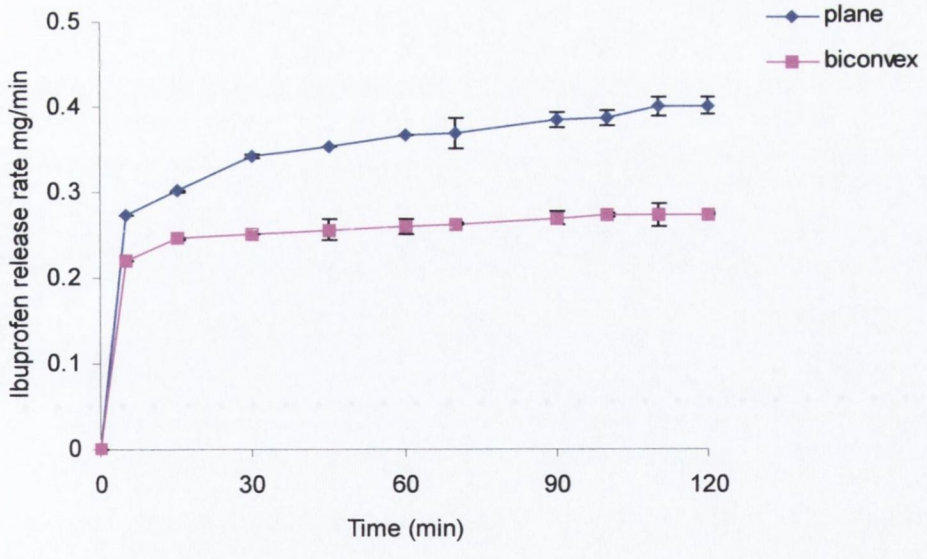

Figure 9.25. Ibuprofen release rate from adipic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at high pressure.

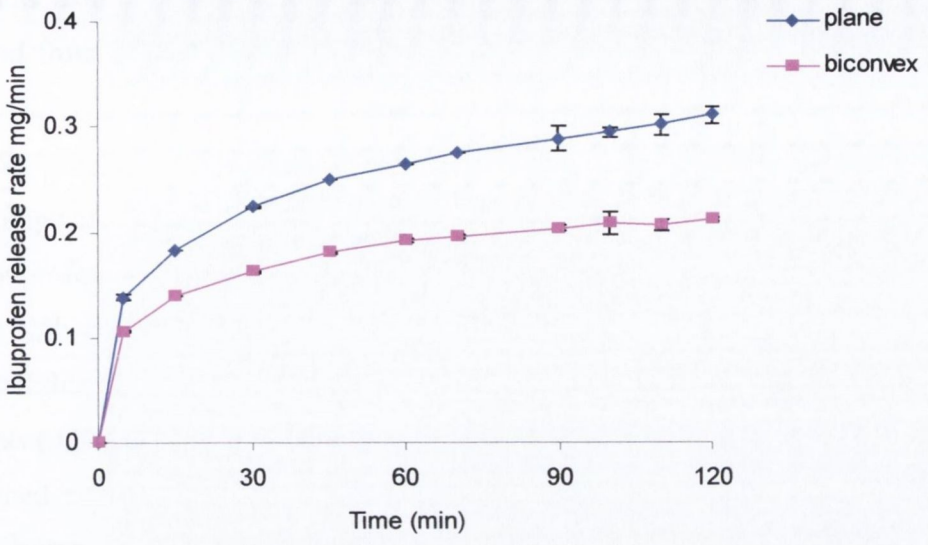

Figure 9.26. Ibuprofen release rate from succinic acid:ibuprofen plane-faced compacts or biconvex compacts compacted at high pressure.

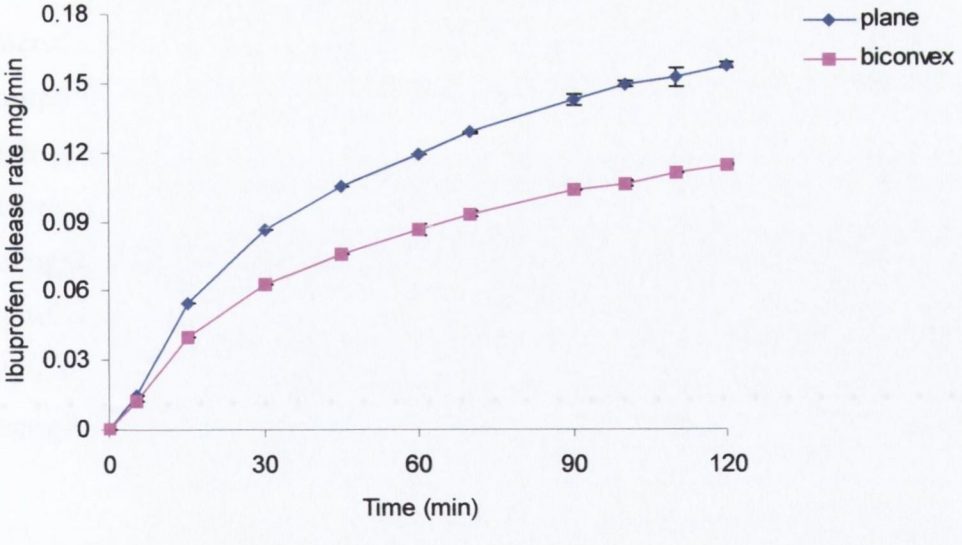

Figure 9.27. Ibuprofen release rate from L-(+)-tartaric acid:ibuprofen plane-faced compacts or biconvex compacts compacted at high pressure.

The ibuprofen dissolution profiles from plane-faced acid excipient:ibuprofen compacts compacted at high pressure was compared to ibuprofen dissolution profiles from acid excipient:ibuprofen biconvex compacts compacted at low pressure (figure 9.28. to 9.30.). These two systems of different compact shape were chosen because

they had the least difference in area, volume and tensile strength. Ibuprofen release rates from adipic acid:ibuprofen plane-faced compacts, compacted at high pressure and from biconvex compacts compacted at low pressure were significantly different ($p \leq 0.05$) for all sampling time points except at five and fifteen minutes. In addition, it was found that ibuprofen release rates from succinic acid:ibuprofen biconvex compacts (compacted at low pressure) were significantly lower ($p \leq 0.05$) than the ibuprofen release rates from succinic acid:ibuprofen plane-faced compacts compacted at high pressure, for all sampling points. The ibuprofen release rates of L-(+)-tartaric acid:ibuprofen biconvex compacts (compacted at low pressure) were also significantly less ($p \leq 0.05$) than the ibuprofen release rates from L-(+)-tartaric acid:ibuprofen plane-faced compacts compacted at high pressure, for all sampling points except at five minutes. The L:I ratio for ibuprofen dissolution from plane-faced compacts compacted at high pressure was greater than the L:I ratio for ibuprofen dissolution from biconvex compacts compacted at low pressure.

The acid excipient release rate from acid excipient:ibuprofen biconvex tablets compacted at low pressure was lower than the acid excipient release rate from plane-faced compacts compacted at high pressure, at all sampling time points.

Therefore, both ibuprofen and acid excipient release rates were lower from biconvex compacts compacted at low pressure than from plane-faced compacts, compacted at high pressure. Earlier results in section 9.2. showed that compacts prepared with a biconvex face and compacted at low pressure had greater porosity and lower tensile strength than plane-faced compacts compacted at high pressure. However, the significant difference in the area of the two differently shaped compacts appears to have a greater influence on the relevant release rates than the porosity or tensile strength characteristics.

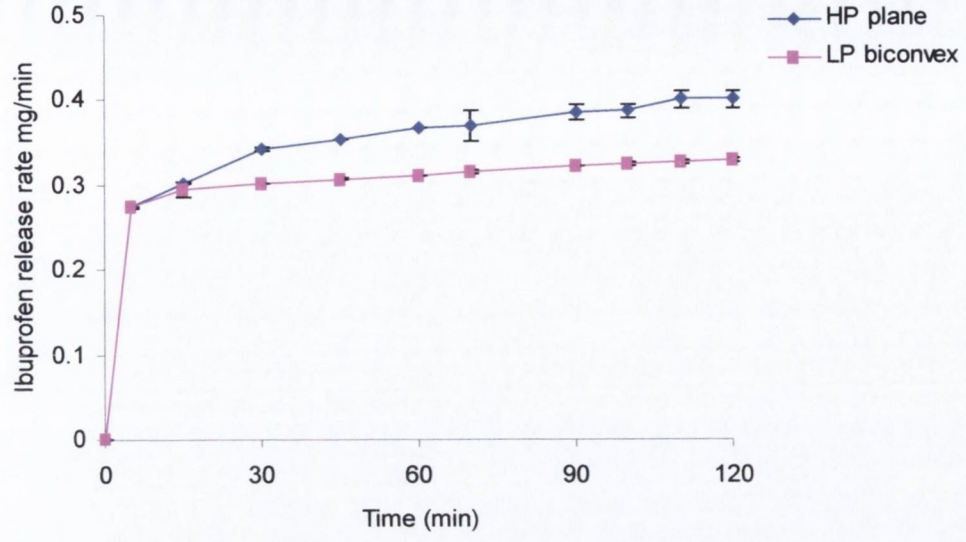

Figure 9.28. Ibuprofen release rate from adipic acid:ibuprofen plane-faced compacts compacted at high pressure (HP), and from adipic acid:ibuprofen biconvex compacts compacted at low pressure (LP).

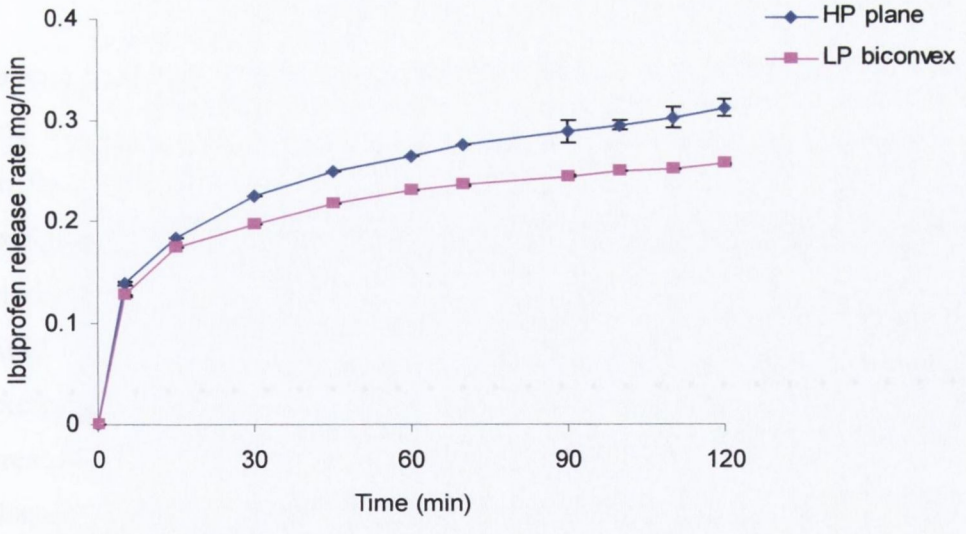

Figure 9.29. Ibuprofen release rate from succinic acid:ibuprofen plane-faced compacts compacted at high pressure (HP), and from succinic acid:ibuprofen biconvex compacts compacted at low pressure (LP).

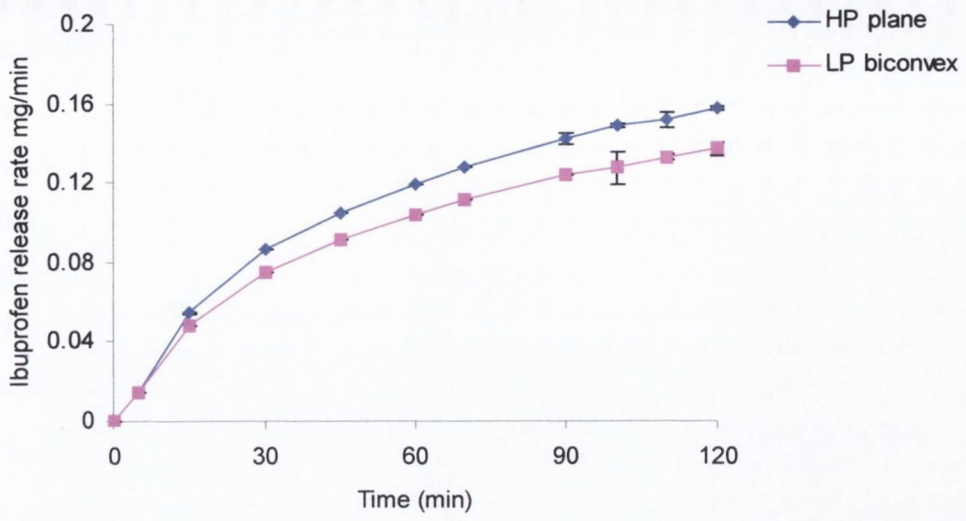

Figure 9.30. Ibuprofen release rate from L-(+)-tartaric acid acid:ibuprofen plane-faced compacts compacted at high pressure (HP), and from L-(+)-tartaric acid acid:ibuprofen biconvex compacts compacted at low pressure (LP).

9.4. CONCLUSION

Ibuprofen dissolution profiles from acid excipient:ibuprofen plane-faced compacts and biconvex compacts showed a positive curvature. This positive curvature was attributed to the recession of the acid excipient from the surface of the disc. As the excipient recedes there is a rise in pH at the surface liquid interface, which leads to an increase in ibuprofen solubility and dissolution.

Acid excipient:ibuprofen compacts compacted at high pressure showed lower acid excipient and ibuprofen release rates than similar compacts compacted at low pressure. This was evident for compacts prepared as either plane-faced or biconvex shaped compacts. This was because the interparticulate porosity of compacts was greater and the tensile strength was less at the lower compaction pressure. Ibuprofen release from compacts prepared at high pressure experienced greater ibuprofen suppression than compacts prepared at low pressure. This was thought to be due to the increase in the uniformity of mix at high compaction pressure. This was evident for compacts prepared as either shape.

The limiting:initial ibuprofen release rate ratio of biconvex compacts was lower than the limiting:initial ibuprofen release rate ratio of plane–faced compacts, at each

compaction pressure. This was because the reducing surface area of the biconvex compact reduced the upward curvature of ibuprofen dissolution. As compared to their similar plane-faced formulation, biconvex compacts prepared with adipic acid showed the greatest reduction in the limiting:initial ibuprofen release rate ratio, while compacts prepared with L-(+)-tartaric acid showed the least. This was because of the differing solubilities between the acid excipient:ibuprofen systems.

These results show that by matching the positive curvature of the acid drug dissolution profile with a reducing biconvex surface area, zero order drug release can be approached.

GENERAL DISCUSSION

Ethylcellulose is a non-toxic, stable, compressible, inert hydrophobic polymer that has been used extensively to prepare pharmaceutical dosage forms (Upadrashta *et al.*, 1993, Neau *et al.*, 1999, Crowley *et al.*, 2004). One of the objectives of this thesis was to characterise the different properties of ethylcellulose, since several properties related either to the material or to the particle might influence the compressibility and the compactibility of the polymer in powder form (Rime *et al.*, 1997), and subsequently drug dissolution from formulations using these polymers. Therefore a number of properties of ethylcellulose powders of different viscosity grades were examined, including particle shape, particle size distribution and particle surface area. In addition, basic ethylcellulose compact characteristics were examined including porosity, tensile strength, surface density, surface roughness, swelling factor and contact angle (in contact with phosphate buffer). The influence of drug loading, disc compaction pressure and ethylcellulose particle size fraction on compact characteristics was also investigated.

SEM photography of ethylcellulose powders showed that powder particles of ethylcellulose 100 cP viscosity grade were more uniform in shape and smoother in appearance, than particles of ethylcellulose 4 cP viscosity grade. There were also a greater number of finer particles present in the ethylcellulose 4 cP powder sample than in the ethylcellulose 100 cP powder sample. This may have a number of implications. Wong and Pilpel (1990) showed that the mixing of powders was influenced by particle shape, while York (1978) showed that the degree of particle slippage and rearrangement taking place during compression increased as the particle size of the powder decreased, and was more extensive for powders composed of non-spherical particles.

The effect of drug loading on ethylcellulose:ibuprofen compact porosity was examined. Compacts were prepared using different ethylcellulose:ibuprofen weight ratios, and different ethylcellulose viscosity grade powders. Results showed that the initial porosity of compacts prepared with ethylcellulose had a tendency to decrease with increasing ibuprofen content.

Experiments also showed that changing the disc compaction pressure did not affect the porosity of compacts prepared with ethylcellulose:ibuprofen (50:50 weight ratio). This was evident for compacts prepared with either ethylcellulose 4 cP or 100 cp

viscosity grade. Desai *et al.* (1965a) similarly reported that poly(vinyl chloride) matrix compacts exhibited constancy of porosity with changes in compression force.

The porosity of ethylcellulose:ibuprofen compacts prepared with different ethylcellulose particle size fractions (and different ethylcellulose viscosity grades) was also determined. The total porosity of compacts prepared with the smallest ethylcellulose particle size fraction was less than the total porosity of compacts prepared with the largest ethylcellulose particle size fraction, for compacts of either ethylcellulose viscosity grade. Closer examination of results showed that as the median ethylcellulose particle size increased the porosity due to air i.e. initial porosity (and consequently total porosity) showed a tendency to increase. This was evident for compacts prepared with either ethylcellulose viscosity grade. Katikaneni *et al.* (1995a) found that the initial relative density of ethylcellulose tablets decreased with decreasing ethylcellulose particle size, while the changes in relative density, attributed to particle rearrangement, increased significantly. This was then reflected in the calculated pore space of compacts prepared with different ethylcellulose particle size fractions i.e. the porosity of compacts decreased with a decrease in ethylcellulose particle size. Lin and Lin (1996) similarly found that compacts of smaller ethylcellulose particle size had less porosity than compacts prepared with ethylcellulose of larger particle size fraction (of the same ethylcellulose viscosity grade).

The initial porosity of compacts prepared with ethylcellulose 4 cP was also less than the initial porosity of compacts prepared with higher ethylcellulose viscosity grades. This was consistent with findings by Shlieout and Zessin (1996). They showed that tablets prepared with different ethylcellulose viscosity grades and a consistent compression force displayed an increase in porosity with an increase in the viscosity grade. They found that the fragmentation rate of ethylcellulose with a low molecular weight was more effective than the rates of those with a higher molecular weight. This was accounted for by the higher compressibility and compactibility of the lower ethylcellulose viscosity grades. Katikaneni *et al.* (1995a) also showed that the porosity in the ethylcellulose tablet structure is dependent on the initial porosity of the powder bed and that plastic deformation is the primary consolidation mechanism. Therefore, the differences in particle morphology, size and area of ethylcellulose 4 cP powders and ethylcellulose 100 cP powders may have also contributed to the porosity difference between compacts of different ethylcellulose viscosity grades.

The tensile strength of ethylcellulose:ibuprofen compacts showed a tendency to decrease with increasing drug loading in compacts prepared with either ethylcellulose viscosity grade (4 cP or 100 cp). These findings were supported by work undertaken by Lin and Lin (1996). They found a slight decrease in ethylcellulose tablet hardness with an increase in drug loading. This may be accounted for by a decrease in the compressibility of the matrix resulting from the higher drug concentration (Katikaneni *et al.*, 1995b). Experiments also found that increasing the disc compaction pressure did not affect the disc tensile strength. This was evident for ethylcellulose:ibuprofen compacts of either ethylcellulose 4 cP or 100 cP viscosity grade. This suggests that these compacts have reached their maximal tensile strength. Katikaneni *et al.* (1995a) has previously shown that ethylcellulose 10 cP compacts prepared with different ethylcellulose particle size fractions, approached maximum achievable hardness at 12 kN.

Further experiments showed that as the ethylcellulose median particle size of ethylcellulose:ibuprofen compacts increased, the tensile strength of compacts showed a tendency to decrease. The increase in tensile strength with a decrease in ethylcellulose particle size is consistent with the theory that smaller particles allow a greater packing density and a greater number of contact points for interparticulate bonding (Katikaneni *et al.*, 1995b). Based on the sensitivity of tablet hardness to the initial particle size it can be concluded that consolidation is via plastic deformation under the tabletting conditions employed.

Compacts prepared with ethylcellulose 4 cP powder had a significantly greater ($p \leq 0.05$) tensile strength than compacts prepared with ethylcellulose 100 cP, for all compact ethylcellulose:ibuprofen weight ratios examined. The dependence of the compressibility and compactibility on the viscosity grade was expected to be due to the increase in polymer order as a result of increased molecular weight. The higher molecular weight grades i.e. higher viscosity grades are inherently more ordered than the lower molecular weight grades because of their longer polymer chains. Results also showed that when ethylcellulose:ibuprofen compacts of either ethylcellulose viscosity grade had similar total porosity values the tensile strength of ethylcellulose 4 cP compacts was higher than the tensile strength of ethylcellulose 100 cP compacts. Shlieout *et al.* (1999) found similar results. He investigated the consolidation behaviour of different ethylcellulose viscosity grades, and compressed each powder to

the same porosity value. A distinctive or a developed irreversible deformation of the ethylcellulose with low molecular weight was measured Electron microscope pictures examined the surfaces of the ethylcellulose tablets of different viscosity grade (but of the same porosity) and found a developed fragmentation process in the lower ethylcellulose viscosity tablets. This can readily explain the better compressibility and compactibility of ethylcellulose with the lower molecular weight.

Lerk *et al.* (1977) established that that the wetting of solid dosage forms is an important initial step in the process of drug dissolution both *in vitro* and *in vivo*. He also determined that the contact angle is one parameter controlling the penetration of liquid into capillaries in capsules and tablets. The determination of contact angles of solids gives a measure of their wettability (Lerk *et al.*, 1977). The contact angle of phosphate buffer in contact with ethylcellulose of each viscosity grade was found to be significantly greater ($p \leq 0.05$) than the contact angle of phosphate buffer in contact with ibuprofen. This means that the ibuprofen compact was more easily wetted by the phosphate buffer than compacts of ethylcellulose. These results were not surprising since previously Upadrashta *et al.* (1993) stated that ethylcellulose is a hydrophobic polymer, which has characteristically high contact angles (Lerk *et al.*, 1977). The difference in wettability between ibuprofen and ethylcellulose compacts may have implications for the wettability of (and for drug release rates from) compacts of varying ethylcellulose:ibuprofen weight ratios.

Results also showed that the contact angle of phosphate buffer in contact with ethylcellulose 4 cP compact (100% w/w) was significantly greater ($p \leq 0.05$) than the contact angle of phosphate buffer in contact with other ethylcellulose viscosity grades (100% w/w). The differences in contact angle of buffer in contact with ethylcellulose 4 cP compacts and other higher viscosity grades compacts established that a difference existed in the surface properties of the compacts prepared with ethylcellulose 4 cP viscosity grade and other higher ethylcellulose viscosity grades. Compacts prepared with ethylcellulose 4 cP viscosity grade were not as easily wetted as compacts prepared with ethylcellulose 100 cp viscosity grade powder. This may have implications for the dissolution of drug from their relative compacts. Other techniques including non-contact laser profilometry and surface density studies confirmed difference in surface characteristics of ethylcellulose:ibuprofen compacts

prepared with different ibuprofen loading, and prepared with different ethylcellulose viscosity grade.

The rate of drug dissolution from dosage forms can be controlled by the extent and rate of liquid absorption by the tablet system. Therefore any factor that influences water uptake will ultimately influence the drug dissolution rate. The water uptake of ethylcellulose compacts (100% w/w) of different viscosity grades was measured by submerging compacts in phosphate buffer and then measuring the percentage increase in disc thickness. It was thought that any increase in disc thickness was linked to relative water uptake in the disc. Results found that the percentage increase in disc thickness was linked to the ethylcellulose viscosity grade, or more accurately the compact porosity. Compacts prepared with ethylcellulose 100 cp (greatest porosity) showed the greatest increase in disc thickness, while compacts prepared with ethylcellulose 4 cP powder showed no increase in disc thickness. Lin and Lin (1996) showed that the water uptake rate of drug loaded ethylcellulose compacts was directly in proportion to the particle size of the ethylcellulose powder and to the porosity of the compact.

One of the purposes of this thesis was to investigate the applications of ethylcellulose as a potential carrier for the preparation of prolonged release formulations, using ibuprofen as a model drug. Therefore, the effect of the polymer-to-drug weight ratio, ethylcellulose viscosity grade, disc compaction pressure and ethylcellulose particle size fraction on ibuprofen release from ethylcellulose:ibuprofen compacts was investigated.

It was observed that as the drug fraction in the ethylcellulose:ibuprofen formulation increased the percentage release of the model drug increased. These results were supported by Dabbagh *et al.* (1996) and Katikaneni *et al.* (1995b) and were attributed to an increase in porosity with an increase in drug concentration, and a concomitant decrease in tortuosity of the matrix (Desai *et al.*, 1966a and Foster and Parrott, 1990a). Conversely, the drug release decreased with increasing ethylcellulose content. When the insoluble excipient has plastic behaviour such as ethylcellulose, it is expected to surround the drug particles and to reduce the number and size of the pores that are present in the compact before dissolution of the drug (initial porosity). Therefore, a decrease in the drug release was expected, due to a decrease in the

effective diffusion coefficient (Soriano *et al.*, 1998) with increasing ethylcellulose content.

The disc compaction pressure did not affect the ibuprofen release rate from ethylcellulose:ibuprofen compacts (of either ethylcellulose 4 cP or 100 cP viscosity grade). This was consistent with findings by Dabbagh *et al.* (1996) who found that the release rate of propranolol hydrochloride from ethylcellulose 7 cP matrix compacts was unaffected by the disc compaction pressure between 78.7 MNm^{-2} and 393.7 MNm^{-2}. This was explained on the basis that the compacts had achieved constancy of porosity between these compaction pressures. This was consistent with findings in chapter five, which showed that ethylcellulose:ibuprofen compacts had reached their maximal tensile strength, and consistent porosity.

Ibuprofen release was also greater from compacts prepared with larger ethylcellulose particle size fractions than smaller ethylcellulose particle size fractions, for compacts formulated with either ethylcellulose 4 cP or 100 cP. Dabbagh *et al.* (1996) found that as the particle size of the ethylcellulose increased the drug release increased. Lin and Lin (1996) showed that the water uptake rate of drug loaded ethylcellulose compacts was directly in proportion to the particle size of the ethylcellulose powder and to the porosity of the compact, in which the porosity increase was also proportional to the drug release rate during dissolution (Usteri *et al.*, 1990).

Greater ibuprofen release was measured from compacts prepared with ethylcellulose 100 cP viscosity grade as compared to compacts prepared with ethylcellulose 4 cP viscosity grade, for each ethylcellulose:ibuprofen formulation examined. Upadrashta *et al.* (1993) found that tablets prepared using different ethylcellulose viscosity grades and a consistent compression force displayed an increase in hardness with a decrease in viscosity grade. Harder tablets were then associated with lower drug dissolution rates. This was also supported by Katikaneni *et al.* (1995b) and is consistent with our earlier findings i.e. compacts prepared with higher viscosity grades displayed greater porosity, and lower hardness than compacts prepared with ethylcellulose 4 cP.

A further objective of this thesis was to apply percolation theory in order to determine whether it is useful to explain release profiles from inert ethylcellulose:ibuprofen matrix compacts, and to compare the proposed interpretations of percolation theory with "classical theories". In addition, we wished to determine which of several model release equations provided the best fit to the ibuprofen release data.

The coefficient of determination and MSC were relatively high for the Higuchi model fit to ibuprofen release data from ethylcellulose:ibuprofen compacts (except those compacts prepared with a 25% w/w or 75% w/w drug loading). According to Higuchi (1963), in the matrix type delivery system the tortuosity and porosity influence the drug release rate. It was evident that as the porosity in the matrix compact increased the tortuosity value decreased for ethylcellulose:ibuprofen compacts. This suggests that with increasing compact porosity the drug diffusional path length becomes less arduous. This was reflected in the drug release rate.

In addition, the tortuosity values for release studies from compacts prepared with ethylcellulose 4 cP were greater than those values determined for release studies from compacts prepared with ethylcellulose of higher viscosity grades. This implies that the drug follows a more lengthened diffusional pathway from compacts of ethylcellulose 4 cP viscosity grade than from compacts prepared with higher ethylcellulose viscosity grades, and was reflected in drug release rates. Desai *et al.* (1966a) and Foster and Parrott (1990a) showed that an increase in release rate generally follows an increase in porosity and a concomitant decrease in the tortuosity of the matrix.

One of the principle drawbacks of the "classical theories" is related to the use of the tortuosity parameter i.e. a theoretical parameter that cannot be experimentally determined. Percolation theory can be used to explain the relevant changes in dissolution kinetics from ethylcellulose compacts of varying drug loads (Bonny and Leuenberger, 1991) and excipient particle size (Caraballo *et al.,* 1993).

Based on percolation theory, the effect of increasing the drug load of the compact was reflected in the formation of a more extensive drug cluster and in a less extensive excipient network. This was used to explain the change in dissolution kinetics of ethylcellulose matrix systems prepared with different drug loadings. Based on a three-dimensional lattice, the lower percolation thresholds were in good agreement with the theoretical site percolation threshold of 0.312 in a simple cubic lattice. Approaching the upper percolation threshold, ethylcellulose was the component reaching a critical volume ratio below which no more coherent network could be found, resulting in the beginning of compact disintegration. Using the concept of two percolation thresholds in the matrix system, the possible range of mixing ratios of

drug and matrix substance can be restricted, giving a basis for more rationale design of dosage form.

According to percolation theory, the use of smaller particle sizes will result in the easier formation of an infinite cluster of this substance. So compacts prepared with the insoluble excipient (ethylcellulose) of smaller particle size will contain a more consistent insoluble infinite cluster i.e. its percolation threshold will decrease due to a more effective distribution. This will determine a slower release rate of ibuprofen than the release rate from compacts prepared with ethylcellulose of larger particle size fraction.

Compacts prepared with the lower ethylcellulose viscosity grade displayed a lower drug release rate than compacts prepared with higher ethylcellulose viscosity grades, even when the same ethylcellulose particle size fraction was used during formulation. Based on percolation theory, the decrease in release rate may be due to the greater compressibility of ethylcellulose 4 cP compacts resulting in the formation of a more continuous infinite insoluble matrix.

The square-root of time model provided a good fit to the release data from ethylcellulose:ibuprofen formulations. This is because drug release from these formulations is based on the assumption that drug diffusion is the primary release mechanism. The poorest fits of the square root of time model were at very high (75% w/w) drug loadings or at very low drug loadings (25% w/w) for all ethylcellulose viscosity grades. These poor fits indicated a change in drug release kinetics from square root of time kinetics. By freeing the time diffusional exponent in model 2 a better fit of dissolution data was achieved than from the square root of time model. As the drug loading in the ethylcellulose:ibuprofen compact increased, the diffusional exponent in model 2 increased implying a gradual change in drug release from Fickian diffusion to zero-order kinetics. Similarly, the diffusional exponent increased when a larger ethylcellulose particle size fraction was used during formulation of ethylcellulose:ibuprofen compacts (50:50 weight ratio) as opposed to a smaller ethylcellulose particle size fraction. The diffusional exponent in model 2 was also consistently higher for model fits of release profiles of formulations prepared with higher ethylcellulose viscosity grades than ethylcellulose 4 cP viscosity grade. Therefore, formulations prepared with higher ethylcellulose viscosity grades loading

were closer to achieving the constant release of ibuprofen as characterised by zero order kinetics, than preparations prepared with lower ethylcellulose viscosity grades. Model 3 proved a better fit to the release profiles from ethylcellulose:ibuprofen compacts prepared with higher drug loads than model 2. It also proved a better fit (than model 2) when fitting release profiles from ethylcellulose:ibuprofen compacts (50% w/w drug loading) prepared with different ethylcellulose particle size fractions (except the release profile from ethylcellulose 4 cP compacts prepared with the ethylcellulose 40–63 μm particle size fraction). This indicates that under these formulation conditions polymer relaxation or swelling becomes a mechanism of drug release to consider. Models that considered erosion as a mechanism of release showed a poor fit to the release data.

One of the objectives of this thesis was to achieve zero-order release of a weakly acidic drug from ethylcellulose matrix tablets in phosphate buffer pH 7.40. Organic acid excipients were used to create an acidic micro-environmental pH inside the polymer matrices, which suppressed ibuprofen dissolution. Due to acid excipient dissolution there was a rise in pH at the compact surface liquid interface, resulting in an increase in ibuprofen solubility and dissolution. It was also expected that as the acid excipient dissolved the porosity of the compact would increase causing a further increase in the ibuprofen dissolution rate. This balanced the increased distances that must be traversed by the ibuprofen molecule out of the matrix compact. As a result the downward curvature of the ibuprofen dissolution profile was reduced and zero-order drug release was approached. This was measured using either the initial release rate to limiting release rate ratio, or the diffusional exponent as determined in Ritger and Peppas (1987).

Compacts prepared with L-(+)-tartaric acid (as opposed to succinic acid or adipic acid) were nearest zero order ibuprofen release. In addition, compacts prepared with higher succinic acid:ibuprofen weight ratios were nearer zero order ibuprofen release than their lower succinic acid:ibuprofen weight ratio counterparts. Formulating matrix compacts with acid excipient sieved less than 40 μm also resulted in a lowering of the initial to limiting ibuprofen release rate ratio. Therefore, the inclusion of acid excipients in ethylcellulose:ibuprofen formulations caused Higuchi drug release to be altered so that it resembled a zero order profile. For each formulation

examined, ibuprofen release from ethylcellulose 100 cP compacts was a step nearer constant drug release than release from ethylcellulose 4 cP compacts.

Additional investigations could include substituting the acid excipient in three component compacts of ethylcellulose:acid excipient:ibuprofen for a pH independent soluble filler such as mannitol. In this manner, the effect of increasing porosity (due to the dissolving excipient) on the release of ibuprofen could be evaluated, independent of the pH effect on ibuprofen solubility and release. The effect of increasing the mannitol:ibuprofen weight ratio and reducing the mannitol particle size, on ibuprofen release could also be examined. Further study could also include investigating the effect of altering the ethylcellulose content within the lower and upper percolation thresholds.

Results showed that by matching the positive curvature of ibuprofen dissolution profiles from acid excipient:ibuprofen compacts with a biconvex surface area, zero-order drug release can be approached. Further study, could determine the optimum drug:excipient ratios and biconvex sizes, which could be used to achieve zero-order drug release.

In summary the present work has shown:

(1) Ethylcellulose (of any viscosity grade) was a good direct compression excipient. The lower viscosity grades of ethylcellulose were more compressible than the higher ethylcellulose viscosity grades, resulting in compacts of higher tensile strength and lower compact porosity. These differences, in addition to differences in surface roughness, surface density and contact angle (with phosphate buffer) have implications for the release of drug from compacts prepared with different ethylcellulose viscosity grades. Results showed that the greatest ibuprofen release rate was from compacts prepared with ethylcellulose 100 cP, while the lowest was from compacts prepared with ethylcellulose 4 cP.

(2) Results showed that as the level of drug concentration in the ethylcellulose:ibuprofen matrix formulations increased, the drug release rate also increased. It was thought that the increase in drug concentration resulted in an increase in compact porosity and a concomitant decrease in the tortuosity of the matrix. Percolation theory was also used to explain the changes in dissolution kinetics over a range of drug loadings. This involved determining the lower and

upper percolation thresholds based on a three dimensional lattice of matrix compacts prepared with either ethylcellulose 4 cP viscosity grade or ethylcellulose 100 cP viscosity grade.

(3) Characterisation of compacts prepared using different particle size fractions of ethylcellulose and consistent compression forces revealed that the initial and total porosity had a tendency to increase with an increase in ethylcellulose particle size. This increase in porosity resulted in faster drug release and a concomitant decrease in the tortuosity value. Based on percolation theory, the use of the smaller ethylcellulose particle size fraction resulted in the formation of a more consistent insoluble infinite cluster, which determined a slower release rate of ibuprofen than the release from compacts prepared with larger ethylcellulose particle size fractions.

(4) By freeing the time diffusional exponent in model 2 a better fit of dissolution data was achieved than when release data was fitted to the square root of time model. The diffusional exponent increased when the drug loading of the formulation increased, or when the median ethylcellulose particle size in the formulation increased. This implies a gradual change in drug release from Fickian diffusion to zero-order kinetics. In addition, the diffusional exponent was higher for model fits of release profiles from formulations prepared with higher ethylcellulose viscosity grades than ethylcellulose 4 cP viscosity grade. Hence, formulations prepared with higher ethylcellulose viscosity grades are closer to achieving the constant release of ibuprofen as characterised by zero-order kinetics. Model 3 also proved a better fit of the release profiles from ethylcellulose:ibuprofen compacts prepared with higher drug loads than model 2. In addition, model 3 proved a better fit (than model 2) when fitting release profiles from ethylcellulose:ibuprofen compacts (50% w/w drug loading) prepared with different ethylcellulose particle size fractions (except the release profile from ethylcellulose 4 cP compacts prepared with the ethylcellulose 40–63 μm particle size fraction). This indicates that under these formulation conditions polymer relaxation or swelling becomes a mechanism of drug release to consider.

(5) The inclusion of acid excipients in ethylcellulose:ibuprofen formulations caused Higuchi drug release to be altered so that it resembled a zero-order profile. For each formulation examined, ibuprofen release from ethylcellulose 100 cP compacts was a step nearer constant drug release than release from ethylcellulose 4 cP compacts

(6) Ibuprofen dissolution profiles from biconvex compacts showed less profile curvature than plane-faced compacts. This was because the reducing surface area of

the biconvex compact reduced the upward curvature of the ibuprofen dissolution profile.

APPENDICES

APPENDIX 1

Calibration curves used to determine concentration of substances in solution

UV calibration curves

Ibuprofen in phosphate buffer pH 7.40

Analytical wavelength: 222 nm

Reference wavelength: 400 nm

Concentration (mg/ml)= (2.0122×10^{-2}* Absorbance) - 1.1110×10^{-3}

Coefficient of determination: 0.9994

HPLC calibration curves

(1) Ibuprofen in phosphate buffer pH 7.40

Mobile Phase: Methanol:1% phosphoric acid (70:30), 0.8ml/min

Aufs: 0.1; λ: 220 nm

Concentration (mg/ml)= (2.8000×10^{-9}* Peak Area) - 1.1113×10^{-6}

Coefficient of determination: 0.9994

(2) Adipic acid in phosphate buffer pH 7.40

Mobile phase: Methanol:1% phosphoric acid (50:50), 0.8ml/min

Aufs: 0.01; λ: 210 nm

Concentration (mg/ml)= (1.6129×10^{-8}* Peak Area) + 2.0782×10^{-5}

Coefficient of determination: 0.9997

(3) Succinic acid in phosphate buffer pH 7.40

Mobile phase: 0.025M phosphoric acid, 0.8ml/min

Aufs: 0.009; λ: 210 nm

Concentration (mg/ml)= (1.5230×10^{-6}* Peak Area) + 1.9882×10^{-3}

Coefficient of determination: 0.9998

(4) L-(+)-tartaric acid in phosphate buffer pH 7.40

Mobile phase: 0.025M phosphoric acid, 0.8ml/min

Aufs: 0.008; λ: 210 nm

Concentration (mg/ml)= (6.0993×10^{-7}* Peak Area) + 1.1121×10^{-3}

Coefficient of determination: 0.9990

APPENDIX 2

Pressure table used with Poresizer 9320

Point	Pressure (p.s.i.a.)	Point	Pressure (p.s.i.a.)	Point	Pressire (p.s.i.a.)	Point	Pressure (p.s.i.a.)
1	10	45	560	89	1440	133	6500
2	15	46	580	90	1460	134	7000
3	20	47	600	91	1480	135	7500
4	25	48	620	92	1500	136	8000
5	30	49	640	93	1520	137	8500
6	35	50	660	94	1540	138	9000
7	40	51	680	95	1560	139	9500
8	45	52	700	96	1580	140	10000
9	50	53	720	97	1600	141	11000
10	55	54	740	98	1620	142	12000
11	60	55	760	99	1640	143	13000
12	65	56	780	100	1660	144	14000
13	70	57	800	101	1680	145	15000
14	75	58	820	102	1700	146	16000
15	80	59	840	103	1720	147	18000
16	85	60	860	104	1740	148	19000
17	90	61	880	105	1760	149	20000
18	95	62	900	106	1780	150	22000
19	100	63	920	107	1800	151	24000
20	110	64	940	108	1820	152	26000
21	120	65	960	109	1840	153	28000
22	130	66	980	110	1860	154	30000
23	140	67	1000	111	1880	155	29000
24	150	68	1020	112	2000	156	27000
25	160	69	1040	113	2050	157	25000
26	180	70	1060	114	2100	158	23000
27	200	71	1080	115	2150	159	21000
28	220	72	1100	116	2200	160	19000
29	240	73	1120	117	2250	161	17000
30	260	74	1140	118	2300	162	15000

31	280	75	1160	119	2400	163	13000
32	300	76	1180	120	2500	164	11000
33	320	77	1200	121	2700	165	9000
34	340	78	1220	122	2900	166	7000
35	360	79	1240	123	3100	167	5000
36	380	80	1260	124	3300	168	3000
37	400	81	1280	125	3500	169	1000
38	420	82	1300	126	3700	170	500
39	440	83	1320	127	4000	171	250
40	460	84	1340	128	4300	172	100
41	480	85	1360	129	4600	173	50
42	500	86	1380	130	5000	174	30
43	520	87	1400	131	5500	175	15
44	540	88	1420	132	6000		

APPENDIX 3

Differential scanning calorimetry thermograms and tables

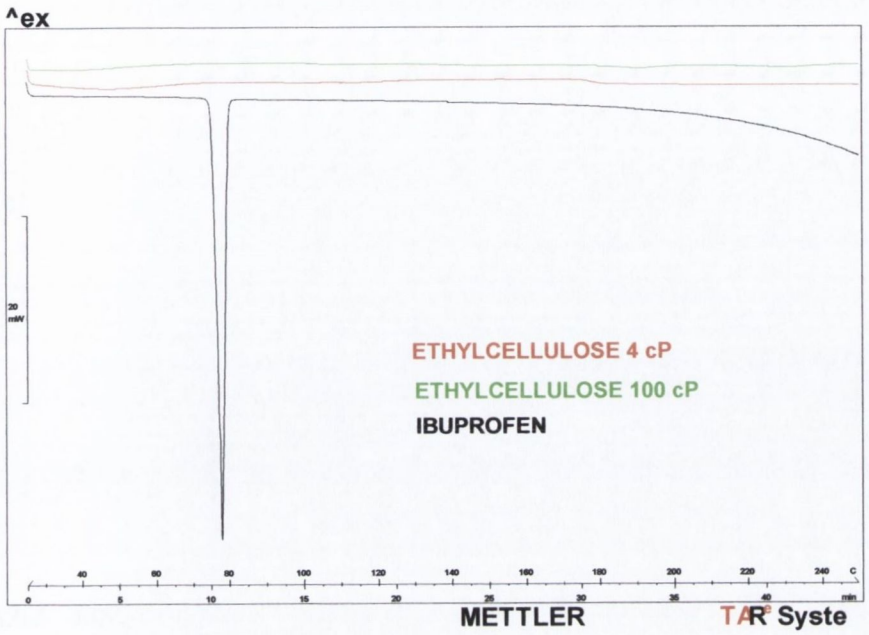

Figure A3.1. DSC thermograms of ethylcellulose 4 cP (100% w/w), ethylcellulose 100 cP (100% w/w) and ibuprofen (100% w/w).

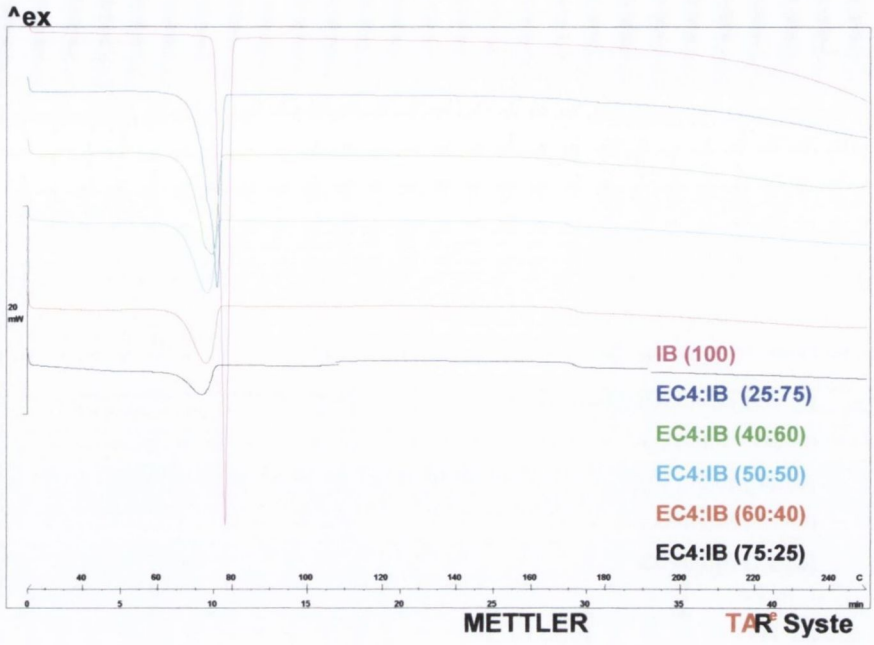

Figure A3.2. DSC thermograms of ibuprofen and ethylcellulose 4 cP:ibuprofen mixtures. EC4 is ethylcellulose 4 cP, IB is ibuprofen. The weight ratio % w/w is indicated in brackets.

Table A3.1.

Onset melting point, peak melting point and normalised melting energy values of ibuprofen in ethylcellulose 4 cP:ibuprofen physical mixtures

Compound(s)	Weight ratio	Onset °C	Peak °C	Energy Jg^{-1}
Ibuprofen	100% w/w	75.49	76.33	128.04
EC:IB	25:75	72.41	75.22	96.53
EC:IB	40:60	67.92	74.08	72.91
EC:IB	50:50	66.10	72.91	52.19
EC:IB	60:40	65.78	72.71	41.65
EC:IB	75:25	64.93	71.78	18.97

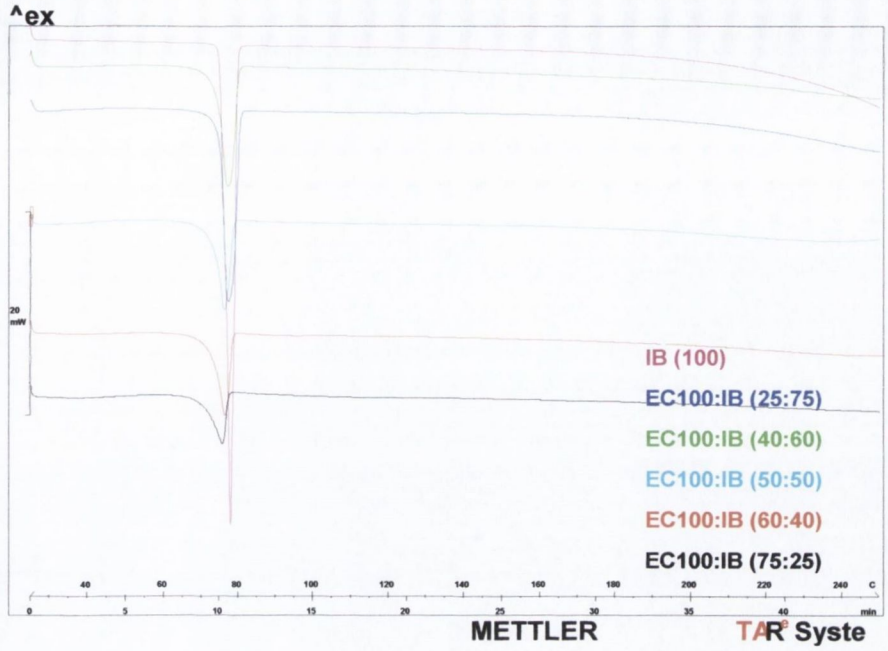

Figure A3.3. DSC thermograms of ibuprofen and ethylcellulose 100 cP:ibuprofen mixtures. EC100 is ethylcellulose 100 cP, IB is ibuprofen. The weight ratio % w/w is indicated in brackets.

Table A3.2

Onset melting point, peak melting point and normalised melting energy values of ibuprofen in ethylcellulose 100 cP:ibuprofen physical mixtures

Compound(s)	Weight ratio	Onset ^{o}C	Peak ^{o}C	Energy Jg^{-1}
Ibuprofen	100% w/w	75.49	76.33	128.04
EC:IB	25:75	75.00	76.77	86.41
EC:IB	40:60	74.27	76.92	61.74
EC:IB	50:50	73.43	76.01	43.52
EC:IB	60:40	72.78	76.18	38.69
EC:IB	75:25	71.23	75.71	27.17

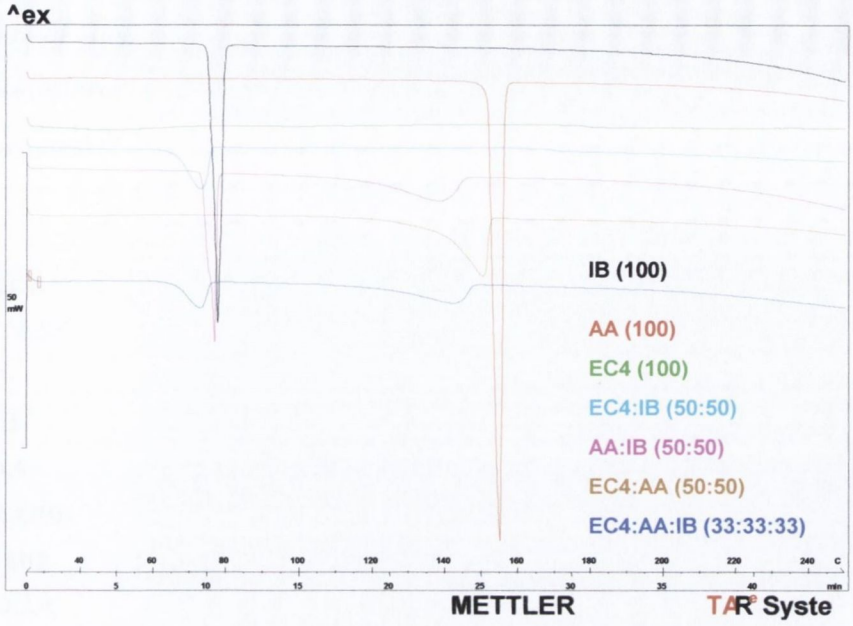

Figure A3.4. DSC thermograms of ethylcellulose 4 cP, ibuprofen, adipic acid and their mixtures. EC4 is ethylcellulose 4 cP, IB is ibuprofen, AA is adipic acid. The weight ratio % w/w is indicated in brackets.

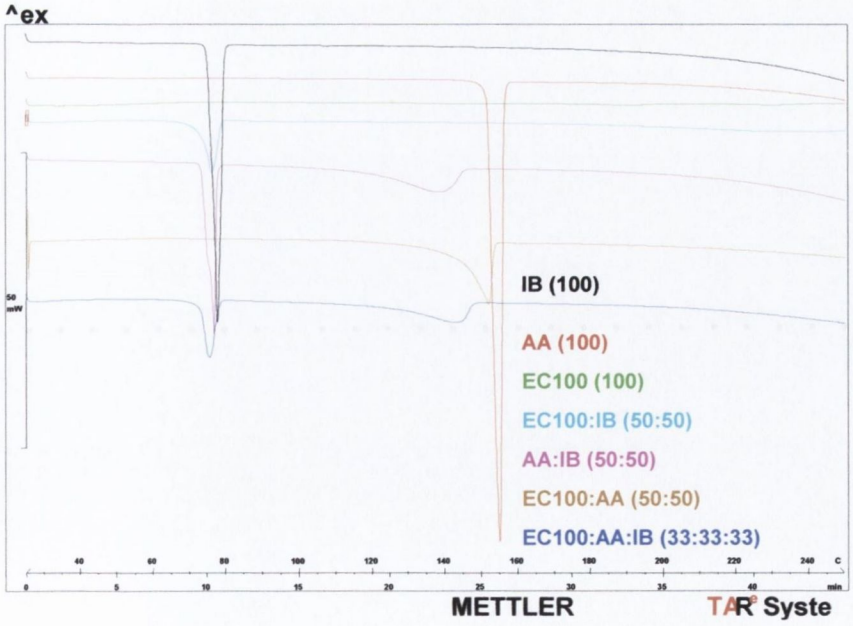

Figure A3.5. DSC thermograms of ethylcellulose 100 cP, ibuprofen, adipic acid and their mixtures. EC100 is ethylcellulose 100 cP, IB is ibuprofen, AA is adipic acid. The weight ratio % w/w is indicated in brackets.

Table A3.3. *Onset melting point, peak melting point and normalised melting energy values of ibuprofen and adipic acid in physical mixtures with and without ethylcellulose (4 cP or 100 cP viscosity grade)*

Compound(s)	Weight ratio % (w/w)	Onset °C IB	Peak °C IB	Onset °C AA	Peak °C AA	Energy Jg^{-1} IB	Energy Jg^{-1} AA
Ibuprofen	100	75.49	76.33			128.04	
Adipic Acid	100			151.40	151.67		256.76
AA:IB	50:50	74.02	75.94	120.84	138.82	73.96	77.27
EC4:IB	50:50	66.10	72.91			52.19	
EC4:AA	50:50			138.32	149.92		119.44
EC4:AA:IB	33:33:33	66.10	72.82	124.74	142.22	35.34	51.72
EC100:IB	50:50	73.43	76.01			43.52	
EC100:AA	50:50			145.38	151.48		101.84
EC100:AA:IB	33:33:33	73.15	75.32	126.93	142.71	34.95	42.77

EC: ethylcellulose (4 is 4 cP viscosity grade, 100 is 100 cP viscosity grade), IB: ibuprofen, AA: adipic acid

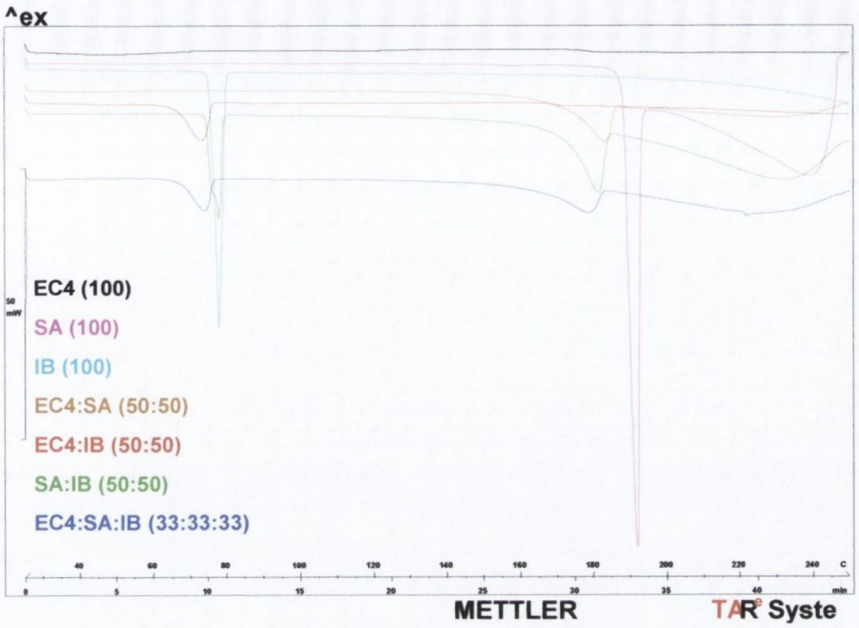

Figure A3.6. DSC thermograms of ethylcellulose 4 cP, ibuprofen, succinic acid and their mixtures. EC4 is ethylcellulose 4 cP, IB is ibuprofen, SA is succinic acid. The weight ratio % w/w is indicated in brackets.

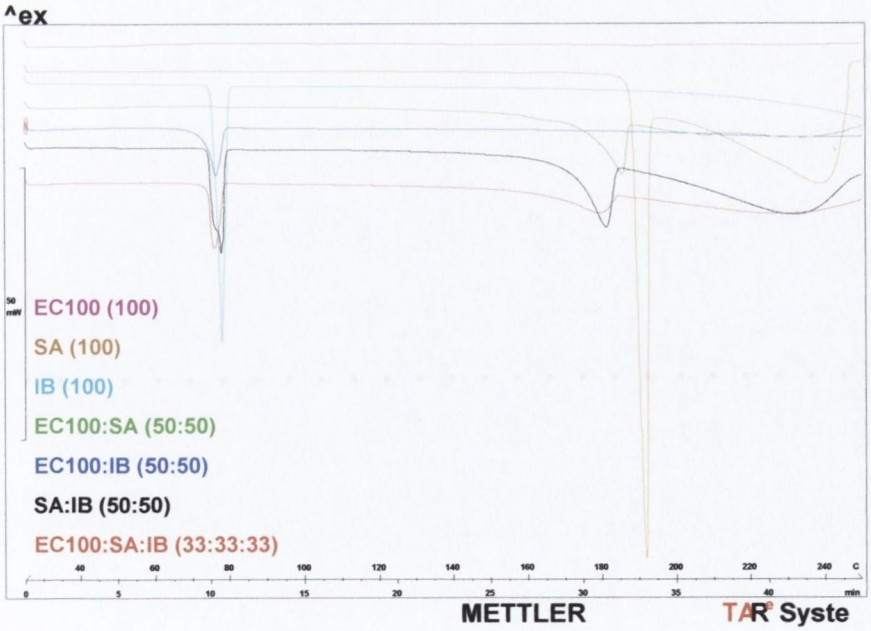

Figure A3.7. DSC thermograms of ethylcellulose 100 cP, ibuprofen, succinic acid and their mixtures. EC100 is ethylcellulose 100 cP, IB is ibuprofen, SA is succinic acid. The weight ratio % w/w is indicated in brackets.

Table A3.4. *Onset melting point, peak melting point and normalised melting energy values of ibuprofen and succinic acid in physical mixtures with and without ethylcellulose (4 cP or 100 cP viscosity grade)*

Sample	Weight ratio % w/w	Onset °C IB	Peak °C IB	Onset °C SA	Peak °C SA	Energy Jg^{-1} IB	Energy Jg^{-1} SA
Ibuprofen	100	75.49	76.33			128.04	
Succinic Acid	100			187.52	187.62		294.27
SA:IB	50:50	74.35	77.17	172.87	180.52	66.68	93.56
EC4:IB	50:50	66.10	72.91			52.19	
EC4:SA	50:50			173.10	182.25		71.73
EC4:SA:IB	33:33:33	67.51	74.02	166.34	177.98	35.06	51.63
EC100:IB	50:50	73.43	76.01			43.52	
EC100:SA	50:50			176.64	184.69		78.41
EC100:SA:IB	33:33:33	74.15	75.49	166.76	178.76	38.22	40.83

EC: ethylcellulose (4 is 4 cP viscosity grade, 100 is 100 cP viscosity grade), IB: ibuprofen, SA: succinic acid

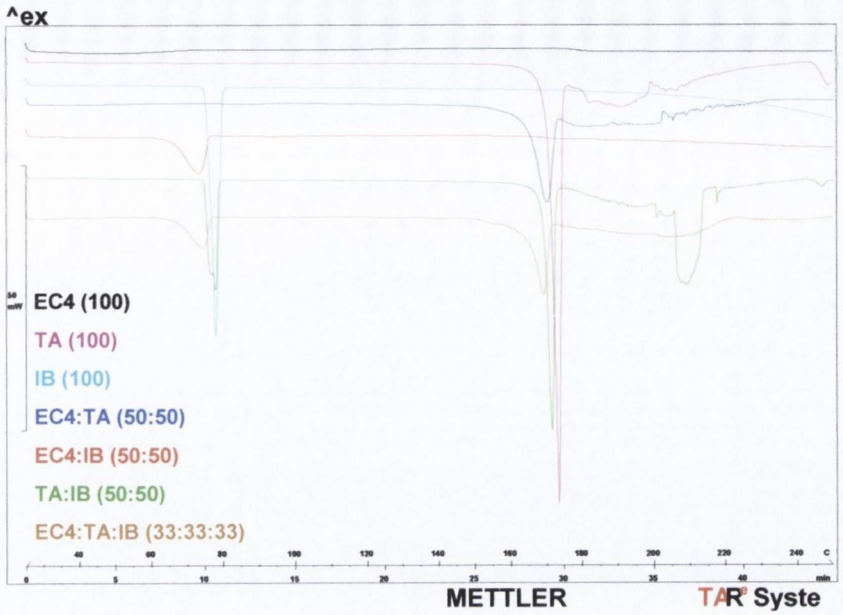

Figure A3.8. DSC thermograms of ethylcellulose 4 cP, ibuprofen, L-(+)-tartaric acid and their mixtures. EC4 is ethylcellulose 4 cP, IB is ibuprofen, TA is L-(+)-tartaric acid. The weight ratio % w/w is indicated in brackets.

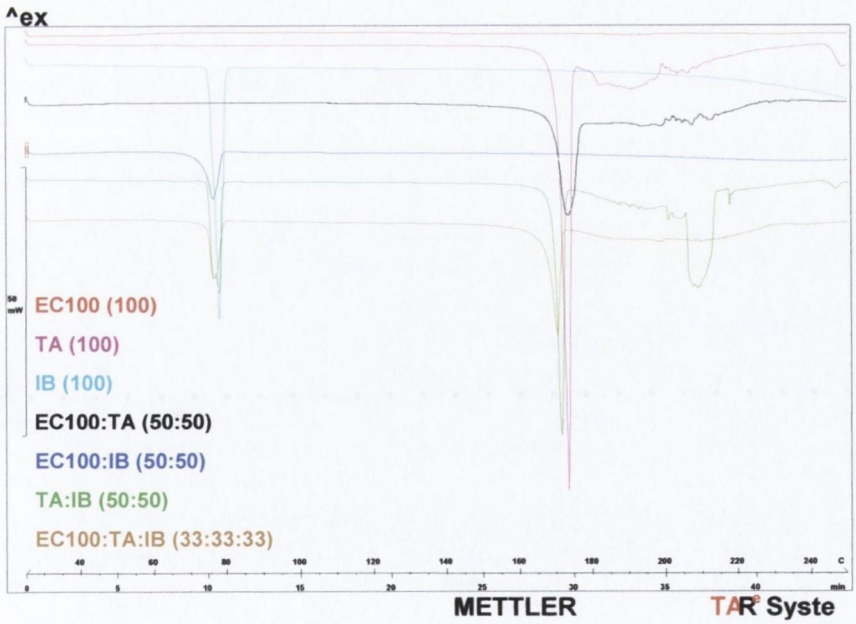

Figure A3.9. DSC thermograms of ethylcellulose 100 cP, ibuprofen, L-(+)-tartaric acid and their mixtures. EC100 is ethylcellulose 100 cP, IB is ibuprofen, TA is L-(+)-tartaric acid. The weight ratio % w/w is indicated in brackets.

Table A3.5. *Onset melting point, peak melting point and normalised melting energy values of ibuprofen and L-(+)-tartaric acid in physical mixtures with and without ethylcellulose (4 cP or 100 cP viscosity grade)*

Sample	Weight ratio % w/w	Onset °C IB	Peak °C IB	Onset °C TA	Peak °C TA	Energy Jg^{-1} IB	Energy Jg^{-1} TA
Ibuprofen	100	75.49	76.33			128.04	
TA	100			170.06	175.61		237.23
TA:IB	50:50	74.11	77.05	168.70	169.23	63.86	115.39
EC4:IB	50:50	66.10	72.91			52.19	
EC4:TA	50:50			164.68	169.10		91.66
EC4:TA:IB	33:33:33	67.21	74.19	164.67	168.45	36.38	68.70
EC100:IB	50:50	73.43	76.01			43.52	
EC100:TA	50:50			169.36	172.28		98.28
EC100:TA:IB	33:33:33	74.94	76.18	167.82	169.99	33.39	75.03

EC: ethylcellulose (4 is 4 cP viscosity grade, 100 is 100 cP viscosity grade), IB: ibuprofen, TA: L-(+)-tartaric acid

APPENDIX 4

Model fits to ibuprofen release data

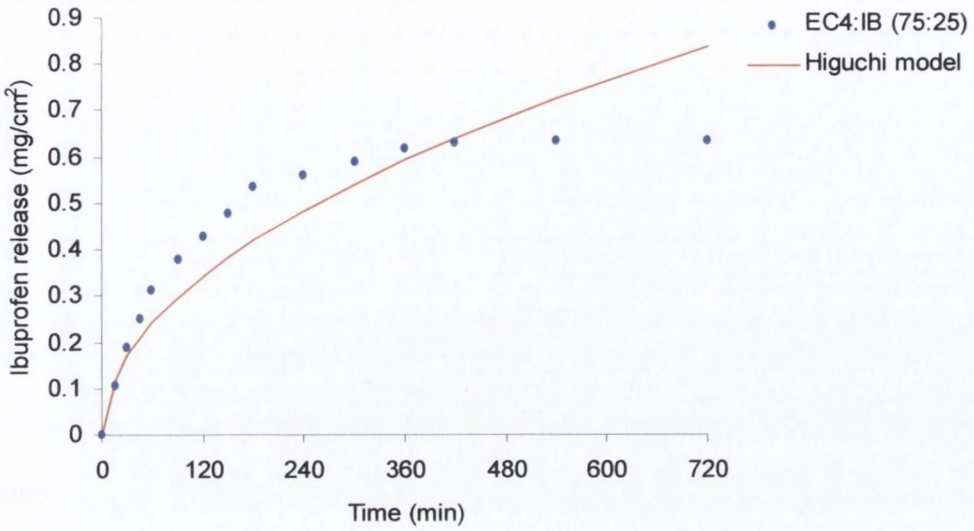

Figure A4.1. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts. EC4: ethylcellulose 4 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

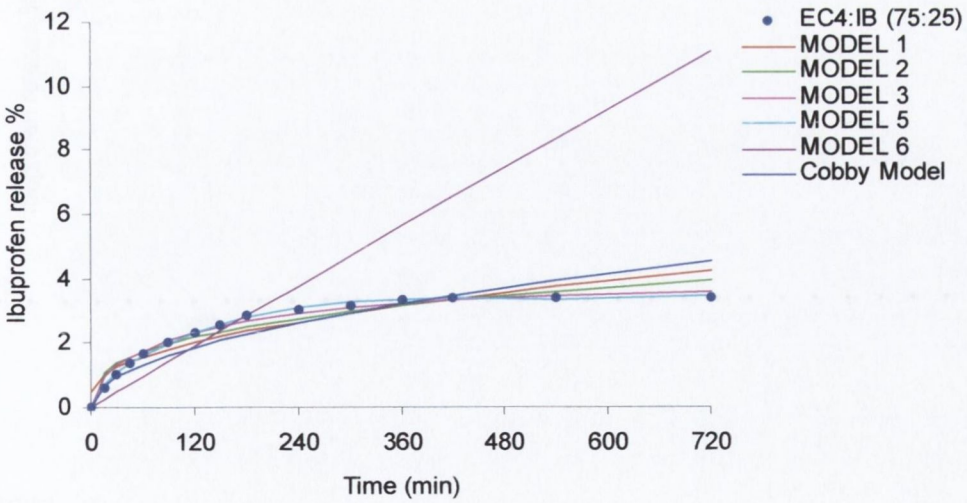

Figure A4.2. Model fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts. EC4: ethylcellulose 4 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

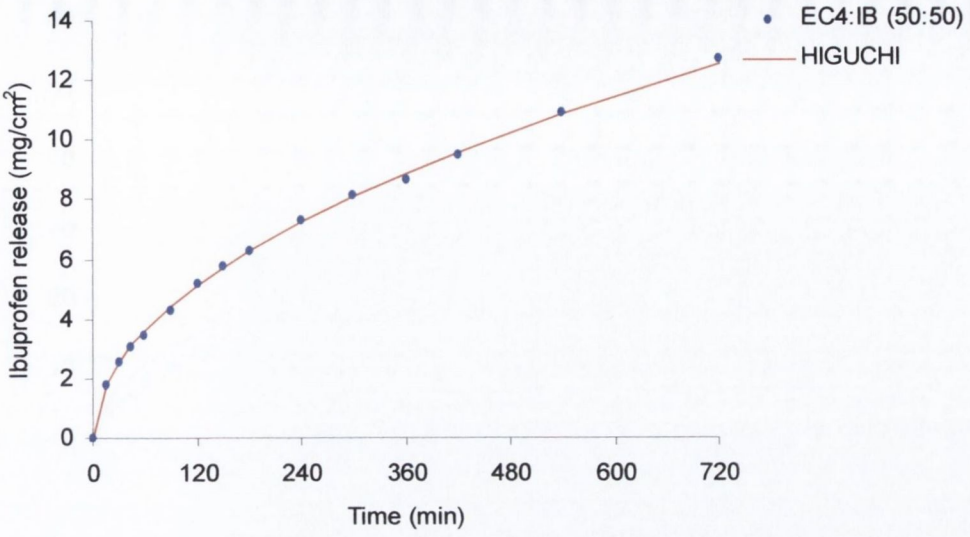

Figure A4.3. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts. EC4: ethylcellulose 4 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

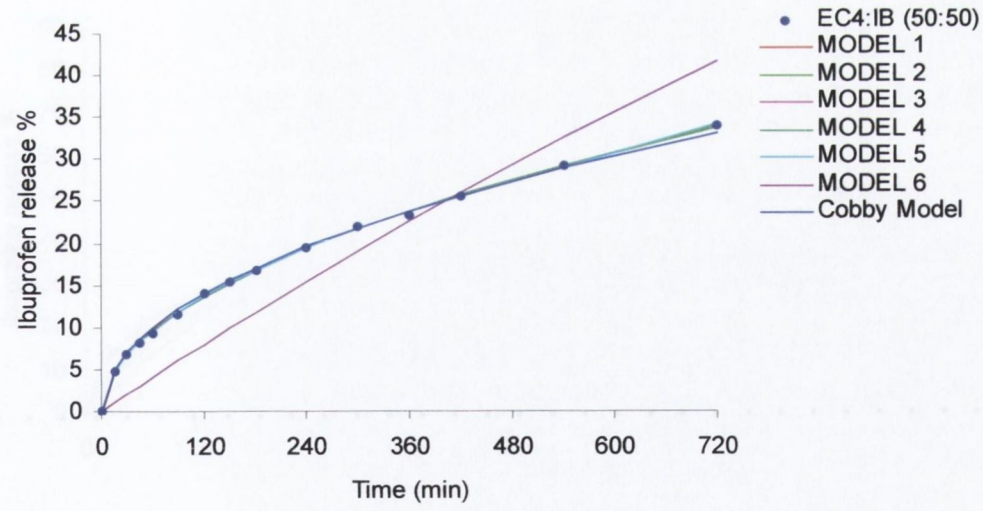

Figure A4.4. Model fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts. EC4: ethylcellulose 4 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

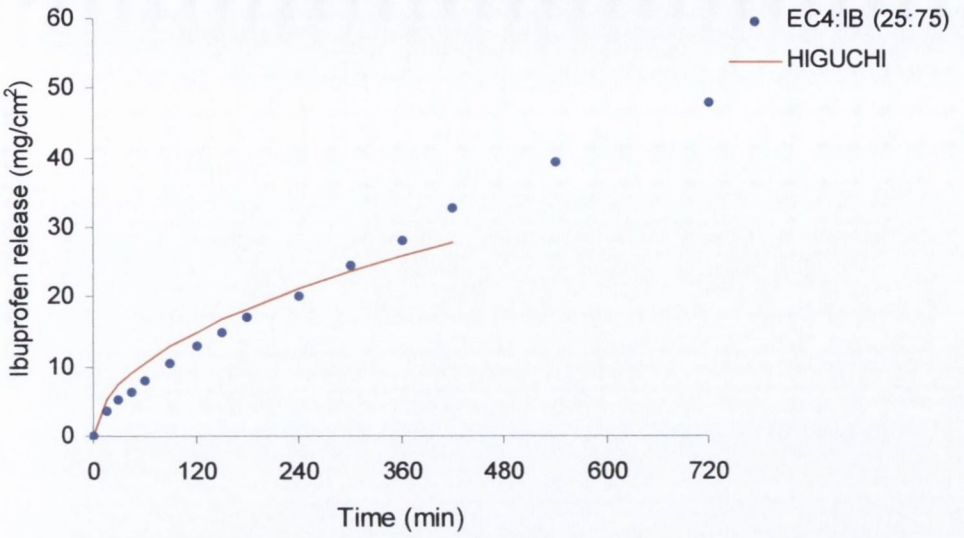

Figure A4.5. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts. EC4: ethylcellulose 4 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

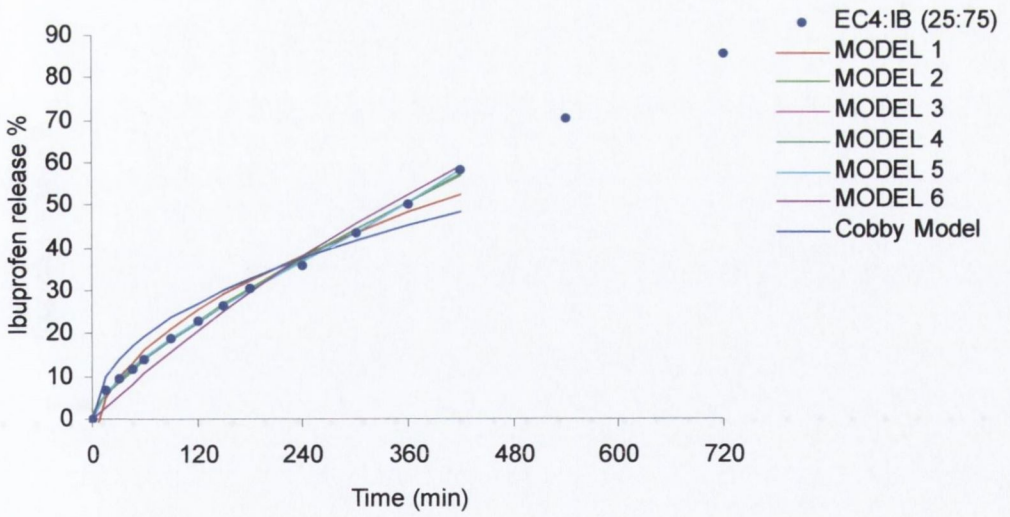

Figure A4.6. Model fits to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts. EC4: ethylcellulose 4 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

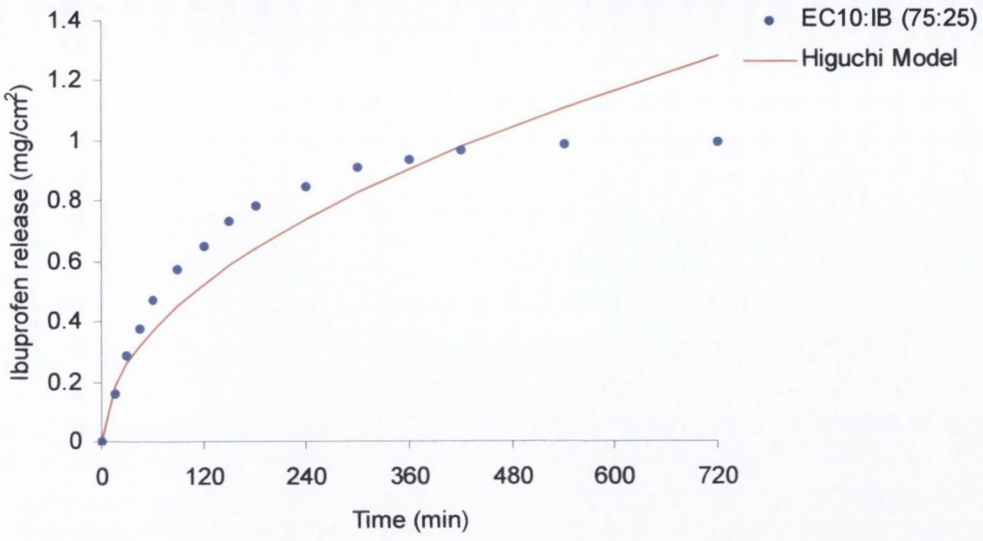

Figure A4.7. Higuchi model fit to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts. EC10: ethylcellulose 10 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

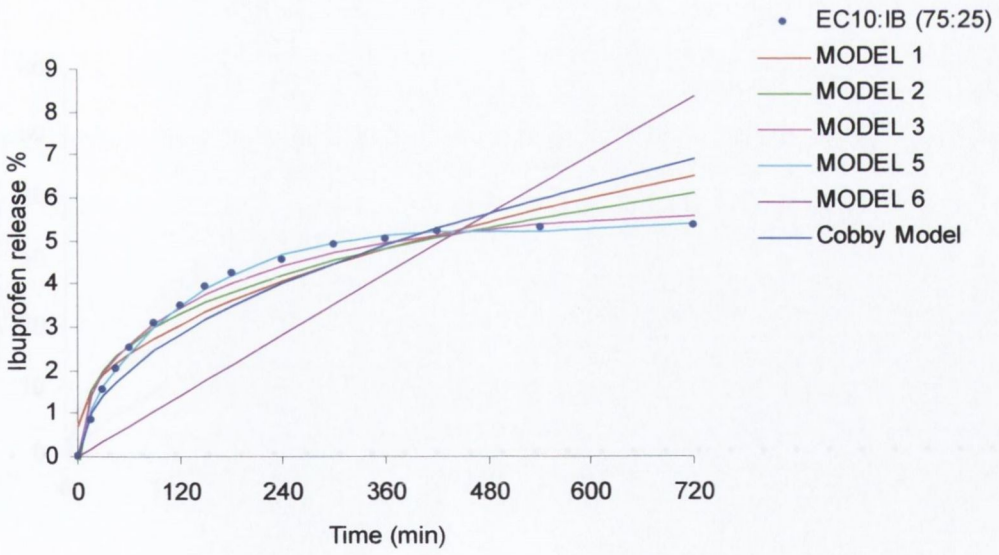

Figure A4.8. Model fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts. EC10: ethylcellulose 10 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

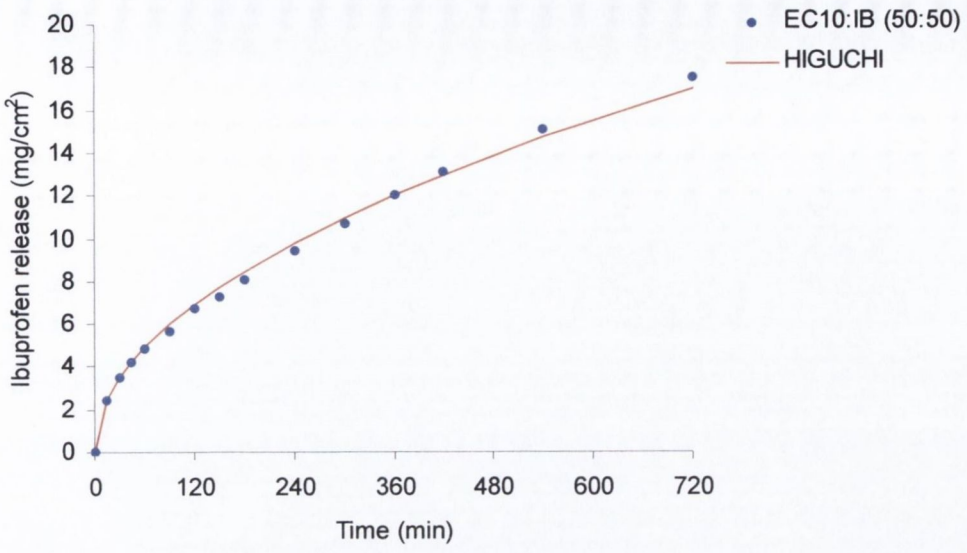

Figure A4.9. Higuchi model fit to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts. EC10: ethylcellulose 10 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

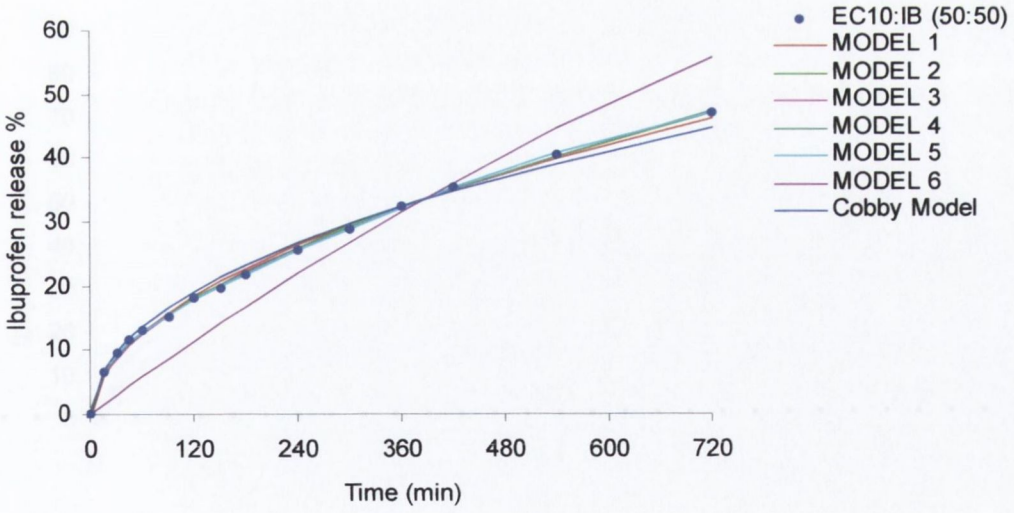

Figure A4.10. Model fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts. EC10: ethylcellulose 10 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

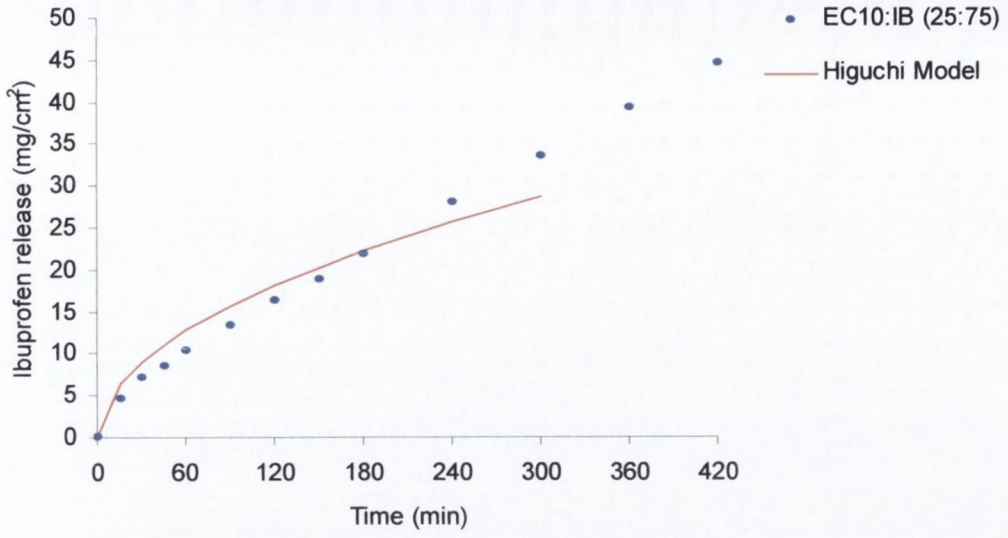

Figure A4.11. Higuchi model fit to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts. EC10: ethylcellulose 10 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

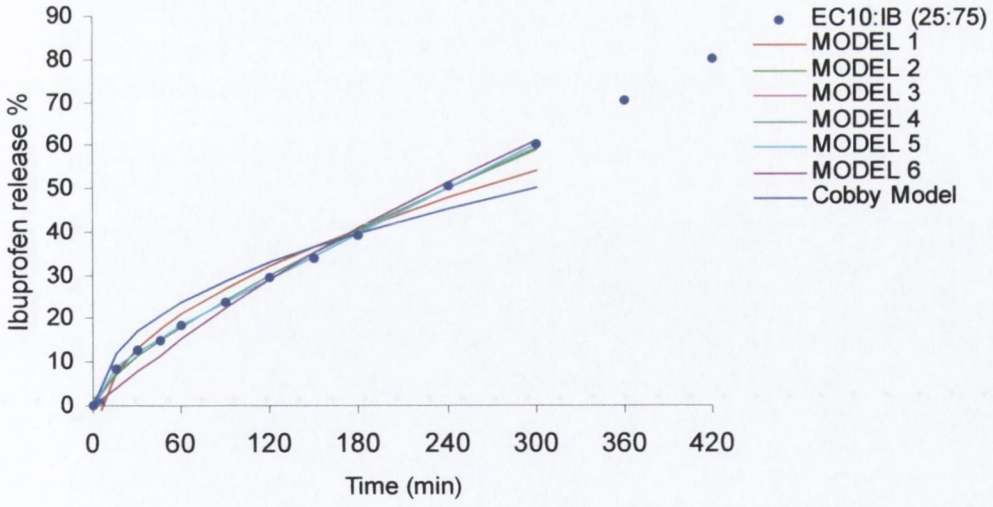

Figure A4.12. Model fits to ibuprofen release data from ethylcellulose 10 cP:ibuprofen compacts. EC10: ethylcellulose 10 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

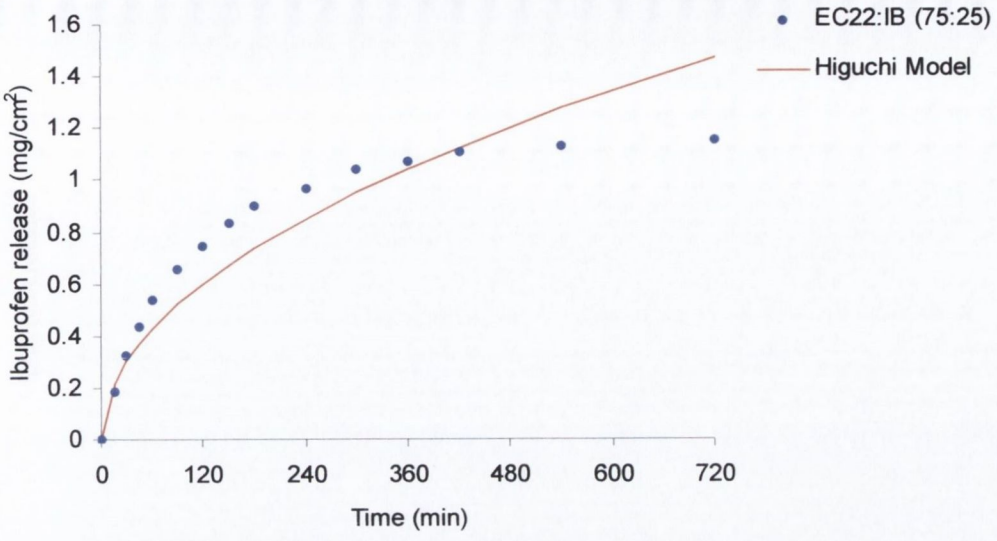

Figure A4.13. Higuchi model fit to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts. EC22: ethylcellulose 22 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

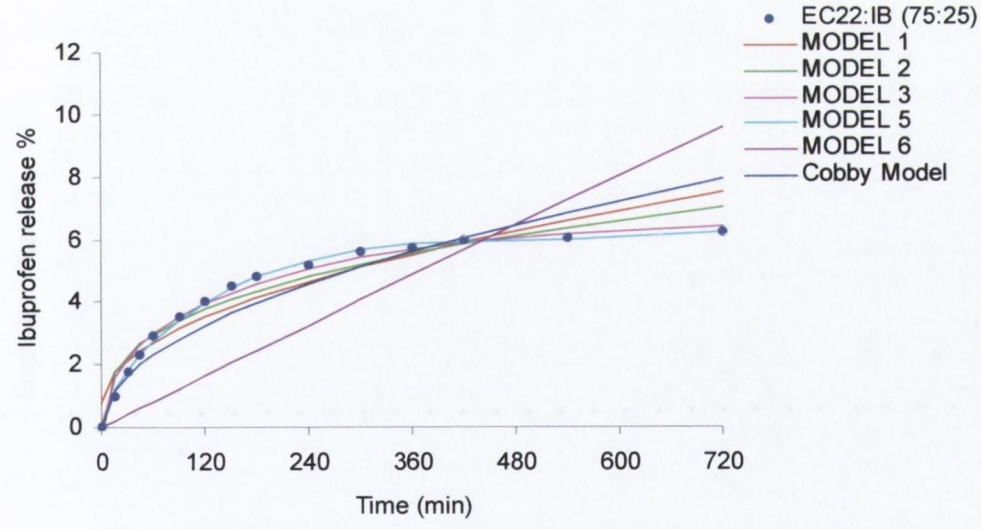

Figure A4.14. Model fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts. EC22: ethylcellulose 22 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

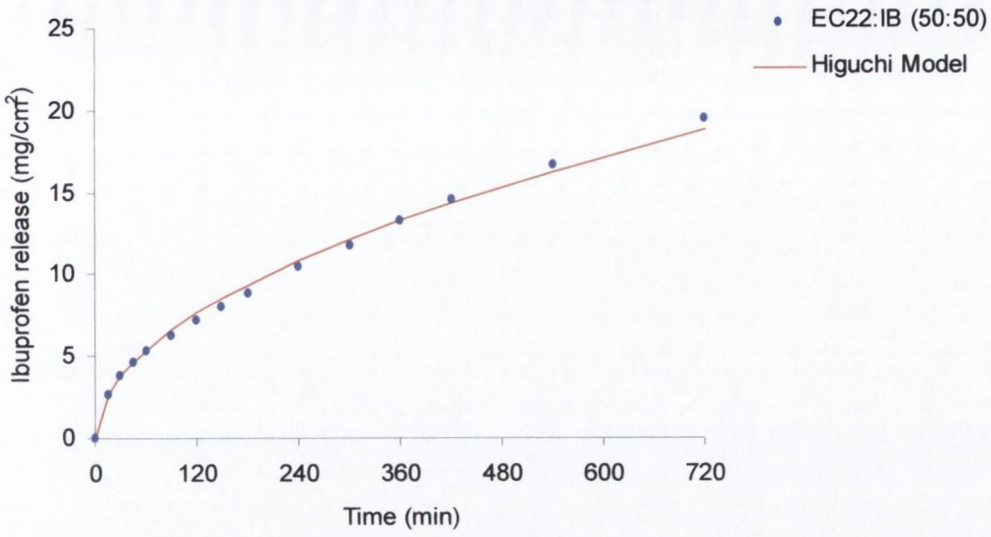

Figure A4.15. Higuchi model fit to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts EC22: ethylcellulose 22 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

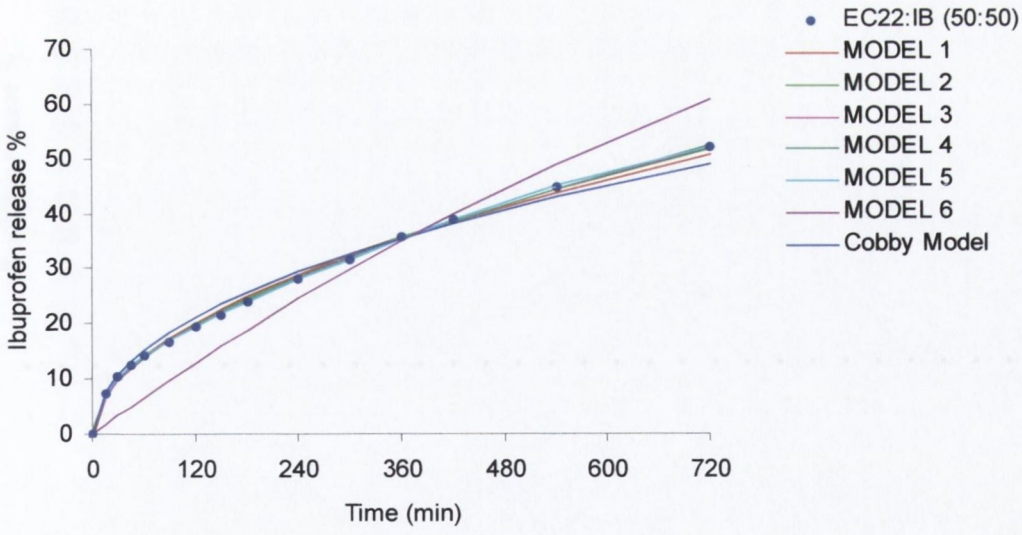

Figure A4.16. Model fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts. EC22: ethylcellulose 22 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

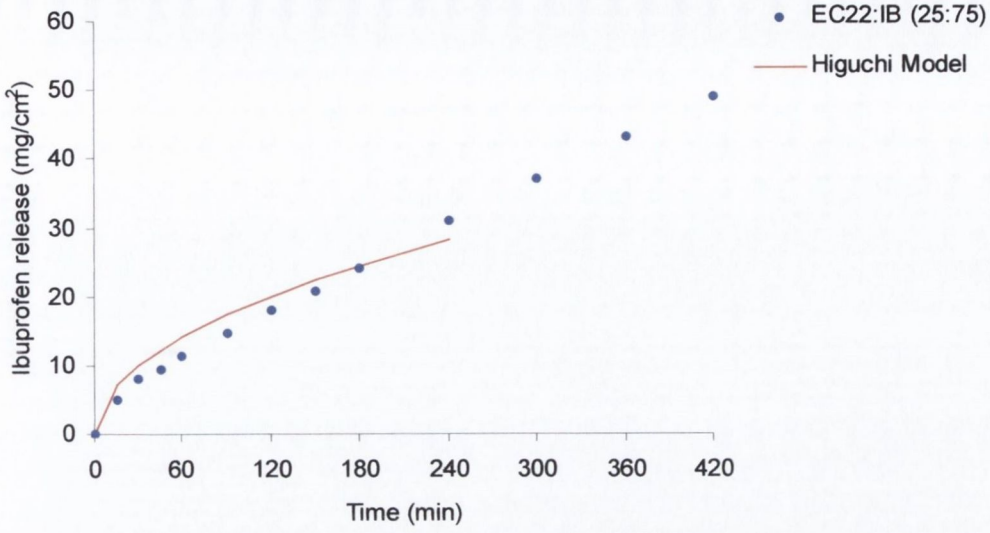

Figure A4.17. Higuchi model fit to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts. EC22: ethylcellulose 22 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

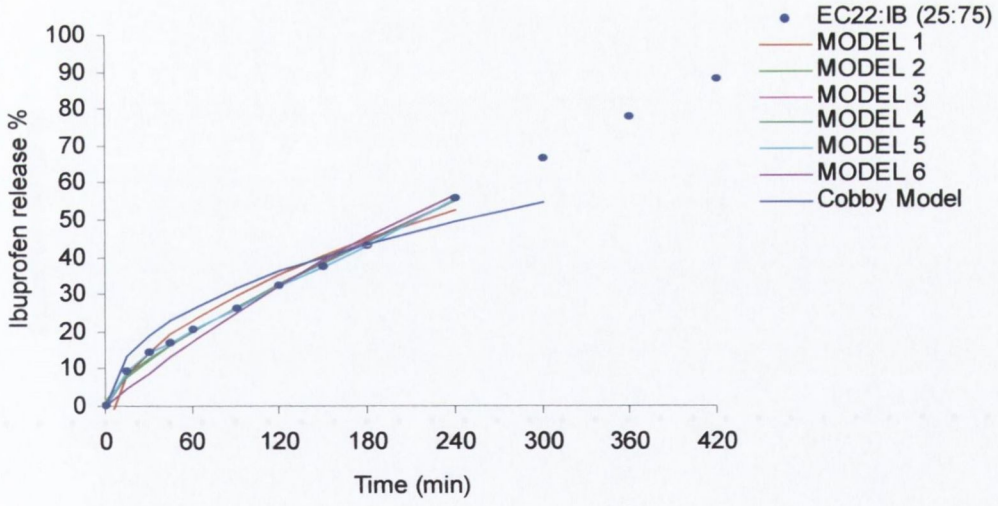

Figure A4.18. Model fits to ibuprofen release data from ethylcellulose 22 cP:ibuprofen compacts. EC22: ethylcellulose 22 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

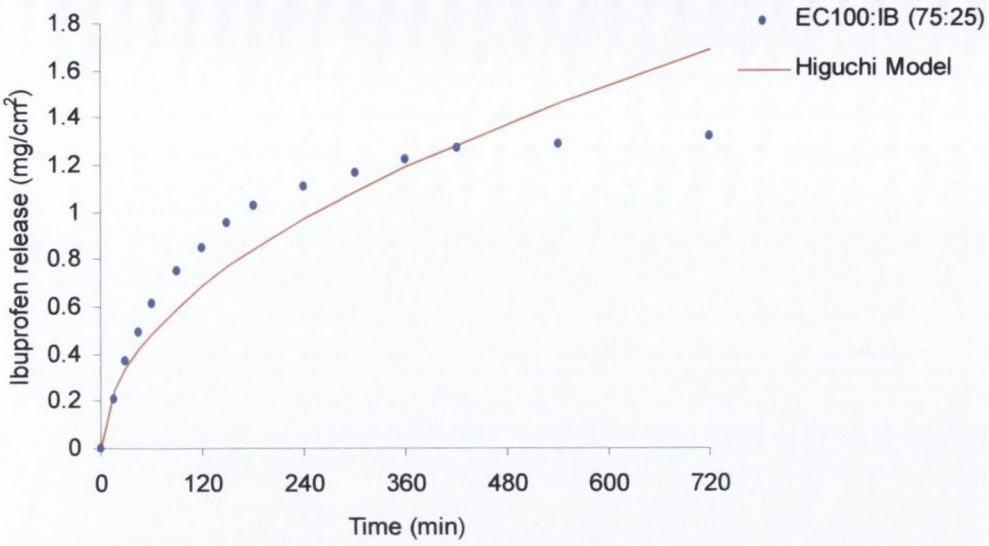

Figure A4.19. Higuchi model fit to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts. EC100: ethylcellulose 100 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

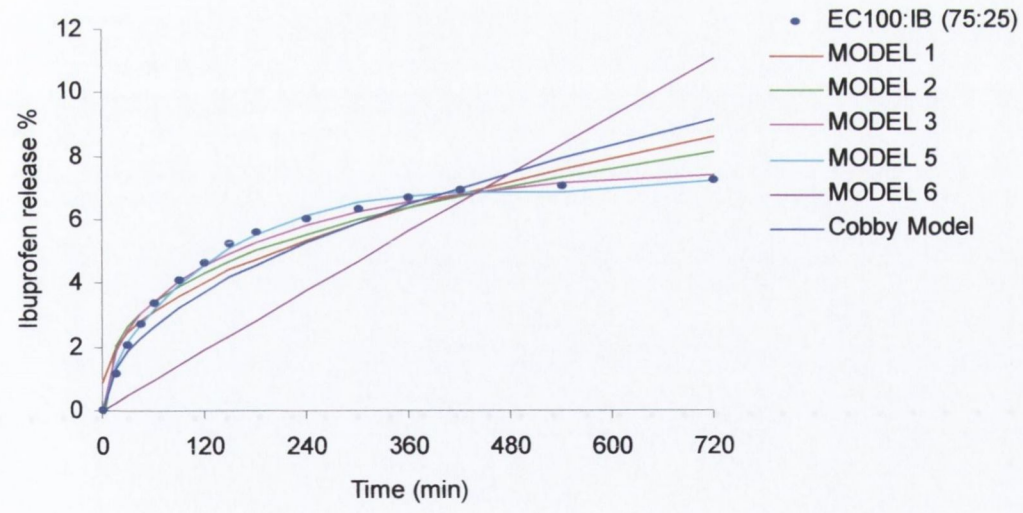

Figure A4.20. Model fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts. EC100: ethylcellulose 100 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

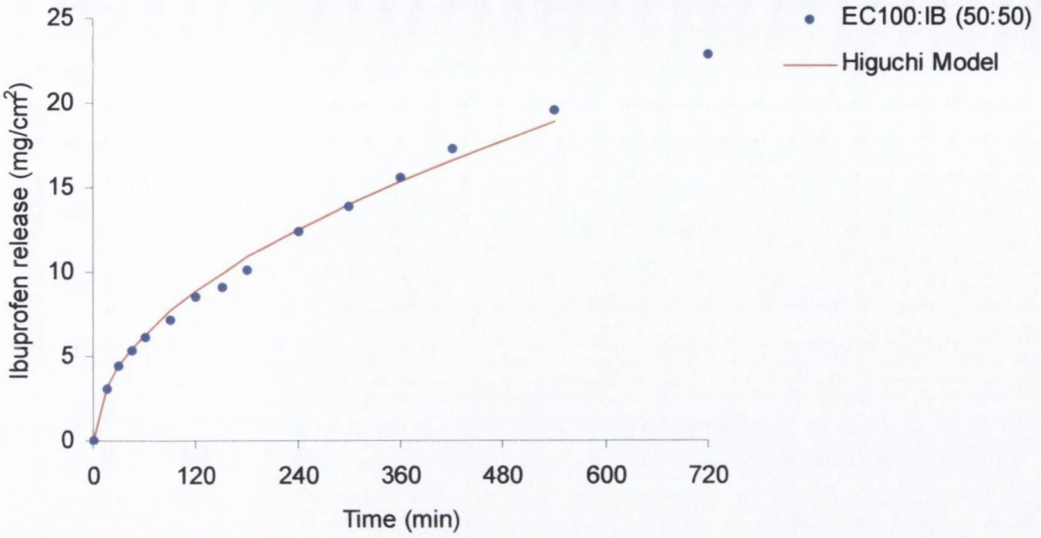

Figure A4.21. Higuchi model fit to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts. EC100: ethylcellulose 100 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

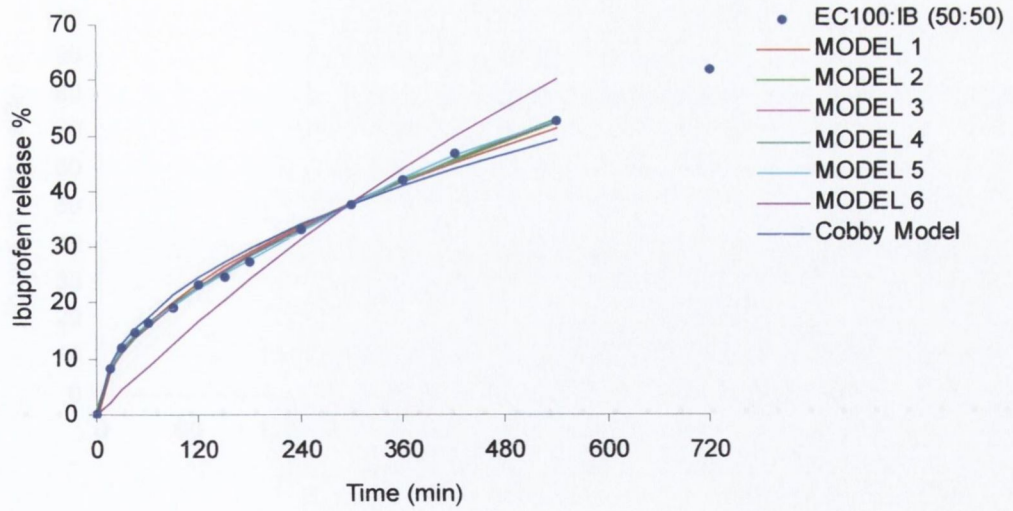

Figure A4.22. Model fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts. EC100: ethylcellulose 100 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction of) drug release.

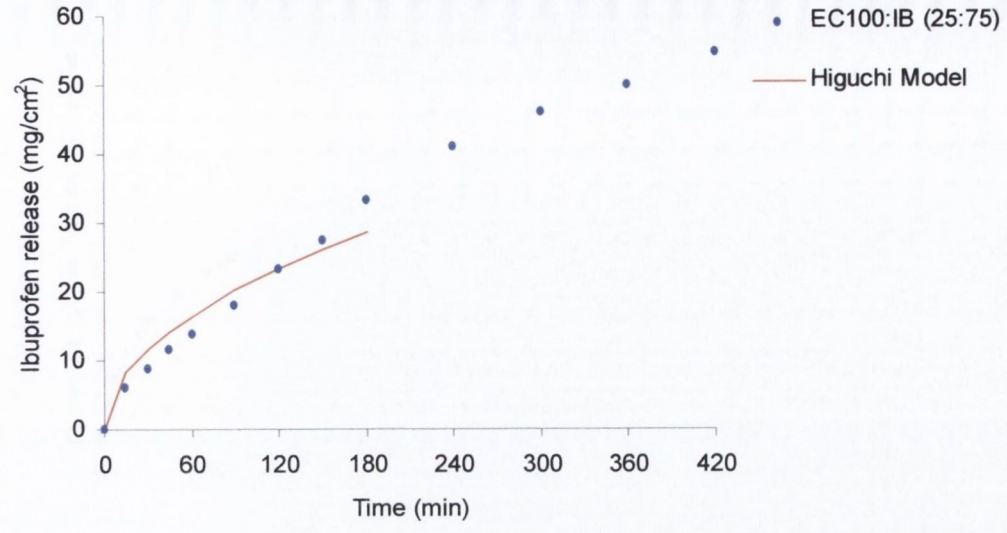

Figure A4.23. Higuchi model fit to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts. EC100: ethylcellulose 100 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets.

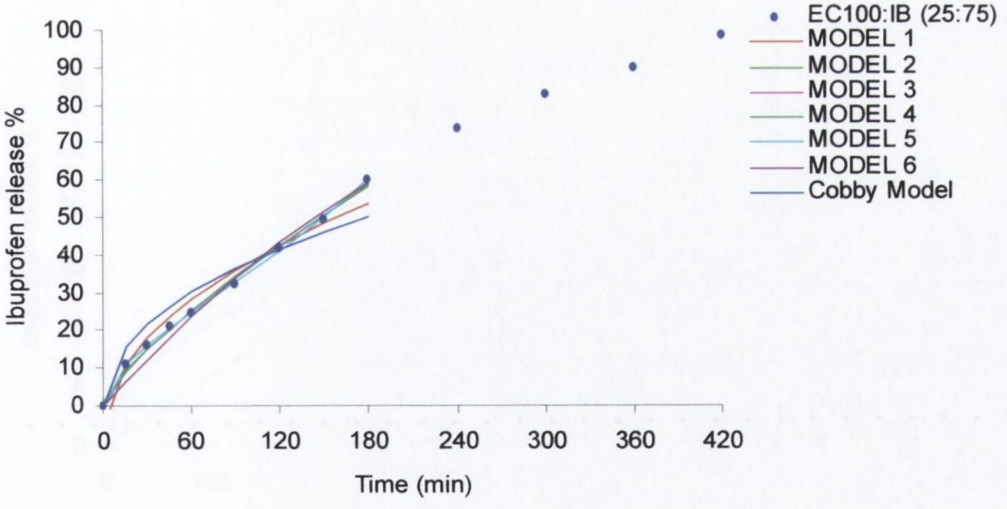

Figure A4.24. Cobby model fit to ibuprofen release data from ethylcellulose 100 cP :ibuprofen compacts. EC100: ethylcellulose 100 cP, IB: ibuprofen. Ethylcellulose:ibuprofen weight ratio is indicated in brackets. The Cobby model is plotted as percentage (as opposed to fraction) of drug release.

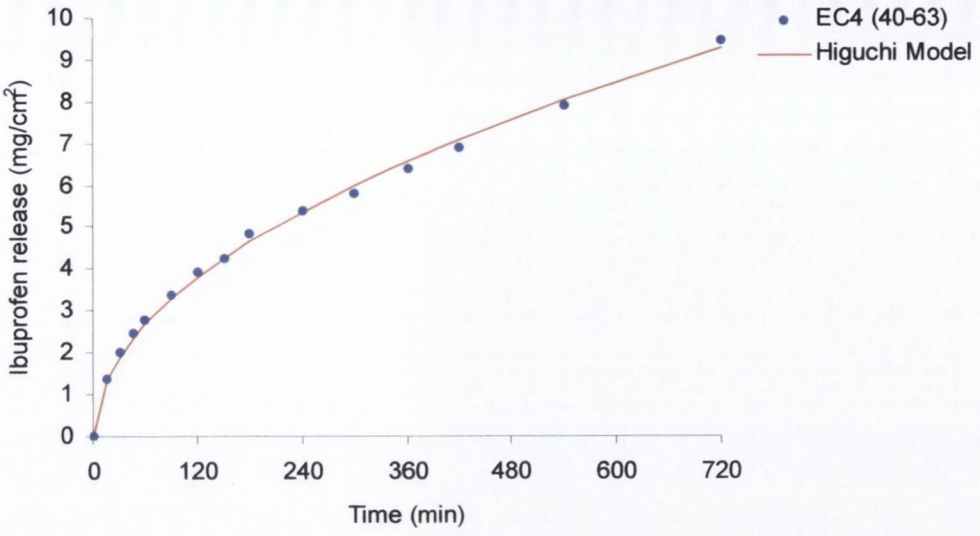

Figure A4.25. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

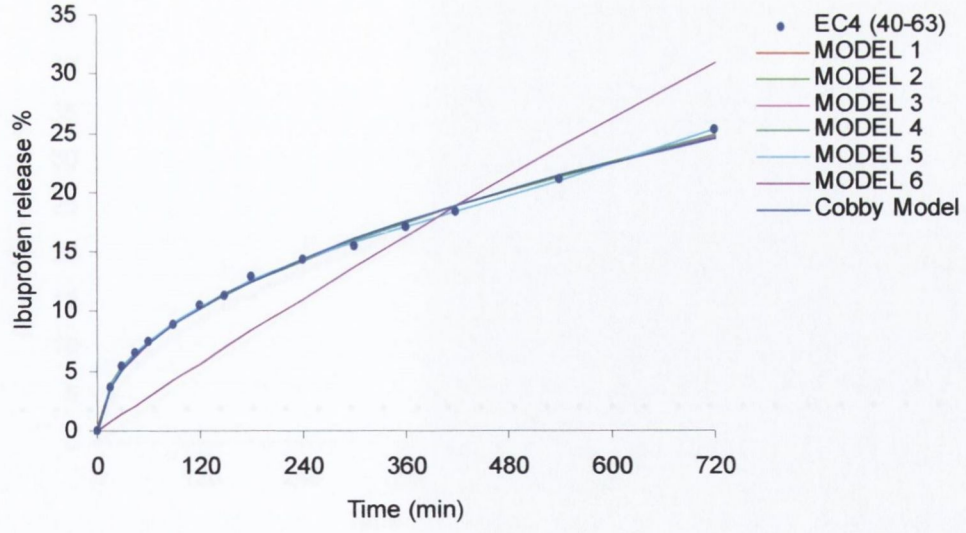

Figure A4.26. Model fits to ibuprofen release data from ethylcellulose 4cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

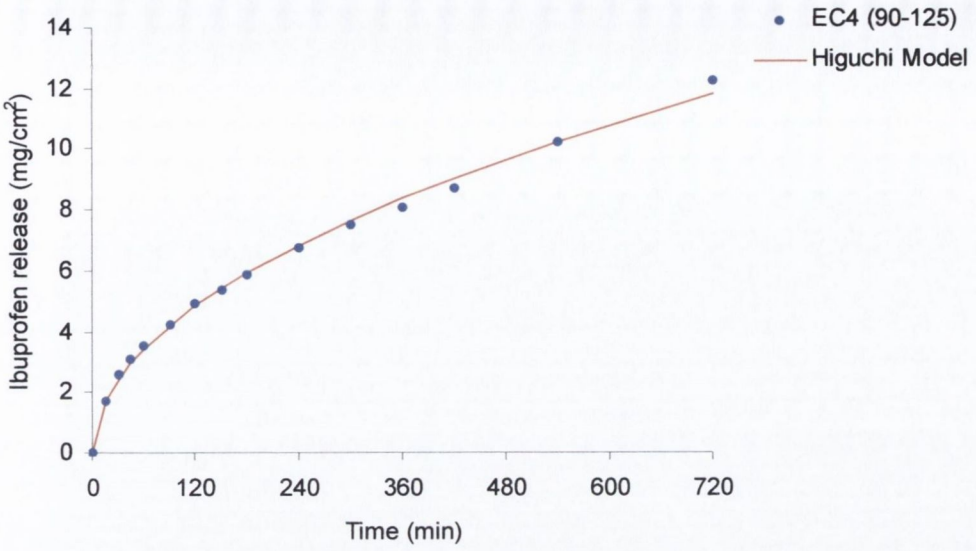

Figure A4.27. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

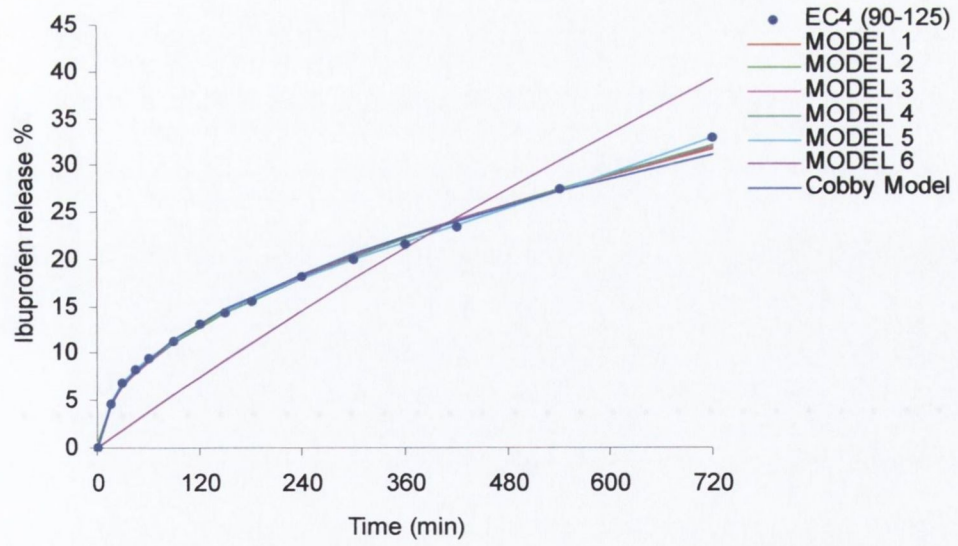

Figure A4.28. Model fits to ibuprofen release data from ethylcellulose 4cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

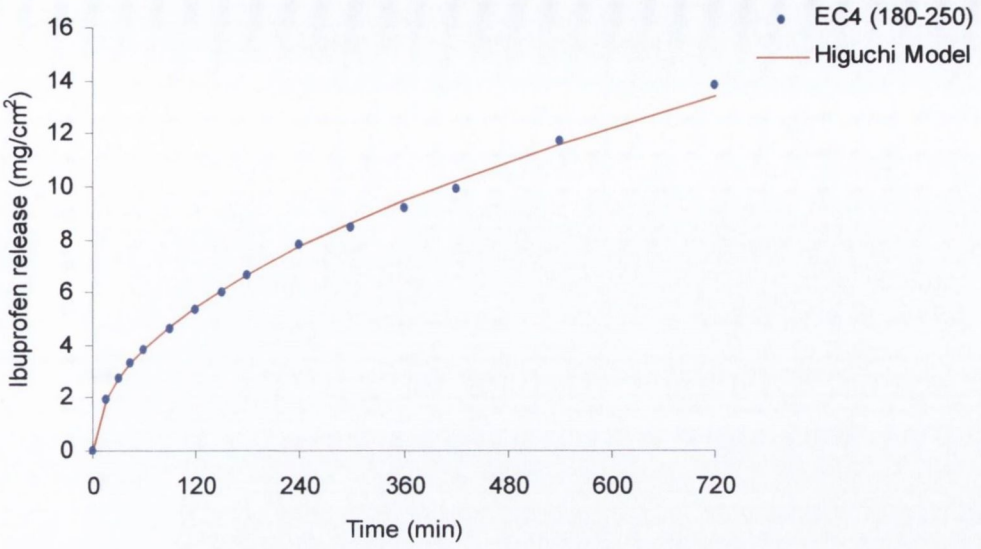

Figure A4.29. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

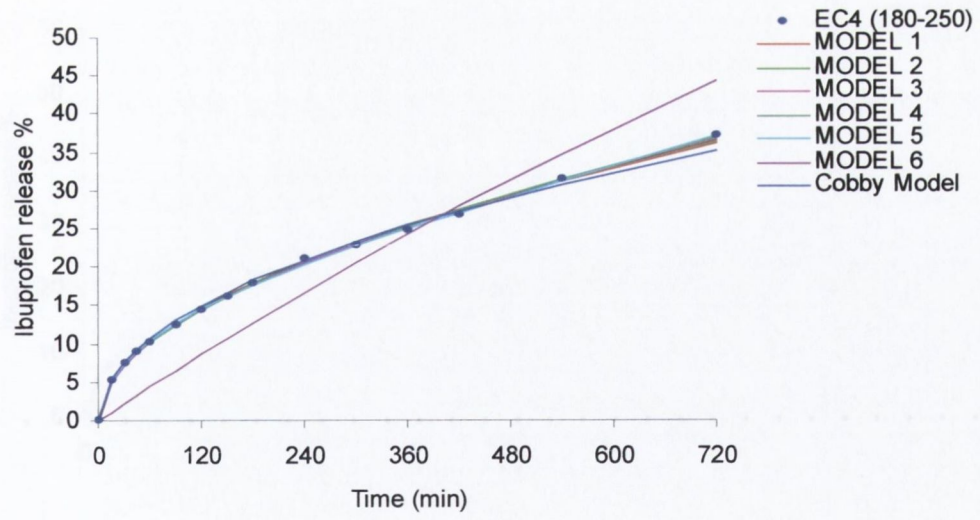

Figure A4.30. Model fits to ibuprofen release data from ethylcellulose 4cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

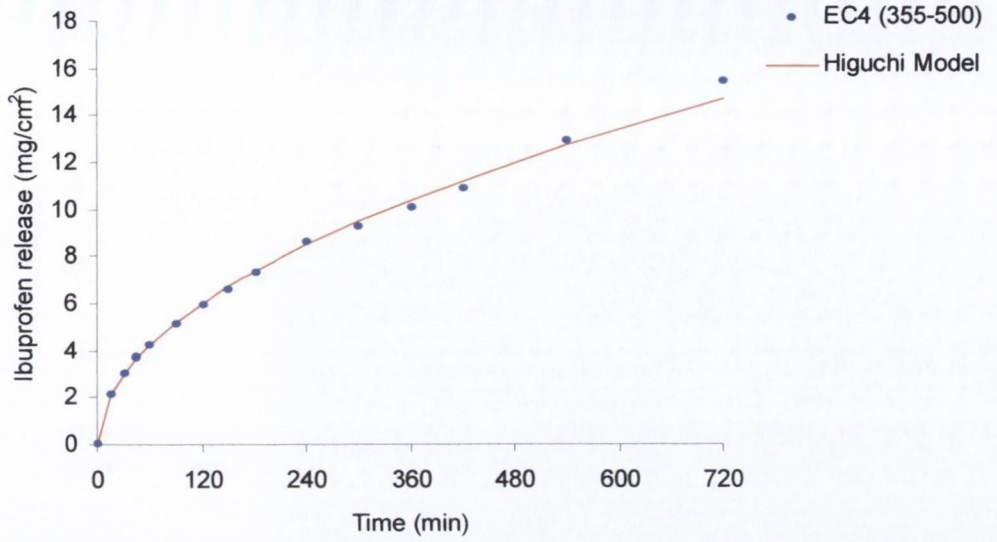

Figure A4.31. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

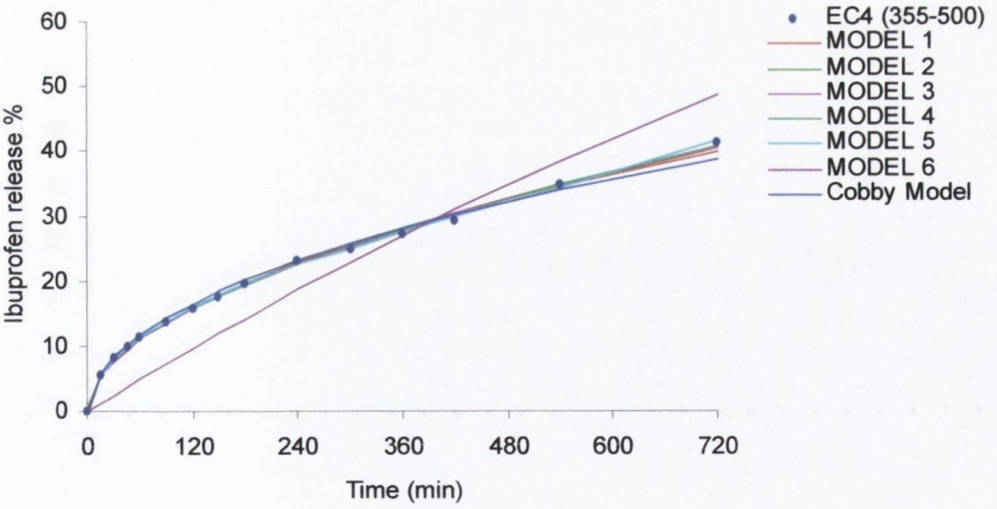

Figure A4.32. Model fits to ibuprofen release data from ethylcellulose 4cP:ibuprofen compacts (50:50 weight ratio). EC4: ethylcellulose 4 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

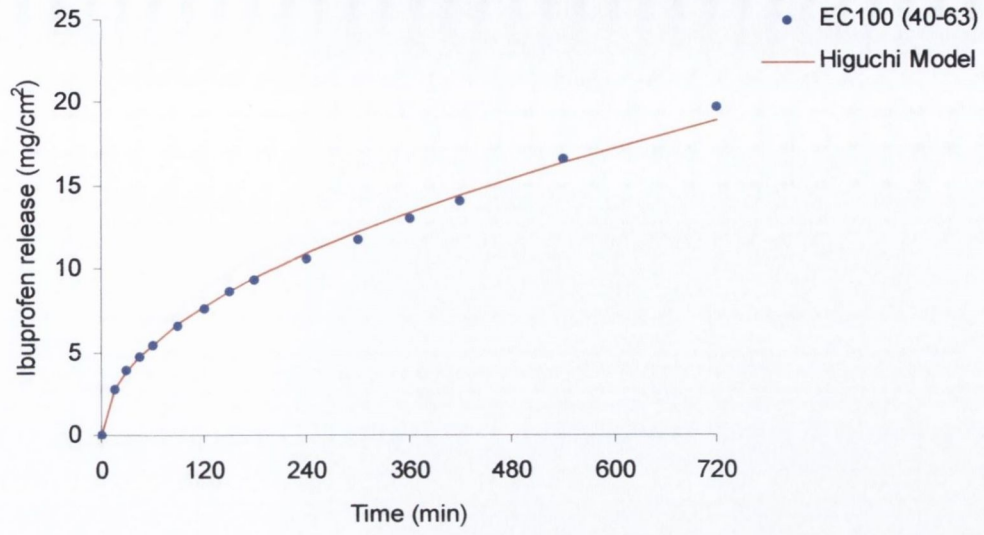

Figure A4.33. Higuchi model fit to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

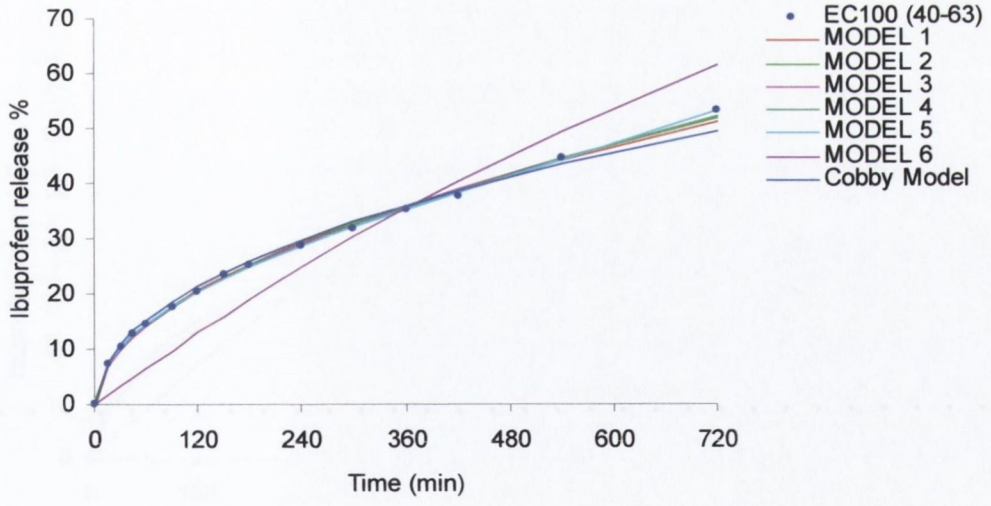

Figure A4.34. Model fits to ibuprofen release data from ethylcellulose 100cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

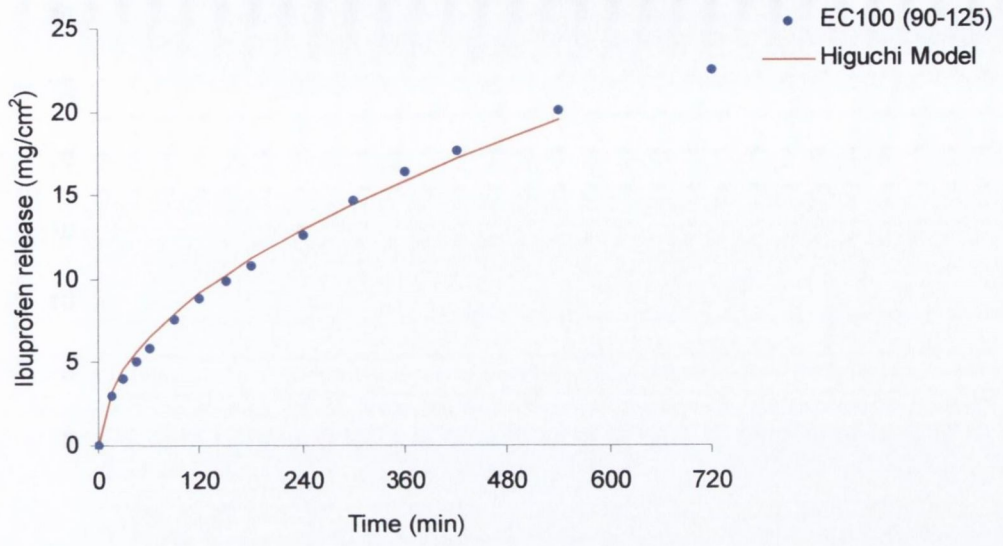

Figure A4.35. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

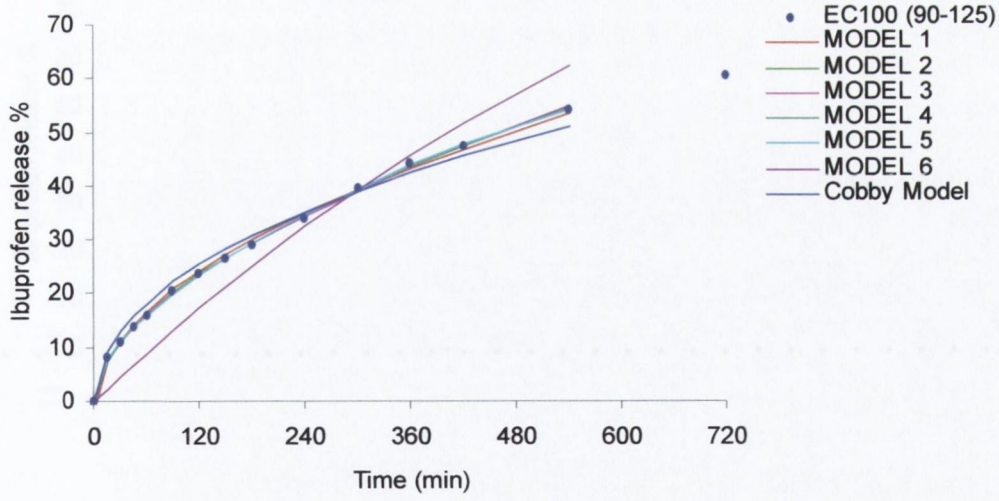

Figure A4.36. Model fits to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

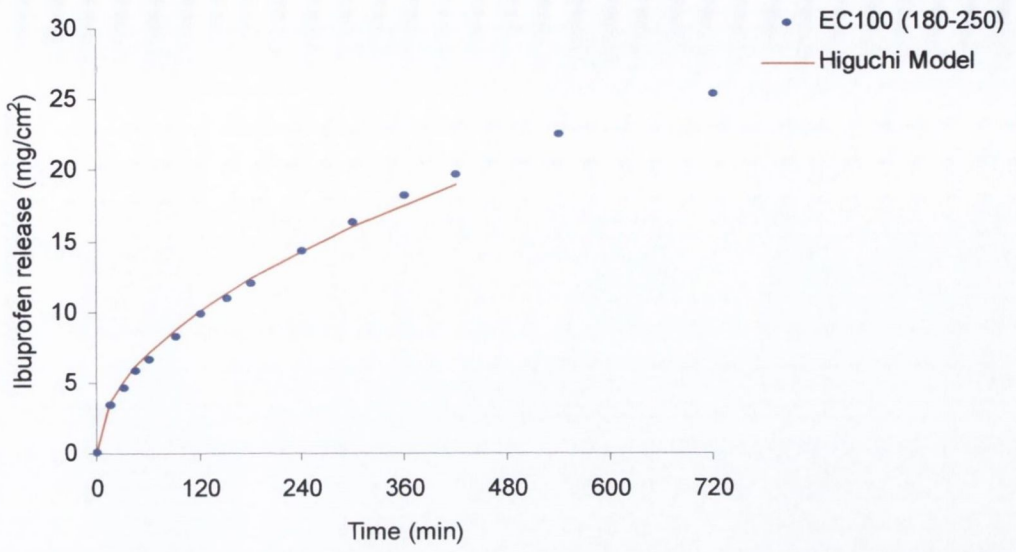

Figure A4.37. Higuchi model fit to ibuprofen release data from ethylcellulose 100 cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

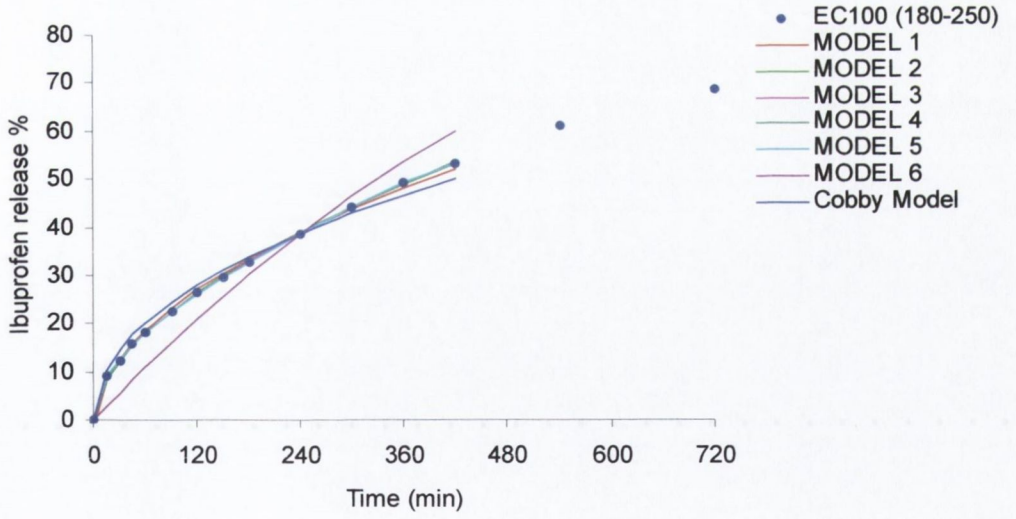

Figure A4.38. Model fits to ibuprofen release data from ethylcellulose 100cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

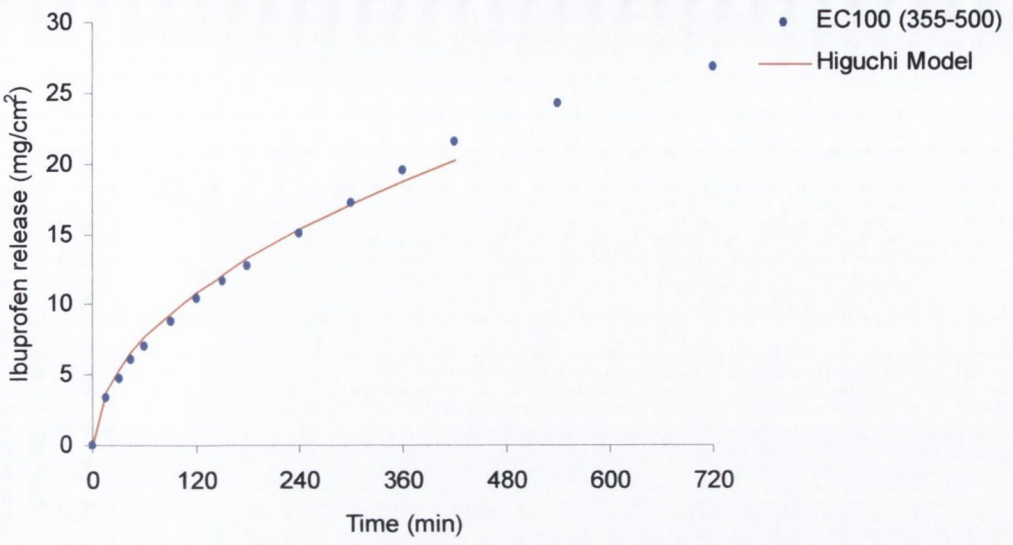

Figure A4.39. Higuchi model fit to ibuprofen release data from ethylcellulose 4 cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets.

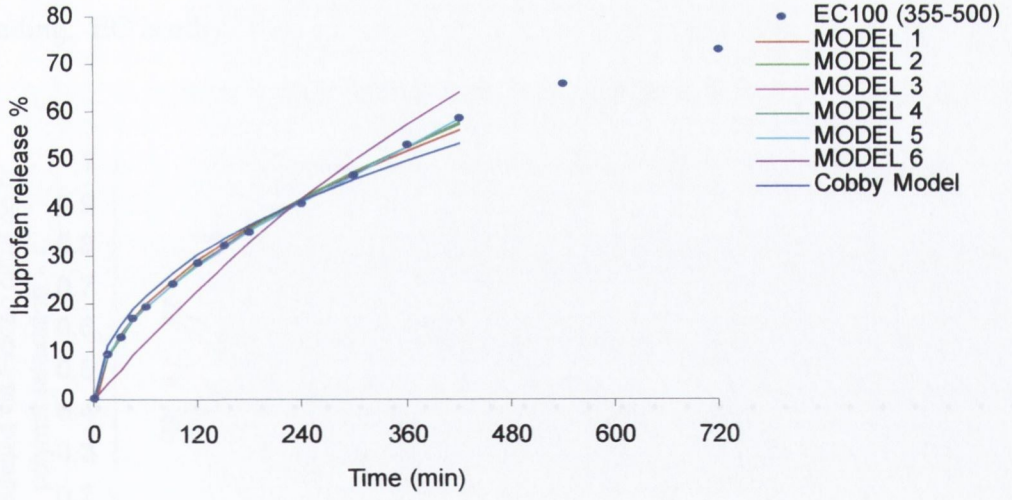

Figure A4.40. Model fits to ibuprofen release data from ethylcellulose 100cP:ibuprofen compacts (50:50 weight ratio). EC100: ethylcellulose 100 cP, IB: ibuprofen. The ethylcellulose particle size fraction is indicated in brackets. The Cobby model and erosion model are plotted as percentage (as opposed to fraction) of drug release.

APPENDIX 5

Plots of fraction of drug released via Fickian diffusion or polymer relaxation

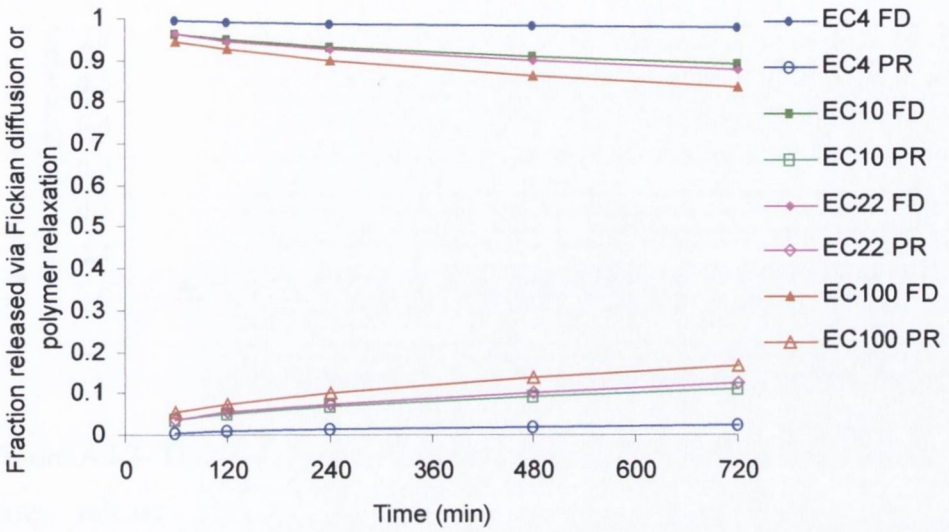

Figure A5.1. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen compacts prepared with a 50% w/w drug loading. EC is ethylcellulose and the number following it is the viscosity grade (cP).

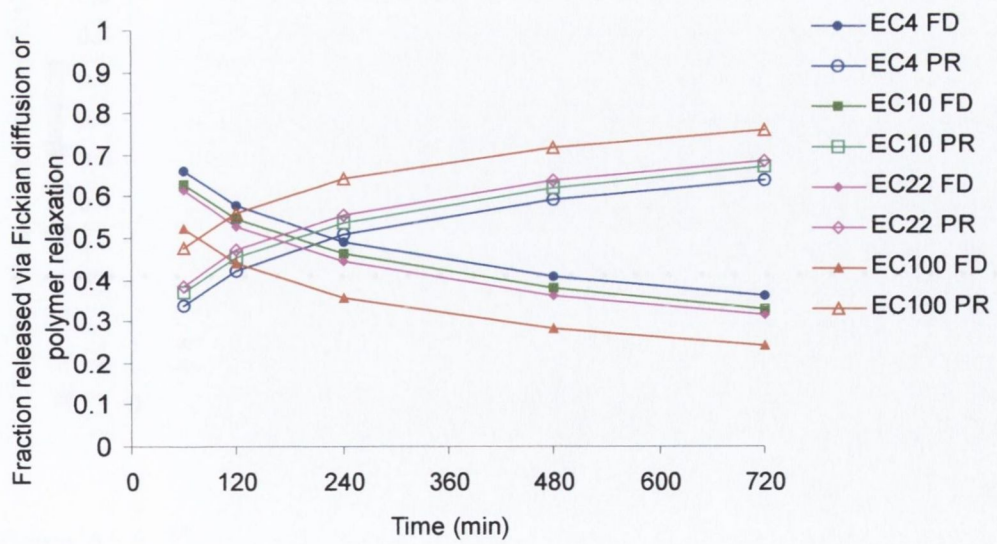

Figure A5.2. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen compacts prepared with a 75% w/w drug loading. EC is ethylcellulose and the number following it is the viscosity grade (cP).

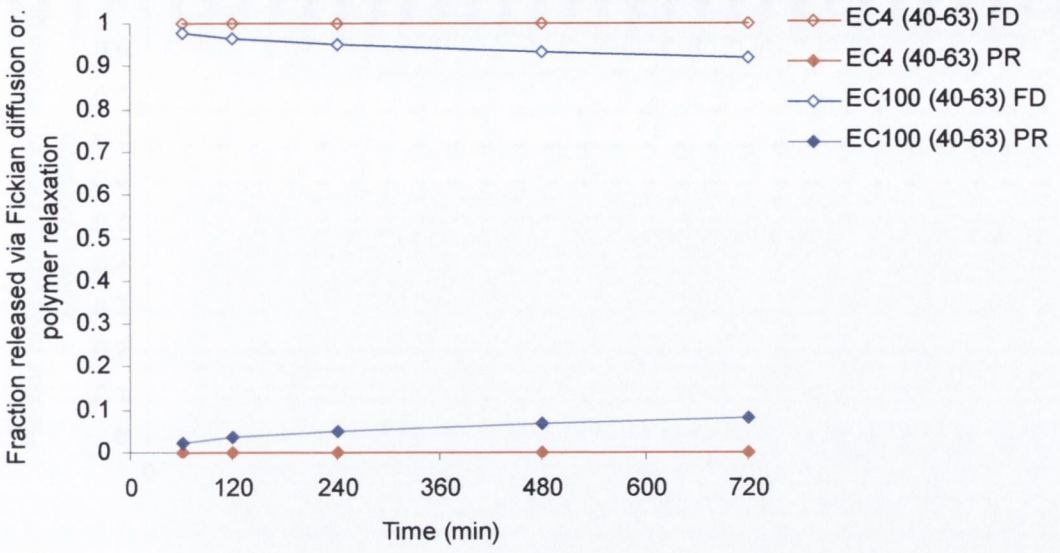

Figure A5.3. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen (50:50 weight ratio) compacts. EC4:ethylcellulose 4 cP, EC100: ethylcellulose 100 cP. The ethylcellulose particle size fraction is indicated in brackets.

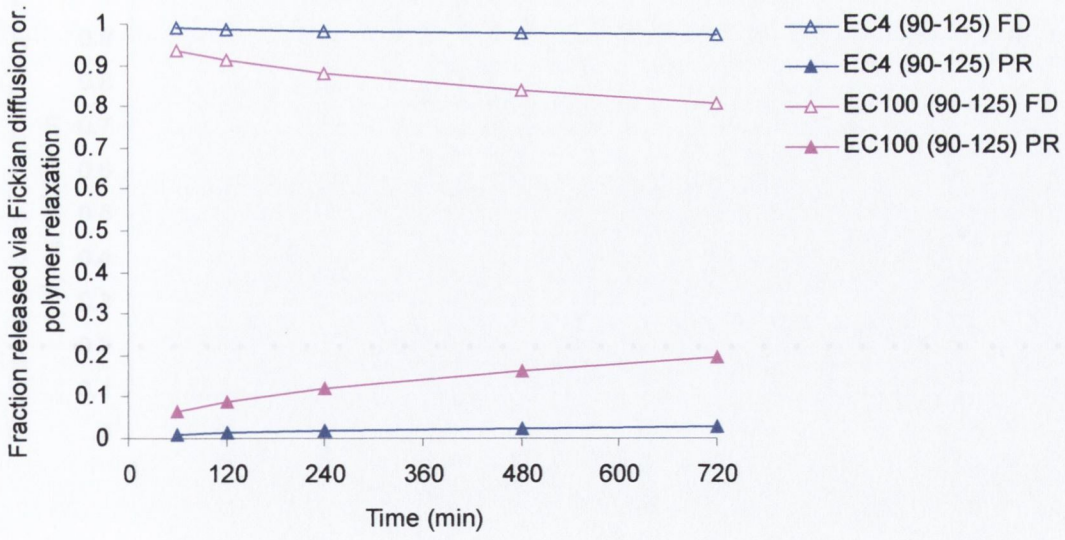

Figure A5.4. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen (50:50 weight ratio) compacts. EC4:ethylcellulose 4 cP, EC100: ethylcellulose 100 cP. The ethylcellulose particle size fraction is indicated in brackets.

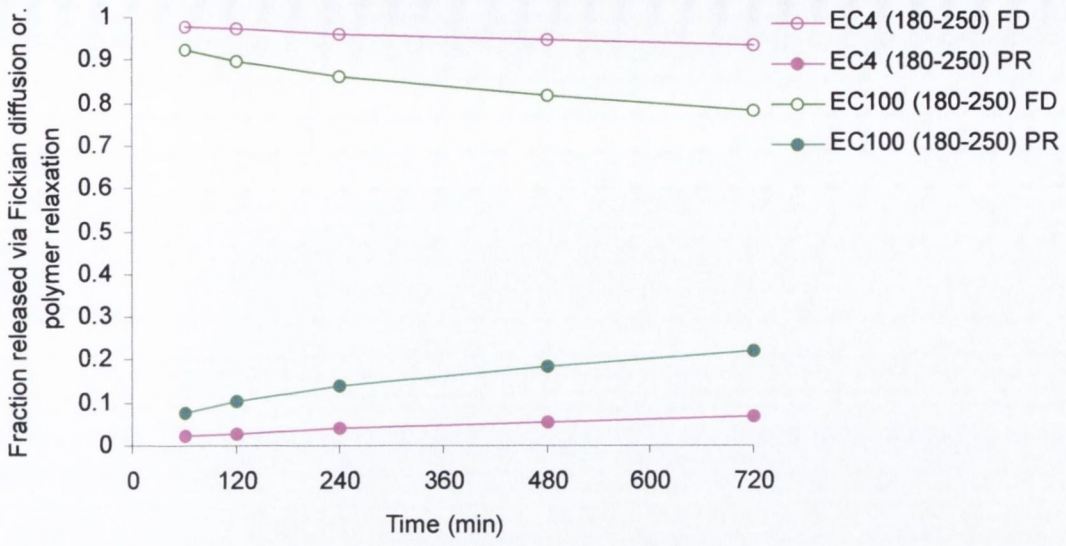

Figure A5.5. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen (50:50 weight ratio) compacts. EC4:ethylcellulose 4 cP, EC100: ethylcellulose 100 cP. The ethylcellulose particle size fraction is indicated in brackets.

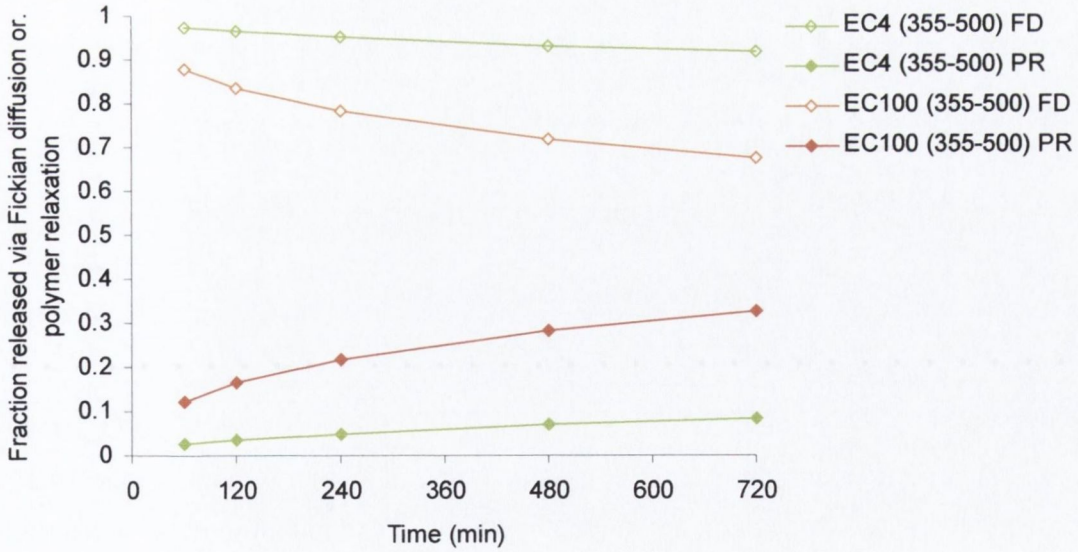

Figure A5.6. The contribution of Fickian diffusion (FD) or polymer relaxation (PR) to drug release from ethylcellulose:ibuprofen (50:50 weight ratio) compacts. EC4:ethylcellulose 4 cP, EC100: ethylcellulose 100 cP. The ethylcellulose particle size fraction is indicated in brackets.

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