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UNDERSTANDING THE ROLE OF LOW GLASS TRANSITION TEMPERATURE EXCIPIENTS IN THE MITIGATION OF AMORPHISATION ON MECHANICAL PROCESSING

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DECLARATION

This thesis is submitted by the undersigned author to the University of Dublin, Trinity College, for the examination for the degree of Doctor of Philosophy. This thesis has not been submitted as an exercise for a degree at any other university and is entirely the work of the undersigned author, except where duly acknowledged and with the aid of editorial advice from Professor Anne Marie Healy. It is agreed that this thesis may be deposited in the University's open access institutional repository, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

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SUMMARY

The aim of this research was to further an understanding of the ability of low glass transition temperature (T_g) crystalline excipients, in particular the dicarboxylic acids, to mitigate the amorphisation of high T_g active pharmaceutical ingredients (APIs) on comilling and to explore the possibility of mitigating amorphisation during other unit processes including blending and compaction. The APIs used were budesonide (BD), sulfadimidine (SDM) and acyclovir (ACV) based on both their high T_g values and their tendency to amorphise on milling at room temperature (RT). The excipients chosen were the dicarboxylic acids succinic acid (SA), glutaric acid (GA), adipic acid (AA) and pimelic acid (PA) in addition to the low T_g polyol mannitol (MAN). The excipients were chosen based on their low T_g values and consequent ability to resist amorphisation on milling. In addition, previous studies have highlighted the ability of the dicarboxylic acids in particular to effect mitigation of amorphisation on comilling. However, the mechanism by which these excipients exert this effect has, to date, not been further explored.

The amorphisation of SDM was initially studied in the absence of a low T_g excipient, in two types of ball mill, a planetary ball mill (PBM) and a vibratory ball mill (VBM). While an increased amorphisation kinetic was observed on milling at RT in the VBM relative to the PBM, both ball mill types led to a similar partial amorphisation (80% amorphous content) of SDM. However, reducing the temperature of the milling operation in both ball mill types led to an increase in the amorphisation of the API. The effect of the milling parameters which affect the level of mechanical energy imparted was assessed relative to the milling temperature in the VBM in a design of experiment analysis. Additionally, the surface chemistry changes on milling of SDM at high and low intensity were assessed by inverse gas chromatography (iGC). Each of the low T_g crystalline excipients were also milled alone and each excipient remained crystalline on milling as demonstrated by PXRD and DSC analysis. However, both MAN and PA underwent polymorphic transformations to metastable polymorphic forms. In addition, the dispersive surface energies on milling of the low T_g excipients were assessed by iGC analysis.

Milling of crystalline BD in the absence of a low T_g excipient in the VBM at both RT and cryo-temperature (CT) led to the amorphisation of the API, leading to a T_g on modulated DSC analysis of 89 °C. In contrast, comilling crystalline BD in the VBM at RT with each of the low T_g dicarboxylic acids led to varying levels of crystalline BD (i.e. mitigation of amorphisation), as quantified by both PXRD and DVS analysis. In

particular, GA was found to completely mitigate amorphisation of BD, followed by PA (72% crystallinity) and AA (21% crystallinity) which exhibited partial abilities to mitigate amorphisation of BD. In contrast, both SA and MAN were unable to mitigate amorphisation of BD to any extent on comilling. In contrast to RT comilling studies, comilling crystalline BD with each of the excipients at CT led to the amorphisation of BD in each case highlighting the importance of the mill temperature in the mitigation of amorphisation on comilling. T_g reduction of the composites formed on comilling at RT and CT was determined by modulated DSC analysis, in addition to spectroscopic evidence for hydrogen bonding interactions. Phase separation from the cryomilled composites was also analysed by DVS analysis. In addition, the solubility of each of the diacid excipients in amorphous BD was determined in addition to the T_g of the glass solutions saturated with excipient formed on co-melt quenching.

Crystalline SDM was partially amorphised in the PBM at RT, and the milled SDM (mSDM) was subsequently comilled with each of the dicarboxylic acids and MAN in the VBM at RT. The level of T_g reduction on comilling was determined by modulated DSC analysis and evidence for hydrogen bonding interactions was assessed by FTIR analysis, which was found to be strongest for GA. The solubility of each of the diacids in amorphous SDM was determined by the zero enthalpy extrapolation method, in addition to the T_g of the glass solutions saturated with excipient formed on co-melt quenching. The thermodynamic properties of liquid SDM: excipient mixtures were assessed by melting point depression analysis which revealed that while MAN was found to be immiscible with SDM in the liquid state, each of the diacids exhibited miscibility. Additionally, the excess thermodynamic functions were computed for the SDM:GA, SDM:AA and SDM:PA composites which revealed similar excess functions of interaction on mixing for all three systems. Crystallisation of SDM from the co-cryomilled SDM:GA and SDM:PA composites was assessed in the DVS, indicating faster crystallisation kinetics from the GA composite. Analysis of the activation energy of crystallisation from the GA and PA composites by non-isothermal kinetics utilising Ozawa/ Kissinger analyses indicated a lower activation energy of crystallisation from the SDM:GA composite relative to SDM:PA.

Two polymorphic forms of crystalline ACV, form I (anhydrous) and form V (3:2 hydrate) were milled in the VBM at both RT and CT. While form I was amorphised at both RT and CT, the form V hydrate was only amorphised at CT. DSC analysis revealed the T_g of amorphous ACV to be 109 °C. Form I ACV was subsequently

comilled with GA, PA and MAN at both RT and CT in the VBM. While comilling at RT with GA led to a cocrystal, comilling with PA led to the regeneration of form I ACV and comilling with MAN led to the amorphisation of ACV. In contrast, comilling at CT led to the amorphisation of ACV in each of the composite systems. The T_g reduction of the co-cryomilled composites was determined by modulated DSC analysis and crystallisation from the co-cryomilled composites was also investigated under humidity accelerated conditions.

Co-blending amorphous SDM did not lead to a hydrogen bonding interaction with GA, in contrast to the interaction observed on comilling. In addition, no polymorphic transformation of β -GA into the metastable α -polymorph was observed on co-blending, in contrast to the comilled composite. The propensity of compaction to lead to the crystallisation of amorphous BD was also studied by compaction of the amorphous composites formed on co-cryomilling BD with each of the diacids SA, GA, AA and PA. However, no crystallisation of BD from the amorphous composites was observed on co-compaction.

The analysis suggested that the ability of the low T_g excipients to drive T_g reduction of the high T_g API down to the temperature of the milling operation was important in terms of their respective abilities to mitigate amorphisation on comilling. The inability of MAN to drive reduction in T_g , and consequent inability to mitigate amorphisation on comilling, was possibly due to immiscibility in the liquid/ glass solution state. However, the relative abilities of the diacids to drive T_g reduction, and subsequent differences in abilities to mitigate amorphisation, could not be accounted for by either a miscibility barrier or to differences in the thermodynamics of interaction on mixing in the liquid/ glass solution state. The difference in the relative abilities of the diacids to drive T_g reduction by mechanical means (relative to the T_g of the saturated glass solutions formed by melt quench) was correlated with the solid-state properties of the diacids in particular their melting point alternation which has been related to differences in the strength of hydrogen bonding in their respective crystalline states. We also interpreted our results in the context of the driven materials theory which attempts to account for mechanically induced phase transformations, both crystalline to amorphous and amorphous to crystalline, utilising the concept of the effective temperature on milling.

Dedicated to my mum, Rita Gallagher

TABLE OF CONTENTS

Acknowledgements.....	i
Abbreviations.....	iii
Selected Presentations and Publications Associated With This Work	vii
ORIGIN AND SCOPE	1
CHAPTER 1 INTRODUCTION.....	5
Overview of The Solid State.....	6
Unit Processes and Formulation Design.....	6
The Crystalline and Amorphous States.....	8
Formation of the Amorphous State – Mechanical vs Thermal Activation	11
Factors Affecting Crystallisation from the Amorphous State	13
Mechanical Activation – Phase Transformations in Single Component	
Systems on Mechanical Processing.....	14
Generation of Static vs Dynamic Disorder on Milling and Solid-State	
Characterisation	14
Mechanical Activation on Milling – Temperature of the Mill Relative to the T_g	
of the Material.....	16
Mechanical Rejuvenation on Milling – Mechanically Induced Ageing and	
Regeneration of Crystalline Order from a Quench-Cooled Glass	19
Mechanical Activation on Compaction and Blending.....	20
Composite Molecular Systems.....	20
Composite Crystalline Systems	21
Composite Amorphous Systems	24
Driven Molecular Alloys – Potential for Mitigation of Amorphisation on	
Comilling.....	26
Towards a Rationalisation of Mechanically Induced Phase Transformations	
– The Effective Temperature on Milling	30
Crystalline to Amorphous Transformations Induced Mechanically	30
Amorphous to Crystalline Transformations Induced Mechanically	31

CHAPTER 2 MATERIALS AND METHODS.....	33
2.1 Materials	34
2.2 Controlled Temperature and Relative Humidity Environments	35
2.3 Unit Operations	36
2.3.1 Milling.....	36
2.3.2 Compaction	37
2.3.3 Blending.....	37
2.3.4 Spray Drying.....	38
2.3.5 Physical Mixture Preparation	38
2.3.6 Melt Quenching.....	38
2.4 Analytical Techniques	38
2.4.1 Differential Scanning Calorimetry	38
2.4.2 Thermogravimetric Analysis	39
2.4.3 Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy.....	40
2.4.4 Near Infrared Reflectance Spectroscopy.....	40
2.4.5 Powder X-Ray Diffractometry	40
2.4.6 Dynamic Vapour Sorption.....	41
2.4.7 Inverse Gas Chromatography (iGC) Surface Energy Analysis	43
2.4.8 BET N ₂ Surface Area Analysis	45
2.4.9 Polarised Hot Stage Microscopy	46
2.4.10 Scanning Electron Microscopy	46
2.4.11 Laser Light Diffraction Particle Size Analysis	46
2.4.12 Experimental Determination of the Solubility of Crystalline Excipients in Amorphous Low Molecular Weight API at 25 °C.....	46
2.4.13 Melting Point Depression Analysis of SDM with Excipients and Computation of the Excess Thermodynamic Functions	47
2.4.14 Determination of the Activation Energy of Crystallisation from Amorphous Composite Systems by Ozawa/ Kissinger Non-Isothermal Crystallisation Kinetics	49
2.4.15 Calculation of the Hildebrand Solubility Parameters	50
2.4.16 Graphing Software and Statistical Analysis	50
2.4.17 Molecular Modelling.....	50

CHAPTER 3 MECHANICAL ACTIVATION STUDIES ON MILLING OF HIGH AND LOW T_g MOLECULAR PHARMACEUTICAL MATERIALS 53

3.1	Introduction.....	54
3.2	Solid State Characterisation of Crystalline and Amorphous Sulfadimidine	55
3.2.1	PXRD Analysis	55
3.2.2	DSC Analysis.....	56
3.2.3	Spectroscopic Analysis	58
3.2.4	Sorption Analysis	61
3.3	Comparison of the Effect of Mill Type and Temperature on Amorphisation Kinetics and Extent of Amorphisation on Milling	64
3.4	Design of Experiment on the Mechanical Activation of Sulfadimidine in the Vibratory Ball Mill	69
3.5	Analysis of Milling Induced Changes to the Surface Chemistry of Sulfadimidine by Inverse Gas Chromatography	79
3.6	Solid State Characterisation and Mechanical Activation Studies of the Low T _g Excipients	86
3.6.1	Mannitol.....	86
3.6.2	The Dicarboxylic Acids	89
3.7	Conclusions.....	100

CHAPTER 4 COMILLING STUDIES WITH BUDESONIDE AND LOW T_g EXCIPIENTS..... 101

4.1	Introduction.....	102
4.2	Solid State Characterisation of Crystalline and Amorphous Budesonide	104
4.2.1	Thermal Analysis	104
4.2.2	Spectroscopic Analysis	105
4.2.3	Sorption Analysis	107
4.3	Comilling Studies of Crystalline Budesonide with Low T _g Excipients at Room temperature.....	108
4.3.1	PXRD Analysis	108
4.3.2	DVS Analysis	111
4.3.3	Thermal Analysis	115

4.4	Co-Cryomilling Studies of Budesonide with Low T_g Excipients.....	120
4.4.1	PXRD Analysis	120
4.4.2	Thermal Analysis	123
4.5	Phase Separation Studies from the Co-Cryomilled Driven Alloys	128
4.5.1	Budesonide and Glutaric Acid Co-Cryomilled Composite.....	128
4.5.2	Budesonide and Pimelic Acid Co-Cryomilled Composite.....	132
4.5.3	Budesonide and Adipic Acid Co-Cryomilled Composite.....	136
4.5.4	Budesonide and Succinic Acid/ Mannitol Co-Cryomilled Composites	
	139	
4.6	Studies on Thermally Co-Activated Budesonide Alloys – Solubility and T_g Reduction	145
4.7	Conclusions.....	149

CHAPTER 5 STUDIES ON THE FORMATION AND PHYSICAL PROPERTIES OF

	SULFADIMIDINE AND LOW T_g EXCIPIENT ALLOYS.....	151
5.1	Introduction	152
5.2	Comilling Studies of Amorphous Sulfadimidine with Low T_g Excipients	153
5.2.1	PXRD Analysis.....	153
5.2.2	DSC Analysis.....	156
5.2.3	FTIR Analysis.....	159
5.3	Studies on the Thermally Co-Activated Sulfadimidine Alloys – Solubility and T_g Reduction	163
5.4	Melting Point Depression Analysis – Miscibility and Excess Thermodynamic Functions of Interactions in the Liquid State	167
5.5	Crystallisation Studies of Sulfadimidine from the Cryomilled Driven Alloys.....	174
5.5.1	DVS Studies	174
5.5.2	Non-Isothermal Crystallisation Kinetics.....	186
5.6	Conclusions.....	191

CHAPTER 6 MECHANICAL ACTIVATION STUDIES ON MILLING OF ACYCLOVIR AND COMILLING WITH LOW T_g EXCIPIENTS.....	193
6.1 Introduction.....	194
6.2 Characterisation of Crystalline Acyclovir.....	196
6.2.1 Thermal Analysis	197
6.2.2 FTIR Analysis.....	198
6.2.3 DVS Analysis	200
6.2.4 SEM Analysis.....	202
6.3 Mechanical Activation Studies of Acyclovir.....	204
6.3.1 Mechanical Activation of Form I (Anhydrous) Acyclovir	204
6.3.2 Mechanical Activation of Form V (3:2 Hydrate) Acyclovir	206
6.4 Comilling Studies of Acyclovir with Low T_g Excipients	209
6.4.1 Comilling Acyclovir with Glutaric Acid	209
6.4.2 Comilling Acyclovir with Pimelic Acid	222
6.4.3 Comilling Acyclovir with Mannitol	226
6.5 Conclusions.....	231
CHAPTER 7 CO-BLENDING AND CO-COMPACTION STUDIES.....	233
7.1 Introduction.....	234
7.2 Characterisation of Blended Sulfadimidine and Co-Blending with Glutaric Acid	235
7.3 Co-Compaction of Budesonide with Dicarboxylic Acids	239
7.4 Conclusions.....	242
CHAPTER 8 GENERAL DISCUSSION	243
Mechanical Activation on Milling and Solid-State Characterisation.....	244
Comilling and Formation of the Driven Molecular Alloys.....	248
Mitigation of Amorphisation on Comilling – Correlation with Experimental Solubility, Calculated Hildebrand Solubility Parameters and T_g Reduction Relative to the Milling Temperature	248
Miscibility and Excess Thermodynamic Functions of Liquid-State Mixtures and Solid-State Properties of the Diacids.....	254

Formation of the Driven Molecular Alloys in the Context of the Driven Materials Theory	260
Phase Separation from the Driven Molecular Alloys	264
Humidity Accelerated Phase Separation from the Cryomilled Driven Alloys	264
Mitigation of Amorphisation on Comilling at Room Temperature – Mechanical Rejuvenation from the Reduced T_g Driven Alloys.....	266
Co-Blending and Co-Compaction Relative to Comilling.....	270
CONCLUSIONS & FUTURE WORK	273
REFERENCES	277
APPENDICES.....	299
A-I Additional Figures.....	299
A-II Characterisation of the Sulfadimidine-Succinic Acid Cocrystal.....	310
A-III Characterisation of the γ -Polymorph of Pimelic Acid	313
A-IV iGC Analysis Conditions.....	315
A-V Quantification of the Excess Thermodynamic Functions	316
A-VI Calculation of the Hildebrand Solubility Parameters.....	319

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ABBREVIATIONS

AA	Adipic acid
ACV	Acyclovir
AN*	Modified Gutmann acceptor number
ATR	Attenuated total reflectance
BCS	Biopharmaceutical Classification System
BET	Brunauer-Emmet-Teller
BD	Budesonide
BPR	Ball to powder mass ratio
ccm	Cubic centimetres per minute
°C	Degrees Celsius
CT	Cryo-temperature
D _{bal}	Ballistic jump
D _{th}	Thermal jump
dm/dt	Rate of change of mass with respect to time
DN	Gutmann donor number
DVS	Dynamic vapour sorption
DOE	Design of experiment
DSC	Differential scanning calorimetry
E _a	Activation energy
FID	Flame Ionisation Detector
G ^E	Excess Gibbs energy
H ^E	Excess enthalpy
ΔH _c	Enthalpy of crystallisation
ΔH _m	Enthalpy of melting
HPLC	High performance liquid chromatography
Hz	Hertz
iGC	Inverse gas chromatography
IND	Indomethacin

J	Joules
K _a	Acid number
K _b	Base number
LLD	Laser light diffraction
MAN	Mannitol
mDSC	Modulated differential scanning calorimetry
m	metre
mg	Milligram
mm	Millimetre
MPD	Melting point depression
mSDM	Milled sulfadimidine
MQ	Melt quench
NIR	Near infrared spectroscopy
N _a	Avogadro's constant
PA	Pimelic acid
PXRD	Powder X-Ray diffraction
R	Universal Gas Constant
RH	Relative humidity
RH _c	Crystallisation relative humidity
RH _{c(10)}	Crystallisation relative humidity at 10% RH/hour ramp rate
RH _g	Glass transition relative humidity
RH _{g(10)}	Glass transition relative humidity at 10% RH/hour ramp rate
RT	Room temperature
SA	Succinic acid
SD	Spray dried
SDM	Sulfadimidine
S ^E	Excess entropy
StD	Standard deviation
T _c	Crystallisation temperature
T _e	Eutectic Temperature

T_g	Glass transition temperature
T_p	Crystallisation peak temperature
TGA	Thermogravimetric Analysis
TRE	Trehalose
T_i^0	Melting transition temperature of pure i th component
T_{mill}	Operational temperature of the mill
T_{eff}	Effective temperature
V_m	Molar volume
V_n	Retention volume
w/v	Weight per volume
w/w	Weight per weight
x_e	Mole fraction at the eutectic composition
x_i	Mole fraction of the i th component
$\Delta_{fus}H_i^0$	Enthalpy of fusion of the pure i th component
ΔE_v	Energy of vaporisation
ΔC_p	Change in constant pressure heat capacity
γ_s^D	Dispersive surface energy of a solid
γ_L^D	Dispersive surface energy of a liquid
γ_i	Activity coefficient of the i th component
α	Alpha
β	Beta
γ	Gamma
δ	Delta
φ	Phi
θ	Theta
%	Percent

SELECTED PRESENTATIONS AND PUBLICATIONS ASSOCIATED WITH THIS WORK

Oral Presentations

All Ireland Schools of Pharmacy, Royal College of Surgeons in Ireland, Dublin, **March 2016** – “*Mechanical Activation – Mitigation of Process Induced Amorphisation and Correlation with Excipient Solubility and Potential for Hydrogen Bonding Interaction*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Cliona Loughnane, Anne Marie Healy]

Poster Presentations

All Ireland Schools of Pharmacy, Trinity College Dublin, Dublin, **April 2014** – “*Investigating Cryo-Milling Induced Amorphisation of Sulfadimidine with Low T_g Excipients*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Anne Marie Healy]

UK and Ireland CRS, University College Cork, Cork, **April 2014** – “*Understanding the Role of Milling Temperature and Composite T_g in Process Induced Amorphisation*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Anne Marie Healy]

AAPS Annual Meeting and Exposition, San Diego, **November 2014** – “*Co-Processing with Low T_g Excipients: Towards a Mechanistic Understanding of the Role of Low T_g Excipients in the Mitigation of Process Induced Amorphisation*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Anne Marie Healy]

All Ireland Schools of Pharmacy Conference, Queen’s University, Belfast, **June 2015** – “*Solid State Interaction as a Mechanism to Prevent Milling Induced Mechanical Activation*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Anne Marie Healy]

CRS Annual Meeting and Exposition, Edinburgh, **July 2015** – “*Mechanical Activation: Milling Induced Solid State Interaction as a Mechanism to Mitigate Process Induced Amorphisation*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Anne Marie Healy]

2016 European Inverse Gas Chromatography (iGC) Symposium, Imperial College London, UK, **October 2016** – “*Revealing Changes in Surface vs Bulk Physicochemical Characteristics of a Mechanically Activated Pharmaceutical Material by Correlation of iGC and DSC Analyses*”. [Kieran Hubert Gallagher, Anne Marie Healy]

AAPS Annual Meeting and Exposition, Denver, Colorado, **November 2016** – “*Mitigation of Process Induced Amorphisation – Correlation with Excipient Solubility in Driven Molecular Alloys and Potential for Hydrogen Bonding Interaction*”. [Kieran Hubert Gallagher, Dolores Serrano Lopez, Cliona Loughnane, Anne Marie Healy]

Publications

Curtin, V., Y. Amharar, K. H. Gallagher, S. Corcoran, L. Tajber, O. I. Corrigan and A. M. Healy (2013). “*Reducing mechanical activation-induced amorphisation of salbutamol sulphate by co-processing with selected carboxylic acids*.” International Journal of Pharmaceutics **456**(2): 508-516.

Amharar, Y., V. Curtin, K. H. Gallagher and A. M. Healy (2014). “*Solubility of crystalline organic compounds in high and low molecular weight amorphous matrices above and below the glass transition by zero enthalpy extrapolation*.” International Journal of Pharmaceutics **472**(1-2): 241-247.

R Serrano, D., K. H Gallagher and A. Marie Healy (2015). “*Emerging nanonisation technologies: tailoring crystalline versus amorphous nanomaterials*.” Current Topics in Medicinal Chemistry **15**(22): 2327-2340.

Amharar, Y., V. Curtin, K. H. Gallagher, E. O'Siochru, P. O'Connell and A.-M. Healy (2016). “*Mitigating unwanted amorphisation: A screening method for the selection of suitable excipients*.” European Journal of Pharmaceutical Sciences **81**: 181-188.

Origin and Scope

Active pharmaceutical ingredients (APIs) are commonly subjected to mechanical processing during routine pharmaceutical manufacture (Hüttenrauch, Fricke et al. 1985, Fisher 2006). One of the key micromeritic properties of an API which affects manufacturability and drug product performance (e.g. dissolution rate) is the particle size. As a consequence, unit processes such as milling are commonly employed in order to effect particle size reduction. However, milling has been shown to lead to the transformation of crystalline materials to higher energy amorphous states or to metastable polymorphic forms, termed mechanical activation (Descamps, Willart et al. 2008). The generation of amorphous regions in a crystalline API may have a significant influence on both the manufacturability and biopharmaceutical properties of the API including altered dissolution and bioavailability properties (Hancock and Zografi 1997). For this reason, the transformation of crystalline API to the amorphous state is, in many instances, an unintentional consequence of the milling operation.

The tendency of a material to amorphise on milling has been suggested to depend on the glass transition temperature (T_g) of the material, relative to the temperature of the milling operation (Descamps, Willart et al. 2006, Descamps, Willart et al. 2007). In particular, it has been noted that milling at a temperature below the T_g tends to lead to the amorphisation of the system, while milling at a temperature at or above the T_g tends to either lead to a polymorphic transformation or to result in the material remaining in the unchanged crystalline state (Dujardin, Willart et al. 2013). As a consequence, many APIs with high T_g values well above RT tend to amorphise when subject to mechanical stress on milling at RT. However, it has been shown that comilling in the presence of a second component can lead to the formation of amorphous glass solutions with a composite T_g intermediate to that of either pure component (Nagahama and Suga 2002). This phenomenon suggests the possibility of reducing the T_g of a high T_g API down towards the temperature of the mill by co-processing with a low T_g crystalline excipient, with consequent promotion of the crystalline form. Indeed, previous studies have highlighted the ability of the dicarboxylic acids in particular to be successful in the mitigation of amorphisation on comilling with a range of high T_g APIs (Curtin, Amharar et al. 2013, Curtin, Amharar et al. 2013). However, the mechanism by which these materials exert this effect has, to date, not been fully explored.

In addition to milling, the API may be subjected to further processing post-milling, which, for the formation of solid compacts, commonly involves blending of the API with excipients followed by compaction of the API: excipient composite. Indeed, blending (in the presence of glass beads) and compaction have been shown to induce the mechanical activation of APIs in addition to milling. In particular, blending of griseofulvin in the presence of glass beads was shown to lead to the amorphisation of the API (Hockerfelt, Nystrom et al. 2009), while many instances of compaction-induced polymorphic transformations to metastable polymorphic forms have been described for pharmaceutical systems such as caffeine and carbamazepine (Lefebvre, Guyot-Hermann et al. 1986, Brittain 2002).

The scope of this thesis will be to:

- Investigate the effect of the type of mill as well as the temperature of the mill relative to the ballistic variables which affect the mechanical energy imparted during milling on the amorphisation of the model high T_g API sulfadimidine, utilising both surface and bulk characterisation techniques.
- Establish the relative abilities of a range of low T_g dicarboxylic acid/ polyol excipients to mitigate the amorphisation of the high T_g APIs budesonide and acyclovir on comilling at both room temperature and cryo-temperature in a vibratory type ball mill.
- Characterise the properties of the alloys formed on comilling in terms of the ability of the excipients to drive T_g reduction and the potential for hydrogen bonding interaction and to characterise crystallisation from the amorphous composites formed on comilling from a crystallographic, spectroscopic and kinetic perspective.
- Correlate the milling parameters, in particular the milling temperature and the variables which affect the mechanical energy imparted during milling, in relation to the phase transformations, both crystalline to amorphous and amorphous to crystalline, that occur on comilling.

- Further an understanding of the mechanism(s) which account(s) for the relative abilities of the low T_g crystalline excipients to mitigate amorphisation on comilling.
- Investigate the potential for the mitigation of amorphisation on co-blending and co-compaction.

CHAPTER 1

INTRODUCTION

OVERVIEW OF THE SOLID STATE

Unit Processes and Formulation Design

Routine drug product manufacturing commonly involves the processing of active pharmaceutical ingredients (APIs) in the solid state, both alone and in the form of composites on co-processing with excipients (Fisher 2006, Wikström, Carroll et al. 2008). Figure 1.1 shows a simplified flow diagram highlighting three key unit processes in the solid-state production of a tablet compact by direct compression. Milling is primarily utilised after crystallisation and isolation of the API in order to control particle size (Bentham, Kwan et al. 2004, Nakach, Authelin et al. 2004). Indeed, the particle size constitutes an important micromeritic property which has been shown to have an influence on the properties of powder systems of pharmaceutical relevance (Bosquillon, Lombry et al. 2001), including:

- Manufacturability – powder flow, blend uniformity, compactability
- Physical/ chemical stability – suspensions, powders for reconstitution
- Biopharmaceutical properties – dissolution, bioavailability

Thus, in many circumstances, a milling operation must be employed post-synthesis in order to achieve the desired particle size range required to ensure optimal micromeritic properties for downstream processing. However, dry milling, especially high energy media milling, has been shown to result in the transformation of crystalline materials into thermodynamically metastable solid-state forms, termed mechanical activation, including metastable polymorphic forms and high-energy amorphous states (Descamps and Willart 2016). The generation of amorphous, disordered material in crystalline systems can have a significant impact on the solid state properties of the API. For example, improved apparent solubility which can be advantageous for solubility limited BCS class II compounds can result from amorphisation (Hancock and Parks 2000). However, the amorphous state is not physically stable and is more prone to both physical and chemical degradation and can have a significant impact on the manufacturing performance of the API (Paluch, Tajber et al. 2012).

During post-milling drug product manufacture, as highlighted in Figure 1.1, the drug will inevitably be mixed with excipients in the development of the final dosage form, and will be subject to blending and compaction steps. It has also been shown that such processes can also lead to the mechanical activation of an API. In particular, it has been shown that compaction can lead to polymorphic transformations to metastable polymorphs due to the very high pressures achieved during the compaction process as has been observed on compaction of caffeine and carbamazepine (Chan and Doelker 1985, Otsuka, Nakanishi et al. 1999). In addition, blending (in the presence of glass beads) has been shown to lead to the surface amorphisation of griseofulvin (Hockerfelt, Nystrom et al. 2009).

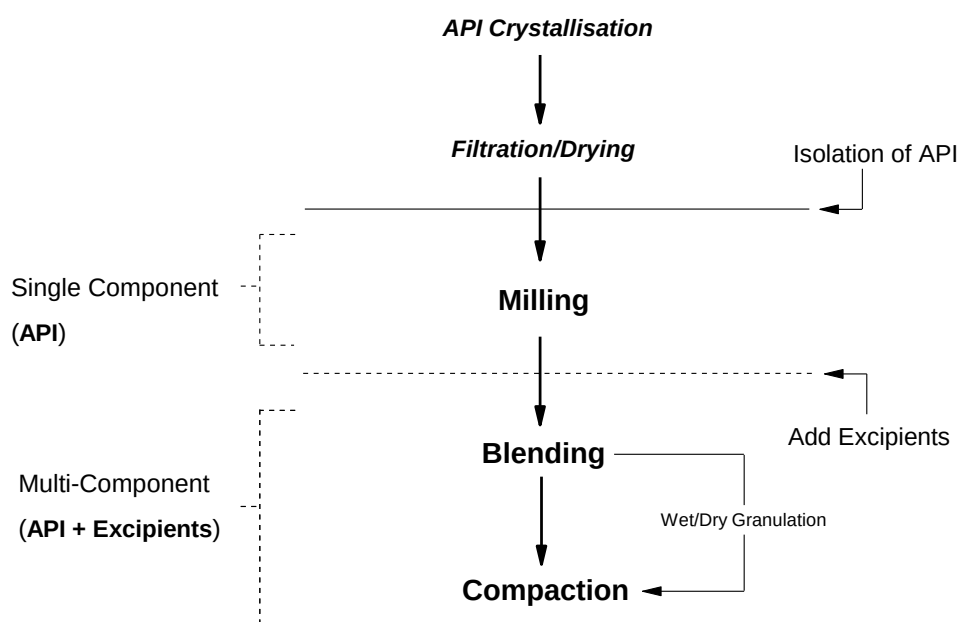


Figure 1.1 Simplified process flow diagram of the main unit operations involved in the formulation of a tablet compact of an API from the post-synthesis solution state.

The above mentioned solid state transformations point to the possibility of the addition of a crystalline functional excipient at the milling stage in order to potentially mitigate amorphisation during milling and possibly also during post milling stages of blending and compaction.

The active pharmaceutical ingredients sulfadimidine (SDM) and budesonide (BD) were chosen in this study as model active pharmaceutical ingredients (APIs), as

both APIs, with T_g values reported to be 78 °C and 89 °C respectively, have previously been shown to undergo amorphisation on milling at room temperature (Dudognon, Willart et al. 2006, Caron, Tajber et al. 2011). Additionally, acyclovir (ACV) was chosen as a third model API. In contrast to both SDM and BD which do not exhibit polymorphism, ACV has been reported to exhibit polymorphism in the form of both true and pseudo-polymorphic forms and thus provided the opportunity to study the effect of co-processing low T_g excipients with a model polymorphic API (Lutker, Quiñones et al. 2011).

The Crystalline and Amorphous States

As drug product formulation and manufacture commonly involves the manipulation of both API and excipients in the solid state, the physicochemical properties of the solid state and the analytical techniques used to characterise the solid state are of great importance in a pharmaceutical context. This was emphasised by Brittain who categorised the physical characterisation techniques used to assess the solid state properties of a powder system from the molecular level to the bulk level (Brittain 1995). Figure 1.2 highlights the properties of the common excipient mannitol from the molecular level to the crystallite level. According to the analysis by Brittain et al., the bulk properties of a powder system such as powder flow and compactability may be affected by the properties of the system at the different levels as shown in Figure 1.2, from the molecular to the individual crystallite to the bulk powder.

At the molecular level, the functional groups present in the molecular structure govern the nature and strength of the inter-molecular interactions in the solid state and in organic molecular materials such interactions are commonly mediated through hydrogen bonding group interactions, in addition to the weaker dipole-dipole interactions and the van der Waals interactions of non-polar groups (Wegiel, Mauer et al. 2013). Vibrational spectroscopy is an importance characterisation tool at the molecular level and allows the characterisation of the nature of the interactions formed in the solid state and in addition changes to the nature of the intermolecular bonding on processing including the formation of hydrogen bonding group interactions in two component systems, in particular API-excipient interactions on processing (Konno, Handa et al. 2008).

The crystalline state is, by definition, characterised by a regular three dimensional order, as described by Newman et al., which can be described as short range order

(SRO) to long range order (LRO) (Newman and Zografi 2014). While SRO extends to nearest (molecule) neighbour and next nearest neighbour, LRO extends over a greater distance at the molecular scale. Intermolecular bonding gives rise to a supramolecular assembly of molecules in a repeating pattern, which gives rise to a crystal lattice structure with long range order in three dimensions with 14 different possible lattice types (Brittain 1995). X-Ray diffractometry, both single crystal and powder (PXRD), is an important characterisation technique allowing the determination of the crystal lattice structure of a molecular crystalline solid (Clas, Faizer et al. 1995). Indeed, PXRD can provide a quick identification technique for the characterisation of polymorphic forms and for the detection of crystalline phases in an amorphous matrix and is thus an important routine characterisation technique in a pharmaceutical context (Di Martino, Conflant et al. 1997).

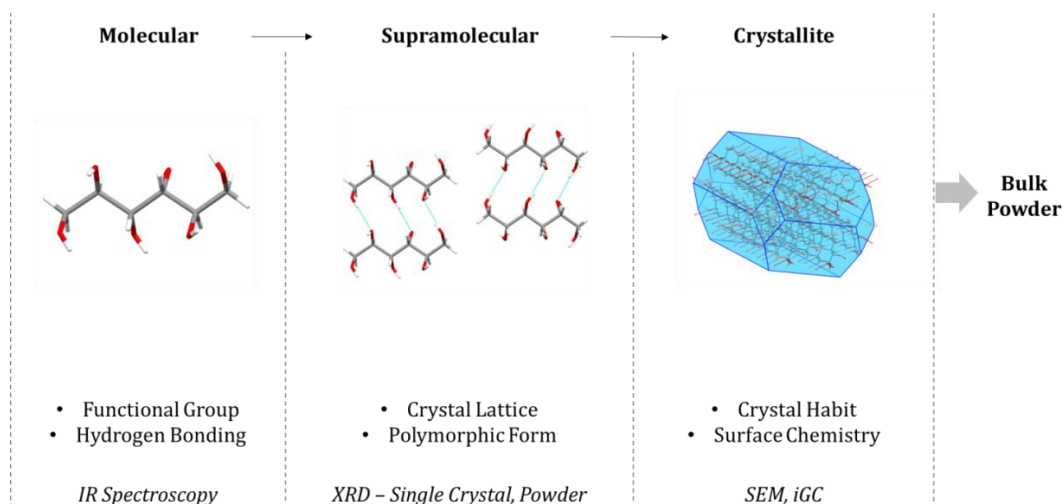


Figure 1.2 Perspective on the emergent solid-state properties of mannitol with common characterisation techniques.

The properties of individual crystallites such as crystal habit and surface energy have also been shown to have an important influence on the physicochemical properties of powder systems (Brittain 1995, Chikhaliya, Forbes et al. 2006). Indeed, while crystal habit and surface chemistry properties can be controlled during the crystallisation step, processing techniques such as blending, milling and compaction have been shown to have significant effects on these properties (York, Ticehurst et al. 1998). Heng et al. highlighted the exposure of different crystal facets on milling of paracetamol (Heng, Thielmann et al. 2006), while Koner et al. compared the compaction properties of mannitol both before and after milling and found that

brittle fracture on milling led to improved compactability of the excipient (Koner, Rajabi-Siahboomi et al. 2015).

Figure 1.3A shows a simplified enthalpy temperature diagram of a pure substance highlighting that below the fusion temperature (T_m) of the material, the crystalline state is the thermodynamically stable state. However, crystallisation is a kinetic phenomenon and the liquid state may persist on cooling below T_m leading to the formation of a supercooled liquid. If the temperature of the system is cooled further at a sufficiently fast rate to prevent nucleation/ crystallisation, eventually the system will undergo a step change in heat capacity associated with a significant increase in the viscosity of the material and a reduction in molecular mobility, leading to the formation of the glass/ amorphous state (Hancock and Zografi 1997). The temperature at which this change occurs is termed the glass transition temperature (T_g). In contrast to the crystalline state, the amorphous state is characterised by a lack of three dimensional long range order and may be characterised by only short-range order of nearest neighbour or next nearest neighbour (Newman and Zografi 2014).

Although crystallisation is thermodynamically favoured, the crystallisation rate low below the T_g is significantly reduced due to the decreased molecular mobility of the system and the T_g thus represents a key characteristic of the amorphous state of an API. Crystallisation is a kinetically controlled process that occurs in two stages, nucleation followed by crystal growth (Trasi and Taylor 2012). Figure 1.3B highlights that the maximum rate of crystallisation normally occurs at a temperature above the T_g and below T_m in the supercooled liquid region. The nucleation rate has also been shown to exhibit a temperature maximum due to competition between thermodynamic and kinetic forces. As described by Trasi et al., the temperature of maximum nucleation usually lies at a lower temperature than T_c , but may occur at a similar temperature to the temperature of maximum crystallisation rate (Trasi and Taylor 2012)

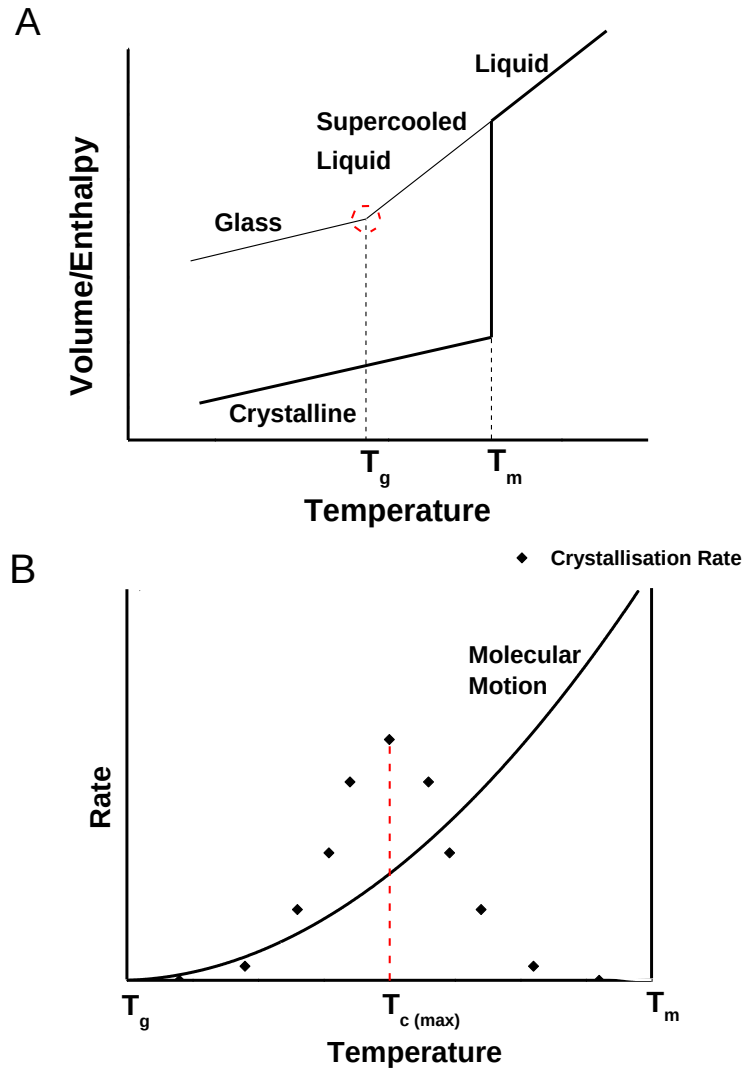


Figure 1.3 A) Enthalpy-temperature diagram highlighting the liquid, supercooled liquid, glass and solid states relative to two key transition temperatures, T_m and T_g and B) the variation in the molecular mobility between T_g and T_m , highlighting the temperature of maximum rate of crystallisation (T_c). [Adapted from reference (Hancock and Zografi 1997)]

Formation of the Amorphous State – Mechanical vs Thermal Activation

As highlighted in Figure 1.3, the amorphous state can be brought about by cooling from the liquid state below the glass transition temperature at a sufficiently fast rate in order to prevent nucleation and crystallisation in the supercooled liquid region (Baird, Van Eerdenbrugh et al. 2010). However, the amorphous state can also be brought about by other means, such as from solution, as highlighted in Figure 1.4. Spray drying is a common pharmaceutical process which can lead to the amorphisation of an API from solution, in particular, if the removal of solvent is sufficiently rapid to prevent nucleation and crystal growth in the increasingly

concentrated solution as the solvent is removed (Corrigan, Healy et al. 2003, Tajber, Corrigan et al. 2005).

In addition to the formation of the amorphous state from molecularly dispersed systems such as from the liquid/ solution state, the amorphous state can also be brought about directly from the crystalline state by the application of a mechanical force, as for example during milling (Colombo, Grassi et al. 2009, Trasi, Boerrigter et al. 2010). As suggested by Willart et al., due to the weaker elastic constants relative to their metallic counterparts, molecular materials more easily undergo vitrification by mechanical means which has important consequences for the unintended formation of the amorphous state during routine processing of pharmaceutical materials (Willart, Descamps et al. 2008).

The particular route by which the amorphous state is formed has been shown to have a significant influence on the properties of the amorphous state produced (Willart, Caron et al. 2004, Caron, Tajber et al. 2011). Hilden et al. highlighted the effect of the rate of cooling on the crystallisation behaviour of the amorphous state brought about by thermal quench (Hilden and Morris 2004). Dujardin et al. compared the amorphous state of glucose formed directly from the crystalline state on milling relative to the amorphous system formed on quenching from the melt (Dujardin, Willart et al. 2008). These authors found that, although the starting material was the anomerically pure α anomer, the amorphous system formed on melt quenching contained both α and β -anomeric forms indicating that the material had undergone mutarotation in the liquid state. However, the amorphous system formed on milling contained only the α anomer. Willart et al. similarly found that milling of anomerically pure α -lactose led to an amorphous system containing only the α anomer in contrast to the melt quenched system which had undergone mutarotation to form an α/β -anomeric mixture (Willart, Caron et al. 2004). These studies highlight that amorphisation by mechanical means represents a fundamentally distinct route of amorphisation relative to formation from the liquid state and in particular suggest that mechanically induced amorphisation represents a direct transformation to the amorphous state without a liquid state intermediate.

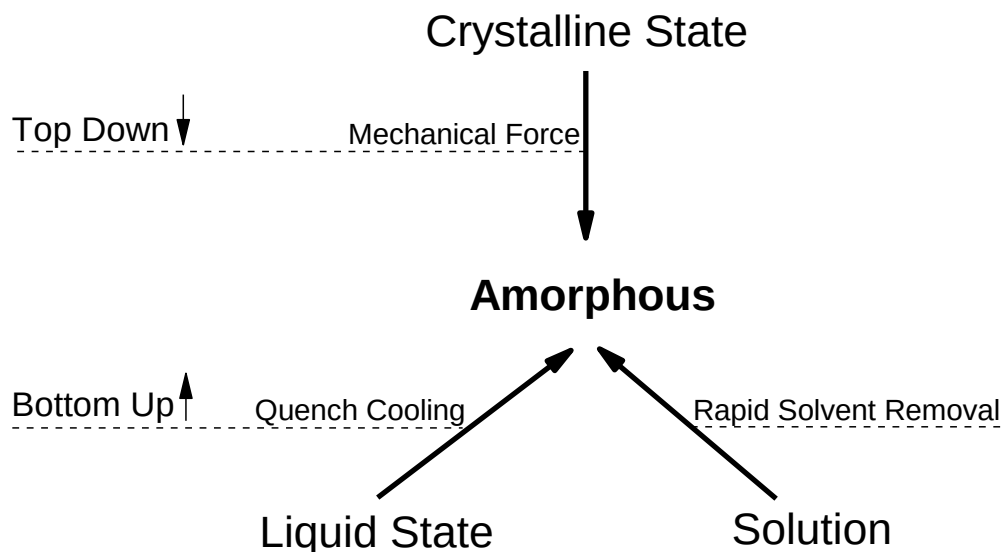


Figure 1.4 Comparison of three common routes of formation of the amorphous state, delineated according to formation from the ordered crystalline state (top down) or from the disordered melt/ solution state (bottom up).

Factors Affecting Crystallisation from the Amorphous State

The amorphous state is metastable from a thermodynamic perspective and will eventually transform to the thermodynamically stable crystalline form (Yu 2001). In addition to the thermodynamic driving force, Bhugra et al. highlighted the importance of the molecular mobility of an amorphous system in terms of the crystallisation rate from the amorphous state (Bhugra and Pikal 2008). Indeed, the thermal history of an amorphous system can have a pronounced effect on the stability of the system towards crystallisation (Kwok, Mauer et al. 2010, Wegiel, Mauer et al. 2013). Yoshioka et al. investigated the effects of physical ageing of indomethacin above and below its T_g on crystallisation from the amorphous state (Yoshioka, Hancock et al. 1994).

Additionally, the different routes of formation, as highlighted in Figure 1.4, can also have an influence on the crystallisation behaviour of the amorphous state produced. Surana et al. compared the resistance to crystallisation of amorphous trehalose brought about by melt quench and spray drying and found an increased resistance to crystallisation in the melt quenched sample (Surana, Pyne et al. 2004). It has

been suggested that the amorphous state brought about by mechanical means may contain nano-crystalline domains and thus crystallisation from milled systems may occur below the T_g on heating in a DSC scan (Descamps and Willart 2016). In addition, a milled amorphous system can also have a high surface area, which can lead to different rates of surface and bulk crystallisation, with fast surface crystallisation relative to slower bulk crystallisation giving rise to a bimodal exothermic crystallisation peak (Chattoraj, Bhugra et al. 2011).

In addition, the presence of a second component can also have a significant effect on the crystallisation behaviour of an amorphous system. For instance, the formation of composite solid dispersion systems between API and high T_g polymer can lead to the stabilisation of the amorphous state. Trasi et al. investigated the impact of polymer excipients on the nucleation and crystal growth of melt-quenched acetaminophen (Trasi and Taylor 2012). However, as highlighted by Taylor et al. alteration of T_g is not the only aspect of a second component on crystallisation (Taylor and Zografi 1997). These authors found that significant inhibition of crystallisation of indomethacin was observed for low levels of PVP, even though the T_g of the system was relatively unchanged to that of pure indomethacin. The authors suggested that hydrogen bonding between the API was an important factor leading to the inhibition of crystallisation.

MECHANICAL ACTIVATION – PHASE TRANSFORMATIONS IN SINGLE COMPONENT SYSTEMS ON MECHANICAL PROCESSING

Generation of Static vs Dynamic Disorder on Milling and Solid-State Characterisation

As described by Wildfong et al., the mechanical driving of a crystalline material is thought to lead to the propagation of cracks in the crystallite surface generated from flaws in the crystal lattice, leading to fragmentation and crystallite size reduction (Hüttenrauch, Fricke et al. 1985, Wildfong, Hancock et al. 2006). However, crystallite size reduction on continued milling eventually reaches a limit, due to the proportionately larger energies required to induced fragmentation in smaller crystallites (Wildfong, Hancock et al. 2006). Beyond this size limit, the mechanical energy of the milling operation may be dissipated instead by inducing dislocations of the crystalline lattice which may accumulate as a function of milling

time. According to the analysis by Wildfong et al., accumulation of lattice dislocations above a critical density may lead to the amorphisation of the material (Wildfong, Hancock et al. 2006). In addition, the authors also highlighted that the persistence of an amorphous state generated on milling also depends on the inherent crystallisation tendency of the material, in addition to the temperature of the milling operation relative to the glass transition temperature of the material and the level of mechanical energy imparted during the milling operation.

The analysis by Wildfong et al. highlights the gradual nature by which the amorphous state is generated on milling resulting from mechanically induced crack propagation, crystallite fragmentation and lattice dislocations. Caron et al. characterised the solid-state amorphisation of α -lactose on milling in a planetary ball mill as a function of milling time (Caron, Willart et al. 2011). These authors quantified the amorphous content of α -lactose by both PXRD and solid-state NMR (^{13}C CP-MAS) analyses. In addition, they also characterised the evolution of the glass transition on DSC analysis as a function of milling time. Interestingly, the authors found that while both PXRD and ss-NMR quantification techniques correlated well with each other in terms of describing the kinetics of amorphisation, both analyses suggested a more rapid amorphisation kinetic relative to the emergence of the T_g in the DSC thermogram. The authors suggested that both ss-NMR and PXRD analyses were sensitive to changes in the milled system such as crystallite fragmentation and the creation of surface defects, termed static defects. Static defects, however, in contrast to a true dynamic disordered amorphous state do not contribute to a T_g in a DSC scan. The authors noted that careful selection and interpretation of analytical techniques is important in order to distinguish static defects from a true dynamic amorphous state.

Newman et al. reviewed the characterisation techniques which are commonly utilised to assess process induced disorder (Newman and Zografi 2014). These authors also stressed the importance of distinguishing between process induced static defects, which are mostly associated with the surface of the milled material, from a true dynamic disordered amorphous state characterised by a lack of the three dimensional periodicity of the crystalline state. In particular, these authors contrasted analytical techniques which detect the amorphous regions directly, such as thermal DSC analysis, from crystallographic analyse, such as PXRD, which detect specifically the crystalline regions of a system from spectroscopic techniques which

are sensitive to both amorphous and crystalline regions (Newman and Zografi 2014).

Inverse gas chromatography (iGC) has been utilised to assess the surface changes to crystalline systems on mechanical processing. Planinšek et al. quantified the surface amorphous content of milled indomethacin by iGC analysis and correlated this with DSC analysis (Planinšek, Zadnik et al. 2010). The milling induced exposure of high energy facets on milling of paracetamol was investigated by Heng et al. (Heng, Thielmann et al. 2006). These authors concluded that paracetamol fractured along the lowest attachment energy plane with the exposure of facets with higher dispersive surface energy. Ho et al. investigated the effect of milling on the surface energy heterogeneity of mannitol as determined by iGC analysis and concluded that mannitol did not fracture along its lowest attachment energy plane on milling, but instead the excipient preferentially fractured along its shortest axis with consequent exposure of a hydrophilic facet associated with the 001 plane (Ho, Naderi et al. 2012). iGC analysis is thus a powerful tool allowing for the selective discrimination of changes to the surface chemistry of milled materials relative to bulk characterisation techniques.

Mechanical Activation on Milling – Temperature of the Mill Relative to the T_g of the Material

The glass transition temperature of an amorphous material is a critical parameter regarding the stability of the material towards crystallisation (Hancock, Shamblin et al. 1995). In the context of milling induced amorphisation, empirical evidence has suggested the importance of the T_g of the material relative to the temperature of the milling operation (T_{mill}) in determining the nature of the phase transformations that occur on milling – namely amorphisation or polymorphic transformation (Descamps, Aumelas et al. 2015). In particular it has been suggested that milling below the T_g generally tends to lead to amorphisation while milling above the T_g generally tends to lead to polymorphic transformations (Descamps, Willart et al. 2007). Indeed, there are many reports in the literature of compounds with a relatively high T_g that have been shown to undergo amorphisation on milling at RT including trehalose, a disaccharide with a T_g of 120 °C, budesonide with a T_g of 89 °C, and griseofulvin with a T_g of 88 °C (Willart, De Gussemme et al. 2001, Willart, Dudognon et al. 2006, Willart, Carpentier et al. 2012).

Dujardin et al. investigated the relationship between the mill temperature and the T_g of the material with α -glucose (Dujardin, Willart et al. 2013). α -Glucose represents an interesting compound in terms of the T_g/T_{mill} correlation as the T_g of α -glucose lies close to RT at 38 °C. Figure 1.5 shows a simplified enthalpy temperature diagram of a material, such as α -glucose, whose T_g is close to RT. Dujardin et al. studied the amorphisation tendency of α -glucose, and found that milling of α -glucose at RT did not lead to the amorphisation of the material, as evidenced by PXRD and DSC analysis. However, when the temperature of the mill was reduced to -15 °C (by placing the mill in a refrigerated room), the material underwent a milling induced crystalline to amorphous transformation, even though all ballistic variables which determine the mechanical energy input were maintained at the same level. In addition to highlighting the importance of the T_g of the material relative to the temperature of the milling operation, Figure 1.5 also highlights the contrast between the direct amorphisation induced by milling relative to the amorphisation by melt quench from the liquid state which leads to mutarotation and the formation of an α/β -anomeric mixture (Dujardin, Willart et al. 2008). These authors also determined the crystallite size reduction as a function of milling time of α -glucose at both RT and at -15 °C. They suggested that reduction of the crystallite size below a critical crystallite size limit, which they determined to be approximately 200 Å for many materials (including both metallic and molecular materials), should lead to the amorphisation of the material. The authors found that on milling at -15 °C, a reduction in the crystallite size below this critical size was observed, while milling at RT did not lead to crystallite size reduction below this level. In addition, as the temperature of the mill at -15 °C was well below the T_g of the system, the reduced molecular mobility at the lower mill temperature inhibited recrystallisation from the milling induced amorphous state.

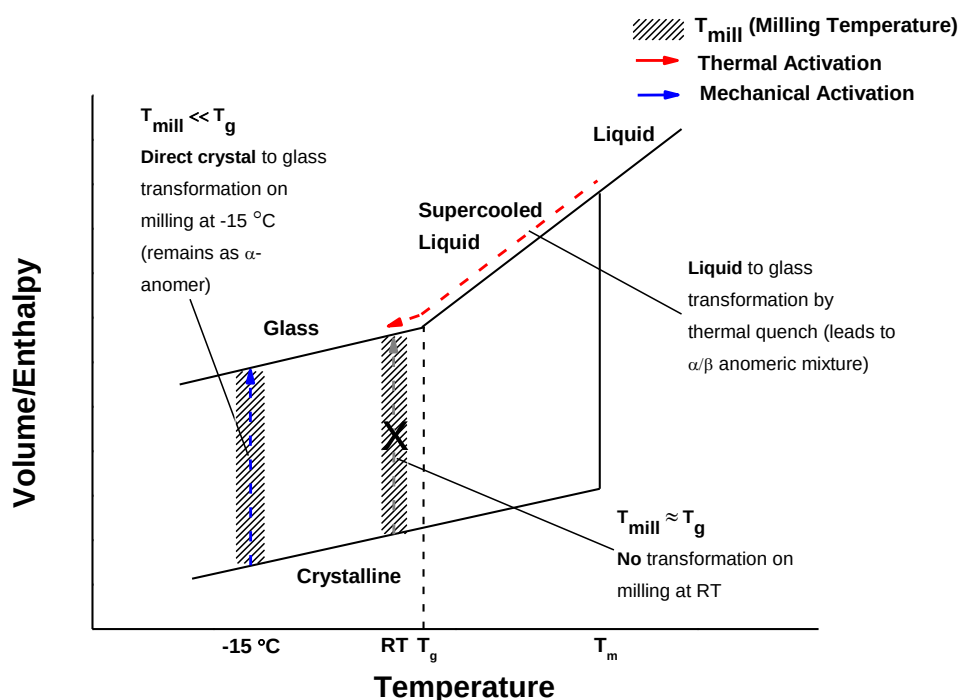


Figure 1.5 Simplified enthalpy temperature diagram of α -glucose highlighting both thermal and mechanical routes to the amorphous state. Note that mechanical activation only results in amorphisation if the the milling temperature is well below the T_g of the material.

In contrast, many low T_g materials have been observed to undergo polymorphic transformation on milling. For example, De Gusseme et al. reported that fananserine, with a T_g of $19\text{ }^{\circ}\text{C}$, underwent a polymorphic transformation on milling at RT to a metastable polymorphic form (De Gusseme, Neves et al. 2008). Sulfathiazole, with T_g of $55\text{ }^{\circ}\text{C}$ has been reported to undergo a transformation to a metastable polymorphic form on milling at RT in the planetary ball mill (Shakhtshneider and Boldyrev 1993). These authors also reported the detection of a partial amorphisation during the initial stages of milling. The polyols sorbitol and mannitol have also been observed to undergo polymorphic transformation on milling to thermodynamically metastable polymorphic forms (Willart, Caron et al. 2007). In an analysis similar to that performed on the structural transformations of α -glucose on milling, Willart et al followed the micro and nano-structural evolution of sorbitol on milling (Willart, Lefebvre et al. 2005). These authors determined the crystallite size of sorbitol as a function of milling time and found that the material never reached the computed critical crystallite size below which amorphisation would be expected to occur. Instead, a critical crystallite size was reached which led to transformation to the metastable polymorph and the authors hypothesised that

this transformation was mediated by a transient amorphous intermediate which could not be detected experimentally.

Mechanical Rejuvenation on Milling – Mechanically Induced Ageing and Regeneration of Crystalline Order from a Quench-Cooled Glass

While many studies have investigated the effects of mechanical driving on the milling induced transformations of crystalline systems, Desprez et al. investigated the effect of mechanical driving on an amorphous API, by milling a previously melt-quenched sample of indomethacin (Desprez and Descamps 2006). The authors milled the amorphous sample of indomethacin, with a T_g of 42 °C, at different rotation speeds in a planetary ball mill at RT, representing different levels of mechanical energy input to the system, at levels of 150 rpm, 200 rpm and 300 rpm. On milling at the highest rotation speed, the authors found that the amorphous API remained PXRD amorphous. However, DSC analysis of the high energy milled amorphous system revealed a different crystallisation pattern relative to the unmilled melt-quenched sample on DSC analysis which, as the authors suggested, indicated that the milling energy had led to a reorganisation of the amorphous state at the molecular level (Desprez and Descamps 2006). In particular, it was found that the milled amorphous sample of indomethacin crystallised into the metastable α polymorph while the unmilled sample crystallised into the stable γ -polymorphic form. The authors concluded that the mechanical energy had altered the molecular level configurational landscape of the amorphous state leading to an accelerated ageing of the amorphous state with consequent crystallisation of the metastable α polymorph on heating. In contrast, it was found that milling the amorphous indomethacin underwent a milling induced crystallisation to the stable γ -polymorphic form on milling at the lowest intensity milling at 150 rpm. In contrast, at 200 rpm, the authors found that the API initially crystallised into the γ -polymorphic form with eventual conversion to the metastable α -polymorphic form on continued milling. These authors highlighted the effect that the mechanical energy of a milling operation may have on the amorphous state itself with observations of accelerated ageing of the amorphous glassy state of indomethacin in addition to a milling induced crystallisation, which they termed “mechanical rejuvenation”, from the amorphous glass, while the polymorphic form that crystallised was found to be highly dependent on the level of mechanical energy imparted to the system.

Mechanical Activation on Compaction and Blending

In addition to milling, compaction has been shown to lead to polymorphic transformations in molecular materials (Brittain 2002). Mazel et al. highlighted the tendency of caffeine to undergo a polymorphic transformation from the metastable form I to the stable form II polymorph on compaction (Mazel, Delplace et al. 2011). In addition, compaction has been shown to lead to fragmentation of crystalline mannitol due to brittle fracture leading to the poor compactability properties of the excipient (Koner, Rajabi-Siahboomi et al. 2015). Interestingly, Thakral et al. highlighted the possibility of compression induced crystallisation from amorphous indomethacin (Thakral, Mohapatra et al. 2015). These authors found that under higher compaction pressures, the surfaces of tablets prepared from amorphous indomethacin underwent crystallisation at a higher rate relative to compacts formed under lower compaction pressures.

Dry mixing in the presence of glass beads has been shown to lead to the amorphisation of griseofulvin (Hockerfelt, Nystrom et al. 2009). These authors suggested that amorphisation occurred without particle size reduction, suggesting that the amorphisation was primarily surface related. In addition, Curtin et al. found that dry mixing of salbutamol sulphate with glass beads in a Turbula mixer at RT led to the complete amorphisation of the API after 24 hours (Curtin, Amharar et al. 2013).

COMPOSITE MOLECULAR SYSTEMS

While mechanical processing can lead to phase transformations in single component systems as highlighted above, co-processing of an API in the presence of a second molecular component can lead to the formation of composites with unique physico-chemical properties of pharmaceutical importance, including cocrystals, molecular salts and co-amorphous composites (Braga, Maini et al. 2013, Löbmann, Grohgan et al. 2013). The definition and the pharmaceutical relevance of mixtures in the solid state were classified by Chiou and Riegelman, who defined the term “solid dispersion” as “the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method” (Chiou and Riegelman 1971). This original definition included

composite systems in the amorphous and crystalline states with both high and low molecular weight carriers. Here we will provide a brief review of commonly encountered composite systems formed between low molecular weight components including the simple crystalline eutectics, cocrystals and molecular salts in addition to co-amorphous composite systems.

Composite Crystalline Systems

Figure 1.6 shows a typical eutectic phase diagram of a two component system, in which both components are miscible in the liquid state and immiscible in the solid state (Chiou and Riegelman 1971, Cherukuvada and Nangia 2012). In the simplest case, at a unique composition corresponding to the eutectic composition, the composite system will display a single melting event at a reduced temperature, the eutectic temperature, relative to the melting temperature of either pure component. Upon cooling from the eutectic melt, each of the components crystallises into their respective crystalline phases as a result of their solid insolubility, resulting in the formation of a eutectic solid. In contrast to a simple physical mixture of the two components, due to the formation from the liquid solution state, the eutectic solid formed can have a significantly altered microstructure (Zhu, Taylor et al. 2010). The altered microstructure of such a solid eutectic system can lead to altered physico-chemical properties including increased dissolution rate of a hydrophobic API in the presence of a hydrophilic second component (Chiou and Riegelman 1971).

Chiou et al. investigated the improved dissolution characteristics of sulfathiazole from a crystalline eutectic dispersion formed with urea, which they attributed to the hydrophilic carrier dispersing leading to a fine crystallite suspension of sulfathiazole with high surface area leading to an increased dissolution rate (Chiou and Niazi 1971). Similarly, the improved dissolution of primidone was investigated in the eutectic solid composite formed with citric acid, a water soluble crystalline excipient (Summers and Enever 1976). Law et al. studied the eutectic formed between fenofibrate and poly(ethylene glycol) (PEG) eutectic mixture formed by the fusion method (Law, Wang et al. 2003). These authors noted the unique microstructure of the composite system leading to increased dissolution rate of the API due to the hydrophilic nature of PEG.

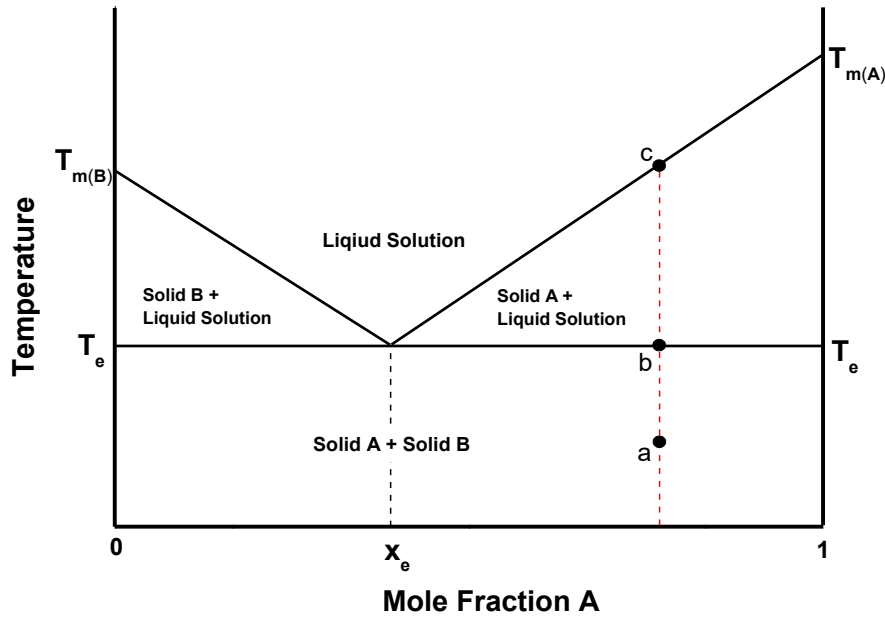


Figure 1.6 Phase Diagram of a hypothetical two component system showing eutectic formation with complete miscibility in the liquid state and negligible solubility in the solid state.

At compositions either side of the eutectic composition, such as the red tie-line shown in Figure 1.6, in which component A is in excess of the eutectic composition, heating a physical mixture at point a below the eutectic temperature eventually leads to a melting event at point b. This is followed by a subsequent liquidus melting of the major component A, at point c. Indeed, the temperature of the liquidus melting event at c, is dependent on the composition of the system with a reduction in the melting temperature of the major component with increasing concentration of the minor component. The compositional dependence of melting point depression has been modelled by the Schroeder-van Laar equation for an ideal mixture (i.e. where cohesive and adhesive interactions are balanced) (Nessim 2000, Rai and Pandey 2004), as shown in Equation 1.1

$$\ln[x_i\gamma_i] = -\frac{\Delta_{fus}H_i^o}{R} \left[\frac{1}{T} - \frac{1}{T_i^o} \right]$$

Equation 1.1

where x_i is the mole fraction of the i th component, γ_i is the activity co-efficient of the i th component ($\gamma_i = 1$ for an ideal mixture), $\Delta_{fus}H_i^o$ is the enthalpy of melting of the

pure i th component, T_i° is the melting temperature of the pure i th component, T is the experimental (liquidus) melting temperature and R is the universal gas constant. While the Schroeder-van Laar equation, where $\gamma_i = 1$, represents an ideal system where cohesive and adhesive forces are balanced, deviation from ideality is commonly observed in real systems, and such deviation from ideality is accounted for by the inclusion of the activity coefficient in Equation 1.1 (Meltzer and Pincus 2012). The activity coefficient has been used to assess the thermodynamics of interaction in the liquid state between miscible components, through computation of the excess thermodynamic functions, i.e. the excess Gibbs energy, G^E , the excess entropy, S^E and the excess enthalpy, H^E which have been interpreted as a measure of the nature of the non-ideal interactions in the liquid state (Gupta, Agrawal et al. 2012). The details of the equations used to compute the excess thermodynamic functions are described in Chapter 2, Section 2.4.13.

In addition to eutectic solids which exhibit a phase separated crystalline microstructure, multi-component systems in the solid state such as cocrystal systems, consisting of a single phase with three dimensional periodicity associated with a crystal lattice structure and with a definite stoichiometry characteristic of the crystalline state are also of pharmaceutical importance (Babu and Nangia 2011). Friščić et al. highlighted the importance of specific H-bonding interactions between API and coformer in cocrystal systems (Friščić and Jones 2009). In a pharmaceutical context, the carboxylic acids such as the dicarboxylic acids, in addition to the substituted aromatic acids have been shown to be useful GRAS (generally regarded as safe) cofomers (Caira, Nassimbeni et al. 1995). According to Cherukuvada et al., the formation of a cocrystal may be favoured when the adhesive interactions between API and conformer are stronger than cohesive forces between like molecules (Cherukuvada and Nangia 2014). Indeed, the formation of cocrystals can lead to significantly altered physicochemical properties such as dissolution and bioavailability in addition to changes in the physical stability of the API (Bruni, Maietta et al. 2013, Bruni, Maietta et al. 2014). While intermolecular interactions in cocrystal systems are largely mediated through non-ionic hydrogen bonds, the formation of molecular salts in pharmaceutical systems has also been described such as that formed between salbutamol sulphate and adipic acid, as described by Paluch et al. (Paluch, Tajber et al. 2011). Indeed, Childs et al. investigated the salt-cocrystal continuum and correlated the likelihood of cocrystal vs salt formation in binary molecular composites with the pKa difference between the two components,

with the greater the pKa difference the greater the ionic/ salt character of the solid composite (Childs, Stahly et al. 2007).

In addition to cocrystal and molecular salt systems, solid solutions have also been reported in molecular systems, in which a second component exists within the crystalline structure of a major component in which the second component either replaces a parent molecule (substitutional) or may be situated in the interstitial spaces between molecules of the parent compound (Cherukuvada and Nangia 2014). Solid solutions are, however, more common in the metallurgical field as with organic molecular composites, only components which are isomorphous lead to the formation of solid solutions as the components must be structurally similar to allow incorporation of the minor substituent into the crystal lattice of the parent molecule (Cherukuvada and Nangia 2014).

Composite Amorphous Systems

As highlighted in Figure 1.6, quench cooling from the melt at a rate fast enough to prevent nucleation and crystallisation of the supercooled liquid can lead to the generation of the amorphous state. In addition, quench cooling from a binary melt solution can lead to the generation of an amorphous glass solution in a manner similar to that previously described for single component systems (Willart, Descamps et al. 2006). Indeed, the formation of a glass solution with a single composite T_g intermediate to that of either pure component provides evidence that the components are miscible and that both components are mixed at the molecular level, in contrast to a simple physical mixture of the two components (Takeda, Murata et al. 1999). The T_g of glass solutions of miscible components shows compositional dependence, as modelled by the Gordon-Taylor law (Gordon, Rouse et al. 1977). The Gordon-Taylor law is based on regular solution theory as applied to binary glass solutions and as such suggests that ideal mixing of two components has no enthalpic contribution as the cohesive and adhesive forces are balanced in an ideal mixture. In contrast, ideal mixing of two miscible components always leads to a positive increase in the entropy of the system (Shamblin, Taylor et al. 1998).

Takeda et al. studied the compositional dependence of the T_g of alcohol-alcohol and alcohol-amine glass solutions formed by the fusion method (Takeda, Murata et al. 1998, Takeda, Murata et al. 1999). These authors found that the excess configurational entropy on mixing in the alcohol-amine glass solutions deviated

significantly (negatively) from that predicted by the regular solution model, while the configurational entropy on mixing of the alcohol-alcohol glass solutions was in much better correlation with the regular solution model. These authors suggested that significant deviation was observed in the alcohol-amine composites due to significant differences in cohesive relative to adhesive interactions leading to structural ordering of like components.

In contrast to a glass solution which displays a single composite T_g intermediate to that of either component, amorphous mixtures that do not display a composite T_g provides an indication that the components are phase separated and not mixed at the molecular level (Korhonen, Pajula et al. 2017). The importance of miscibility in the formation of molecular level solutions has been emphasised by Shamblin in the formation of co-lyophilised amorphous sugar mixtures (Shamblin, Taylor et al. 1998). Indeed, solubility parameters have been used as a predictive tool of the miscibility of two components in the liquid state and by extension the amorphous state from calculation based methods based on the Fedors group contribution theory (Fedors 1974, Marsac, Shamblin et al. 2006). Liquid miscibility and by extension miscibility in the amorphous state of binary composites has been suggested if the difference in the solubility parameters of the two components is less than 7 MPa^{1/2} units while a difference of greater than 7 MPa^{1/2} units suggests immiscibility (Janssens and Van den Mooter 2009, Korhonen, Pajula et al. 2017).

While two components may be miscible in the amorphous state, it has been shown that one of the components may show limiting solubility in the second component, in particular if one of the components is highly resistant to amorphisation, as shown by Curtin et al. in the case of the diacids (Curtin, Amharar et al. 2013). These authors found that a reduced T_g glass solution on co-melt quenching was formed only across a limited composition range of the diacids glutaric acid, adipic acid and pimelic acid with a range of APIs including sulfadimidine and salbutamol sulphate (Curtin, Amharar et al. 2013). In particular, these diacids remain crystalline when melt quenched alone and thus when co-melt quenched with API result in a glass solution only up to a certain composition – termed the solubility composition associated with a maximally reduced T_g . Amharar et al., however, devised a novel method for the determination of the solubility composition of the diacids in amorphous low molecular weight API matrix termed the zero melting enthalpy extrapolation method (Amharar, Curtin et al. 2014).

DRIVEN MOLECULAR ALLOYS – POTENTIAL FOR MITIGATION OF AMORPHISATION ON COMILLING

While the original definition by Chiou and Riegelman referred only to solid dispersions brought about by the fusion and/ or solvent methods, the formation of composite molecular systems on milling has been extensively reported in the literature (Shakhtshneider, Vasilchenko et al. 1996, Nagahama and Suga 2002, Allesø, Chieng et al. 2009). Indeed, the term driven materials/ driven alloys has been used in order to distinguish the composite alloy systems formed by mechanical means from those formed by non-mechanical (bottom up) methods such as quenching from the binary melt or from the solution state (Descamps, Willart et al. 2006). The formation of hydrogen bonded cocrystal synthons on comilling has been extensively reported in the literature and indeed the mechanosynthesis of cocrystals has been suggested as a green alternative to the screening of cocrystal forms relative to solvent based methods (Rehder, Klukkert et al. 2011, Bruni, Maietta et al. 2014).

In a comprehensive review, Friščić et al. suggested that the mechanism for the formation of cocrystal systems on milling can occur either through the molecular diffusion of one of the components in the vapour state followed by deposition onto the solid surface of the second component, through the formation of a eutectic melt (liquid) intermediate between two components with low melting temperatures or through the formation of a composite amorphous (glass solution) intermediate (Friščić and Jones 2009). In the first instance, Kuroda et al. reported on the formation of a cocrystal on exposure of 2,2'-biphenol to p-benzoquinone vapours and also suggested that the rate of formation was significantly enhanced if the two components were briefly milled. In relation to the second mechanism, the formation of a eutectic melt (liquid) intermediate on co-grinding was observed by Davey et al. in the formation of a cocrystal between benzophenone ($T_m = 48\text{ }^{\circ}\text{C}$) and diphenylamine ($T_m = 53\text{ }^{\circ}\text{C}$) through the formation of a liquid state intermediate between both components due to the reduced eutectic melting of $13\text{ }^{\circ}\text{C}$ on contact, below the operational temperature (i.e. room temperature) of grinding.

However, in composite systems consisting of components which are both non-volatile and which have melting temperatures well above the operational temperature of the mill, the authors suggested that the formation of a cocrystal

system is likely to proceed through the generation of a composite amorphous intermediate induced by the mechanical energy of the mill (Friščić and Jones 2009). Jayasankar et al. highlighted the formation of a cocrystal between carbamazepine and saccharin on comilling at RT while, in contrast, the authors noted the formation of a co-amorphous composite on comilling at CT (Jayasankar, Somwangthanaroj et al. 2006). Characterisation of the post-milling co-crystallisation of the cryomilled amorphous composite indicated that crystallisation of the cocrystal occurred via an amorphous intermediate. Indeed, the authors also noted that the T_g of the composite formed on co-cryomilling carbamazepine and saccharin was 41 °C and suggested the importance of the T_g of the amorphous composite, relative to the temperature of the milling operation (T_{mill}), in determining whether the comilling operation led to the formation of an amorphous composite on co-cryomilling, or the formation of a crystalline cocrystal on comilling at RT close to the T_g of the system. Bruni et al. investigated the formation of a bumetanide cocrystal with 4-aminobenzoic acid and similarly suggested that the formation of the cocrystal on dry grinding, in the absence of a liquid drop of solvent, occurred via an amorphous composite intermediate (Bruni, Maietta et al. 2014).

In addition to the formation of cocrystal systems on comilling in which adhesive intermolecular interactions are primarily formed through non-ionic hydrogen bonds, comilling has also been shown to lead to the formation of molecular salts. As reported by Hasa et al., comilling vincamine with citric acid led to the formation of a molecular salt between the two components (Hasa, Perissutti et al. 2013). Paluch et al. reported on the formation of amorphous salts with defined stoichiometry between the dicarboxylic acid succinic acid and the zwitterionic compound ciprofloxacin in the planetary ball mill (Paluch, McCabe et al. 2013). Hu et al. performed an extensive comilling study of the sulfonamide sulfathiazole (STZ) with a variety of organic carboxylic acids (Hu, Gniado et al. 2014). STZ, with a T_g of 55 °C, has been shown to undergo a polymorphic transformation on milling at RT with evidence for a partial initial amorphisation (Shakhtshneider and Boldyrev 1993). On comilling, Hu et al. found that STZ formed either a cocrystal with glutaric acid, a salt with malonic acid or co-amorphous composites with both citric acid and tartaric acid.

While Hu et al. did not report on the T_g s of the co-amorphous composites produced on comilling STZ with either citric acid or tartaric acid, the ability of the milling operation to drive the formation of amorphous glass solutions between two

components leading to the formation of amorphous composites with composition dependent glass transition temperatures have been described, for example, by Nagahama et al. who comilled deoxycholic acid and tri-*O*-methyl- β -cyclodextrin (TMCD) at RT and found that a single intermediate T_g was formed which varied with the composition of the system (Nagahama, Suga et al. 2000, Nagahama and Suga 2002). Indeed, a maximum T_g was observed at the equimolar composition which they correlated with a strong interaction between the two components. These authors correlated the compositional dependence of the T_g with the Gordon-Taylor law and found that the system deviated from the predicted values. These observations importantly highlight the ability of the milling operation to drive the formation of amorphous composite systems with a single compositional dependent T_g . Löbmann et al. similarly reported on the formation of co-amorphous composites between the two APIs glipizide and simvastatin prepared by ball milling and determined the variation in the T_g of the composite and found a good correlation of the compositional dependence of the T_g with the Gordon-Taylor law (Löbmann, Strachan et al. 2012).

As previously described, the T_g of a system marks an important transition in terms of the kinetic stability of the amorphous state towards crystallisation (Hilden and Morris 2004). Indeed, we have highlighted the importance of the T_g of the system being milled, relative to the temperature of the mill, in particular in single component systems in terms of the amorphous/ crystalline outcome of a milling operation, as investigated by Dujardin et al. and their milling studies of α -glucose (Dujardin, Willart et al. 2013). Caron et al compared the properties of composites formed by thermal and mechanical activation between mannitol (MAN, $T_g = 13\text{ }^{\circ}\text{C}$) and trehalose (TRE $T_g = 120\text{ }^{\circ}\text{C}$) in particular focusing on the compositional dependence of the T_g of the amorphous composites produced by both routes (Caron, Willart et al. 2007). Miscibility in the amorphous state between the two components was indicated by the formation of an amorphous composite with a single T_g on co-melt quenching across the entire composition range. In contrast to co-melt quenching, comilling both components only led to the formation of an amorphous glass solution for compositions where the T_g was above T_{mill} (i.e. compositions with low content of MAN and high content of TRE). As the concentration of MAN was increased to the point where the T_g of the composite approached the temperature of the mill (where the T_g was recorded to be $35\text{ }^{\circ}\text{C}$) further increasing the composition of MAN led to the crystallisation of MAN in the metastable α -polymorphic form without any further reduction in the T_g of the

composite. This study highlights the importance of the T_g of the composite system formed on comilling, relative to the temperature of the mill, in determining the amorphous/ crystalline nature of the composite system formed on comilling.

Importantly, in the particular case of the MAN and TRE composite, the authors did not report any crystallisation of the high T_g component (TRE) when the T_g of the composite was reduced to T_{mill} . The concept of comilling a low T_g material with a high T_g material in order to destabilise the amorphous state of the high T_g component, potentially mitigating the amorphisation of the high T_g component, has been explored by previous authors (Balani, Ng et al. 2010, Curtin, Amharar et al. 2013, Curtin, Amharar et al. 2013, Amharar, Curtin et al. 2014). In particular comilling the APIs sulfadimidine and salbutamol sulphate, each with T_g s well above RT and which tend to amorphise on milling, with the diacid glutaric acid (GA) led to the **complete mitigation of amorphisation** in the planetary ball mill (Curtin, Amharar et al. 2013, Curtin, Amharar et al. 2013). In contrast to GA, comilling with either pimelic acid (PA) and adipic acid (AA) led to partial amorphisation while comilling with succinic acid (SA) did not mitigate amorphisation to any extent. These authors correlated the ability of glutaric acid to mitigate amorphisation with the proximity of the calculated Hildebrand solubility parameters of the excipient and API mixture. In addition, the authors determined the experimental solubility of the diacids in the amorphous APIs and found that GA was more soluble than AA. These authors subsequently suggested that the greater level of mitigation of amorphisation on comilling with GA was due to the greater solubility of GA in the amorphous API relative to AA. In a separate work, Amharar et al. proposed that the determination of T_g reduction of co-melt quenched composites could be used as a predictive tool in addition to using the Hildebrand solubility parameter as a method to predict the ability of the low T_g excipient to mitigate amorphisation on comilling (Amharar, Curtin et al. 2016). Co-blending salbutamol sulphate with the diacids in the presence of glass beads (termed dry mixing) led to the partial mitigation of amorphisation of the API (Curtin, Amharar et al. 2013). These authors similarly correlated the solubility composition of the diacids in the amorphous API with their relative capacity to mitigate amorphisation on co-processing, with GA exhibiting both the highest solubility in amorphous salbutamol sulphate and, in addition, the greatest ability to mitigate amorphisation on co-blending.

TOWARDS A RATIONALISATION OF MECHANICALLY INDUCED PHASE TRANSFORMATIONS – THE EFFECTIVE TEMPERATURE ON MILLING

Crystalline to Amorphous Transformations Induced Mechanically

In the previous sections we have detailed the phase transformations that occur in driven molecular systems on milling and on comilling in molecular alloy systems. Willart et al. reviewed the general physical theories/ frameworks which have been suggested by various authors and which attempt to account for crystalline to amorphous phase transformation on driving (Willart and Descamps 2008). A commonly suggested mechanism for milling induced amorphisation is the generation of local hot-spots within the mill leading to melting and subsequent vitrification from the melt (De Gusseme, Neves et al. 2008). However, as described above, studies by Willart et al. suggested that milling of α -lactose led to anomerically pure amorphous α -lactose in contrast to the melt quenched system which had undergone mutarotation in the liquid state, indicating that amorphisation on milling had not proceeded through a liquid (melt) intermediate followed by subsequent vitrification (Willart, Caron et al. 2004).

In addition, Willart et al. assessed the theory proposed by Okamoto et al. who described that the mechanical energy of the milling operation **adds to** the thermal motion of the system leading to a melt event on milling below T_g (Okamoto, Lam et al. 1999, Willart and Descamps 2008). However, it has consistently been shown that reducing the temperature of the mill (and consequently the temperature of the system) even down to cryo-temperatures leads to an increased amorphisation tendency which, as Willart et al. outlined, appears to contradict the analysis that the mechanical energy imparted to the system adds to the thermal dynamic mobility of the system (Willart, Caron et al. 2004, Willart and Descamps 2008).

In contrast, the driven materials theory describes a **competition** between a thermal molecular mobility of the system which is a function of the temperature of the system and which tends to restore the system to the thermodynamically stable crystalline state (if the milling temperature is maintained below the equilibrium melt/ fusion temperature of the system), and a ballistic jump parameter related to the effect of the mechanical energy on the molecular level configuration of the system which tends to lead to a more disordered state (Martin and Bellon 1996, Descamps and Willart 2016). A competition between the restorative “thermal jump”

parameter, D_{th} and a disordering “ballistic jump” parameter, D_{bal} , occurs on milling according to Equation 1.4. This equation predicts that a material being milled at real temperature equal to T_{mill} , behaves as though the system were at an effective temperature T_{eff} which is related to T_{mill} by consideration of the ballistic and thermal jump parameters:

$$T_{eff} = T_{mill} \left(1 + \frac{D_{bal}}{D_{th}} \right)$$

Equation 1.2

The ballistic jump in this term is dependent on the milling parameters, for example the speed of rotation of the solar disk of the planetary ball mill and an increase in the milling intensity leads to an increase in D_{bal} and a consequent increase in T_{eff} . The thermal jump is dependent on the material properties and actual temperature of the system, T_{mill} , and a reduction in the T_{mill} leads to a reduction in the D_{th} and an increase in the T_{eff} . Thus, at low enough milling temperatures and high enough milling intensity, a transformation to a disordered state may be achieved such that the T_{eff} is displaced above the equilibrium phase transition (melting) temperature of the material.

Such mechanically induced phase transformations to the amorphous state are said to occur under non-equilibrium conditions, i.e. amorphisation occurs where the temperature of the system is below the equilibrium melt temperature of the system and thus involves a direct transformation from crystalline to amorphous transformation without a liquid (melt) intermediate. Most importantly, the driven materials theory provides a framework to consider mechanically induced phase transformations where the mechanical energy input (the ballistic effect) is considered **relative** to the temperature of the mill and which is consistent with the experimental observation of increased amorphisation tendency with reduction in the milling temperature.

Amorphous to Crystalline Transformations Induced Mechanically

While the driven materials theory utilises the effective temperature concept to describe crystalline to amorphous transformations on milling according to Equation 1.2, Willart et al. also explored the concept of the effective temperature in order to

account for the milling induced amorphous to crystalline transformation observed on milling glassy indomethacin (Desprez and Descamps 2006). In particular these authors studied the effect of varying the mechanical driving force on the amorphous state of glassy indomethacin, with a T_g of 42 °C, and suggested that crystallisation from the amorphous state was driven by the mechanical energy of the mill. However, in contrast to the crystalline to amorphous transformation described by the driven materials theory outlined above, whereby the effective temperature is displaced relative to the equilibrium melt transition temperature, the effective temperature of the system regarding an amorphous to crystalline is not displaced relative to an equilibrium transition temperature. These authors suggested that such a transformation would be best described by kinetic parameters related to the material itself and in particular could be related to the activation energy associated with nucleation and crystal growth, as described by the Arrhenius correlation with temperature, shown in Equation 1.3.

$$r(T) \propto \exp\left(\frac{-\Delta E}{k_b T}\right)$$

Equation 1.3

Thus, under the appropriate milling (ballistic and temperature) conditions, the effect of the ballistic shocks on the molecular configuration of the system can not only affect the ageing of the milled glass, as in the case of indomethacin, but can also paradoxically **facilitate** nucleation and subsequent crystallisation of the material, also observed in the case of indomethacin. In the analysis Willart et al., mechanically induced crystallisation from the amorphous state is described as a phenomenon distinct to the phenomenon of amorphisation from the crystalline state, relying on an effective temperature on milling which is displaced relative to the glass transition temperature of the material. Such a transformation is also highly dependent on the milling conditions, including ballistic parameters and milling temperature. In totality, the analysis by Willart and Descamps et al. attempts to frame the experimentally observed phase transformations in **molecular** systems on mechanical driving, including crystalline to amorphous and amorphous to crystalline transformations, in the context of a physical theory based framework.

CHAPTER 2

MATERIALS AND METHODS

2.1 MATERIALS

Material	Supplier
Sulfadimidine (SDM)	Sigma Aldrich, Ireland
Budesonide (BD)	Kemprotec Ltd., U.K.
Acyclovir (ACV)	Kemprotec Ltd., U.K.
Succinic Acid (SA)	Sigma Aldrich, Ireland
Glutaric Acid (GA)	Sigma Aldrich, Ireland
Adipic Acid (AA)	Sigma Aldrich, Ireland
Pimelic Acid (PA)	Sigma Aldrich, Ireland
Mannitol (MAN)	Sigma Aldrich, Ireland
Water (HPLC grade)	Elix3 connected to a Synergy UV system, Millipore, U.K.
Water (Deionised, for iGC and DVS)	Sigma Aldrich, Ireland
Ethanol (96%)	Cooley Distillery, Ireland
Ethanol (>99.8%, for iGC)	Sigma Aldrich, Ireland
Nitrogen gas (highly pure)	BOC, Ireland
Liquid Nitrogen	BOC, Ireland
Methane (highly pure, for iGC)	BOC, Ireland
Heptane (>99.8%, for iGC)	Sigma Aldrich, Ireland
Octane (>99.8%, for iGC)	Sigma Aldrich, Ireland
Nonane (>99.8%, for iGC)	Sigma Aldrich, Ireland
Decane (>99.8%, for iGC)	Sigma Aldrich, Ireland
Undecane (>99.8%, for iGC)	Sigma Aldrich, Ireland

Isopropanol (>99.8%, for iGC)	Sigma Aldrich, Ireland
Acetone (>99.8%, for iGC)	Sigma Aldrich, Ireland
Ethyl Acetate (>99.8%, for iGC)	Sigma Aldrich, Ireland
Chloroform (>99.8%, for iGC)	Sigma Aldrich, Ireland
Dichloromethane (>99.8%, for iGC)	Sigma Aldrich, Ireland
Potassium Carbonate	Sigma Aldrich, Ireland
Magnesium Carbonate	Sigma Aldrich, Ireland
Sodium Chloride	Sigma Aldrich, Ireland
Potassium Chloride	Sigma Aldrich, Ireland
Phosphorous Pentoxide	Sigma Aldrich, Ireland

2.2 CONTROLLED TEMPERATURE AND RELATIVE HUMIDITY ENVIRONMENTS

Controlled relative humidity environments were generated by the use of saturated salt solutions of known fixed relative humidity as detailed by Greenspan, and set out in the table below (Greenspan 1977). 200 ml screw cap jars were used to hold the saturated salt solutions in individual plastic holders with powder samples held in separated individual glass vials.

Table 2.1 Saturated salt solutions prepared for the maintenance of controlled relative humidity conditions according to Greenspan (Greenspan 1977).

Salt	Relative Humidity (%)	Mass of Salt (g)	Mass of Water (g)
P ₂ O ₅	0	5	0
MgCl ₂	33	3	3
K ₂ CO ₃	43	3	1.5
NaCl	75	3	3
KCl	85	3	3

Controlled humidity jars thus prepared were kept in controlled temperature environments in ovens maintained at both 25 °C and 40 °C. Samples on storage (not on stability studies) were stored in a similar manner over P₂O₅ in a temperature controlled refrigerated room at 4 °C.

2.3 UNIT OPERATIONS

2.3.1 Milling

Planetary Ball Milling

The Retsch PM 100 Planetary Ball Mill (PBM) (Haan, Germany) was used for the preparation of mechanically activated SDM and BD. The active pharmaceutical ingredient (API) was loaded into a 50 ml stainless steel milling chamber with three stainless steel balls (ϕ = 25 mm) at a 40:1 ball to powder mass ratio (BPR). The acceleration of the solar disk was set to 400 rpm in each case. Each milling operation consisted of a 20 minute milling period interrupted with a 10 minute pause period to prevent excessive heat generation. The sample was loaded and unloaded from the milling chamber under dry nitrogen atmosphere (RH < 2 %). Planetary ball milling experiments were either conducted at room temperature (RT) or in a controlled temperature room at 4 °C. For milling experiments performed at 4 °C, the mill was maintained in the controlled temperature room overnight in order to equilibrate the temperature before the milling operation was conducted.

Vibratory Ball Milling

The Retsch Cryomill (Haan, Germany) was used for vibratory ball milling (VBM) experiments for both room temperature and cryo-temperature (CT) milling. Unless otherwise stated, powders were loaded into a 25 ml stainless steel milling chamber with three stainless steel balls (ϕ = 12 mm) at a BPR of 40:1. All milling experiments were conducted at 25 Hz frequency, with a milling period of 3 minutes interrupted with a pause period of 3 minutes to prevent excessive heat generation. All samples were loaded and unloaded from the milling chamber under dry nitrogen

atmosphere ($RH < 2\%$). The temperature of the mill was recorded using an IR thermometer during RT milling studies.

The Retsch Cryomill was also used for cryo-temperature milling studies. A 50 litre liquid nitrogen pressurised tank, with a pressure maximum of 1.2 bar was used to supply liquid nitrogen to the milling chamber. The milling chamber was dipped into liquid nitrogen for 3 minutes prior to placing into the Cryomill in order to cool the chamber to liquid nitrogen temperature. A further precooling of 3 minutes was employed in the Cryomill. Milling experiments were conducted with a milling period of 3 minutes interrupted with a pause period of 2 minutes. Subsequent to cryomilling experiments the temperature of the chamber was allowed to equilibrate at room temperature and opened under dry nitrogen atmosphere.

2.3.2 Compaction

Compacts of the composites formed on comilling crystalline BD with SA, GA and AA at 50% w/w in the VBM at CT were prepared using a Natoli NP-RD10 (Saint Charles, MO, USA) laboratory-scale single punch tablet press, with an Enerpac (Menomonee Falls, WI, USA) AC RC53 piston working in the range from 0 to 10 tonnes with standard flat faced 8-mm diameter punch and die tooling. Pressure was either released immediately after the desired pressure was reached or a dwell time of 10 seconds was employed. The upper and lower punches were lubricated with a dusting of magnesium stearate and compacts were pushed out of the bottom die using the bottom punch. A compaction force of 75 MPa was used for all compaction experiments. Following compaction, the tablets were crushed with a pestle and mortar for subsequent solid state analysis.

2.3.3 Blending

The Turbula Mixer (W. A. Bachofen, Basel, Switzerland) was used for blending experiments in which both crystalline SDM was blended alone and in which planetary ball milled SDM was co-blended with crystalline β -GA at 50% w/w at a rotational speed of 64 rpm for up to 24 hours. A total of 0.5 g of powder was placed into 50 ml glass jars under nitrogen atmosphere which were positioned securely into a large glass tumbler. All experiments were conducted at room temperature.

2.3.4 Spray Drying

The Buchi-290 Mini Spray Dryer was used for spray drying experiments. Systems were spray dried from a 70% v/v (ethanol: water) solution in the case of both SDM and GA at a concentration of 0.4% w/v, or from a 96% v/v (ethanol: water) solution for BD at a concentration of 1.0% w/v. All solutions were freshly prepared immediately prior to spray drying. An inlet temperature of 78 °C was used in the open mode configuration for all spray drying experiments with nitrogen as the atomising gas. An outlet temperature of 48 °C, 51 °C and 50 °C was recorded for SDM, GA and BD spray drying experiments respectively. An aspirator setting of 100%, in addition to a gas flow rate of 400 L/ hour and a pump rate of 30% was used for all spray drying experiments. A high efficiency Büchi cyclone was used for all spray drying experiments, which was emptied of powder using a spatula and an anti-static gun (Zerostat, Sigma Aldrich, UK).

2.3.5 Physical Mixture Preparation

Physical mixtures of API and excipient were prepared by gentle mixing in an agate mortar and pestle.

2.3.6 Melt Quenching

Physical mixtures of API and excipient were prepared in the agate mortar and pestle. The sample was loaded into a DSC pan and sealed hermetically under nitrogen atmosphere. The pan was then placed onto a hotplate under a nitrogen purge at the required melt/ eutectic temperature for 10 seconds, followed immediately by quench cooling in liquid nitrogen.

2.4 ANALYTICAL TECHNIQUES

2.4.1 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) analysis was carried out in the standard mode using a Mettler Toledo DSC 821^e model (Ohio, United States) with nitrogen as the inert purge gas. Samples (7-10 mg) were packed into aluminium pans, sealed and pierced to form three vent holes. A heating rate of 10 °C/min was used in the

temperature range 25-210 °C unless otherwise stated. The instrument was calibrated with highly pure indium. Mettler Toledo STARe software (Version 6.10) on a Windows NT operating system was used for data analysis. All scans were run at least in duplicate.

Modulated DSC analysis was conducted on a DSC Q200 (TA Instruments, Delaware, United States) apparatus for the determination of both T_g and ΔC_p values. A scanning rate of 2 °C/min was used with a period and amplitude of modulation of 60 s and 0.8 °C respectively unless otherwise stated. Samples (2-3 mg) were placed into standard aluminium pans. The temperature and cell constant were calibrated using highly pure indium while the heat capacity was calibrated with a sapphire disc. Universal Analysis software (TA Instruments) was used for data analysis. All modulated scans were run at least in triplicate.

Quantification of Amorphous Content by DSC Analysis

A calibration curve was developed with cryomilled amorphous SDM as the amorphous standard using unmilled crystalline SDM as the crystalline standard. The cryomilled SDM sample was sieved through a 180 µm sieve in order to eliminate large agglomerates and ensure a homogenous physical mix. Physical mixtures were prepared at 10%, 20%, 50% and 70% w/w compositions of amorphous SDM in crystalline SDM. Each of the calibration standards were run at least in triplicate in the Mettler Toledo DSC. Quantification of the enthalpy of crystallisation was performed using the Mettler Toledo STARe software (Version 6.10).

2.4.2 Thermogravimetric Analysis

Thermogravimetric analysis (TGA) was conducted on a Q50 TGA (TA Instruments, Delaware, United States) apparatus. Aluminium pans were tared and samples (5-7 mg) were placed into the aluminium pans prior to analysis. Scans were recorded over a temperature range from 25–300 °C unless otherwise stated at a heating rate of 10 °C/min. Universal Analysis software (TA Instruments) was used for data analysis. All scans were run at least in triplicate.

2.4.3 Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy

Infrared spectra were recorded on a PerkinElmer Spectrum 1 FTIR Spectrometer. Spectrum software (v5.0.1) was used for evaluation of the recorded spectra. Each spectrum was scanned in the range 650-4000 cm^{-1} with a resolution of 4 cm^{-1} and a minimum of four scans were collected and averaged for each sample.

2.4.4 Near Infrared Reflectance Spectroscopy

NIR spectra were recorded using a Buchi NIR (Flawil, Switzerland) system with an NIR reflectance attachment. Spectra were recorded in the 10000-4000 cm^{-1} range with a resolution of 8 cm^{-1} using 27 co-added scans. The sample was placed in a glass vial and repositioned following every 3 scans in order to ensure homogenous representation of the sample. NIRCal software was used to collate the data and for the preparation of calibration curves for the quantification of amorphous content.

Quantification of Amorphous Content by NIR Analysis

The amorphous content of SDM was determined by NIR analysis by the preparation of two calibrations curves, NIR-1 and NIR-2. The amorphous standard used for both calibration curves was cryomilled amorphous SDM, which was sieved through a 180 μm sieve. For the preparation of NIR-1, the crystalline standard was prepared from the cryomilled amorphous standard by crystallising the cryomilled sample in the DVS. For the preparation of the NIR-2 calibration curve, the crystalline standard was unmilled crystalline SDM raw material. Physical mixtures of amorphous and crystalline standards for each calibration curve were prepared at 10% intervals from 10-90% w/w amorphous content by mixing in an agate mortar and pestle. Spectra were recorded in the 10000-6000 cm^{-1} range and the entire range was used for the preparation of the calibration curves. NIRCal software was used to generate calibration curves and both Standard Normal Variate (SNV) and second derivative pre-treatments were applied, as described previously (Curtin, Amharar et al. 2013).

2.4.5 Powder X-Ray Diffractometry

Powder X-ray diffraction (PXRD) analysis was performed on samples flattened onto a low background silicon sample holder using a Rigaku Miniflex II desktop X-ray

diffractometer (Rigaku, Tokyo, Japan). The PXRD patterns were recorded from 5° to 40° on the 2θ scale at a step of 0.05° s⁻¹. The X-ray tube, composed of Cu anode ($\lambda_{\text{CuK}\alpha} = 1.54 \text{ \AA}$), was operated under a voltage of 30 kV and a current of 15 mA. Data analysis was conducted using X'Pert HighScore Plus Version 2.2a.

Estimation of Amorphous Content by PXRD Analysis

The amorphous content of BD in the composites formed on comilling BD with GA, AA and PA was estimated as described previously (Caron, Willart et al. 2011, Curtin, Amharar et al. 2013) by determination of the area under the curve of the Bragg peaks associated with crystalline BD at 6.2° and 12.1° 2θ both before and after crystallisation in the DVS. The area under the curve of each peak was input into Equation 2.1

$$\% \text{ Amorphous Content (PXRD)} = 100 \times \left(1 - \frac{A_p}{A_c}\right)$$

Equation 2.1

where A_p represents area of the individual peak in the comilled composite before crystallisation in the DVS and A_c represents the area of the same peak in the composite after crystallisation in the DVS. The amorphous content was thus determined by averaging the amorphous content values determined from each individual peak.

2.4.6 Dynamic Vapour Sorption

Dynamic vapour sorption (DVS) analysis was conducted on samples (20-25 mg) using the DVS Advantage (Surface Measurement Systems, London, UK) apparatus. The analysis temperature was $25.0 \pm 0.1 \text{ °C}$ and water (HPLC grade, Sigma-Aldrich, Ireland) was used as the probe vapour. All samples were dried at 0% P/P_0 for at least an hour and then the partial vapour pressure was increased by increments of 10% P/P_0 up to 90% followed by a similar stepwise desorption to 0% P/P_0 . At each vapour pressure step, the sample mass was allowed to reach equilibrium, defined as $dm/dt \leq 0.002 \text{ mg/minute}$ over 10 minutes before moving to the next step. All experiments were performed at least in duplicate.

Quantification of Amorphous Content by DVS Analysis

Amorphous content quantification by DVS was conducted on milled BD and on comilled BD: excipient composites using Equation 2.2, in a manner similar to that described previously (Curtin, Amharar et al. 2013, Curtin, Amharar et al. 2013)

$$\% \text{ Amorphous Content (DVS)} = 100 \times \frac{\Delta m \times m_s}{m_d} \times \frac{1}{\Delta m_a}$$

Equation 2.2

Where Δm is the difference in the mass uptake between the first and second sorption cycles of the API at 30% RH (20% RH for BD:PA composite), m_s is the sample mass in the DVS, m_d is the mass of API in the overall sample mass and Δm_a is the difference in mass uptake between the first and second sorption cycles of the amorphous milled standard at 30% RH (20% RH for PA composite). The amorphous standard used for DVS quantification was planetary ball milled BD for 15 hours (Dudognon, Willart et al. 2006).

Determination of the Glass Transition Relative Humidity (RH_g) and Crystallisation Relative Humidity (RH_c)

The RH_{g10} (the glass transition relative humidity determined at 10% RH/ hour) of an amorphous sample was determined by running the sample in the DVS, with water as the probe vapour, using a kinetic ramp of 10% RH/ hour from 0% to 90% P/P₀. A regression line was fit to the linear portions of the profile representing surface adsorption and bulk absorption using Origin software (Version 9.0). The co-ordinates of the point of intersection of the two linear equations were determined. The x co-ordinate, representing time, was used to determine the RH value at that time-point, which was the RH_{g10}. Each measurement was run at least in triplicate and the average of three measurements reported as the RH_{g10}.

The RH_{c10}, i.e. the crystallisation relative humidity as determined from the 10% RH/ hour kinetic ramp, was evaluated by determining the point of inflection of the profile, i.e. the time point where $dm/dt = 0$. From this time point, the corresponding RH value was determined which represented the RH_{c10}. Each measurement was run

at least in triplicate. For the determination of the RH_{c0} , this procedure was repeated for lower kinetic ramp rates, i.e. 2%, 4%, 6% RH/ hour. The RH_c from each of these ramp rates was then utilised to prepare graphs of ramp rate (x-axis) vs RH_c (y-axis). A regression line was fit to the experimental RH_c values. The RH_{c0} was thus determined from this graph as the y-axis intercept.

2.4.7 Inverse Gas Chromatography (iGC) Surface Energy Analysis

Surface characterisation of the solid state of powder systems was carried out using an SMS-iGC 2000 (Surface Measurement Systems Ltd., London, UK). All powders for iGC analysis were packed into (300 x 3 mm internal diameter) pre-silanised glass columns. Silanised glass wool was packed into each end of the column in order to plug the powder into the column. Prior to measurements, all samples were held at the column temperature (details for each system shown in Appendix A-IV) for 1 hour prior to analysis at 0% RH and under helium purge in order to equilibrate the temperature of the system and to remove any surface moisture/ solvent from the surface of the powder. A higher column temperature of 323 K (50 °C) was used for SDM samples (both milled and unmilled) as the retention times of the higher alkanes (decane and undecane) were too strongly retained with a column temperature of 303 K (30 °C to allow accurate analysis of their retention peaks. All solvents used as probe vapour were maintained in an oven at 305 K. Probe vapours used in iGC experiments included the non-polar alkanes heptane, octane, nonane, decane and undecane in addition to the polar probes acetone, ethyl acetate, chloroform, isopropanol and dichloromethane. Methane gas was used as the internal standard. 100 µl of a mixture of probe vapour and helium carrier gas was injected during each run with an injection concentration of 0.05% v/v of the saturated probe vapour pressure, unless otherwise stated. In addition, methane was used as the internal standard and to calculate the dead volume. A flame ionisation detector was used to detect the elution of the probe vapour from the column.

Dispersive Surface Energy – Schulz Method

The determination of the dispersive component of surface energy was determined by the Schulz method, as described previously (Planinšek, Trojak et al. 2001). Equation 2.3 shows the relationship between the retention volume of a non-polar probe, V_n , and the dispersive component of surface energy, γ_s^D .

$$RT\ln(V_n) = 2aN_a\sqrt{\gamma_S^D\gamma_L^D} + c$$

Equation 2.3

where a represents the cross sectional surface area of the probe molecule, γ_S^D are γ_L^D the dispersive components of the surface free energy of the solid and probe molecule respectively, V_n is the net retention volume of the probe molecule, R is the universal gas constant, T is the temperature and N_a is Avogadro's constant. When Equation 2.3 is used to generate a plot as shown in Figure 2.1, the dispersive surface energy can be obtained from the slope of the line. In addition, the specific acid-base free energies of polar probe molecules can also be determined by assessing their retention volumes relative to the non-polar line, as shown in Figure 2.1.

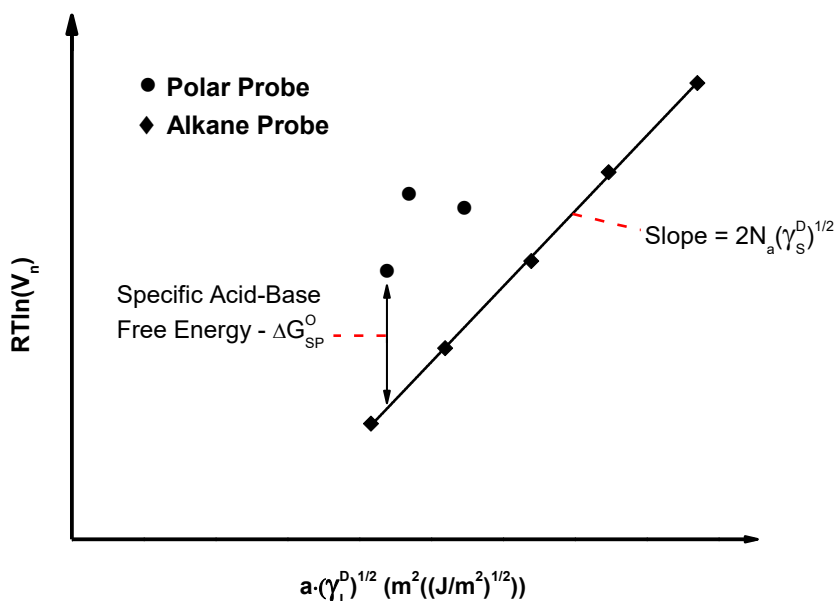


Figure 2.1 Standard iGC plot for the determination of the dispersive surface energy component (γ_S^D) and the specific acid-base free energy (ΔG_{SP}^0)

Surface Acid-Base Chemistry – Gutmann K_a/K_b Method

The specific acid-base free energies as determined in the previous section were subsequently used in the determination of the surface Lewis acid (K_a) and Lewis base (K_b) numbers of unmilled and milled SDM systems. The K_a and K_b values were

determined by the Gutmann approach where the values are related to the specific free energies of the polar probes according to Equation 2.4

$$-\Delta G = K_a(DN) + K_b(AN^*)$$

Equation 2.4

where ΔG is the specific free energy of interaction of the polar probe as determined by iGC analysis and DN and AN^* represent the donor number and modified acceptor numbers of the polar probe and are a measure of the electron donating and accepting character of the probe respectively. Determination of the regression line of the plot of $(\Delta G/AN^*)$ vs (DN/AN^*) yields a slope with the value of K_a and an intercept with the value of K_b .

Surface Phase Transition – Heat of Sorption

Heat of sorption analysis was conducted on milled amorphous SDM in a manner similar to that described by Surana et al. (Surana, Randall et al. 2003). Columns were packed in a similar manner to that described in the previous section and conditioned at 303 K and 0% RH under helium gas flow for 1 hour. Subsequently, the column temperature was heated to either 62 °C or 66 °C and equilibrated for 30 minutes. Decane probe was used as the probe vapour in the infinite dilution range ($P/P_o = 0.05\%$) with methane as the internal standard. The temperature was raised for the next injection and maintained at the temperature for 30 minutes before injection. This was repeated until the column temperature of 80 °C was achieved.

2.4.8 BET N₂ Surface Area Analysis

The specific surface area (SAA) of powder systems was determined by the Brunauer-Emmett-Teller (BET) method using a Micromeritics Gemini VI 2385C (Micromeritics, Norcross, GA, USA) surface area and pore size analyser. Nitrogen gas was used as the analytical adsorptive gas and helium was used for free space measurement. All samples were degassed in a Micromeritics Smartprep degasser at 30 °C for 12 hours prior to analysis. The amount of surface-adsorbed nitrogen was determined in the range 0.05-0.3 P/P_o , with an equilibration time of 10 seconds.

Evacuation was carried at a rate of 500 mmHg/ min over a time of 1 minute. Saturation P_0 was determined before each measurement.

2.4.9 Polarised Hot Stage Microscopy

The eutectic melting of ACV in molten GA was recorded on an Olympus BX35 (Tokyo, Japan) upright polarising microscope with a Linkam (Epsom, UK) hot stage attachment with liquid nitrogen used as both the stage coolant and for the generation of a nitrogen gas purge of the hot stage. Linksys 32 software was used for image analysis. Physical mixtures prepared in an agate mortar and pestle of crystalline form I ACV and crystalline β -GA were loaded onto a glass slide and covered with a cover slip. The temperature scan rate was 10 °C/ minute from 25 °C to 250 °C with an image capture rate of 1 frame per second.

2.4.10 Scanning Electron Microscopy

Images of powder samples were taken at various magnifications by SEM using a Zeiss Supra Variable Pressure Field Emission Scanning Electron Microscope (Germany) equipped with a secondary electron detector at 5k kV. Samples were prepared by placement on aluminium stubs under nitrogen atmosphere followed by gold sputter coating prior to analysis.

2.4.11 Laser Light Diffraction Particle Size Analysis

Particle size distributions of powder samples were determined by laser diffraction using a Malvern Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, U.K.). A Scirocco dry powder feeder apparatus was used to disperse the powder samples at 1 bar pressure. An obscuration of 1-3% was obtained using a vibration rate of 75%. d_{50} and d_{90} values were determined from the particle size distribution.

2.4.12 Experimental Determination of the Solubility of Crystalline Excipients in Amorphous Low Molecular Weight API at 25 °C

The solubilities of the diacids in SDM, BD and ACV were determined by the zero enthalpy extrapolation method, as previously described (Curtin, Amharar et al. 2013). Amorphous glass solutions of crystalline API and crystalline diacid were

prepared in the composition range 90% w/w diacid in API to 50% w/w diacid in API, by the melt quench method as described in Section 2.3.6.

As BD undergoes degradation on melting ($\approx 250\text{ }^{\circ}\text{C}$), physical mixtures of diacid with BD were heated to $180\text{ }^{\circ}\text{C}$ on a hot plate. Composites at or above 50% w/w of diacid in BD displayed a liquidus melt of BD at or below $180\text{ }^{\circ}\text{C}$ in the presence of each of the diacids. A similar procedure was followed for the determination of the solubility of GA in ACV, as ACV similarly degrades on melting but shows a reduced liquidus temperature of melting in the presence of GA at or below $180\text{ }^{\circ}\text{C}$. As SDM has previously been shown to avoid degradation on melting, the melt-quenched composites were prepared by heating to $210\text{ }^{\circ}\text{C}$. The eutectic melts were subsequently quench-cooled in liquid nitrogen (to prevent crystallisation of BD on cooling) and subsequently annealed for 48 hours under desiccant at $25\text{ }^{\circ}\text{C}$ before thermal analysis.

The annealed samples were then subject to a DSC heating scan at $20\text{ }^{\circ}\text{C}/\text{minute}$ (a fast scan rate was used to prevent crystallisation of the amorphous API) and the enthalpy of melting of the crystalline diacid, in excess of the solubility composition, was determined for each composition. The enthalpy of melting values (y-axis) were then plotted against their respective composition values (x-axis) and a linear regression line was evaluated and extrapolated to the abscissa to yield the solubility composition.

2.4.13 Melting Point Depression Analysis of SDM with Excipients and Computation of the Excess Thermodynamic Functions

The Schroeder-van Laar equation (Equation 2.5, where $\gamma_i = 1$) describes a two component system assuming both components are completely miscible in the liquid state and completely immiscible in the solid state (the components in Equation 2.5 are described in Section (Reddi, Satuluri et al. 2011). The presence of an increasing amount of a second component leads to increasing depression of the melting point of the major component. If the system behaves ideally, the cohesive and adhesive forces are balanced and the experimental melting point depression data should correlate with that predicted by the Schroeder-van Laar equation where the activity co-efficient, γ_i , is equal to unity (Meltzer and Pincu 2012).

$$\ln[x_i\gamma_i] = -\frac{\Delta_{fus}H_i^0}{R} \left[\frac{1}{T} - \frac{1}{T_i^0} \right]$$

Equation 2.5

where x_i is the mole fraction of the i th component, γ_i is the activity co-efficient of the i th component ($\gamma_i = 1$ for an ideal mixture), $\Delta_{fus}H_i^0$ is the enthalpy of melting of the pure i th component, T_i^0 is the melting temperature of the pure i th component, T is the experimental (liquidus) melting temperature and R is the universal gas constant. However, deviation from ideality is commonly observed in real systems due to differences in the cohesive/adhesive intermolecular forces and such deviation is accounted for by modification of the Schroeder-van Laar by the inclusion of the activity coefficient (Sharma, Kant et al. 2003). The activity coefficient thus determined from experimental melting point depression data can then be used to assess quantitatively the nature of the cohesive/ adhesive interaction on mixing in the liquid state between the two components, by computation of the excess thermodynamic functions from the activity coefficient data (Sharma, Tandon et al. 2004), namely the excess Gibbs energy (G^E) determined from Equation 2.6, the excess entropy (S^E) from Equation 2.7, and the excess enthalpy (H^E) from Equation 2.8.

$$G^E = RT[x_1 \ln \gamma_{11} + x_2 \ln \gamma_{12}]$$

Equation 2.6

$$S^E = -R \left[x_1 \ln \gamma_{11} + x_2 \ln \gamma_{12} + x_1 T \left(\frac{\partial \ln \gamma_{11}}{\partial T} \right)_P + x_2 T \left(\frac{\partial \ln \gamma_{12}}{\partial T} \right)_P \right]$$

Equation 2.7

$$H^E = -RT^2 \left[x_1 \left(\frac{\partial \ln \gamma_{11}}{\partial T} \right)_P + x_2 \left(\frac{\partial \ln \gamma_{12}}{\partial T} \right)_P \right]$$

Equation 2.8

where x_i is the mole fraction of the i th component, γ_{li} is the activity coefficient in the liquid state of the i th component and $\delta \ln \gamma_{li} / \delta T$ is the variation of the natural logarithm of the activity coefficient in the liquid state of the i th component as a function of temperature. The computation of the $\delta \ln \gamma_{li} / \delta T$ term is detailed in Appendix A-V.

2.4.14 Determination of the Activation Energy of Crystallisation from Amorphous Composite Systems by Ozawa/ Kissinger Non-Isothermal Crystallisation Kinetics

The activation energy (E_a) of crystallisation from the amorphous co-cryomilled equimolar composites formed with SDM:GA and SDM:PA was determined by non-isothermal crystallisation methods, in a similar manner to that described by Baghel et al. (Baghel, Cathcart et al. 2016). In particular, the cryomilled composites were analysed in the DSC Q200 as described in Section 2.4.1 using linear heating rates of 1, 2, 3, 5 and 10 °C/ minute. Equation 2.9 shows the Kissinger equation

$$\ln\left(\frac{\beta}{T_p^2}\right) = \ln\left(\frac{AR}{E_a}\right) - \frac{E_a}{RT_p}$$

Equation 2.9

where β represents the linear heating rate, T_p represents the peak of the crystallisation exotherm from DSC analysis, A is the pre-exponential factor and R is the universal gas constant Equation 2.9 was used for the determination of the E_a of crystallisation from the slope of the linear plot obtained by plotting $\ln(\beta/T_p^2)$ vs $1/T_p$. In addition, the E_a was determined by the Ozawa model, as previously described (Seefeldt, Miller et al. 2007, Baghel, Cathcart et al. 2016) Equation 2.10 shows the Ozawa equation for the determination of the activation energy.

$$\ln(\beta) = -1.052\left(\frac{E_a}{RT_p}\right) + c$$

Equation 2.10

The E_a of crystallisation was determined from the slope of the linear plot formed by plotting $\ln(\beta)$ vs $1/T_p$.

2.4.15 Calculation of the Hildebrand Solubility Parameters

The Hildebrand solubility parameters of each API and each excipient were determined using the Fedors group contribution method (Fedors 1974). The method involves the summation of vaporisation enthalpies of structural fragments in each compound along with the molar volume and determined using Equation 2.11

$$\delta = \left(\frac{\Delta E_v}{V_m} \right)^{1/2}$$

Equation 2.11

where ΔE_v is the energy of vaporisation and V_m is the molar volume. Detailed calculations of the Hildebrand solubility parameters of the materials used in this thesis are shown in Appendix A-VI.

2.4.16 Graphing Software and Statistical Analysis

Both Excel and Origin were used for graphing, and for linear regression analyses and second order polynomial curve fitting. Minitab (Software Version) was used for design of experiment analysis.

2.4.17 Molecular Modelling

The CCDC (Cambridge Crystal Structural Database) was used for the determination of calculated PXRD patterns from the single crystal XRD data, associated with the following Refcodes together with the associated polymorphic form in parenthesis:

Sulfadimidine – **SULFN018**;

Succinic Acid – **SUCACB07** (α) and **SUCACB10** (β);

Glutaric Acid – **GLURAC06** (α) and **GLURAC07** (β);

Adipic Acid – **ADIPAC05** (α) and **ADIPAC** (β);

Pimelic Acid – **PIMELA** (α) and **PIMELA01** (β);

Mannitol – **DMANTL08** (α), **DMANTL07** (β) and **DMANTL10** (δ).

In addition, Mercury software was used for the visualisation of molecular structures and for the calculation of BFDH morphology maps.

CHAPTER 3

MECHANICAL ACTIVATION STUDIES ON MILLING OF HIGH AND LOW T_g MOLECULAR PHARMACEUTICAL MATERIALS

3.1 INTRODUCTION

Commonly employed comminution processes such as high energy media milling may lead, in addition to particle size reduction, to solid state transformations of molecular pharmaceutical materials, leading to direct transformations from the crystalline to amorphous state or from a stable to metastable crystalline polymorphic form (Hüttenrauch, Fricke et al. 1985). The glass transition temperature of the material being milled, relative to the temperature of the mill, has been shown to be an important characteristic in determining the amorphisation/polymorphic transformation outcome of a milling operation (Descamps, Willart et al. 2007). In addition the type of mill and the level of mechanical energy imparted have been shown to affect the solid-state transformations of milled materials (Abdellaoui and Gaffet 1994, Koner, Rajabi-Siahboomi et al. 2015).

In this chapter, the milling induced amorphisation of the high T_g material sulfadimidine will be investigated. Quantification of amorphous content will be undertaken by two separate methods i.e. thermal analysis by DSC and spectroscopic analysis by NIR. We will compare two types of mill, a planetary type versus a vibratory type ball mill, on the rate and extent of amorphisation of sulfadimidine on milling at room temperature. In addition the effect of reducing the milling temperature on the extent of amorphisation of sulfadimidine in both mill types will be assessed.

The impact of three milling variables which affect the mechanical energy input on milling in a vibratory ball mill on the amorphisation tendency of sulfadimidine relative to the temperature of the mill will also be investigated, in a 2^4 factorial design of experiment. Additionally, inverse gas chromatography will be utilised to characterise the specific changes to the surface chemistry of sulfadimidine on high and low intensity milling. A range of low T_g crystalline excipients will also be milled, including the dicarboxylic acids succinic acid, glutaric acid, adipic acid and pimelic acid and the polyol, mannitol. The materials will be assessed for evidence of milling induced amorphisation/polymorphic transformation in addition to changes to the surface properties of the materials, including the determination of the dispersive surface energy after milling by inverse gas chromatographic analysis.

3.2 SOLID STATE CHARACTERISATION OF CRYSTALLINE AND AMORPHOUS SULFADIMIDINE

Amorphous sulfadimidine (SDM) was prepared by the melt quench method by heating crystalline SDM above its melting point to 210 °C under nitrogen atmosphere followed immediately by quench cooling in liquid nitrogen. In addition, amorphous SDM was prepared by the spray drying method, as described previously (Caron, Tajber et al. 2011). SDM was also amorphised by milling in both a planetary ball mill for 12 hours at RT, and in addition in the vibratory ball mill at CT for 60 minutes.

3.2.1 PXRD Analysis

Figure 3.1 (a) shows the PXRD diffractogram of unmilled crystalline SDM, with characteristic Bragg peaks associated with the crystalline nature of the unmilled material. In contrast, both the melt quench and spray dried systems displayed no corresponding Bragg peaks in their respective diffractograms, indicating that both processing methods had led to the amorphisation of SDM. Figure 3.1(d) similarly displayed an amorphous halo pattern for the cryomilled SDM system, in contrast to the system milled in the PBM at RT for 18 hours (e) which displayed Bragg peaks associated with crystalline SDM, indicating a partial amorphisation on milling in the PBM at RT. Indeed, such partial amorphisation on milling of SDM at RT in the PBM has previously been described by Caron et al. (Caron, Hu et al. 2013).

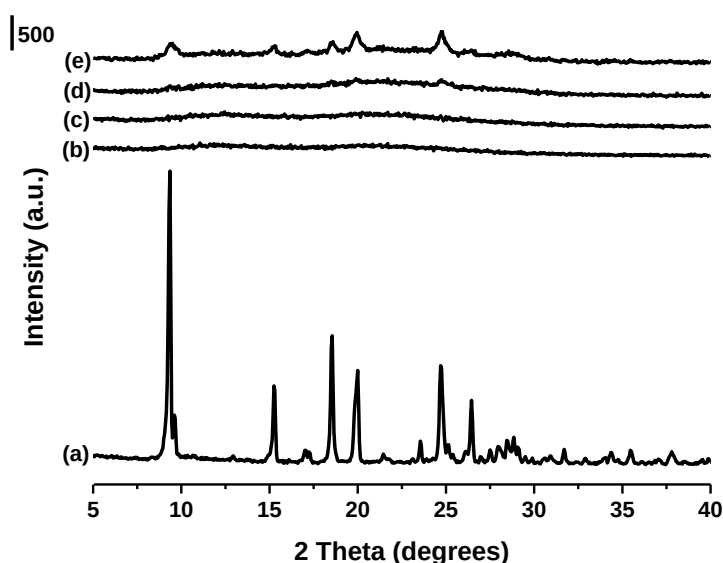


Figure 3.1 PXRD diffractograms of (a) unmilled crystalline SDM, (b) melt quenched SDM, (c) spray dried SDM, (d) SDM milled in the VBM at CT for 60 minutes and (e) SDM milled in the PBM at RT for 18 hours.

3.2.2 DSC Analysis

DSC analysis of the melt quenched (MQ) SDM system, as shown in Figure 3.2 (e), displayed a clear T_g in the total heat flow signal at $78.1\text{ }^{\circ}\text{C}$ ($\pm 0.3\text{ }^{\circ}\text{C}$) which correlates with the previously reported T_g of SDM (Caron, Tajber et al. 2011). The enthalpy of crystallisation occurred at $150\text{ }^{\circ}\text{C}$ in the MQ sample with a subsequent melt at $198\text{ }^{\circ}\text{C}$. In contrast, the spray dried system similarly displayed a T_g at $78\text{ }^{\circ}\text{C}$, however, the crystallisation temperature was lower for the spray dried system at $120\text{ }^{\circ}\text{C}$, indicating the effect of the route of formation on the crystallisation behaviour of the system. Thermograms (b) and (c) indicate bimodal exotherms for the SDM which was subjected to PBM milling at RT for 18 hours and cryomilling for 1 hour, indicating fast surface crystallisation followed by slow bulk crystallisation (Chattoraj, Bhugra et al. 2011). As the crystallisation exotherm in the milled systems covered the expected glass transition temperature region associated with amorphous SDM, modulated heat flow DSC analysis was conducted on the milled amorphous systems, with the reversing heat flow signals shown in the inset of Figure 3.2. The enthalpy of crystallisation of the cryomilled system was determined to be $49.3\text{ (}\pm 0.9\text{) J/g}$, compared to $36.8\text{ (}\pm 1.7\text{) J/g}$ for the planetary ball milled material, indicating a greater level of amorphous content in the cryomilled system. The cryomilled amorphous SDM sample was used to prepare a calibration curve for

the quantification of amorphous content using the enthalpy of crystallisation, as shown in Figure 3.3 and as described in Chapter 2, Section 2.4.1.

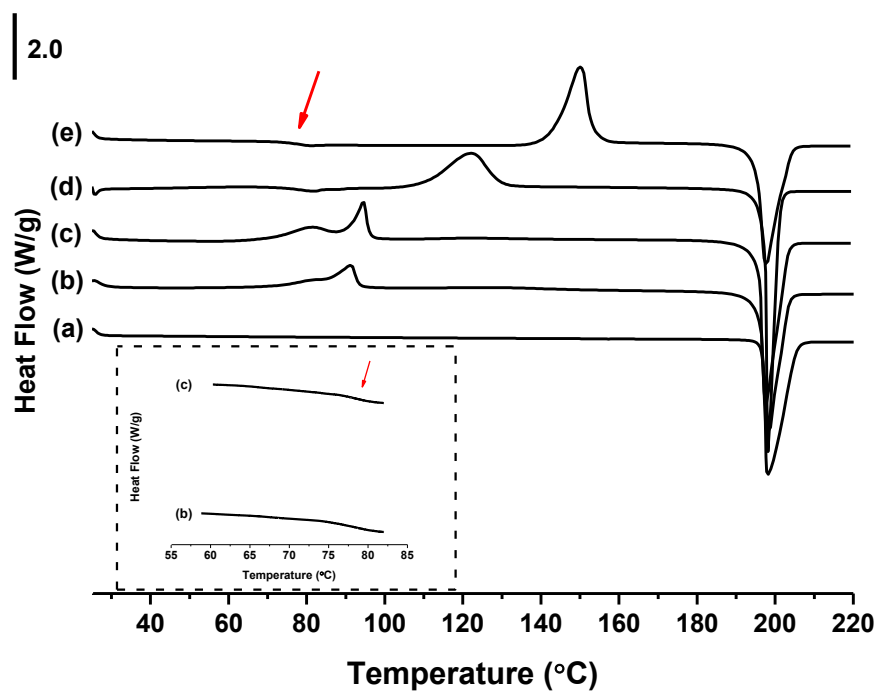


Figure 3.2 DSC thermograms of (a) crystalline SDM (b) SDM milled in the PBM at RT for 18 hours (c) SDM milled in the VBM at CT for 60 minutes (d) SDM spray dried and (e) melt quenched SDM. Red arrows indicated glass transition events in the DSC thermograms.

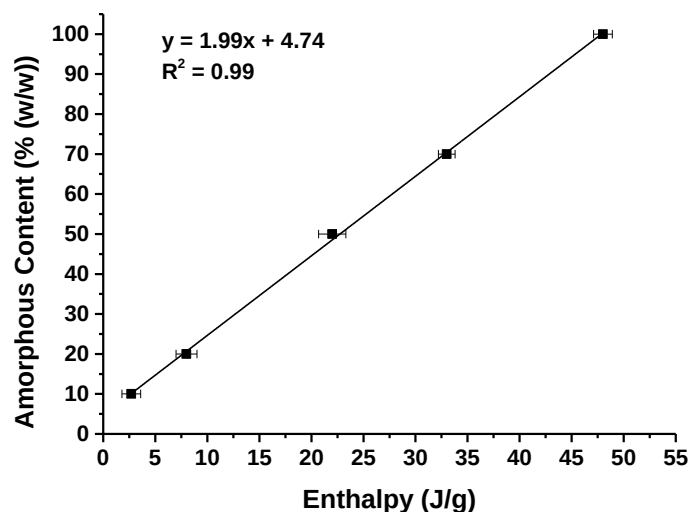


Figure 3.3 Calibration curve of SDM derived from enthalpy of crystallisation (ΔH_c) on DSC analysis.

3.2.3 Spectroscopic Analysis

3.2.3.1 FTIR

The molecular structure of SDM, as shown in Figure 3.4, has a number of both hydrogen bond donor and acceptor groups. The sulfonamide functionality, as a hydrogen bond accepting group, has been shown to be particularly sensitive to hydrogen bonding interactions and has played an important role in the formation of solid-state composites including cocrystals on both spray drying and milling, in particular with the aromatic acids such as p-aminosalicylic acid (Caira, Nassimbeni et al. 1995, Caira 2007, Grossjohann, Serrano et al. 2015). In addition to the sulfonamide group, the structure also contains an amine group located at the para position on the aromatic ring also capable of forming hydrogen bond interactions, primarily as a hydrogen bond donor.

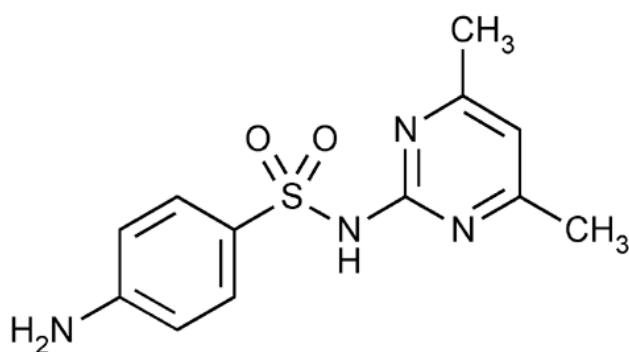


Figure 3.4 Molecular structure of sulfadimidine.

Figure 3.5A shows the FTIR spectra in the 3800–3000 cm^{-1} region for unmilled crystalline SDM in addition to the melt quenched, spray dried and milled systems. The unmilled crystalline SDM system displayed three peaks in this region at 3445 cm^{-1} and 3333 cm^{-1} associated with antisymmetric and symmetric stretching of the N-H amine group located at the para position of the aromatic ring respectively, in addition to a peak at 3234 cm^{-1} associated with stretching of the sulfonamide N-H group (Grossjohann, Serrano et al. 2015). Figure 3.5B shows the FTIR spectra in the 1800–650 cm^{-1} region, with a peak at 1150 cm^{-1} in the unmilled crystalline SDM system associated with the $\text{S}=\text{O}_2$ sulfone stretching vibration, as well as an antisymmetric stretching peak of the $\text{S}=\text{O}_2$ group at 1310 cm^{-1} . Comparison of the unmilled crystalline spectrum with the melt quenched system indicated peak shifts

in the N-H amine (located at the para position of the aromatic ring) stretching peaks, in particular, of the N-H antisymmetric stretching peak, from 3333 cm^{-1} to 3360 cm^{-1} and from 3445 cm^{-1} to 3476 cm^{-1} (as highlighted by red arrows in Figure 3.5A). These peak shifts in the hydrogen bonding amine group were possibly associated with the amorphous nature of the melt quenched system as a result of the breakdown of the hydrogen bonded framework relative to the crystalline system (Taylor 1998). Similar changes were also observed in both the spray dried and cryomilled systems, similarly indicating the amorphous nature of these systems. In contrast, the SDM system milled in the planetary ball mill only displayed partial peak shifts in the $3800\text{--}3000\text{ cm}^{-1}$ region, consistent with PXRD evidence of partial amorphisation on milling at RT as shown in Figure 3.1.

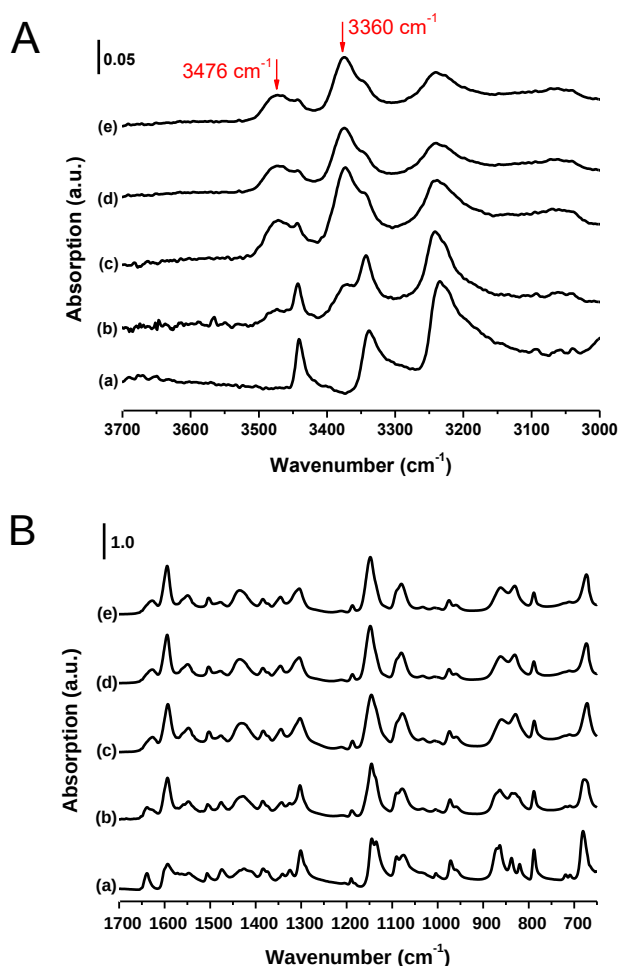


Figure 3.5 FTIR spectra in A) the $3700\text{--}3000\text{ cm}^{-1}$ region (red arrows indicate peak positions referred to in the discussion text) and B) the $1700\text{--}650\text{ cm}^{-1}$ region of (a) crystalline SDM (b) SDM milled in the PBM at RT for 18 hours (c) SDM milled in the VBM at CT for 60 minutes (d) spray dried SDM and (e) melt quenched SDM.

3.2.3.2 Near Infra-Red – Quantification of Amorphous Content

Figure 3.6A shows the NIR spectra of both unmilled crystalline SDM and the cryomilled amorphous system. Differences between the two spectra were observed, particularly in the 5500-7000 cm^{-1} region. NIR analysis was used for the quantification of amorphous content of milled SDM by the generation of two calibration curves. For the generation of the first calibration curve, termed NIR-1, cryomilled SDM recrystallised in the DVS was used as the crystalline standard, while for the second calibration curve, termed NIR-2, unmilled crystalline SDM was used as the crystalline standard. Cryomilled PXRD amorphous SDM was used as the amorphous standard for both calibration curves. Particle size analysis revealed a similar d50 for the unmilled and milled materials (12 μm and 11 μm respectively) as shown in Figure A-I.1. However, the d90 of the milled system was larger (64 μm compared to 28 μm for the unmilled material) possibly due to the generation of agglomerates on milling, as shown in Figure A-I.2. The calibration curve was determined from 0-100% crystalline content in steps of 10% w/w using the entire spectral range from 4000–10000 cm^{-1} applying Standard Normal Variate (SNV) analysis and second derivative pre-treatments, in a manner similar to that previously described (Curtin, Amharar et al. 2013).

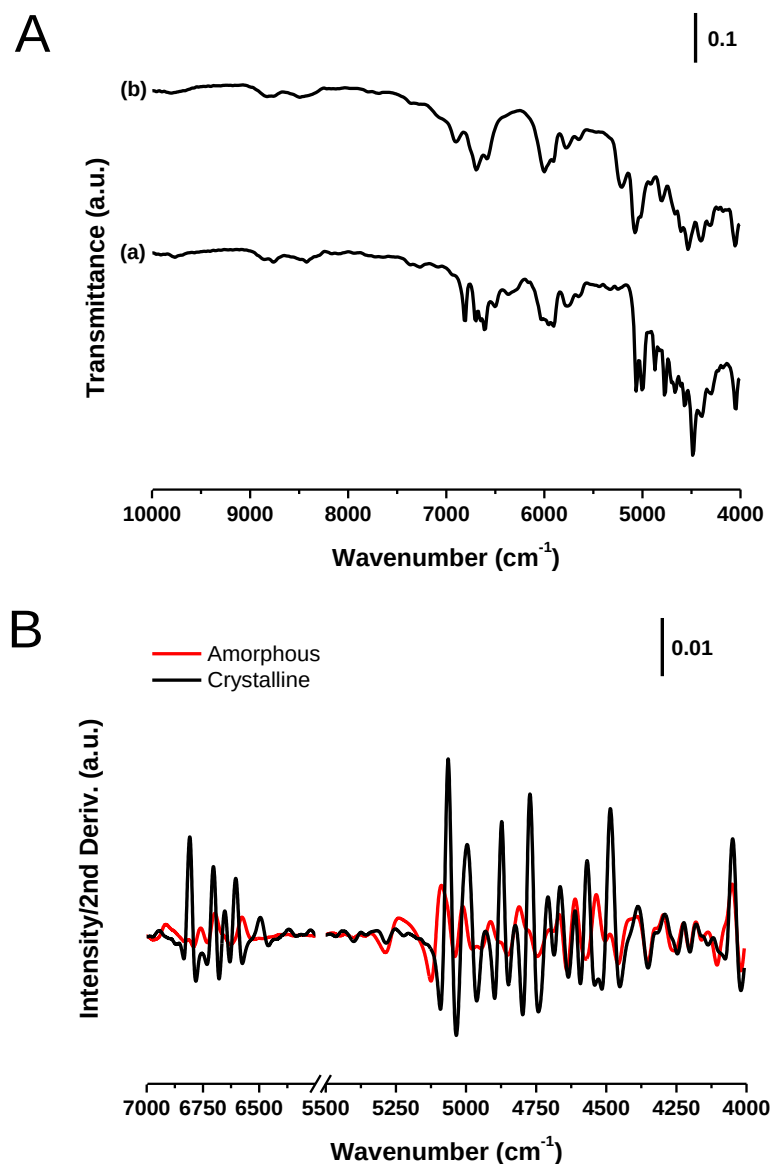


Figure 3.6 A) (a) crystalline unmilled SDM and (b) cryomilled amorphous SDM. B) NIR 2nd derivative spectra of unmilled crystalline SDM (black line) and cryomilled amorphous SDM (red line).

3.2.4 Sorption Analysis

3.2.4.1 Dynamic Vapour Sorption

Cryomilled amorphous SDM was subjected to a stepwise sorption analysis in the DVS of 10% RH per step in the range from 0 to 90% RH with water as the probe vapour, as shown in Figure 3.7A. Analysis of the sorption profile indicated a mass loss event at 80% RH for the cryomilled material, associated with a crystallisation event. In contrast, in the second sorption cycle, no further mass loss event was observed, suggesting that full crystallisation had occurred in the first sorption cycle.

The cryomilled amorphous SDM system was also subjected to a kinetic ramp, with water as the probe vapour, at a ramp rate of 10%/hour from 0 to 90% RH, as shown in Figure 3.7B. The sorption profile revealed a concave slope, characteristic of the amorphous state, which has been associated with initial surface adsorption of water vapour at lower RH values, followed by bulk absorption of water vapour into the amorphous bulk at higher RH values. The RH_{g10} was determined, as shown in Figure 3.7B, by extrapolation of the two linear portions of the profile and was determined to be 40.7% RH ($\pm 0.6\%$). In addition, the RH_{c10} was determined from the kinetic ramp as the RH value associated with the inflection point of the ramp, i.e. where dm/dt reached a value of zero. The RH_{c10} was determined to be 75.3% RH ($\pm 0.2\%$).

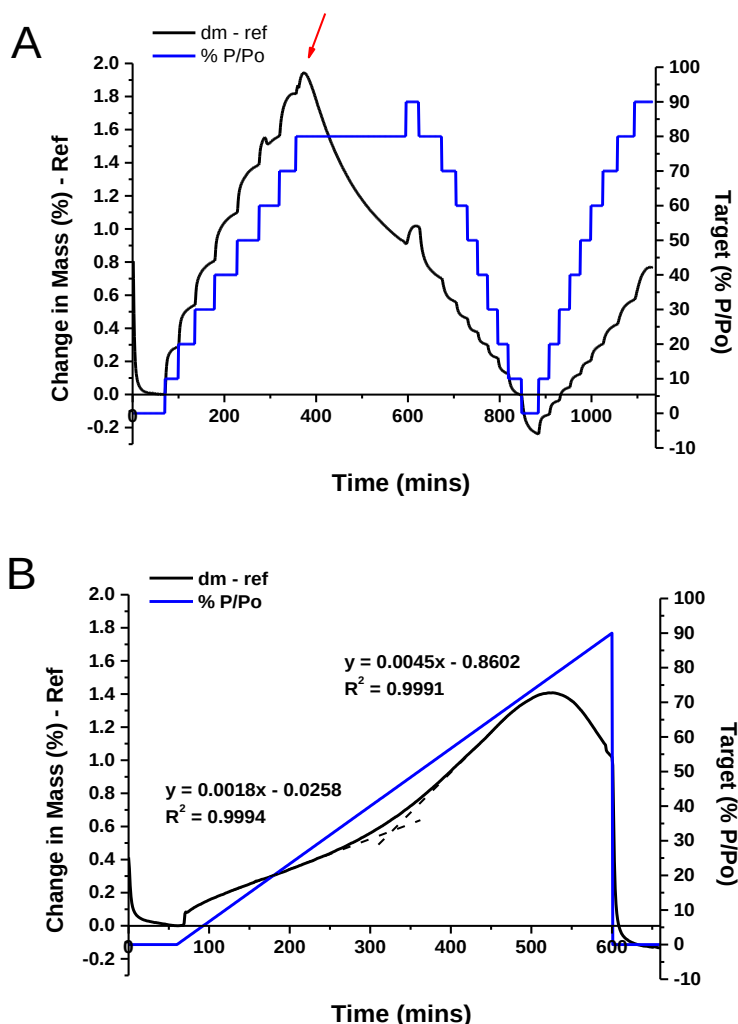


Figure 3.7 A) Stepwise DVS sorption isotherm from 0-90% RH of SDM milled in the VBM at CT for 60 minutes. B) Kinetic ramp at 10% RH/hour from 0% to 90% of SDM milled in the VBM at CT for 60 minutes. Red arrow indicates onset of mass loss event.

3.2.4.2 Inverse Gas Chromatography

Unmilled crystalline SDM was characterised by iGC analysis with both non polar alkane probes for the determination of the dispersive component of surface energy, as well as with five polar probes for the determination of the specific acid-base component of the surface energy, as shown in Figure 3.8 (Dove, Buckton et al. 1996). The dispersive surface energy value of the unmilled SDM system was determined to be $48 (\pm 0.8) \text{ mJ/m}^2$, determined at 50°C . The Gutmann K_a value was determined, as shown in Figure 3.8B, from the Gutmann plot to be $0.134 (\pm 0.002)$. In contrast, the K_b value was negative, indicating negligible surface basic character (Grimsey, Feeley et al. 2002, Heng, Thielmann et al. 2006).

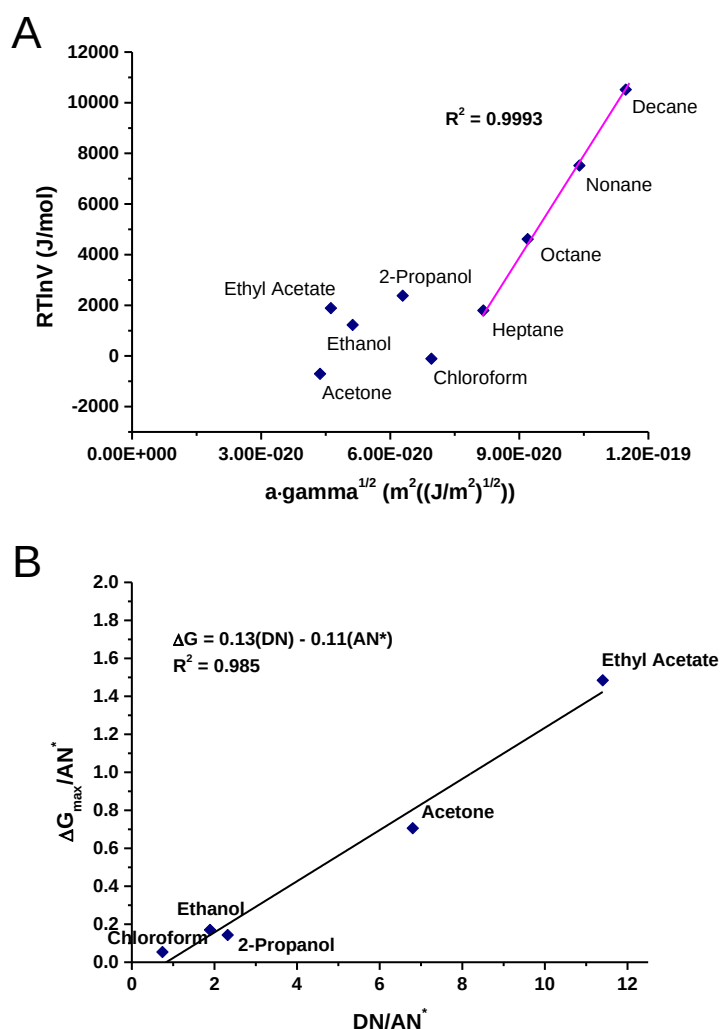


Figure 3.8 A) iGC surface energy analysis of unmilled crystalline SDM and B) Gutmann acid/base plot of unmilled crystalline SDM

3.3 COMPARISON OF THE EFFECT OF MILL TYPE AND TEMPERATURE ON AMORPHISATION KINETICS AND EXTENT OF AMORPHISATION ON MILLING

PXRD analysis, shown in Figure 3.1, indicated the presence of Bragg peaks in the diffractogram of the SDM system on milling in the planetary ball mill at RT. In contrast, we also showed that milling of SDM in a different ball mill type, the vibratory ball mill, led to an amorphous system on milling at CT. In order to compare the time-dependent amorphisation of SDM between the two types of ball mills (planetary vs vibratory) at the same milling temperature, the amorphous content of SDM was determined as a function of milling time at room temperature in both mill types. DSC and NIR (NIR-1 calibration curve) were used to quantify amorphous content of SDM at each time point. Figure 3.9A and B show the total heat flow DSC scans of each of the milling time points for the PBM and VBM RT milled systems respectively.

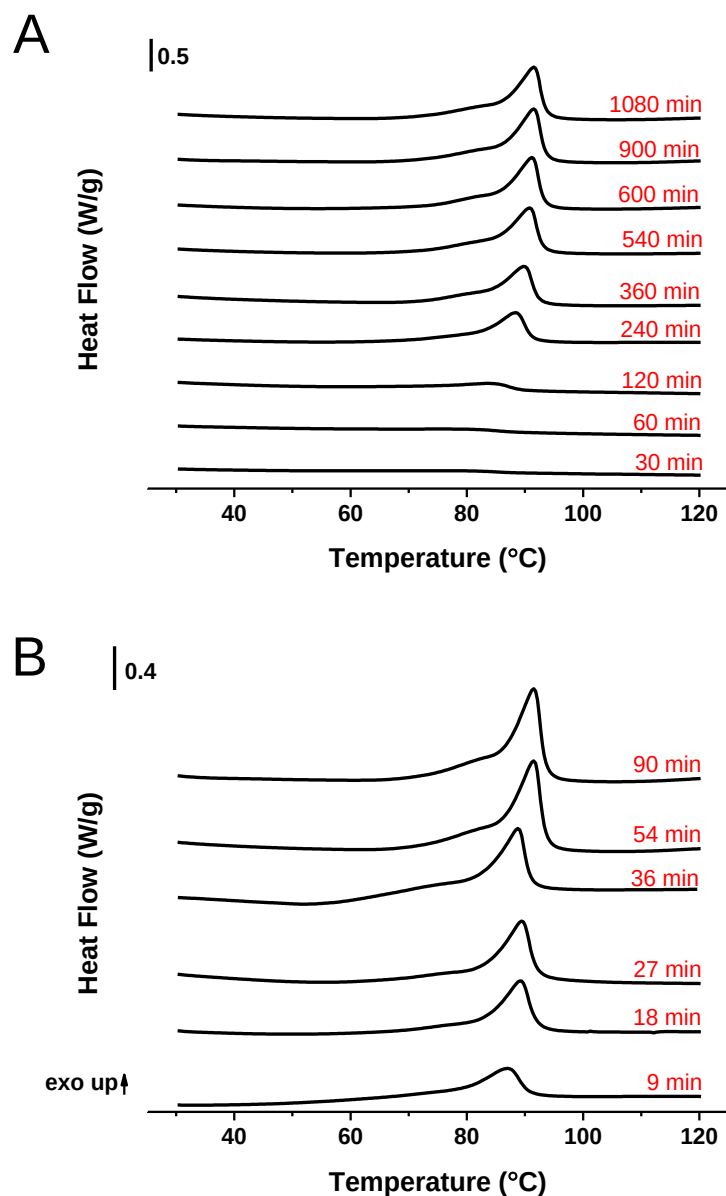


Figure 3.9 A) DSC thermograms of SDM milled in the PBM at RT for 18 hours and B) DSC thermograms of SDM milled in the VBM at RT for 90 minutes.

Figure 3.10 shows the level of amorphous content in the SDM milled systems as a function of time on milling in both the PBM and VBM at RT as quantified by DSC and NIR. Interestingly, a similar level of amorphisation was reached in both mill types, approximately 80% amorphous content, as shown in Table 3.1. This level of amorphous content was reached after approximately 6 hours on milling in the PBM, while the same level of amorphous content was achieved after approximately 60 minutes in the VBM, indicating faster kinetics of amorphisation in the vibratory type ball mill. Abdellaoui et al. investigated the mechanical energy input during milling in both vibratory type and planetary type ball mills (Abdellaoui and Gaffet 1995,

Abdellaoui and Gaffet 1996). However, these authors found that the level of mechanical energy input was dependent on the specific mill design and varied considerably between different types of vibratory and planetary ball mills, thus precluding a simple comparison of the two ball mill types used in this study in terms of the mechanical energy input relative to the kinetics of amorphisation of SDM.

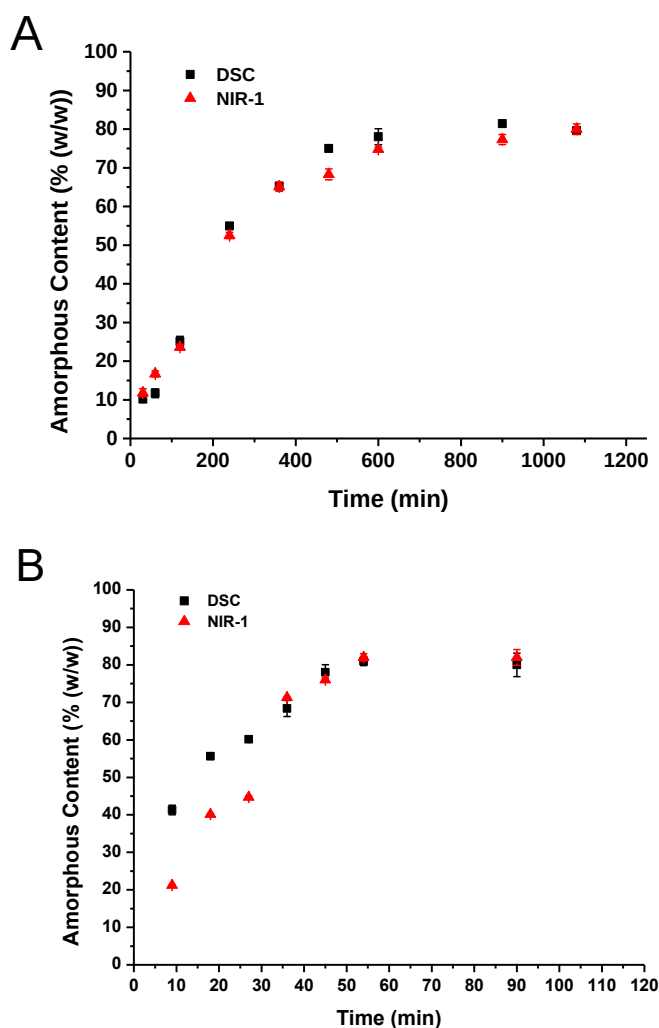


Figure 3.10 Amorphous content values as quantified by DSC and NIR-1 calibration curves for SDM milled A) in the PBM at RT for 18 hours and B) in the VBM at RT for 90 minutes

As a similar level of amorphisation of SDM was observed on milling at RT in both ball mill types, the effect of milling temperature on the extent of amorphisation of SDM was investigated. As previously described, reducing the milling temperature in the VBM to CT led to a PXRD amorphous system in contrast to the RT milled system,

as shown in Figure 3.11. Comparison of the extent of amorphisation of SDM in the PBM after 18 hours of milling at 4°C relative to RT, as shown in Table 3.1, indicates that reducing the temperature of the milling operation led to an approximately 12% greater level of amorphisation. Figure 3.11 shows the PXRD diffractograms of both PBM milled systems, highlighting the reduced intensity of the Bragg peaks of the SDM system milled in the PBM at 4 °C.

The increased amorphisation tendency on milling of molecular materials with reducing milling temperature has been highlighted by many authors (Feng, Pinal et al. 2008, Kaminska, Adrjanowicz et al. 2013). Sulfathiazole, with a reported T_g of 59 °C (Bianco, Tewes et al. 2013), has been shown to undergo a polymorphic transformation on milling at RT (Shakhtshneider and Boldyrev 1993). In contrast, Hu et al. studied the transformations of sulfathiazole on milling at both RT and CT and found that, while milling at RT induced a polymorphic transformation to a metastable polymorph, milling at CT led to the amorphisation of the compound (Hu, Macfhionnghaile et al. 2013). Dujardin et al. provided mechanistic insights into the relationship between the amorphisation tendency of α -glucose, with a T_g of 42 °C, and the milling temperature (Dujardin, Willart et al. 2013). These authors correlated crystallite size reduction on milling at both RT, close to T_g and at -15 °C, relative to a critical crystallite size below which amorphisation was favoured and found that at the lower milling temperature the crystallite size was reduced below the critical crystallite size and, in addition, as the lower temperature was well below T_g , crystallisation from the amorphous state generated was impeded due to reduced molecular mobility.

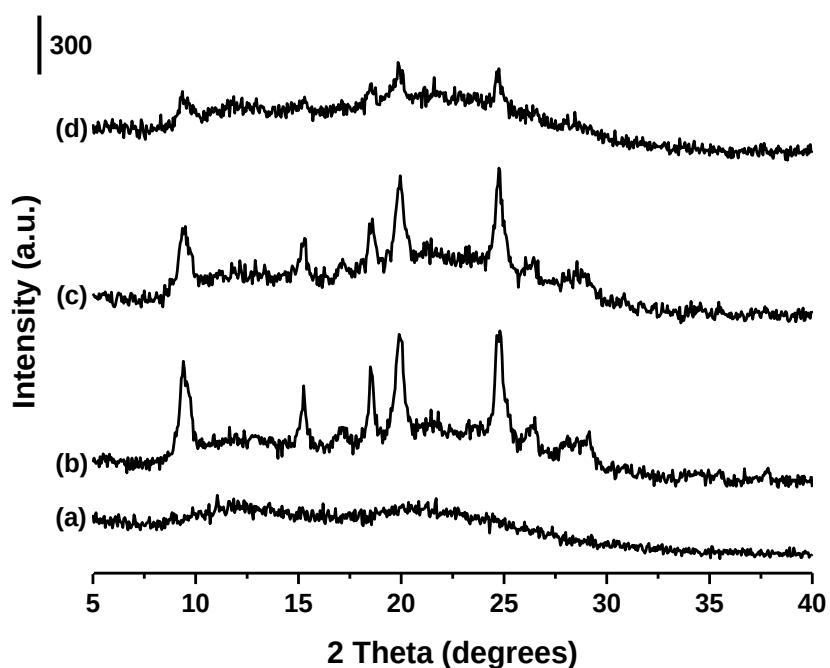


Figure 3.11 PXRD diffractograms of SDM milled in (a) the VBM at CT for 60 minutes (b) the VBM at RT for 60 minutes (c) the PBM at RT for 18 hours and (d) the PBM at 4 °C for 18 hours.

Table 3.1 Amorphous content values of SDM as determined by DSC and NIR-1 on milling in the PBM at both RT and 4 °C and on milling in the VBM at both RT and CT.

Mill Type	T_{mill} (°C)	% Amorphous Content DSC (Std)	% Amorphous Content NIR-1 (Std)
PBM	RT	78 (1.1)	82 (0.9)
	4	91 (0.7)	93 (0.3)
VBM	RT	81 (1)	80 (0.8)
	CT	100 (0)	99 (0.6)

3.4 DESIGN OF EXPERIMENT ON THE MECHANICAL ACTIVATION OF SULFADIMIDINE IN THE VIBRATORY BALL MILL

As highlighted by Burmeister et al., the mechanical energy imparted during milling is an important factor in determining the nature of the physical transformations that occur on milling (Burmeister and Kwade 2013). Burgio et al. investigated the various factors which affect the mechanical energy imparted on milling in the planetary ball mill on milling of metallic alloys (Burgio, Iasonna et al.). Utilising the assessment by Burgio et al. in the planetary ball mill, Koner et al. assessed the mechanical energy input on milling the low T_g excipient, mannitol, in a planetary ball mill by changing three milling variables of over two (high and low) levels – namely the milling time, the ball to powder mass ratio (BPR) and the rotation speed of the solar disk (Koner, Rajabi-Siahboomi et al. 2015).

The study by Koner et al. focused on the fragmentation behaviour of a crystalline **low T_g material** resistant to amorphisation on milling. In this study, the relationship between three milling parameters which affect the level of mechanical energy input on milling in a vibratory ball mill were investigated relative to the mill temperature, on the amorphisation of the model high T_g compound, SDM, in a statistical factorial design of experiment (DOE). Factorial experimental design may consist either of a full factorial experimental design (2^n), in which each of the design points is performed, or, in the case where the number of possible variables is considered to many to be investigated feasibly (e.g. where 5 variables are of interest) a fractional factorial DOE may be performed (2^{n-m}). As this study consisted of four variables, constituting a total of 16 unreplicated runs, a full factorial design of experiment was chosen in order to assess the entire design space of the study. The DOE was unreplicated as each of the design points was run only once in order to reduce the number of runs performed.

The milling parameters chosen were **frequency of vibration (f)** with a high of 25 Hz and a low of 15 Hz. In addition, two other variables were investigated which have been shown to have an impact on energy input, namely the **ball diameter (ϕ)**, with a high of 12 mm and low of 10 mm, and **ball to powder mass ratio (BPR)**, with a high value of 40:1 and a low value of 20:1 (Burgio, Iasonna et al.). The **temperature of the mill (T_{mill})** was selected as the fourth variable, with a high level at RT and low level at CT. Table 3.2 summarises the chosen variables of the

DOE with associated units and high and low values of each variable. Table 3.3 highlights the design points and run order of the 16 runs of the DOE together with the amorphous content values as determined by DSC and NIR analysis. The particular choice of high and low variable values chose for the DOE was based on preliminary feasibility studies which indicated the scope of the design space, in particular with regard the low energy milling variables and the associated generation of amorphous SDM under these conditions.

Table 3.2 Factors with high and low level values and associated units for the unreplicated 2^4 factorial design of experiment on the amorphisation of SDM in the vibratory ball mill.

Variable	Low (-)	High (+)	Unit
Frequency (f)	15	25	s^{-1}
Temperature of Mill (T_{mill})	CT*	RT (20-38 °C)	°C
Ball Diameter (ϕ)	10 (x5 balls)	12 (x3 balls)	mm
Ball to Powder Mass Ratio (BPR)	20:1	40:1	n/a

*Actual temperature during cryomilling was not determined experimentally

Table 3.3 Design points, run order, factors and amorphous content values for the unreplicated 2^4 factorial DOE on the amorphisation of SDM in the vibratory ball mill.

Design Point	Run Order	f	ϕ	BPR	T_{mill}	% Amorphous Content (StD, n = 3)		
						DSC	NIR-1	NIR-2
1	2	+	+	+	-	88.2 (0)	89.2 (0.8)	90.5 (0.1)
2	14	+	+	+	+	68.2 (1.1)	71.3 (0.1)	71.3 (0.10)
3	15	+	+	-	-	75.2 (0.7)	69.5 (1.3)	77.4 (0)
4	13	+	+	-	+	52.5 (0.2)	53.7 (1.0)	59.3 (1.1)
5	12	+	-	+	-	60.1 (0.7)	57.8 (2.2)	59.5 (0.3)
6	6	+	-	+	+	49.0 (0.4)	50.2 (2.2)	52.4 (0.7)
7	10	+	-	-	-	22.1 (0.5)	27.2 (1.3)	35.1 (0.8)
8	5	+	-	-	+	18.4 (0.8)	25.2 (1.6)	24.8 (0.3)
9	16	-	+	+	-	22.1 (0.2)	34.0 (0.7)	28.5 (2.3)
10	9	-	+	+	+	17.5 (1.0)	27.7 (1.0)	34.9 (1.4)
11	3	-	+	-	-	7.2 (0.5)	7.7 (2.0)	23.1 (0.5)
12	11	-	+	-	+	6.8 (0.2)	7.0 (1.8)	18.7 (0.5)
13	8	-	-	+	-	6.6 (0.2)	10.4 (1.8)	11.9 (0.6)
14	1	-	-	+	+	6.1 (0.2)	6.6 (1.2)	16.5 (1.8)
15	7	-	-	-	-	4.8 (0)	1.1 (0.6)	12.9 (0.4)
16	4	-	-	-	+	4.8 (0)	1.1 (0.7)	14.3 (0.3)

The number of balls was chosen such that the total weight of the 10mm balls was approximately equal to the total weight of the 12 mm balls (5x10 mm balls = 20 g and 3x12 mm balls = 20.5 g). This allowed the same mass of powder to be used for the 20:1 BPR for both 5x10 mm ball runs and 3x12 mm ball runs, and similarly the same mass of API to be used for the 40:1 BPR. The milling time chosen was based on the amorphisation kinetics described in Section 3.3, whereby 50% amorphisation of SDM was observed after 36 minutes at RT (as determined by DSC) which represented both a relatively short milling time and a sufficient level of amorphisation which would allow discrimination of the effects of the variables on amorphous content.

Amorphous content was determined by DSC analysis from the enthalpy of crystallisation using the calibration curve described in Section 3.2.2 and also by NIR analysis using the calibration curves NIR-1 and NIR-2, as described in Section 3.2.3.2. DSC analyses for each of the 16 runs are shown in Figure 3.12. In particular, Figure 3.12A shows the DSC thermograms of each of the high frequency (25 Hz) runs, while Figure 3.12B shows the DSC thermograms of each of the low frequency

(15 Hz) runs. In addition, Figures A-I.3A and A-I.3B in Appendix A-I highlight the PXRD diffractograms for each of the high and low frequency runs respectively. In addition comparison of the DSC analysis with the analysis of both of the NIR analysis, NIR-1 and NIR-2 is shown in Figure 3.13. Note that, in the design points with low frequency (15 Hz) milling, from design point 9 to 16, the NIR-2 calibration curve consistently over-estimates the level of amorphous content relative to DSC analysis and relative to NIR-1 which shows a better correlation with the DSC quantification results (shown in Table 3.3). In contrast, in the first 9 design points corresponding to high frequency 25 Hz milling (with corresponding greater level of amorphous content), both the NIR-1 and NIR-2 calibration curves correlate well with DSC quantification results. Owing to the good correlation between NIR-1 and the DSC analysis (relative to the apparent over-estimation of amorphous content with NIR-2), amorphous content values generated from the NIR-1 calibration curve were subsequently used in the design of experiment analysis.

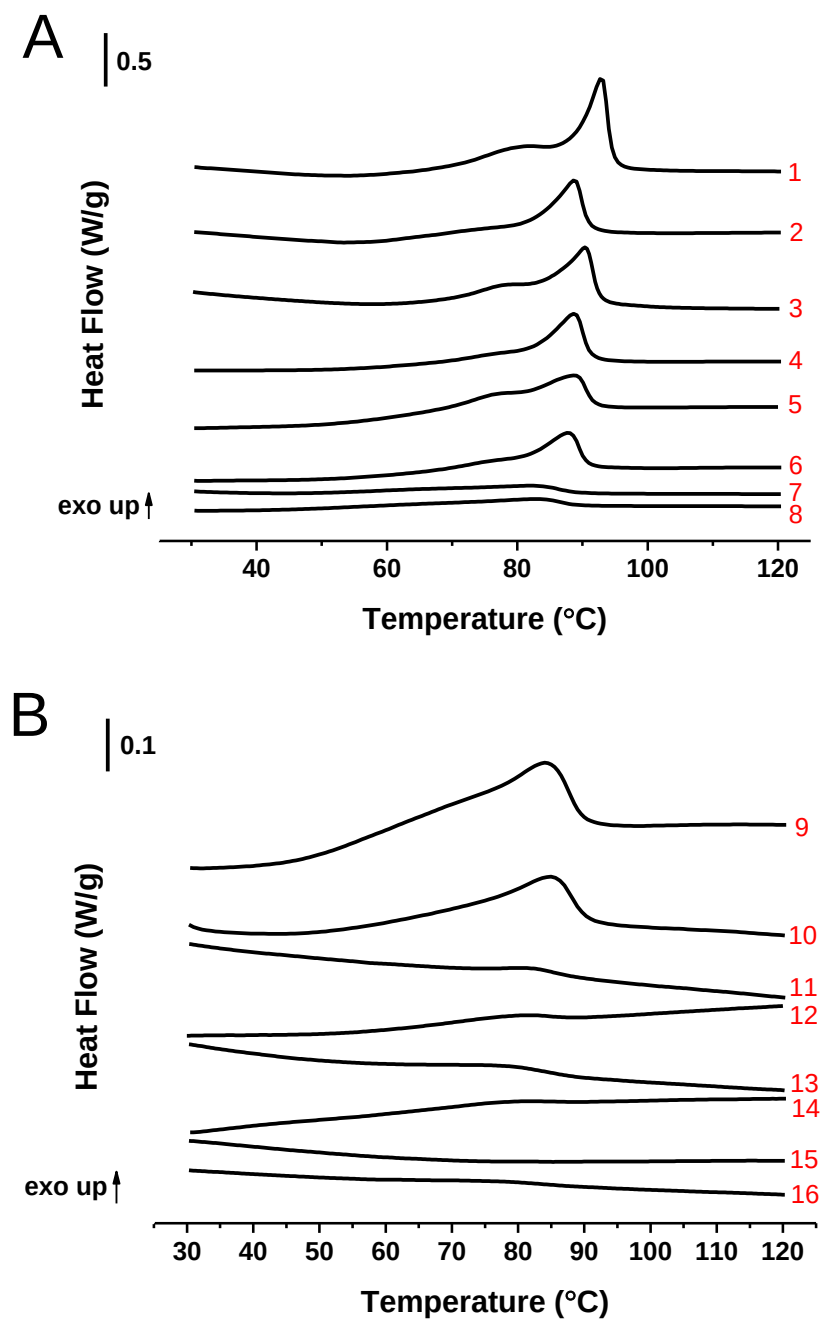


Figure 3.12 DSC thermograms of each of the DOE design points showing A) high frequency (25 Hz) runs and B) low frequency (15 Hz) runs.

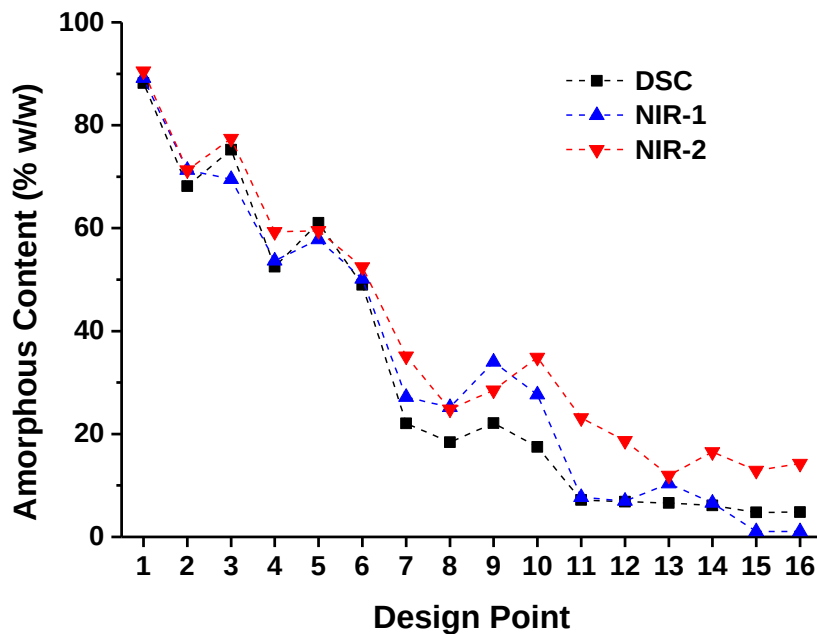


Figure 3.13 Amorphous content values for each of the DOE design points as quantified by DSC and both NIR calibration curves – NIR-1 (using previously milled (and crystallised in the DVS) crystalline SDM as crystalline standard) and NIR-2 (using unmilled crystalline SDM as crystalline standard).

Figure 3.14 shows the main effects and the 2, 3 and 4-way interaction effects between the four variables considered in the study design. Each of the effects from the Minitab output shown in Figure 3.14 are displayed in a main effects plot shown in Figure 3.15. The frequency variable had the greatest influence on amorphous content with an effect of 43.6, followed by ball diameter with an effect of 22.6, followed by the ball to powder mass ratio with an effect of 19.3. In contrast, the fourth main effect, T_{mill} , had a negative effect on amorphous content indicating that as the temperature of the mill was reduced the amorphisation of SDM was increased.

Minitab Output

Analysis of Variance

Source	DF	Adj SS	Adj MS	Effect
Model	15	11971.1	798.07	*
<u>Linear</u>	4	11307.0	2826.75	*
Frequency	1	7590.3	7590.33	43.6
Ball Diameter	1	2037.4	2037.39	22.6
Ball:Powder Mass Ratio	1	1495.8	1495.76	19.3
Tmill	1	183.5	183.53	-6.7
<u>2-Way Interactions</u>	6	475.8	79.31	*
Frequency*Ball Diameter	1	272.5	272.53	8.3
Frequency*Ball:Powder Mass Ratio	1	60.3	60.31	3.8
Frequency*Tmill	1	66.0	65.99	-4.0
Ball Diameter*Ball:Powder Mass Ratio	1	12.0	11.98	1.7
Ball Diameter*Tmill	1	46.6	46.63	-3.4
Ball:Powder Mass Ratio*Tmill	1	18.4	18.41	-2.1
<u>3-Way Interactions</u>	4	186.3	46.59	*
Frequency*Ball Diameter*Ball:Ratio	1	159.0	159.01	-6.3
Frequency*Ball Diameter*Tmill	1	27.0	26.96	-2.6
Frequency*Ball:Powder Mass Ratio*Tmill	1	0.2	0.18	0.2
Ball Diameter*Ball:Powder Mass Ratio*Tm	1	0.2	0.19	0.2
<u>4-Way Interactions</u>	1	1.9	1.92	*
Frequency*Ball Diameter*Ball:Powder Mass Ratio*Tmill	1	1.9	1.92	0.7
Error	0	*	*	
Total	15	11971.1		

Figure 3.14 Minitab output from the DOE of the main effects and 2, 3 and 4-way interactions of the four milling variables on amorphous content of SDM in the VBM for 36 minutes.

The design of experiment analysis allowed the determination of the two-way interaction effects between each of the ballistic variables relative to the milling temperature. Figure 3.15 highlights the interaction effects plot indicating that as the temperature was reduced, each of the main ballistic variables had a greater amorphisation tendency with the frequency variable having the strongest interaction with mill temperature. Figure 3.15 also highlights the positive interaction effect between frequency and ball diameter variables, indicating that the frequency variable had a greater effect on amorphous content of SDM with increasing ball diameter. In addition, Figure 3.16 shows a cube plot highlighting the fitted mean amorphous content values for each of the study design points.

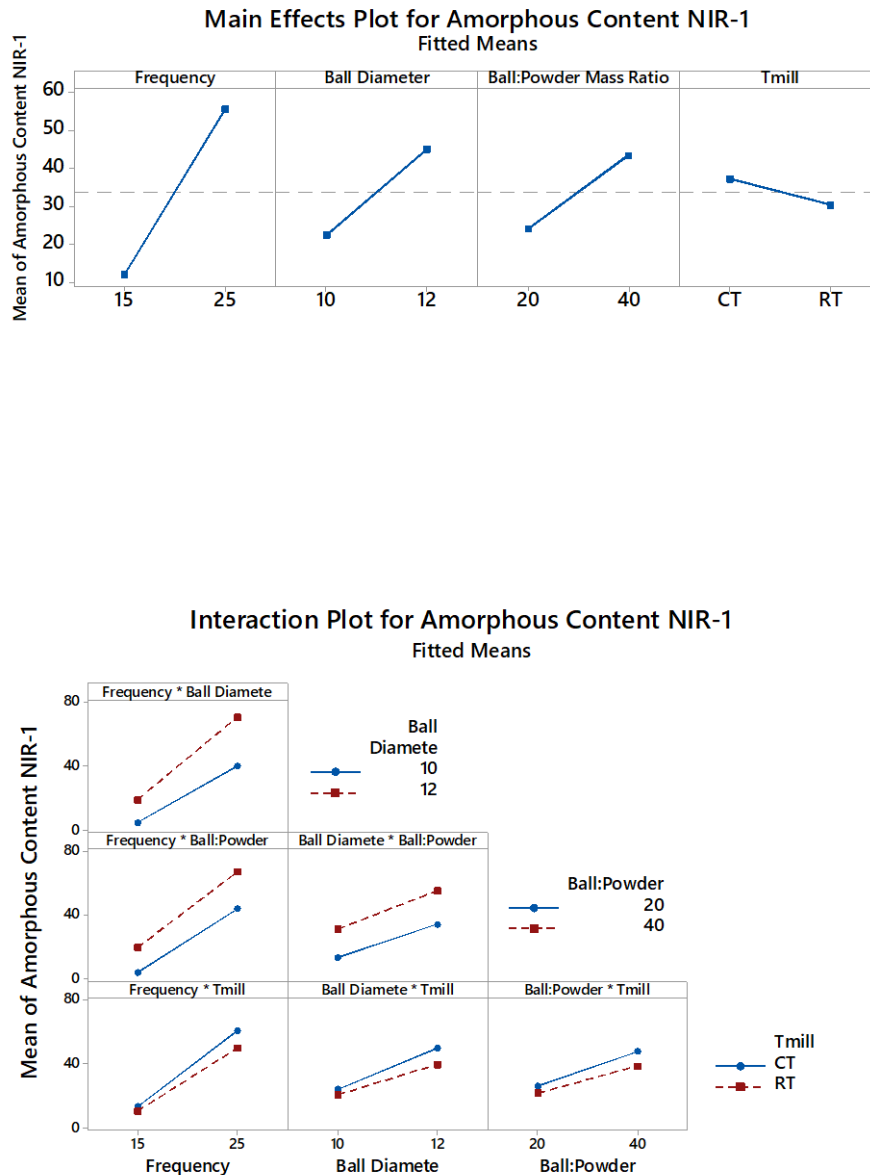


Figure 3.15 Main effects plot indicating the influence of changing the level of each of the four factors on amorphous content of SDM Interaction plot showing the two-way interactions between each of the four main effects.

Cube Plot (fitted means) for Amorphous Content NIR-1

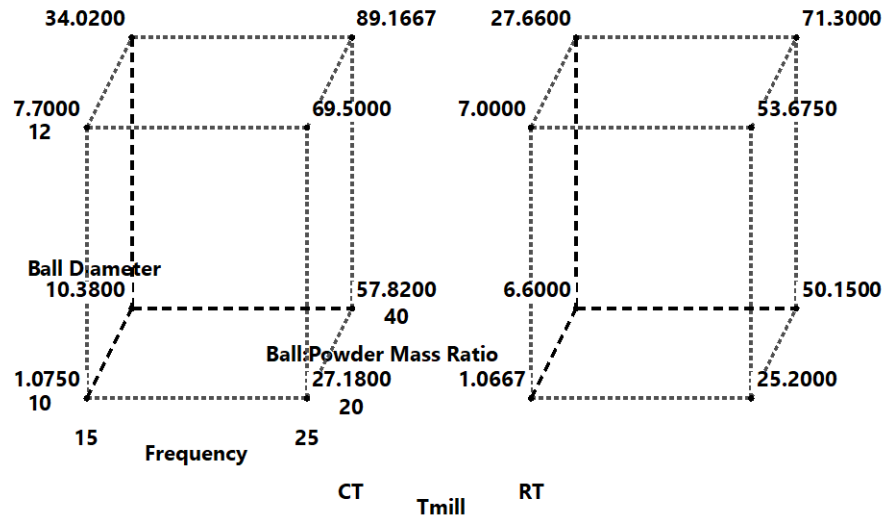


Figure 3.16 Cube plot highlighting interaction effects on fitted mean amorphous content of SDM.

Figure 3.17 shows the Minitab output from a reduced model analysis, in which only the four main variables were included and the remaining 2, 3 and 4-way interaction effects were used for the estimation of a standard error (S) value of the model. The model summary indicates an S value of 7.8 with a good R^2 value of 94.5% both suggesting a good fit of the data to the regression model, while the reduced model also allowed the calculation of a regression equation of amorphous content relative to each of the main variables, also shown in Figure 3.17. The residual plots from the reduced model analysis are shown in Figure 3.18. The normal probability plot shows good linearity, indicating a normal distribution of effects while only one of the deleted residuals was slightly greater than 2. The versus order plot does not reveal any unusual pattern in the run order, indicating lack of bias associated with the run order in the DOE.

Minitab Output (Reduced Model)

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	4	11307.0	2826.75	46.82	0.000
Linear	4	11307.0	2826.75	46.82	0.000
Frequency	1	7590.3	7590.33	125.72	0.000
Ball Diameter	1	2037.4	2037.39	33.75	0.000
Ball:Powder Mass Ratio	1	1495.8	1495.76	24.78	0.000
Tmill	1	183.5	183.53	3.04	0.109
Error	11	664.1	60.37		
Total	15	11971.1			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
7.76999	94.45%	92.44%	88.26%

Regression Equation in Uncoded Units

Amorphous Content NIR = **-206.5 + 4.356 Frequency + 11.28 Ball Diameter + 0.967 Ball:Powder Mass Ratio - 3.39 Tmill**

Fits and Diagnostics for Unusual Observations

Obs	Amorphous Content NIR	Fit	Resid	Std Resid
16	1.07	-12.40	13.47	2.09 R

R Large residual

Figure 3.17 Minitab output of the reduced model analysis with only the four main factors included

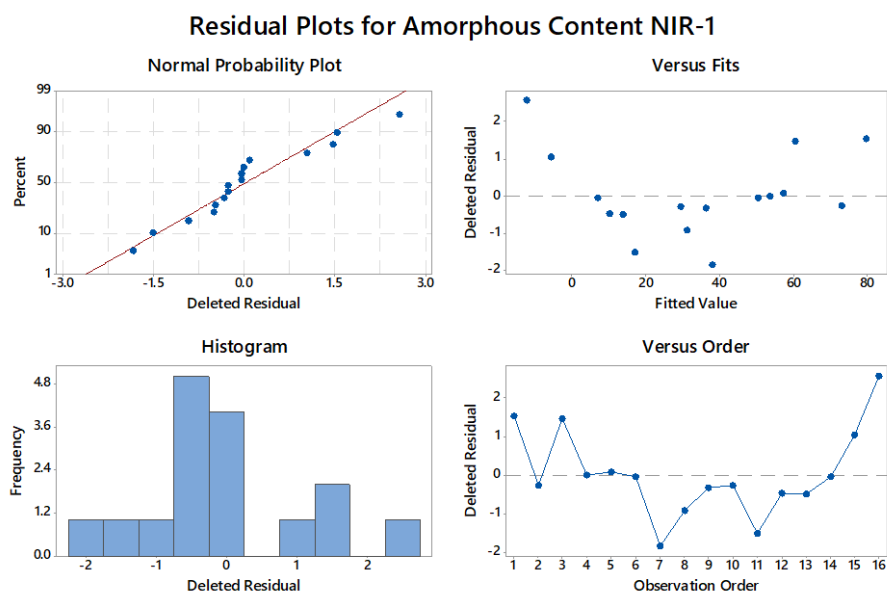


Figure 3.18 Residual plots from the reduced model analysis.

3.5 ANALYSIS OF MILLING INDUCED CHANGES TO THE SURFACE CHEMISTRY OF SULFADIMIDINE BY INVERSE GAS CHROMATOGRAPHY

Pharmaceutical processing and in particular milling has been shown to lead to significant changes to the solid surface of many materials - both APIs, including paracetamol and indomethacin, as well as excipients, such as mannitol. As highlighted in the previous section, the design of experiment analysis led to the generation of systems with varying levels of amorphous content as quantified by the bulk characterisation techniques, DSC and NIR. In order to further probe the surface characteristics of SDM on milling, we selected two systems from the design of experiment study, milled under high frequency (25 Hz, design point 2) and low frequency (15 Hz, design point 14) milling conditions, with amorphous contents, as quantified by DSC and NIR, highlighted in Table 3.3. Figure 3.19A shows the total and reversing heat flow DSC thermograms of SDM milled in the VBM for the system described by design point 2 in Table 3.3, with amorphous content, as quantified by DSC and NIR-1 of 68% and 71% respectively. The total heat flow DSC scan indicated a bimodal crystallisation exotherm with an initial peak at 72 °C followed by a bulk exothermic peak at 87 °C, while the reversing heat flow signal displayed a T_g event at 78 °C. In contrast, Figure 3.19B shows the total and reversing heat flow scans of the low frequency milled SDM system (design point 14), indicating a slight exotherm in the temperature region possibly associated with crystallisation of amorphous SDM with an exothermic peak at 79 °C but no detectable T_g in the reversing heat flow signal.

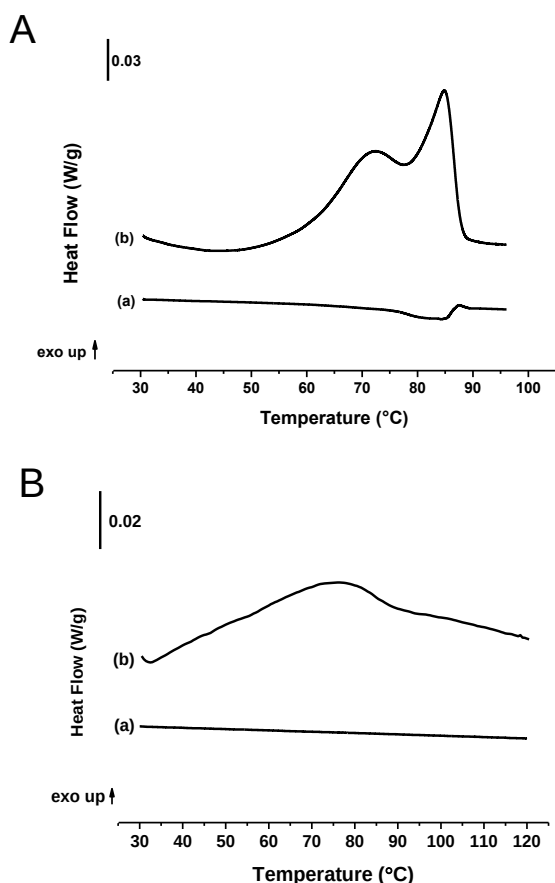


Figure 3.19 A) mDSC thermograms of DOE design point 2 SDM milled in the VBM for 36 minutes showing (a) reversing heat flow signal and (b) total heat flow signal. B) mDSC thermograms of DOE design point 14 SDM milled in the VBM for 36 minutes showing (a) reversing heat flow signal and (b) total heat flow signal.

The high frequency milled SDM system was analysed by heat of sorption analysis using decane as the probe vapour from 66 °C to 80 °C, as shown in Figure 3.20A, with methane gas as the internal standard, similar to the analysis of the surface transitions of amorphous sucrose described by Surana et al. (Surana, Randall et al. 2003). The retention plot indicated a decreasing decane retention volume with increasing column temperature while the initial peak at 0.7 minutes associated with the methane internal standard remained relatively unchanged. The retention volumes were plotted as a function of temperature as a heat of sorption plot, as shown in Figure 3.20B. The heat of sorption plot was further analysed using the Phase Transition analysis method from the Advanced iGC Excel Macro (iGC 2000, SMS UK). The analysis indicated a surface phase transition event at 69 °C, as shown in

Figure 3.20B, and shown in Table 3.4. In addition, in order to assess the possibility of a surface transition at lower temperatures, a heat of sorption analysis was

performed with decane as the probe vapour from 62 °C to 80 °C (indicating an extension of the green line to in Figure 3.20B to higher values), as shown in Appendix A-I, Figure A-I.5. However, the analysis indicated a phase transition event at a similar temperature of 70 °C.

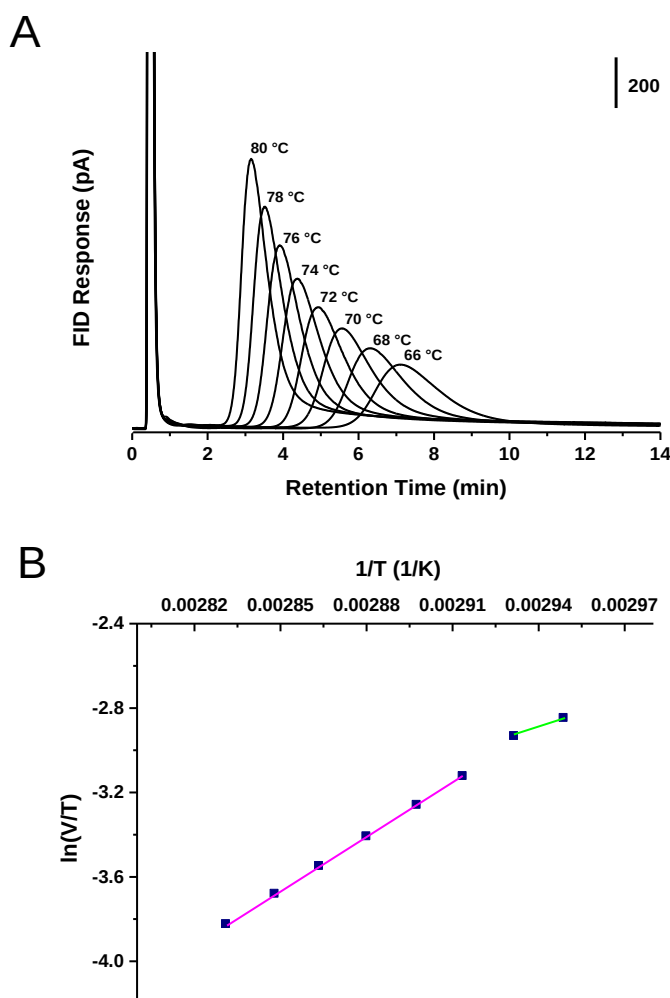


Figure 3.20 A) Heat of sorption retention volume plot with decane as the probe vapour from 66 °C to 80 °C and methane gas as the internal standard. **B)** Heat of sorption plot with a phase transition at 69 °C as determined by the Phase Transition analysis from the iGC Excel Macro.

The dispersive surface energy of the high frequency milled SDM system was determined at 50 °C, both before the heat of sorption analysis (i.e. before in-situ crystallisation in the iGC column) and, in addition, subsequent to the heat of sorption analysis. As shown in Table 3.4, the dispersive surface energy of the high frequency milled amorphous SDM increased to 62 mJ/m² from a value of 48 mJ/m² for the unmilled crystalline SDM system. In contrast, analysis of the high frequency

milled SDM system after heat of sorption analysis indicated a dispersive surface energy value of 56 mJ/m². This indicates that the surface energy of the high frequency milled system after recrystallisation was activated relative to the unmilled system. Figure 3.21 compares the surface energy plots for the crystalline unmilled SDM starting material relative to the surface energy plot of the high frequency milled SDM system after heat of sorption analysis.

Table 3.4 iGC analysis of unmilled crystalline SDM and SDM milled in the VBM for 36 minutes with conditions of DOE design point 2 and design point 14.

SDM System	γ_s^D (mJ/m²) (StD)	Surface Transition (°C) (StD)	Bulk T_g DSC (°C) (StD)	K_a (StD)
Unmilled Crystalline SDM	48 (0.8)	-	-	0.134 (0.002)
Design Point No. 2 Before Crystallisation	62 (2.2)	69 (2.1)	78 (0.4)	-
Design Point No. 2 After Crystallisation	56 (1.4)	-	-	0.15 (0.001)
Design Point No. 14	55 (1.5)	-	-	0.147 (0.002)

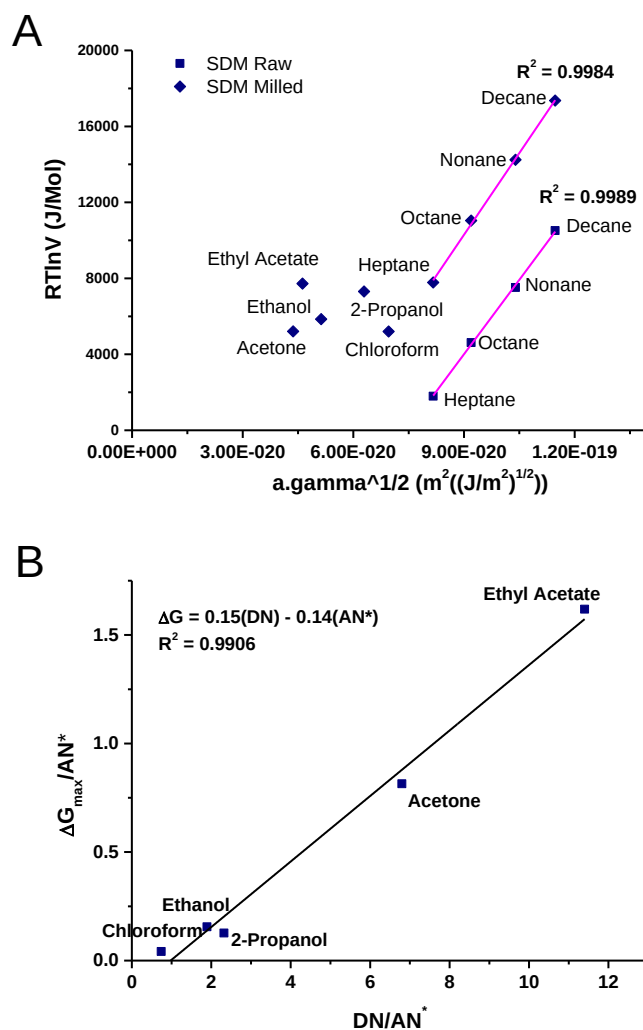


Figure 3.21 A) iGC surface energy and acid base plot of SDM milled according to DOE design point 2 after heat of sorption analysis. and B) Gutmann acid base plot

Figure 3.22 shows the surface energy plot of the SDM low frequency (15 Hz) milled sample, for which the surface energy was determined to be 55 mJ/m², and therefore likely to be only an activated as opposed to fully amorphous surface. However, an increase in the K_a value from 0.134 (unmilled) to 0.147 was also noted. There was no indication of surface transition on heat of sorption, however heat of sorption analysis may not be sensitive enough to detect such a low level of amorphous content. Further work is required to detect the surface amorphous character by iGC of such low levels of amorphous content.

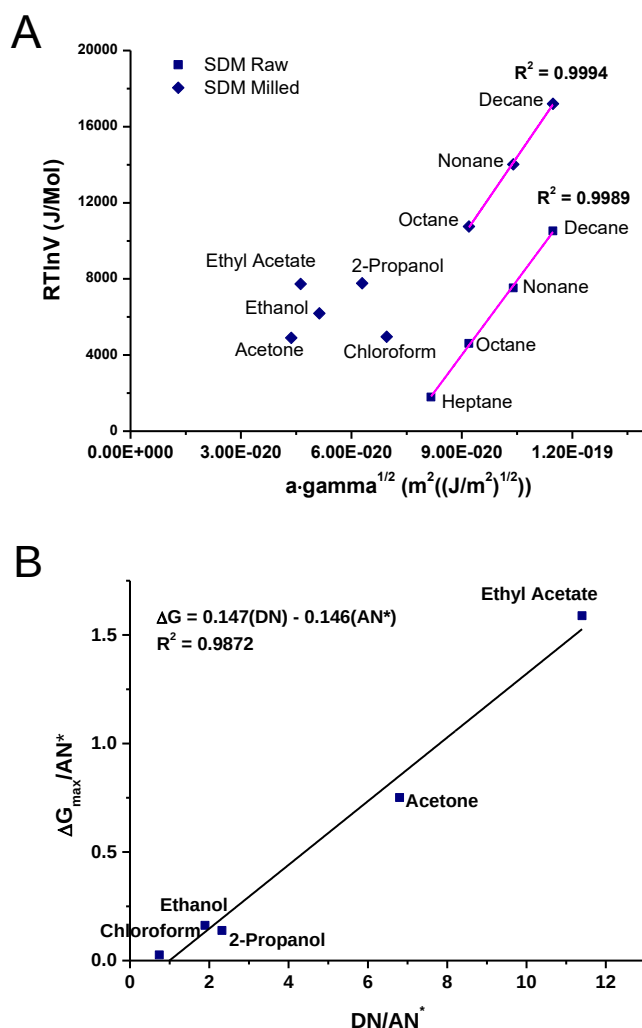


Figure 3.22 A) iGC surface energy and acid base plot and B) Gutmann acid-base plot of SDM milled according to DOE design point 14 milling conditions.

Figure 3.23 shows SEM images of SDM milled in the VBM at RT and in the PBM at RT, in addition to SDM milled in the VBM at CT. The particle sizes appear to range around 20 μm . However, the morphology of the particles is difficult to interpret due to the effect of the milling process. The BFDH morphology map of SDM from the Cambridge Structural database (CSD) using Mercury software was calculated and is shown in Figure 3.23. The analysis indicates that the aromatic N-H group is primarily associated with the 001 face, indicating that the increase in the K_a number, as determined by iGC analysis, could be associated with milling induced cleavage along this plane (Heng, Thielmann et al. 2006).

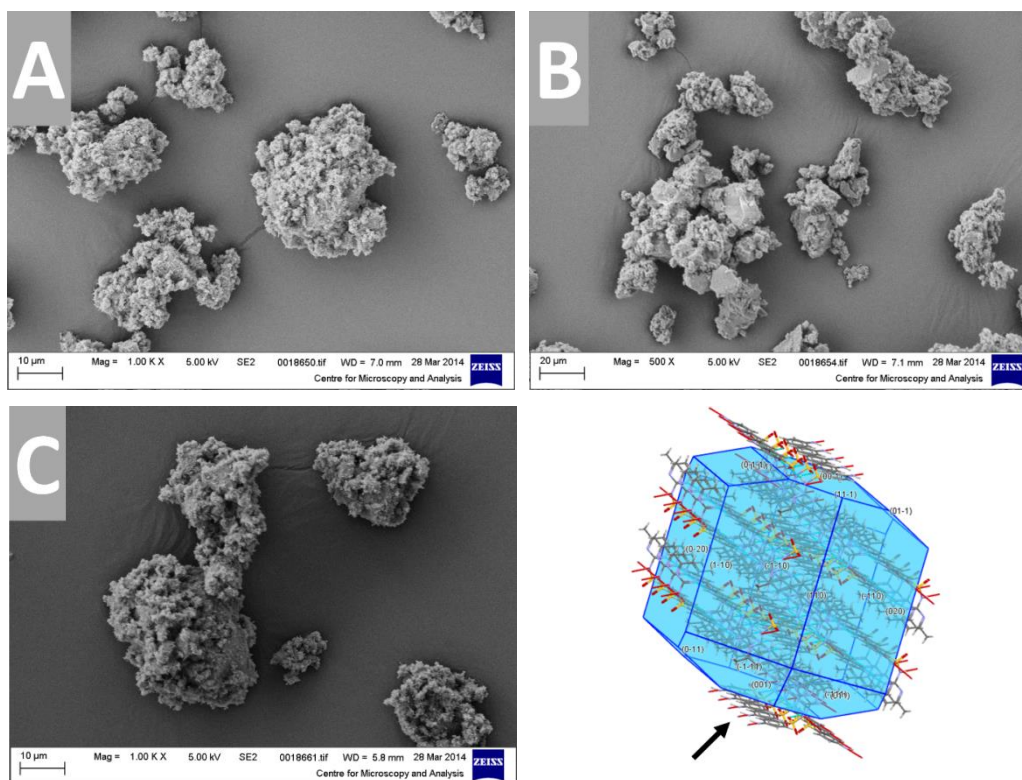


Figure 3.23 SEM images of A) SDM milled in the VBM at RT for 60 minutes B) SDM milled in the PBM at RT for 18 hours and C) SDM milled in the VBM at CT for 60 minutes. Inset shows the BFDH morphology of SDM (refcode SULFN018) as determined using Mercury software.

3.6 SOLID STATE CHARACTERISATION AND MECHANICAL ACTIVATION STUDIES OF THE LOW T_g EXCIPIENTS

In addition to crystalline to amorphous transformations on milling, many materials have been shown to either undergo polymorphic transformations to metastable polymorphic forms or to remain in the stable crystalline form on milling (Dujardin, Willart et al. 2013, Descamps, Aumelas et al. 2015). In particular, it has been noted that such transformations appear to occur in materials which exhibit a low glass transition temperature. As this study involves the comilling of high and low T_g materials with the aim of mitigating amorphisation of the high T_g component, we will firstly characterise the structural changes that occur on milling of the low T_g excipients alone in terms of their tendency to undergo amorphisation/polymorphic transformations and in terms of changes to their solid-state surface characteristics on milling.

3.6.1 Mannitol

The solid state characteristics of mannitol (MAN) have been well documented and three solid-state polymorphic forms have been characterised (α , β and δ) with the β polymorph being the thermodynamically stable form at standard temperature and pressure (Cares-Pacheco, Vaca-Medina et al. 2014). Figure 3.24 shows PXRD diffractograms of β -polymorphic MAN, in addition to the metastable α polymorph generated from the single crystal data in the Cambridge Crystallographic Data Centre (CCDC) database. As shown in Figure 3.24, unprocessed MAN was in the β -polymorphic form. Crystalline β -MAN was milled in the planetary ball mill at RT for 12 hours leading to a milling induced polymorphic transformation to the metastable α -polymorphic form as shown in Figure 3.24 (d). The milling induced β to α polymorphic transformation of MAN was previously described by Willart et al. (Willart, Caron et al. 2007). These authors highlighted the importance of the low T_g of the material at 13 °C, in terms of the inability of the milling operation to amorphise MAN. Indeed, the polymorphic transformation of the structurally related polyol sorbitol, with a T_g of 0 °C has been ascribed to the existence of a transient amorphous intermediate on milling (Willart, Lefebvre et al. 2005). Willart et al. followed the structural and nano-structural changes of sorbitol on milling and correlated the polymorphic transformation with a critical crystallite size below

which polymorphic transformation was favoured and which was situated above a critical crystallite size associated with amorphisation (Willart, Lefebvre et al. 2005).

Figure 3.25 shows the DSC thermograms for the unmilled and milled MAN systems. The thermograms reveal a slight decrease in the melting point of the α -polymorphic milled system at $167.2 (\pm 0.3) ^\circ\text{C}$ compared to the melting point of the β polymorph at $168.4 (0.4) ^\circ\text{C}$. The reduced melting point of the α polymorph of MAN is in agreement with previous findings, resulting from the monotropic nature of the β -polymorph (Burger, Henck et al. 2000).

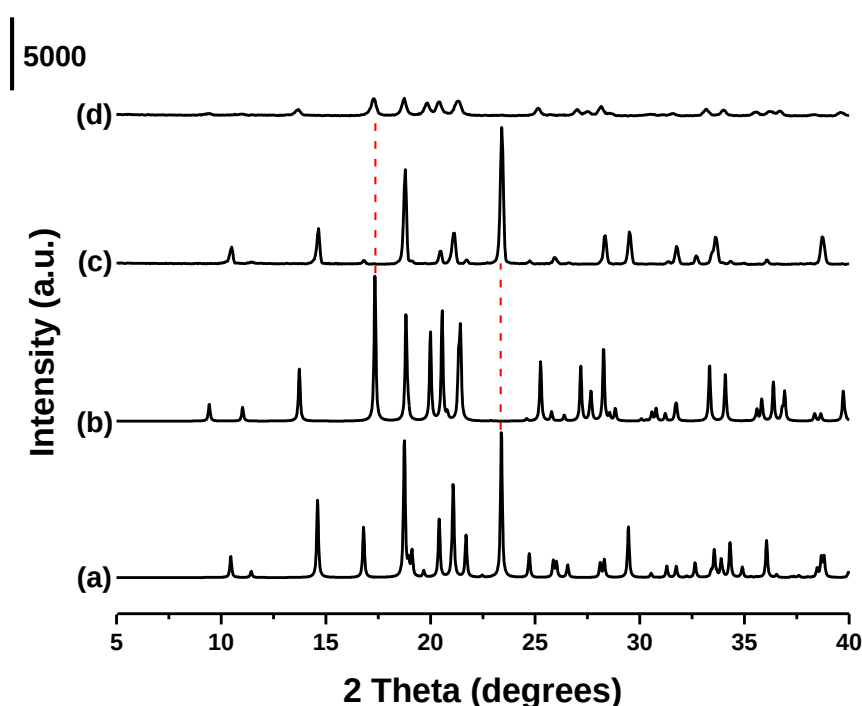


Figure 3.24 PXR D diffractograms showing (a) the CCDC generated single crystal structure of β -MAN (b) the CCDC generated single crystal structure of α -MAN (c) unprocessed β -MAN and (d) β -MAN milled in the PBM at RT for 12 hours. Red lines indicate peaks associated with crystalline MAN.

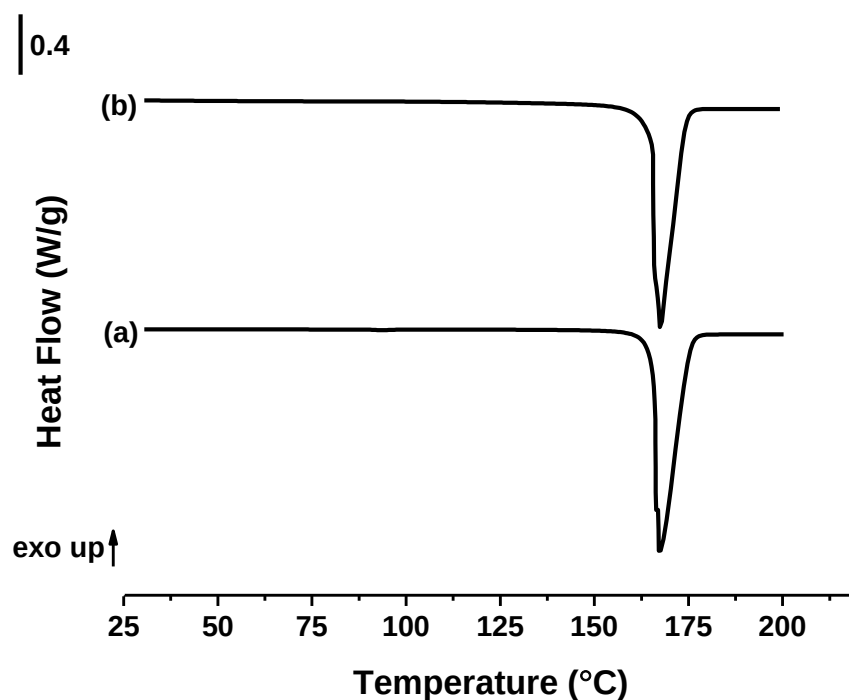


Figure 3.25 DSC thermograms of (a) crystalline β -MAN and (b) MAN milled in the PBM at RT for 12 hours.

The dispersive surface energy of β -polymorphic MAN starting material was determined by iGC analysis as highlighted in Figure 3.26 and in Table 3.4. The value was in good agreement with previously reported surface energy of β -MAN of 40 mJ/m² (Cares-Pacheco, Vaca-Medina et al. 2014). In addition, the dispersive surface energy of the milled excipient which, according to PXRD, had transformed to the α polymorph was also determined by iGC analysis and was found to undergo a large increase to 72 mJ/m². Cares-Pacheco et al. also determined the dispersive surface energy of α -MAN crystallised from solution and reported the value to be 74.9 mJ/m² which was similarly in good agreement with our analysis. The specific surface area of MAN before and after milling was also determined by N₂ BET analysis, as shown in Table 3.5, and indicated a large increase in surface area of MAN on milling from 0.68 to 8.66 m²/g.

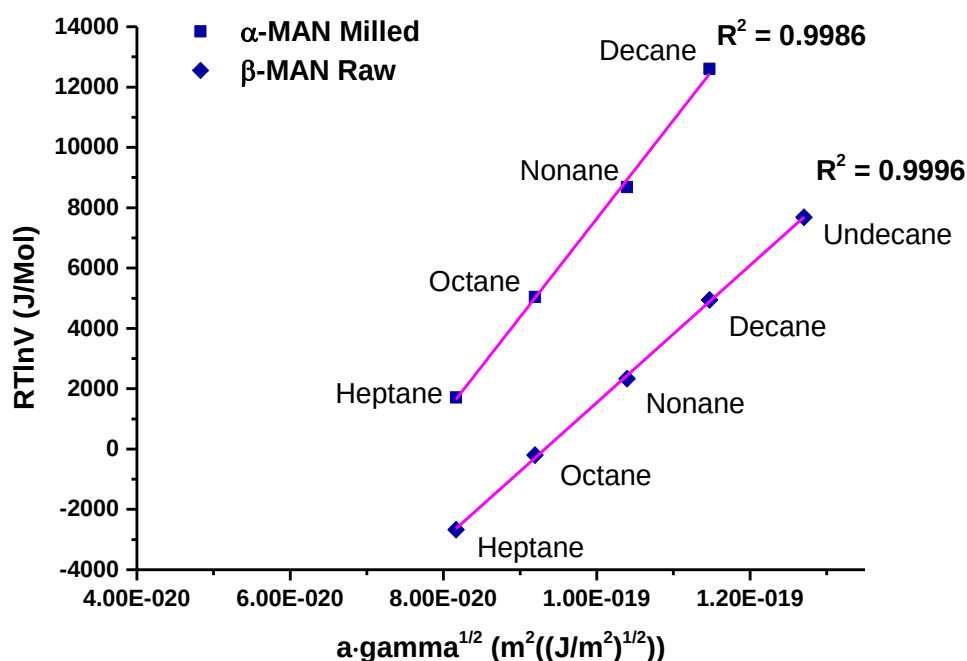


Figure 3.26 Surface energy plots for raw crystalline β -MAN and MAN milled in the PBM at RT for 12 hours.

Table 3.5 Dispersive surface energy values as determined by iGC analysis and specific surface area values as determined by N_2 BET analysis of each of the excipients MAN, SA, GA, AA and PA both before milling and after milling alone in the PBM at RT for 12 hours.

	γ_s^D (mJ /m ²) (StD, n=2)		Surface Area (m ² /g) (StD, n=3)	
	Before	After	Before	After
Mannitol	36.2 (0.8)	72.2 (2.3)	0.68 (0.04)	8.66 (0.02)
Succinic Acid	-	46.7 (1.8)	0.24 (0.08)	5.39 (0.07)
Glutaric Acid	-	34.8 (0.5)	0.17 (0.09)	2.41 (0.12)
Adipic Acid	-	38.8 (0.3)	0.81 (0.03)	2.26 (0.07)
Pimelic Acid	-	33.9 (0.2)	0.72 (0.03)	2.59 (0.06)

3.6.2 The Dicarboxylic Acids

3.6.2.1 Glutaric Acid

Glutaric acid (GA), exhibits two known polymorphic forms, the metastable α polymorph and the stable β polymorph (McNamara, Childs et al. 2006). GA exhibits enantiotropic behaviour under standard conditions of pressure and temperature. However, it exhibits monotropic behaviour at pressures above 63 kPa with the β -polymorphic form the only stable polymorph above this pressure (Espeau, Négrier

et al. 2013). Figure 3.27 shows the diffractogram of unmilled β -GA as well as the CCDC generated PXRD pattern from the single crystal XRD structure of α -polymorphic GA. β -GA was milled alone in the PBM at RT for 12 hours and the sample remained crystalline and in the β -polymorphic form, as shown in Figure 3.27 (c). In addition, β -GA was milled in the VBM at CT for 45 minutes and similarly remained in the β -polymorphic form on milling. GA was also spray dried as a 1% solution in 70% ethanol in water. In contrast to milling, spray drying GA under these conditions led to the generation of a mixture of α and β -polymorphic forms as shown in Figure 3.27 (e).

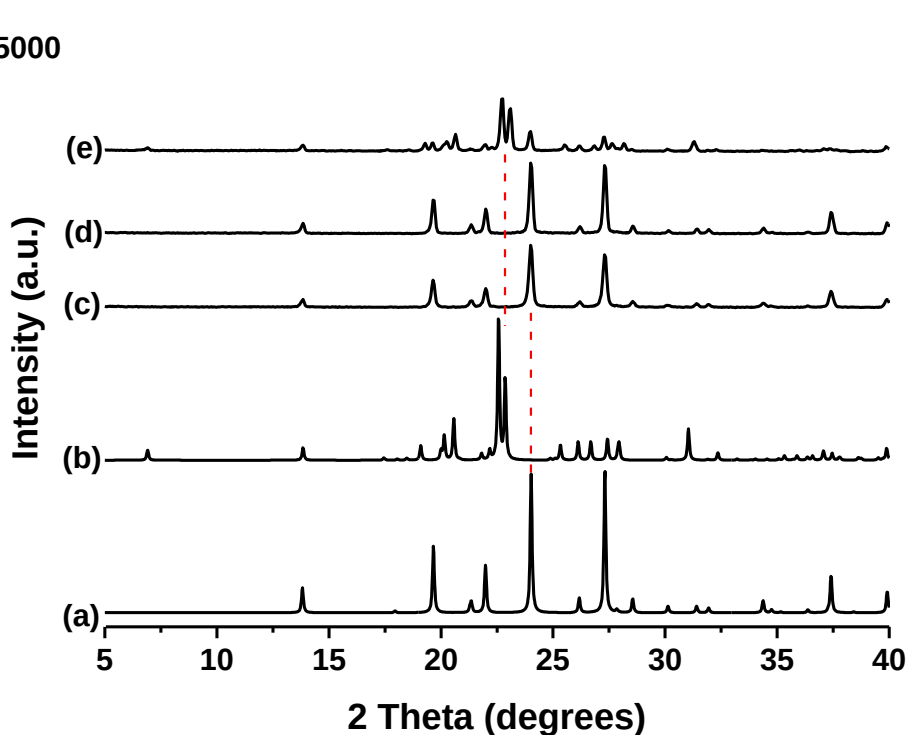


Figure 3.27 PXRD diffractograms of (a) unmilled crystalline β -GA (b) the CCDC generated single crystal structure of α -polymorphic GA (c) GA milled in the PBM at RT for 12 hours (d) GA milled in the VBM at CT for 45 minutes and (e) spray dried GA from a 1% solution in 70% ethanol in water. Red lines indicate Bragg peaks associated with crystalline GA.

Figure 3.28 (a) reveals DSC thermograms of unmilled β -GA with an endothermic signal at 76 °C associated with the polymorphic transition from the stable polymorphic form β to the metastable high temperature polymorphic form α , followed by a melt endotherm at 98 °C. In addition Figure 3.28 reveals the DSC thermograms of β -GA milled in the PBM at RT for 12 hours in addition to β -GA

cryomilled in the VBM at CT for 45 minutes and the spray dried sample. Both the milled systems revealed an endotherm at 76 °C associated with a polymorphic transition to the metastable α polymorph, consistent with the PXRD finding that GA remained in the stable β -polymorphic form on milling at both RT and CT. In contrast a much smaller endotherm was present in the spray dried system associated with the polymorphic transition to the α -polymorphic form, which was consistent with the PXRD analysis which indicated that the spray dried system containing both α and β -polymorphic forms of GA.

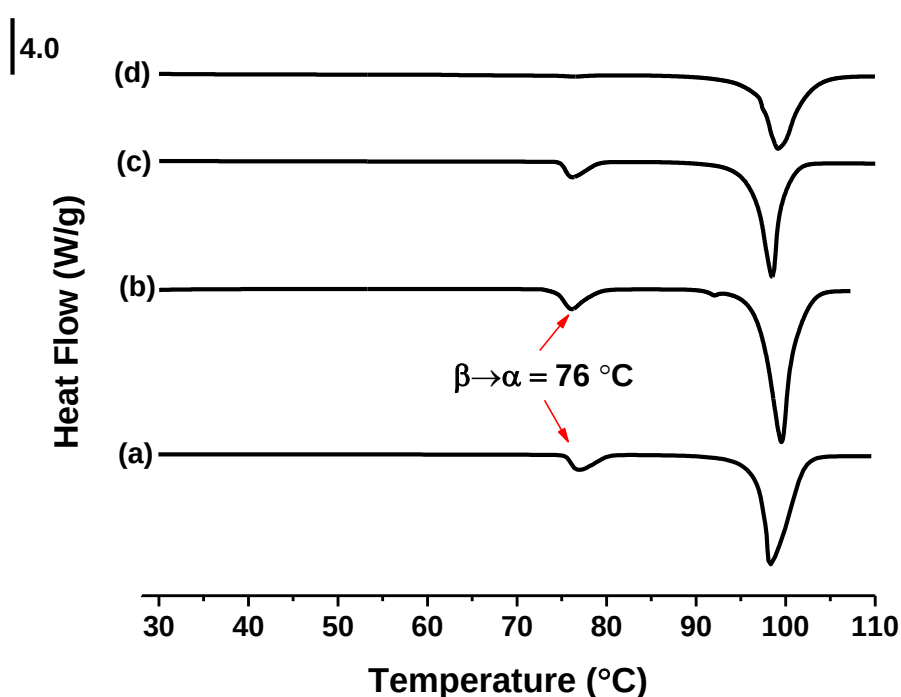


Figure 3.28 DSC thermograms of (a) unprocessed crystalline β -GA, (b) GA milled in the PBM at RT for 12 hours, (c) GA milled in the VBM at CT for 45 minutes and (d) spray dried GA.

The dispersive surface energy of GA milled in the PBM at RT for 12 hours was analysed by iGC analysis using the non-polar alkane probes from heptane to undecane as shown Figure 3.29. The dispersive surface energy was determined to be 34.8 mJ/m² as highlighted in Table 3.5, with a good R^2 correlation of 0.9995. In addition, the specific surface area of both unmilled and milled β -GA was determined by N₂ BET analysis as shown in Table 3.5. The results suggested an increase in the surface area from 0.17 m²/g to 2.41 m²/g on milling in the PBM at RT. The dispersive surface energy of the unmilled form was not determined due to very low

retention volume of the non-polar probes, possibly due to the small surface area and limited potential for interaction in the sample prior to milling.

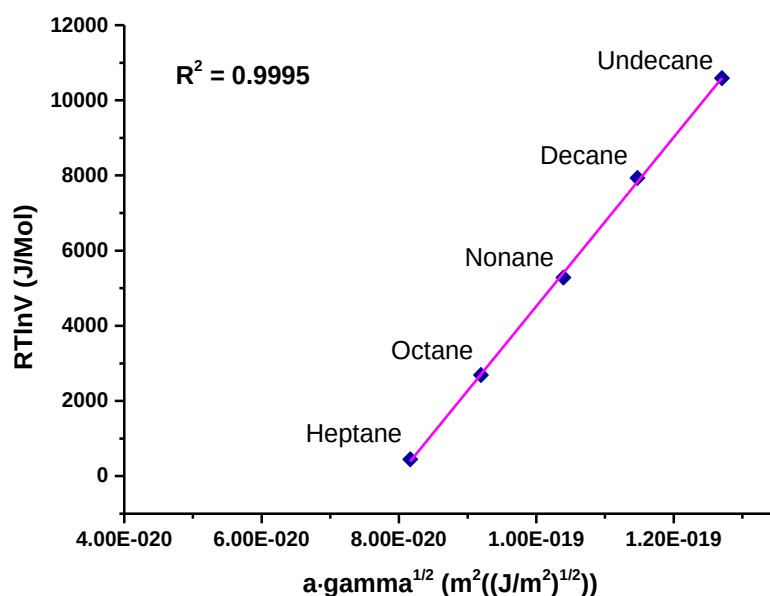


Figure 3.29 iGC surface energy plot of β -polymorphic GA milled in the planetary ball mill for 12 hours.

Figure 3.30 shows the DVS stepwise sorption isotherms with water as the probe vapour of both β -GA milled in the PBM at RT for 12 hours, as well as the spray dried GA system. In contrast to the spray-dried system, no mass loss event was observed in either the first or second sorption cycle of the milled sample. Analysis of the spray dried system indicated a mass loss event at 50% RH in the first cycle, while no such mass loss event was observed in the second sorption cycle. The sorption cycle shown in Figure 3.30B was only run up to 70% RH in contrast to that shown in Figure 3.30A which was run up to 90% w/w RH. Thus, the sorption cycle shown in Figure 3.30B does not reveal the large increase in mass uptake of GA at either the 80% or 90% RH.

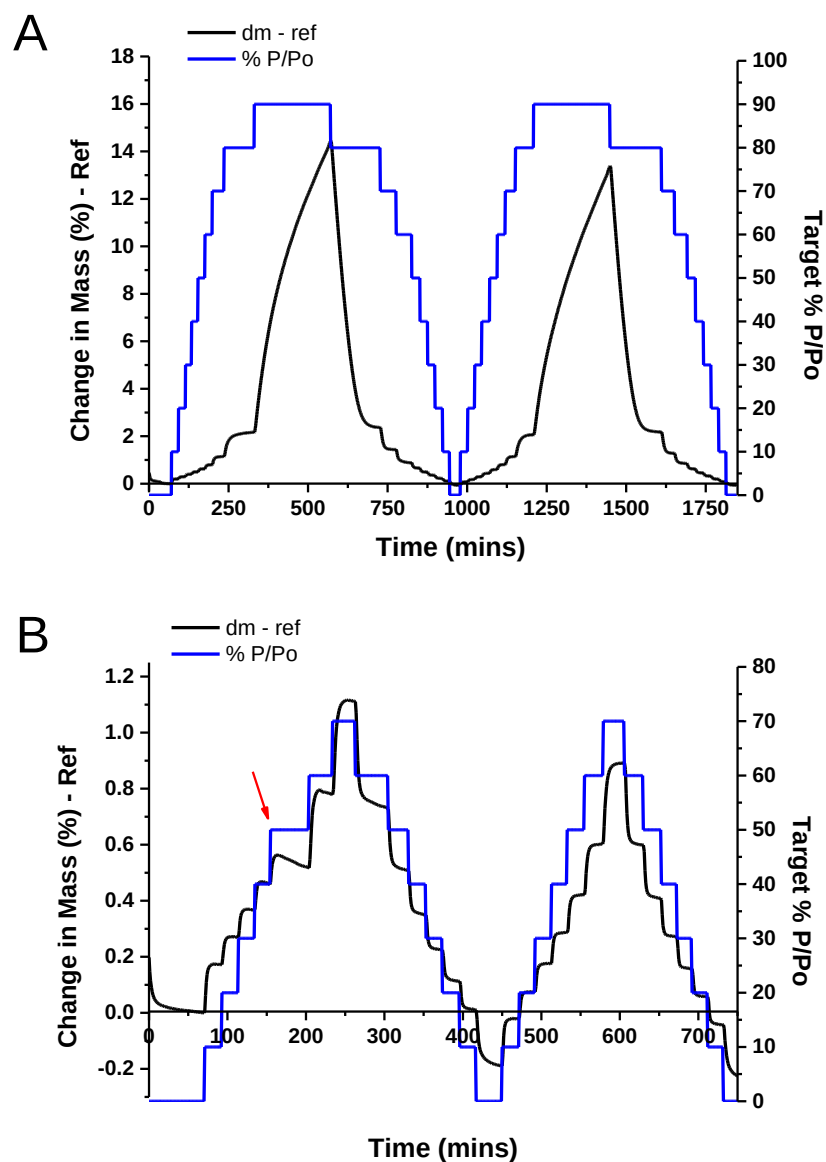


Figure 3.30 DVS stepwise sorption isotherms of A) crystalline β -polymorphic GA and B) spray dried GA containing a mixture of α and β -polymorphic forms. (Red arrow indicates a mass loss event associated with polymorphic conversion)

In order to further investigate the nature of the mass loss event that occurred on DVS analysis, the spray dried GA system was held at 25 °C and 75% RH over saturated NaCl solution and monitored by PXRD analysis over two hours as shown in

Figure 3.31. The PXRD analysis revealed the conversion of the metastable α -polymorphic form to the stable β polymorph over the two hour time period. This suggests that the mass loss event in the DVS was most likely due to the humidity-induced polymorphic conversion to the stable β polymorph.

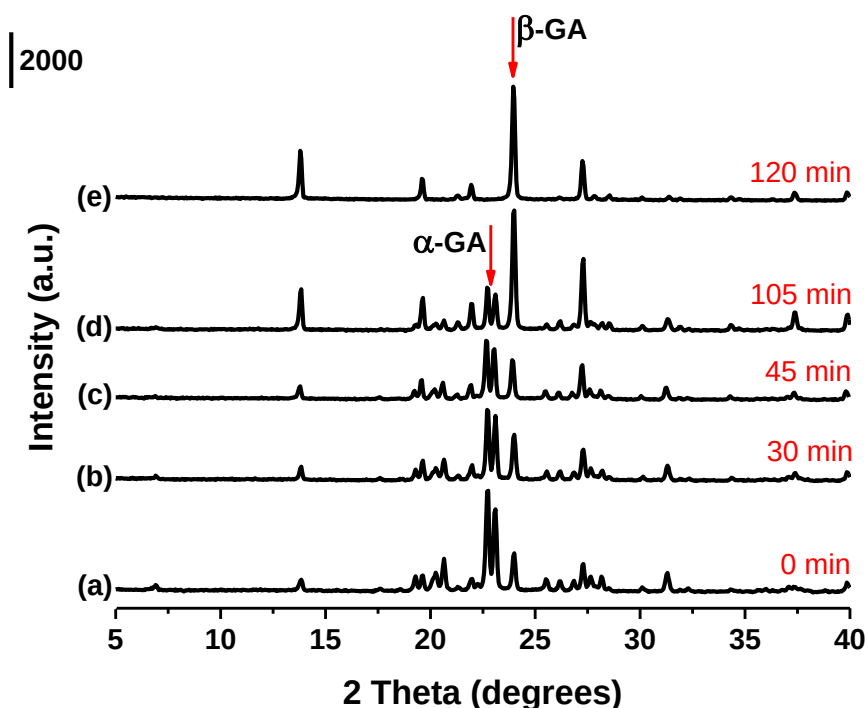


Figure 3.31 PXRD diffractograms of spray dried GA containing a mixture of α and β -polymorphic forms held at 25 °C and 75 % RH from 0 to 120 minutes.

3.6.2.2 Pimelic Acid

As described by Burger et al., pimelic acid (PA) has three known polymorphic forms, described as α , β , and γ , with the β -polymorphic form being the thermodynamically stable form at standard pressure and temperature (Burger, Henck et al. 1996). Figure 3.32 shows the PXRD diffractograms of unmilled PA as well as the CCDC generated structures of the α and β -polymorphic forms. PXRD evidence suggested that the unmilled crystalline PA was in the β -polymorphic form. In contrast to GA which did not show any tendency to undergo a polymorphic transformation when milled, PA underwent a partial polymorphic transformation to the metastable α polymorph when milled in the PBM at RT. The PXRD diffractograms of the systems milled in the VBM at both RT and CT similarly suggested that PA underwent a polymorphic transformation to the metastable α polymorph. Interestingly, the PXRD diffractogram of the CT milled system indicated that PA underwent a greater level of polymorphic transformation than the RT milled system with the intensity of the Bragg peaks associated with the β polymorph significantly reduced relative to the RT milled system.

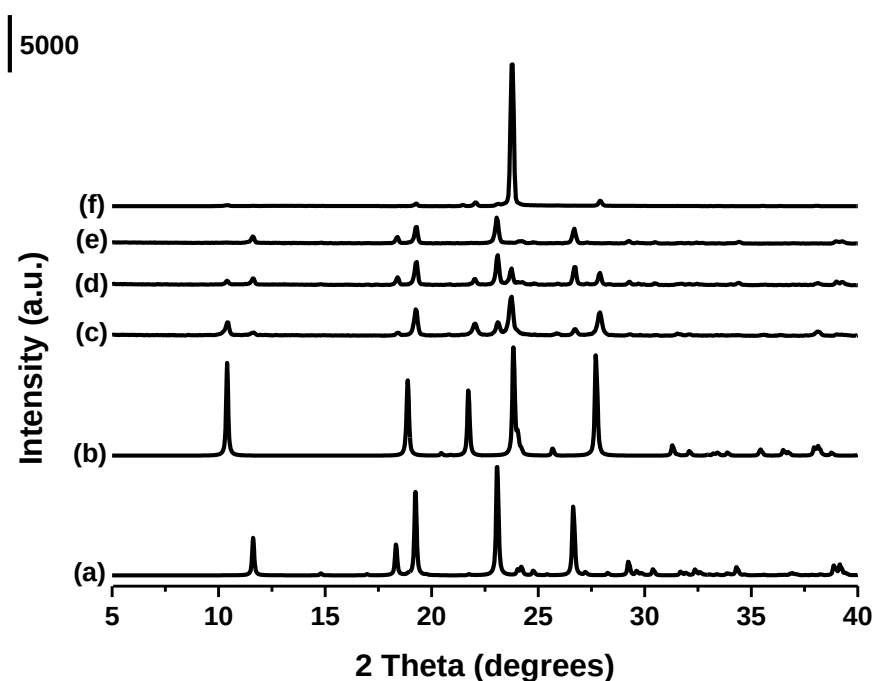


Figure 3.32 PXRD diffractograms showing (a) CCDC generated crystal structure of α -polymorphic PA (b) CCDC generated crystal structure of β -polymorphic PA (c) PA milled in the PBM at RT for 12 hours (d) PA milled in the VBM at RT for 36 minutes (e) PA milled in the VBM at CT for 36 minutes and (f) raw crystalline PA.

DSC analysis of raw unmilled PA revealed three endothermic events at 87 °C, 98 °C and 105 °C. These have previously been attributed to a transformation to the metastable α polymorph and a subsequent transformation from the α polymorph to γ -polymorphic form, indicating the enantiotropic nature of PA (Burger, Henck et al. 1996). No file is deposited with the CCDC associated with the γ -polymorph of PA. However the PXRD diffractogram and d-spacing values of the Bragg peaks of the γ polymorph have been published previously by Burger et al. and are shown in Appendix A-III.

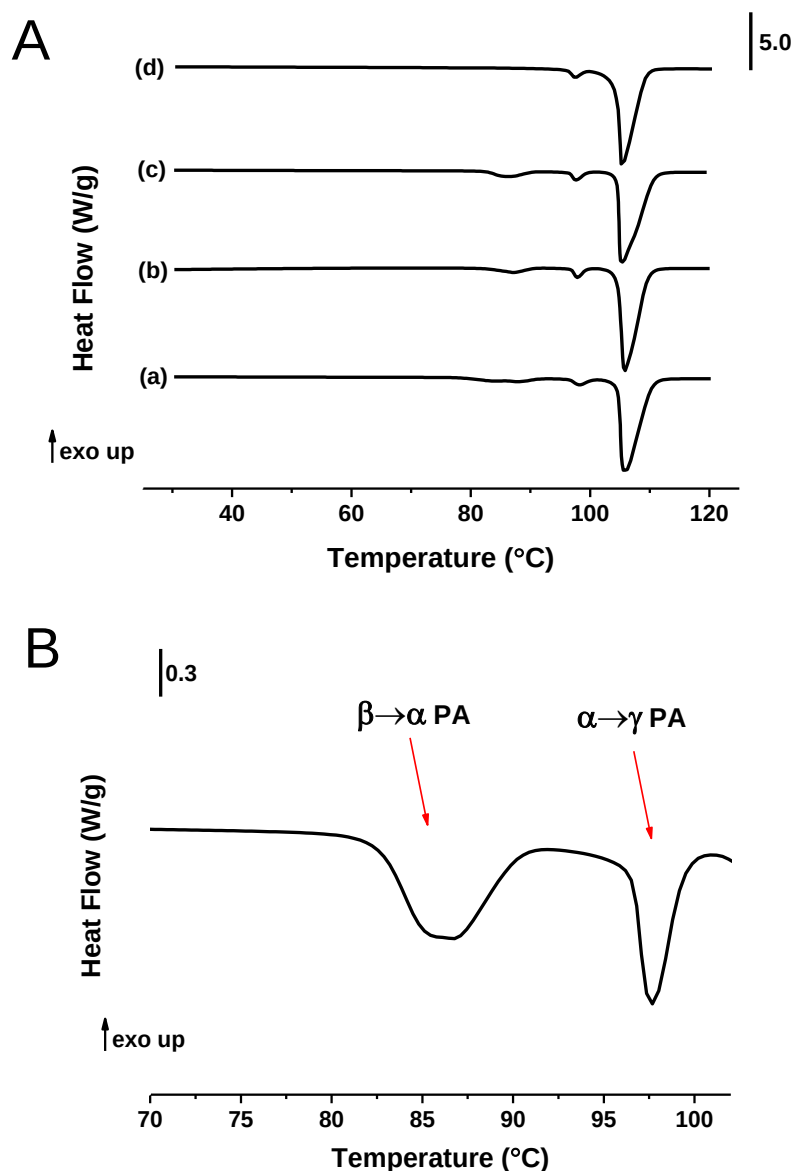


Figure 3.33 A) DSC thermograms of (a) crystalline unmilled PA (b) PA milled in the PBM at RT for 12 hours (c) PA milled in the VBM at RT for 36 minutes and (d) PA milled in the VBM at CT for 36 minutes. B) DSC thermogram of unprocessed crystalline β -polymorphic PA indicating transition endotherms to metastable α and γ -polymorphic forms at 86 and 97 °C respectively.

The surface energy was determined for the PA PBM milled for 12 hours, and is shown in Figure 3.34, with an R^2 value of 0.9995. However, as for GA, the surface energy could not be determined for the unmilled raw PA due to low retention volume, possibly associated with low surface area of the unmilled system. The dispersive surface energy value was similar to GA at 34 mJ/m². The specific surface area of unmilled PA and the PA system milled in the PBM at RT for 12 hours was determined, by N₂ BET analysis, to be 0.72 m²/g and 2.59 m²/g respectively.

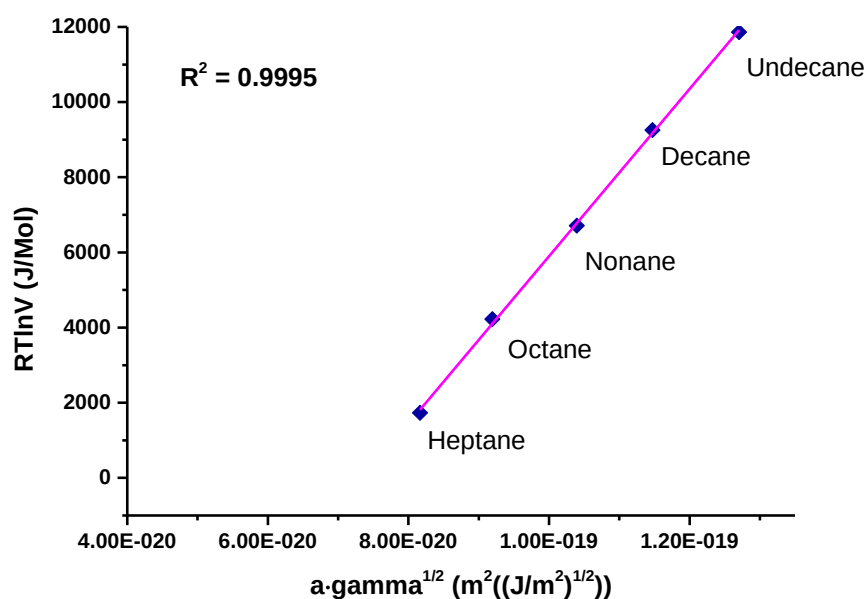


Figure 3.34 iGC surface energy plot of PA milled in the PBM at RT for 12 hours.

3.6.2.3 Succinic Acid and Adipic Acid

Figure 3.35A and B reveal the PXRD diffractograms of the α and β -polymorphic forms of succinic acid (SA) and adipic acid (AA) respectively, as generated from the CCDC structural database single crystal data. Analysis of the PXRD diffractogram of unmilled SA indicates that the starting material was in the thermodynamically stable β polymorph form. Additionally, on milling in the PBM at RT for 12 hours and in the VBM at RT for 45 minutes, SA remained both crystalline and in the β -polymorphic form with no evidence of any Bragg peaks associated with the α polymorph in either of the milled systems. Analysis of the PXRD diffractogram of unmilled crystalline AA indicated that it was in the thermodynamically stable β -polymorphic form. On milling in the PBM at RT for 12 hours and in the VBM at RT for 45 minutes AA remained both crystalline and as the stable β polymorph.

The dispersive surface energy of PBM milled SA and AA were also determined by iGC analysis, as shown in Figure 3.36 and Table 3.5. As for both GA and PA, the dispersive surface energies of unmilled SA and AA could not be determined due to low retention volumes. However, the dispersive surface energy of milled SA was found to be the largest of the diacids at $46.7 \text{ mJ}/\text{m}^2$. Similarly, Luner et al. determined the dispersive surface energy of SA on milling in an impact mill to be $43 \text{ mJ}/\text{m}^2$ (Luner, Zhang et al. 2012). In contrast, the dispersive surface energy of

milled AA was lower than SA at 38.8 mJ/m² but higher than either GA or PA. Table 3.5 also highlights the specific surface areas of milled SA and AA indicating that SA underwent the greatest increase in surface area on milling of the four diacids studied.

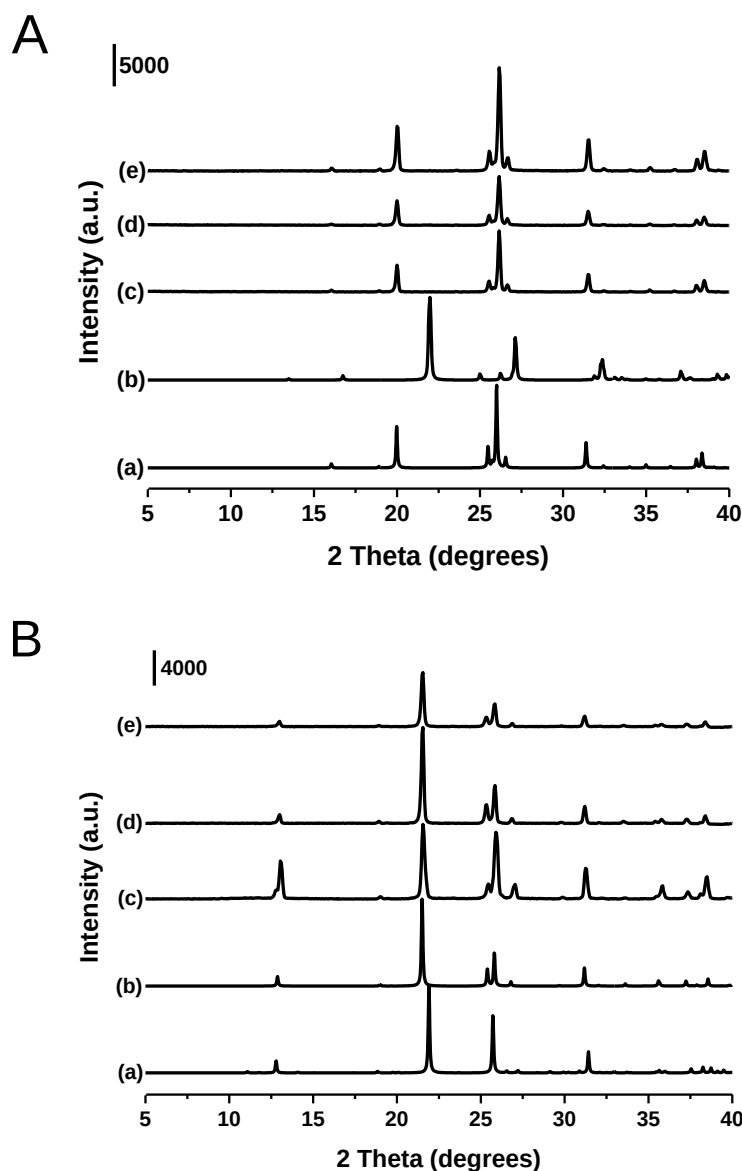


Figure 3.35 A) PXRD diffractograms of (a) CCDC generated single crystal structure of β -polymorphic SA (b) CCDC generated single crystal structure of α -polymorphic SA (c) unmilled crystalline SA (d) SA milled in the PBM at RT for 12 hours and (e) SA milled in the VBM at RT for 45 minutes. B) PXRD diffractograms of (a) CCDC generated single crystal structure of α -polymorphic AA (b) CCDC generated single crystal structure of β -polymorphic AA (c) unmilled crystalline AA (d) AA milled in the PBM at RT for 12 hours and (e) AA milled in the VBM at RT for 45 minutes.

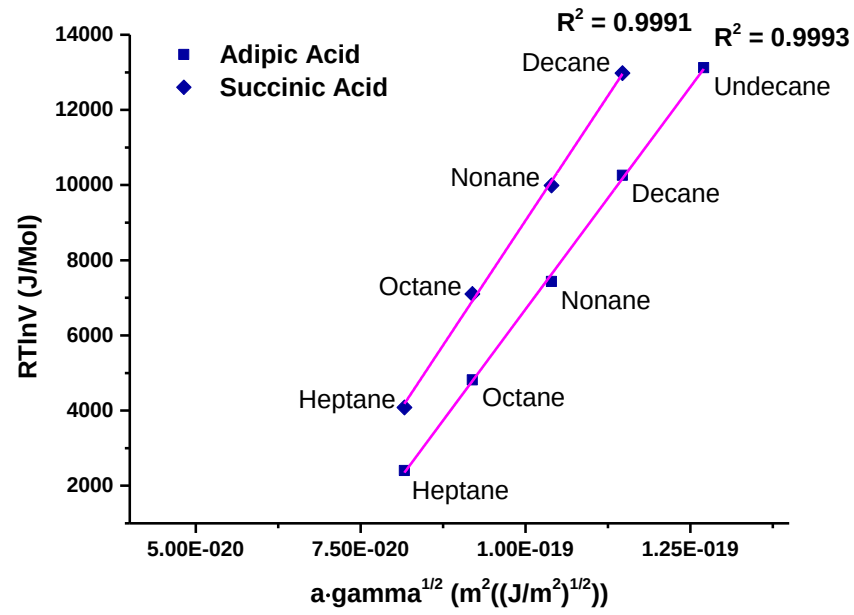


Figure 3.36 iGC surface energy plot of AA and SA milled separately in the PBM at RT for 12 hours.

3.7 CONCLUSIONS

The amorphisation of the model active pharmaceutical ingredient SDM in two ball mill types, the planetary ball mill and the vibratory ball mill was investigated with quantification of amorphous content determined by both DSC and NIR analyses. Although a similar level of amorphisation of SDM of 80% was found in both ball mill types, the vibratory ball mill resulted in much faster amorphisation kinetics relative to the planetary type ball mill. We also conducted a design of experiment analysis into the factors which affect the mechanical energy input relative to the milling temperature. Frequency was found to have the greatest effect on amorphous content followed by ball diameter and ball to powder mass ratio. Negative interaction effects were observed for each of the main ballistic factors relative to the mill temperature, indicating that as the temperature of the mill was reduced, each of the ballistic factors has a greater impact on the amorphisation of SDM.

In addition, bulk amorphous characterisation of high and low frequency milled SDM was performed by DSC analysis while surface characterisation was performed by iGC analysis. A significant increase in the surface energy associated with surface amorphisation of the high frequency milled system to 62 mJ/m² was observed relative to 48 mJ/m² for the unmilled crystalline material. In addition, heat of sorption analysis revealed a surface transition event which correlated with the exotherm observed on DSC analysis associated with surface crystallisation. No surface transition was evident on heat of sorption analysis of the low frequency milled system. However milling at low frequency led to an increase in the dispersive surface energy to 55 mJ/m² relative to the unmilled system. iGC analysis also suggested a similar increase in the Gutmann K_a number for both high and low frequency milled SDM systems.

Milling of a range of low T_g crystalline excipients was also performed. The observed polymorphic transformation of β -MAN to the metastable α polymorph as well as the dispersive surface energy values of the unmilled and milled systems, were in good agreement with previously reported results. Of the dicarboxylic acids, PA underwent a partial polymorphic transformation to the metastable α polymorph on milling, in contrast to glutaric acid, succinic acid and adipic acid all of which remained in the stable β -polymorph on milling.

CHAPTER 4

COMILLING STUDIES WITH BUDESONIDE AND LOW T_G EXCIPIENTS

4.1 INTRODUCTION

Budesonide is a hydrophobic steroid with low aqueous solubility, primarily administered by the pulmonary and oral routes for the treatment of inflammatory disorders such as asthma and Crohn's disease. Due to its poor solubility, and given that it is administered via the airways in the dry powder form, the particle size represents a critical characteristic of the solid-state form of the API from a formulation and bioavailability perspective (Hvizdos and Jarvis 2000). Tajber et al. have shown that the micromeritic properties of budesonide may be controlled by tuning of the conditions on spray drying (Tajber, Corrigan et al. 2009). However, spray drying has been shown to lead to the amorphous state of the API, characterised by a relatively high T_g of 89 °C (Nolan, Tajber et al. 2009). Micronisation by milling offers another formulation strategy to effect particle size control. However, due in part to its high T_g , budesonide has been shown to undergo mechanical activation in the planetary ball mill, resulting in the direct transformation from the crystalline to amorphous state (Dudognon, Willart et al. 2006).

In this chapter, the amorphisation tendency of budesonide in the vibratory ball mill on both room and cryo-temperature milling will be investigated. Additionally, crystalline budesonide will be comilled with a range of low T_g excipient dicarboxylic acids and a polyol in the vibratory ball mill at room temperature. The driven alloys formed will be assessed in terms of their crystallographic, thermal and sorption characteristics by PXRD, DSC and DVS analyses respectively. In addition, the amorphous content of budesonide in the comilled composites will be determined from the PXRD and DVS analyses, allowing the establishment of the relative order of the ability of the low T_g excipients to mitigate amorphisation on comilling at room temperature.

Co-cryomilling studies of budesonide with each of the low T_g excipients will also be performed, allowing a comparison of the effect of milling temperature on the solid-state properties of the driven alloys. The humidity induced phase separation of the alloys will be determined by DVS analysis and the composites will be analysed before and after crystallisation for crystallographic and morphological changes on crystallisation. Changes in the spectroscopic properties by FTIR analysis of the co-cryomilled composites before and after crystallisation will also be performed in

order to assess the potential for hydrogen bonding interaction on co-processing. The solubility of the diacids in amorphous budesonide will then be determined by the zero enthalpy extrapolation method and, in addition, the T_g of the co-thermally activated alloys will be determined, allowing for a comparison of the T_g reduction formed on co-mechanical versus co-thermal activation.

4.2 SOLID STATE CHARACTERISATION OF CRYSTALLINE AND AMORPHOUS BUDESONIDE

4.2.1 Thermal Analysis

Figure 4.1 shows the DSC thermograms of crystalline BD, BD milled for 15 hours in the PBM at RT and spray dried BD. The spray dried sample revealed a step change at 89 °C (± 0.6 °C) in the total heat flow signal associated with a glass transition event, with a subsequent crystallisation exotherm at 128 °C (± 0.8 °C).

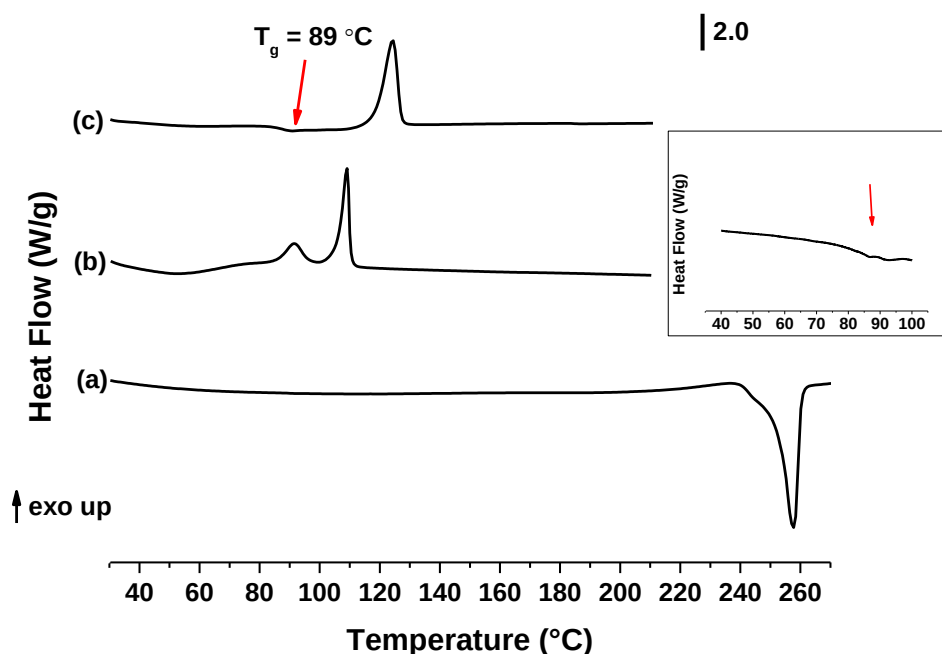


Figure 4.1 Total heat flow DSC thermograms showing (a) crystalline BD (b) BD milled in the PBM at RT for 15 hours and (c) spray dried BD. Inset highlights the reversing heat flow mDSC signal (2 °C/ minute) of PBM milled BD. Red arrows highlight glass transition events in the DSC thermograms.

In contrast, BD milled at RT in the PBM displayed a bi-modal crystallisation exotherm, at a reduced temperature relative to that observed in the spray dried sample with a T_c of 90 °C (± 0.9 °C) and 110 °C (± 0.7 °C), indicative of initial faster crystallisation of surface amorphous regions, followed by bulk crystallisation associated with the higher temperature exotherm (Chattoraj, Bhugra et al. 2011). The difference in the crystallisation behaviour on DSC analysis indicated the effect of route of formation on the physical properties of the amorphous state of BD. The

total heat flow signal for the milled sample did not reveal a T_g event due to the lower temperature surface crystallisation exotherm obscuring the region where the glass transition event was observed in the spray dried sample. As a result, the milled sample was analysed by modulated DSC analysis and the reversing heat flow signal, shown in the inset of Figure 4.1, revealed a step change at 89 °C (± 0.5 °C), indicating that the milling operation had led to the direct transformation of BD from the crystalline state into an amorphous state characterised by a step change in the reversing heat flow signal (i.e. a dynamic disorder).

4.2.2 Spectroscopic Analysis

The molecular structure of BD is shown in

Figure 4.2. The structure contains two carbonyl groups with one attached directly to the steroid ring structure (the quinonoid carbonyl) and the other attached to an aliphatic side chain (the alkyl carbonyl) in addition to two aliphatic hydroxyl groups. Budesonide thus contains both hydrogen bond donor (O-H) and hydrogen bond acceptor (O-H and C=O) groups which afford the potential for hydrogen bonding group interactions with excipients during processing (Bandi, Wei et al. 2004).

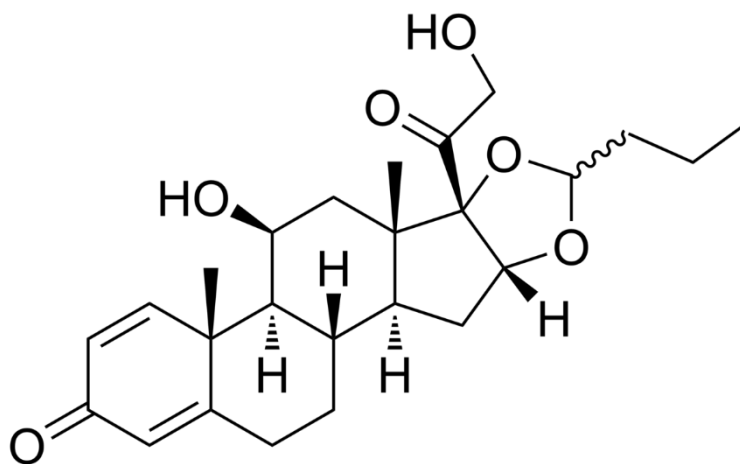


Figure 4.2 Molecular structure of budesonide.

Figure 4.3 reveals the FTIR spectrum of crystalline BD, in addition to both the spray dried and PBM milled forms of the API, which were shown to be amorphous by DSC. The peaks in the infrared spectrum of BD have previously been assigned in a study

reported by Ali et al. (Ali, Edwards et al. 2007). Figure 4.3 (a) shows the spectrum of crystalline BD revealing peaks in the 1600 to 1800 cm^{-1} region associated with C=O stretching. One of the peaks occurred at a lower wavenumber of 1666 cm^{-1} , and is associated with the quinonoid carbonyl, with a higher wavenumber peak at 1723 cm^{-1} being attributed to the alkyl carbonyl, as suggested by Ali et al. In addition, the 3400 -3600 cm^{-1} region, which is associated with O-H stretching, displayed a broad peak at 3492 cm^{-1} . Additionally, the C-O stretching peak was observed at 1096 cm^{-1} . These represent the key regions of the BD spectrum associated with hydrogen bonding groups. The spectra of the PBM milled and spray dried systems are also shown in Figure 4.3. The O-H stretching peak was shifted to a lower wavenumber in both amorphous systems from 3492 to 3423 cm^{-1} , while the quinonoid C=O peak underwent a shift from 1666 to 1655 cm^{-1} . Also, the C-O peak underwent a peak shift from 1096 to 1086 cm^{-1} on amorphisation.

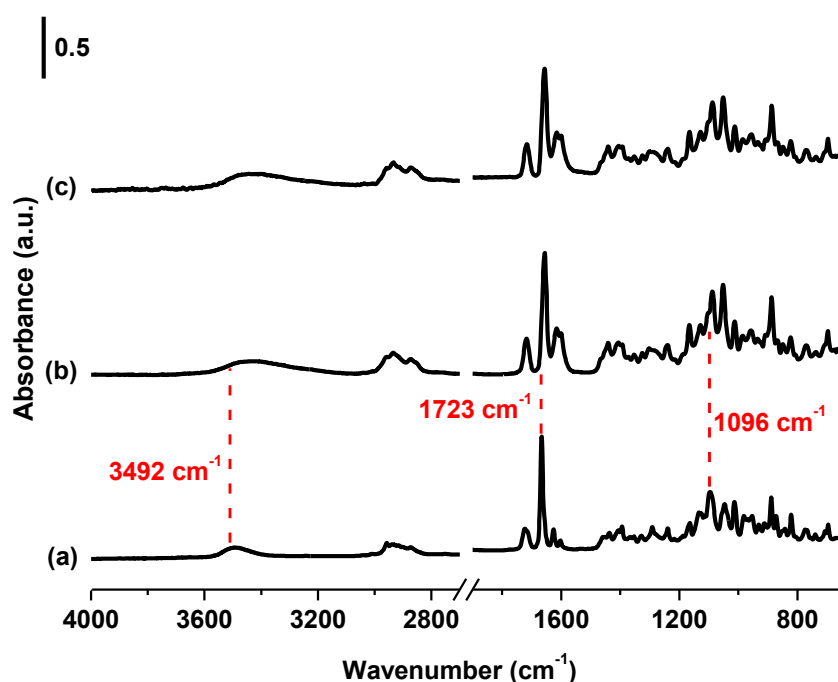


Figure 4.3 FTIR spectra of (a) crystalline BD and (b) BD milled in the PBM at RT for 15 hours and (c) spray dried BD. Dashed red lines highlight those peaks referred to in the text.

4.2.3 Sorption Analysis

Figure 4.4 shows the step sorption profile of the BD system milled in the PBM for 15 hours at RT. While the first sorption cycle did not reveal any mass loss event, a mass loss event was observed in the desorption cycle at 80% RH and 70% RH. The low tendency of water to act as a plasticiser of amorphous BD is most likely due to the compound's very low aqueous solubility.

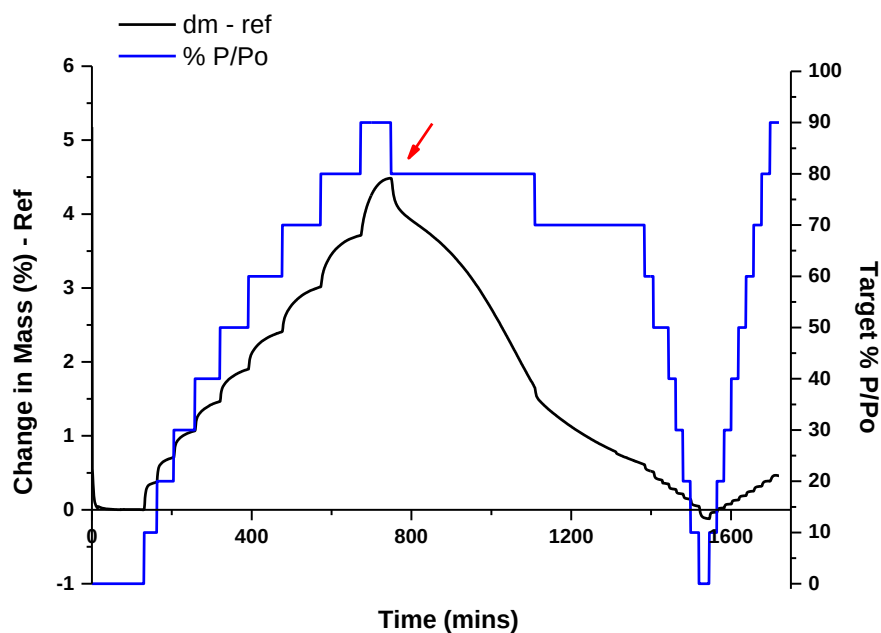


Figure 4.4 DVS stepwise sorption plot of BD milled in the PBM at RT for 15 hours, with water as the probe vapour. Red arrow indicates a mass loss event associated with crystallisation of BD.

4.3 COMILLING STUDIES OF CRYSTALLINE BUDESONIDE WITH LOW T_g EXCIPIENTS AT ROOM TEMPERATURE

4.3.1 PXRD Analysis

Crystalline BD was milled alone and comilled with each of the diacids, SA, GA, AA and PA and the polyol MAN at a 50% w/w composition in the VBM at RT for 60 minutes. Figure 4.5 (a) and (b) shows the PXRD diffractograms of crystalline starting material and BD milled alone respectively. A diffuse halo was observed on milling alone at RT, an indication that the material had undergone a milling induced crystalline to amorphous transformation. The milling time required for amorphisation of BD in the VBM appeared to be significantly less than the prolonged milling time required for the amorphisation of BD in the PBM, as previously described (Dudognon, Willart et al. 2006).

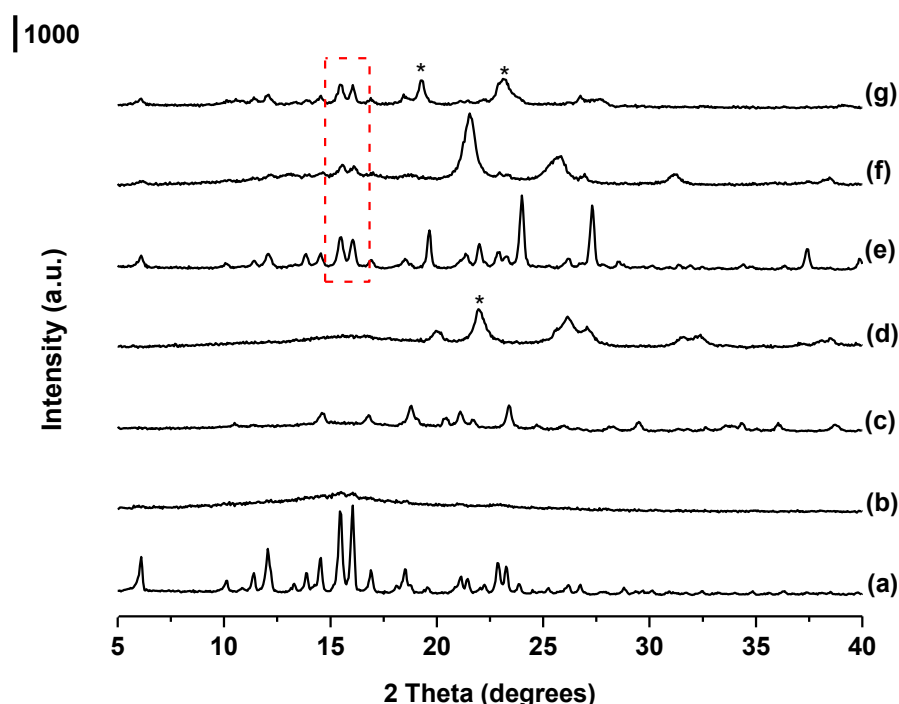


Figure 4.5 PXRD diffractograms of (a) crystalline BD, (b) BD milled in the VBM at RT for 60 minutes and crystalline BD comilled with (c) MAN, (d) SA, (e) GA, (f) AA and (g) PA at 50% w/w in the VBM at RT for 60 minutes. * Indicates peaks associated with α -polymorph of excipient. Red box indicates Bragg peaks associated with crystalline BD in the region 12.5° – 14.5° 2 θ .

As described in Chapter 3, milling in the VBM also led to much faster amorphisation kinetics for SDM relative to PBM milling, as quantified by NIR, PXRD and DSC. However, PBM milled BD was used as the amorphous standard when quantifying amorphous content of BD in order to ensure that the reduced milling time is in fact leading to a true amorphous state BD on milling. When comilled with crystalline β -polymorphic MAN, Figure 4.5 (c), no Bragg peaks associated with crystalline BD were observed in the diffractogram, indicating that comilling with MAN was unsuccessful at mitigating amorphisation of the API at RT. Comilling crystalline BD with SA, shown in Figure 4.5 (d), similarly did not yield any trace of crystalline BD in the diffractogram.

The PXRD diffractograms shown in Figure 4.5 (e), (f) and (g) for the BDGA, BDAA and BDPA RT comilled composites respectively, in contrast to the BDMAN and BDSA composites, revealed the presence of Bragg peaks in the 15-16° 2 θ region associated with crystalline BD, highlighted in the red box. However, the Bragg peaks of crystalline BD in the BDAA composite appeared of a reduced intensity relative to the BDGA and BDPA composites. The amorphous content of BD in each of these three systems was estimated by analysis of the integrated Bragg peaks due to crystalline BD at 6.3°, 12.2° and 15.4° 2 θ . These estimates of amorphous content are shown in . The amorphous content of BD in the comilled composites was determined to be 82% ($\pm$ 9%) on comilling with AA, 35% ($\pm$ 8%) on comilling with PA and 0% on comilling with GA. Thus the PXRD estimates indicated that, while comilling with GA led to the complete mitigation of amorphisation of BD at RT, both AA and PA led to partial mitigation of amorphisation on comilling, with PA leading to a greater level of mitigation of amorphisation relative to AA. Curtin et al. investigated the ability of the three diacids GA, AA and PA to mitigate amorphisation of salbutamol sulphate on comilling in the planetary ball mill at RT (Curtin, Amharar et al. 2013). They found that while GA led to the complete mitigation of amorphisation of salbutamol sulphate on comilling, both AA and PA led to partial mitigation with PA leading to a greater level of mitigation of amorphisation of salbutamol sulphate (% amorphous content on comilling with PA = 42% w/w) than AA (% amorphous content on comilling with AA = 46% w/w). Thus, the relative ability of the three diacids to mitigate amorphisation of crystalline BD in the vibratory ball mill at RT correlated reasonably well with their ability to mitigate amorphisation of salbutamol sulphate in the planetary ball mill at RT.

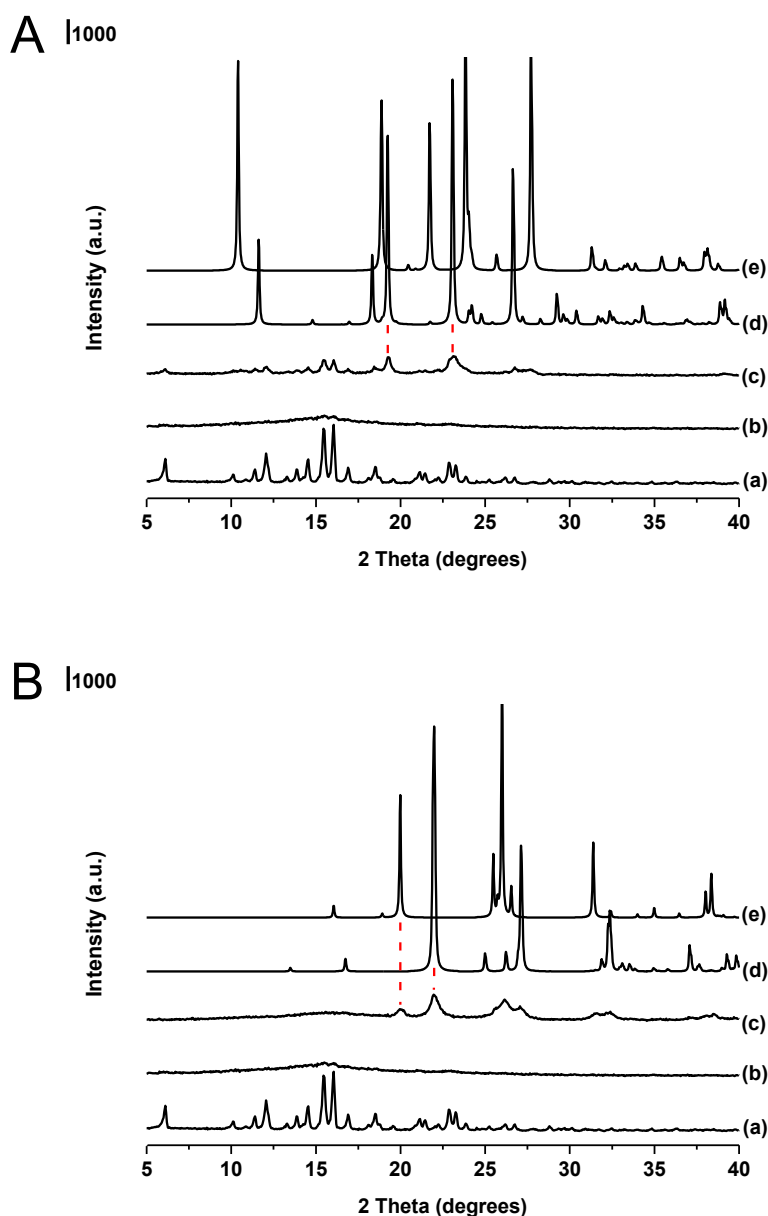


Figure 4.6 A) PXRD diffractograms of (a) crystalline BD, (b) VBM RT milled BD, (c) VBM RT comilled 50% w/w BDPA and CCDC generated PXRD patterns of (d) α -polymorphic PA and (e) β -polymorphic PA and B) PXRD diffractograms of (a) crystalline BD, (b) VBM RT milled BD, (c) VBM RT comilled 50% w/w BDSA and PXRD patterns generated from CCDC single crystal data of (d) α -polymorphic SA and (e) β -polymorphic SA. Red lines indicate peaks associated with crystalline excipient.

While only three of the composite systems revealed evidence for crystalline BD on PXRD analysis, each of the composites revealed Bragg peaks associated with crystalline excipient. Figure 4.6A indicates that PA underwent a complete transformation to the α -polymorphic form, even though the starting material used was the thermodynamically stable β -polymorphic form. The diffractogram showed

no trace of the β polymorph of PA in the comilled system. Figure 4.6 (b) reveals peaks associated with both α and β -polymorphs of SA in the BDSA comilled composite, indicating that SA underwent a partial polymorphic transformation to the metastable polymorph on comilling with BD at RT. In contrast, GA was present in the β -polymorphic form both before milling and after 60 minutes of comilling. PXRD analysis of the composites formed on comilling BD with GA, AA and MAN indicated that each of the excipients were present in the stable β -polymorphic form, as shown in Appendix A-1, in addition to Bragg peaks associated with crystalline BD.

4.3.2 DVS Analysis

While PXRD analysis could be used to identify crystallinity in the composites, in order to further characterise the amorphous phase of the composite systems formed on comilling BD at RT, DVS analysis was conducted on each of the comilled systems using water as the probe vapour. Each of the composite systems was exposed to a stepwise isotherm of 10% per step from 0 – 90% RH at 25 °C. The sorption profile of the BDGA comilled composite revealed no mass loss event at any RH value up to 90% in the sorption or desorption step. This suggested that, in conjunction with the PXRD crystalline nature of the system, the system was fully crystalline on comilling at RT.

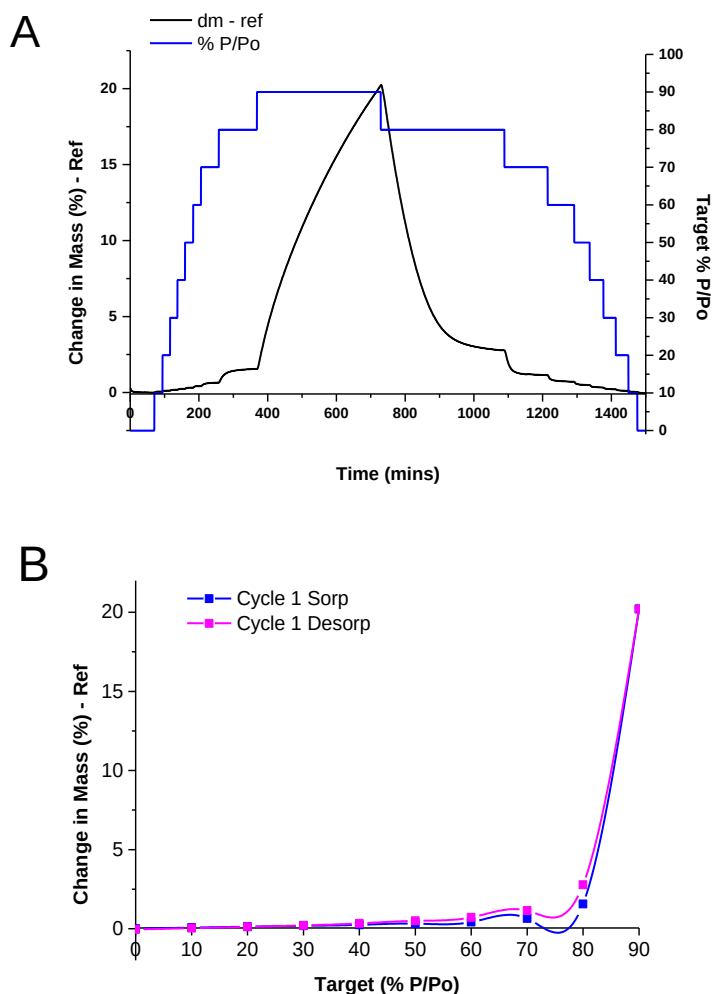


Figure 4.7 DVS A) stepwise and B) isotherm plots of crystalline BD comilled with GA in the VBM at RT at 50% w/w for 60 minutes.

Figure 4.8A shows the DVS analysis of the BDPA RT comilled composite which showed an initial mass loss event at 30% RH, with further mass loss events at 40, 50, 60 and 70% RH. The mass loss events indicated the crystallisation of the amorphous phase BD in the composite system, which was estimated by PXRD analysis to be 35% ($\pm 8\%$) w/w. Interestingly however, the onset crystallisation RH was significantly reduced relative to amorphous BD milled alone (90% RH), indicating that comilling with PA had led to the formation of a composite system which was plasticised more easily by water vapour. DVS analysis of the BDAA RT comilled composite, shown in Figure 4.8B, indicated a single mass loss event, associated with crystallisation of BD, at 80% RH.

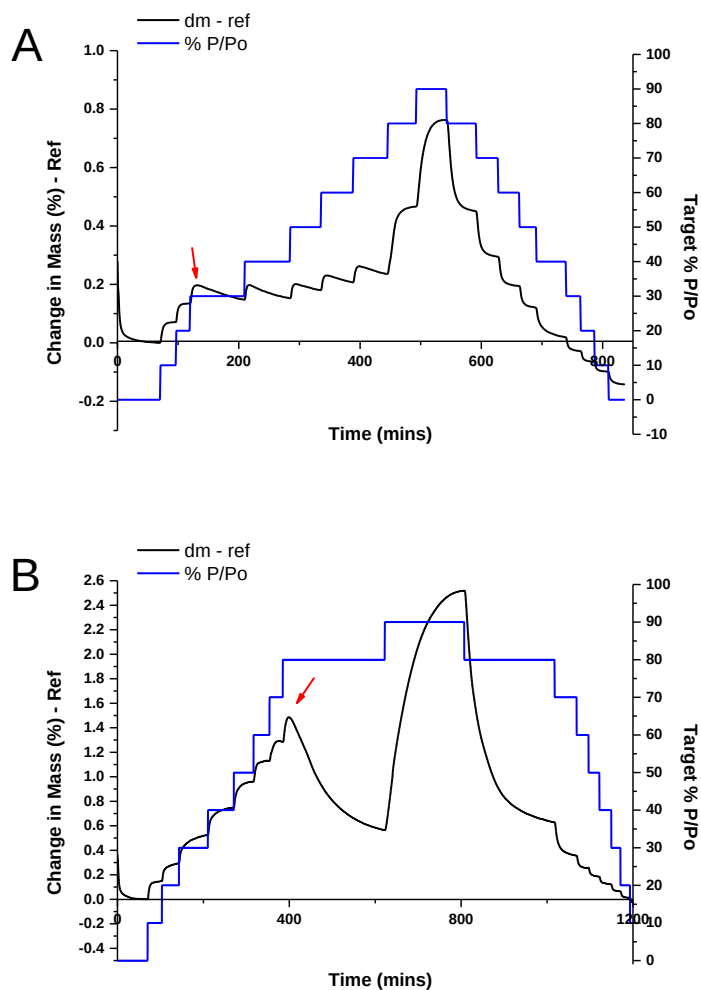


Figure 4.8 DVS stepwise sorption plots of crystalline BD comilled with A) PA and B) AA in the VBM at RT at 50% w/w composition for 60 minutes. Red arrows indicate onset of mass loss events.

The sorption plot of the composite formed on comilling BD with SA, shown in Figure 4.9A, indicated a mass loss event at 90% RH. The stepwise sorption plot of the RT comilled BDMAN system (Figure 4.9F) showed no mass loss event over the entire humidity range, indicating that MAN, in contrast to the diacids, may have led to the stabilisation of the amorphous phase of BD to plasticisation by water vapour on comilling.

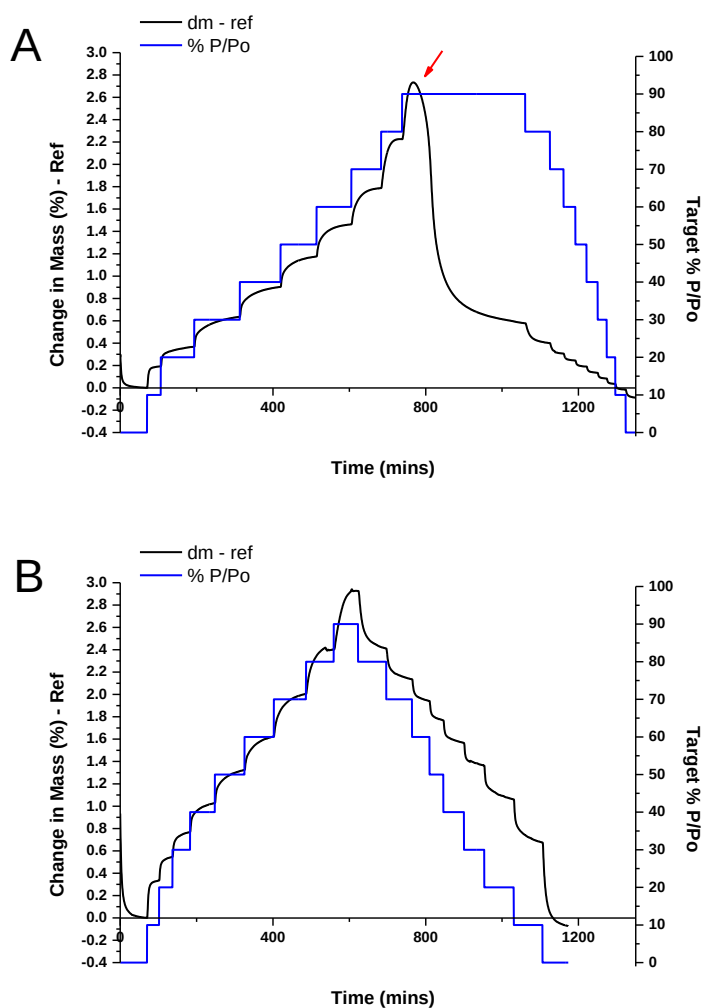


Figure 4.9 DVS stepwise sorption plots of crystalline BD comilled with A) SA and B) MAN in the VBM at RT at 50% w/w for 60 minutes. Red arrow indicates onset of a mass loss event.

The sorption isotherms of the BD: excipient RT comilled composites, shown for comparison in Figure 4.10, were used to quantify the amorphous content of BD in each of the milled composites at 30% RH as shown in . As the BDPA composite showed a mass loss event at 30% RH, the amorphous content was determined at 20% RH for this system. The amorphous standard used to quantify the amorphous content was BD milled for 15 hours in the PBM at RT, as such a prolonged milling time has previously been reported to fully amorphise BD (Dudognon, Willart et al. 2006). The DVS quantification results confirmed the relative order in which the diacids were successful at mitigating amorphisation of BD at RT, as suggested by the estimations from PXRD analysis. While comilling at RT with GA led to the complete mitigation of amorphisation of BD, comilling with both PA and AA led to partial mitigation of amorphisation with PA showing a greater level of amorphous content

reduction (% amorphous content = 28% w/w) relative to AA (% amorphous content = 79% w/w). In contrast, neither SA nor MAN were successful at mitigating amorphisation to any extent. These quantification results are in reasonably good agreement with the PXRD estimates of amorphous content.

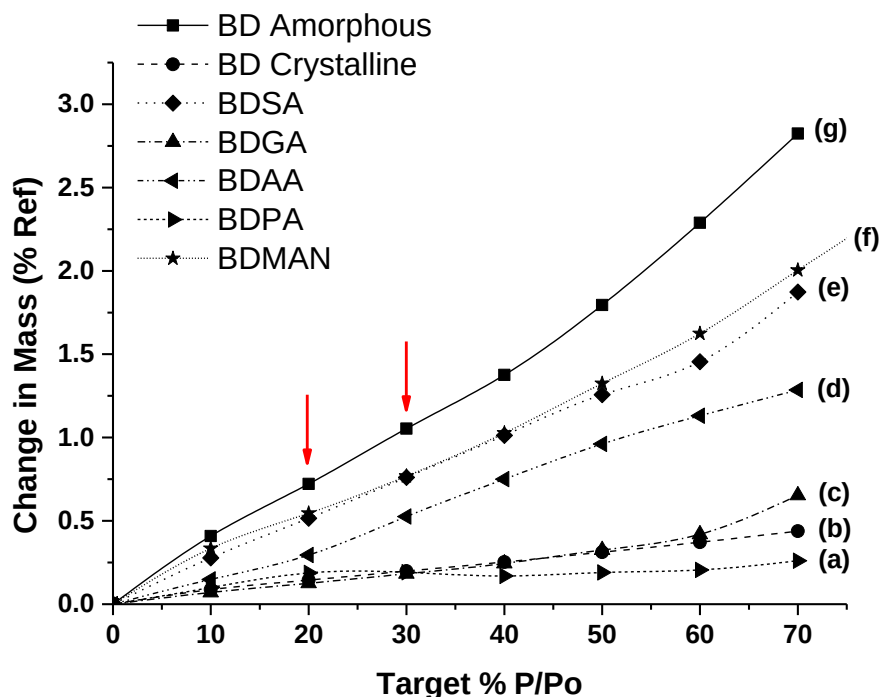


Figure 4.10 Sorption isotherms from 0-70% RH of (b) crystalline BD, (g) VBM RT (60 minutes) milled amorphous BD and crystalline BD comilled with (a) PA, (c) GA, (d) AA, (e) SA and (f) MAN at 50% w/w in the VBM at RT for 60 minutes. Red arrows indicate the target P/Po (20% and 30%) at which amorphous content were determined.

4.3.3 Thermal Analysis

Figure 4.11 (f) shows the total heat flow DSC thermogram of BD milled alone for 60 minutes at RT revealing a bimodal crystallisation exotherm with T_c values, detailed in , of 86 °C (crystallisation of surface amorphous regions) and 103 °C (crystallisation of bulk amorphous regions). On comilling with MAN at RT, the crystallisation exotherm was increased to a higher temperature ($T_c = 117$ °C) relative to either the surface or bulk crystallisation exotherms of the BD system milled alone. In addition, as a result of the crystallisation exotherm being pushed to a higher temperature, a glass transition event was observed in the total heat flow signal of the BDMAN composite at 88 °C (± 0.7 °C) (Figure 4.12A, inset) indicating that MAN did not result in T_g reduction on comilling with BD in spite of the low T_g of

MAN of 13 °C (Willart, Dudognon et al. 2006). In contrast, Caron et al reported the T_g lowering effect of MAN when comilled with the high T_g material trehalose ($T_g = 120$ °C) (Caron, Willart et al. 2007). Analysis of the melt endotherm of the comilled BDMAN composite revealed no decrease in the T_m of the composite ($T_m = 167.8$ °C (± 0.6 °C)) relative to crystalline MAN, which displayed a $T_m = 168.4$ (± 0.4) °C, as shown in Figure 4.11 (f), indicating immiscibility between BD and MAN in the liquid state.

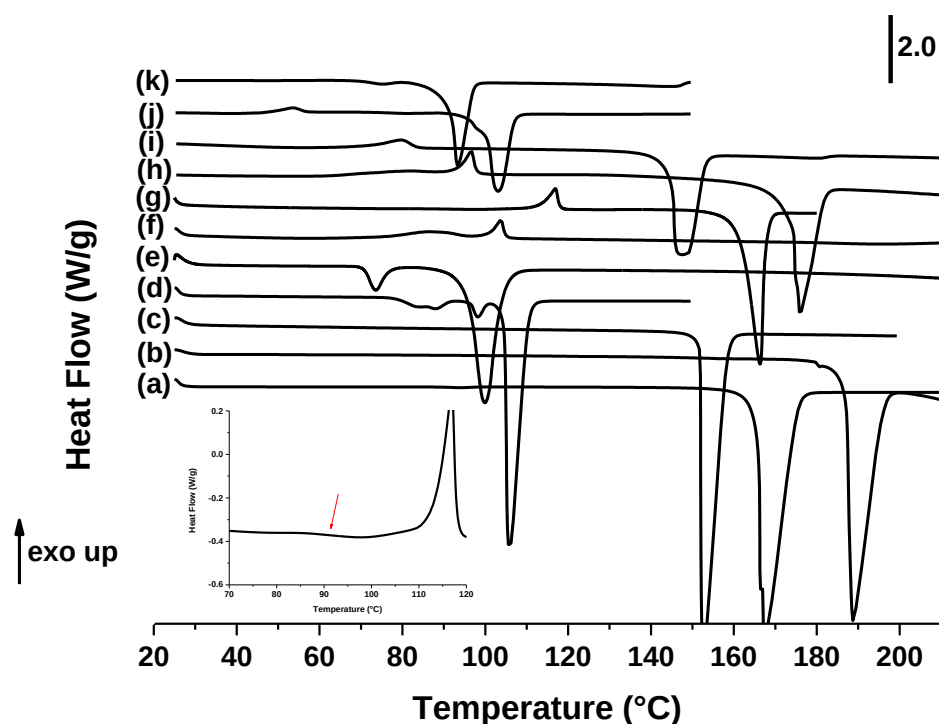


Figure 4.11 Total heat flow DSC thermograms of (a) crystalline MAN, (b) crystalline SA, (c) crystalline AA, (d) crystalline PA, (e) crystalline GA, (f) BD milled in the VBM at RT for 60 minutes and crystalline BD comilled in the VBM at RT at 50% w/w for 60 minutes with crystalline (g) MAN, (h) SA, (i) AA, (j) PA and (k) GA. Inset thermogram highlights the BDMAN RT comilled composite revealing a T_g in the total heat flow signal. (Red arrow indicates glass transition event in the DSC thermogram.)

In contrast to MAN, comilling with SA at RT displayed a single crystallisation exotherm with a $T_c = 96$ °C in the total heat flow signal, shown in Figure 4.11 (h). In addition, analysis of the melt endothermic peak of the comilled BDSA system (subsequent to the crystallisation exotherm) indicated a reduced T_m at 176 °C relative to crystalline SA of 189 °C, indicating the formation of a eutectic melt, and miscibility between SA and BD in the liquid state.

The composite formed on RT comilling BD with AA at 50% w/w showed a single crystallisation exotherm with a $T_c = 79\text{ }^{\circ}\text{C}$, while the composite formed with PA displayed an exothermic peak with a $T_c = 55\text{ }^{\circ}\text{C}$. In contrast, the composite formed on comilling GA with crystalline BD did not reveal any crystallisation exotherm, indicating a completely crystalline system on comilling. Interestingly, in addition to SA, each of the composites formed with GA, AA and PA led to T_m reduction relative to the T_m of the excipient, as detailed in Table 4.1, an indication of miscibility in the liquid state between each of the diacids and BD, in contrast to the polyol MAN which displayed no T_m reduction in the presence of BD relative to the T_m of the pure substance ($168\text{ }^{\circ}\text{C}$).

Table 4.1 Amorphous content, thermal and crystallographic characteristics of milled BD and comilled BD: excipient composites in the VBM at RT.

	$T_c\text{ (}^{\circ}\text{C)}$ (StD)	$T_m\text{ (}^{\circ}\text{C)}$ (StD)	$T_g\text{ (}^{\circ}\text{C)}$ (StD)	% Amorphous Content PXRD (StD)	% Amorphous Content DVS (StD)	Excipient Polymorph
BD	86 (0.3) / 103 (0.5)	***	89 (0.8)	*	94 (2)	-
SA	-	189 (0.2)	-	-	-	β
GA	-	98 (0.1)	-	-	-	β
AA	-	152 (0.2)	-	-	-	β
PA	-	106 (0.3)	-	-	-	β
MAN	-	168 (0.2)	-	-	-	β
BDSA	96 (0.9)	176 (0.2)	75 (0.6) / 89 (0.6)	*	106 (7)	α/β
BDGA	**	93 (0.3)	45 (0.8)	0 (0)	2 (1)	β
BDAA	79 (0.4)	147 (0.5)	67 (0.8)	82 (9)	79 (5)	β
BDPA	55 (0.8)	103 (0.3)	42 (0.5)	35 (8)	28 (6)	α
BDMAN	117 (0.1)	168 (0.2)	88(0.4)	*	97 (2)	β

*No Bragg peaks associated with crystalline BD. **Fully crystalline on comilling at RT. ***BD degrades on melting.

The glass transition temperature represents a critical parameter in terms of the stability of the amorphous phase generated during the milling operation towards crystallisation (Descamps, Willart et al. 2007). Indeed, the reduction in the T_g of the API on comilling with low T_g excipient is hypothesised in the current context to be essential to the mechanism by which the excipient may potentially result in the

mitigation of amorphisation on comilling. However, the crystallisation exotherms for the BD: excipient composites, as well as BD milled alone, obscured the T_g in the total heat flow signals shown in Figure 4.11 (with the exception of the BDMAN composite). The T_g values were therefore determined by modulated DSC analysis and are shown in Figure 4.12 and are also detailed in . The reversing heat flow signal of the BDMAN composite indicated that the T_g of the composite was the same as that observed in the total heat flow signal, at 89 °C, and was also the same as amorphous BD milled alone, confirming the inability of MAN to effect a reduction in the T_g of BD on comilling at RT.

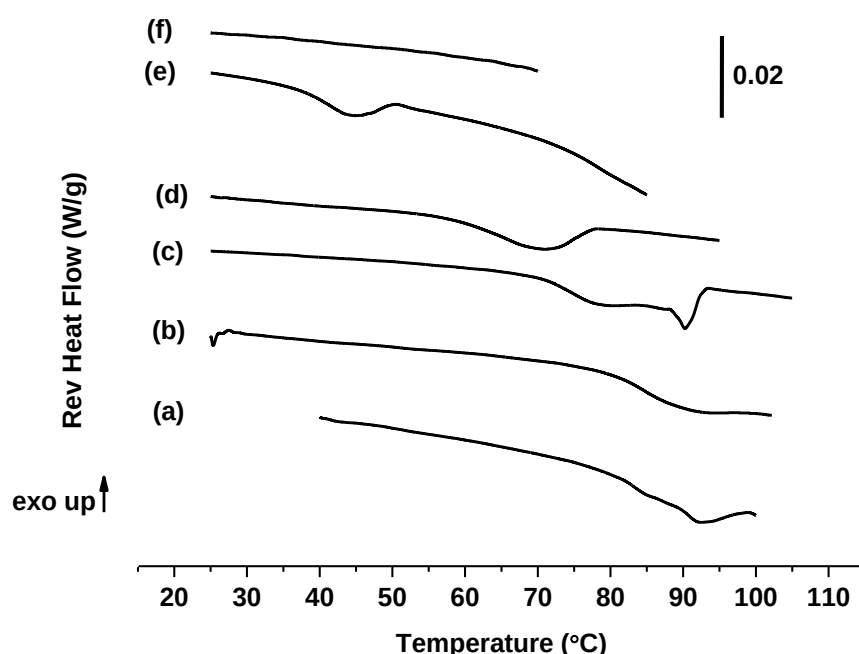


Figure 4.12 Reversing heat flow modulated DSC thermograms of (a) BD milled in the VBM at RT for 60 minutes and crystalline BD comilled in the VBM at RT at 50% w/w for 60 minutes with crystalline (b) MAN, (c) SA, (d) AA, (e) PA and (f) GA.

In contrast, the BDSA comilled composite displayed a T_g at 75 °C with a second enthalpic relaxation event at 89 °C indicating that the RT comilled system possibly consisted of both a composite BDSA phase with a slightly reduced T_g , together with separate phases of amorphous BD and crystalline SA (shown to be present in both the α and β -polymorphic form by PXRD analysis). Comilling crystalline BD with AA at RT led to a T_g reduction to 68 °C, relative to 89 °C for BD milled alone. In contrast PA resulted in a T_g reduction to 42 °C on comilling at RT. The reversing heat flow

signal for GA showed no sign of a glass transition event, again providing an indication that the system was completely crystalline on comilling. As a result, planetary ball milled amorphous BD was comilled with crystalline β -GA at 50% w/w at RT. After 9 minutes of comilling, the T_g of the sample was determined to be 45 °C, as highlighted in . As shown in Appendix A-I Figure A-I.8, PXRD analysis indicated that comilling amorphous BD with crystalline GA for 60 minutes led to the regeneration of crystalline BD.

4.4 CO-CRYOMILLING STUDIES OF BUDESONIDE WITH LOW T_g EXCIPIENTS

4.4.1 PXRD Analysis

Budesonide was milled alone for 45 minutes in the VBM at CT. PXRD analysis of the cryomilled system, as shown in Figure 4.13A (b) revealed a broad halo characteristic of the amorphous state indicating that a crystalline to amorphous transformation had occurred.

BD was also comilled at CT with each of the diacids, SA, GA, AA and PA and the polyol MAN at CT for 45 minutes at a 50% w/w composition. Figure 4.13A (c) shows the diffractogram for the BDMAN co-cryomilled composite indicating no peaks associated with crystalline BD. However, peaks associated with crystalline MAN were observed indicating that the excipient remained crystalline on comilling at CT. A comparison of the diffractograms of the RT and CT BDMAN comilled composites, shown in Figure 4.13B (e) and (f) respectively, revealed that the Bragg peaks associated with MAN were broader and apparently reduced in intensity on comilling at CT relative to the RT comilled composite. However, the Bragg peaks were comparable between the two systems, with no new Bragg peaks evident in the CT comilled system, indicating that, as for the RT comilled composite, the CT comilled composite contained MAN in the β -polymorphic form (i.e. MAN had not undergone any polymorphic transformation on comilling with BD at CT).

Figure 4.13A (d) shows the PXRD diffractogram for the BDSA co-cryomilled composite. As for the BDSA composite comilled at RT, the CT system does not contain any peaks associated with crystalline BD. However, broad peaks were evident in the diffractogram associated with crystalline SA. Figure 4.13B (a) and (b) compares the BDSA RT and CT comilled composites respectively and indicates that the CT comilled composite, similar to the RT composite, contained peaks associated with both α and β -polymorphic forms of SA. This indicates that on comilling at both RT and CT, SA underwent a partial transformation to the α -polymorph. However, similar to the BDMAN system, the Bragg peaks associated with crystalline SA appeared to be reduced in intensity relative to the RT comilled composite.

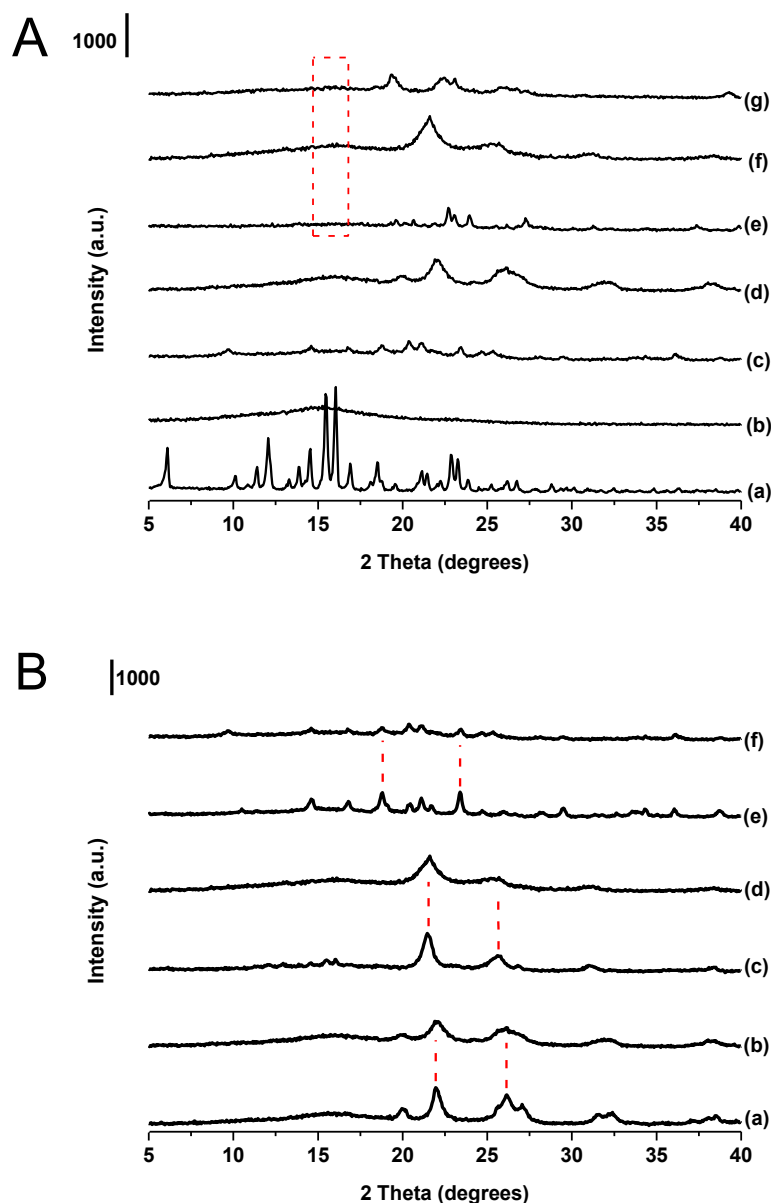


Figure 4.13 PXRD diffractograms of A) (a) crystalline BD (b) BD milled in the VBM at CT and BD comilled in the VBM at CT at 50% w/w with (c) MAN, (d) SA, (e) GA, (f) AA and (g) PA (red box indicates region where Bragg peaks associated with crystalline BD would be expected in the region 12.5° – 14.5° 2θ) and B) the composites formed on comilling crystalline BD at 50% w/w with (a) SA at RT, (b) SA at CT, (c) AA at RT, (d) AA at CT, (e) MAN at RT and (f) MAN at CT. (Red lines indicate Bragg peaks associated with crystalline excipient.)

The comilled composite formed between BD and AA, shown in Figure 4.13A (f) was PXRD amorphous for BD but revealed a broad peak at 21.6° 2θ associated with crystalline β -polymorphic AA. Figure 4.13B (c) and (d) compares the PXRD diffractograms of the BDAA composites formed at RT and CT respectively. The peak associated with β -polymorphic AA appeared broader and of reduced intensity compared to that observed in the RT comilled system, similar to the observation for

SA and MAN comilled composites While reduced intensity Bragg peaks associated with crystalline BD were detected in the RT BDAA comilled composite, no such peaks were observed in the composite comilled at CT. The observed reduction in intensity and broader nature of the peaks associated with the crystalline excipients (AA, SA and MAN) could be due to the lower temperature of the mill resulting in a greater crystallite size reduction of the excipient and thus greater peak broadening in PXRD analysis (Dujardin, Willart et al. 2013).

The diffractogram shown in Figure 4.13A (e) shows the PXRD diffractogram of the composite formed on co-cryomilling crystalline BD with GA. In contrast to the RT comilled system, no peaks associated with crystalline BD were detected on comilling at CT. Interestingly, peaks associated with crystalline GA were observed in the diffractogram associated with both the α and β -polymorphic forms, as highlighted in Figure 4.14 (a), with the Bragg peaks at 22.3° 2θ being characteristic of the α -polymorph while the Bragg peak at 23.2° 2θ is characteristic of the β -polymorph.

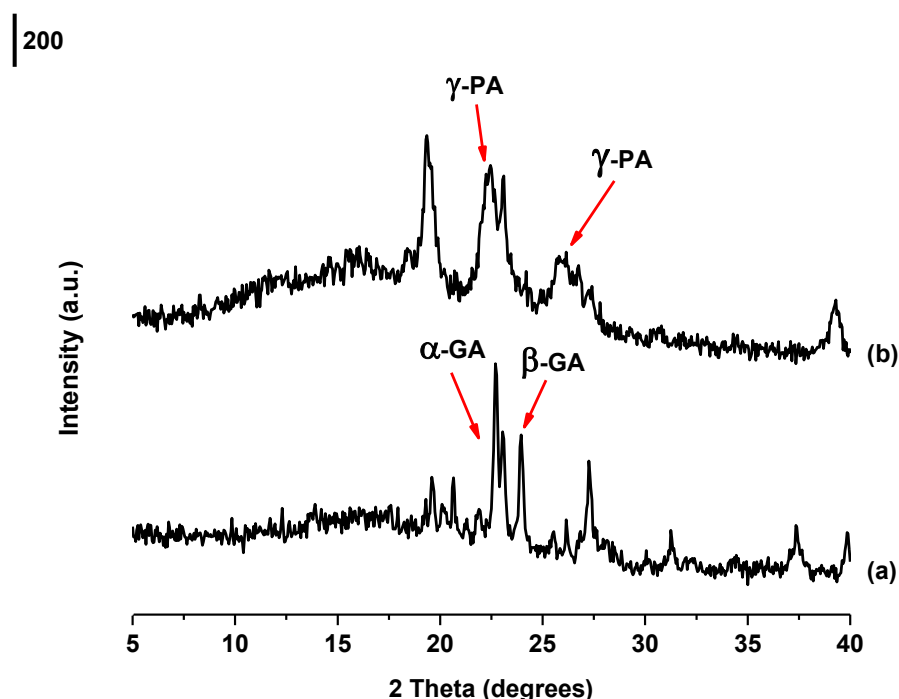


Figure 4.14 PXRD diffractograms of (a) crystalline BD comilled in the VBM at CT at 50% w/w for 45 minutes with (a) GA and (b) PA.

Analysis of the diffractogram for the BDPA co-cryomilled composite in Figure 4.13A (g) indicated no PXRD Bragg peaks associated with crystalline BD, in contrast to the RT comilled system (shown in Figure 4.5). However, peaks associated with the γ -polymorph of pimelic acid were observed, as highlighted in Figure 4.14 (b). The Bragg peaks of the γ -polymorphic form of PA are assigned in Appendix A-III.

4.4.2 Thermal Analysis

Figure 4.15 (f) shows the total heat flow thermogram of BD cryomilled alone for 45 minutes revealing a bi-modal exothermic crystallisation event associated with surface ($T_c = 94\text{ }^{\circ}\text{C}$) and bulk ($T_c = 111\text{ }^{\circ}\text{C}$) crystallisation, which was similar to that observed for BD milled alone at RT in both the PBM (shown in Figure 4.1) and VBM (shown in Figure 4.11). However, a comparison of the T_c values reported in and indicates that both the surface and bulk crystallisation exotherms were higher for the cryomilled BD system relative to the RT milled system.

The thermogram shown in Figure 4.15 (b) of the composite formed on co-cryomilling BD with MAN revealed a single crystallisation event with a $T_c = 120\text{ }^{\circ}\text{C}$, which is significantly higher than the bulk crystallisation exotherm of BD cryomilled alone ($T_c = 111\text{ }^{\circ}\text{C}$). The crystallisation exotherm is also slightly higher than the exotherm observed in the BDMAN composite comilled at RT ($T_c = 117\text{ }^{\circ}\text{C}$). In addition, due to the higher crystallisation temperature of the BDMAN composite, a T_g event was observed in the total heat flow signal of the CT comilled composite at $88\text{ }^{\circ}\text{C}$, shown in the inset of Figure 4.15, indicating that on comilling at CT, as well as at RT, MAN was unable to effect a T_g reduction of BD. The composite formed on co-cryomilling with AA, shown in Figure 4.15(h), revealed a crystallisation exotherm with a T_c of $88\text{ }^{\circ}\text{C}$, while the BDSA composite revealed a crystallisation exotherm with a T_c of $98\text{ }^{\circ}\text{C}$, relatively higher than the composite formed with AA. A comparison of the T_c values of the systems comilled at RT (shown in Table 4.1) reveals that the T_c of the CT comilled systems are higher than those observed for the RT comilled systems.

Thermal analysis of the co-cryomilled BDGA composite, shown in Figure 4.16A (j) revealed a single exothermic crystallisation event, with a T_c of $66\text{ }^{\circ}\text{C}$, associated with a crystallisation event, which contrasts with the composite formed at RT, which was crystalline and showed no crystallisation exotherm on DSC analysis. Interestingly, the composite formed on co-cryomilling BD with PA revealed a crystallisation

exotherm with a $T_c = 67^\circ\text{C}$, indicating that both GA and PA reduced the crystallisation of amorphous BD on comilling to a similar extent. Additionally, a comparison of the T_c of the BDPA composite comilled at RT, with a value of 55°C (Table 4.1), reveals that the co-cryomilled has a higher T_c .

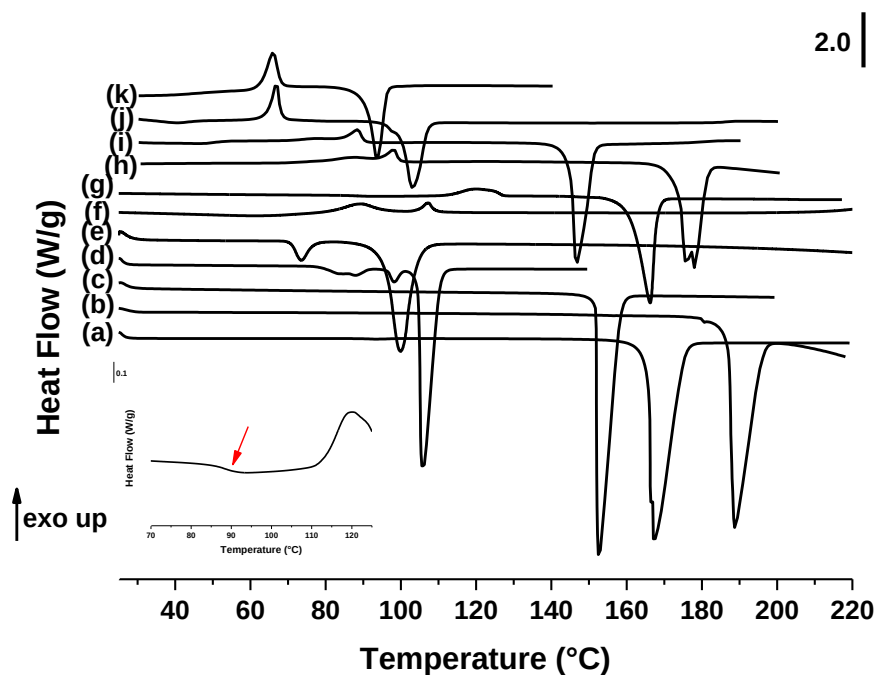


Figure 4.15 Total heat flow thermograms of (a) crystalline MAN, (b) crystalline SA, (c) crystalline AA, (d) crystalline PA, (e) crystalline GA, (f) BD milled in the VBM at CT for 45 minutes and crystalline BD comilled in the VBM at CT at 50% w/w for 45 minutes with (g) MAN, (h) SA, (i) AA, (j) PA and (k) GA. (Red arrow indicates glass transition event in the DSC thermogram.)

Table 4.2 Thermal and crystallographic characteristics of milled BD, unmilled crystalline excipients and comilled 50% w/w BD: excipient composites in the VBM at CT.

	T_c (°C) (StD)	T_m (°C) (StD)	T_g (°C) (StD)	Excipient Polymorph
BD	94 (0.3) /111 (0.4)	*	89 (0.4)	-
SA	-	189 (0.2)	-	β
GA	-	98 (0.1)	-	β
AA	-	152 (0.2)	-	β
PA	-	106 (0.3)	-	β
MAN	-	168 (0.2)	-	β
BD:SA	98 (0.9)	176 (0.3)	72 (0.5)	α/β
BD:GA	66 (1.2)	94 (0.1)	43(0.6)	α/β
BD:AA	88 (0.5)	147 (0.2)	58 (0.9)	β
BD:PA	67 (0.7)	104 (0.1)	43 (0.8)	γ
BD:MAN	120 (0.2)	167 (0.2)	88 (0.4)	β

*BD degrades on melting

As the crystallisation event in the total heat flow signals shown in Figure 4.15 obscured the glass transition temperature region (with the exception of the BDMAN composite), the BD: excipient co-cryomilled composites were analysed by modulated DSC analysis, with the reversing signal of the systems shown in Figure 4.16 and detailed in Table 4.2.

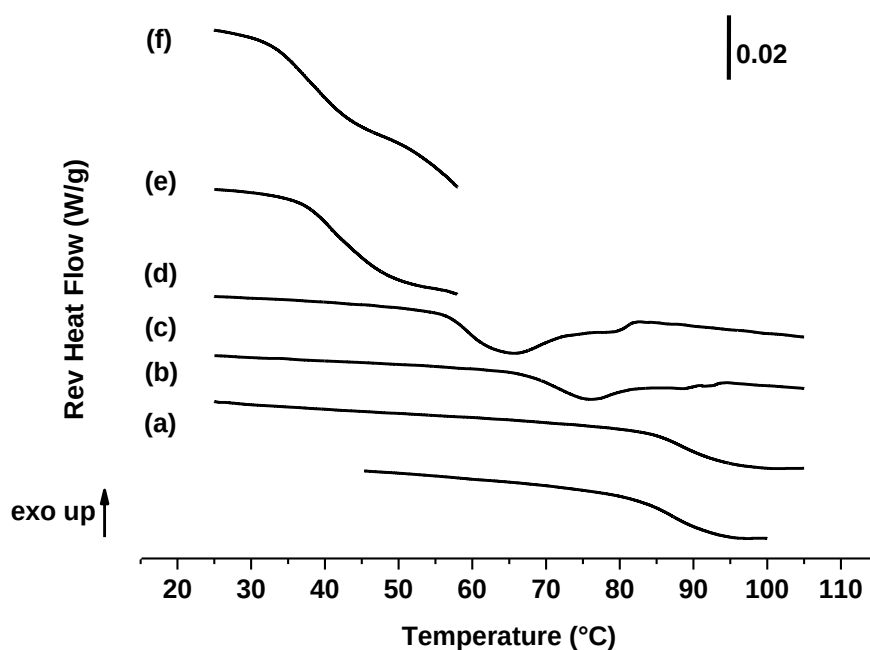


Figure 4.16 Reversing heat flow modulated DSC thermograms of (a) VBM CT milled BD for 45 minutes and crystalline BD comilled in the VBM at CT at 50% w/w for 45 minutes with (b) MAN, (c) SA, (d) AA, (e) PA and (f) GA.

Interestingly, both GA and PA showed a similarly reduced T_g on co-cryomilling (relative to BD cryomilled alone) of 43 °C. This correlated with the similarly reduced crystallisation exotherm observed in the total heat flow scans of both composites. Additionally, the T_g of the BDPA composite formed at CT was similarly reduced to that formed at RT (shown in , $T_g = 42$ °C) indicating a similar level of T_g reduction at both RT and CT comilling with PA. In contrast, comilling with SA at CT led to a T_g reduction to 72 °C, as shown in the reversing signal in Figure 4.16 (d). This value is less than that observed on comilling at RT, which appeared to show two T_g events at 75 °C and 89 °C. In contrast, comilling with AA at CT led to a T_g of 58 °C, compared to a T_g reduction at RT of 67 °C.

Interestingly, the T_g reduction of the BD: excipient composites broadly correlated with the relative ability of the excipients to mitigate amorphisation on comilling at RT, as described in Section 4.3. Both GA and PA both reduced the T_g of the API to the greatest extent on comilling at CT, and, on RT comilling, both GA and PA led to the greatest mitigation of amorphisation on comilling. Comilling at RT with AA led to a T_g reduction to 67 °C, and led to partial mitigation of amorphisation, but less than that observed on comilling with either GA or PA. In contrast, SA led to a partial T_g

reduction to 78 °C on comilling at RT and, in addition, showed no capacity to mitigate amorphisation on comilling at RT as quantified by DVS analysis.

4.5 PHASE SEPARATION STUDIES FROM THE CO-CRYOMILLED DRIVEN ALLOYS

Mechanical activation of BD on milling at both RT and CT led to the formation of an amorphous state characterised by a T_g of 89 °C. Comilling the API at RT with the diacids GA, PA and AA led to varying degrees of mitigation of amorphisation of BD at RT, as described in Section 4.3. However, comilling at CT led to the amorphisation of BD for all systems studied. The 50% w/w co-cryomilled composites were analysed in the DVS in order to assess their phase separation properties using water as the probe vapour. The aim was to characterise the crystallographic, morphological and spectroscopic characteristics of the crystallisation process from the driven alloys, and in addition, to compare the low T_g excipients in terms of their influence on the sorption properties and stability of amorphous BD on comilling.

4.5.1 Budesonide and Glutaric Acid Co-Cryomilled Composite

Figure 4.17A shows the stepwise sorption plot of the 50% w/w BDGA CT comilled composite, revealing a single mass loss event at 50% RH associated with crystallisation of the amorphous API. This is in contrast to the RT comilled system, shown in Figure 4.7A, which did not display any mass loss event as BD was fully crystalline on comilling at RT. In contrast to BD cryomilled alone, which underwent a crystallisation event at 90% RH in the second sorption cycle, the reduction in the crystallisation RH indicated that the amorphous composite formed on comilling with GA led to an alloy which was more sensitive to plasticisation by water, possibly due to a reduction in the RH_g and consequently the RH_c of amorphous BD on comilling.

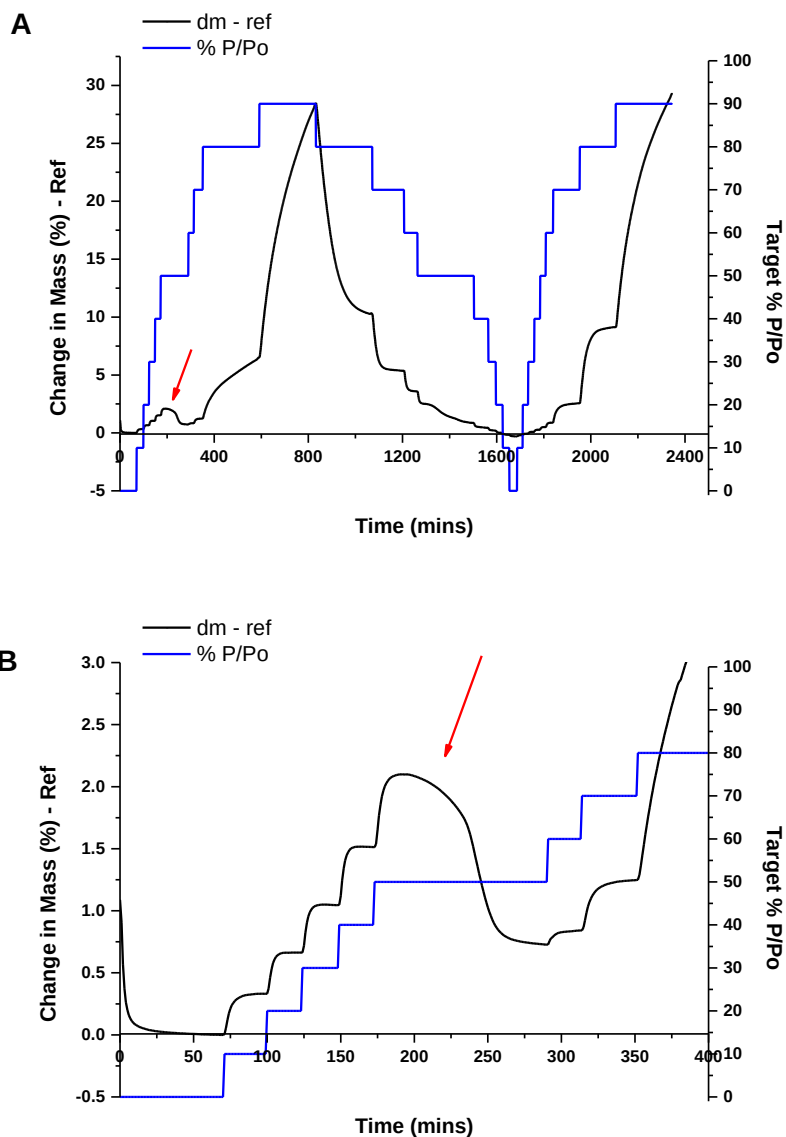


Figure 4.17 DVS change in mass plots of the composite formed on comilling crystalline BD with GA in the VBM at CT at 50% w/w. Red arrows indicate onset of mass loss events associated with crystallisation.

Analysis of the PXRD pattern of the composite before and after crystallisation, shown in Figure 4.18 (b) and (c) respectively, confirmed that BD had undergone an amorphous to crystalline transformation. In addition, an increase in the peak intensity of the Bragg peak at $24^\circ 2\theta$, characteristic of the β -polymorph of GA was observed in the system after DVS analysis. The Bragg peaks associated with α -polymorphic GA in the co-cryo-milled amorphous composite (Figure 4.18 (b)) disappeared on crystallisation in the DVS. No mass loss event was observed in the second sorption cycle shown in Figure 4.17A, indicating that complete crystalline had occurred in the first sorption cycle.

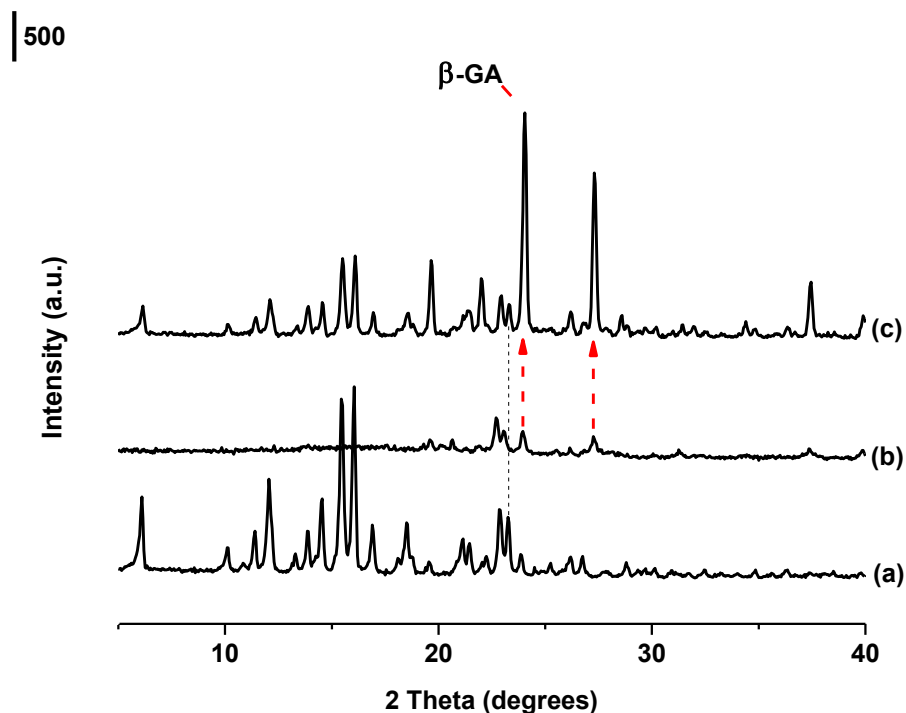


Figure 4.18 PXRD diffractogram of (a) crystalline BD and the composite formed on comilling crystalline BD with GA in the VBM at CT at 50% w/w (b) before and (c) after crystallisation in the DVS. Red arrows indicate Bragg peaks associated with β -GA, while the black dashed line indicates Bragg peaks associated with α -GA.

The FTIR spectra of the co-cryomilled amorphous BDGA composite, shown in Figure 4.19, was determined in order to assess the potential for the formation of hydrogen bonding interaction between both components on comilling, as indicated by peak shifts associated with hydrogen bonding groups. In addition, the FTIR spectrum was also recorded after crystallisation in the DVS. Analysis of the O-H stretching region of GA on formation of the co-cryomilled amorphous composite at 2954 cm^{-1} (Figure 4.19B (d)) indicated the disappearance of the O-H stretching peak on comilling. Analysis of the carbonyl stretch of GA in the cryomilled composite before crystallisation indicated an increase from 1687 cm^{-1} to a higher wavenumber by 6 cm^{-1} as shown in Figure 4.19C (d), while the (quinonoid) carbonyl group of BD underwent a slight shift of 4 cm^{-1} to a lower wavenumber from 1656 cm^{-1} to 1652 cm^{-1} as shown in Figure 4.19C (d). The alkyl carbonyl group of BD was obscured by the carbonyl group of GA. In addition, the C-O stretching peak of GA at 1206 cm^{-1} underwent a peak shift to 1198 cm^{-1} in the co-cryomilled composite, as shown in

Figure 4.19D (d). On crystallisation, the O-H stretch of GA appeared, as shown in Figure 4.19B (e) and the carbonyl group of GA shifts to a lower wavenumber from 1693 cm^{-1} before crystallisation to 1689 cm^{-1} after crystallisation, as shown in Figure 4.19C (e). In addition, the C-O stretch of GA reverted back to 1242 cm^{-1} , as shown in Figure 4.19D (e). FTIR analysis thus indicated evidence for H-bonding interaction on comilling between GA and BD, with involvement of the hydroxyl and carbonyl groups.

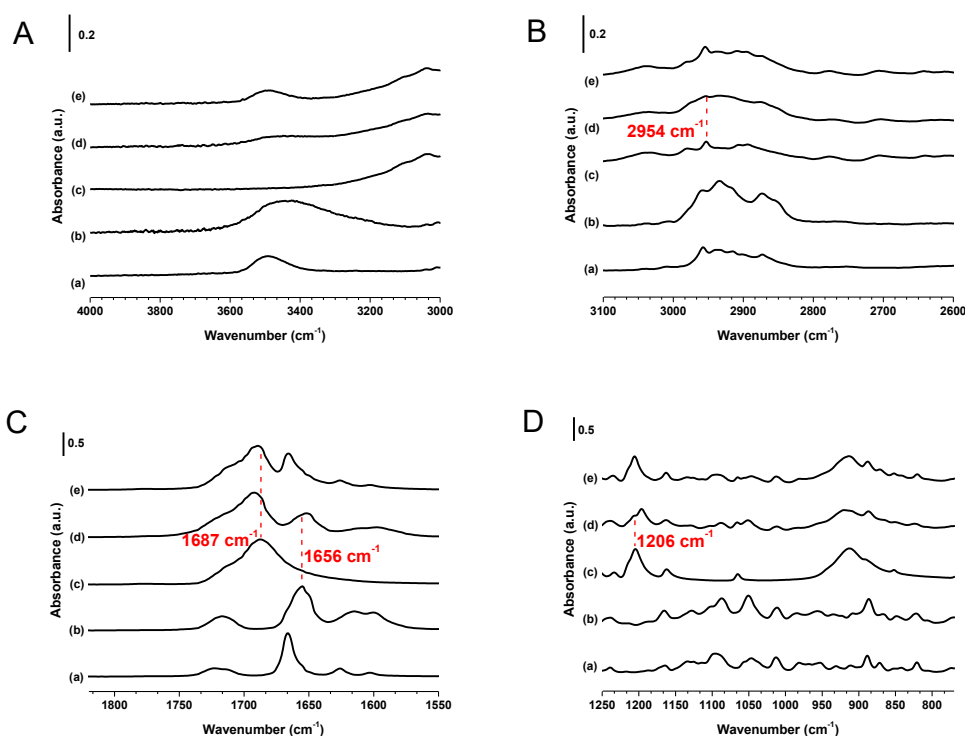


Figure 4.19 FTIR spectra of (a) crystalline BD, (b) BD milled in the VBM at CT, (c) GA milled in the VBM at CT and the composite formed on comilling crystalline BD with GA in the VBM at CT at 50% w/w (d) before and (e) after crystallisation in the DVS. Red dashed lines indicate peak positions referred in the text above.

The BDGA co-cryomilled composite was also analysed by SEM microscopy before and after crystallisation, and the images are shown in Figure 4.20. The morphology of the composite before crystallisation (Figure 4.20 A-C) revealed a smooth matrix within which appeared to be embedded small and larger crystallites. The smooth matrix could be due to BD, as PXRD analysis of the composite suggested BD was amorphous, while the crystallites could be due to GA, which was shown to be in the α and β -polymorphic form. After crystallisation (Figure 4.20 D-F), the matrix

appeared rougher, and larger crystals were observed embedded throughout the rough matrix.

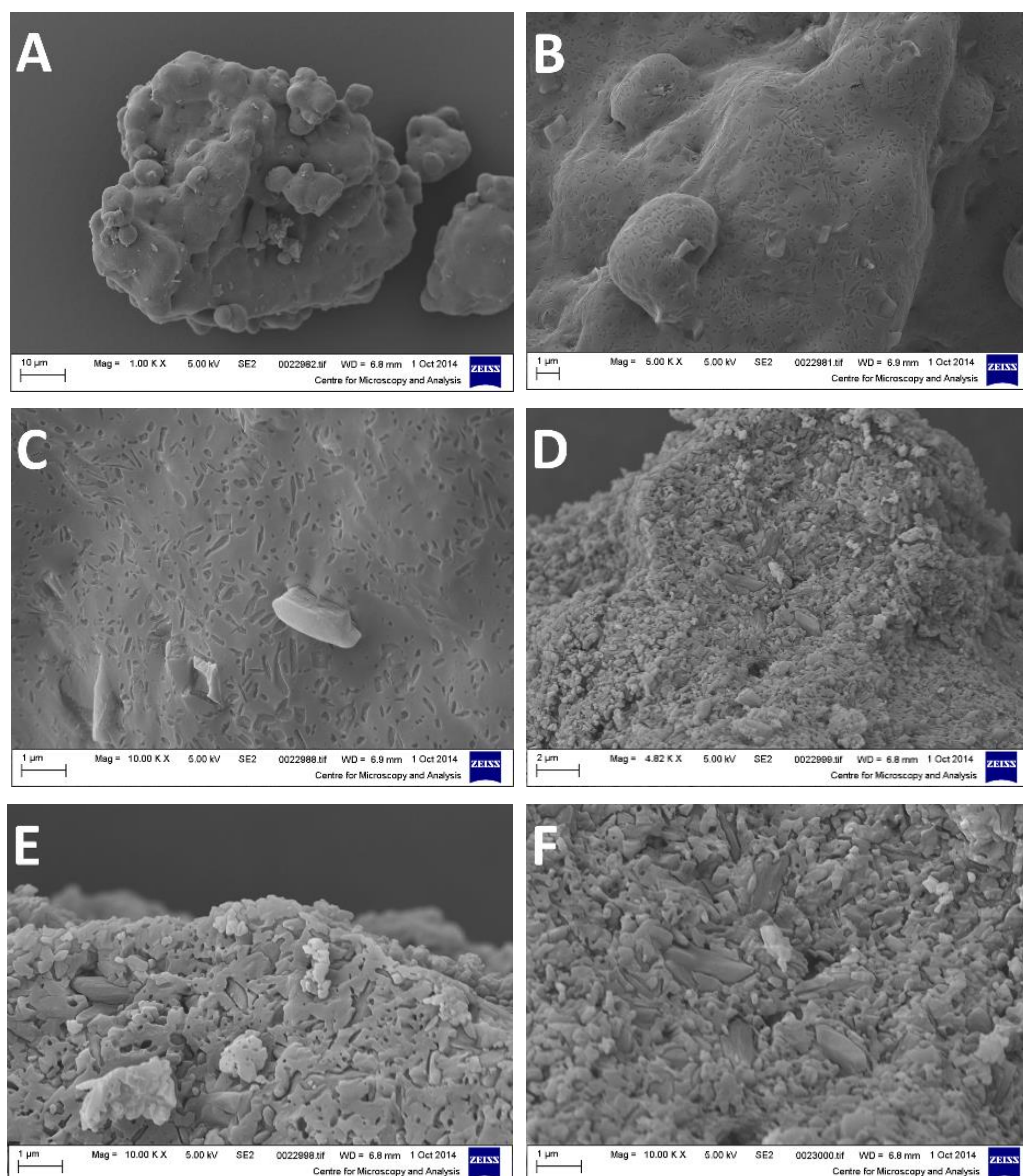


Figure 4.20 SEM images of the composite formed on comilling crystalline BD with GA in the VBM at CT at 50% w/w (A-C) before and (D-F) after crystallisation in the DVS.

4.5.2 Budesonide and Pimelic Acid Co-Cryomilled Composite

The stepwise sorption plot of the BDPA co-cryomilled composite is shown in Figure 4.21. A mass loss event was observed at 40% RH in the first sorption cycle, followed by subsequent mass loss events at both 50 and 60% RH. This indicated that the crystallisation event at 40% was incomplete with subsequent crystallisation occurring at the higher RH values. In the second sorption cycle, no

mass loss event was observed, indicating that full crystallisation had occurred in the first sorption cycle. The onset of crystallisation at 40% RH indicates that, relative to GA, comilling PA with BD had led to a reduction in the RH_c and an increased sensitivity of amorphous BD to plasticisation by water. However, the mass loss event observed with GA was a single mass loss event, while the mass loss event observed with PA occurred over a range of RH steps, an indication of faster kinetics of crystallisation for the BDGA comilled composite.

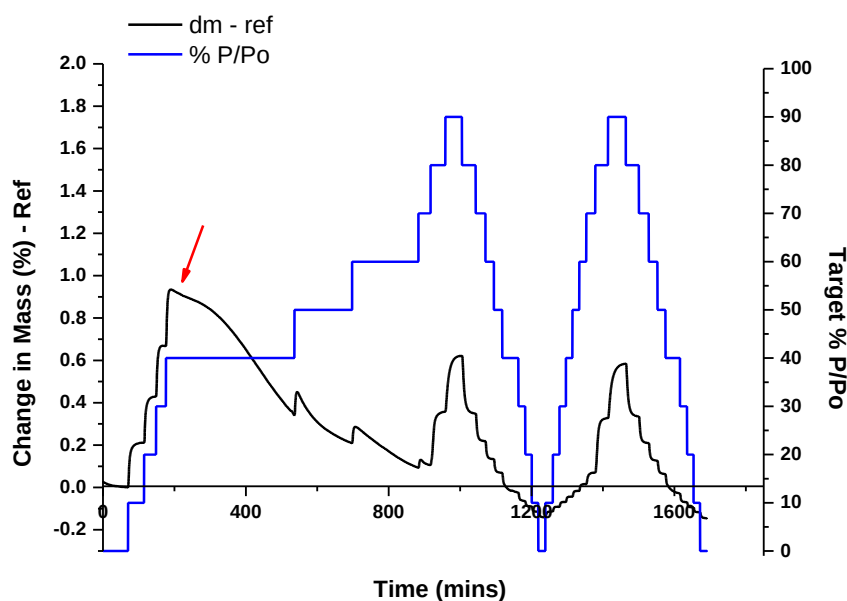


Figure 4.21 DVS change in mass plot of the composite formed on comilling crystalline BD with PA in the VBM at CT at 50% w/w. Red arrow indicates mass loss event.

PXRD analysis of the composite was performed before and after DVS analysis and the diffractograms are shown in Figure 4.22. While before crystallisation, no Bragg peaks associated with crystalline BD were observed, indicating BD was amorphous, only peaks associated with γ -polymorphic PA were detected, as described in Appendix A-III. The diffractogram after DVS analysis confirmed that BD had undergone crystallisation during the analysis, while analysis of the Bragg peaks associated with PA revealed that PA had also crystallised out from the cryomilled amorphous composite but into the α -polymorphic form. This is in spite of the fact that the β -polymorphic form is the thermodynamically stable form at RT. The diffractogram of the RT comilled BDPA composite also revealed that PA was in the α -polymorphic form on comilling at RT.

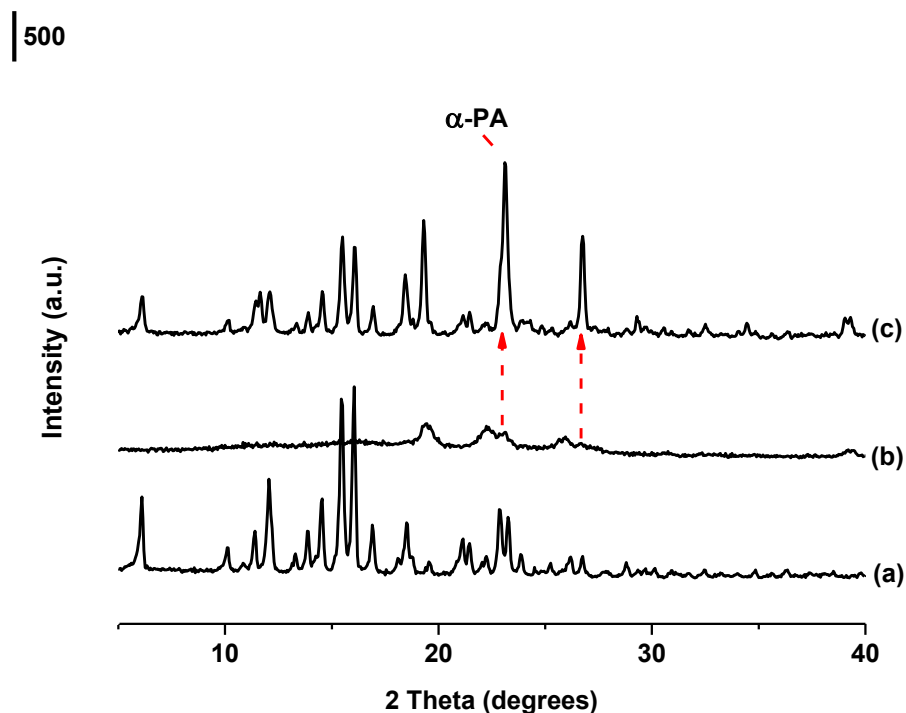


Figure 4.22 PXRD diffractogram of (a) crystalline BD and the composite formed on comilling crystalline BD with PA in the VBM at CT at 50% w/w (b) before and (c) after crystallisation in the DVS. Red arrows indicate Bragg peaks associated with α -PA.

The FTIR spectra of the BDPA co-cryomilled composite, before and after crystallisation in the DVS is shown in Figure 4.23. The stretching O-H region of the hydroxyl group of BD in the cryomilled amorphous composite at 3447 cm^{-1} , as shown in Figure 4.23A (d), is broad and of reduced intensity relative to amorphous BD but does not reveal a peak shift, and the O-H stretching region of PA at 2953 cm^{-1} , shown in Figure 4.23B (d), similarly does not reveal any peak shift in the co-cryomilled composite, in contrast to the GA composite. The C=O group of PA underwent a shift to a higher wavenumber from 1688 to 1693 cm^{-1} in the co-cryomilled amorphous composite, as shown in Figure 4.23C (d), possibly indicating some level of H-bonding on co-cryomilling. However, no peak shift was observed in the quinonoid carbonyl group of BD at 1655 cm^{-1} , as shown in Figure 4.23C (d). In contrast to the GA system, the C-O group of PA at 1200 cm^{-1} did not undergo a peak shift on co-cryomilling. The FTIR analysis thus suggests that PA does not undergo as significant H-bonding with the API on comilling relative to GA.

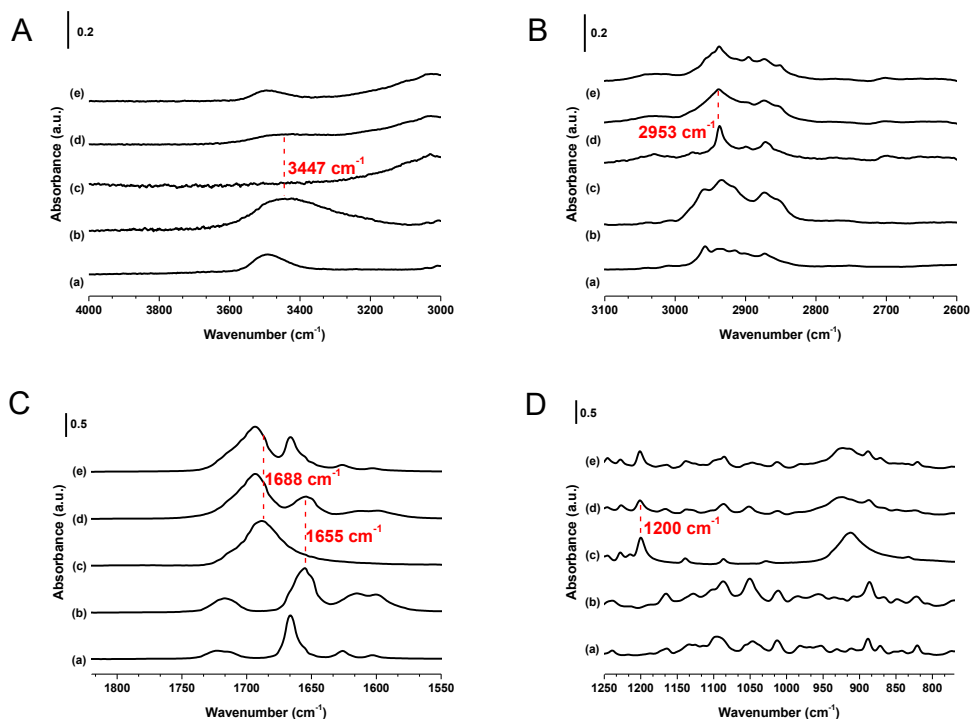


Figure 4.23 FTIR spectra (a) crystalline BD, (b) BD milled in the VBM at CT, (c) PA milled in the VBM at CT and crystalline BD comilled with PA in the VBM at CT at 50% w/w (d) before and (e) after crystallisation in the DVS. Red lines indicate peak positions associated with functional groups discussed above.

In addition, the BDPA co-cryomilled composite was analysed by SEM analysis both before and after crystallisation in the DVS, as shown in Figure 4.24. The system appeared to have a smooth surface texture with crystallites embedded in the surface, somewhat similar to the BDGA system. After crystallisation, the texture appears rougher with two distinct crystalline phases apparent, one rough textured crystalline matrix, which was also observed in the BDGA system after crystallisation and is most likely crystalline BD, and a separate crystalline system with larger crystals, possibly due to crystalline PA, embedded within the rough matrix, which as shown by PXRD is in the α -polymorphic form.

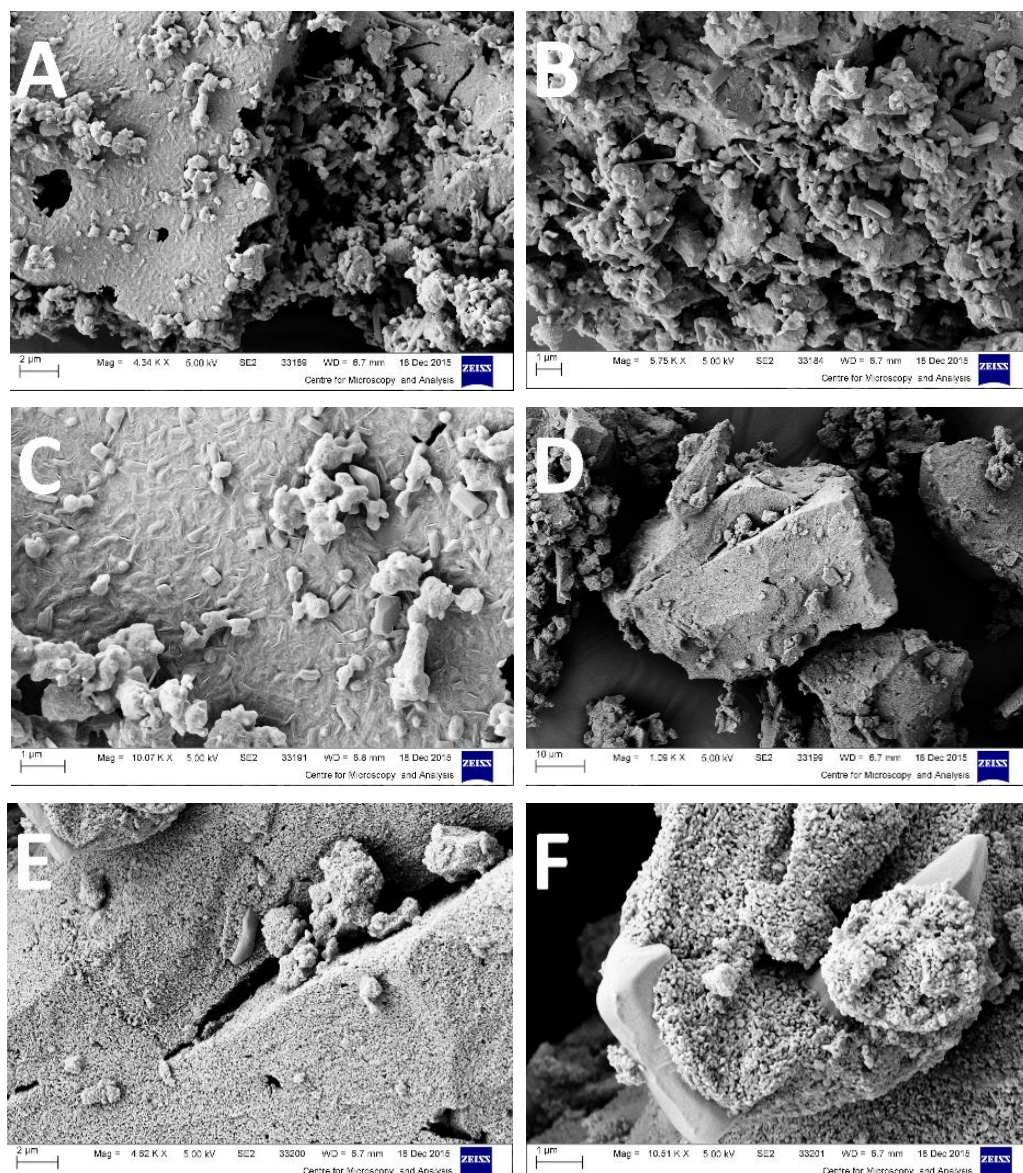


Figure 4.24 SEM images of the composite formed on comilling crystalline BD with PA in the VBM at CT at 50% w/w (A-C) before crystallisation and (D-F) after crystallisation in the DVS.

4.5.3 Budesonide and Adipic Acid Co-Cryomilled Composite

The stepwise sorption plot of the BDAA 50% w/w co-cryomilled composite is shown in Figure 4.25. A mass loss event was observed at 80% RH in the first sorption cycle, and a further mass loss event was observed on increasing to 90% RH. No further mass loss event was observed in the second sorption cycle indicating that complete crystallisation of the amorphous composite had occurred in the first sorption cycle. Relative to BD cryomilled alone, the BDAA amorphous composite showed an increased sensitivity to plasticisation by water but not to the same extent as comilling with either GA or PA, which displayed an onset of crystallisation at 50% and 40% RH respectively.

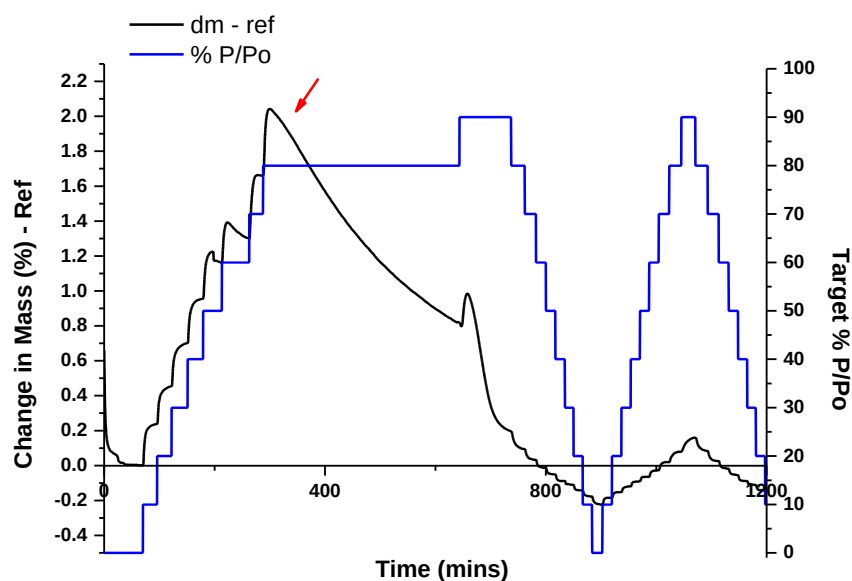


Figure 4.25 DVS change in mass plot of the composite formed on comilling crystalline BD with AA in the VBM at CT at 50% w/w. Red arrow indicates onset of mass loss event associated with crystallisation.

PXRD analysis, shown in Appendix A-1 Figure A-I.10, indicated Bragg peaks associated with crystalline of BD in the composite after DVS analysis. In addition, the Bragg peaks associated with β -polymorphic AA had increased in intensity relative to the broad β -polymorphic peaks observed in the amorphous cryomilled composite before crystallisation (shown in Figure 4.13B).

FTIR analysis, indicated a peak shift in the C=O stretching peak of AA (Figure 4.26C), with a shift to a higher wavenumber from 1688 – 1694 cm^{-1} on co-cryomilling, while after crystallisation the peak had reduced to 1690 cm^{-1} . The O-H stretching peak of AA, shown in Figure 4.26B, indicated the disappearance of the peak in the co-cryomilled composite relative to the composite after crystallisation which displayed a peak at 2953 cm^{-1} . Additionally, the C-O stretching peak of AA at 1191 cm^{-1} increased to 1195 cm^{-1} on co-cryomilling. However, there was no shift in the quinonoid C=O group of BD at 1654 cm^{-1} . Similarly, the broad O-H stretching peak of BD at 3423 cm^{-1} did not appear to undergo a shift on co-cryomilling; however the peak in the co-cryomilled composite was of a low intensity.

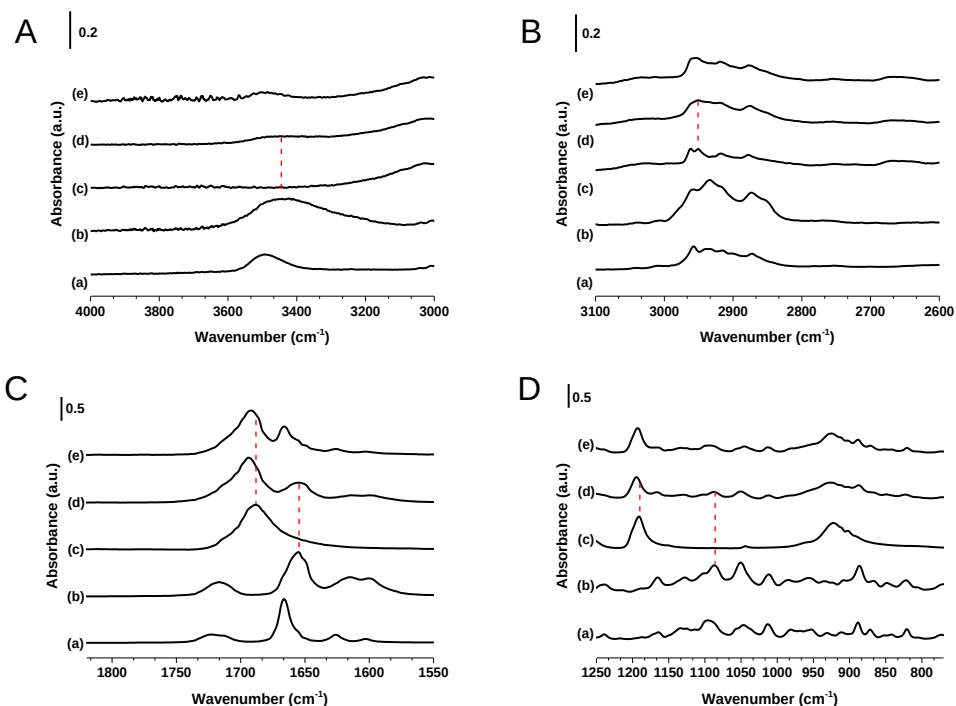


Figure 4.26 A-D FTIR analysis of (a) crystalline BD, (b) BD milled in the VBM at CT for 45 minutes, (c) AA milled in the VBM at CT for 45 minutes and crystalline BD comilled with AA at 50% w/w for 45 minutes (d) before and (e) after crystallisation in the DVS. Red lines indicate peak positions associated with functional groups discussed in the text.

SEM analysis was also performed on the BDAA co-cryomilled composite before and after crystallisation in the DVS. Before crystallisation, as shown in Figure 4.27A-C, the composite system appeared to consist of two morphologically distinct regions which did not appear to be homogeneously dispersed as was observed for the BDGA or BDPA co-cryomilled composites. One of the regions appeared to consist of a needle like morphology, which was possibly due to AA, together with an apparently smooth surfaced matrix, which was possibly due to amorphous BD. After crystallisation, the composite, shown in Figure 4.27 D-F, appeared to consist of two separate morphological regions, one with a needle like morphology, similar to the composite before crystallisation, as well as a rough textured matrix, possibly due to crystalline BD.

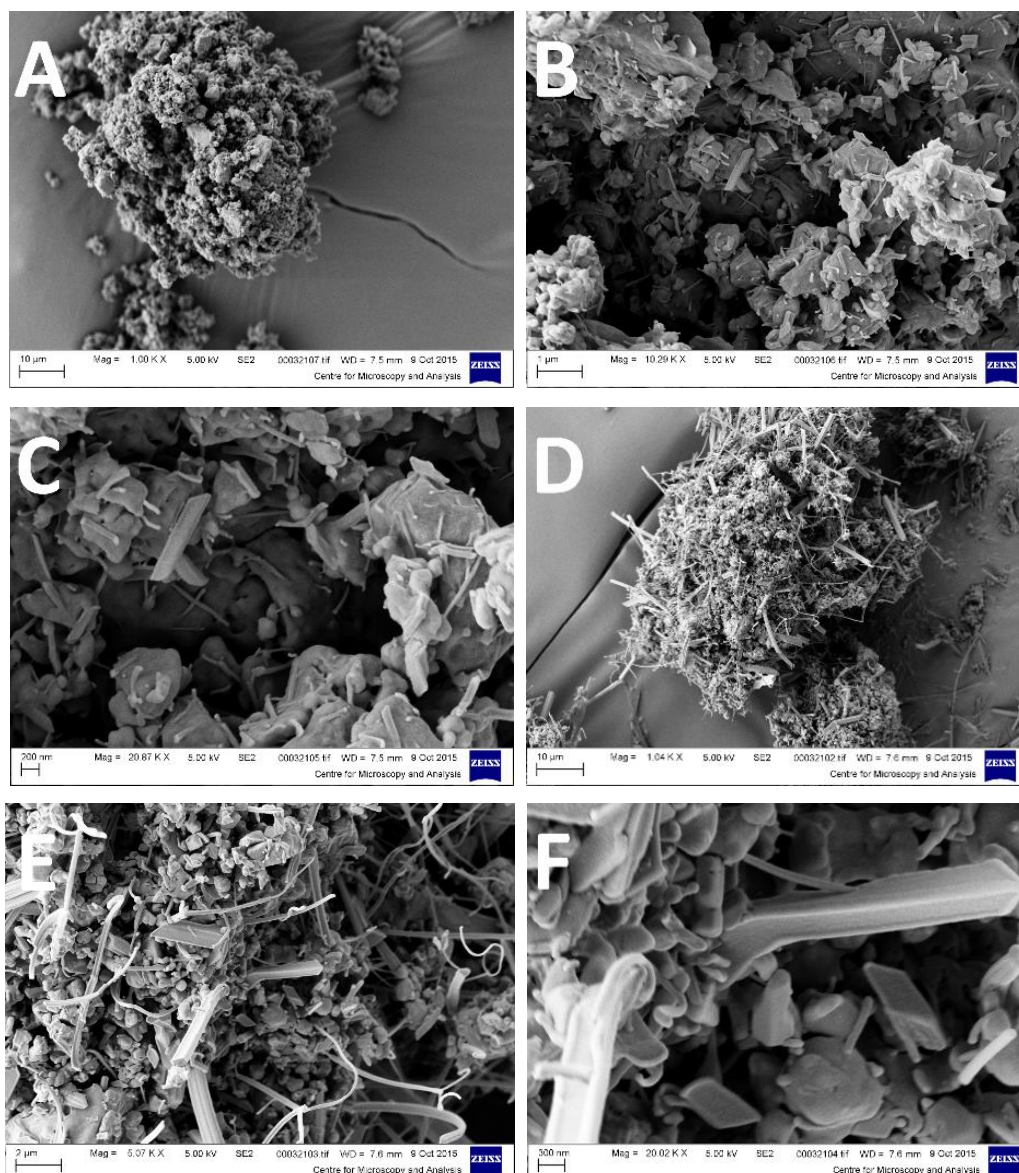


Figure 4.27 SEM images showing the composite formed on comilling crystalline BD with AA in the VBM at CT at 50% w/w (A-C) before crystallisation and (D-F) after crystallisation in the DVS.

4.5.4 Budesonide and Succinic Acid/ Mannitol Co-Cryomilled Composites

In contrast to the DVS isotherm of the RT comilled BDSA composite (shown in Figure 4.9A) which showed a mass loss event at 90% RH, co-cryomilled BDSA showed no mass loss event on DVS analysis at 25 °C, as shown in Figure 4.28A. This suggests that comilling BD with SA at CT may have led to a more stable amorphous composite towards water vapour induced crystallisation than the comilled composite formed at RT. This correlates with the increased thermal stability of the CT comilled BD: excipient composites, as suggested by the generally increased T_c on DSC analysis relative to their RT comilled counterparts (T_c values shown in and

respectively). Similarly, the composite formed on comilling BD with MAN at CT showed no mass loss event on DVS analysis (Figure 4.28B).

Interestingly, the BDMAN co-cryomilled composite showed evidence of a hysteresis effect. Young and Nelson analysis may be applied to sorption isotherms which do not show complex phase transformations such as crystallisation/hydrate formation etc. and in which the main sorption mechanism and formation of hysteresis effects is due to surface and/or bulk sorption of water (Bianco, Tewes et al. 2013). Such analysis allows for the quantitative discrimination of the surface vs. bulk sorption mechanism of the material. As neither the BDSA or BDMAN composites underwent a crystallisation event during sorption analysis, Young and Nelson analysis was performed on the isotherm data shown in Figure 4.29, in order to compare the mechanism of water sorption uptake in the these two co-cryomilled composites. In addition, Young and Nelson analysis was also applied to the cryomilled BD isotherm for comparison.

The Young and Nelson component plots from the three systems are shown in Figure 4.29 and the constants E (indicating strength of interaction with the probe molecule), A (indicating surface adsorption) and B (indicating bulk absorption) are shown in Table 4.3. The plots reveal that the BDMAN composite showed increased bulk absorption of water vapour relative to either BD milled alone or the BDSA co-cryomilled composite, while the BDSA composite showed a significantly reduced level of bulk absorption of water relative to BD milled alone. In contrast, the A constant for each of the three systems were comparable, an indication that the systems showed similar surface adsorption characteristics. The increased bulk water absorption in the BDMAN composite is surprising given the stability of the amorphous composite formed with the excipient on comilling at both RT and CT. However, given that the T_g of BD was not reduced on comilling at either milling temperature, the two components are likely to be phase separated and thus any absorption of water by MAN would be unlikely to have an effect on the stability of the amorphous phase BD towards crystallisation.

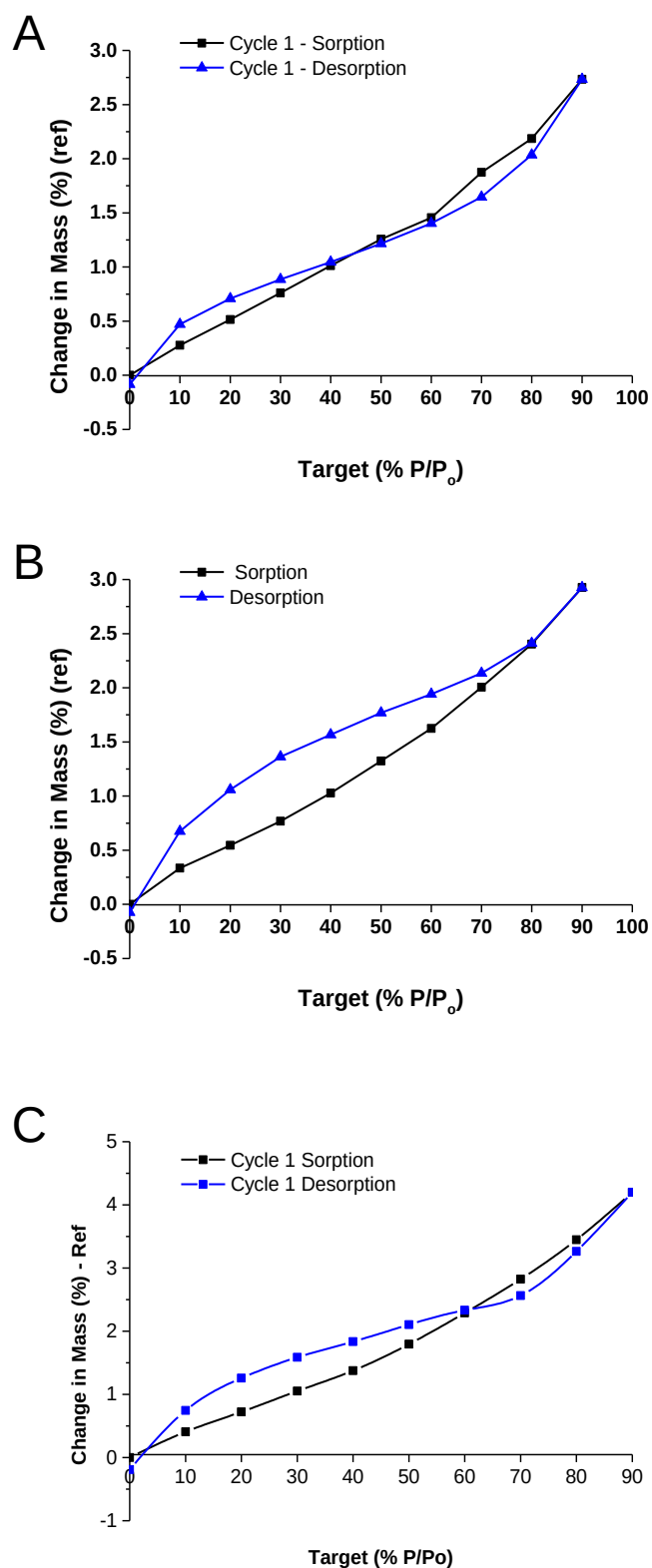


Figure 4.28 DVS isotherm plots of the composites formed on comilling crystalline BD in the VBM at CT at 50% w/w with A) SA and B) MAN.

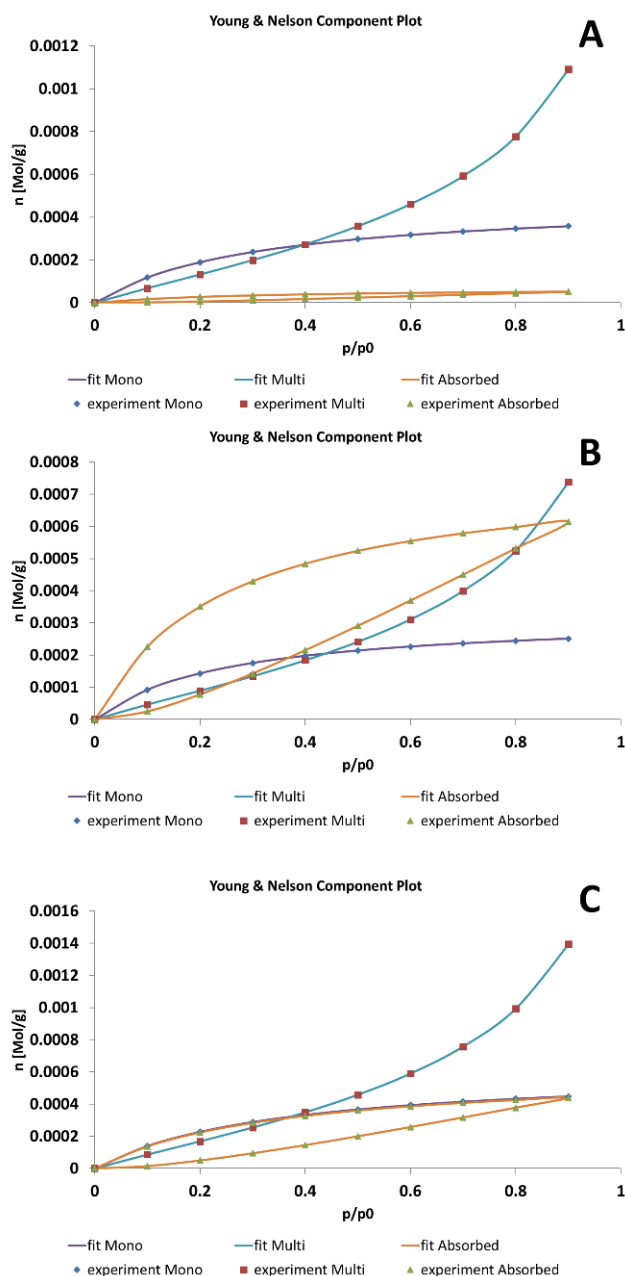


Figure 4.29 Young and Nelson component plots of A) BD comilled with SA in the VBM at CT at 50% w/w for 45 minutes, B) BD comilled with MAN in the VBM at CT at 50% w/w and C) BD milled alone in the VBM at CT for 45 minutes.

Table 4.3 Constants from the Young and Nelson component plots described in Figure 4.29

	E	A	B	R ²
BD	0.256	4.607×10^{-4}	5.021×10^{-4}	0.997
BDSA	0.234	3.67×10^{-4}	5.916×10^{-5}	0.997
BDMAN	0.198	2.56×10^{-4}	6.974×10^{-4}	0.999

The FTIR spectrum of the co-cryomilled BDMAN system (Figure 4.30) displayed no peak shifts in the O-H stretching region of MAN at 3285 and 3397 cm^{-1} . In addition, no change in either BD carbonyl peak at 1725 cm^{-1} (associated with the alkyl carbonyl group) or at 1656 cm^{-1} (associated with the quinonoid carbonyl group) was observed on comilling with MAN, nor any change in the C-O bond of MAN at 1080 cm^{-1} relative to unprocessed β -polymorphic MAN. The lack of any evidence of interaction from the FTIR analysis further suggests the phase separated nature of the comilled composite formed between BD and MAN.

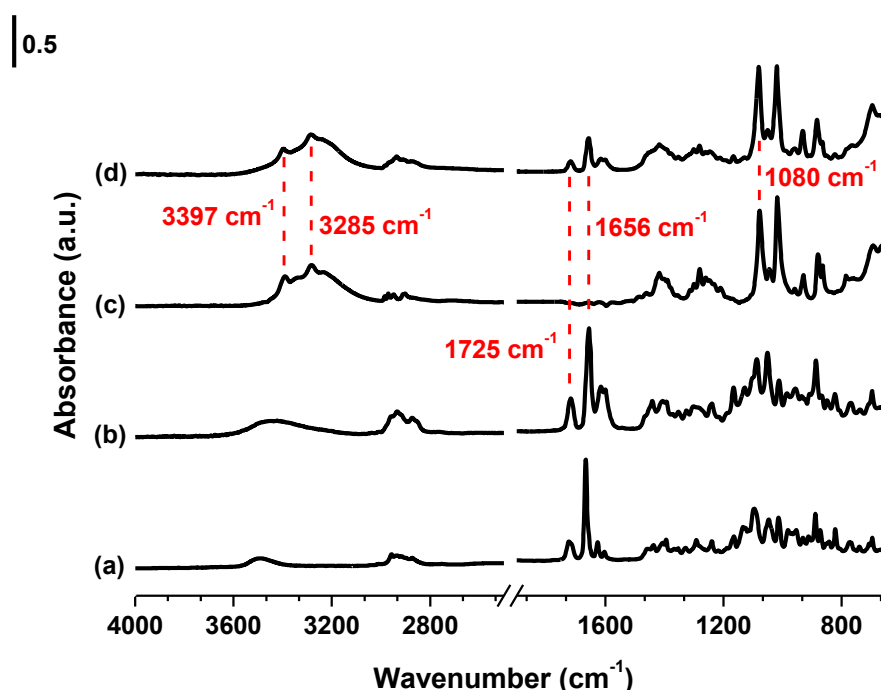


Figure 4.30 FTIR spectra of (a) crystalline BD, (b) amorphous BD milled in the VBM at CT, (c) crystalline β -MAN and (d) crystalline BD comilled with MAN at 50% w/w in the VBM at CT. Red lines indicate peak positions associated with functional groups discussed in the text.

The co-cryomilled BDSA system was maintained at 40 °C and 75% RH for 24 hours. PXRD analysis indicated Bragg peaks associated with crystalline BD and, in addition, Bragg peaks associated with crystalline β -polymorphic SA (Appendix A-1, Figure A-1.10). Subsequent analysis by SEM (Figure 4.31) both before and after crystallisation was undertaken in order to characterise the morphological characteristics of the composite system. The SEM images revealed two apparently distinct and separate morphological regions both before and after crystallisation, with one needle like morphology, possibly due to crystalline AA, which surrounded

a matrix that appeared relatively smooth before crystallisation and relatively rougher after crystallisation, possibly due to amorphous and crystalline BD respectively. The morphology appeared somewhat similar to that observed in the BDAA co-cryomilled composite, shown in Figure 4.27.

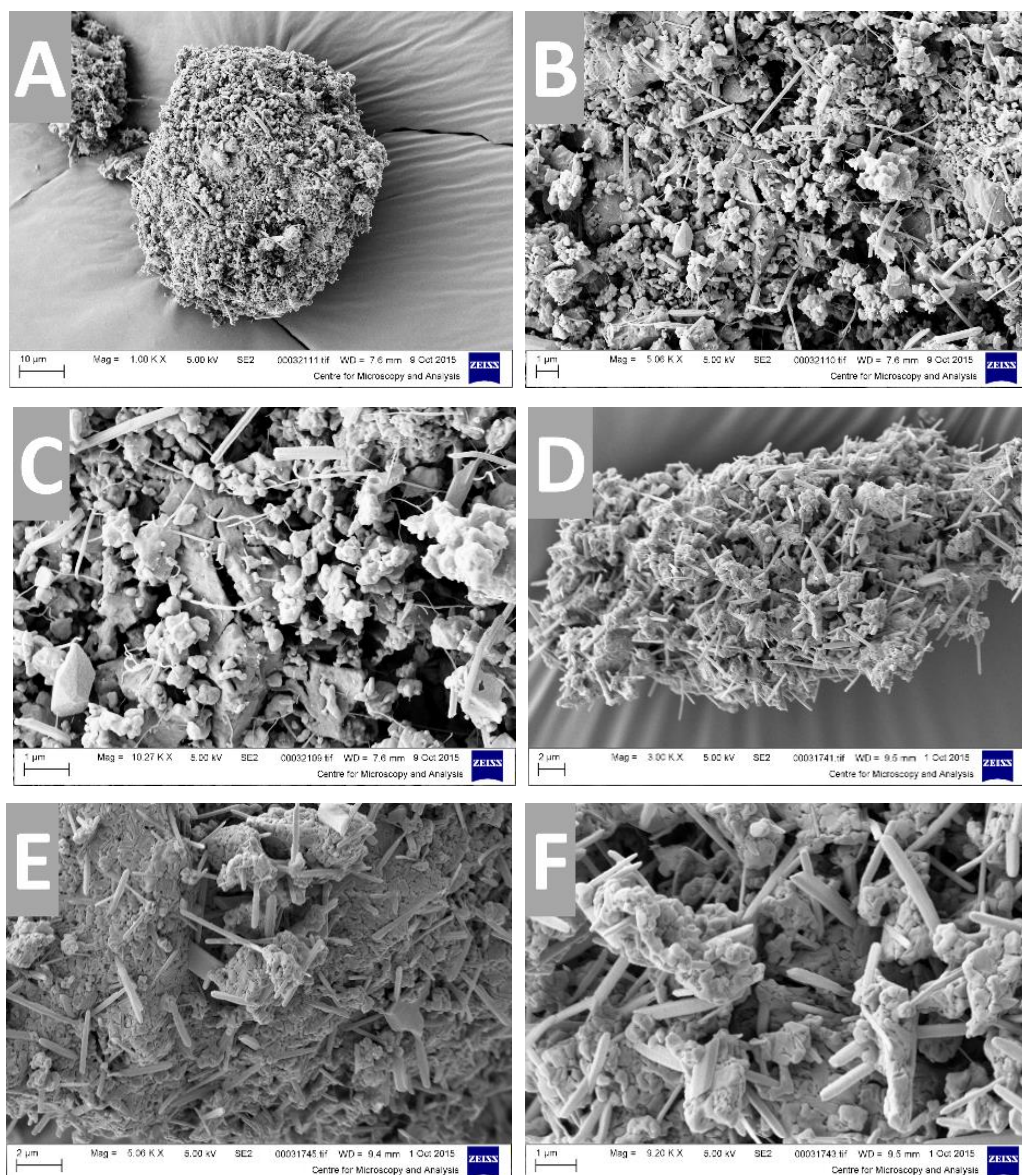


Figure 4.31 SEM images of the composite formed on comilling crystalline BD with SA in the VBM at CT at 50% w/w (A-C) before crystallisation and (D-F) after crystallisation at 40 °C and 75% RH for 12 hours.

4.6 STUDIES ON THERMALLY CO-ACTIVATED BUDESONIDE ALLOYS – SOLUBILITY AND T_g REDUCTION

The solubility of each of the diacids in amorphous BD was determined by the zero enthalpy extrapolation method. Due to the lack of miscibility displayed between BD and MAN, in contrast to the diacids on thermal analysis, BD could not safely be melted without degradation due to the lack of a reduced eutectic melting of BD in the presence of MAN and thus was not amenable to solubility determination. Figure 4.32 shows the determination of the solubility value of each of the diacids in amorphous BD by extrapolation of the heat of fusion values of the melt quench systems in the composition range 50% - 90% w/w diacid in BD.

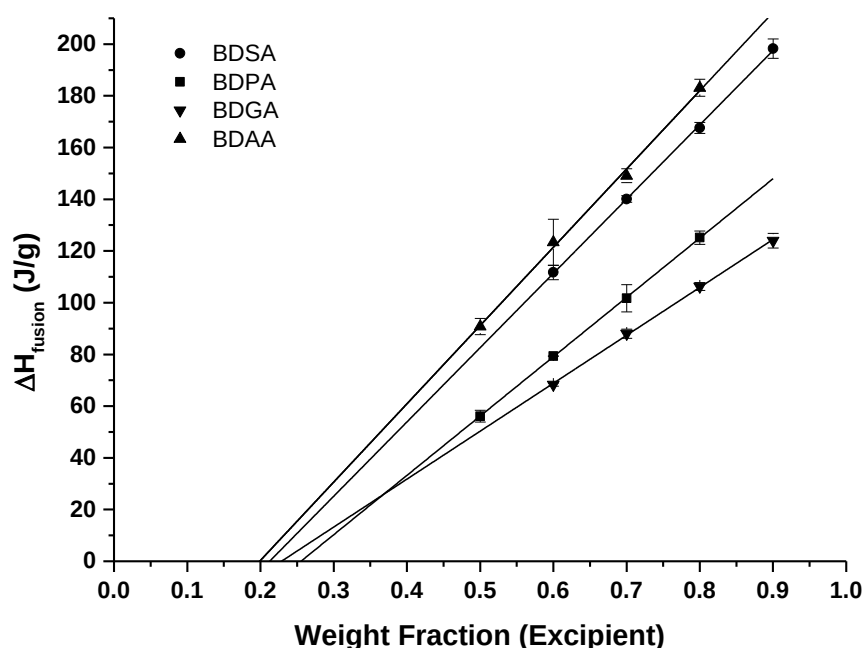


Figure 4.32 Zero enthalpy extrapolation plots for the determination of the solubility of the diacids SA, GA, AA and PA in amorphous BD

Table 4.4 highlights the slope and intercept values of the linear regression equations from the solubility lines shown in Figure 4.32, together with the solubility limit determined from the regression analysis. Analysis of the solubility compositions revealed that PA showed the highest solubility in amorphous BD at 26% w/w. In spite of the fact that GA mitigated amorphisation to the greatest extent on comilling, the solubility of GA in amorphous BD was determined to be 23%,

while that of SA was determined to be 21% w/w. In contrast to PA and GA, SA did not mitigate amorphisation of BD to any extent on comilling at RT. The solubility of AA in amorphous BD was the lowest of all the diacids with a value of 20% w/w.

The T_g values of the 50% w/w BD: diacid co-melt quench composites, as determined from modulated heat flow DSC analysis shown in Figure 4.33A, are also shown in Table 4.4. As the 50% w/w composition was above the solubility of each of the diacids in amorphous BD, the T_g s determined from the 50% w/w composites reflected the maximally reduced T_g of amorphous BD saturated with diacid. However, a difference in the level of T_g reduction on comilling SA with BD at either RT (shown in , $T_g = 75/89\text{ }^\circ\text{C}$) or CT (shown in , $T_g = 72\text{ }^\circ\text{C}$) was observed, relative to the T_g of the melt quench composite ($T_g = 53\text{ }^\circ\text{C}$). Similarly, with the composite formed between BD and AA, a difference was observed between the T_g values of the comilled and co-melt quenched composites. In contrast, comparison of the T_g reduction formed on comilling PA, at either RT or CT, with the T_g reduction of the co-melt quench composite revealed that PA reduced the T_g of amorphous BD on comilling to a similar extent as for the melt-quench system. The composite formed on comilling GA with BD at CT also showed a similar level of T_g reduction as the co-melt quench composite (the RT comilled composite was completely crystalline and did not display a T_g).

Table 4.4 Slope, intercept and R^2 values determined from the zero enthalpy extrapolation determination of the solubility of the diacid excipients in amorphous BD together with the calculated T_g of the diacids and the experimental T_g for each BD:excipient melt quench 50% w/w composite.

	Slope	Intercept (J/g)	R^2	Solubility at 25 $^\circ\text{C}$ (% w/w)	T_g^* ($^\circ\text{C}$)	T_g of 50% w/w MQ Alloy ($^\circ\text{C}$) ($\pm\text{SD}$)
Succinic Acid	287.3	-61.05	0.9995	21	49*	53 (1.1)
Glutaric Acid	185.3	-42.3	0.9994	23	-14*	39 (1.9)
Adipic Acid	302.8	-60.2	0.9974	20	25*	48 (0.9)
Pimelic Acid	229.5	-58.6	0.9999	26	-8*	40 (0.2)

* Calculated T_g based on the $0.7(T_m)$ rule

In addition, the T_g s of the diacids, as calculated from the $0.7(T_m)$ rule, are also shown in Table 4.4. Analysis of the T_g of the BDSA composite reveals that the experimentally determined T_g of the composite had a value of $53\text{ }^\circ\text{C}$. However, the predicted T_g of SA was determined to be $49\text{ }^\circ\text{C}$. Given that SA is present in the

saturated amorphous API at only 21% w/w, the actual T_g is likely to be below 49 °C and highlights the limitation of the 0.7 T_m rule as an accurate estimate of the T_g of the diacids.

Figure 4.33B shows the PXRD diffractograms of the co-mechanically activated (at CT) alloy of BDGA over a composition range that covers (i.e. above, below and at) the experimentally determined solubility composition of GA in amorphous BD, i.e. 23% w/w. Above the solubility composition, at 50% w/w, crystalline GA was present with evidence of both α and β -polymorphic peaks, while at the solubility composition (i.e. 23% w/w GA in BD) only a very small trace of the peaks associated with crystalline GA were observed. The 13% w/w GA in BD composite revealed a halo pattern characteristic of the amorphous state. This analysis supports both the solubility value of 23% w/w determined here for GA in amorphous BD, and also supports the zero enthalpy extrapolation method for the accurate determination of experimental solubility of crystalline excipient in amorphous API.

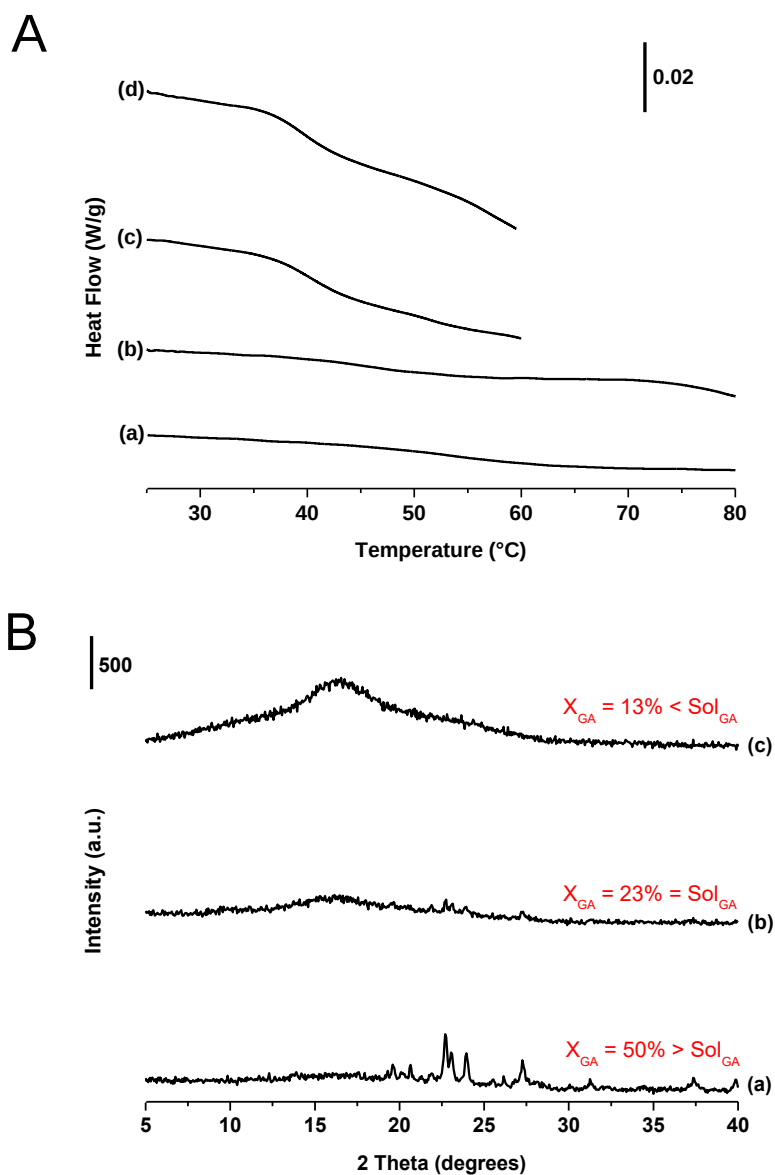


Figure 4.33 A) Reversing heat flow modulated DSC thermograms of co-melt quenched composites at 50% w/w with BD and (a) SA (b) AA (c) PA and (d) GA. B) PXRD diffractograms of crystalline BD comilled in the VBM at CT for 45 minutes with GA at compositions (a) above the solubility composition at 50% w/w (b) at the solubility composition of 23% w/w and (c) below the solubility composition at 13% w/w.

4.7 CONCLUSIONS

In this chapter the amorphisation of crystalline BD in the vibratory type ball mill at both RT and CT was investigated. The relative abilities of a range of low T_g excipients, in particular the diacids SA, GA, AA and PA and the polyol MAN to mitigate amorphisation of crystalline BD on comilling at both RT and CT was studied. While GA led to the complete mitigation of amorphisation of BD on comilling at RT as quantified by DVS and PXRD, both AA and PA led to partial mitigation of amorphisation with PA exhibiting a greater ability to mitigate amorphisation relative to AA. In contrast, neither SA nor MAN were successful at mitigating amorphisation. None of the excipients were successful at mitigating amorphisation on comilling at CT.

In addition, the level of T_g reduction of BD on comilling at both RT and CT with each of the low T_g excipients was determined by modulated DSC analysis. While no reduction in T_g on comilling was observed with MAN at either RT or CT, both GA and PA led to similar levels of T_g reduction at both RT and CT. In contrast, while both SA and AA led to a greater level of T_g reduction relative to MAN, neither led to the same level of T_g reduction observed with either GA or PA on comilling at either RT or CT. The reduction in T_g appeared to correlate broadly with the relative ability of the diacids to mitigate amorphisation of crystalline BD on comilling.

The co-cryomilled BD: excipient alloys were characterised by vibrational spectroscopic analysis for evidence for hydrogen bonding group interactions. The analysis revealed the strongest evidence for interaction between BD and GA on co-cryomilling in addition to evidence for an interaction with PA. Humidity accelerated phase separation of the co-cryomilled alloys revealed that while both GA and PA led to the plasticisation of amorphous BD to a greater extent on comilling than either AA, SA or MAN, crystallisation from the GA composite was faster than from the PA composite.

The solubility of each of the diacid excipients in amorphous BD was also determined by the zero enthalpy extrapolation method. Interestingly, the solubility compositions did not appear to reflect the relative abilities of the diacid excipients to mitigate amorphisation as has previously been suggested. In addition, the T_g values of the BD: excipient glass solutions saturated with diacid excipient (i.e. at a composite above the solubility composition) formed on co-melt quenching were

also determined. Interestingly, comparison of the level of T_g reduction formed on comilling BD with the diacids relative to the T_g of the glass solutions formed on co-melt quenching indicated that while both GA and PA on comilling led to similar levels of T_g reduction relative to the co-melt quenched composites, neither SA nor AA were able to reduce the T_g of BD on comilling to the same extent as the composites formed on co-melt quenching.

CHAPTER 5

STUDIES ON THE FORMATION AND PHYSICAL PROPERTIES OF SULFADIMIDINE AND LOW T_g EXCIPIENT ALLOYS

5.1 INTRODUCTION

Sulfadimidine is a sulfonamide class antibiotic which, as shown, has a T_g above room temperature of 78 °C. Previous studies have highlighted the tendency of SDM to undergo a crystalline to amorphous transformation on milling (Caron, Tajber et al. 2011). Comilling studies with sulfadimidine to date have revealed that, due to the presence of hydrogen bond donor and acceptor groups in the molecule, in particular the sulfonamide and aromatic amine groups, it can undergo intermolecular hydrogen bonding interactions with, for example, the aromatic acids on comilling, leading to the formation of cocrystal products (Caira, Nassimbeni et al. 1995, Grossjohann, Serrano et al. 2015). In addition, comilling crystalline SDM with the diacids, glutaric acid and adipic acid was shown to lead to the complete and partial mitigation of amorphisation of sulfadimidine respectively in the planetary ball mill, while comilling with succinic acid was shown to be unsuccessful in this regard (Curtin, Amharar et al. 2013).

In this chapter the physical transformations of amorphous sulfadimidine when comilled with a range of low T_g excipients will be investigated. In particular, the extent of T_g reduction on comilling will be assessed, in addition to spectroscopic analysis for milling induced hydrogen bonding interactions, and the crystallographic solid state transformations of both sulfadimidine and excipient on comilling will be determined. The sorption characteristics and crystallisation behaviour of the amorphous composites formed on co-cryomilling will be determined by dynamic vapour sorption analysis in addition to the determination of the activation energy of crystallisation from the driven alloys formed with glutaric acid and pimelic acid.

In addition to the physical characterisation of the driven alloys formed between sulfadimidine and the low T_g excipients, glass solutions will be prepared by thermal activation. The solubility of the diacids in amorphous sulfadimidine will be determined by the zero enthalpy extrapolation method and the T_g of the melt quench composites will be determined. A thermodynamic assessment, by melting point depression analysis, of the mixing behaviour in the liquid state will be performed, with subsequent computation of the excess thermodynamic functions, in order to quantify and compare the nature and extent of specific interactions formed between sulfadimidine and the diacids on mixing in the liquid state.

5.2 COMILLING STUDIES OF AMORPHOUS SULFADIMIDINE WITH LOW T_g EXCIPIENTS

Previous studies have highlighted the ability of certain diacids, in particular GA, to mitigate amorphisation on comilling with crystalline SDM in a planetary ball mill at RT (Curtin, Amharar et al. 2013). In addition, the previous chapter in this thesis illustrated the relative capacity of the diacids SA, GA, AA and PA, in addition to the polyol MAN, to mitigate amorphisation of BD, a structurally unrelated compound, in a vibratory ball mill at RT. In order to further investigate the physical properties of the amorphous composites formed on comilling between amorphous API and the low T_g excipients, SDM was initially amorphised in the PBM which, as described in Chapter 3, led to the generation of a partially amorphous system with an amorphous content of 78-80% as determined by NIR and DSC. This (partially) amorphous sample of SDM (which we will identify as mSDM for brevity) was then co-milled at 50% w/w with the diacids SA, GA, AA and PA and the polyol MAN in the VBM at RT.

5.2.1 PXRD Analysis

Figure 5.1A (e) and (f) shows the PXRD diffractograms of the composite formed on comilling mSDM with GA after 3 and 36 minutes of milling. Bragg peaks in the region $22-23^\circ 2\theta$, characteristic of the α -polymorph of GA, were evident in the composite after 36 minutes of milling, while the peak at $24.1^\circ 2\theta$, characteristic of the β -polymorph of GA, had disappeared. This suggests that a milling induced polymorphic conversion of GA to the metastable α -polymorph had occurred. GA was not observed to undergo any polymorphic transformation when milled alone either in the PBM at RT for 12 hours or in the VBM at RT or CT. In contrast, no change (either reduction or increase) in the Bragg peaks associated with SDM had occurred over the same period. However, as highlighted in Chapter 3, SDM does not fully amorphise when milled at RT in either the VBM or PBM and thus we would not expect to see any further reduction in peak intensity on milling. Figure 5.1B highlights the polymorphic transformation of GA to the metastable polymorph over the first 18 minutes of the comilling study. Full conversion to the metastable α -polymorph was achieved after 18 minutes of milling with the milling-time dependent decrease in the peaks associated with the β -polymorph clearly

correlated with the concomitant increase in the intensity of the peaks associated with the α -polymorph.

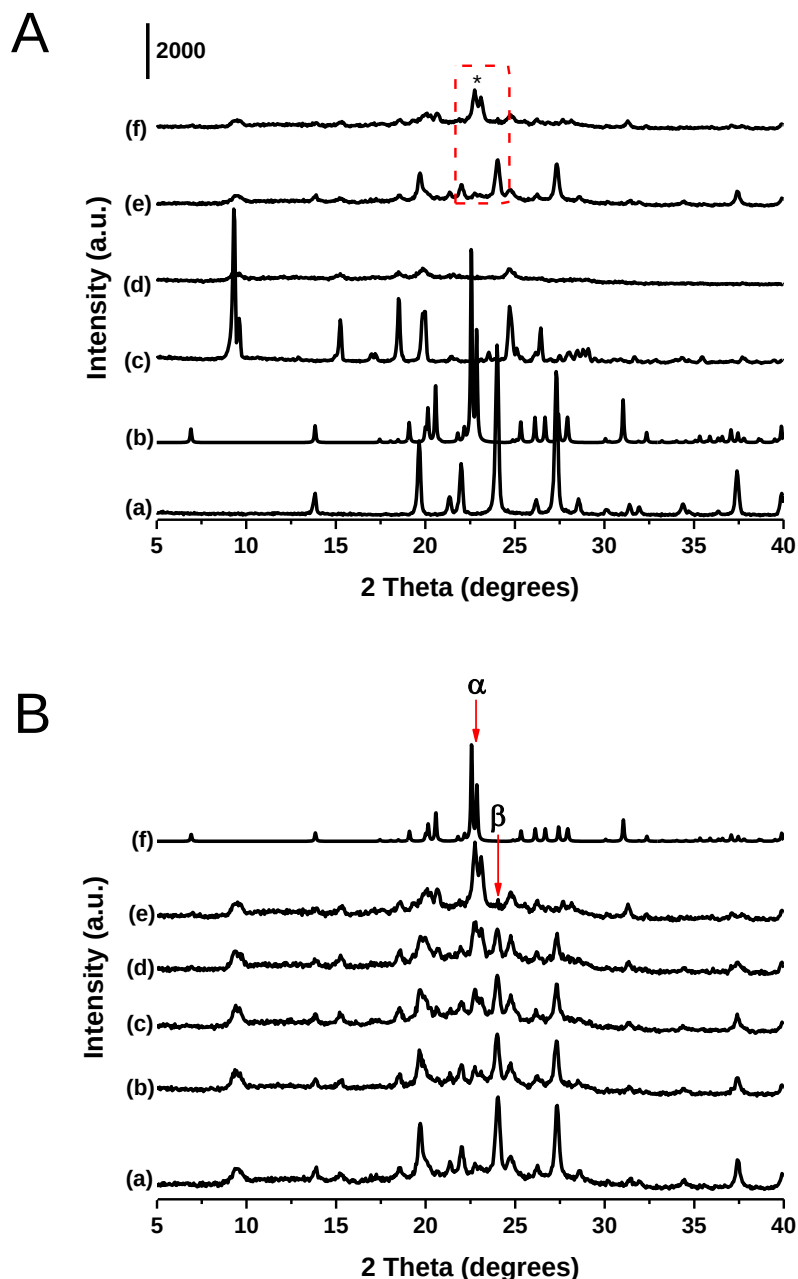


Figure 5.1 A) PXR D diffractograms of (a) GA β -polymorphic generated from the single crystal data obtained from the CCDC, (b) GA α -polymorphic generated from the single crystal data obtained from the CCDC, (c) crystalline SDM, (d) SDM milled in the PBM at RT for 12 hours (mSDM), (e) mSDM comilled with 50% w/w GA in the VBM at RT after 3 minutes and (f) mSDM comilled with 50% w/w GA in the VBM at RT after 36 minutes. Red box indicates Bragg peaks associated with the α and β -polymorphic forms of GA. B) PXR D diffractograms of mSDM comilled with 50% w/w GA in the VBM at RT after (a) 3, (b) 6, (c) 9, (d) 12, (e) 15, (e) 18 minutes and (f) CCDC generated α -polymorphic GA.

mSDM was then comilled with the crystalline diacids SA, AA and PA and crystalline MAN at RT and 50% w/w composition for 36 minutes. The PXRD patterns after 36 minutes of milling are shown in Figure 5.2. Comilling mSDM with SA also showed evidence for a partial polymorphic conversion of the excipient to the metastable α -polymorph on comilling at RT, with the presence of the peak at $22^\circ 2\theta$ indicative of the α -polymorph. In addition, Bragg peaks associated with α -polymorphic PA were observed in the PXRD diffractogram on comilling although the starting material was in the β -polymorphic form. Both AA and MAN remained in the stable β -polymorphic form on comilling. A slight reduction in the intensity of the SDM Bragg peaks on comilling with both SA and MAN was noted, indicating that comilling with these excipients may have facilitated the amorphisation of SDM.

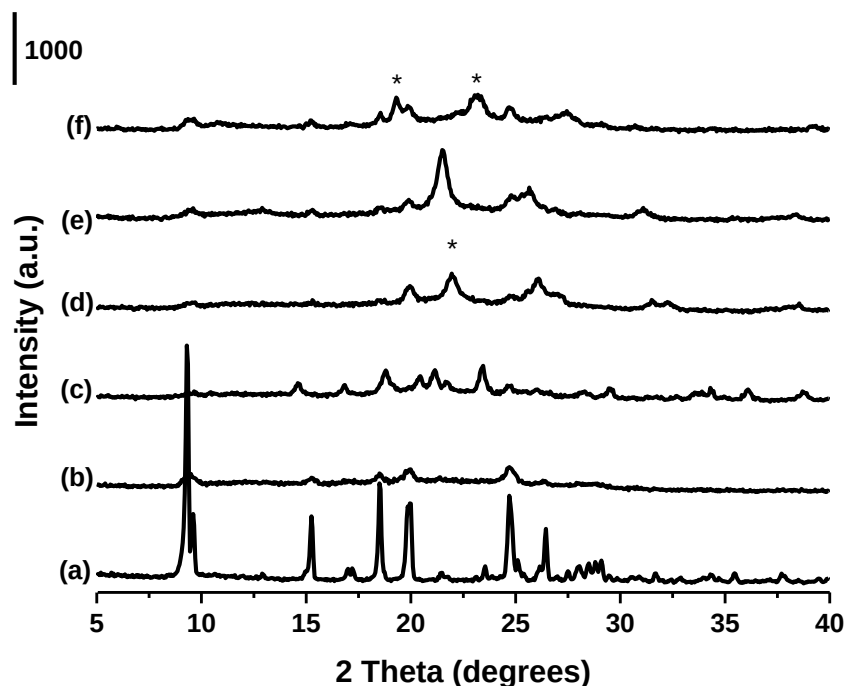


Figure 5.2 PXRD diffractograms of (a) crystalline SDM, (b) SDM milled in the PBM at RT for 12 hours (mSDM), and mSDM comilled in the VBM at RT at 50% w/w for 36 minutes with (c) MAN, (d) SA, (e) AA and (f) PA. * Indicates Bragg peaks associated with alpha polymorph of excipient.

Many low T_g materials have been shown to undergo polymorphic transformations on milling, including sorbitol ($T_g = 0^\circ\text{C}$), mannitol ($T_g = 13^\circ\text{C}$) and fananserine ($T_g = 19^\circ\text{C}$) (Willart, Lefebvre et al. 2005). Indeed, the polymorphic conversions observed in single component systems have been hypothesised to occur by the formation of transient surface amorphous regions but, due to the instability of the

amorphous state of the low T_g excipients, have not been experimentally observed. It appears that the presence of the amorphous API during comilling with mSDM may be facilitating the polymorphic conversion of the excipient, by the formation first of a binary amorphous composite in which GA (SA or PA) is molecularly dispersed, promoting the transformation of the excipient to the metastable polymorph.

5.2.2 DSC Analysis

The capacity of the low T_g excipients to reduce the T_g of API on comilling is theorised to be an essential component in the strategy for the mitigation of milling induced amorphisation. Previous authors have highlighted the capacity of the milling operation to effect the formation of binary amorphous systems with composite T_g values intermediate to either pure component (Nagahama, Suga et al. 2000, Dudognon, Willart et al. 2006). In this regard, the thermal characteristics of the composites formed on comilling mSDM with each of the low T_g excipients in the VBM at RT at 50% w/w were determined by DSC analysis. Figure 5.3 shows the total heat flow signal of the composite formed after 3 and 36 minutes of milling mSDM with crystalline GA. After 3 minutes of milling, the crystallisation temperature (T_c) was reduced from 92 to 53 °C. After 36 minutes of milling the composite displayed a T_c = 51 °C and, in addition, the endothermic event at 72 °C associated with the β to α -polymorphic transformation of GA was no longer present in the thermogram, providing further evidence of the milling induced polymorphic conversion of GA to the metastable α -polymorph, which was revealed by PXRD analysis. Table 5.2 shows the T_g values as determined from the reversing signal of modulated DSC scans, indicating that the T_g was reduced after 3 minutes of milling. However, analysis of the heat capacity change at T_g revealed a ΔC_p of 0.16 J/°C·g relative to the ΔC_p of the composite milled for 18 minutes and 36 minutes of approximately 0.4-0.5 J/°C·g.

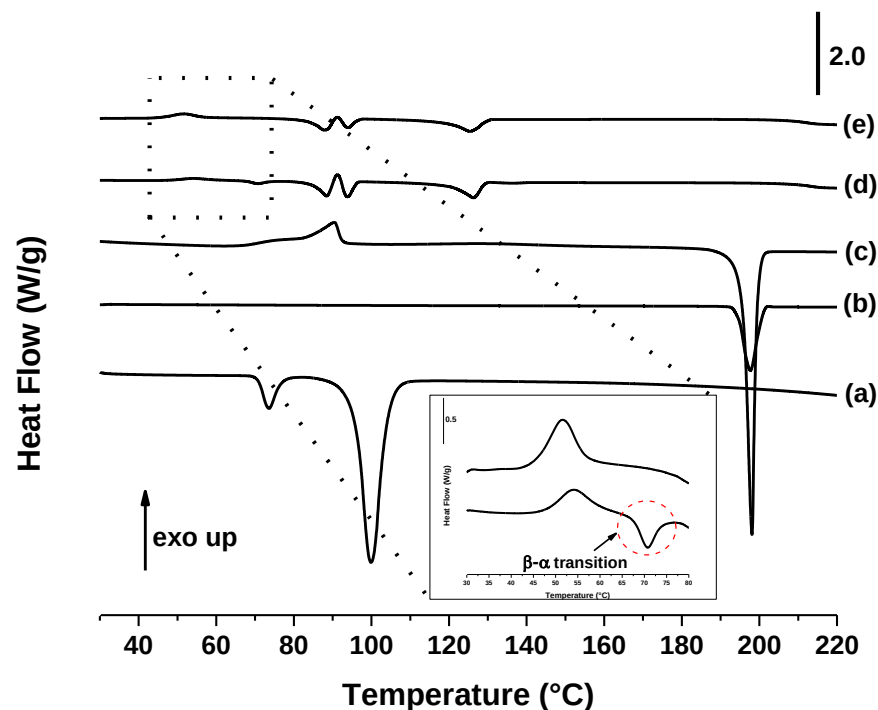


Figure 5.3 Total heat flow DSC thermogram of (a) crystalline GA, (b) crystalline SDM, (c) SDM milled in the PBM at RT for 12 hours (mSDM), and mSDM comilled with GA in the VBM at RT at 50% w/w for (d) 3 minutes and (e) 36 minutes. Inset highlights the reduction in the crystallisation exotherm of the SDMGA comilled composite and the disappearance of the β - α polymorphic transition endotherm in the composite milled for 36 minutes.

As shown in Figure 5.4 (g) and detailed in Table 5.2, the total heat flow DSC thermogram of the composite formed on comilling mSDM with crystalline MAN after 36 minutes of milling displayed a crystallisation exotherm with a T_c at 91 °C, which remained close to that of mSDM itself ($T_c = 93$ °C, Figure 5.4 (f)), indicating that MAN had not resulted in any destabilisation of the amorphous API on comilling. Indeed, analysis of the reversing heat flow signal of the composite in Figure 5.5 (b) indicated that the T_g was only slightly reduced from 78 to 76 °C. Comilling mSDM with the diacids SA and AA led to a reduction in the T_c from 93 °C to 88 and 78 °C respectively (as detailed in Table 5.1), and a reduction in the T_g of mSDM to 68 and 60 °C respectively (as detailed in Table 5.2). As the 36-minute milling time is relatively short and in order to determine if any further T_g reduction would be observed on further comilling with SA, mSDM was comilled in the planetary ball mill at RT with SA at 50% w/w for 12 hours, and the reversing heat flow thermogram is shown in Figure 5.5 (c). The T_g of the 12 hour comilled composite was determined to be 67 °C, the same as the 36 minute comilled composite in the VBM at RT.

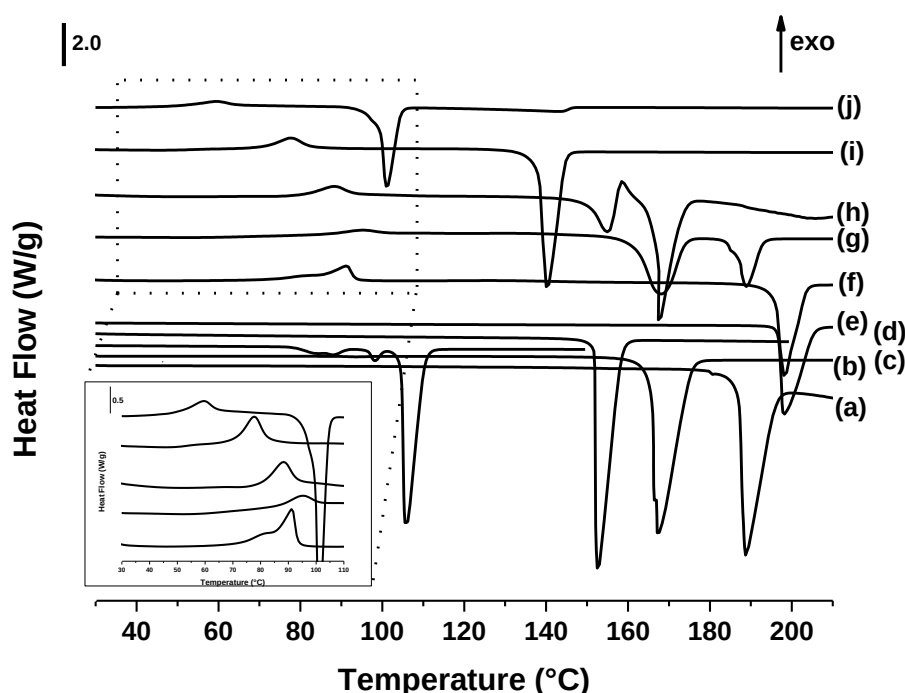


Figure 5.4 Total heat flow DSC thermograms of crystalline (a) SA, (b) MAN, (c) PA, (d) AA, (e) SDM and (e) SDM milled in the PBM at RT for 12 hours (mSDM) and mSDM comilled in the VBM at RT at 50% w/w for 36 minutes with (g) MAN, (h) SA, (i) AA and (j) PA. Inset highlights the crystallisation exotherms of the comilled composites.

Table 5.1 Endothermic and exothermic thermal transition temperatures of each of the DSC thermograms shown in Figure 5.4.

	T_c (°C) (StD)	T_{m1} (°C) (StD)	T_{m2} (°C) (StD)
SDM Unmilled (e)	-	198 (0.3)	-
SDM Milled (f)	93 (0.4)	197 (0.7)	-
SA (a)	-	189 (0.2)	-
AA (d)	-	152 (0.1)	-
PA (c)	-	106 (0.3)	-
MAN (b)	-	168 (0.2)	-
SDM:SA (h)	88 (0.7)	155 (0.2)	168 (0.6)
SDM:AA (i)	78 (0.3)	141 (0.2)	-
SDM:PA (j)	60 (0.5)	101 (0.2)	143 (0.2)
SDM:MAN (g)	91 (0.4)	168 (0.6)	189 (0.7)

Interestingly, comilling mSDM with PA for 36 minutes led to a T_c reduction to 60 °C, shown in Figure 5.4 (j), which was higher than that observed for the SDMGA

composite. However, analysis of the reversing heat flow signal in Figure 5.5 (f) indicates that the T_g was reduced to 46 °C, close to the T_g reduction observed in the SDMGA system of 44 °C.

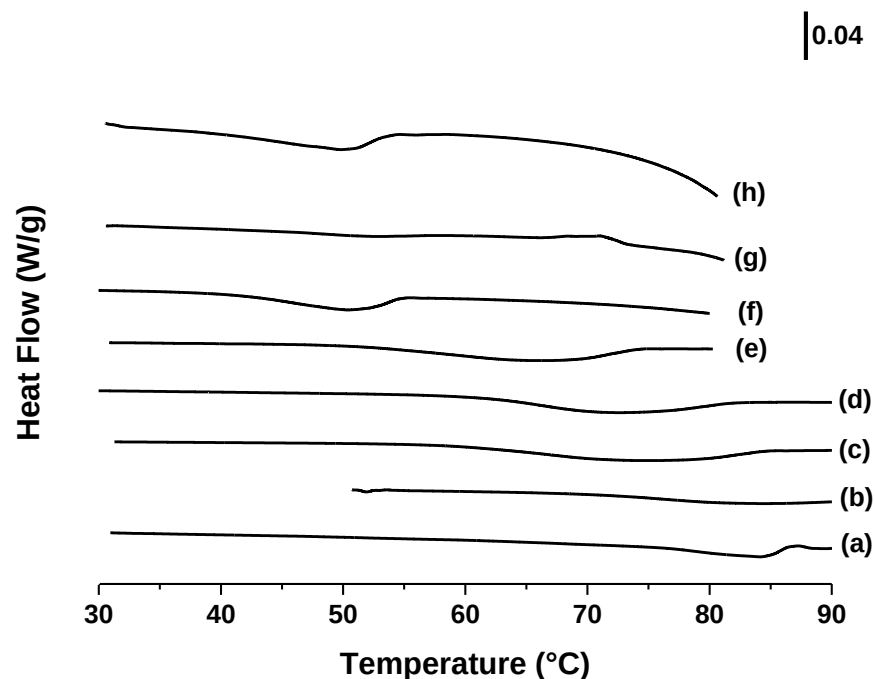


Figure 5.5 Reversing heat flow modulated DSC thermograms of (a) SDM milled in the PBM at RT for 12 hours (mSDM) and mSDM comilled in the VBM at RT at 50% w/w for 36 minutes with (b) MAN, (c) SA, (e) AA, (f) PA and with GA after (g) 3 minutes and (h) 36 minutes. (c) shows the reversing heat flow signal of crystalline SDM comilled with GA at 50% w/w in the PBM at RT after 12 hours.

Table 5.2 Thermal analysis of the composites formed on comilling mSDM with the low T_g excipients in the VBM at RT after 3, 18 and 36 minutes of milling.

	3 min	18 min	36 min	
	T_g (°C) (StD)	T_g (°C) (StD)	T_g (°C) (StD)	T_c (°C) (StD)
Succinic Acid	67.7 (0.3)	65.9 (0.8)	67.5 (1.0)	88.4 (0.9)
Glutaric Acid	44.7 (0.5)	43.9 (1.1)	44.1 (0.7)	51.3 (1.2)
Adipic Acid	60.4 (0.3)	58.8 (58.8)	59.9 (0.5)	77.7 (0.6)
Pimelic Acid	45.5 (0.8)	45.8 (0.9)	45.7 (0.2)	59.5 (0.4)
Mannitol	76.8 (1.1)	76.4 (0.8)	75.6 (0.7)	91.6 (0.9)

5.2.3 FTIR Analysis

Intermolecular interactions in amorphous composite systems have been shown to be of great significance in affecting the stability of the amorphous state. Figure 5.6 compares the FTIR spectra in the region 4000-650 cm^{-1} of the composites formed

between mSDM with GA in the VBM after 3, 9 and 18 minutes of milling, relative to crystalline and amorphous SDM and milled crystalline GA. The appearance of a shoulder in the C=O peak associated with GA in the 1700 cm^{-1} region was evident, suggesting the formation of a milling-induced hydrogen bond between the API and excipient.

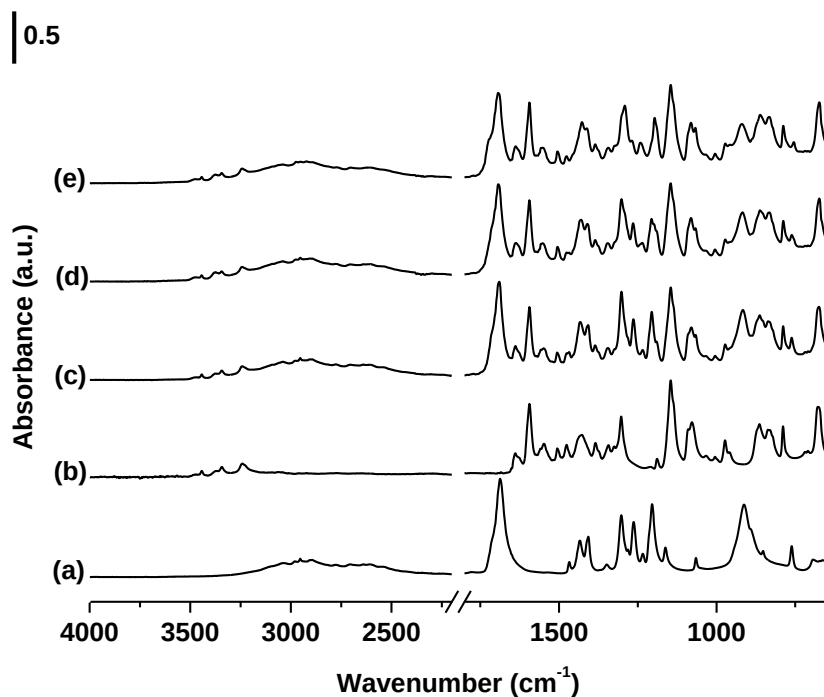


Figure 5.6 FTIR spectra of (a) GA milled in the VBM at RT for 36 minutes (b) SDM milled in the PBM at RT for 12 hours (mSDM), (c) mSDM comilled with crystalline GA in the VBM at RT for (c) 3, (d) 9, and (e) 18 minutes.

Figure 5.7 highlights the FTIR spectral regions associated with the hydrogen bonding groups of SDM and GA in systems subjected to between 3 and 18 minutes of comilling. Peak shifts in the O-H stretching region associated with the hydroxyl group of GA were evident, with the appearance of a peak at 2924 cm^{-1} and the disappearance of the peak at 2955 cm^{-1} . In addition, Figure 5.7B reveals the C=O stretching region associated with the carbonyl group of GA with the appearance of a shoulder at 1725 cm^{-1} which is strongly suggestive of a hydrogen bonding interaction. Additionally, the carbonyl peak shifts by 5 cm^{-1} to a higher wavenumber, from 1688 cm^{-1} to 1693 cm^{-1} . The S=O₂ antisymmetric stretching region at 1300 cm^{-1} , shown in Figure 5.7C, also showed evidence of a milling induced interaction with SDM with a shift to a lower wavenumber, from 1310 cm^{-1}

to 1290 cm^{-1} . The sulfonamide functional group of SDM has been shown to be particularly sensitive to hydrogen bonding interactions and has been suggested to be important in cocrystal formation on comilling (Grossjohann, Serrano et al. 2015). Figure 5.7D reveals the shift in the spectral region associated with the C-O group of GA at 1210 cm^{-1} with a shift to a lower wavenumber of 1195 cm^{-1} .

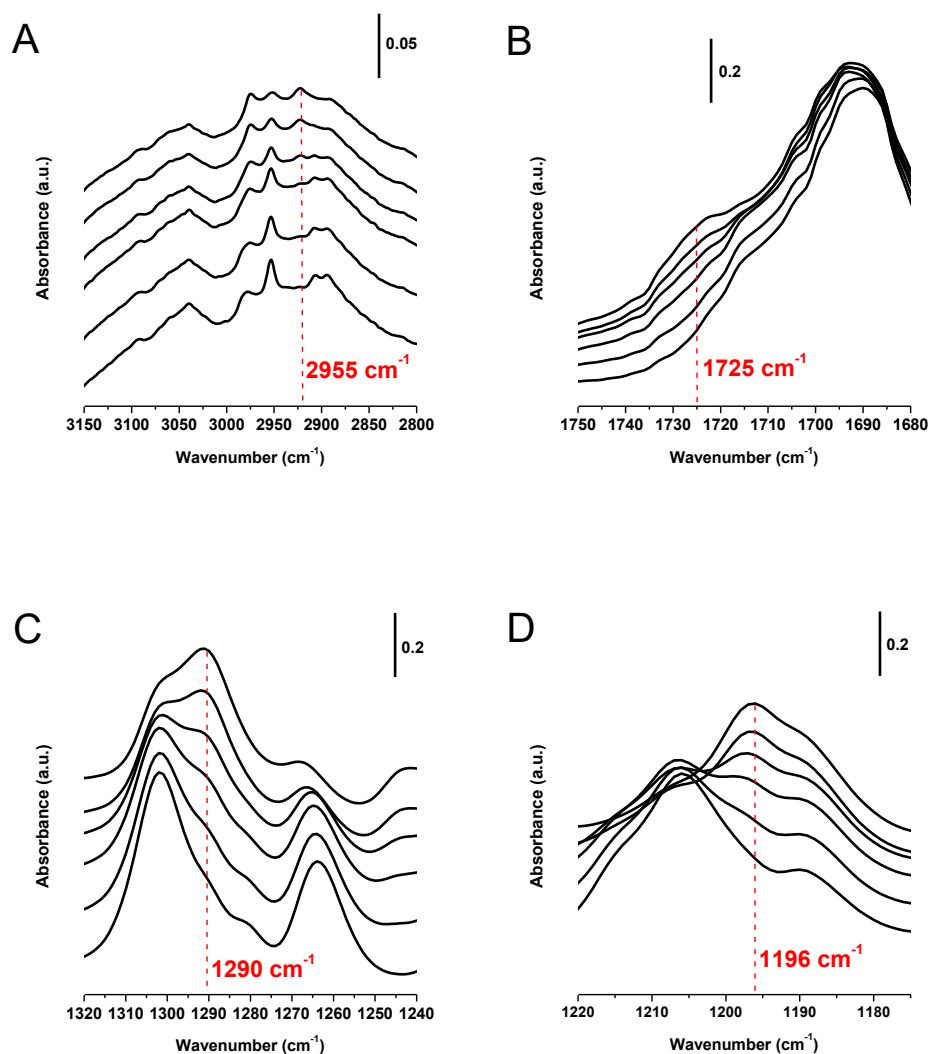


Figure 5.7 FTIR spectra of mSDM comilled with GA in the VBM at RT at 50% w/w after (from bottom to top) 3, 6, 9, 12, 15 and 18 minutes of milling. Red lines indicate peak positions referred to in the discussion text.

In contrast to GA, the diacids PA, AA and SA did not show as strong an interaction with mSDM on comilling, with no significant peak shifts observed in the O-H stretching region. However, a shift in the carbonyl peak of the diacids of between 4 and 6 cm^{-1} to a higher wavenumber was observed, indicating the possibility of some

level of interaction on comilling with mSDM with the FTIR spectra shown in Appendix A-I, Figure A-I.11.

Figure 5.8 reveals the FTIR spectrum of the composite formed on comilling mSDM with MAN. No peak shifts were observed in either the O-H stretching region of MAN, in particular the peaks at 3282 and 3390 cm^{-1} (red dashed lines). In addition, the C-O stretching peak of MAN at 1070 cm^{-1} did not show any shift on comilling with mSDM. The S=O₂ antisymmetric stretching peak of SDM at 1310 cm^{-1} similarly showed no change over the 36-minute milling period.

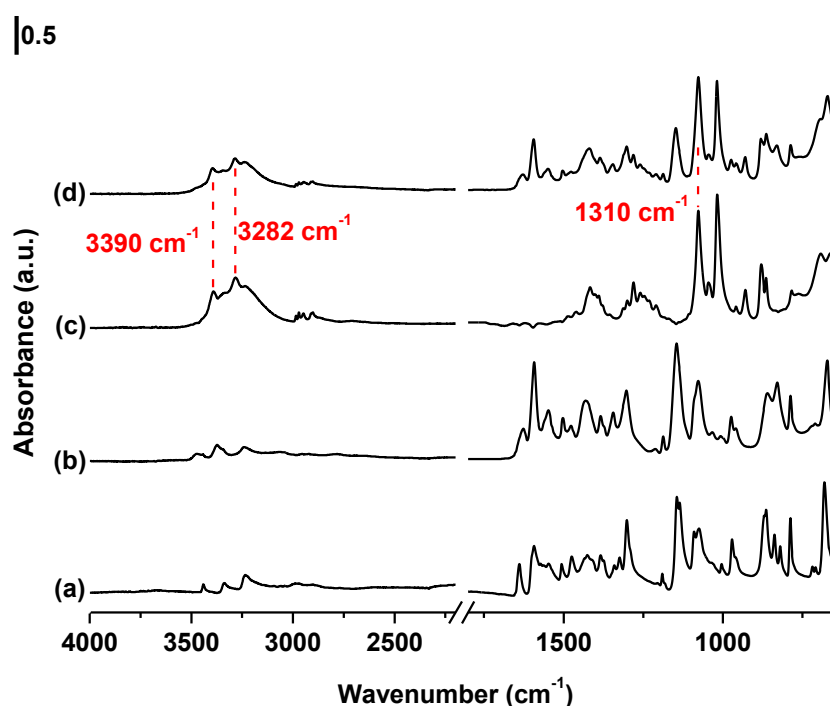


Figure 5.8 FTIR spectra of (a) crystalline SDM (b) SDM milled in the PBM at RT for 12 hours (mSDM), (c) β -MAN and (d) mSDM comilled with crystalline β -MAN for 36 minutes in the VBM at RT at 50% w/w. Red lines indicate peak positions referred to in the discussion text.

5.3 STUDIES ON THE THERMALLY CO-ACTIVATED SULFADIMIDINE ALLOYS – SOLUBILITY AND T_g REDUCTION

Section 1.2 focused on the formation of amorphous composite systems between high and low T_g molecular materials on mechanical activation/mechanical driving. However, binary amorphous systems can also be brought about by melt quench from the co-melt solution state. Figure 5.9 highlights the compositional dependence of the T_g of the amorphous melt quench composite formed between SA and SDM. As shown in Chapter 3, pure amorphous SDM has a T_g of 78 °C. Formation of a molten mixture of SA and SDM, followed by melt quench of the system, led to successive reduction in the T_g as a function of increasing composition of SA. Such compositional dependence of T_g in composite amorphous systems is commonly modelled with, for example, the Gordon-Taylor equation, which is based on the regular solution theory as applied to glass solutions (Gordon, Rouse et al. 1977). However, the lack of experimental data regarding the pure amorphous state of the diacids impeded such analysis in these systems. In the particular case of the diacid composite systems, the T_g was only reduced to a particular value (49 °C in the case of SDMSA) and then levelled off with no further decrease in the T_g of SDM with increasing concentration of SA (red line shown in Figure 5.9, Figure A-I.12 Appendix A-I shows the reversing heat flow signals of the corresponding SDM:SA MQ composites).

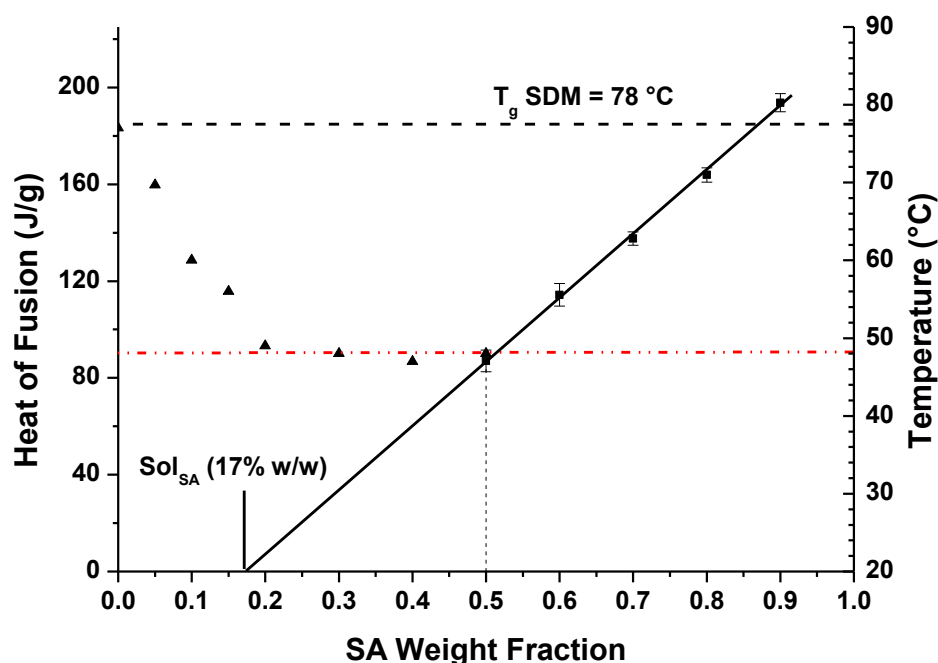


Figure 5.9 Zero enthalpy extrapolation curve (■) for the determination of the solubility of SA in amorphous SDM together with the experimentally determined T_g values (▲) of SDMSA melt quenched composites. Red lines indicates the maximally reduced T_g of SDM:SA melt quenched composite at or above solubility limit.

PXRD analysis revealed that the composite above this critical composition contained crystalline SA (mixture of both α and β -polymorph, data not shown). Thus, above the composition of maximum T_g reduction, SA existed, at least in part, in the crystalline state.

The composition of SA in SDM, at which point the T_g was maximally reduced and beyond which crystalline SA began to separate out, may be considered the “solubility composition” of the excipient in the amorphous state API. The solubility of SA in amorphous SDM, as shown in Figure 5.9, was determined by extrapolating the experimentally determined heat of fusion values associated with crystalline SA at compositions above the solubility composition (in the composition range from 50 to 90% w/w SA in SDM) to the abscissa (i.e. according to the “zero enthalpy extrapolation” method as shown in Chapter 2, Section 2.4.12). The slope and intercept values of the linear regression equations are shown in Table 5.3 along with the R^2 values for each of the SDM: diacid composites. In addition, the solubility composition of MAN in SDM, which was previously determined (Amharar, Curtin et al. 2014) is shown.

Table 5.3 Slope, intercept and R^2 values determined from the zero enthalpy extrapolation determination of the solubility of each excipient in amorphous SDM together with the calculated/ experimental T_g of the excipients and the experimental T_g for each SDM:excipient melt quench composite at 50% w/w.

	Slope	Intercept (J/g)	R^2	Solubility at 25 °C (% w/w)	T_g of Excipient (°C)	T_g of 50% w/w MQ Alloy (°C) ($\pm$ SD)
SDM:SA	262.9	-44.7	0.9984	17	49*	49 (1.2)
SDM:GA	172.3	-55.2	0.9975	32	-14*	43 (1.2)
SDM:AA	288.3	-54	0.9995	19	25*	47 (0.7)
SDM:PA	272	-101.9	0.9973	37	-8*	43 (1.6)
SDM:MAN	275.6* *	-9.7**	0.9996* *	3.5**	13	29 (1.1)/ 78 (0.6)

*Calculated using the 0.7(T_m) Rule [(Fukuoka, Makita et al. 1989)] **From reference (Amharar, Curtin et al. 2014)

Analysis of the solubility values reveals PA to have the highest solubility in amorphous SDM (37% w/w) followed by GA with a value of 32% w/w. Both AA and SA exhibited lower solubility values of 19 and 17% w/w in amorphous SDM respectively. Interestingly, the T_g of the SA composite is the same as the T_g of SA predicted by the 0.7 T_m rule, (Fukuoka, Makita et al. 1989) even though the composition only contains 17% w/w SA. Thus, the true T_g of SA is likely to be less than 49 °C, highlighting the limitation of the rule in the estimation of the T_g of the diacid excipients.

In addition, the T_g values of the co-melt quench alloys at 50% w/w were determined, and are shown in Figure 5.10. As the solubility of each of the diacids was determined to be below 50% w/w in amorphous SDM, the T_g of the 50% w/w alloy represents the maximally reduced T_g of each composite (i.e. of SDM saturated with excipient). Additionally, each of the SDM: diacid composites were also comilled at 50% w/w and the level of T_g reduction determined for each of the comilled composites, shown in Table 5.2. Interestingly, on co-melt quench each of the diacids led to the formation of a single reduced T_g value to within a narrow temperature range from 43 °C with both GA and PA, to 47 °C with AA and 49 °C with SA. Comparison of the T_g reduction formed on comilling with each of the excipients at the same composition (50% w/w) revealed that while both GA and PA reduced the T_g on comilling to a similar extent as the co-melt quench composites (44 and 46 °C

respectively), comilling with SA and AA only led to a T_g reduction to 60 and 66 °C respectively.

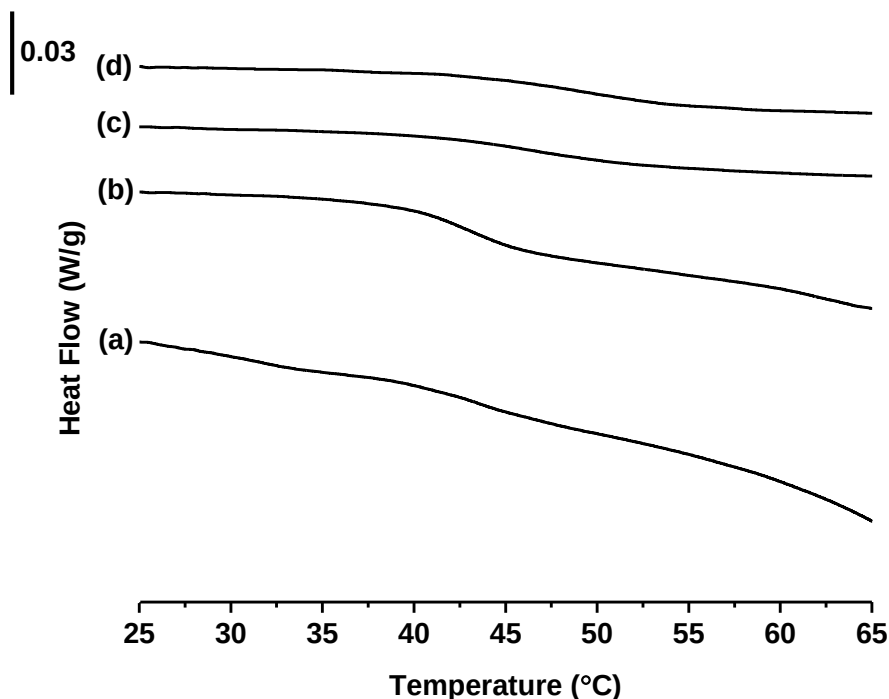


Figure 5.10 Reversing heat flow modulated DSC thermograms of co-thermally activated (melt quench) 50% w/w composites of SDM and (a) GA, (b) PA, (c) AA and (d) SA.

In comparison, on co-melt quenching MAN with SDM at 50% w/w, the amorphous composite produced contained two T_g events at 29 and 78 °C, as detailed in Table 5.3. This behaviour suggested limited miscibility of MAN in SDM, in both the co-melt solution state, and subsequently in the amorphous state produced by melt quench of the melt. Additionally, MAN did not result in any T_g reduction on comilling with mSDM, as described in Section 5.2.2.

5.4 MELTING POINT DEPRESSION ANALYSIS – MISCIBILITY AND EXCESS THERMODYNAMIC FUNCTIONS OF INTERACTIONS IN THE LIQUID STATE

In Section 5.3, the glass transition temperature and solubility compositions of amorphous composite systems formed by fast cooling of the liquid (molten) mixtures of SDM and diacid/polyol excipients were determined. In Section 5.2 the formation of amorphous composite systems by mechanical driving was assessed and the level of T_g reduction of amorphous SDM on comilling was determined. Spectroscopic analysis also revealed evidence for a H-bonding interaction in the amorphous composites formed on comilling with the diacids, in particular with GA. However, comparison of the co-mechanically and co-thermally activated alloys suggested a difference in terms of T_g reduction for the amorphous alloys formed with the diacids SA and AA in contrast to both GA and PA which showed comparative T_g reduction on comilling and co-melt quenching. In contrast comilling with MAN did not result in any level of T_g reduction on comilling with amorphous SDM.

We have hypothesised that effecting a T_g reduction on comilling is an essential component in the context of mitigation of amorphisation on comilling. Thermodynamic assessments of the mixing characteristics and the quantitative determination of the nature and extent of interactions in amorphous glass solutions have previously been determined using calculation based methods for lyophilised blends of amorphous sugars and for solid dispersion systems (Shamblin, Taylor et al. 1998, Vasanthavada, Tong et al. 2005). However, as the diacids could not be amorphised the lack of any experimental data for their amorphous state characteristics significantly undermines the accuracy of a calculations based approach for these systems.

Table 5.4 shows a range of physical characteristics of the crystalline excipients SA, GA, AA, PA and MAN in addition to crystalline SDM, including molecular weight, melting temperature and melting (fusion) enthalpy. In addition, Table 5.4 includes the calculated Hildebrand solubility parameters of each of the materials, the calculation of which are shown in Appendix A-VI. Melting point depression analysis was performed on physical mixtures of GA, AA, PA and MAN with crystalline SDM in order to provide an assessment of the thermodynamics of mixing between SDM and

the low T_g excipients in the liquid solution state. Figure 5.11A-D shows the DSC scans determined with increasing concentration of each of the excipients.

Table 5.4 Physical characteristics and calculated Hildebrand solubility parameters of SDM, SA, GA, AA, PA and MAN.

	M_w (g/mol)	T_m (K)	$\Delta_{fus}H^\circ$ (J/mol)	δ^* (MPa ^{1/2})
Sulfadimidine	278.3	471.4	35930	25.7
Succinic Acid	118.1	462	31649	27.0
Glutaric Acid	132.1	371.5	21563	25.8
Adipic Acid	146.1	425.25	36045	24.9
Pimelic Acid	160.2	378.4	28790	24.1
Mannitol	182.2	441.2	54823	38.2

* Calculated Hildebrand solubility parameter

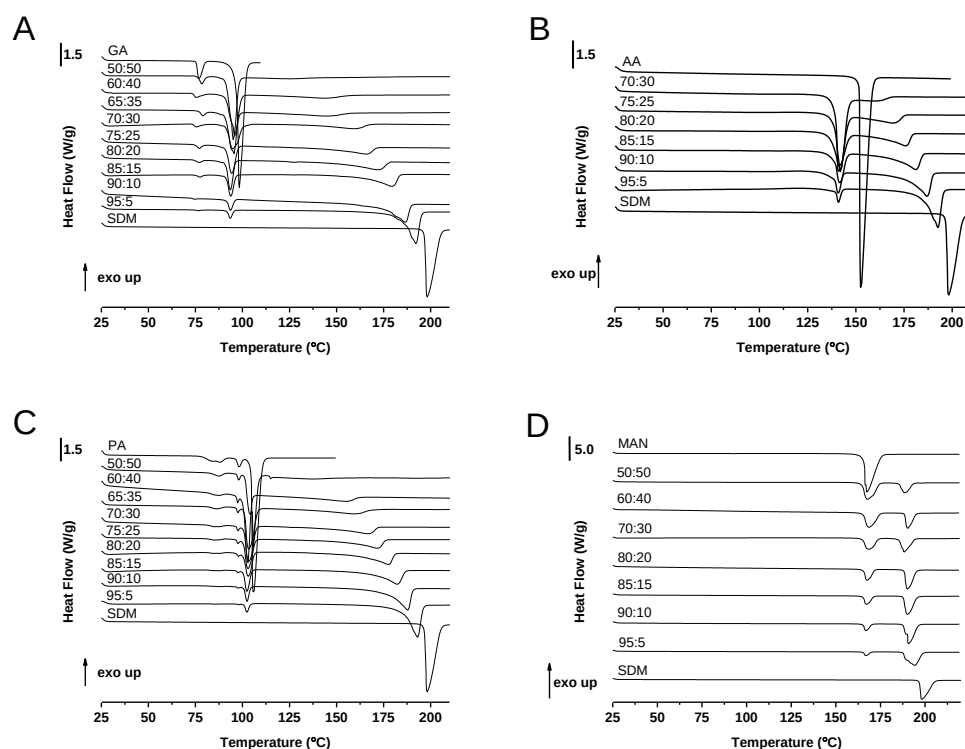


Figure 5.11 DSC thermograms showing heating scans of physical mixtures of crystalline SDM with A) GA, B) AA, C) PA and D) MAN.

As shown in Figure 5.11, each of the diacids led to a successively reduced liquidus melt temperature of SDM with increasing composition of excipient, an indication that the diacids and SDM were miscible in the liquid state. As described in Appendix A-II, physical mixtures of SDM and SA on heating to the eutectic melting of

SA led to the crystallisation of a cocrystal from the melt solution, and was thus not amenable to melting point depression analysis. Additionally, the melt endotherm of each of the diacids in the composite systems was reduced relative to the pure diacid, indicating a reduced eutectic melting temperature in each case. In particular, the T_m of AA was reduced to 141 °C in the SDM:AA composites from 152 °C for pure AA. Additionally, the T_m of GA was reduced to 94 °C in the SDM:GA composites from 98 °C for pure GA and the T_m of PA was reduced to 101 °C in the SDM:PA composites from 106 °C for pure PA. Thus, the reduction in the eutectic T_m of the AA composite was interestingly almost twice that of either composite formed with GA or PA and SDM.

In contrast, the melting temperature of MAN in the SDM:MAN composites was not reduced relative to pure MAN at 168 °C. The melting temperature of SDM displayed melting point depression up to the 90:10 composition after which no further decrease in the melting point of the composite system occurred indicating limited (partial) miscibility. Utilising the physical data shown in Table 5.4, the Schroeder-van Laar equation, as detailed in Chapter 2, Section 2.4.13, was used to determine the theoretical melting point depression of SDM in an ideal mixture, as detailed in Table 5.5 and shown graphically in Figure 5.12 (Reddi, Satuluri et al. 2011).

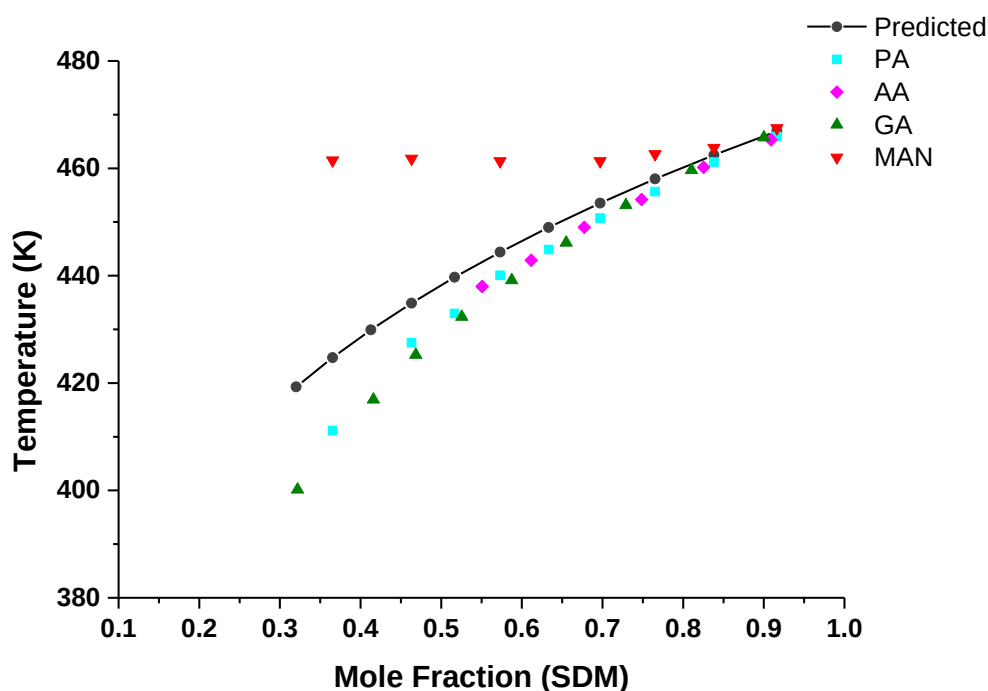


Figure 5.12 Predicted melting point depression of SDM (black line) from the ideal solubility equation and experimental melting point depression values of SDM in the presence of the excipients GA, AA, PA and MAN.

Table 5.5 Predicted melting point depression values of SDM derived from the ideal solubility equation together with experimental melting point depression values and computed activity co-efficients (γ) of mixtures of SDM with GA, AA, PA and MAN from the Schroeder-Van Laar equation.

X_{SDM}	$T_{SDM(P)}^*$ (K)	$T_{SDM(E)}^{**}$ (K)				$\ln\gamma_{(SDM)}$			$\ln\gamma_{(GA)}$	$\ln\gamma_{(AA)}$	$\ln\gamma_{(PA)}$
		GA	AA	PA	MAN	GA	AA	PA			
0.5	419.5	400.2	-	411.2	461.2	-0.5	-	-0.336	0.889	-	1.185
0.6	430.2	416.9	-	427.5	461.1	-0.32	-	-0.171	1.299	-	1.675
0.65	435.4	425.3	-	433	-	-0.236	-	-0.153	1.156	-	1.881
0.7	440.5	432.3	438	440.1	461.5	-0.185	-0.102	-0.096	1.729	1.085	2.135
0.75	445.5	439.2	442.9	440.9	-	-0.141	-0.098	-0.09	1.961	1.4	2.371
0.8	450.6	446.2	449	450.7	461.3	-0.095	-0.067	-0.06	2.233	1.659	2.664
0.85	455.6	453.2	454.2	455.7	462.3	-0.053	-0.057	-0.049	2.564	2.018	3.002
0.9	460.8	459.7	460.2	461.2	463.8	-0.023	-0.031	-0.027	3.002	2.507	3.464
0.95	466	465.8	465.3	466	467.5	-0.005	-0.024	-0.019	3.718	3.261	4.2

*Predicted melting point (values shown relative to the mole fraction (X_{SDM}) of SDMGA system) **Experimental melting point

In an ideal liquid mixture, the adhesive and cohesive forces are balanced (Shamblin, Taylor et al. 1998). However, in real mixtures deviation from ideality is commonly observed due to specific interactions leading to unbalanced cohesive and adhesive intermolecular bonding (Reddi, Satuluri et al. 2011). Figure 5.12 shows graphically the comparison of the expected melting point of ideal solutions and the experimentally determined melting points of each of the composite systems. While MAN showed only a slight decrease in the melting point of SDM, the T_m of SDM in the presence of each of the diacids GA, AA and PA showed a negative deviation from the ideal solubility line, indicating that the mixtures with the diacids, although miscible, do not behave ideally, which is an indication of specific interactions on mixing in the liquid state. Deviation from ideal behaviour was accounted for by the inclusion of the activity coefficient in the Schroeder-van Laar equation, the specifics of which are detailed in Chapter 2, Section 2.4.13. From the experimental melting point values of the composites formed with miscible components (the diacids in this case) the activity coefficients were determined, in a manner similar to that reported by Meltzer et al. who investigated the eutectic alloys formed between tartaric and citric acid (Meltzer and Pincu 2012). The values of the activity coefficients thus determined are shown in .

The experimentally determined activity coefficients have been used to compute the excess thermodynamic functions for eutectic mixtures of miscible molecular systems, allowing a quantitative assessment of the thermodynamics of mixing in the liquid state (Sharma, Tandon et al. 2004, Reddi, Satuluri et al. 2011). A shows the excess Gibbs energy (G^E) plot for the SDM/GA, PA and AA composites, which is positive across the composition range studied for each system. In contrast, C indicates that the excess enthalpy of interaction (H^E) was negative, an indication of an exothermic (hydrogen bonding) interaction on mixing in the liquid state between the diacids and SDM. However, as shown in B, the excess entropy, S^E , on mixing with SDM was negative for each of the diacids and it was the negative entropic contribution which led to an overall positive G^E over the composition range. This behaviour has previously been attributed to the cohesive forces between like components being stronger than the adhesive forces formed between unlike components (Rai and Pandey 2004). This could be due to the ability of the diacids to form relatively strong carboxyl group dimers in the liquid state.

The exothermic nature of the interaction on mixing with AA was more negative, as indicated by a more negative H^E curve, relative to either GA or PA as shown in

Figure 5.13C. This could explain the greater level of reduction in the eutectic melting temperature of AA on mixing relative to either GA or PA with SDM, as noted above where the eutectic melting temperature of the SDM:AA composite was reduced by almost twice that of either the SDM:GA or SDM:PA composites. Gupta et al. correlated a negative H^E formed in the eutectic melt between β -naphthol and vanillin with FTIR spectroscopic evidence for interaction in the crystalline eutectic formed on cooling (Gupta, Agrawal et al. 2012). However, in the current context, we are not forming a crystalline eutectic system below the eutectic T_m , characterised by a phase separated crystalline-crystalline microstructure but rather, an amorphous glass solution characterised by a single composite T_g , indicative of mixing of both components at the molecular level. Importantly, the compositions considered in this MPD analysis included the solubility composition of each of the diacids in amorphous SDM at RT, as shown in Figure 5.13A-C, thus allowing an analysis of the thermodynamics of mixing in the liquid state close to this composition.

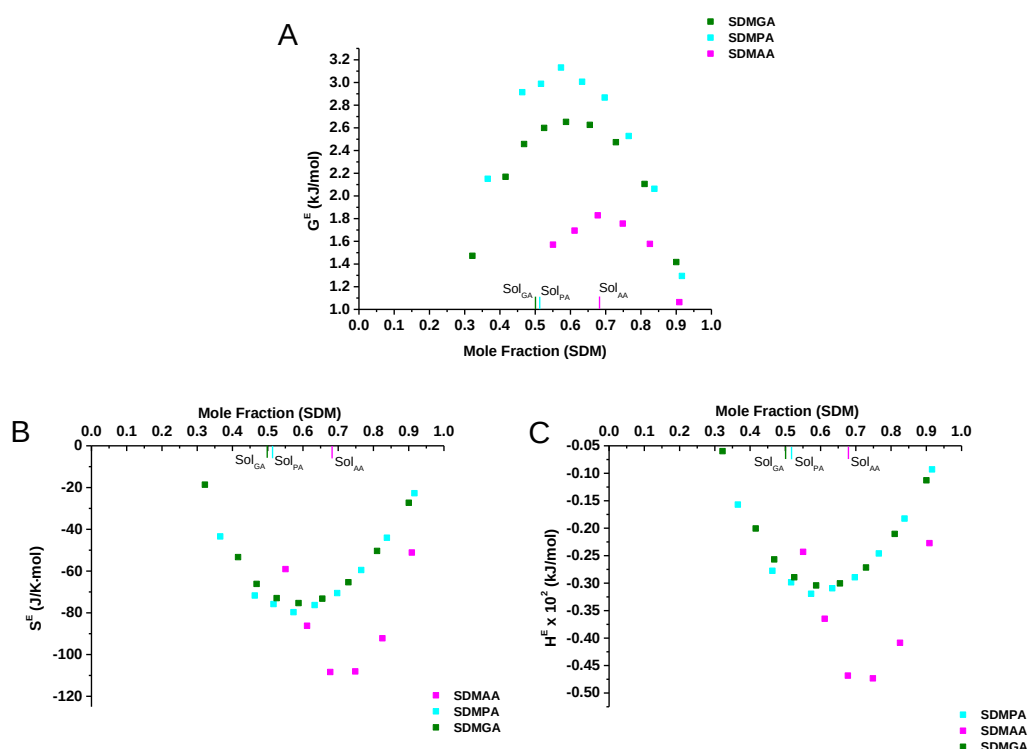


Figure 5.13 Excess thermodynamic functions computed from the activity co-efficients of mixtures of SDM with GA, AA and PA showing A) the excess Gibbs energy, G^E B) the excess entropy, S^E and C) the excess enthalpy, H^E of mixing.

The computed excess thermodynamic functions provide both a qualitative and quantitative insight into the thermodynamics of mixing in the liquid state. They also

allow a comparison between the diacids into the thermodynamic nature of the interactions formed in particular with SDM on mixing. Most importantly, the analysis suggests that, in addition to there being no miscibility barrier to mixing (in contrast to MAN) between the diacids and SDM, the thermodynamics of mixing are comparable for each of the three diacids with each excipient having a favourable (exothermic) H^E on mixing, thus suggesting that there is additionally no thermodynamic barrier to mixing with any of these diacids. In addition, as noted by Sharma et al., the strength of the MPD approach to assessing the thermodynamics of interaction is that it is based on experimental evidence and does not require theoretical assumptions common to many calculation-based approaches (Sharma, Kant et al. 2003).

5.5 CRYSTALLISATION STUDIES OF SULFADIMIDINE FROM THE CRYOMILLED DRIVEN ALLOYS

5.5.1 DVS Studies

The amorphous state produced on mechanical and co-mechanical activation is metastable from a thermodynamic perspective, and will inevitably undergo a transformation to the crystalline state (Hilden and Morris 2004). However, although crystallisation is thermodynamically favoured, the timescale over which the transformation occurs can often be determined by kinetic rather than thermodynamic factors (Lim, Ng et al. 2013). The humidity induced crystallisation behaviour of the amorphous composites formed on comilling SDM with the diacid excipients GA, PA and SA in the VBM at CT were assessed in the DVS in order to characterise both the effect of the excipient on crystallisation of SDM from the amorphous state relative to SDM milled alone, and to compare the relative stability of the diacid composites formed on comilling. In addition, as water was used as the probe vapour the results have both a theoretical and practical relevance, as humidity may be considered a variable condition during milling, and is known to have a significant influence on the properties of amorphous solids, and potentially on the nature of the solid state transformations of a milling and/or comilling operation (Kwok, Mauer et al. 2010).

5.5.1.1 *Sulfadimidine and Glutaric Acid Co-Cryomilled Composite*

Crystalline SDM was comilled with GA at 50% w/w in the VBM at CT for 54 minutes. PXRD analysis of the composite (shown in Figure 5.16 (a)) revealed Bragg peaks associated with both α and β -polymorphic GA with no peaks associated with crystalline SDM. The stepwise sorption plot of the co-cryomilled SDMGA composite is shown in Figure 5.14A. The plot revealed two mass loss events, the first at 50% RH and the second at 70% RH. In addition, Figure 5.14B shows the kinetic sorption plot (10% RH/ hour) for the SDMGA composite. Similar to the stepwise sorption plot, the kinetic plot reveals two mass loss events. The curvature of the mass uptake before the first mass loss event was associated with initial surface adsorption and subsequent bulk absorption at higher RH of the amorphous regions of the sample (shown to be amorphous by PXRD). The RH_{g10} (the glass transition relative humidity determined from 10% RH/ hour ramp) was determined by extrapolation

of the two linear portions associated with surface and bulk sorption as shown in Figure 5.14B and detailed in Table 5.6. The RH_{c10} (the crystallisation relative humidity determined from 10% RH/ hour ramp) was determined from the first mass loss event (where dm/dt reaches 0). Relative to SDM milled alone, comilling with GA effected a reduction in the RH_{g10} of SDM from 41 to 30% RH and a reduction in the RH_{c10} from 75 to 54% RH.

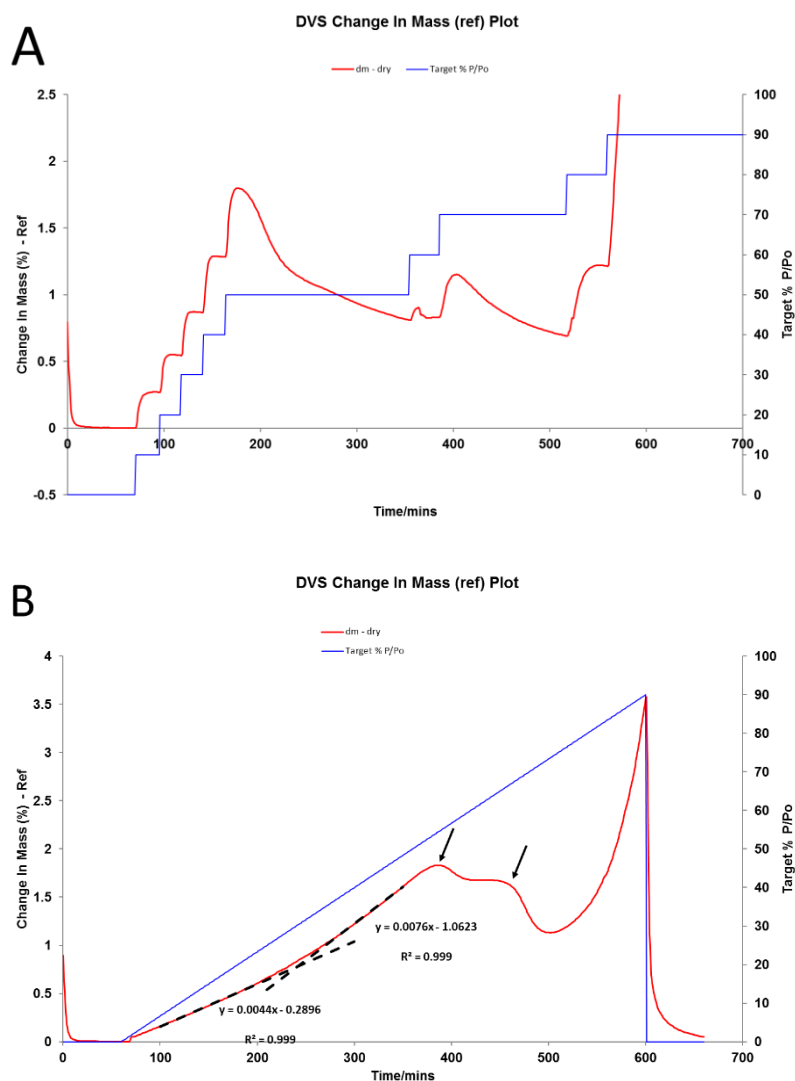


Figure 5.14 DVS analysis of the composite formed on comilling crystalline SDM with GA in the VBM at CT at 50% w/w for 54 minutes showing the A) change in mass plot and B) kinetic ramp at 10% RH/ hour with water as probe vapour.

Table 5.6 Comparison of the calculated RH_g and RH_c values for cryomilled SDM and SDM co-cryomilled 50% w/w w GA, PA and SA composites determined from the 10%/ hour kinetic ramp with water as the probe vapour.

	RH_{c10} (%) (StD)	RH_{g10} (%) (StD)
SDM	75.3 (0.2)	40.7 (0.6)
SDMGA	53.7 (0.7)	29.9 (1.1)
SDMPA	59.4 (0.4)	-
SDMSA	75.4 (0.2)	38.7 (0.1)

SEM analysis of the cryomilled SDMGA composite before and after crystallisation in the DVS, shown in Figure 5.15, indicated a significant change in morphology on crystallisation. Before crystallisation, the surface appeared to consist of a smooth matrix with small crystallites embedded throughout. After crystallisation, the matrix appeared rough and embedded crystals were larger relative to those observed prior to crystallisation. Similar changes in the morphology of the co-cryomilled BDGA system were observed on crystallisation in the DVS shown in Chapter 4.

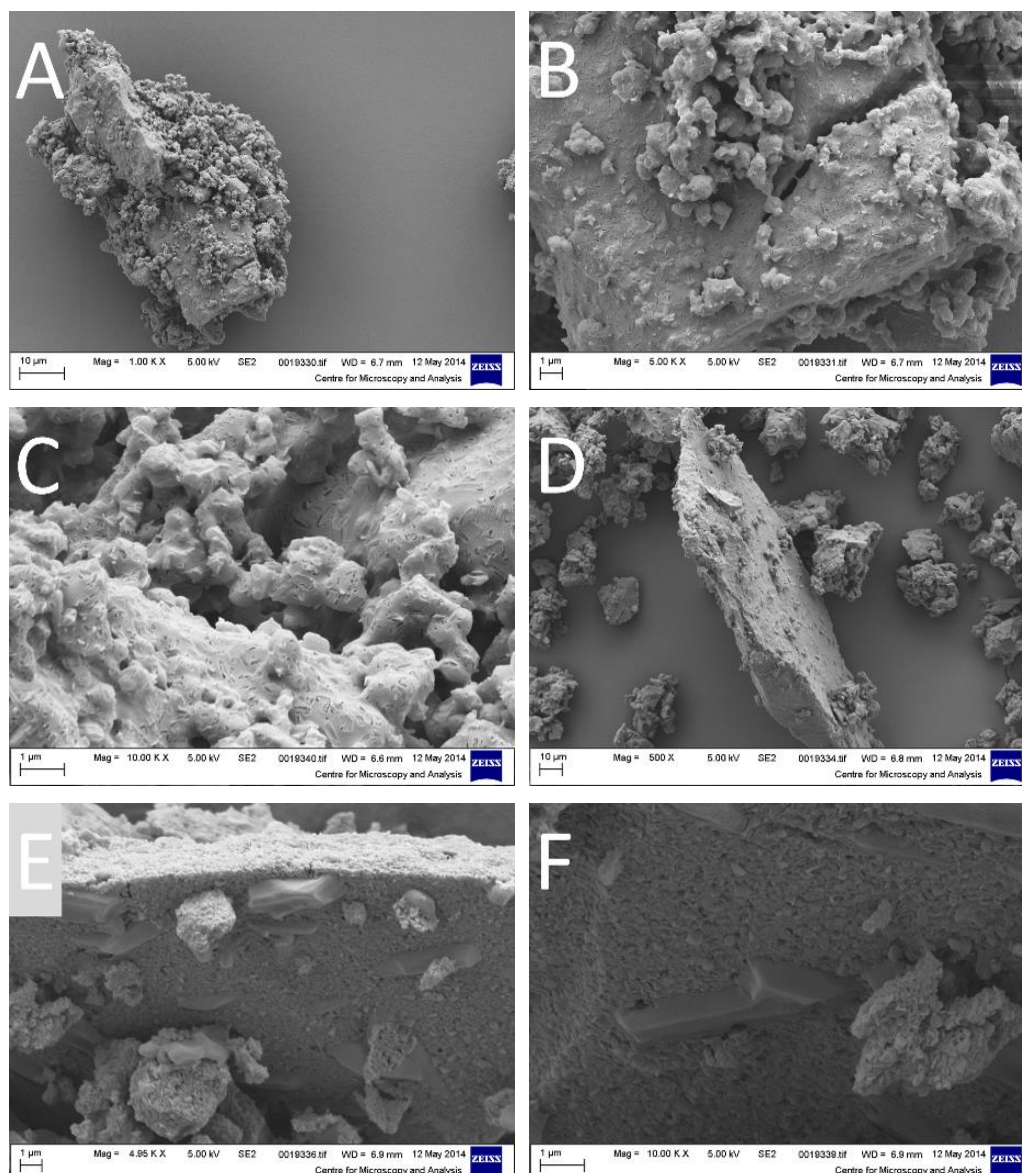


Figure 5.15 SEM images showing the composite formed on comilling crystalline SDM with GA at 50% w/w in the VBM at CT (A-C) before and (D-F) after crystallisation in the DVS.

In order to further probe the crystallographic changes occurring during the two mass loss events observed in the DVS sorption plots, the cryomilled SDMGA amorphous composite was held at both 43% RH (over saturated K_2CO_3 solution) and 75% RH (over saturated NaCl solution) at 25 °C. Figure 5.16 shows the PXRD trace after 4 hours at 43% RH, showing evidence of an increase in Bragg peaks associated with crystalline SDM and crystalline beta GA relative to the system before crystallisation. However, α -GA peaks at 22-23° 2θ were still evident in the trace. A comparison of the PXRD trace of the composite held at 75% RH after 4 hours indicated complete transformation to the β -polymorph and an apparent increase in the intensity of the SDM peaks.

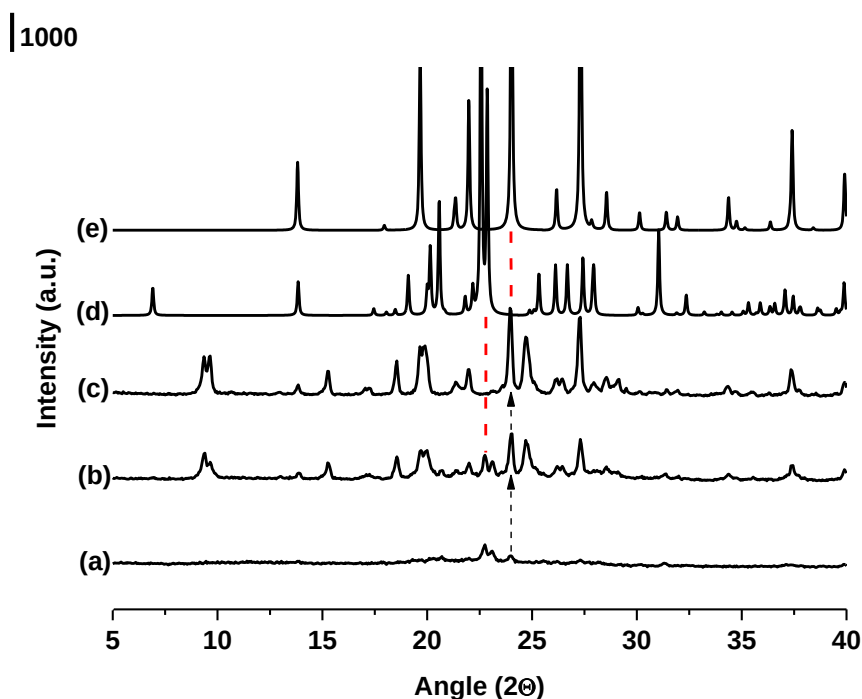


Figure 5.16 PXRD diffractograms of the composite formed on comilling crystalline SDM with GA at 50% w/w in the VBM at CT (a) before crystallisation, (b) after 3 hours maintained at 25 °C and 43% RH, (c) after 3 hours maintained at 25 °C and 75% RH and PXRD patterns of d) α -GA generated from single crystal data from the CCDC and (e) β -GA generated from single crystal data from the CCDC. Red lines indicate Bragg peaks associated with crystalline GA.

Figure 5.17 reveals FTIR analysis of the SDMGA co-cryomilled composite in the spectral regions associated with A) the aromatic amine and sulfonamide group N-H stretching of SDM and B) the C=O stretching region associated with the carbonyl group of GA. The gradual shift to lower wavenumbers of the N-H stretching peaks of SDM observed after 100 and 205 minutes at 43% RH in Figure 5.17A is characteristic of a crystallisation process, which appeared to be complete after 205 minutes. In addition, a gradual reduction in the shoulder of the carbonyl peak of GA after 100 and 205 minutes at 43% RH correlated with the crystallisation of GA into the β -polymorph from the co-cryomilled amorphous composite. Together with the PXRD data, this suggests that full crystallisation of SDM may have occurred at the 43% RH mass loss event, while the mass loss event at 75% RH may not be due to an amorphous to crystalline transformation, but instead due to polymorphic transformation of residual α -polymorphic GA to the thermodynamically stable β -polymorphic form. It would appear that the amorphous composite formed on co-

cryomilling SDM with GA not only had a reduced T_g , RH_g and RH_c but indeed that the crystallisation of the API from the amorphous composite was being driven by the concomitant crystallisation of the low T_g excipient.

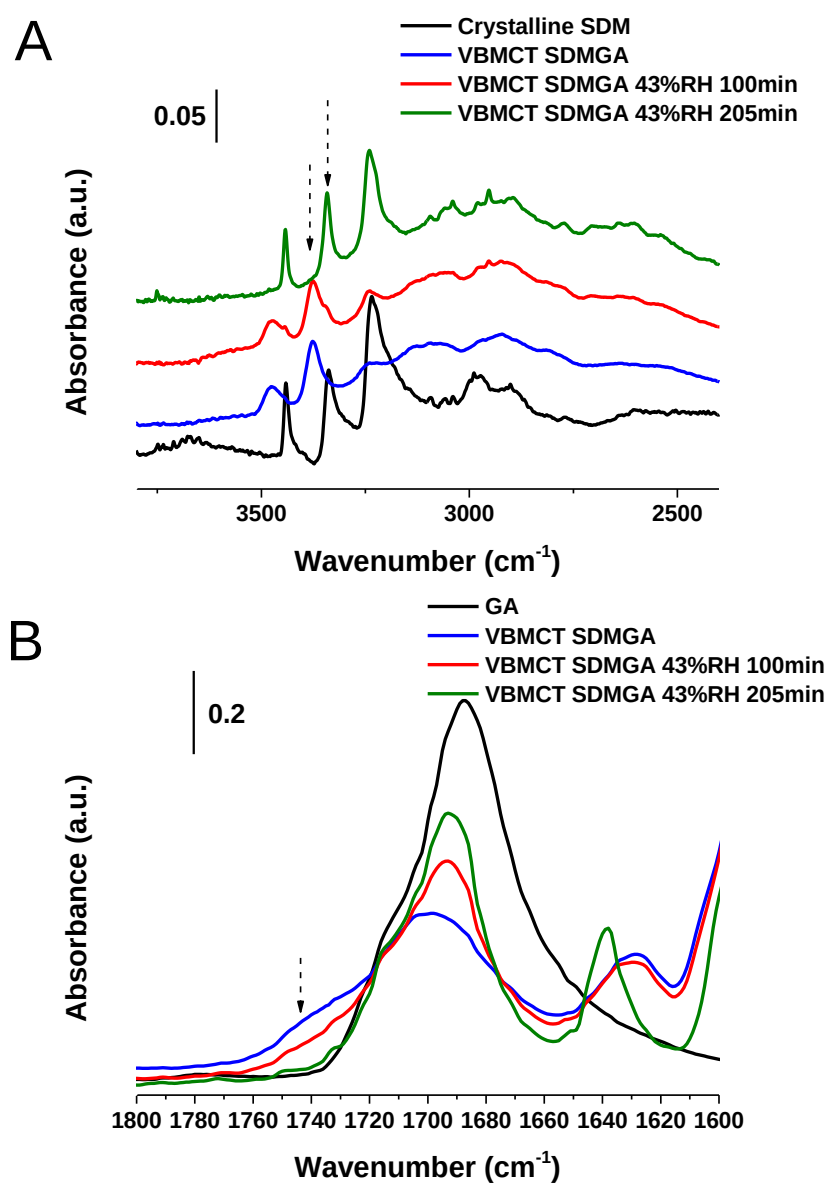


Figure 5.17 FTIR spectra in the A) 3600-2400 cm^{-1} and B) 1800-1600 cm^{-1} region of the composite formed on comilling crystalline SDM with GA in the VBM at CT at 50% w/w before crystallisation and after 100 and 205 minutes maintained at 25 °C and 43% RH.

5.5.1.2 Sulfadimidine and Pimelic Acid Co-Cryomilled Composite

Crystalline SDM was co-cryomilled for 54 minutes with PA in the VBM at CT at 50% w/w. The PXRD diffractogram of the co-cryomilled composite is shown Figure 5.18 (a), and shows no evidence of Bragg peaks associated with crystalline SDM

indicating that SDM was fully amorphised in the comilling operation. Trace evidence of γ -polymorphic PA was evident in the diffractogram (Characterisation of γ -polymorphic PA is shown in Appendix A-III).

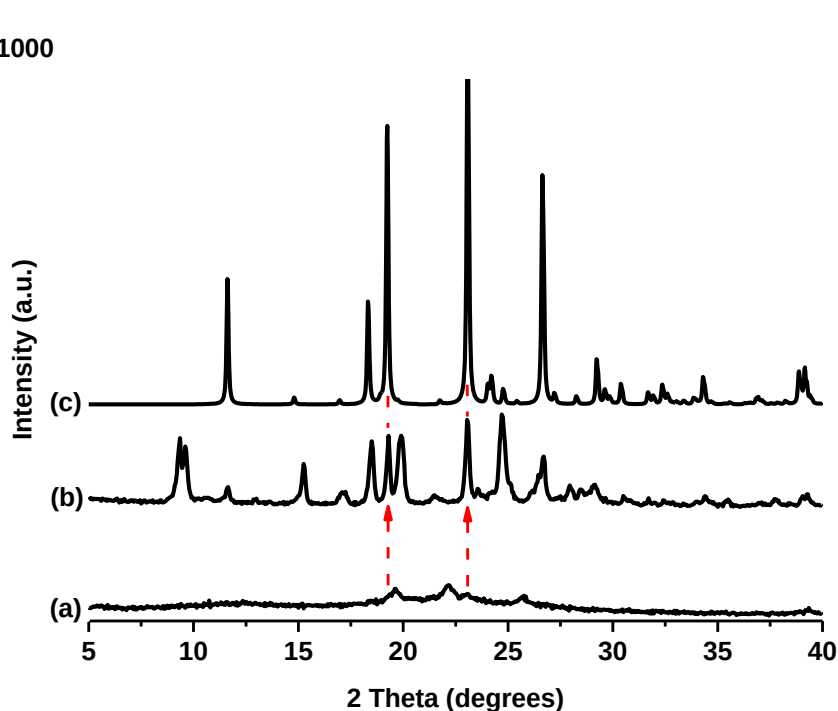


Figure 5.18 PXR D diffractogram the composite formed on comilling crystalline SDM with PA in the VBM at CT at 50% w/w for 54 minutes (a) before crystallisation and (b) after crystallisation in the DVS and (c) the CCDC generated PXR D diffractogram of α -polymorphic PA. Red arrows indicate Bragg peaks associated with crystalline PA.

Figure 5.19A shows the stepwise sorption plot of the composite from 0-90% RH, indicating the onset of a mass loss event at 40% RH. The isotherm plot is shown in Figure 5.19B. The mass loss event continued to occur on increasing from 40 to 50% RH, while on increasing to 60% RH a more significant mass loss event was observed. No further mass loss event was apparent up to 80% RH indicating that full crystallisation had occurred by this stage.

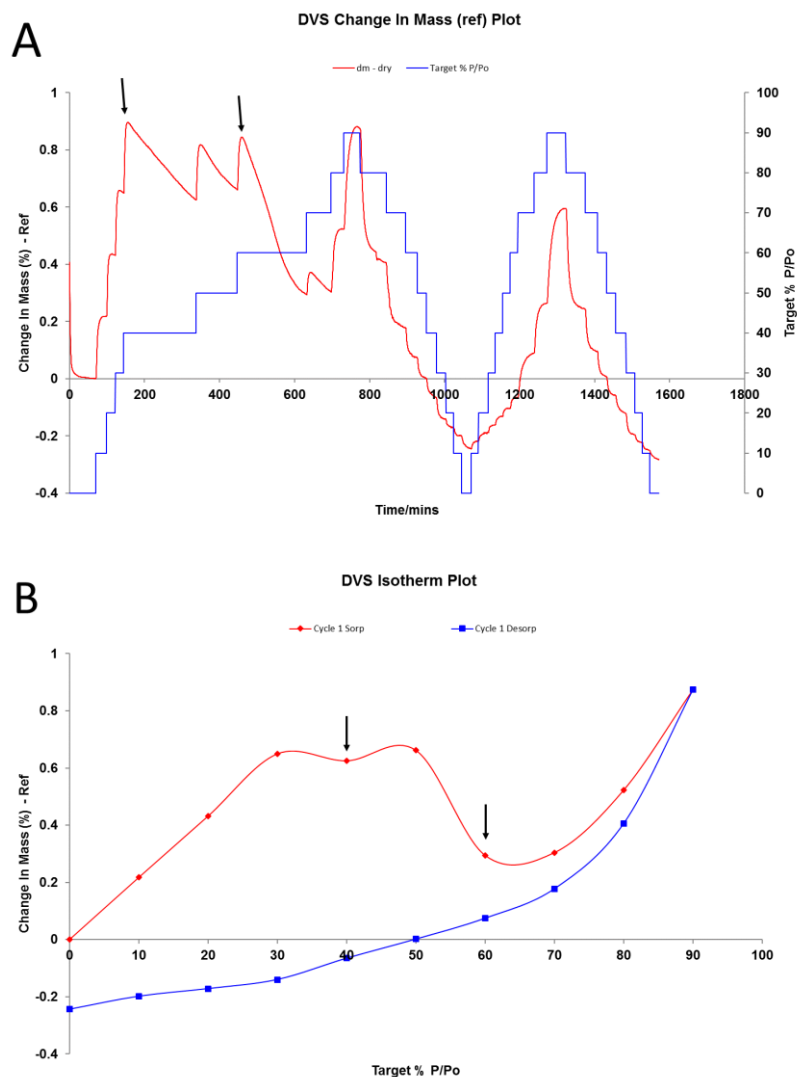


Figure 5.19 DVS analysis showing the A) change in mass plot and B) isotherm plot of the composite formed on comilling crystalline SDM with PA in the VBM at CT at 50% w/w for 54 minutes using water as the probe vapour.

The kinetic ramp (10% RH/ hour) is shown in Figure 5.19B. In contrast to the SDMGa system, the initial sorption profile before the crystallisation event was a straight line, possibly indicating equal rates of surface and bulk sorption and thus did not allow for the determination of the RH_g . However, the RH_{c10} was determined from the point of inflection where $dm/dt = 0$. The RH_{c10} of the SDMPa composite at 59% RH was reduced relative to amorphous SDM (75% RH) but was higher than the RH_{c10} of the SDMGa co-cryomilled composite (54% RH). PXRD analysis of the composite before and after crystallisation in the DVS, as shown in Figure 5.18, indicated that the composite had indeed undergone a crystallisation event, with the

presence of Bragg peaks associated with crystalline SDM and with α -polymorphic PA.

The change in slope of the kinetic ramp before the inflection point could be due to slow initial crystallisation kinetics at lower RH values (between 40 and 50% RH as shown from the stepwise sorption plot) followed by faster crystallisation kinetics at a higher RH value (60% RH from the stepwise sorption plot). This contrasts with the mass loss events observed in the SDMGA system, which appeared to be two separate and distinct events, while in the SDMPA system the multiple mass loss events appear to be due to a continuous crystallisation process.

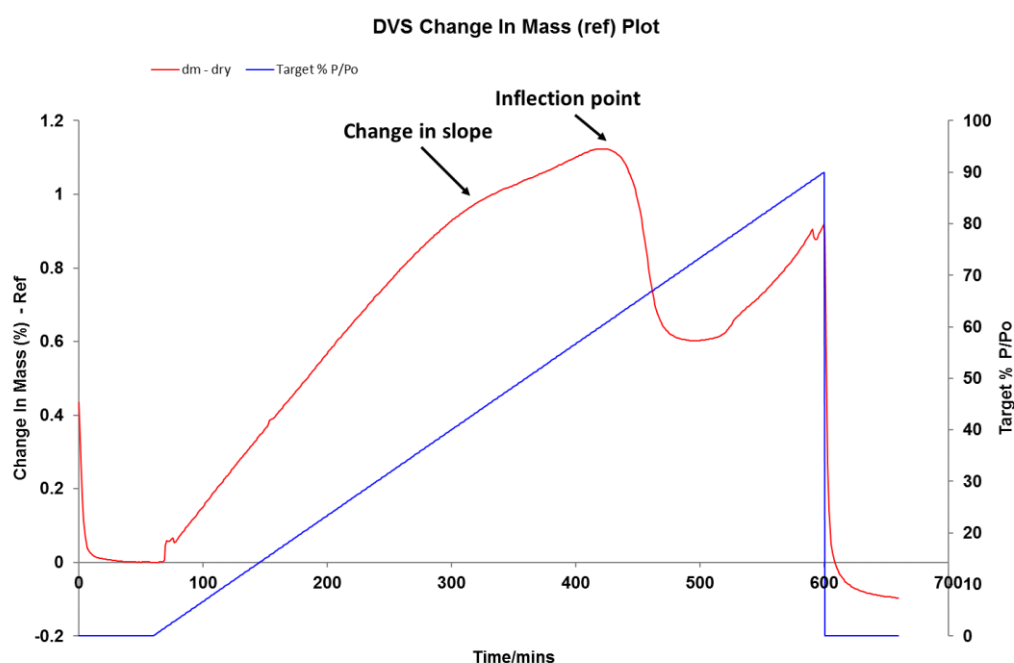


Figure 5.20 DVS kinetic ramp (10% RH/ hour) of the co-cryomilled SDMPA 50% w/w composite.

5.5.1.3 Sulfadimidine and Succinic Acid Co-Cryomilled Composite

Crystalline SDM was comilled with SA in the VBM at CT at 50% w/w for 54 minutes. DVS analysis of the co-cryomilled composite shown in Figure 5.21A indicated a mass loss event at 80% RH, similar to that observed for SDM milled alone. A clear distinction was also observed in the sorption profile before the inflection associated with crystallisation, associated with initial surface adsorption at lower RH values and subsequent bulk absorption of water into the amorphous matrix at higher RH values. The RH_{g10} was determined from the point of inflection to be 39%, which

indicates a slight reduction in the RH_{g10} relative to amorphous SDM, which has a RH_{g10} of 41% RH. The RH_{c10} was determined from the point of inflection to be 75%, similar to amorphous SDM milled alone. PXRD analysis of the composite after DVS analysis indicated the presence of β -polymorphic SA along with crystalline SDM, as shown in Appendix A-I, Figure A-I.13.

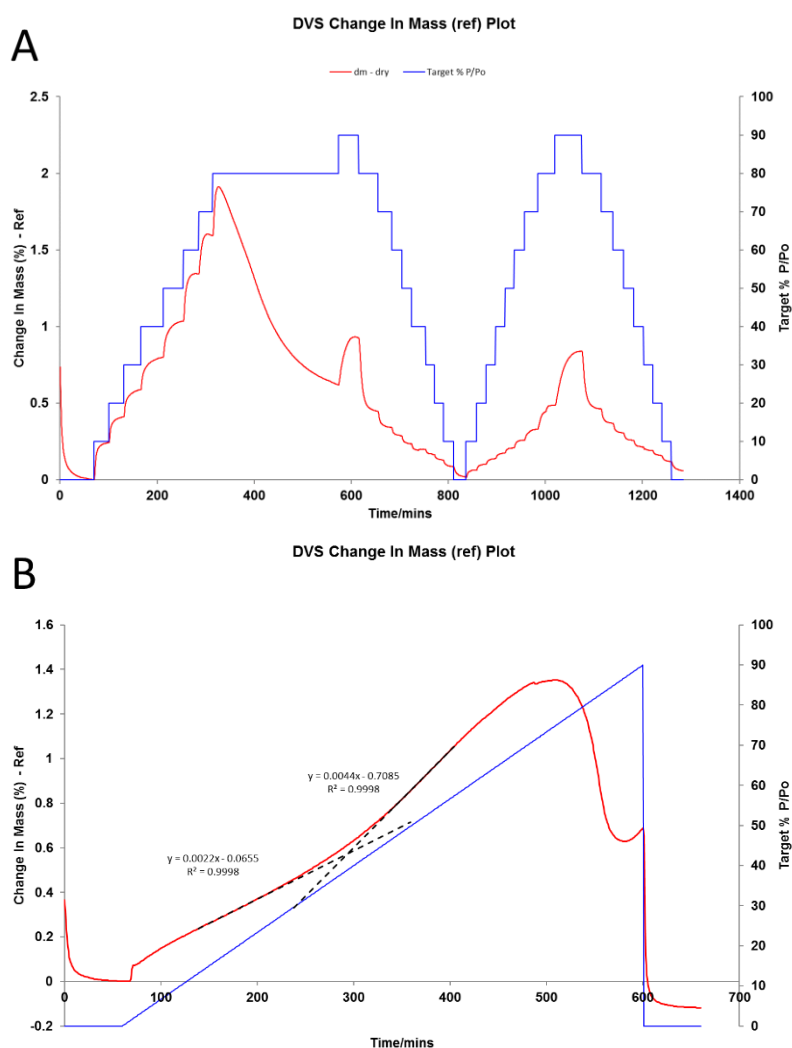


Figure 5.21 DVS analysis of the composite formed on comilling crystalline SDM with SA in the VBM at CT at 50% w/w for 54 minutes showing the A) change in mass plot and B) kinetic ramp at 10%/ hour using water as the probe vapour.

5.5.1.4 Comparison of Isobaric Crystallisation of SDMGA and SDMPA Composites at RH_{c0}

In order to compare the kinetics of crystallisation of the SDMGA and SDMPA co-cryomilled composites in the DVS, while taking into account the effect of %RH on the rate of crystallisation, the RH_{c0} of the 50% w/w co-cryomilled SDMGA and

SDMPA composites was determined. This was accomplished by evaluating the RH_c at 6% and 10% ramp rates for the SDMPA composite and at 2%, 6%, 8% and 10% ramp rates for the SDMGA composite and subsequently extrapolating to 0% RH/hour ramp rate as illustrated in Figure 5.22. The extrapolation procedure indicated the RH_{c0} of SDMPA to be 53% RH which was consistent with the mass loss event observed at the 60% RH step in the sorption plot shown in Figure 5.19. The RH_{c0} for the SDMGA co-cryomilled composite was determined to be 43% RH which was also consistent with the first mass lost event at 50% RH shown in Figure 5.14.

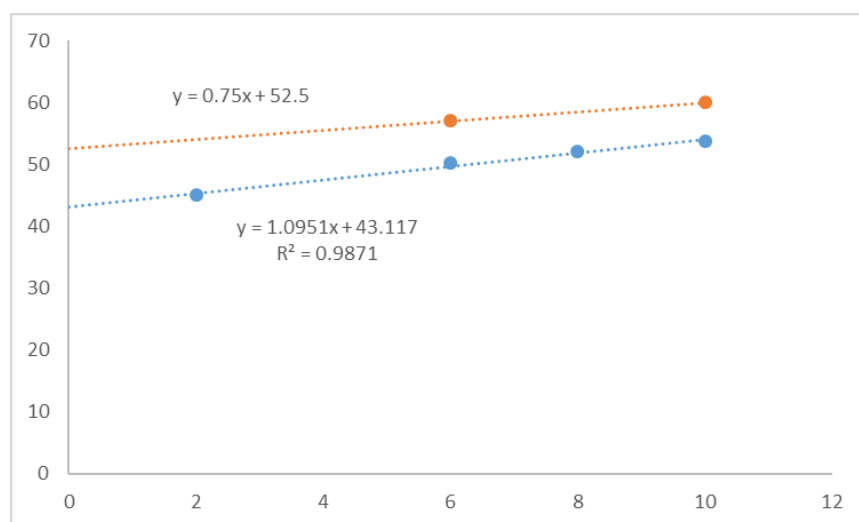


Figure 5.22 Determination of the RH_{c0} by extrapolation of the 10% and 6% (PA) and 10%, 8%, 6% and 2% of GA co-cryomilled SDM composites

Additionally, GA and PA were co-cryomilled with crystalline SDM at their respective solubilities as determined in Section 0, by the zero enthalpy extrapolation method. Comparison of the PXRD diffractograms of the composites at 50% w/w and at their respective solubility compositions (32% for GA and 37% for PA) are shown in Figure 5.23. The diffractograms revealed the disappearance of the Bragg peaks associated with either excipient at the experimentally determined solubility, corroborating the solubility values. Interestingly, 32% w/w GA in SDM and 37% w/w PA in SDM correspond to a 1:1 molar ratio respectively. Comparison of the crystallisation kinetics was subsequently determined from their respective maximally saturated solubility compositions, corresponding to a 1:1 molar ratio in each case, when held at 53% RH and 43% RH respectively. The time taken to reach 0.002 dm/dt was determined to be 470 minutes for the SDMPA system and 160 minutes for the SDMGA system, as shown in Figure 5.24.

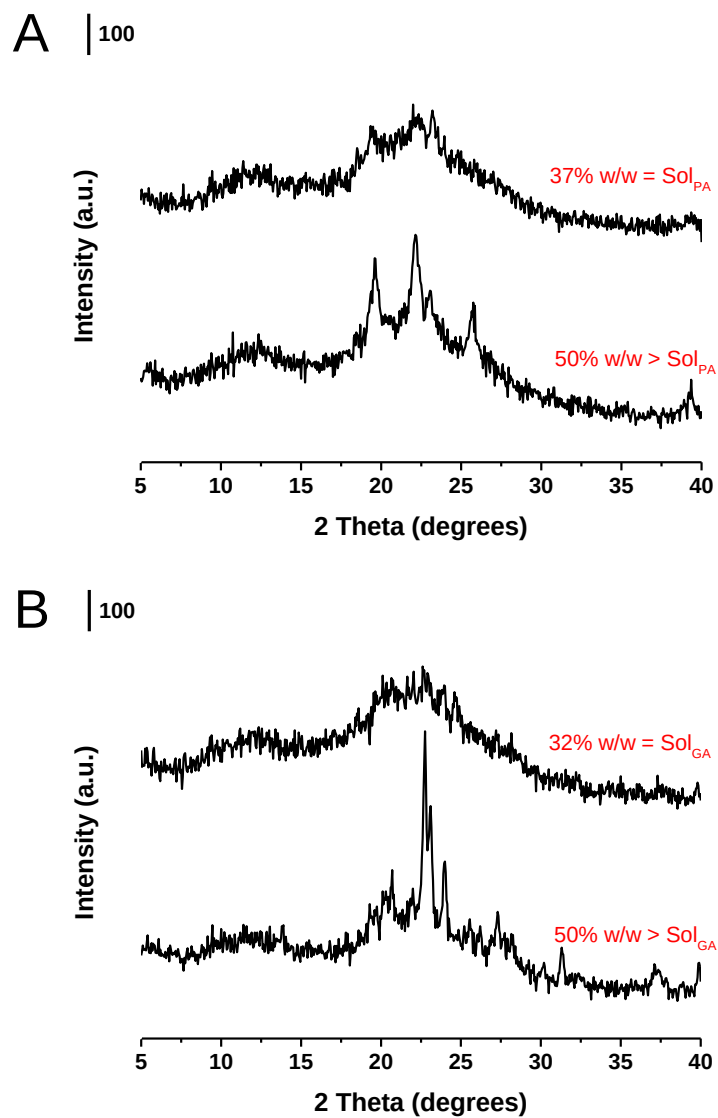


Figure 5.23 PXR D diffractograms of the composites formed on co-cryomilling for 54 minutes A) SDM with crystalline PA at both 50% and 37% w/w and B) SDM with crystalline GA.

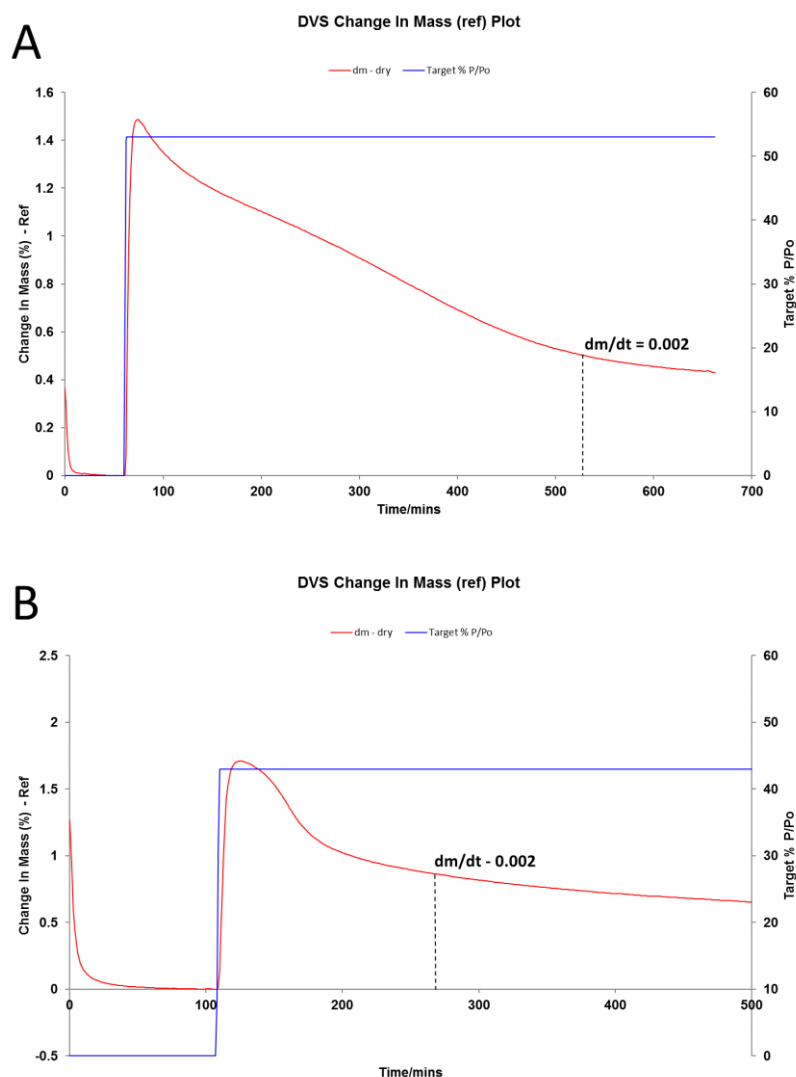


Figure 5.24 DVS isobaric studies showing the composite formed on co-cryomilling in the VBM at CT SDM with A) PA at 37% w/w at 53% RH for 10 hours and B) GA at 32% w/w at 43% RH for 10 hours.

5.5.2 Non-Isothermal Crystallisation Kinetics

Both GA and PA showed the capacity to reduce the T_g of mSDM on comilling to a similar extent (43 °C, Table 5.2). However, in this study and in previous studies (Curtin, Amharar et al. 2013, Curtin, Amharar et al. 2013) GA has consistently demonstrated a greater capacity to mitigate amorphisation of a range of (structurally diverse) APIs on comilling. DVS stability studies indicated that co-cryomilling with GA reduced the RH_{c0} of SDM to a greater extent than PA (43% relative to 53% respectively). Analysis of humidity induced crystallisation upon exposure to the critical RH of the SDMGA and SDMPA co-cryomilled composites also suggested faster kinetics of crystallisation for the SDMGA system. These observations suggest that, given that GA and PA reduced the T_g of both APIs to a

similar extent on comilling, the greater capacity of GA to mitigate amorphisation could have a kinetic basis.

The crystallisation behaviour of the composites formed on comilling SDM with GA and PA at their respective solubilities (corresponding to a 1:1 molar ratio in each case) were further investigated by determination of the activation energy of crystallisation from non-isothermal DSC crystallisation kinetic studies. DSC analysis was performed at varying heating rates and both Ozawa and Kissinger plots were constructed in order to determine the activation energy of crystallisation from the amorphous composites. DSC analysis of the 32% SDMGA co-cryomilled amorphous composite is shown in Figure 5.25 and Figure 5.26, while the results are tabulated in Table 5.7. The analysis of the SDMPA system is shown in Figure 5.27 and Figure 5.28 and tabulated in Table 5.8.

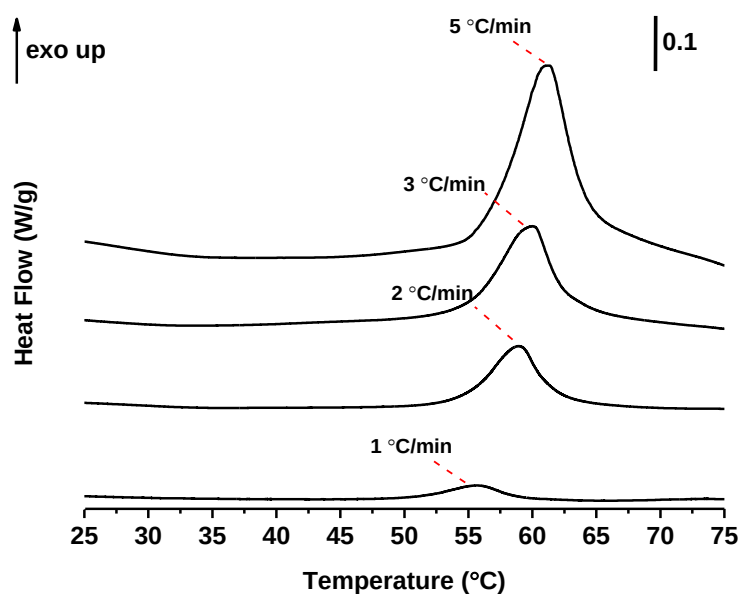


Figure 5.25 DSC thermograms of the composite formed on co-cryomilling SDM with GA at the solubility limit of GA in SDM (32% w/w) at different scan rates.

Table 5.7 Determination of the activation energy (E_a) of crystallisation from the peak maximum of DSC scans of the 32% (1:1 molar ratio) co-cryomilled SDMGA amorphous composite

Heating Rate (β , K/min)	1	2	3	5	E_a (kJ/mol) Kissinger	E_a (kJ/mol) Ozawa
Peak Max (T_p , °C)	56	58.8	60.2	61.4		
Peak Max (T_p , K)	329.2	332	333.3	334.6		
SD	0.17	0.13	0.05	0.21		
$1/T_p \times 10^{-3}$ (1/K)	3.038	3.012	3	2.989		
$\ln(\beta/T_p^2)$	-11.59	-10.92	-10.52	-10.01	260.4	252.8
$\ln(\beta)$	0	0.693	1.099	1.609		

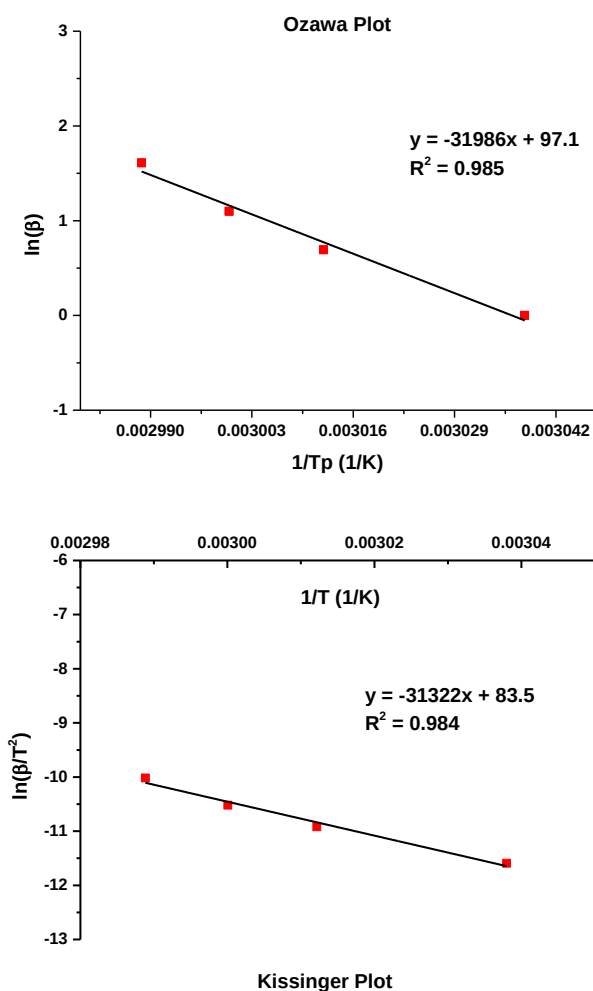


Figure 5.26 Kissinger and Ozawa plots for of the SDMGA 32% w/w (1:1 molar ratio) co-cryomilled amorphous composite.

The analysis suggests that the E_a for the SDMGA system is considerably lower, with a value of 260 kJ/mol from the Kissinger plot analysis compared to the SDM:PA system with a value of 326 kJ/mol. Also, good correlation was found between both the Ozawa and Kissinger plots. Analysis of the activation energy of crystallisation from the driven alloys formed between SDM and GA or PA shows that the E_a for crystallisation is significantly lower for the GA composite. This correlates with the observed faster crystallisation kinetics of the SDM:GA system from DVS studies, as a lower E_a of crystallisation means the composite has a lower energy barrier to overcome, leading to faster nucleation and crystallisation kinetics (Van Eerdenbrugh, Baird et al. 2010).

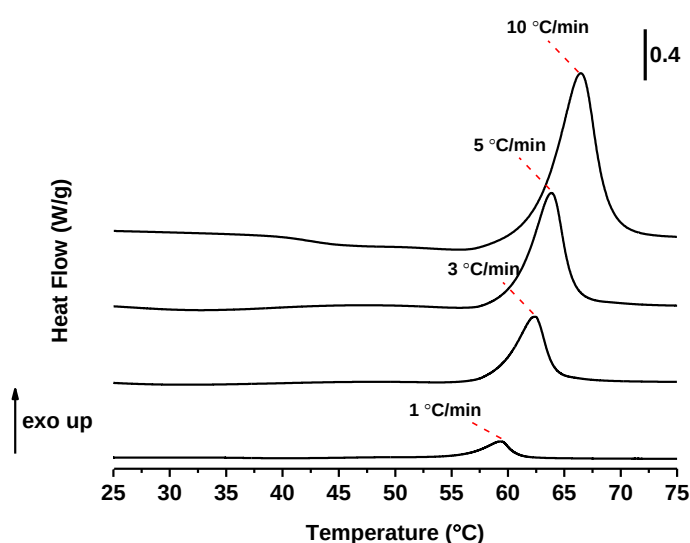


Figure 5.27 DSC thermograms of the composite formed on co-cryomilling SDM with PA at the solubility limit of PA in SDM (37% w/w) at different scan rates.

Seefeldt et al. investigated the kinetics of crystallisation from the amorphous composite formed between nicotinamide and carbamazepine on co-melt quenching (Seefeldt, Miller et al. 2007). They correlated the activation energy for the formation of a cocrystal from the binary amorphous composite by isothermal and non-isothermal methods and found good correlation between the two methods. However, the route of formation of the alloy is known to strongly affect the properties of the amorphous state produced. Indeed, in this study we have highlighted the differences in the physical properties of the alloys formed on comilling and co-melt quenching of SDM, including T_g reduction. In this study, we have focused on an assessment of the crystallisation behaviour from the driven alloy in the context of understanding the unique characteristics of the amorphous

composite brought about by mechanical means, rather than from the solution state such as via melt quenching.

Table 5.8 Determination of the activation energy (E_a) of crystallisation from the peak maximum of DSC scans of the 37% (1:1 molar ratio) co-cryomilled SDMPA amorphous composite.

Heating Rate (β , K/min)	1	3	5	10	E_a (kJ/mol) Kissinger	E_a (kJ/mol) Ozawa
Peak Max (T_p , °C)	59.7	62.7	64.1	66.2		
Peak Max (T_p , K)	332.8	335.8	337.3	339.3		
SD	0.04	0.02	0.01	0.22		
$1/T_p \times 10^{-3}$ (1/K)	3.004	2.978	2.964	2.947		
$\ln(\beta/T_p^2)$	-11.62	-10.53	-10.03	-9.35	326.1	315.3
$\ln(\beta)$	0	1.099	1.609	2.303		

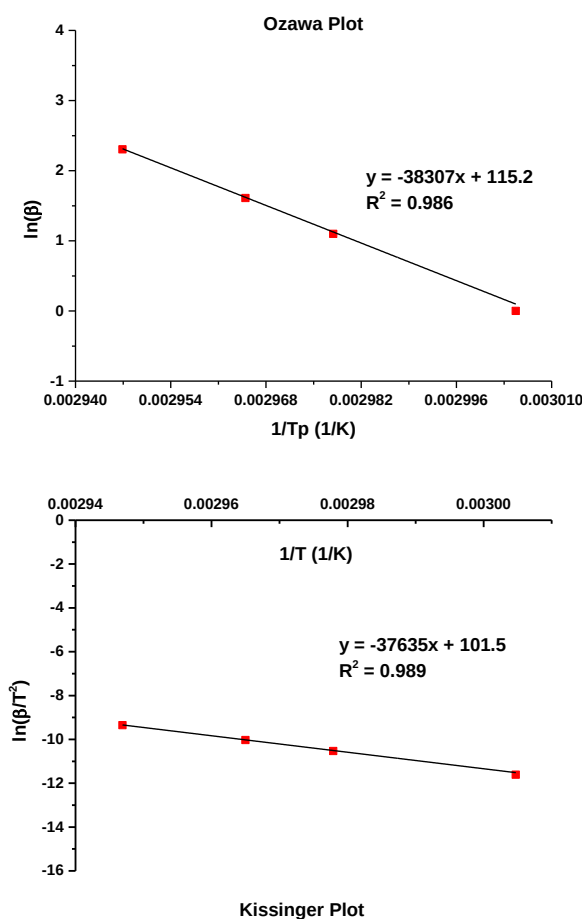


Figure 5.28 Kissinger and Ozawa plots for of the SDMPA 37% w/w (1:1 molar ratio) co-cryomilled amorphous composite.

5.6 CONCLUSIONS

While in Chapter 3 we studied the amorphisation of SDM on milling alone, in this chapter we studied the formation of glass solutions between amorphous SDM and the low T_g excipients SA, GA, AA, PA and MAN on mechanical driving at RT in terms of the spectroscopic, thermal and crystallographic characteristics of the driven alloys formed. While no T_g reduction was observed on comilling amorphous SDM with MAN, both GA and PA reduced the T_g of amorphous SDM to the greatest extent on comilling of each of the diacids. In contrast, while both SA and AA reduced the T_g of amorphous SDM to a greater extent than MAN, neither reduced the T_g to the same extent as either GA or PA. Spectroscopic analysis revealed evidence for hydrogen bonding interactions between amorphous SDM and the diacids, with the strongest interaction observed on comilling with GA. In contrast, no interaction was observed on comilling with MAN. Additionally, crystallographic analysis revealed the transformation of GA, SA and PA to metastable polymorphic forms on comilling with amorphous SDM.

The solubility of each of the diacid excipients in amorphous SDM was determined by the zero enthalpy extrapolation method which revealed PA to have the highest solubility in amorphous SDM followed by GA, AA and SA. In addition we determined the T_g s of the saturated glass solutions formed on co-melt quenching SDM with the diacid excipients at a composition above their solubility compositions. Comparison with the T_g reduction observed on comilling revealed that both SA and AA were unable to drive T_g reduction of SDM on comilling to the same extent as the saturated glass solutions formed on co-melt quenching. In contrast no such deviation was observed on comilling with either GA or PA. Melting point depression analysis of SDM in the presence of MAN, AA, GA and PA revealed limited miscibility between MAN and SDM while AA, GA and PA all exhibited miscibility in the liquid state. Thermodynamic analysis of mixing in the liquid state with quantitative analysis of the excess thermodynamic functions on mixing SDM with AA, GA and PA revealed similar interactions on mixing in the liquid state with each of the diacid excipients.

Co-cryomilled composites were formed between SDM and SA, GA and PA. DVS analysis revealed that while SA did not lead to a reduction in the crystallisation RH, both GA and PA led to the plasticisation of amorphous SDM on comilling with faster crystallisation kinetics from the GA composite relative to the PA composite. Non-

isothermal crystallisation kinetics revealed that the activation energy of crystallisation from the co-cryomilled SDM:GA and SDM:PA amorphous composites was lower for the GA composite, consistent with the humidity accelerated crystallisation kinetics which suggested that the crystallisation kinetics from the GA composite were faster relative to the composite formed on comilling with PA in spite of similar levels of T_g reduction on comilling, as determined by modulated DSC analysis.

CHAPTER 6

MECHANICAL ACTIVATION STUDIES ON MILLING OF ACYCLOVIR AND COMILLING WITH LOW T_g EXCIPIENTS

6.1 INTRODUCTION

Acyclovir is an anti-viral compound with a complex solid-state chemistry comprising six known polymorphic forms – four anhydrous polymorphs in addition to two pseudopolymorphic hydrates, with the 3:2 hydrate the commercially used form (Nart, França et al. 2015). Acyclovir has been described as a BCS Class IV compound with poor aqueous solubility and permeability characteristics, consequently leading to poor oral bioavailability. As a result of its poor physicochemical characteristics, comilling studies with acyclovir have been performed with various excipients highlighting the propensity of acyclovir to form cocrystal adducts on comilling with, for example, glutaric acid and fumaric acid, leading to alteration in the physicochemical properties of the drug (Bruni, Maietta et al. 2013, Sarkar and Rohani 2015). In addition, the formation of a cocrystal with tartaric acid on comilling has also been described as well as the formation of a co-amorphous composite with citric acid, with a composite glass transition temperature of 68 °C (Masuda, Yoshihashi et al. 2012).

In this chapter, anhydrous polymorphic form I acyclovir will be prepared from the commercially available form V 3:2 hydrate. The solid state properties of the two polymorphic forms in the crystalline state will be assessed. In addition, the milling induced amorphisation of acyclovir in the vibratory ball mill at both room temperature and cryo-temperature will be investigated, in order to compare the amorphisation tendency of the two polymorphic forms in relation to the milling temperature. In addition, the glass transition temperature of mechanically activated acyclovir will be determined.

The comilling studies with low T_g excipients of previous chapters will be extended to acyclovir. The solubility of glutaric acid in amorphous acyclovir will be determined by the zero enthalpy extrapolation method. Comilling studies of anhydrous acyclovir with glutaric at room temperature will assess the propensity for the formation of the previously described cocrystal in a vibratory type ball mill. Both the anhydrous and hydrate forms of acyclovir will be comilled with glutaric acid at cryo-temperature. The anhydrous form of acyclovir will also be comilled with both pimelic acid and mannitol at room temperature in order to assess their respective abilities to mitigate amorphisation of acyclovir on comilling. In addition, the anhydrous form of acyclovir will be comilled with both pimelic acid and

mannitol at cryo-temperature. The co-cryomilled composites will be assessed in terms of their thermal characteristics, in particular to assess the ability of the excipient to drive the reduction of the glass transition temperature of acyclovir on comilling, in addition to spectroscopic analysis for hydrogen bonding interaction and crystallographic analysis of co-crystallisation from the co-cryomilled amorphous composites.

6.2 CHARACTERISATION OF CRYSTALLINE ACYCLOVIR

The solid-state properties of acyclovir (ACV) have been described by Karolewicz et al as having low solubility and low permeability and is thus classified as a BCS class IV compound (Karolewicz, Nartowski et al. 2016). Figure 6.1 highlights the various known solid state forms of ACV as described by (Lutker, Quiñones et al. 2011). These authors highlighted the interconversion of the different polymorphs and pseudopolymorphs of ACV, with four anhydrous forms at RT and two hydrate forms, including the 2:3 hydrate which is the commercially used form of ACV.

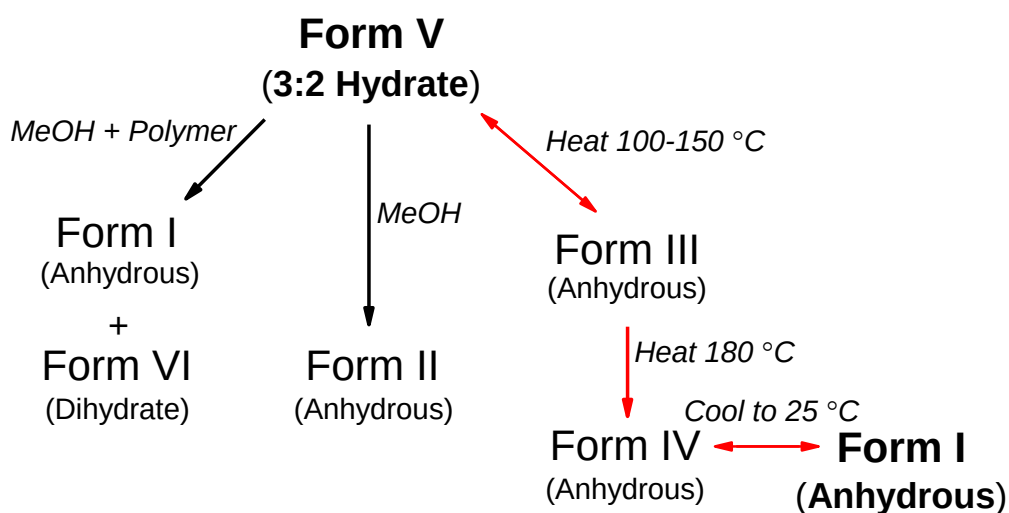


Figure 6.1 Schematic of the various known solid state forms of acyclovir with associated methods of preparation and transformations between the different forms. [Adapted from reference (Lutker, Quiñones et al. 2011)].

Form I ACV was prepared from the commercial form V 3:2 hydrate by heating the hydrate on a hot plate at 200 °C for 3 hours. Lutker et. al have previously shown that heating ACV to 180 °C did not lead to any degradation of the API (Lutker, Quiñones et al. 2011). In addition, TGA analysis (shown in Figure 6.3) did not reveal any evidence for degradation below the melt temperature of 250 °C. Figure 6.2 shows the PXRD diffractogram of both the commercial form V starting material (a) in addition to the anhydrous form I (b). The Bragg peaks of form I anhydrous ACV were in good agreement with those previously reported, with Bragg peaks at 8.6°

and $28.8^\circ 2\theta$ characteristic of the anhydrous form I polymorph (Kristl, Srčić et al. 1996). Additionally, no Bragg peaks associated with the form V hydrate were present in the diffractogram, indicating that full conversion to the anhydrous form had occurred after 3 hours.

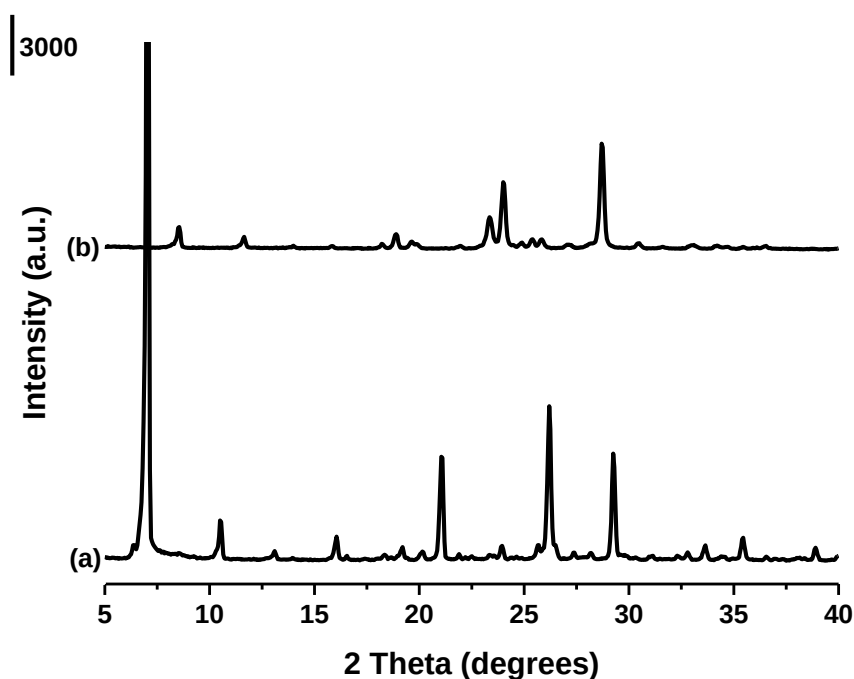


Figure 6.2 PXRD diffractograms of (a) crystalline form V (3:2 hydrate) ACV and (b) crystalline form I (anhydrous) ACV formed by heating form V ACV at 200°C for 3 hours.

6.2.1 Thermal Analysis

Figure 6.3A highlights the DSC thermogram of (a) form V ACV displaying a broad endotherm associated with loss of the water of hydration on heating in the DSC scan, followed by an endothermic event at 172°C associated with the high temperature polymorphic conversion to the form IV anhydrous polymorph, described in Figure 6.1. The melt endotherm at 252°C is immediately followed by another broad endotherm associated with the degradation of ACV on melting (Lutker, Quiñones et al. 2011). Figure 6.3B (a) shows the TGA scan of the hydrate, with a mass loss of 5.3% w/w associated with the loss of water of hydration. However, the TGA scan indicated that the mass loss event was not complete until 135°C .

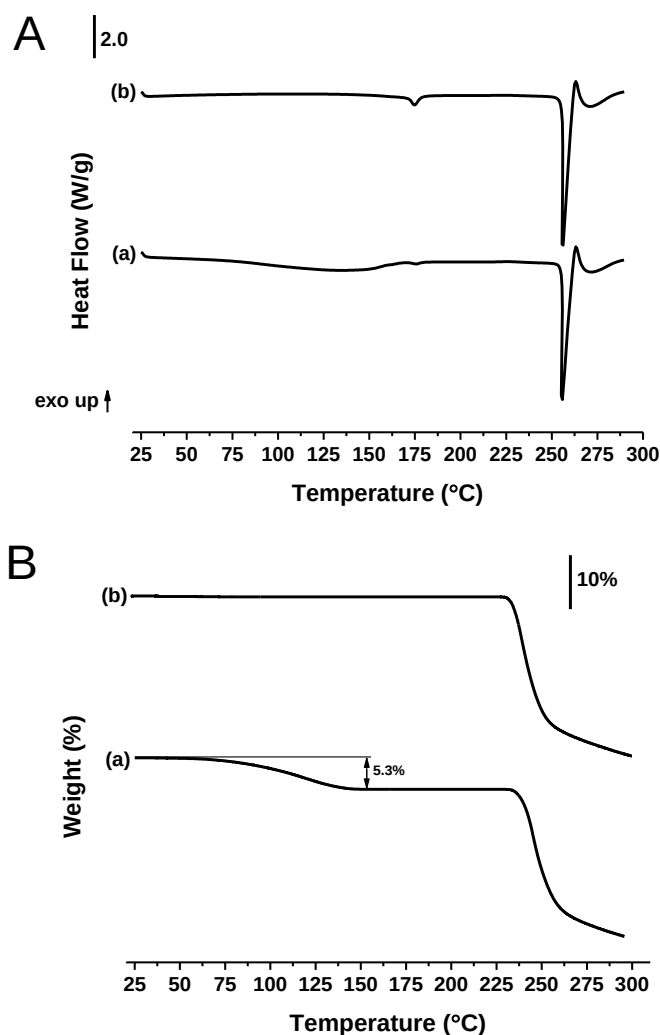


Figure 6.3 A) DSC thermograms of crystalline form V ACV and (b) form I ACV. B) TGA thermograms for (a) crystalline form V ACV and (b) crystalline form I ACV.

Figure 6.3A (b) highlights the DSC thermogram of form I ACV indicating a single endothermic peak at 172 °C associated with a polymorphic transformation to the form IV polymorph, followed by a melting event at 252 °C, similar to form V ACV. Additionally, no mass loss event was observed in the TGA scan as shown in Figure 6.3B (b), in contrast to the form V hydrate starting material, further indicating that full conversion to the form I polymorph (and complete loss of the water of hydration) had been achieved.

6.2.2 FTIR Analysis

The molecular structure of ACV is shown in Figure 6.4. The guanosine analogue has a number of hydrogen bond donor groups including the aliphatic O-H group on the

ether side chain and, in addition, an NH_2 amino group attached to the heterocyclic ring together with a heterocyclic N-H group. Hydrogen bond donor groups include the C=O group on the heterocyclic ring.

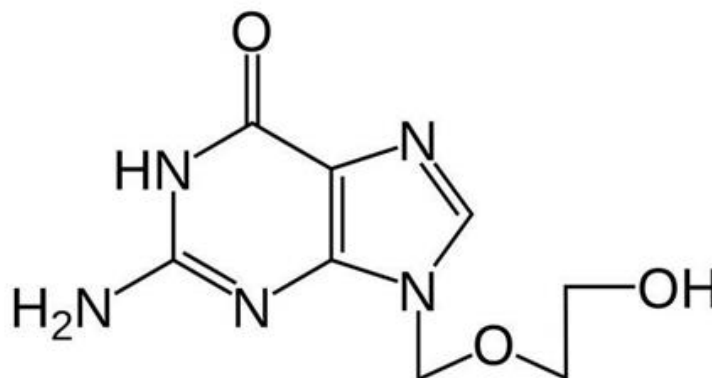


Figure 6.4 Molecular structure of acyclovir.

Figure 6.5 reveals the FTIR spectra of both the crystalline form I (anhydrous) and form V (3:2 hydrate) ACV. The $3600\text{--}3000\text{ cm}^{-1}$ spectral region associated with O-H and N-H stretching vibrations is complex due to the many O-H and N-H bonds present in the ACV structure. However, significant differences in the exact peak positions was observed on comparison of both polymorphic forms, possibly associated with both the presence of water in the hydrate and in the different hydrogen bonding network present in the two polymorphic forms (Sohn and Kim 2008, Lutker, Quiñones et al. 2011). The $1750\text{--}1600\text{ cm}^{-1}$ region represents another important region in the spectrum in terms of hydrogen bonding interactions, associated with the carbonyl C=O bond. Differences in the carbonyl stretching peak were observed for the hydrate at 1709 cm^{-1} , relative to the form I polymorph at 1689 cm^{-1} in the crystalline systems.

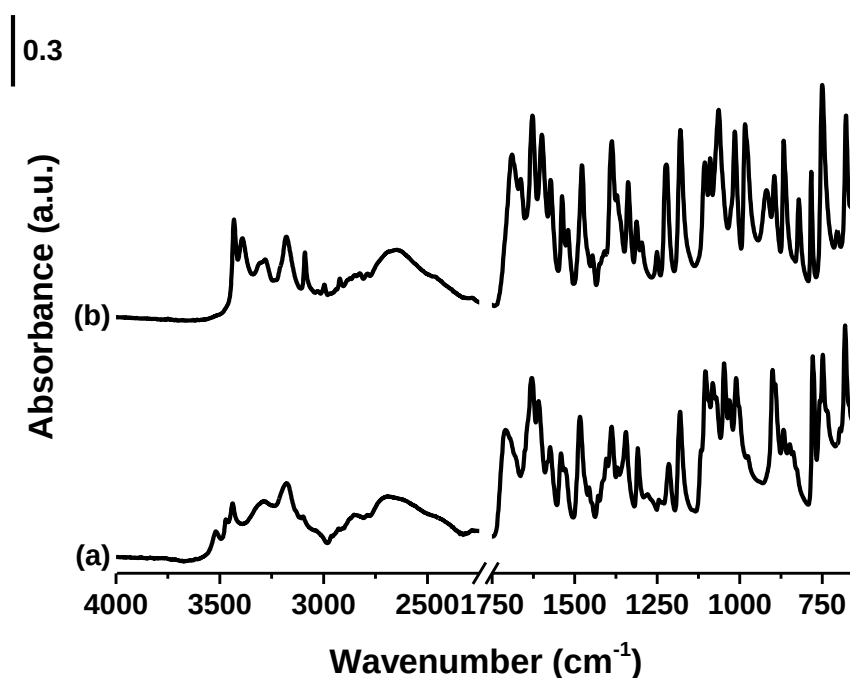


Figure 6.5 FTIR spectra of (a) crystalline form V (3:2 hydrate) ACV and (b) crystalline form I (anhydrous) ACV.

6.2.3 DVS Analysis

Form V ACV was subjected to a stepwise DVS sorption analysis, with water as the probe vapour, from 0% to 90% RH in 10% RH per step, as shown in Figure 6.6. The sorption profile indicated an initial mass loss event during the initial drying stage, during which the sample was purged with dry nitrogen gas. This mass loss event was most likely associated with the loss of water of hydration as the mass loss was reversed during the first step at 10% P/P_0 . The sorption profile shown in Figure 6.6B highlights that from 10% to 90% RH only a slight hysteresis was observed, while the total percent change in mass from 10% to 90% RH was 0.2% w/w indicating a limited tendency of the surface of the form V ACV hydrate to sorb water vapour.

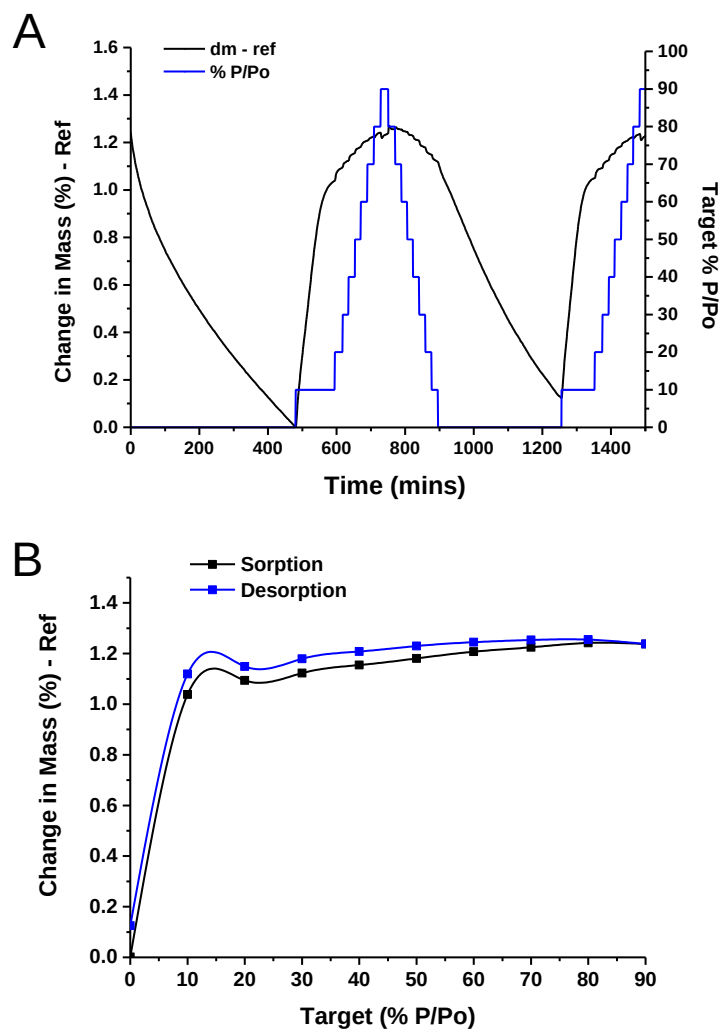


Figure 6.6 A-B) DVS stepwise sorption isotherm of crystalline form V ACV from 0-90% in 10% RH steps.

Figure 6.7 highlights the DVS stepwise sorption plot of form I anhydrous ACV with water as the probe vapour from 0% to 90% RH. In contrast to the sorption behaviour of the hydrate shown in Figure 6.6, the anhydrous form I ACV underwent a large mass uptake at 80% and 90% RH with a total uptake of 5.3% w/w. This level of water uptake indicates the regeneration of the 3:2 hydrate (i.e. form V ACV) at 80% RH.

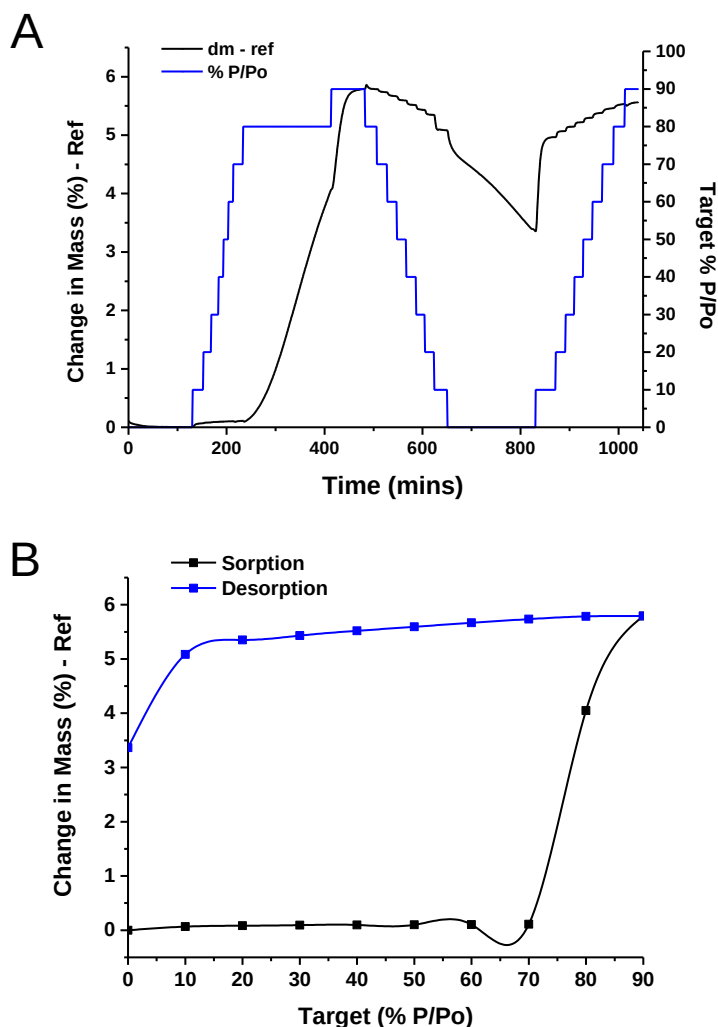


Figure 6.7 A-B) DVS stepwise sorption isotherm of crystalline form I ACV.

6.2.4 SEM Analysis

SEM analysis was performed on both the unprocessed form V ACV and form I ACV which, as described, was produced by heating the form V polymorph on a hot plate at 200 °C for 3 hours. The images shown in Figure 6.8A-C show the form V ACV unprocessed particles with a column-like morphology and a smooth surface. In contrast, the images shown in Figure 6.8E-F are of the form I ACV, indicating a similar overall morphology and size. However, the surface appears rough and pitted, possibly due to the loss of water of hydration on heating to 200 °C.

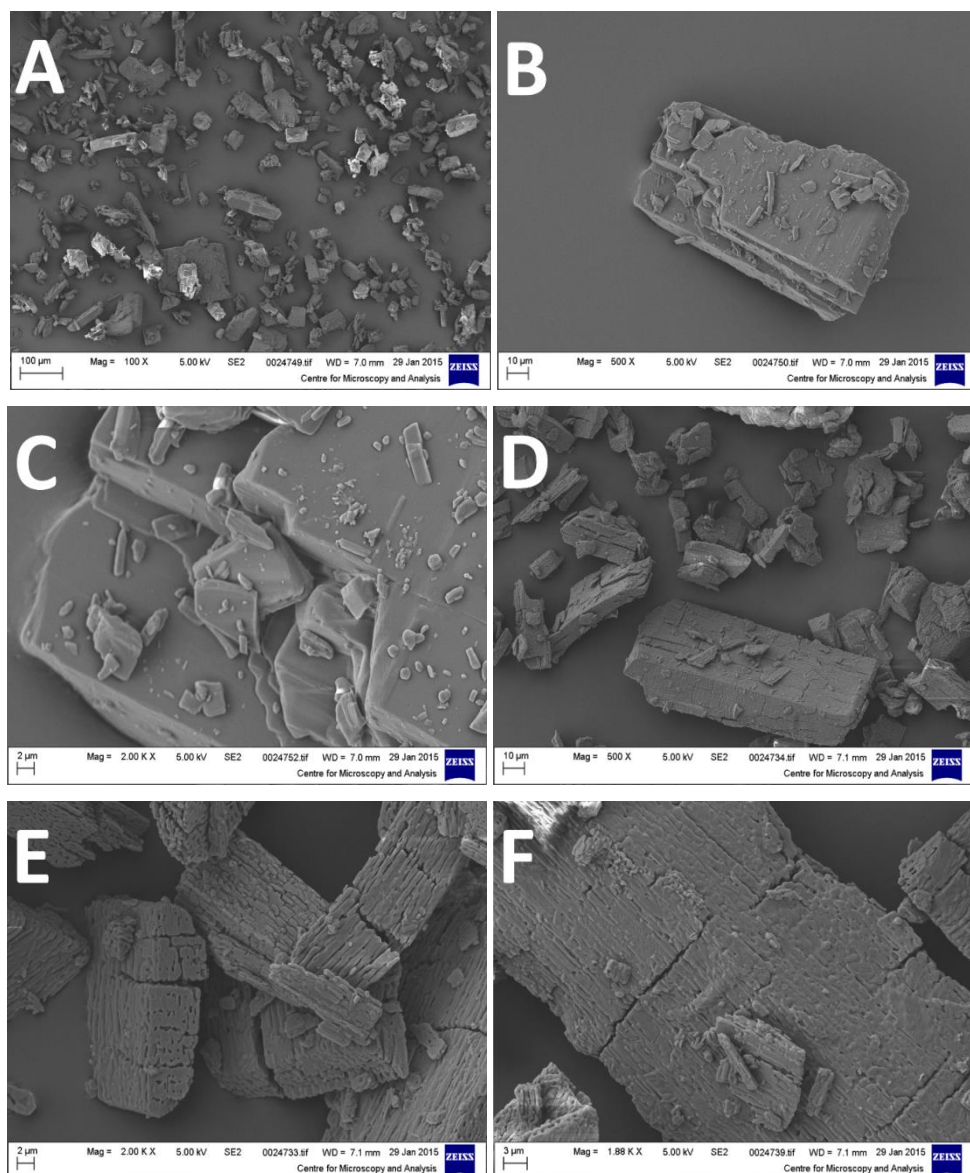


Figure 6.8 A-C) SEM images of crystalline form V ACV. D-F) SEM images of crystalline form I ACV.

6.3 MECHANICAL ACTIVATION STUDIES OF ACYCLOVIR

6.3.1 Mechanical Activation of Form I (Anhydrous) Acyclovir

Anhydrous form I ACV was milled in the vibratory ball mill at RT for 54 minutes. Figure 6.9A shows the PXRD diffractograms of the RT milled system with increasing milling time, indicating a gradual reduction in the intensity of the Bragg peaks associated with the crystalline material, suggestive of a milling induced transformation to the amorphous state (Lefort, De Gusseme et al. 2004). Form I ACV was also milled in the VBM at CT for 54 minutes. As shown in Figure 6.9B, the PXRD diffractogram of the cryomilled system revealed a halo pattern. The absence of any Bragg peaks associated with crystalline API in the diffractogram was indicative of a milling induced crystalline to amorphous transformation on milling at CT.

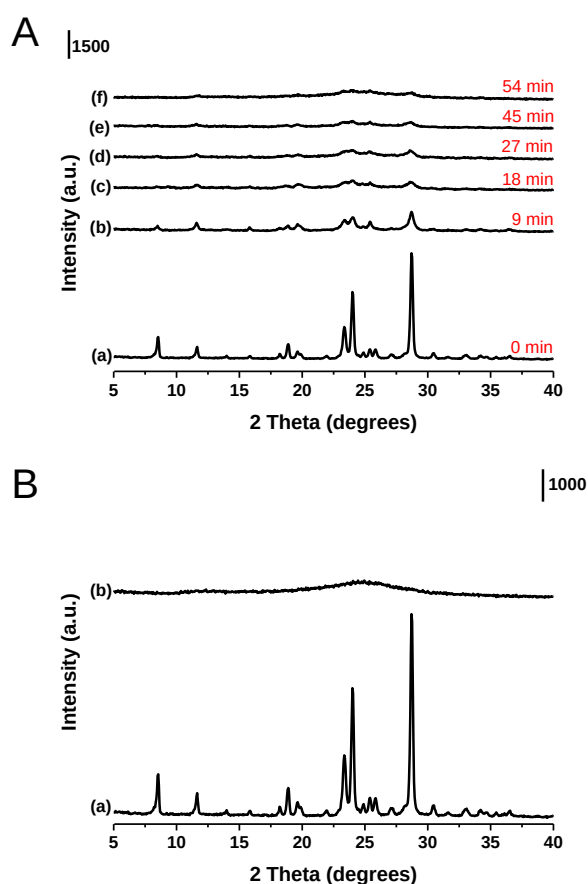


Figure 6.9 A) PXRD diffractograms of form I ACV milled in the VBM at RT from 0-54 minutes of milling. B) PXRD diffractograms of (a) crystalline form I ACV and (b) form I ACV milled in the VBM at CT for 54 minutes.

While PXRD evidence suggested a milling induced transformation of form I ACV on milling at RT and CT to the amorphous state, the systems were further analysed by DSC and TGA analysis, as shown in Figure 6.10A and Figure 6.10B respectively. The DSC thermogram of the cryomilled system displayed a bimodal crystallisation exotherm with an initial peak at 101 °C followed by a subsequent peak at 118 °C. The bimodal nature of the milled system suggests initial fast surface crystallisation, followed by slower crystallisation of the bulk amorphous regions (Chattoraj, Bhugra et al. 2012). The sample was also analysed by modulated heat flow DSC analysis with the reversing signal shown in the inset, indicating a T_g event at 109.2 °C (± 0.6 °C). The DSC thermogram of the RT milled form I ACV similarly indicated a bimodal crystallisation exotherm with a fast surface exothermic peak 97 °C followed by an exothermic peak at 117 °C due to slower crystallisation of the bulk. The RT milled system was analysed by modulated DSC analysis with the reversing heat flow signal shown in the inset of Figure 6.10A, indicating a T_g event at 109.6 °C (± 0.5 °C), similar to the cryomilled system. The generation of a glass transition event in the reversing heat flow signals provided further evidence that the milling operation had led to the generation of amorphous ACV at both RT and CT, as indicated by PXRD analysis. TGA analysis, shown in Figure 6.10B, revealed that, relative to the unmilled crystalline form I polymorph starting material, the CT milled system displayed a mass loss of 2.9% w /w at 100 °C relative to the RT milled system which revealed a mass loss of 2.1% w/w at the same temperature. This could be due to the sorption of water vapour by the amorphous regions generated during the milling operation at both RT and CT (Baird, Olayo-Valles et al. 2010).

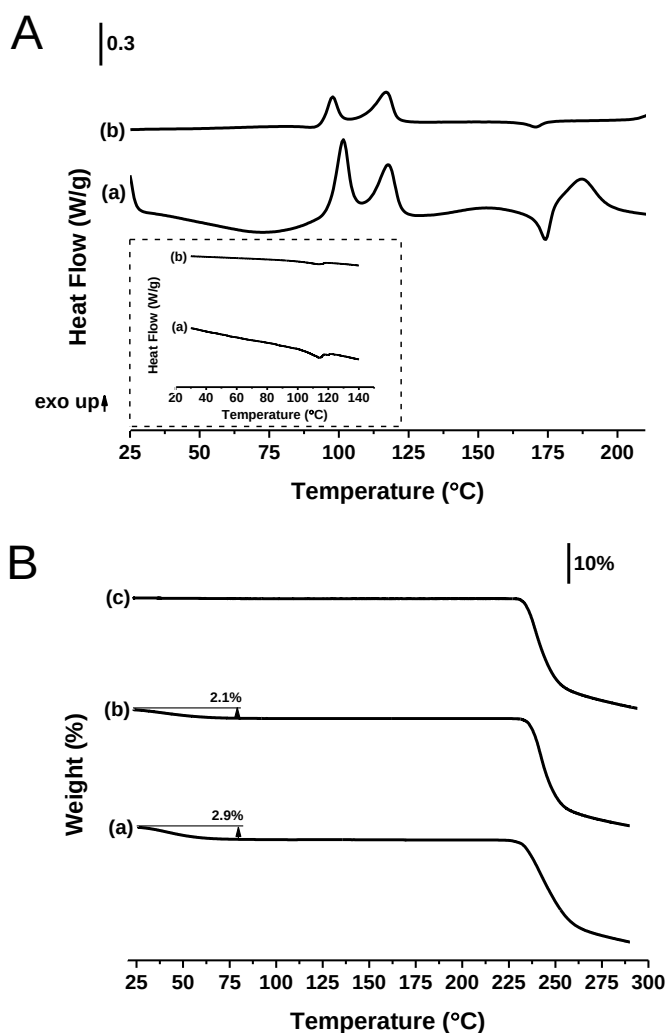


Figure 6.10 A) DSC thermograms of crystalline form I ACV milled in the VBM for 54 minutes at (a) CT and (b) RT. Inset highlights the reversing heat flow signals determined from a modulated DSC run. B) TGA thermograms of form I ACV milled in the VBM form 54 minutes at (a) CT and (b) RT and (c) unmilled crystalline form I ACV.

6.3.2 Mechanical Activation of Form V (3:2 Hydrate) Acyclovir

Form V ACV (3:2 hydrate) was milled in the VBM for 54 minutes at both RT and CT. Figure 6.11 reveals the PXRD analysis of both the unmilled crystalline form V ACV starting material, as well as the RT and CT milled systems. The diffractogram of the RT milled system revealed Bragg peaks associated with the crystalline form V polymorph. In contrast, the diffractogram of the CT milled system indicated no Bragg peaks associated crystalline API, indicating that milling at CT had led to the amorphisation of the API. Willart et al. compared the amorphisation tendency of trehalose anhydrous and trehalose dihydrate, and similarly found that the hydrate form was more resistant to amorphisation relative to the anhydrous form (Willart, De Gusseme et al. 2001). These authors suggested that the water of hydration was

acting as a plasticiser during milling, effectively reducing the T_g of any amorphous API that was generated during milling leading to an increased crystallisation tendency relative to the anhydrous material.

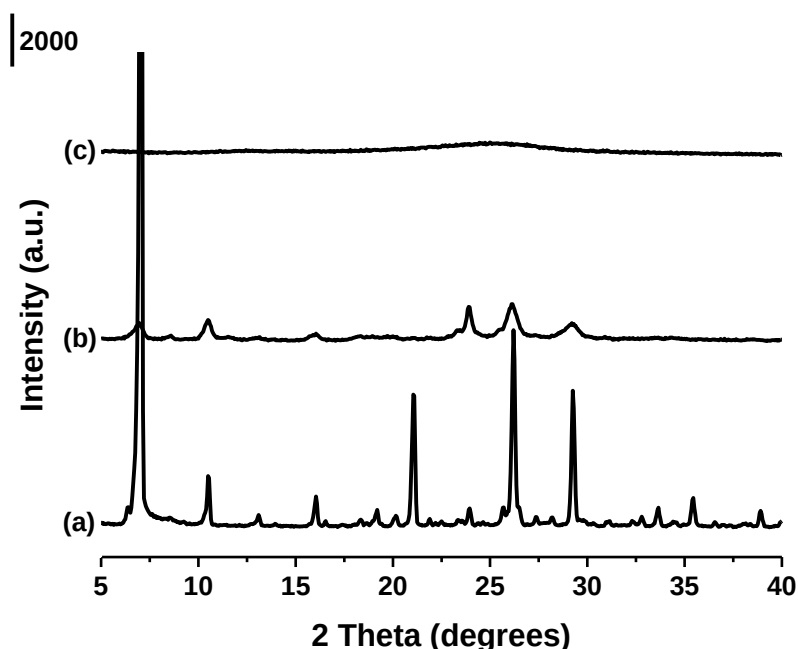


Figure 6.11 PXRD diffractograms of (a) crystalline form V ACV and form V ACV milled in the VBM for 54 minutes at (b) RT and (c) CT.

Figure 6.12A shows the DSC thermograms of the RT and CT milled form V ACV systems. The system milled at CT revealed an exothermic peak at 114 °C associated with crystallisation from the milled amorphous state. In contrast, Figure 6.12A (b) shows the DSC thermogram of the form V ACV milled at RT for 54 minutes. Interestingly, no exothermic peak was detected suggesting that the system was crystalline after milling at RT, which was consistent with PXRD analysis shown in Figure 6.11. However, an endothermic peak was observed at 116 °C. The endothermic peak in the RT milled system was possibly associated with transformation of the crystalline form V hydrate to form III ACV, as suggested by Figure 6.1. Interestingly, the same endothermic peak was not observed in the DSC scan of the unmilled crystalline form V hydrate, as shown in Figure 6.3A (a). However, comparison of the TGA thermograms of the RT milled form V hydrate and the unmilled form V hydrate as shown in Figure 6.12B (b) and (c) respectively, indicates that the milled hydrate lost its water of hydration at a lower temperature

during the TGA scan, at approximately 100 °C relative to the unmilled hydrate which retained its water of hydration until approximately 135 °C. Consequently, the broad endotherm associated with the loss of water of hydration could obscure the polymorphic transformation to the form III polymorph of unmilled form V ACV, as shown in Figure 6.3A (b). Figure 6.12B (a) shows the TGA scan of the cryomilled amorphous form V hydrate, showing a 5% w/w loss at approximately 60 °C, lower than either (b) or (c), possibly due to the amorphous nature of the system.

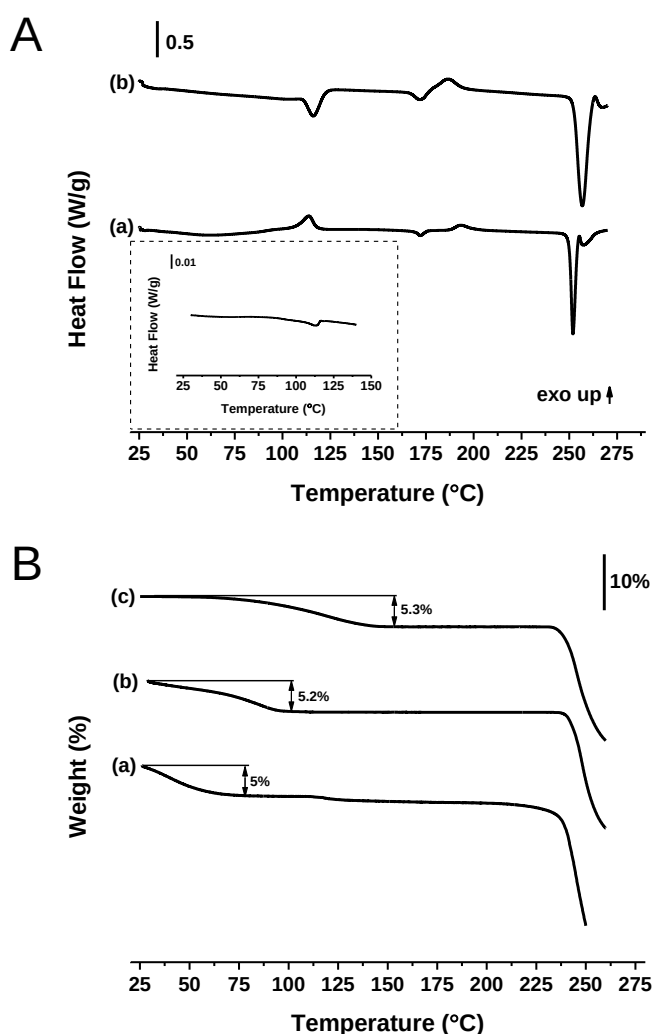


Figure 6.12 A) DSC thermograms of form V ACV milled in the VBM for 54 minutes at (a) CT and (b) RT. Inset shows the reversing heat flow signal of the CT milled sample. B) TGA thermograms of form V ACV (a) milled in the VBM for 54 minutes at CT (b) milled in the VBM at RT for 54 minutes and (c) unmilled crystalline form V ACV.

6.4 COMILLING STUDIES OF ACYCLOVIR WITH LOW T_g EXCIPIENTS

6.4.1 Comilling Acyclovir with Glutaric Acid

6.4.1.1 Solubility of Glutaric Acid in Amorphous Acyclovir

As highlighted in the previous section, ACV has been shown to undergo degradation on heating to its melting point at approximately 250 °C, thus precluding the preparation of amorphous ACV by the melt quench method. However, DSC analysis of a physical mixture of form I ACV with crystalline β -GA (at 70% w/w GA in ACV), as shown in Appendix A-I Figure A-I.14, indicated an initial endotherm at 92 °C associated with melting of GA, followed by a second endotherm at 170 °C, possibly associated with the liquidus melting of ACV into molten GA, an indication that the materials are miscible in the liquid state. Figure 6.13 shows hot-stage polarised microscopy images on heating of the same physical mixture to 180 °C at a scan rate of 10 °C/ min. The images suggest the increasing disappearance of birefringence associated with crystalline ACV at 170 °C, indicating a reduced liquidus melting temperature of ACV in the presence of GA.

The reduced melting point of ACV in the presence of GA allowed the preparation of melt quench composites by quench cooling from the liquid mixture at 180 °C, without heating to the melting/ degradation point of ACV, allowing the determination of the solubility of GA in amorphous ACV by the zero enthalpy extrapolation method (Amharar, Curtin et al. 2014) as shown in Appendix A-1, Figure A-I.15. The solubility composition of GA in amorphous SDM was determined to be 39% w/w.

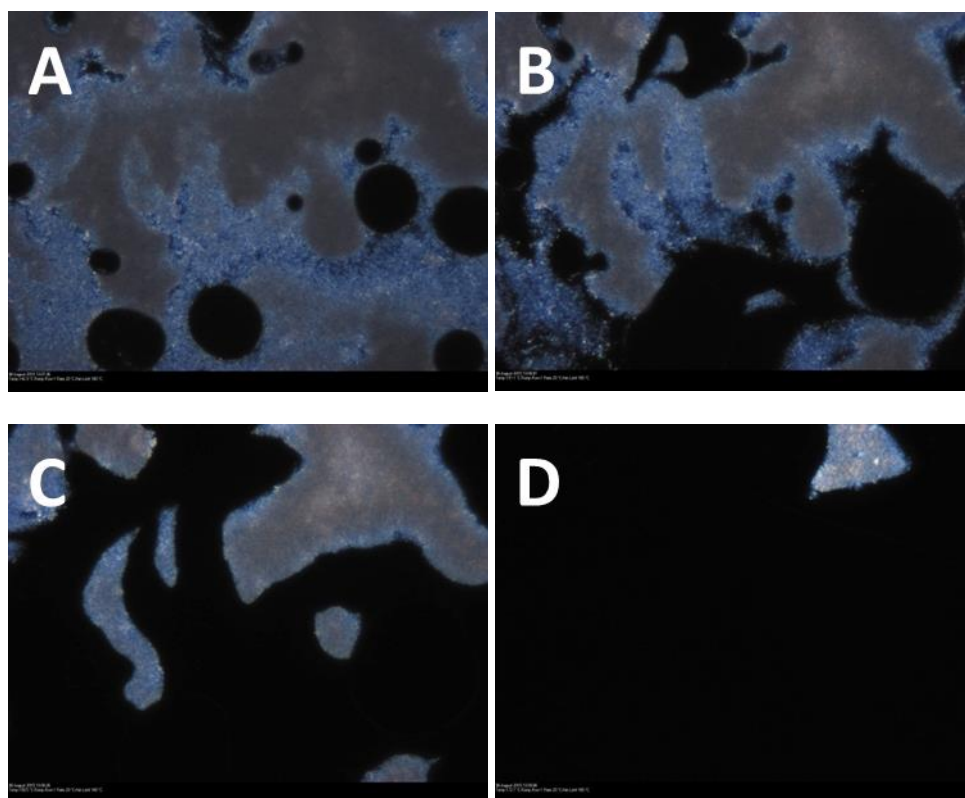


Figure 6.13 Hot stage polarised microscopy images of the 70% w/w physical mixture of GA in form I ACV heated at 10 °C/ min scan rate to 180 °C at temperatures of (A) 140 °C (B) 150 °C (C) 160 °C and (D) 170 °C

6.4.1.2 Comilling Form I (Anhydrous) Acyclovir with Glutaric Acid at Room Temperature

Crystalline β -GA was comilled at 36% w/w, corresponding to a 1:1 molar ratio, with form I anhydrous ACV in the VBM at RT for 54 minutes. PXRD analysis of the comilled system is shown in Figure 6.14 after 9 and 54 minutes of comilling. While each of the Bragg peaks in the diffractogram after 9 minutes of milling were associated with each of the starting materials, analysis of the diffractogram after 54 minutes of milling indicates the formation of a new crystalline form, with Bragg peaks at 10.8° and 26.1° 2θ not associated with either starting material. Previous studies have highlighted the formation of 1:1 molar cocrystal between ACV and GA on comilling in a planetary ball mill (Bruni, Maietta et al. 2013). The Bragg peaks of the diffractogram after 54 minutes correlate with those reported by Bruni et al., thus confirming the formation of the ACV:GA cocrystal on comilling in the VBM at RT (Bruni, Maietta et al. 2013). Interestingly, these authors indicated a milling time of 12 hours in the planetary ball mill for the formation of the ACV:GA cocrystal, relative to our studies in the VBM which led to cocrystal formation after 54 minutes.

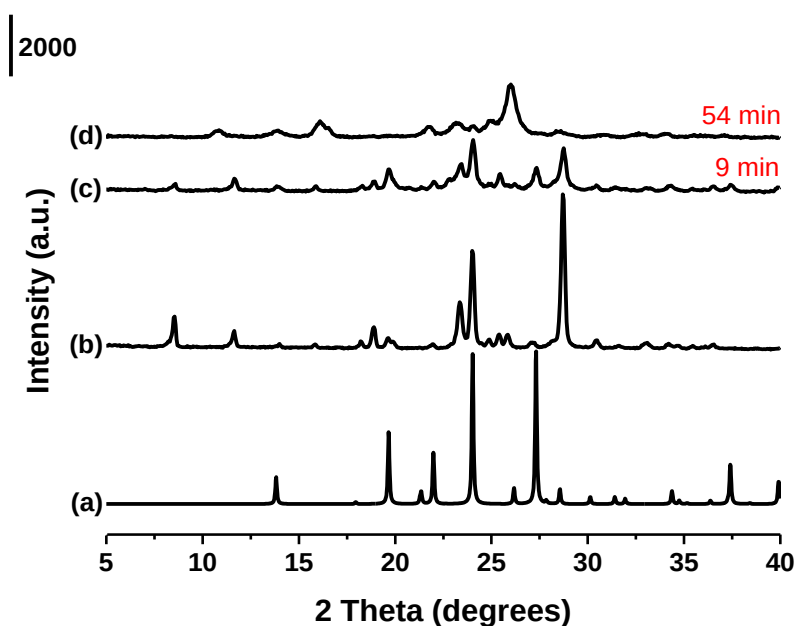


Figure 6.14 PXRD diffractograms of (a) crystalline β -GA (b) crystalline form I ACV and crystalline form I ACV comilled with β -GA in the VBM at RT at 36% w/w GA in ACV after (c) 9 minutes and (d) 54 minutes of milling.

Figure 6.15 (c) shows DSC thermogram of the cocrystal system formed on comilling form I ACV with β -GA at RT. A melt endotherm of the cocrystal was observed at 163 °C, which is consistent with previous findings (Bruni, Maietta et al. 2013).

Figure 6.16 shows the FTIR spectra of the cocrystal system formed on comilling form I ACV with GA at 36% w/w in the VBM at RT. The spectrum of the comilled system, shown in Figure 6.16 (d) indicates the presence of peaks in the 3600–3000 cm^{-1} region associated with O-H/ N-H stretching, in particular a new peak at 3423 cm^{-1} , distinct from either of the starting materials. In addition, a distinct peak in the 1750–1600 cm^{-1} region associated with the C=O stretching region was observed in the cocrystal system at 1645 cm^{-1} . Changes in the spectral regions associated with these hydrogen bonding groups is indicative of strong hydrogen bonding group interactions in the cocrystal system formed on comilling.

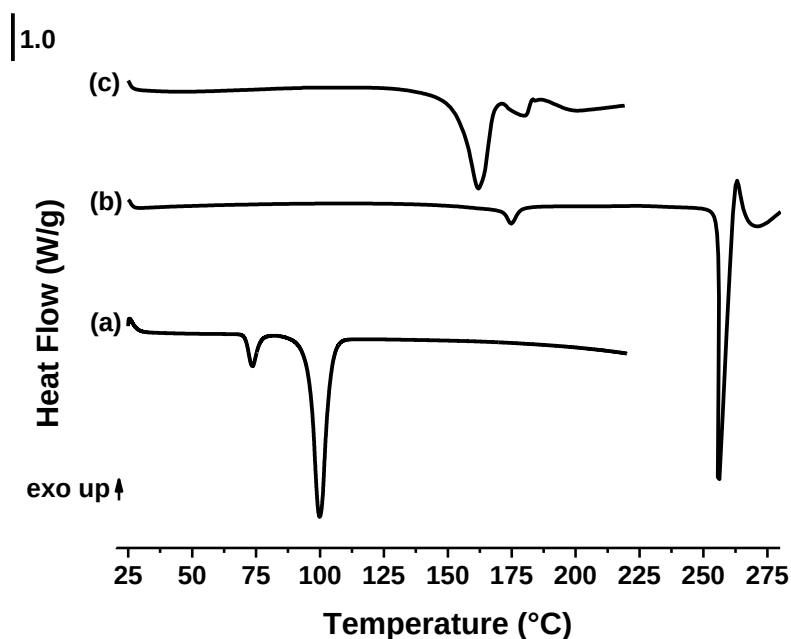


Figure 6.15 DSC thermograms of (a) crystalline β -GA (b) crystalline form I ACV and (c) crystalline form I ACV comilled with β -GA in the VBM at RT at 36% w/w GA in ACV for 54 minutes.

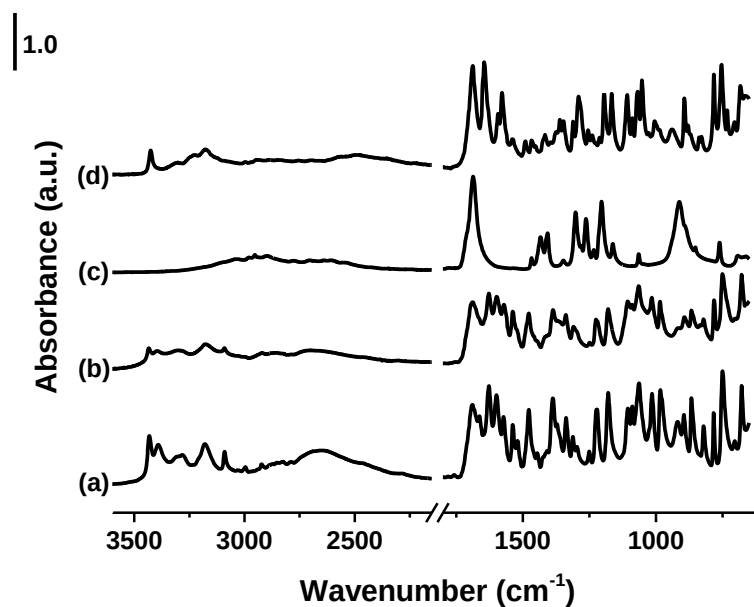


Figure 6.16 FTIR spectra of (a) crystalline form I ACV (b) form I ACV milled in the VBM at RT for 54 minutes (c) β -GA milled in the VBM at RT for 54 minutes and (d) crystalline form I ACV comilled with β -GA in the VBM at RT at 36% w/w (GA in ACV).

The ACV:GA cocrystal system formed on comilling at RT was subjected to stepwise sorption analysis in the DVS, with water as the probe vapour, from 0% to 90% P/P_0 .

at 10% per step as shown in Figure 6.17. The first sorption cycle led to a total water mass uptake of 1.1% w/w at 90% RH, with evidence of a slight mass loss event at the 90% RH step in the first sorption cycle of 0.1% w/w, possibly due to a small level of amorphous content in the milled system. In contrast, in the second sorption cycle, no mass loss event was observed with a total water mass uptake at 90% RH of 1.0% w/w. In contrast to the DVS sorption profiles of unmilled crystalline form I and form V ACV shown in Figure 6.6 and Figure 6.7, the cocrystal system formed with GA was stable to changes in relative humidity across the relative humidity range from 0% to 90% P/P₀.

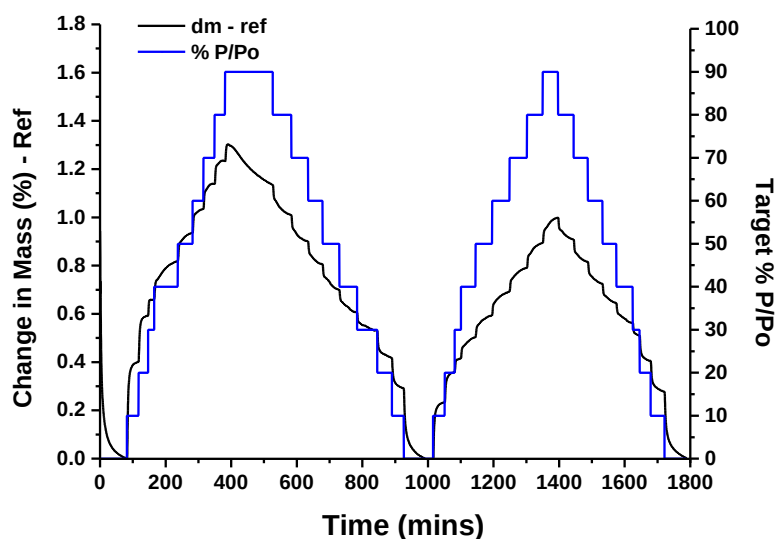


Figure 6.17 DVS analysis of the cocrystal formed on comilling β -GA at 36% w/w (1:1 molar ratio) in crystalline form I ACV in the VBM at RT for 54 minutes.

6.4.1.3 Comilling Acyclovir with Glutaric Acid at Cryo-Temperature

6.4.1.3.1 Comilling with Form I (Anhydrous) Acyclovir

Crystalline β -GA was comilled with form I ACV at both 36% w/w and 50% w/w compositions in the VBM at CT for 54 minutes. The PXRD diffractograms of the co-cryomilled composites, together with the diffractograms of crystalline form I ACV and the CCDC generated crystal structures of α and β -polymorphic GA are shown in Figure 6.18. Interestingly, the diffractogram of the 50% w/w co-cryomilled composite contains Bragg peaks associated with both α and β -polymorphic forms of GA, in contrast to the 36% w/w (equimolar) co-cryomilled composite which was

PXRD amorphous, suggesting that the solubility of GA in amorphous ACV lies between these two compositions. This corroborates the solubility composition determined for GA in amorphous ACV by the zero enthalpy extrapolation method which was determined to be 39% w/w. In addition, GA in excess of the solubility composition underwent a partial milling induced transformation to the metastable α -polymorph, which was also observed on co-cryomilling with BD and SDM in previous chapters.

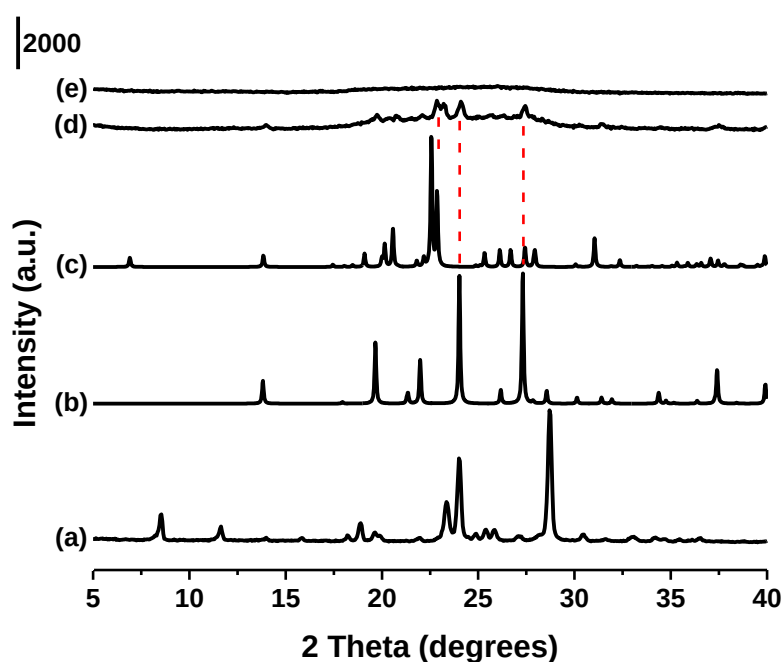


Figure 6.18 PXRD diffractograms of (a) crystalline form I ACV (b) CCDC generated crystal structure of β -GA (c) CCDC generated crystal structure of α -GA (d) crystalline form I ACV comilled with β -GA at 50% w/w in the VBM at CT for 54 minutes and (e) crystalline form I ACV comilled with β -GA at 36% w/w (GA in ACV) in the VBM at CT for 54 minutes. Red lines indicate Bragg peaks associated with crystalline GA.

Figure 6.19 (c) reveals the DSC thermogram of the 50% w/w ACV:GA co-cryomilled composite indicating a crystallisation exotherm at 80 °C, followed by two endothermic peaks at 98 °C and 164 °C. The endothermic peak at 164 °C suggests that the crystallisation event at 80 °C led to the formation of the ACV-GA cocrystal, as a similar endothermic event was observed in the RT comilled system shown in Figure 6.15. This suggests that as the cocrystal forms a 1:1 molar ratio corresponding to 36% w/w GA in ACV, the endotherm at 98 °C resulted from the melting of crystalline GA in excess of this composition. The inset of Figure 6.19 also highlights the reversing heat flow signal from a modulated DSC scan of the 50%

w/w co-cryomilled ACV:GA composite, with a glass transition event highlighted at 48.3 °C (± 0.7 °C).

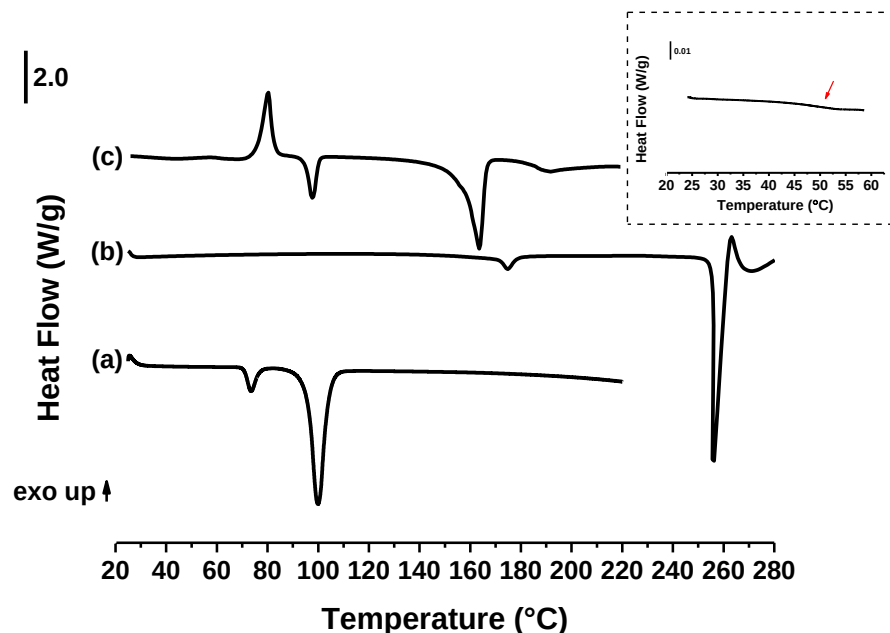


Figure 6.19 DSC thermograms of (a) crystalline β -GA (b) crystalline form I ACV and (c) crystalline form I ACV comilled with β -GA at 50% w/w at CT for 54 minutes. Inset shows the reversing heat flow signal of (c), with the T_g event highlighted at 48 °C. Red arrow indicates the glass transition event in the reversing heat flow signal.

The 36% w/w co-cryomilled ACV:GA composite was subjected to stepwise sorption analysis in the DVS, with water as the probe vapour, from 0% to 90% P/P₀ at 10% per step, as shown in Figure 6.20A. Interestingly, the sorption plot indicated a significant mass uptake event of 2% w/w at the 40% RH step, possibly due to crystallisation of the form V hydrate. Subsequently, at 80% RH, a mass loss event of 3.6% w/w was observed. The loss of this amount of water is consistent with the complete loss of water of hydration from the 3:2 hydrate of form V ACV thus indicating that the mass uptake event at 40% RH was due to the crystallisation of the form V hydrate. Interestingly, the second sorption cycle did not lead to any further mass loss/ uptake events, indicating that the mass loss event at 80% RH led to the generation of the ACV:GA cocrystal, as indicated by the stable nature of the cocrystal towards water vapour induced phase transformations, relative to native ACV.

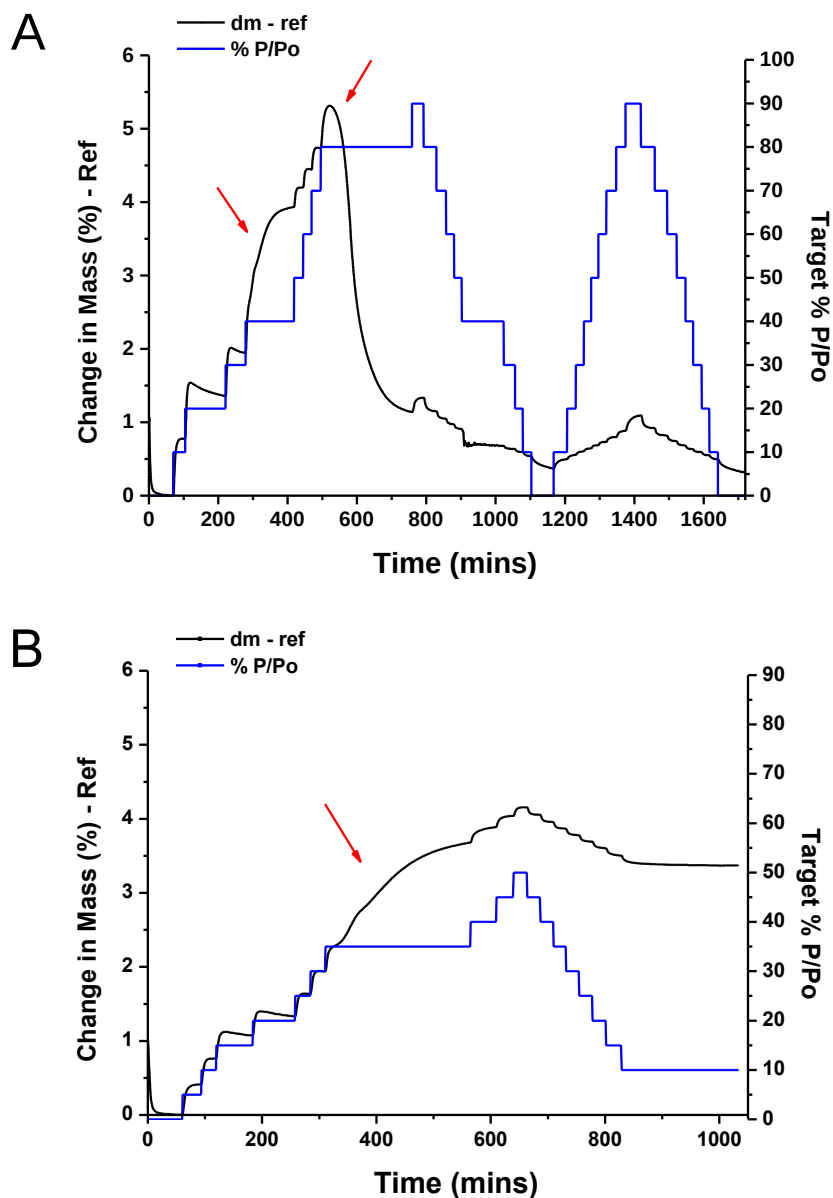


Figure 6.20 Stepwise DVS isotherm of crystalline form I ACV comilled with β -GA in the VBM at CT at 36% w/w for 54 minutes with A) 10% RH per step from 0-90% RH and B) 5% RH per step from 0-60% RH. Red arrows indicate mass uptake (hydrate formation) and mass loss (co-crystal formation) events.

Additionally as shown in Figure 6.20B, the co-cryomilled 36% w/w composite was subjected to a sorption cycle of 5% RH per step from 0% to 60%, with a mass uptake event observed at 35% RH of 1.9% w/w followed by a desorption cycle to 10% RH. The mass uptake at the end of the desorption cycle at 10% RH was 3.8% w/w, which further correlates with the crystallisation of the 3:2 hydrate in the first sorption cycle at the 35% RH step.

Figure 6.21 (A-C) shows SEM images of the composite formed on co-cryomilling β -GA with form I ACV at 36% w/w for 54 minutes and (D-F) the same composite after crystallisation into the cocrystal in the DVS. Before crystallisation, the surface of the particles appear coarse and pitted, in contrast to the system after crystallisation which appear to have a smoother surface with a more defined structure.

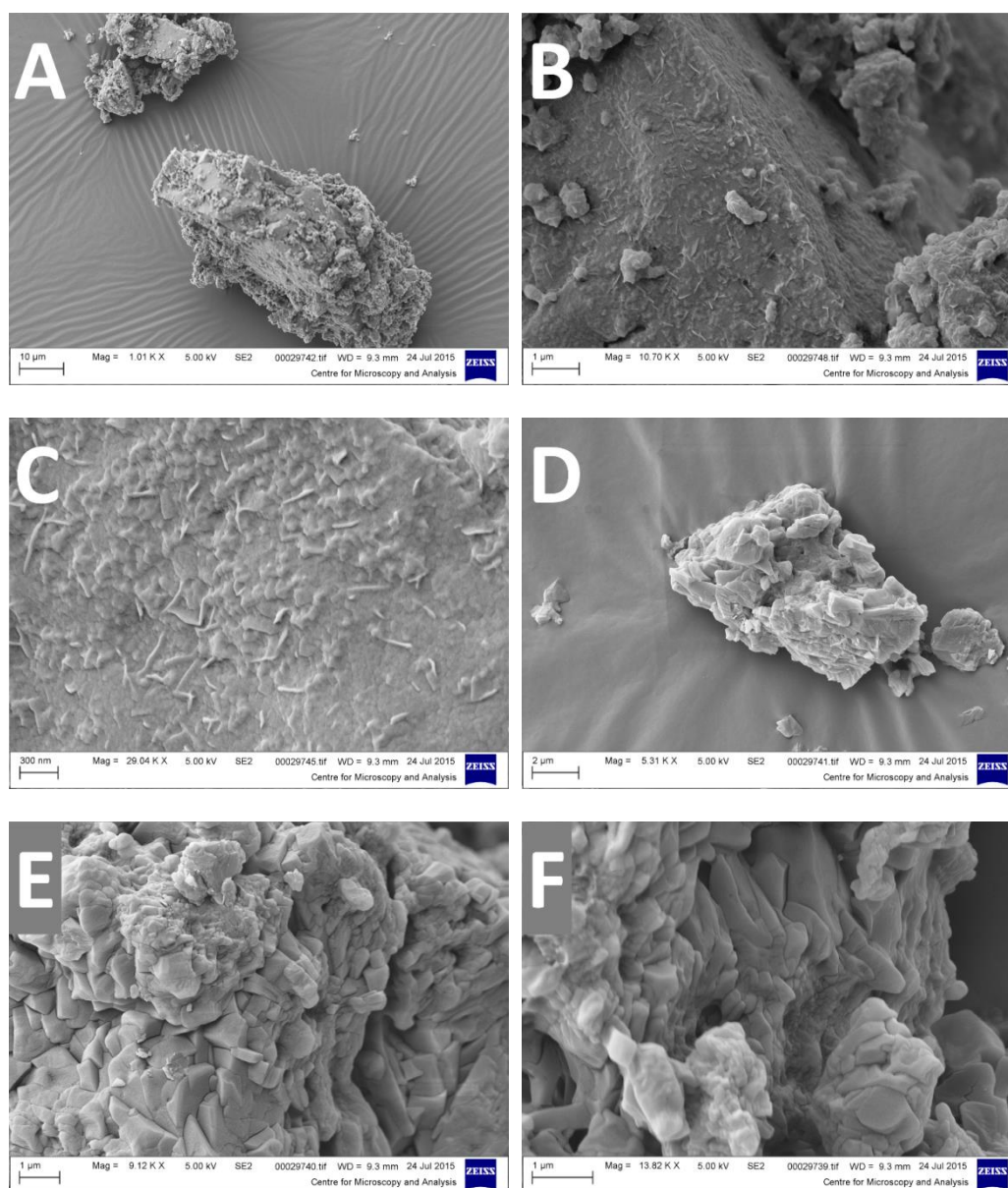


Figure 6.21 SEM images showing the amorphous composite formed on comilling GA with form I ACV at 36% w/w in the VBM at CT for 54 minutes (A-C) before and (D-F) after DVS analysis from 0-90% RH.

6.4.1.3.2 Comilling with Form V (3:2 Hydrate) Acyclovir

Crystalline β -GA was comilled with form V ACV (3:2 hydrate) at 50% w/w in the VBM at CT for 54 minutes. Figure 6.22 (d) shows the PXRD diffractogram of the co-cryomilled composite with Bragg peaks associated with both α and β -polymorphic GA. In contrast, the diffractogram did not display any Bragg peaks associated with crystalline ACV, indicating that comilling with β -GA at CT led to the amorphisation of ACV after 54 minutes.

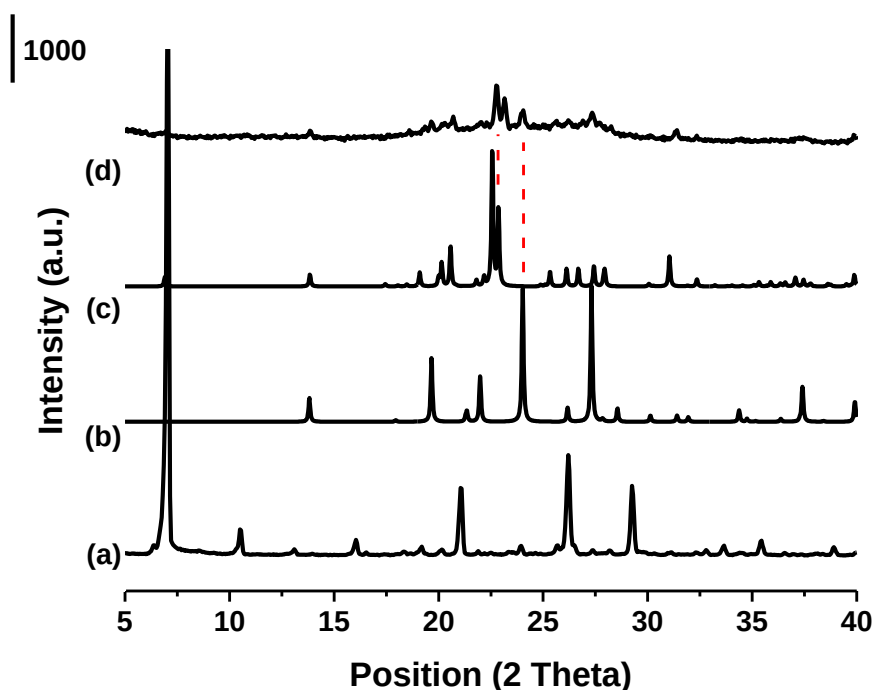


Figure 6.22 PXRD diffractograms of (a) crystalline form V ACV (b) CCDC generated crystal structure of β -GA (c) CCDC generated crystal structure of α -GA and (d) form V ACV comilled with β -GA in the VBM at CT at 50% w/w for 54 minutes. Red lines indicate Bragg peaks associated with crystalline GA.

The co-cryomilled composite formed on comilling form V ACV with GA was held at 25 °C and 43% RH in order to assess the crystallisation characteristics of the system under controlled stability testing conditions. Figure 6.23A shows the PXRD diffractograms of the system, indicating that after two hours at 43% RH increase in PXRD peak at 26.2° 2θ associated with form V ACV. In addition there was an increase in the intensity of the peak associated with β -polymorphic GA at 23.9° 2θ. Further concomitant growth of the β -polymorphic GA peak with the Bragg peak associated with crystalline form V ACV 3:2 hydrate occurred between 2 and 9 hours.

This analysis suggests, similar to the crystallisation from the SDM:GA co-cryomilled composites, that the crystallisation of β -GA appears to undergo a concomitant crystallisation with the API from the amorphous composite; in this case crystallisation of the form V ACV 3:2 hydrate. No further increase in intensity between 9 hours and 4 days was observed, indicating full crystallisation up to 9 hours on stability.

The co-cryomilled composite was also held at 40 °C and 43% RH, with PXRD diffractograms of the system shown in Figure 6.23B. After 2 hours, crystallisation of form V ACV and β -GA was observed. However after 3 hours, PXRD analysis indicated the transformation of the system to the ACV:GA cocrystal, with characteristic peaks at 10.8° and 26.1° 2 θ .

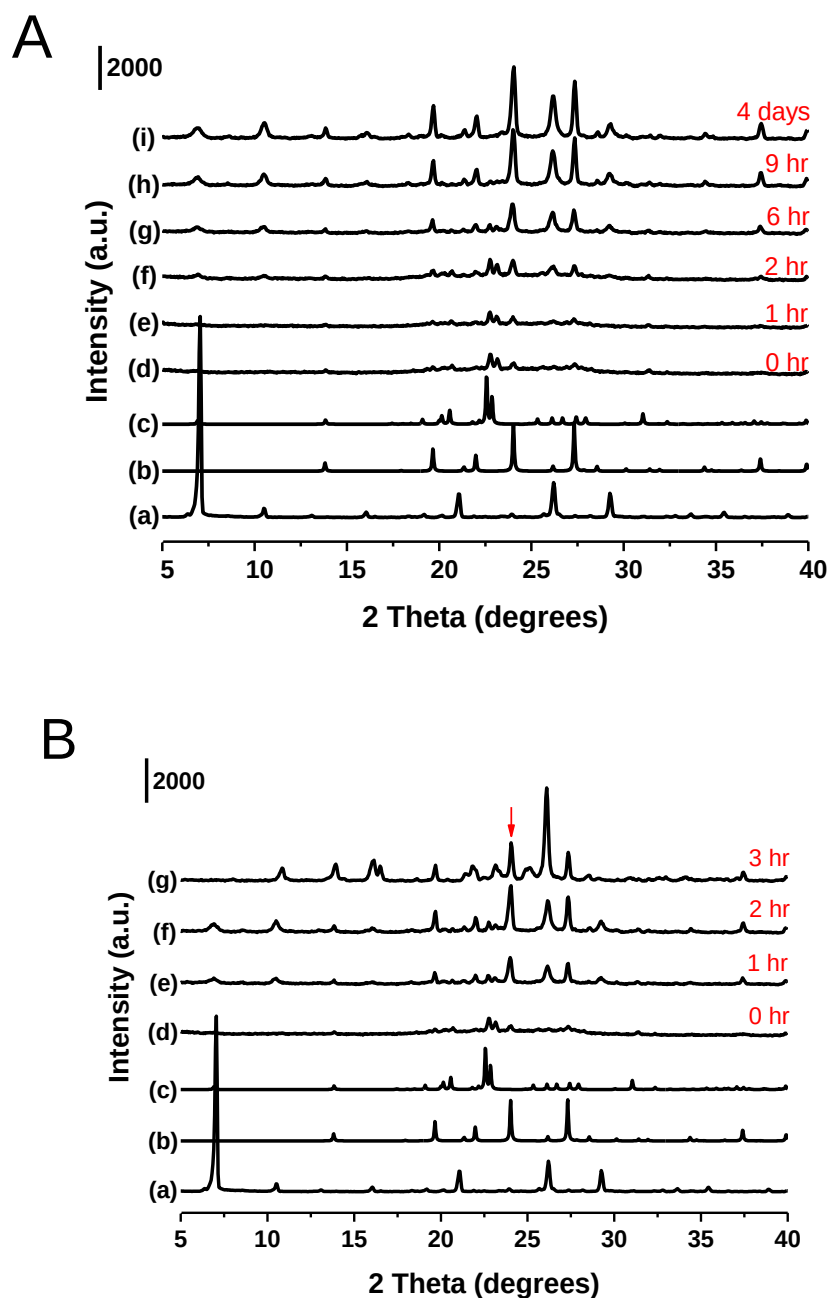


Figure 6.23 A) PXRD diffractograms (a) crystalline form V ACV (b) CCDC generated single crystal structures of β -GA (c) CCDC generated single crystal structures of α -GA (d-i) form V ACV comilled with β -GA at 50% w/w in the VBM at CT held at 43% RH and 25 °C. B) PXRD diffractograms of (a) (a) crystalline form V ACV (b) CCDC generated single crystal structures of β -GA (c) CCDC generated single crystal structures of α -GA (d-g) form V ACV comilled with β -GA at 50% w/w in the VBM at CT held at 43% RH and 40 °C. [Intensity of reference diffractograms (a-c) in both A and B have been reduced to scale for clarity]. Red arrow indicates Bragg peak at 23.9° 2 θ associated with β -GA.

Figure 6.24 (a) shows the TGA scan of the co-cryomilled form V ACV:GA composite indicating a mass loss of 1.4% w/w up to 100 °C, possibly due to loss of water sorbed into the amorphous ACV generated on co-cryomilling. In addition, the TGA

scans of the co-cryomilled composite held at 25 °C and 43% RH are shown, indicating a mass loss of 2.4% RH, consistent with the water loss from the 3:2 hydrate on heating to 100 °C. The TGA scan of the cocrystal formed from the co-cryomilled composite held at 40 °C and 43% RH after 3 hours indicates a minimal mass loss at 100 °C of 0.2% w/w (figure 6.24 (d)).

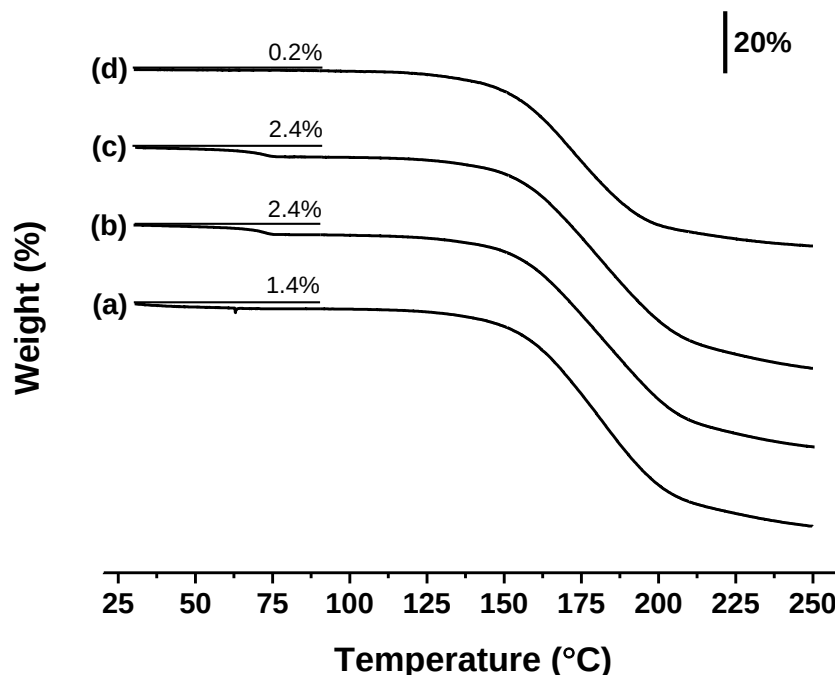


Figure 6.24 TGA thermograms of (a) β -GA comilled with form V ACV at 50% w/w in the VBM at CT and held at (b) 25 °C and 43% RH for 9 hr (c) 25 °C and 43% RH for 4 days and (d) 40 °C and 43% RH for 3 hr

Figure 6.25A (d) shows the FTIR spectrum of the co-cryomilled form V ACV:GA composite. In comparison to the spectra for β -GA and either form V or form I ACV, significant overlap in the carbonyl stretching region and the O-H/ N-H stretching regions prohibited an accurate assessment of peak shifts which would suggest hydrogen bonding in the milling-induced amorphous composite. However, as shown in Figure 6.25B (d), the concomitant nature of the crystallisation of ACV and GA together with the generation of the cocrystal from the amorphous composite after 3 hours at 43% RH and 25 °C suggests the possibility of hydrogen bonding both in the amorphous composite and in the cocrystal system that forms on crystallisation (Masuda, Yoshihashi et al. 2012).

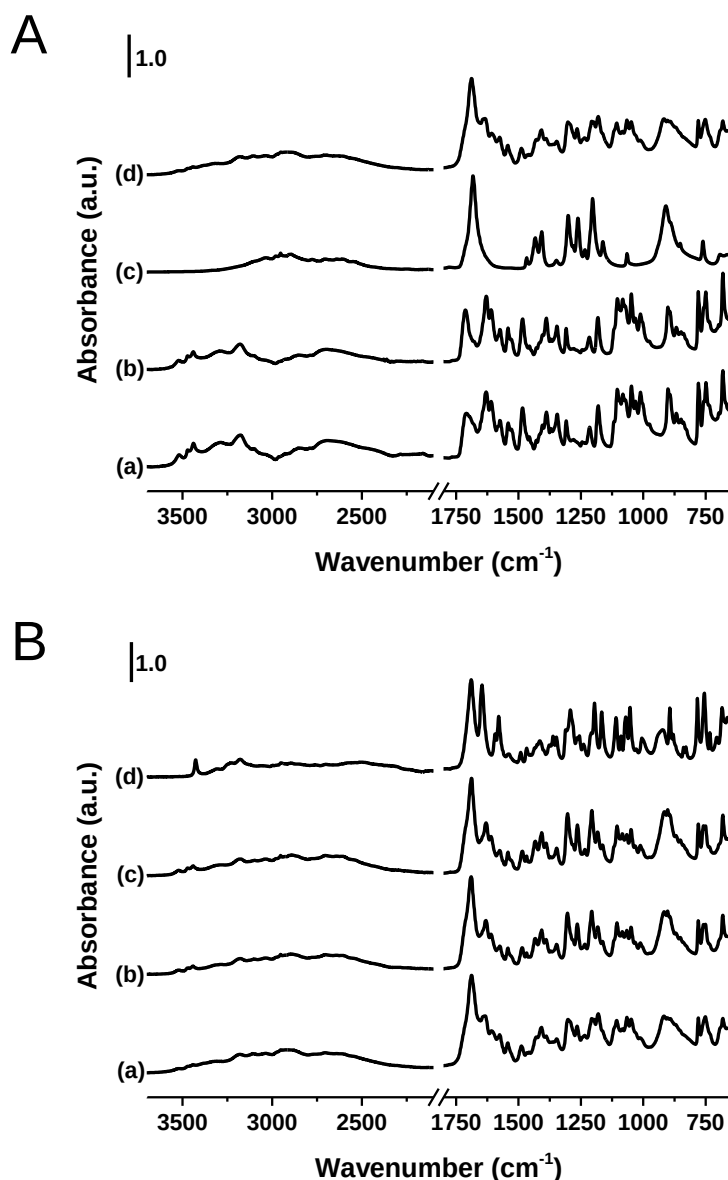


Figure 6.25 A) FTIR spectra of (a) crystalline form I ACV (b) crystalline form V ACV (c) β -polymorphic GA and (d) form V ACV comilled in the VBM at CT with β -GA at 50% w/w for 54 minutes. B) FTIR spectra of form V ACV comilled with β -GA at 50% w/w in the VBM at CT for 54 minutes held at 43% RH and 40 °C after (a) 0 hr (b) 1 hr (c) 2 hr and (d) 3 hr.

6.4.2 Comilling Acyclovir with Pimelic Acid

Form I ACV was comilled with β -PA at 50% w/w in the VBM at both RT and CT for 54 minutes. Figure 6.26 (b) shows the DSC signal of the system comilled at CT displaying a crystallisation exotherm at 68 °C with an enthalpy of crystallisation (ΔH_{cr}) of 16.8 J/g (± 0.9 J/g). The system was also analysed by modulated heat flow DSC analysis, as shown in the inset, and revealed a T_g event at 54.2 °C (± 0.7 °C),

indicating that comilling form I ACV with β -PA led to a T_g reduction of ACV from 109 °C to 54 °C. In contrast, the DSC signal of the RT comilled system, shown in Figure 6.26 (c) showed a slight exotherm at 68 °C with a ΔH_{cr} of 4.1 J/g (± 1.8 J/g).

Figure 6.27A shows the PXRD diffractograms of the form I ACV:PA composite formed on comilling in the VBM at RT. Bragg peaks associated with form I ACV were observed in the diffractogram. This suggests that comilling with PA was at least partially successful at mitigating amorphisation of form I ACV on comilling at RT. Bragg peaks associated with the α polymorph of PA were also evident in the diffractogram of the RT comilled system. Figure 6.27B highlights the PXRD diffractogram of the ACV:PA composite comilled in the VBM at CT which, in contrast to the RT comilled system, contained no Bragg peaks associated with crystalline ACV. However, Bragg peaks associated with α -polymorphic PA were evident in the PXRD diffractogram.

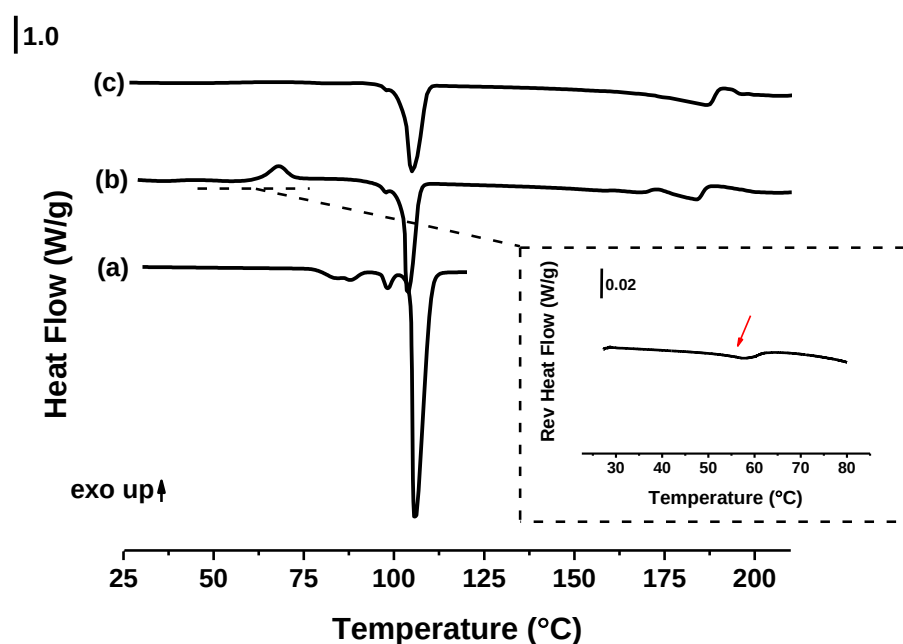


Figure 6.26 DSC thermograms of (a) crystalline β -PA and form I ACV comilled with crystalline PA at 50% w/w for 54 minutes at (b) CT and (c) RT. Inset shows the reversing heat flow signal and T_g event of the CT comilled system. Red arrow indicates glass transition event in the reversing heat flow signal.

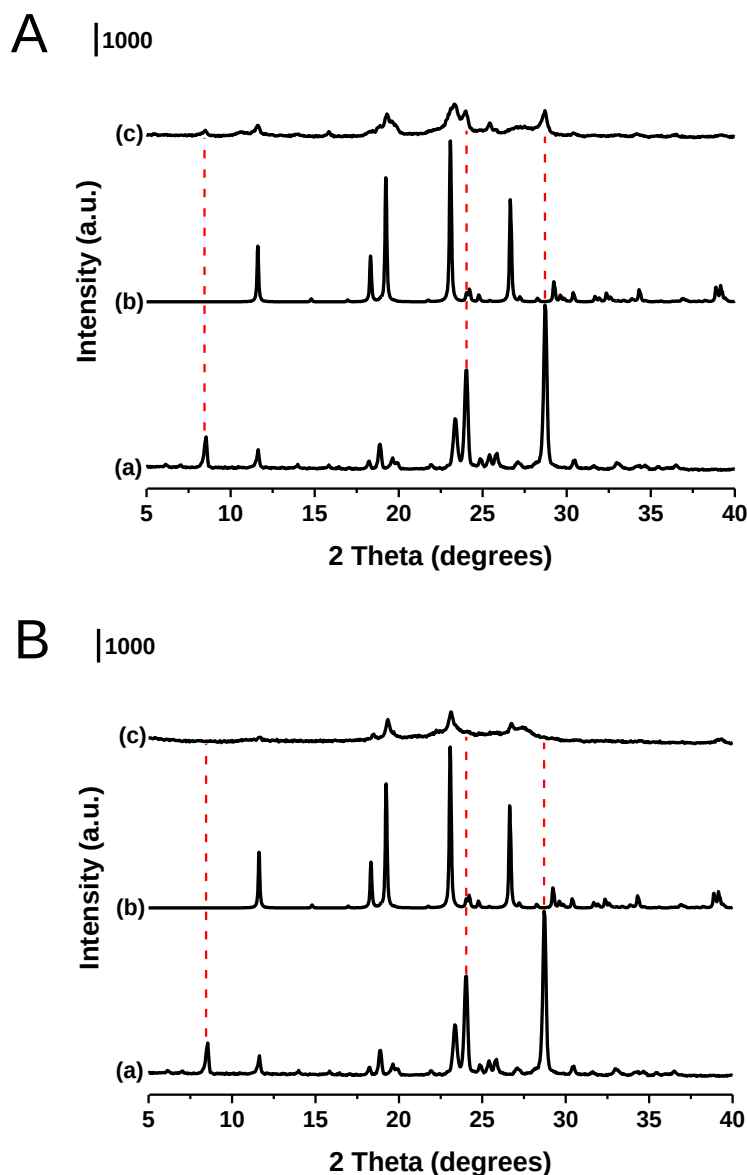


Figure 6.27 A) PXR D diffractograms of (a) crystalline form I ACV (b) CCDC generated structure of α -PA and (c) form I ACV comilled with β -PA in the VBM at RT at 50% w/w for 54 minutes. B) PXR D diffractograms of (a) crystalline form I ACV (b) CCDC generated single crystal structure of α -PA and (c) form I ACV comilled with β -PA in the VBM at CT at 50% w/w for 54 minutes. Red lines indicate Bragg peaks associated with crystalline form I ACV.

Figure 6.28 shows the stepwise DVS sorption profile, with water as the probe vapour, of the form I ACV:PA composite formed on comilling in the VBM at CT at 50% w/w, in steps of 10% RH from 0% to 90% RH. The analysis reveals a mass uptake of 2.4% w/w at 60% P/P₀, possibly associated with the generation of the 3:2 form V hydrate from amorphous ACV. In contrast to the ACV:GA composite which displayed a mass uptake/ crystallisation at 40% RH followed by cocrystal formation at 80% RH, the ACV:PA co-cryomilled composite does not form a cocrystal.

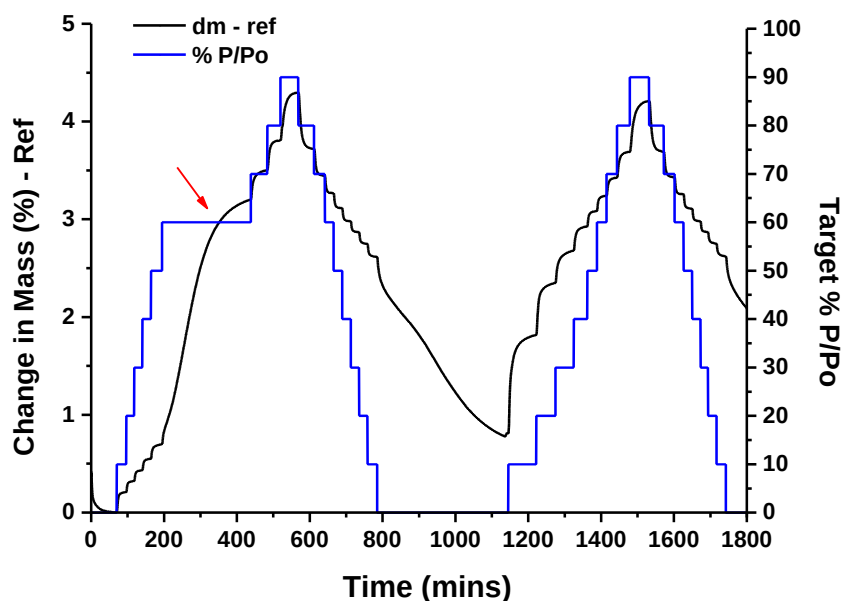


Figure 6.28 DVS stepwise sorption plot of form I ACV comilled with β -PA in the VBM at CT at 50% w/w for 54 minutes. Red arrow indicates onset of mass increase possibly associated with crystallisation event and hydrate formation.

Figure 6.29 highlights the FTIR spectra of the form I ACV:PA 50% w/w comilled composites at both RT and CT. The FTIR spectrum indicated a crystalline nature and form I ACV in the comilled system at RT, further suggesting the ability of PA to lead to the regeneration of form I ACV on comilling at RT, in contrast to the broad diffuse region of the CT comilled system due to amorphisation of ACV.

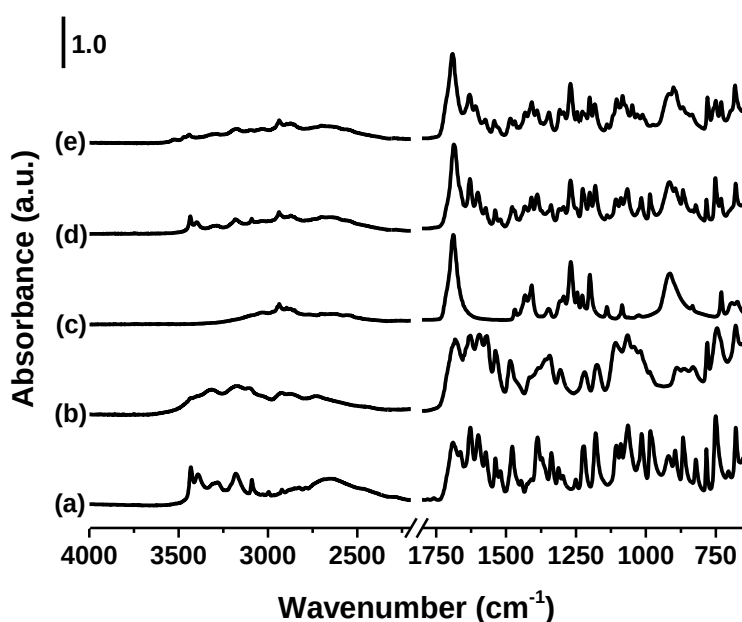


Figure 6.29 FTIR spectra of (a) form I anhydrous ACV (b) form V 3:2 hydrate ACV (c) β -polymorphic PA (d) form I ACV comilled with β -PA in the VBM at RT at 50% w/w for 54 minutes (e) form I ACV comilled with β -PA in the VBM at CT at 50% w/w for 54 minutes.

6.4.3 Comilling Acyclovir with Mannitol

β -MAN was comilled with form I ACV at 50% w/w in the VBM at both RT and CT for 54 minutes. Figure 6.30A shows the PXRD diffractograms of unmilled crystalline form I ACV, together with the CCDC generated structure of β -polymorphic MAN and the RT comilled composite. The diffractogram of the comilled composite at RT does not contain any Bragg peaks associated with crystalline ACV, indicating that comilling with β -MAN led to the amorphisation of form I ACV at RT. However, Bragg peaks associated with β -MAN were observed in the diffractogram. However, due to the low T_g of MAN, the compound does not undergo amorphisation on milling. Figure 6.30B (d) shows the PXRD diffractogram of the form I ACV:MAN CT comilled composite. As for the comilled composite at RT, comilling at CT with β -MAN led to the amorphisation of form I ACV. However, Bragg peaks associated with both the β and δ -polymorphic forms of MAN were observed in the diffractogram, indicating that on comilling at CT, β -MAN underwent a partial polymorphic transformation to the metastable δ polymorph in contrast to comilling at RT.

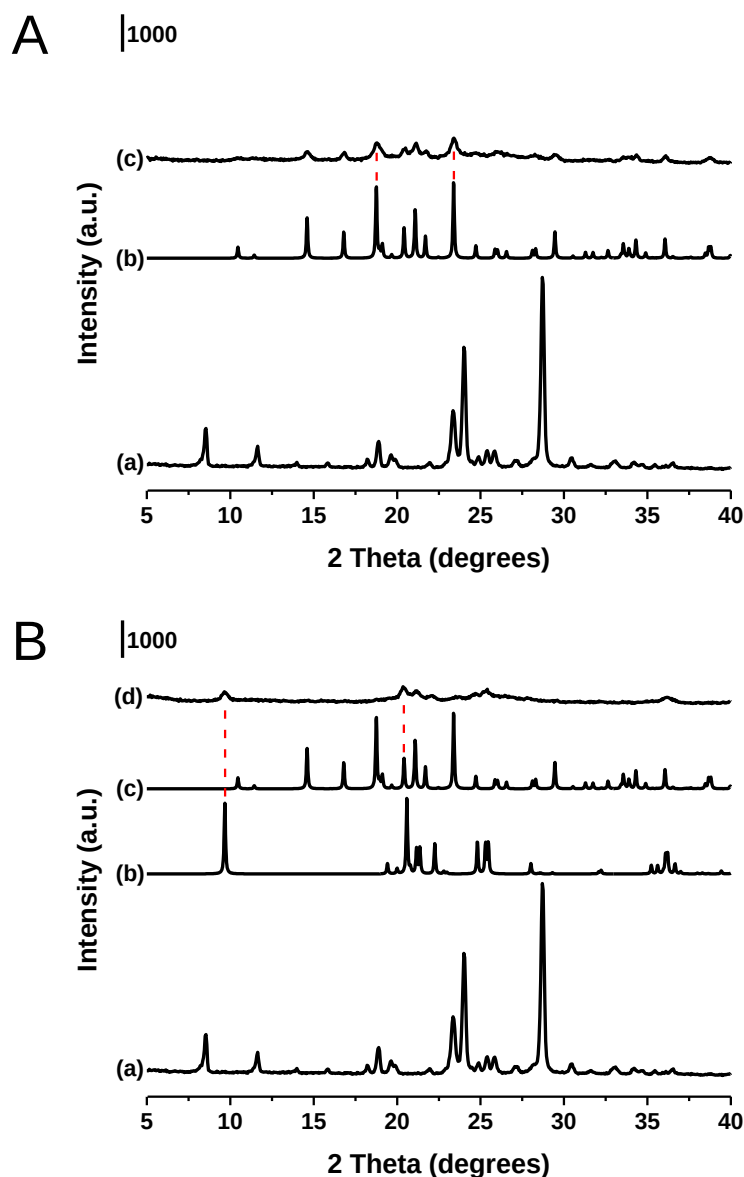


Figure 6.30 A) PXR D diffractograms of (a) crystalline form I ACV (b) CCDC generated crystal structure of β -MAN (c) crystalline form I ACV comilled with β -MAN at 50% w/w at RT for 54 minutes. B) PXR D diffractograms of (a) crystalline form I ACV (b) CCDC generated crystal structure of δ -MAN (c) CCDC generated crystal structure of β -MAN and (d) crystalline form I ACV comilled with β -MAN at CT for 54 minutes.

Figure 6.31 (a) and (b) show the DSC thermograms of unmilled crystalline β -MAN and the form I ACV:MAN CT comilled composite respectively. The CT comilled composite shows an exothermic peak at 113 °C, followed by an endothermic peak associated with melting of crystalline MAN at 167 °C. In contrast, the melt endotherm of β -MAN occurred at 168 °C, indicating lack of a reduced eutectic melting of MAN in the presence of ACV. This indicates that the two components are unlikely to be miscible in the liquid state, which in turn indicates that they are likely

to be immiscible in the glass solution state. The inset of Figure 6.31 highlights the reversing heat flow signal from a modulated heat flow scan of the CT form I ACV: MAN comilled composite, indicating a glass transition event at $101 (\pm 0.8) ^\circ\text{C}$. This suggests that β -MAN led to only a slight reduction in the T_g of form I ACV on comilling from $109 ^\circ\text{C}$. However, as the T_g of MAN has been determined to be $13 ^\circ\text{C}$, this does not represent a significant level of T_g reduction on comilling and could be due to the limited miscibility of the two components in the liquid/ glass solution state.

Figure 6.31 (c) highlights the DSC thermogram of the form I ACV: MAN RT comilled composite. The thermogram indicates a crystallisation exotherm at $108 ^\circ\text{C}$ which was reduced relative to that of the CT comilled composite. However, the endotherm associated with the melt of crystalline MAN was similar at $167 ^\circ\text{C}$.

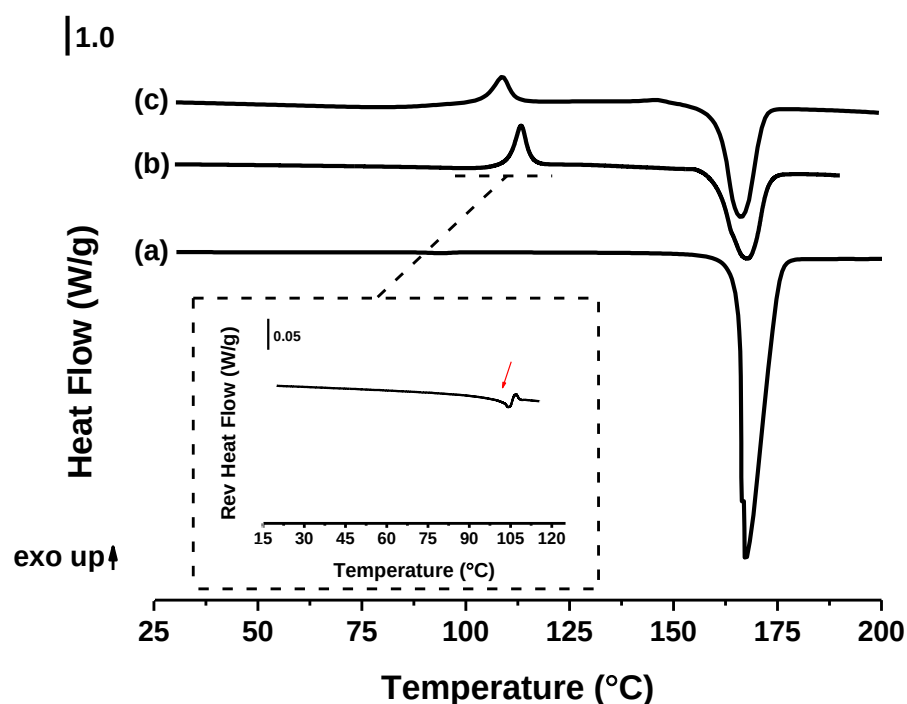


Figure 6.31 DSC thermograms of (a) crystalline β -MAN and form I ACV comilled with MAN at 50% w/w in the VBM for 54 minutes at (b) CT and (c) RT. Inset shows the reversing heat flow signal and T_g event of the CT comilled system. Red arrow indicated glass transition event in the reversign heat flow signal.

Figure 6.32 shows the stepwise DVS sorption isotherm, with water as the probe vapour, of the form I ACV:MAN RT comilled composite in 10% RH/ per step from 0% to 90% RH. The profile reveals a mass loss event at 60% RH possibly associated

with a crystallisation event. Interestingly, crystallisation of the 3:2 hydrate from the co-cryomilled ACV:GA and ACV:PA composites in the DVS led to mass uptake events, associated with the incorporation of the water of hydration into the crystal lattice of the hydrate. However, in the case of the ACV:MAN co-milled composite, a very large uptake of water had occurred of 5.6% at 50% RH, prior to the mass loss event at 60% RH. As only 2.7% w/w uptake of water is required to form the 3:2 hydrate, crystallisation into the hydrate from the ACV:MAN composite led to the expulsion of water from the amorphous comilled composite. Indeed, subsequent to the mass loss event shown in Figure 6.32, at 0% RH under dry nitrogen flow, the continuous mass loss is consistent with the loss of water of hydration from the crystalline hydrate, as shown in Figure 6.6.

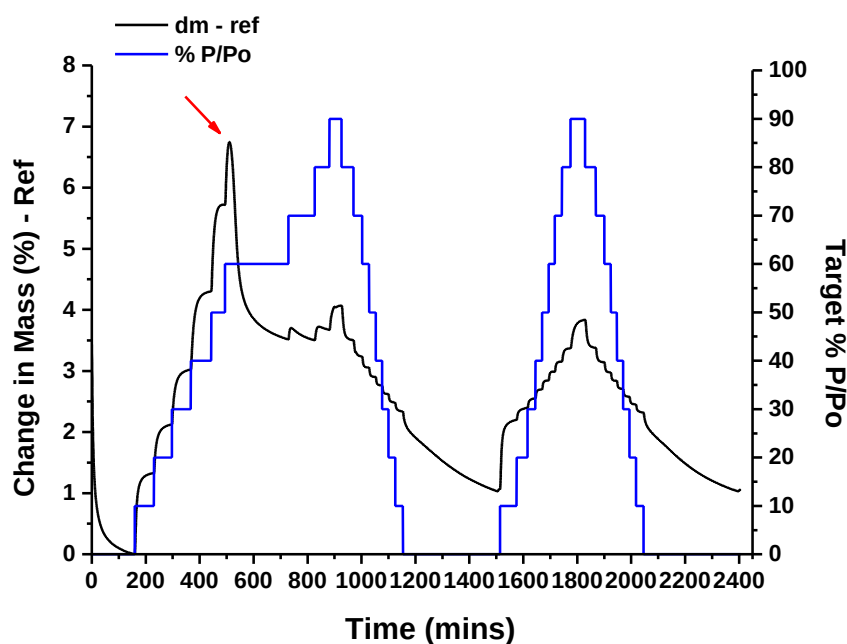


Figure 6.32 DVS stepwise sorption profile of form I ACV comilled with MAN at 50% w/w composition in the VBM at RT for 54 minutes. Red arrow indicates onset of mass loss event.

Figure 6.33 shows the FTIR spectra of the form I ACV:MAN comilled composites formed at RT and CT. Comparison of the O-H stretching region at 3393 cm^{-1} and C-O stretching at 1077 cm^{-1} of MAN in the RT comilled composite revealed no peak shift, indicating a lack of hydrogen bonding on comilling. In contrast, the CT comilled composite showed a broad diffuse spectrum in the O-H stretching region. However, this could be due to the partial transformation to the δ -polymorphic form, as shown in Figure 6.30B.

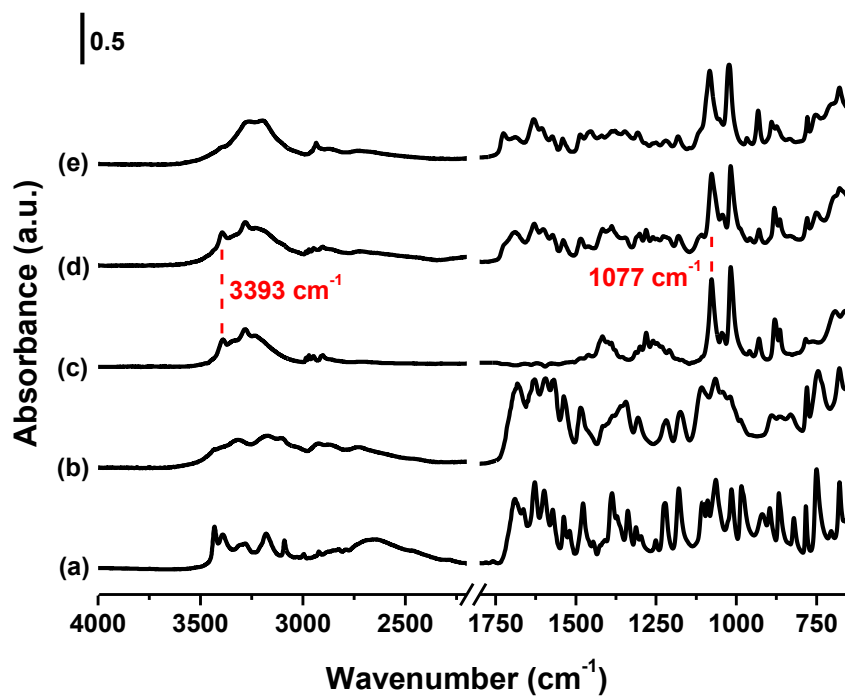


Figure 6.33 FTIR spectra of (a) form I anhydrous ACV (b) form V 3:2 hydrate ACV (c) β -polymorphic MAN and form I ACV comilled with β -MAN at 50% w/w for 54 minutes in the VBM at (d) RT and (e) CT. Red lines indicate peak positions referred to in the discussion text.

6.5 CONCLUSIONS

The anhydrous form I polymorph of acyclovir was prepared from the commercially available form V hydrate. Room temperature milling of the form V hydrate of acyclovir did not lead to the amorphisation of the compound, in contrast to the anhydrous form I polymorph which was amorphised on milling at room temperature, as evidenced by DSC and PXRD analysis. Both forms were amorphised on milling at cryo-temperature and the glass transition temperature of the cryomilled amorphous state was determined to be 109 °C for both polymorphic forms.

Comilling of form I acyclovir with glutaric acid at room temperature in the vibratory ball mill led to the generation of an equimolar cocrystal after 54 minutes compared to the 12 hours required for the formation of the cocrystal in the planetary ball mill reported previously. Comilling form I acyclovir with mannitol at room temperature led to the amorphisation of the API. In contrast, the composite formed on comilling form I acyclovir with pimelic acid contained evidence of the form I polymorph, indicating that the pimelic acid was at least partly successful at mitigating amorphisation of acyclovir on comilling with the regeneration of the starting polymorphic form of the API.

Co-cryomilling form I anhydrous acyclovir with glutaric acid led to the amorphisation of the API with a reduced T_g of 48 °C. Crystallisation studies from the co-cryomilled composite indicated a concomitant crystallisation of the β polymorph of glutaric acid, together with the 3:2 hydrate of acyclovir at 43% RH and 25 °C. However, conversion to the cocrystal was observed on increasing either the temperature to 40° C or the humidity to 80% RH. Co-cryomilling form I anhydrous acyclovir with both mannitol and pimelic acid led to the amorphisation of acyclovir. However, co-cryomilling with pimelic acid led to the formation of a reduced T_g composite with a value of 54 °C. In contrast, co-milling with mannitol only led to a T_g reduction to 101 °C, in spite of the low T_g of mannitol of 13 °C. Humidity induced crystallisation from the co-cryomilled composites formed with both pimelic acid and mannitol led to the regeneration of the form V polymorph of acyclovir, as evidenced by DVS analysis.

CHAPTER 7

CO-BLENDING AND CO-COMPACTION STUDIES

7.1 INTRODUCTION

Blending and compaction processes are routinely employed in the pharmaceutical industry with the aim of generating homogenous API: excipient blends followed by the formation of tablet compacts respectively. As blending and compaction processes are usually employed subsequent to the milling operation, unintentionally generated amorphous regions, generated during milling, may be subject to blending and compaction processes in the presence of excipients. In previous chapters we have highlighted the ability of the milling operation to drive hydrogen bonding group interactions between amorphous sulfadimidine and various excipients. It is thus of importance to assess the propensity of the blending process to drive similar interactions between amorphous API and excipient, which may have consequences for the properties of the amorphous state of the API on co-processing. In addition previous studies have highlighted increased crystallisation rates from the amorphous state of APIs (e.g. indomethacin) on application of a compression force (Thakral, Mohapatra et al. 2015). It is thus also of interest, in the context of mitigating amorphisation on co-processing, to investigate the propensity of a compression force to drive crystallisation of API from API: excipient composite systems formed on comilling.

In this chapter the effect of processing crystalline sulfadimidine in the Turbula mixer alone, in the absence of excipient will be assessed. Subsequently, previously amorphised sulfadimidine will be co-blended with glutaric acid, in order to assess both the ability of the excipient to drive crystallisation of amorphous sulfadimidine on co-blending and, in addition, to assess the potential for the co-blending process to drive a hydrogen bonding interaction with amorphous sulfadimidine, as was observed in the comilled system in Chapter 5.

As previous studies have highlighted the tendency for compaction to induce crystallisation from amorphous indomethacin, the ability of the high pressures generated during compaction to drive the crystallisation of BD from the reduced T_g BD: diacid composites formed on co-cryomilling will be assessed, in order to assess the propensity for the compaction process to drive crystallisation of amorphous API in the presence of low T_g excipient.

7.2 CHARACTERISATION OF BLENDED SULFADIMIDINE AND CO-BLENDING WITH GLUTARIC ACID

SDM was processed alone, without glass beads, in a Turbula mixer at RT by placing 0.5 g of powder into a 50 ml glass vial, which was then secured in place inside a large glass tumbler. The sample was processed in the Turbula mixer for 24 hours at RT at 64 rotations per minute. Figure 7.1 shows the DSC thermograms of SDM both before and after processing alone in the Turbula mixer. No exothermic peak was detected in the DSC signal, indicating that crystalline SDM was not amorphised. Each of the thermograms displayed an exothermic peak at 198 °C, associated with the melting point of crystalline SDM.

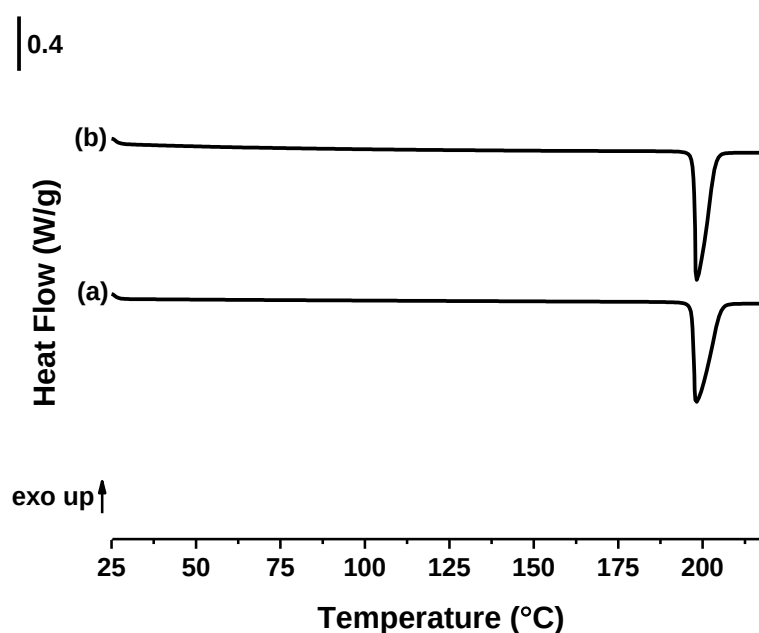


Figure 7.1 DSC thermograms of (a) unprocessed crystalline SDM and (b) SDM blended alone in the Turbula mixer for 24 hours.

Figure 7.2 highlights the surface energy plot of crystalline unmilled SDM together with the plot of the SDM system blended in the Turbula mixer for 24 hours at RT. While the dispersive surface energy of the unmilled crystalline SDM was determined to be 48 mJ/m², as shown in Chapter 3, Section 3.2.4, the dispersive surface energy of the mixer-processed SDM system was determined to be 56 mJ/m² indicating that processing for 24 hours in the Turbula mixer led to the activation of

the surface of the particles. It should be note that, as shown in Figure 7.2, the retention volumes of the non-polar probes were similar for the unprocessed and processed SDM systems. This contrasts with the surface energy plots of the milled SDM systems, as shown in Figure 3.22 and 3.23 in Chapter 3, Section 3.5 even though a similar mass of powder was used in each case. This difference is most likely due to the increase in surface area of the milled systems associated with particle size reduction leading to increased surface area for interaction with the non-polar probes and consequently increased retention volumes (Thielmann, Burnett et al. 2007)

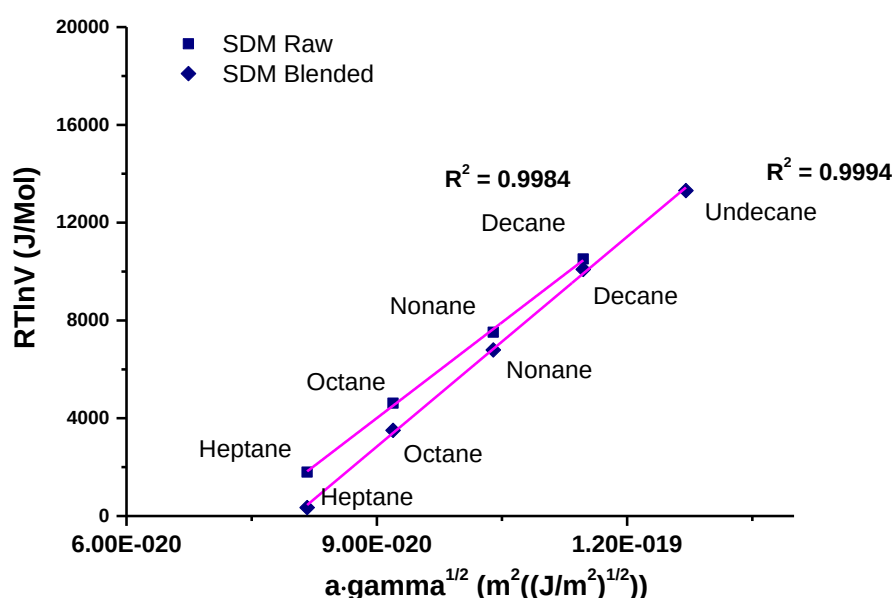


Figure 7.2 Surface energy plots of unprocessed SDM and SDM blended alone in the Turbula mixer for 24 hours.

In Chapter 5, the properties of the composite systems formed on comilling the dicarboxylic acid excipients with previously milled amorphous SDM was assessed. In order to investigate the composite system formed on co-blending, amorphous (planetary ball milled) SDM (mSDM) was co-blended with β -GA at 50% w/w at RT for 24 hours at 64 revolutions per minute. Figure 7.3 highlights the PXRD diffractograms of the co-blended system after 20 minutes of co-blending and after 24 hours. In contrast to the properties of the alloy formed on comilling amorphous SDM with β -GA which showed polymorphic transformation of β -GA to the α -polymorphic form, no such transformation was observed to occur on co-blending.

This analysis also highlights that after 24 hours of co-blending, in the absence of glass beads or mixing media, SDM was still amorphous indicating that GA was unable to mitigate amorphisation of SDM on co-blending under the conditions of this study.

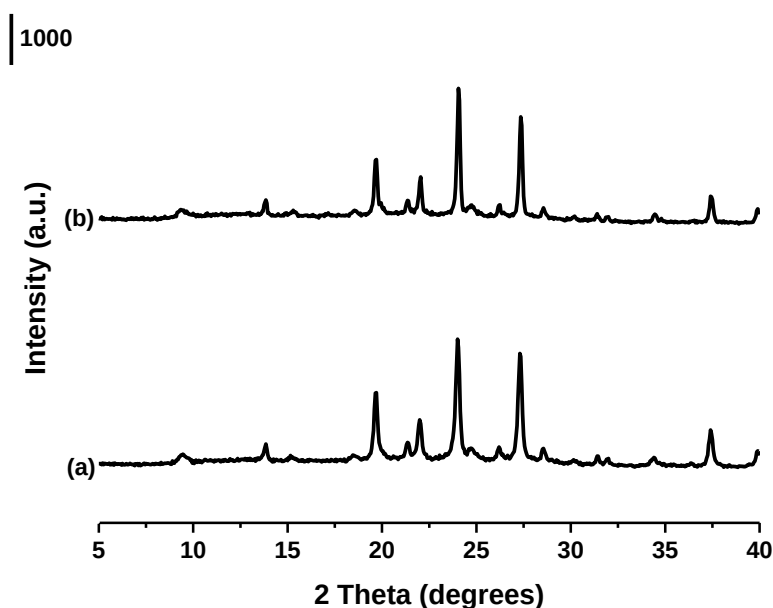


Figure 7.3 PXRD diffractograms of planetary ball milled SDM co-blended with β -GA at 50% w/w at RT for (a) 20 minutes and (b) 24 hours.

Figure 7.4 shows the FTIR spectra of a physical mixture of mSDM and crystalline β -GA mixed in an agate mortar and pestle, together with the spectra of mSDM co-blended with β -GA at 50% w/w for 24 hours at RT and mSDM comilled with β -GA at 50% w/w in the VBM at RT for 36 minutes. Figure 7.4A highlights the shoulder observed for the carbonyl peak at 1725 cm^{-1} in the comilled composite, while Figure 7.4B highlights the shift in the C-O group of GA from 1210 to 1195 cm^{-1} on comilling and the shift in the S=O antisymmetric stretching peak of SDM from 1300 - 1290 cm^{-1} relative to the physical mixture. Similar shifts in hydrogen bonding groups were not observed in the co-blended system, as highlighted in Figure 7.4, which exhibited a similar spectrum to that of the physical mixture formed in the agate pestle and mortar. Curtin et al. reported on the ability of GA to partially mitigate amorphisation of salbutamol sulphate on co-mixing in the Turbula mixer in the presence of glass beads (Curtin, Amharar et al. 2013). Importantly in the current study we co-blended amorphous API with GA in the absence of mixing media.

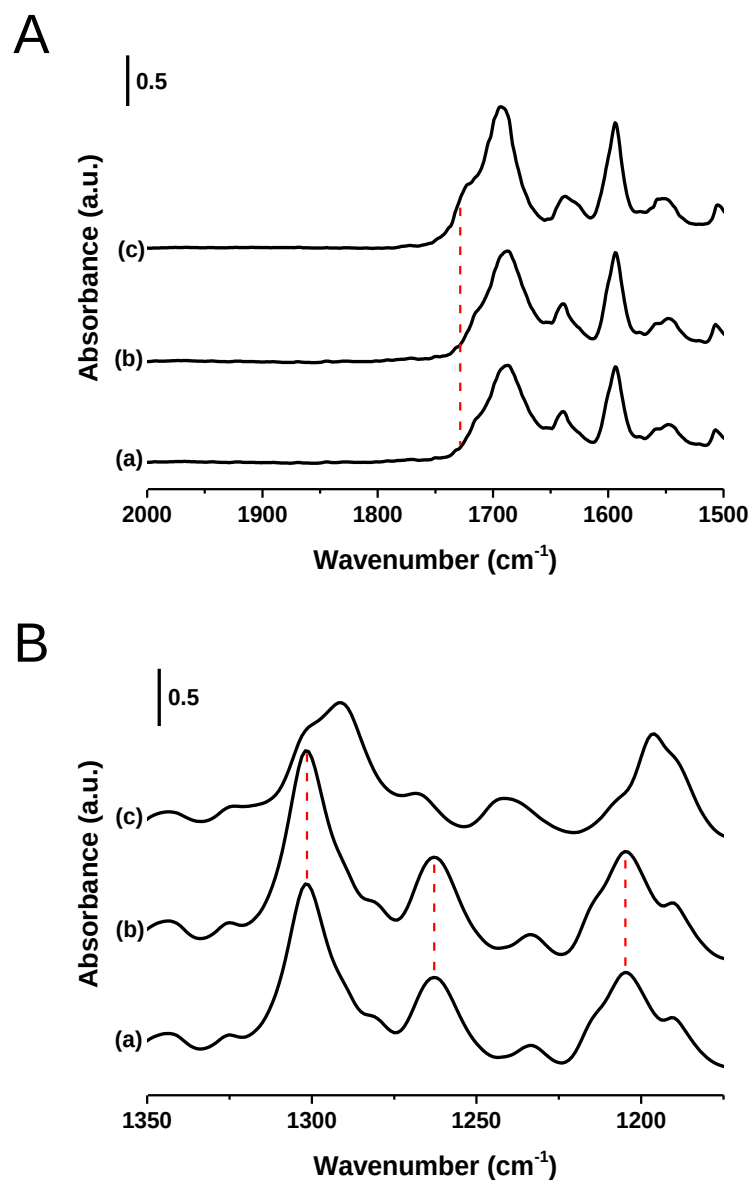


Figure 7.4 A-B) FTIR spectra of (a) physical mix of planetary ball milled SDM and crystalline β -GA at 50% w/w (b) planetary ball milled SDM co-blended with β -GA at 50% w/w in the Turbula mixer for 24 hours and (c) planetary ball milled SDM comilled with β -GA at 50% w/w in the VBM at RT. (Red dashed lines indicated peak positions referenced in the text).

7.3 CO-COMPACTION OF BUDESONIDE WITH DICARBOXYLIC ACIDS

As described by Espeu et al., GA exhibits enantiotropic behaviour at standard temperature and pressure. However, at elevated pressures, above 63 MPa, GA exhibits monotropic behaviour with the beta polymorph being the only stable polymorph above this pressure. Spray drying GA led to the generation of a mixed α/β polymorphic system, as shown in Figure 7.5. The spray dried GA system was compacted at 75 MPa for a dwell time of 10 seconds. As shown in Figure 7.5, compacting at 75 MPa led to an increased in the Bragg peaks associated with the β -polymorph of GA and a reduction in the Bragg peaks associated with the α polymorph.

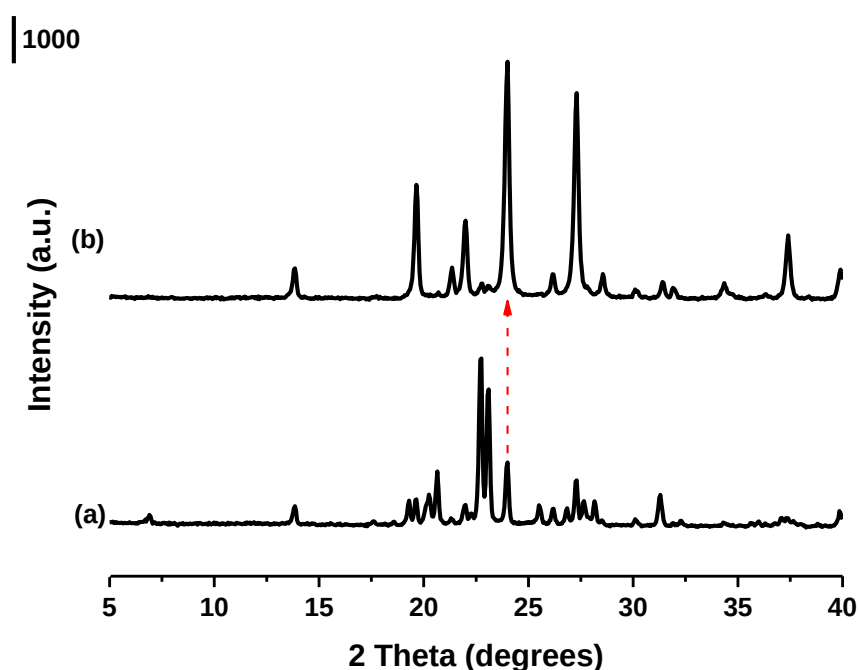


Figure 7.5 PXRD diffractograms of (a) GA spray dried from 70% ethanol solution at 78 °C and (b) spray dried GA after compaction at 75 MPa for a dwell time of 10 seconds. (Red arrow indicates Bragg peak associated with β -polymorphic GA).

Many pharmaceutical systems have been shown to undergo polymorphic transformations on compaction including caffeine and carbamazepine (Lefebvre, Guyot-Hermann et al. 1986, Mazel, Delplace et al. 2011, Juban, Briançon et al. 2016). However, investigations have also been conducted on the effect of compaction

pressures on the stability/ crystallisation tendency of amorphous systems. Thakral investigated the increased crystallisation tendency of amorphous indomethacin on compaction (Thakral, Mohapatra et al. 2015). These authors found that higher compression pressures led to increased crystallinity of indomethacin, particularly on the surface of the compacts formed. Adrjanowicz studied the kinetics of crystallisation of indomethacin in the super-cooled liquid state on compaction, and found an increased crystallisation rate which they attributed to the effect of the compression pressure on the thermodynamic driving force for crystallisation (Adrjanowicz, Grzybowski et al. 2013). Interestingly, Worku et al. investigated the impact of compression forces on the hydrogen bonding interactions in solid dispersion systems formed between naproxen and PVP-VA 64 formed by spray drying and found that compression increased the stability of the solid dispersion due to the compaction pressure facilitating the hydrogen bonding interaction (Worku, Aarts et al. 2014).

In order to assess the propensity of a compression force to drive crystallisation of amorphous BD: diacid excipient composites formed on co-cryomilling, the co-cryomilled BD: diacid composites (50% w/w) were compacted at 75 MPa for 10 seconds dwell time. Figure 7.6A shows the BD:GA co-cryomilled composite both before and after compaction. No evidence of crystalline BD was observed in the PXRD diffractograms. In addition, the diffractogram also suggested that the compression force did not lead to the crystallisation of β -GA, in contrast to the situation shown in Figure 7.5, where the compression force led to the growth of β -GA from the spray dried system. Figure 7.6B shows the PXRD diffractograms of the BD:AA and BD:SA 50% w/w co-cryomilled composites both before and after compaction at 75 MPa with a 10 seconds dwell time. Similarly to the BD:GA system, no PXRD evidence for crystalline BD was observed in these systems. While this analysis indicated that high compression forces did not lead to increased crystallisation of the API from the amorphous state under the limited set of conditions of this study, further work is required to assess the impact of high pressure on the physical properties of amorphous molecular alloys in terms of the effect on the destabilisation of the amorphous API, and the propensity to drive crystallisation from amorphous composite systems with low T_g excipients.

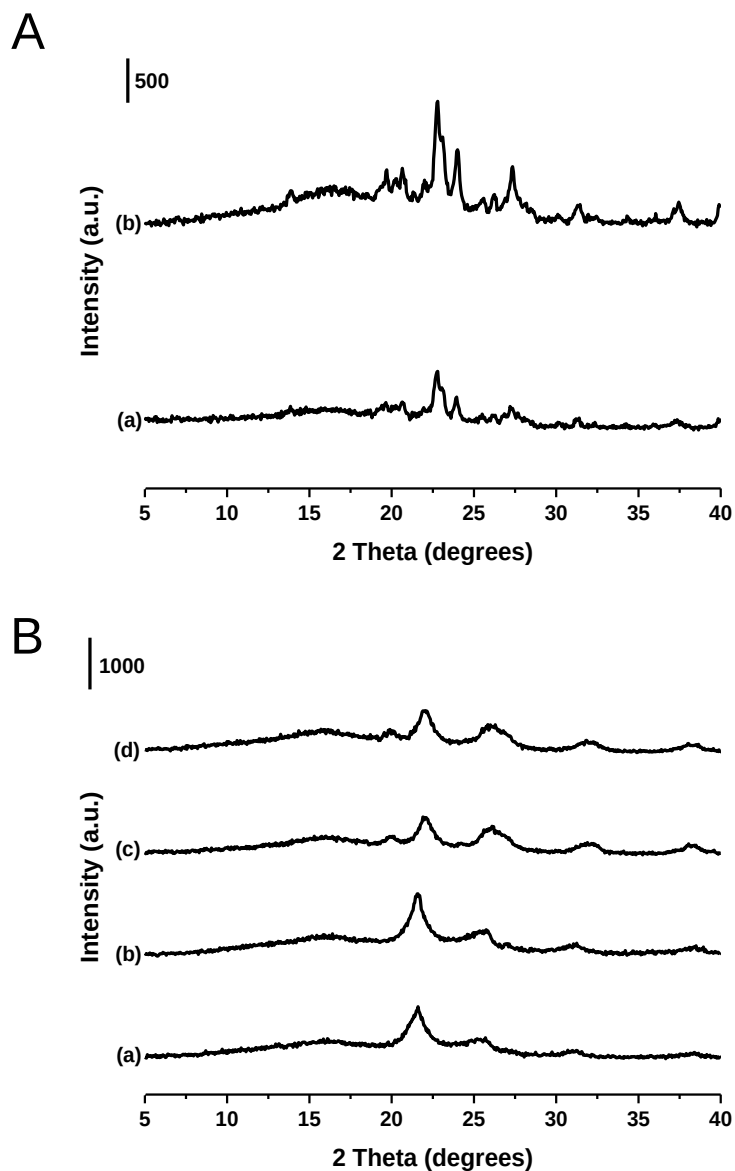


Figure 7.6 A) PXRD diffractograms of (a) BD comilled with GA at 50% w/w in the VBM at CT and (b) co-cryomilled BD:GA 50% w/w composite after compaction at 75 MPa for a dwell time of 10 seconds. B) PXRD diffractograms of (a) BD comilled with AA at 50% w/w in the VBM at CT and (b) co-cryomilled BD:AA 50% w/w composite after compaction at 75 MPa for a dwell time of 10 seconds (c) BD comilled with AA at 50% w/w in the VBM at CT and (d) co-cryomilled BD:SA 50% w/w composite after compaction at 75 MPa for a dwell time of 10 seconds.

7.4 CONCLUSIONS

In this chapter previously amorphised (in the planetary ball mill) SDM was co-blended with the low T_g crystalline excipient, β -GA, in a Turbula mixer at RT for 24 hours. In contrast to results presented in previous chapters which suggested the formation of a milling-induced hydrogen bonding interaction between GA and amorphous SDM as evidenced by spectroscopic analysis, no such interaction was observed on co-blending under the conditions used in this study. In addition, while comilling led to the polymorphic transformation of β -GA to the metastable α polymorph in the presence of amorphous SDM, no such transformation was observed to occur on co-blending. This suggests the importance of the mechanical energy imparted during a milling operation in driving the observed phase transformations between amorphous API and excipient. The propensity of a compression force to lead to the crystallisation of BD from reduced T_g amorphous BD: diacid composites formed on co-cryomilling was also investigated. However, the analysis did not reveal any crystallisation of BD from the amorphous composites on the application of a compression force. Further studies are required to explore the effect of compression forces on the crystallisation tendency from amorphous composite systems.

CHAPTER 8

GENERAL DISCUSSION

MECHANICAL ACTIVATION ON MILLING AND SOLID-STATE CHARACTERISATION

Many factors are known to influence the solid-state transformations of molecular materials on mechanical driving, including material factors such as the T_g of the material in addition to milling variables including the temperature of the mill, the type of mill and the mechanical energy imparted during the milling operation (Abdellaoui and Gaffet 1996, Shakhtshneider, Danède et al. 2007, Descamps, Aumelas et al. 2015). The amorphisation of SDM ($T_g = 78\text{ °C}$) in both a vibratory (VBM) and a planetary (PBM) type ball mill at RT was compared. Both the VBM and PBM led to a similar steady-state partial amorphisation of SDM of 80% w/w on milling at RT, which correlates with previous findings by Curtin et al., who reported that SDM was partially amorphised, to a similar extent, on milling in the PBM at RT (Curtin, Amharar et al. 2013). However, the kinetics of amorphisation appeared to be faster in the VBM, achieving the steady-state 80% amorphous content after approximately 60 minutes of milling. This compares to the PBM which took approximately 6 hours to achieve the same steady-state level of amorphisation. In addition to the type of ball mill, the temperature of the milling operation has been shown to play a crucial role in affecting phase transformations to high energy amorphous states on mechanical driving, with an increased amorphisation tendency at lower milling temperatures (Descamps, Willart et al. 2007, Tao, Sun et al. 2009, Hu, Macfhionnghaile et al. 2013). We also investigated the impact of milling temperature on the amorphisation of SDM in both the VBM and PBM. While both mill types led to a steady-state partially (80%) amorphous system on milling at RT, in contrast milling in the PBM at 4 °C led to a partially amorphous system of 93% amorphous content after 18 hours. On milling SDM in the VBM at CT the generation of a PXRD amorphous system was observed.

In order to further explore the relationship between the variables that affect the mechanical energy imparted during milling with the milling temperature, we conducted a 2^4 factorial design of experiment investigation in the vibratory ball mill to examine the effect of three ballistic variables, the frequency of vibration (f), the ball to powder mass ratio (BPR) and the ball diameter (φ), each of which are known to affect the mechanical energy imparted during milling, **relative to** the temperature of the milling operation, T_{mill} , on the amorphisation of SDM (Burgio, Iasonna et al. , Burmeister and Kwade 2013). Determination of the main effects

(ME) allowed a comparison of the influence of each of the factors on amorphisation, with frequency of vibration having the greatest influence on amorphisation (ME = 43.6), relative to each of the other ballistic variables ball diameter (ME = 22.6) and ball to powder mass ratio (ME = 19.3). In contrast to the ballistic variables, the temperature of the mill T_{mill} had a negative effect reflecting the fact that as the temperature is reduced the amorphous content increased, which is in line with previous findings. The effect of the temperature on amorphous content (ME = -6.7) was of lower magnitude than the ballistic variables.

The design of experiment allowed the determination of the interaction effects (IE) between each of the main variables with the largest interaction observed for frequency: ball diameter (IE = 8.3). As suggested by Abdellaoui et al., the kinetic energy of the balls, and thus the mechanical energy imparted per impact, is a function of both the ball mass (determined by the ball diameter) and the ball velocity (determined by the frequency of vibration) (Abdellaoui and Gaffet 1995). In contrast to the interaction effects between the ballistic variables, the interaction effects for each of the ballistic variables and T_{mill} were negative. This suggests that as the temperature of the mill was reduced, each of the ballistic factors had a greater impact on the amorphisation of SDM. In particular, the strongest interaction with T_{mill} was found for the frequency variable (IE = -4.0). Similarly, decreasing the T_{mill} to CT also had an influence on amorphising tendency of the ball diameter variable (IE = -3.4) while the ball to powder mass ratio showed the lowest interaction with T_{mill} (IE = -2.1).

The driven materials theory accounts for the relationship between the mechanical energy imparted during milling, determined by the ballistic variables, and the temperature of the milling operation relative to the tendency to drive the amorphisation of the material being milled (Descamps and Willart 2016). The model describes a **competition** between ballistic effects which drive the system towards a disordered high energy state and the temperature dependent molecular mobility of the system which tends to restore the system to the thermodynamically favoured crystalline state. According to Equation 8.1, the ballistic shocks imparted during a milling operation lead to a ballistic jump parameter, D_{bal} . In addition the equation includes a restorative thermal jump parameter D_{th} , which is dependent on the temperature of the system, i.e. the temperature of the milling operation, T_{mill} .

$$T_{eff} = T_{mill} \left(1 + \frac{D_{bal}}{D_{th}} \right)$$

Equation 8.1

Each of the three parameters combine according to Equation 8.1 to yield an effective temperature of milling, T_{eff} . Equation 8.1 predicts that if the ballistic variables (which determine D_{bal}) of the milling operation are maintained at a constant level and T_{mill} is reduced, the reduction in the milling temperature leads to a greater effective temperature of milling. As suggested by Descamps et al., if the effective temperature is increased relative to the equilibrium melt temperature of the material being milled, there is a greater tendency to drive the molecular dissociation of the system towards a higher energy amorphous state, analogous to a melting event, as thermal restoration is unable to overcome the disordering force of the milling operation. Importantly, the transformation to the amorphous state can be achieved even if the actual temperature of the system is below the melt temperature of the material, thus allowing a **direct transformation** to the amorphous state.

In addition to the quantification of bulk amorphous regions by DSC and NIR, inverse gas chromatography (iGC) in particular has been utilised to assess changes to the solid surfaces of processed materials (Cares-Pacheco, Vaca-Medina et al. 2014). Milling has been shown to induce significant changes to the solid-state surface characteristics of crystalline materials including the generation of surface amorphous regions in addition to crystallite fragmentation with the exposure of high energy crystal facets (Feeley, York et al. 1998, Grimsey, Feeley et al. 2002). From the design of experiment study, the bulk amorphous characteristics of SDM milled at high frequency milling (25 Hz) were characterised. Analysis indicated 68% w/w amorphous content as quantified by DSC. In addition, DSC analysis revealed a bimodal crystallisation exotherm with the initial exothermic peak at 72 °C which has been associated with fast crystallisation of surface amorphous regions (Chattoraj, Bhugra et al. 2011). The dispersive surface energy of this milled amorphous SDM was determined to be 62 mJ/m², higher than that of the unmilled crystalline material, which had a dispersive surface energy of 48 mJ/m². In addition, heat of sorption analysis indicated a phase transition at 69 °C, consistent with the DSC exotherm, and associated with surface crystallisation. Subsequent to the heat of sorption analysis, the dispersive surface energy was reduced to 56 mJ/m²,

indicating an increase in the surface energy of the milled crystalline system relative to unmilled crystalline starting material. The surface energy of a low frequency (15 Hz) milled system from the design of experiment study was also determined for which DSC analysis indicated a low amorphous content of 6% w/w. While no phase transformation was detected on heat of-sorption analysis, the surface energy had increased to 55 mJ/m², similar to that of the high energy milled system.

IGC has also been utilised to assess changes to the surface acid-base chemistry of processed materials (Mohammadi-Jam and Waters 2014). In a manner similar to that employed by Heng et al. in the assessment of milling induced changes to the surface properties of paracetamol, we determined the Lewis acid K_a values by the Gutmann method for both unmilled SDM and in addition the two milled SDM samples after enthalpy of sorption analysis (Heng, Thielmann et al. 2006). Relative to the unmilled starting material which had a K_a number of 0.135, analysis of the high frequency milled system indicated an increase in the K_a number to 0.15. This suggests an increase in the acid character of the surface of SDM on milling, possibly associated with exposure of the aromatic N-H group of SDM which acts as a Lewis acid electron acceptor, suggesting the exposure of the 001 plane of SDM, as determined by BFDH morphology analysis. Similarly, analysis of the K_a value of the low frequency milled system indicated an increase from 0.135 to 0.147, similar to the high energy frequency milled system.

In addition to the quantification of amorphous content by DSC analysis, the amorphous content in the design of experiment study was also quantified by NIR analysis. Two calibration curves were prepared with NIR analysis, one with unmilled crystalline SDM as the crystalline standard and the other with milled recrystallised SDM as the crystalline standard. It was noted that when the NIR calibration curve was constructed with unmilled SDM for the crystalline standards, there was a consistent over-estimation of the amorphous content, relative to DSC quantification - by up to 15% - for the systems with **low levels of amorphous content** (i.e. the low frequency (15 Hz) milled systems). This finding is consistent with the study reported by Caron et al. who compared the amorphisation kinetics of lactose on milling using both PXRD and ss-NMR relative to DSC analysis (Caron, Willart et al. 2011). During the initial stages of milling, these authors reported that both PXRD and ss-NMR analyses overestimated the level of amorphous content in the milled system when compared to quantifications based on the emergence of the T_g by DSC analysis. These authors suggested that during the initial stages of milling,

both PXRD and ss-NMR were sensitive to static effects induced by the milling process. Newman et al. reviewed the common solid-state characterisation techniques (Newman and Zografi 2014). In particular they contrasted techniques which detect changes associated the amorphous regions (thermal analysis), with those techniques that characterise the crystalline regions (PXRD analysis) and those that characterise both the amorphous and crystalline regions (spectroscopic analyses). When milled crystalline SDM was used as the crystalline standard, better correlation with the DSC results was observed, as shown in Chapter 3. In contrast, in systems with high levels of amorphous content the two NIR calibration curves were **both in good agreement** with the DSC results. Thus, deviation of the NIR amorphous content values from DSC data was only observed in systems with low levels of amorphous content. IGC analysis however revealed that even in low energy milled systems significant surface changes were observed, similar to the high energy milled system.

COMILLING AND FORMATION OF THE DRIVEN MOLECULAR ALLOYS

Mitigation of Amorphisation on Comilling – Correlation with Experimental Solubility, Calculated Hildebrand Solubility Parameters and T_g Reduction Relative to the Milling Temperature

In this work, each of the four diacids SA, GA, AA and PA and the polyol MAN were comilled with crystalline BD at 50% w/w in the vibratory ball mill at RT. Table 8.1 shows the amorphous content of BD on milling alone and on comilling at RT with each of the excipients. PXRD analysis revealed evidence of crystalline BD on comilling with AA, GA and PA, in contrast to the systems formed on comilling with SA and MAN which were PXRD amorphous for BD. Quantification of the crystalline content of BD in each of the systems by DVS analysis indicated that GA was the most successful diacid at mitigating amorphisation of crystalline BD with 98% crystallinity on comilling, followed by PA (72% crystallinity) and then AA (21% crystallinity). In contrast, DVS analysis revealed that both SA and MAN were unsuccessful at mitigating amorphisation of BD to any extent on comilling. This analysis establishes the relative ability of the four diacids and MAN to mitigate amorphisation on comilling in a vibratory ball mill at RT. These results are broadly in line with previous findings of comilling the diacids with SDM in a planetary ball

mill undertaken by Curtin et al., who found GA to completely mitigate amorphisation followed by AA which showed partial ability to mitigate amorphisation, while SA did not mitigate amorphisation to any extent (Curtin, Amharar et al. 2013). Similarly, the same authors found that on comilling with salbutamol sulphate in a planetary ball mill at RT, GA completely mitigated amorphisation, with lesser mitigation of amorphisation achieved with PA and less again with AA (Curtin, Amharar et al. 2013).

Table 8.1 Summary of the comilling experiments with BD and the BD: excipient alloys at both RT and CT in addition to the experimental solubilities of the diacids in BD and the difference in the calculated Hildebrand solubility parameters between the excipients and BD.

	PXRD Evidence of Crystalline BD		Amorphous Content DVS (% w/w)	$\Delta\delta$ (MPa ^{1/2})	Solubility (% w/w)
	CT	RT	RT		
Budesonide	no	no	94	-	-
BD:SA	no	no	106	1.1	21
BD:GA	no	yes	2	0.1	23
BD:AA	no	yes	79	1.0	20
BD:PA	no	yes	28	1.8	26
BD:MAN	no	no	97	12.3	-

Curtin et al. correlated the increased ability of GA to mitigate amorphisation of SDM on comilling relative to AA to their experimentally determined solubilities in SDM, as determined by the zero enthalpy extrapolation method (Amharar, Curtin et al. 2014). However, analysis of the experimentally determined solubility values of each of the diacids in BD do not correlate well with their respective abilities to mitigate amorphisation on comilling. In particular, PA exhibited greater solubility in amorphous BD than GA, while GA was more successful at mitigating amorphisation than PA. In addition, the solubility of GA (23% w/w) was only 2% more than the solubility of SA (21%) in amorphous BD. However, GA was able to completely mitigate amorphisation on comilling with crystalline BD at RT while SA was unable to mitigate amorphisation of crystalline BD to any extent on comilling.

In addition, the calculated Hildebrand solubility parameters have also been suggested to be a predictor of the ability of a low T_g excipient to mitigate amorphisation on comilling (Curtin, Amharar et al. 2013, Amharar, Curtin et al. 2016). Table 8.1 shows the difference between the Hildebrand solubility

parameters of each of the excipients and BD (calculation of the Hildebrand solubility parameters shown in Appendix A-VI). However, comparison across the range of diacids suggests that PA has a $\Delta\delta$ of 1.8 MPa^{1/2} which is actually greater than that of either SA ($\Delta\delta$ = 1.1 MPa^{1/2}) or AA ($\Delta\delta$ = 1.0 MPa^{1/2}), but nonetheless PA showed a greater ability to mitigate amorphisation relative to AA, while SA did not mitigate amorphisation to any extent. The Hildebrand solubility parameters have been used to predict miscibility in two component systems, where systems have been assumed miscible if the $\Delta\delta$ is less than 7 MPa^{1/2} units (Greenhalgh, Williams et al. 1999). The solubility parameter approach therefore appears to correlate with the inability of MAN to mitigate amorphisation, but neither the experimental solubility compositions nor the Hildebrand solubility parameters appear to accurately reflect the **relative ability of the diacids** to mitigate amorphisation of BD on comilling.

Crystalline BD was also comilled with each of the diacid excipients and MAN in the VBM at CT, as shown in Table 8.1. In contrast to comilling at RT, reducing the temperature of the mill, T_{mill} , to CT led to the amorphisation of BD in each of the systems, as evidenced by PXRD analysis. Dujardin et al. highlighted the importance of the temperature of the milling operation T_{mill} , **relative to T_g of the system**, in determining the amorphous/ crystalline outcome on milling of α -glucose, which has a T_g close to RT of 38 °C (Dujardin, Willart et al. 2013). As highlighted in Figure 8.1, on milling α -glucose at RT, close to the T_g of the system, the system remained crystalline on milling. However, reducing the milling temperature to -15 °C (where $T_{mill} = T_g - 35$ °C) led to the amorphisation of the material.

These authors attributed these findings to reduced molecular mobility of amorphous α -glucose when T_{mill} was situated well below RT resulting in reduced recrystallisation kinetics from the amorphous state generated, combined with greater crystallite size reduction at lower T_{mill} relative to a critical crystallite size below which bulk transformation to the amorphous state was favoured.

In contrast to α -glucose, BD has a T_g well above RT at 89 °C, and consequently amorphised on milling in the VBM at both RT and CT. As highlighted in Figure 8.1, while comilling BD with GA at CT led to the amorphisation of BD, the T_g of the co-cryomilled composite were determined to be reduced from 89 °C to 43 °C. While the reduced T_g of the amorphous composite formed on comilling BD with GA was unlikely to be close to T_{mill} on co-cryomilling, the T_g of 43 °C was reduced close to T_{mill} on comilling at RT, where the temperature of the mill was measured and found to vary from 20 °C to 38 °C. This analysis highlights the importance of the ability of

the diacid to reduce the T_g of the API towards T_{mill} , in terms of the ability of the excipient to mitigate amorphisation on comilling. Studies with acyclovir (ACV) similarly suggested the importance of the T_g of the composite formed on comilling relative to T_{mill} in determining the amorphous/ crystalline outcome of the comilling operation. Milling of form I anhydrous ACV at both RT and CT led to the amorphisation of the API with a glass transition temperature of 109 °C, which, similar to BD, is well above T_{mill} at either RT or CT. Comilling form I ACV with MAN led to the amorphisation of ACV at RT and resulted in T_g reduction to 101 °C. In contrast, comilling form I ACV with PA at RT led to the regeneration of form I (anhydrous) ACV as evidenced by PXRD analysis, while comilling with PA at CT led to an amorphous composite with a T_g reduced to 54 °C. Comilling form I ACV with GA at RT led to the generation of an ACV:GA cocrystal, while comilling with GA at CT led to an amorphous composite with a T_g reduced to 48 °C from 109 °C.

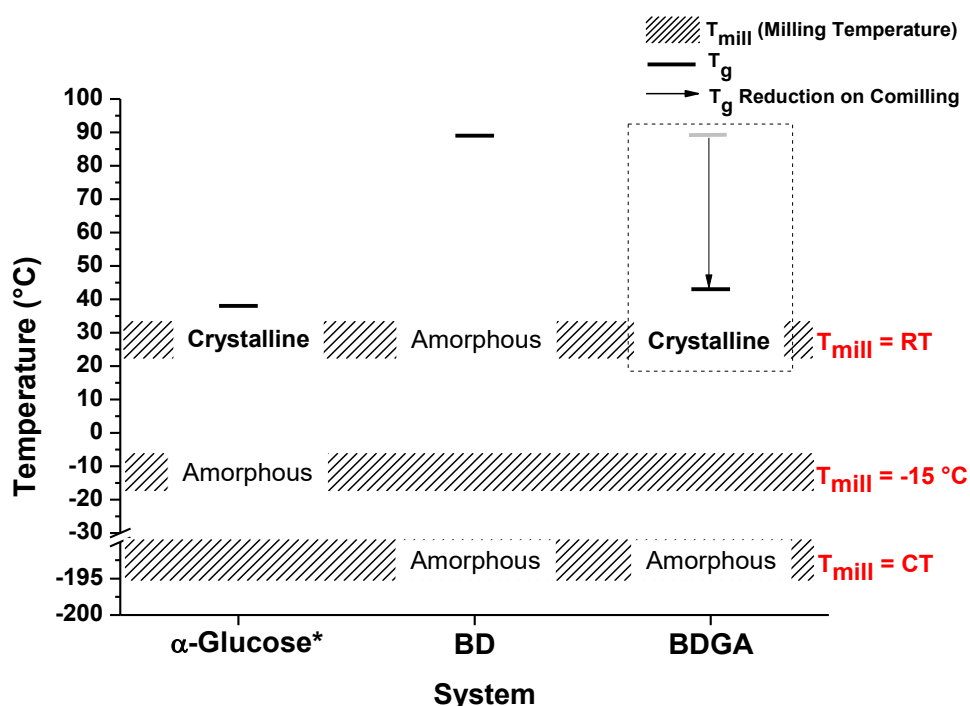


Figure 8.1 Structural transformations induced on milling of α -glucose, BD and, in addition, the BDGA comilled alloy, highlighting the relationship between the T_g of the system relative to the milling temperature, T_{mill} on the amorphous/crystalline nature of the system on (co)milling. [* α -glucose data from reference (Dujardin, Willart et al. 2013)]

While these findings highlight the apparent importance of the ability of the low T_g excipient to drive the T_g of the API towards T_{mill} in determining their ability to mitigate amorphisation on comilling, the diacids exhibited a limited solubility in the

amorphous APIs used in this study, and as a result, are only capable of reducing the T_g down to the composition at which the amorphous API is saturated with diacid excipient (Amharar, Curtin et al. 2014). This solubility composition importantly sets a limit on the maximum level of T_g reduction that may be expected on comilling with the diacids, and consequently, a limit on the extent to which the T_g may be reduced relative to T_{mill} . The solubility compositions of each of the diacid excipients in amorphous BD were determined by the zero enthalpy extrapolation method as shown in Table 8.2. The T_g values of the glass solutions formed by co-melt quenching BD with each of the diacids at 50% w/w were also determined, as this composition is above the maximum solubility composition in each case and thus represents the maximally reduced T_g s of the amorphous composites formed between amorphous BD and the diacids. Table 8.2 also shows the T_g values of the composites formed on comilling BD with each of the excipients at 50% w/w composition in the VBM at both RT and CT.

Table 8.2 Summary of the T_g of the molecular alloys formed on comilling and co-melt quenching SDM and BD with the diacids and MAN relative to the experimentally determined solubilities of the excipients in amorphous API and the difference in the calculated Hildebrand solubility parameters between excipient and API.

	T_g RT Milled (°C)		T_g CT Milled (°C)	T_g Melt Quench (°C)		$\Delta\delta$ (MPa ^{1/2})		Solubility (% w/w)	
	SDM	BD	BD	SDM	BD	SDM	BD	SDM	BD
SA	68	75/89	72	49	53	1.3	1.1	17	21
GA	44	45*	43	43	39	0.1	0.1	32	23
AA	60	67	58	47	48	0.6	1.0	19	20
PA	46	42	43	43	40	1.6	1.8	37	26
MAN	76	89	89	29/7 8	-	12.5	12.3	3	-

* Determined by comilling milled amorphous BD with GA in the VBM at RT

Figure 8.2A highlights the level of T_g reduction with the diacids and MAN on comilling with BD relative to the maximally reduced T_g of the glass solutions formed on melt quenching. Figure 8.2A shows the T_g reduction on comilling BD with each of the excipients both at RT and CT relative to the T_g of budesonide milled alone and relative to T_{mill} . In addition, the maximally reduced T_g values of the glass solutions formed on co-melt quenching are also highlighted. Interestingly, both GA and PA reduced the T_g of BD by the greatest extent, and indeed were able to fully to reduce

the T_g to values close to those of the saturated glass solutions formed on co-melt quenching, indicating that milling had formed a saturated glass solution of either excipient in amorphous BD. In contrast, both AA and SA appeared unable to reduce the T_g of BD on comilling to the same level as the T_g of the saturated glass solution formed on co-melt quenching. Importantly, the ability of the diacids to drive T_g reduction on comilling broadly correlated with their respective abilities to mitigate amorphisation on comilling with BD at RT.

In Chapter 5, the relative abilities of the low T_g excipients to drive the reduction in T_g of previously amorphised SDM on comilling in the VBM at RT was established. Additionally, the solubility of each of the diacids in amorphous SDM was determined, and in addition we also determined the glass transition temperatures of the saturated glass solutions (at 50% w/w composition) formed on co-melt quenching as shown in Table 8.2. Interestingly, a similar correlation was observed as for comilling with BD, in which both SA and AA were unable to drive T_g reduction of amorphous SDM to the T_g of the saturated glass solution formed by melt quenching. Indeed, the T_g reduction observed on comilling amorphous SDM with the diacids also correlated with previous findings by Curtin et al., who found GA to be the most successful at mitigating amorphisation of SDM on comilling in the planetary ball mill at RT, followed by AA, while SA was unable to mitigate amorphisation to any extent on comilling.

Following on from the research by Curtin et al., Amharar et al. hypothesised that co-melt quench T_g reduction could be used to predict the ability to mitigate amorphisation on comilling by assuming that a similar level of T_g reduction would be observed on comilling (Amharar, Curtin et al. 2016). However, while this correlation applies in the case of MAN, this analysis suggests that this assumption cannot be made as co-melt quenching and comilling both SDM and BD with the diacids SA and AA led to differences in T_g reduction. It is also interesting to note that the same pattern of T_g reduction across the four diacids was observed with two structurally distinct APIs with significant implications for the relative ability of these diacids to mitigate amorphisation on comilling.

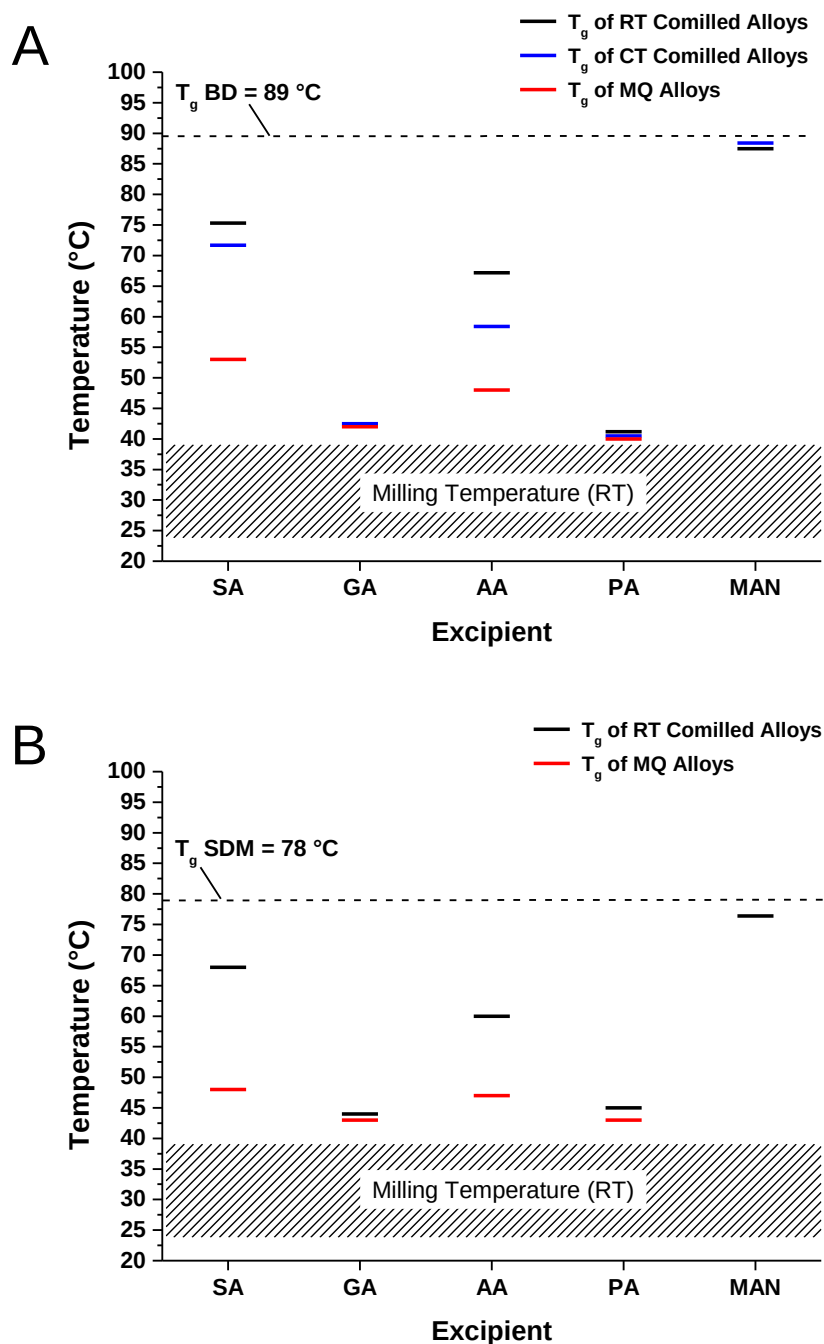


Figure 8.2 Difference in the T_g of the comilled composites relative to the T_g of the co-melt quenched composites (at 50% w/w composition) relative to the milling temperature formed on comilling excipient with (A) crystalline BD and (B) amorphous SDM.

Miscibility and Excess Thermodynamic Functions of Liquid-State Mixtures and Solid-State Properties of the Diacids

In Chapter 3, the miscibility of MAN in SDM in the liquid state by melting point depression analysis was determined. The analysis indicated limited miscibility in the liquid state between the two components. Indeed, as highlighted in Chapter 4,

DSC analysis of BD:MAN composites indicated a lack of a reduced (eutectic) melting of MAN, similarly indicating a lack of miscibility between the two components in the liquid state. The lack of liquid-state miscibility of either API with MAN also suggests immiscibility in their respective glass solutions (Marsac, Shamblin et al. 2006). Lack of miscibility in the glass solutions formed on comilling could account for the inability of MAN to reduce the T_g of amorphous SDM and BD on comilling, as highlighted in Figure 8.2. Indeed, the lack of miscibility between MAN and both APIs was well predicted by the disparity of their respective Hildebrand solubility parameters. A difference of more than 7 MPa^{1/2} has been suggested to be evidence for immiscibility, and a difference of greater than 12 MPa^{1/2} was determined for both APIs and MAN, as shown in Table 8.2 (Forster, Hempenstall et al. 2001).

In contrast to the inability of MAN to reduce the T_g on comilling with the either SDM or BD in this study, Caron et al. found that MAN and trehalose (TRE) formed a reduced T_g glass solution on co-melt quenching over the entire composition range investigated (Caron, Willart et al. 2007). When they compared this to the system formed on comilling across the composition range, an amorphous glass solution with a reduced T_g (relative to TRE alone, $T_g = 120\text{ }^{\circ}\text{C}$) was formed only for the compositions that had a T_g higher than approximately $40\text{ }^{\circ}\text{C}$ (close to the milling temperature range), with a further increase in the composition of MAN leading to crystallisation of MAN into the α -polymorph and no further decrease in the T_g of the milled composite. This study highlighted both the ability of MAN, a low T_g material with a T_g of $13\text{ }^{\circ}\text{C}$ to drive the reduction in T_g on comilling with a high T_g material, and also the critical role of the milling temperature relative to the T_g of the composite that forms on comilling in affecting the solid-state phase transformations in the system during co-processing. The authors also found that (for the composition corresponding to that which led to T_g reduction to $40\text{ }^{\circ}\text{C}$) while MAN crystallised out into the metastable α polymorph, trehalose remained in a reduced T_g amorphous glass solution, indicating that even though MAN reduced the T_g of the composite to T_{mill} , it did not lead to the regeneration of crystalline trehalose on comilling.

In contrast to MAN, each of the diacids GA, AA and PA displayed melting point depression with SDM over the composition range studied, indicating miscibility with SDM in the liquid state (as shown in Appendix A-II, co-melting SA in the presence of SDM led to the generation of a cocrystal, thus impeding melting point depression analysis in this system). In addition, DSC analysis of the BD: diacid

composites shown in Chapter 4 revealed a reduced eutectic melting with each of the diacids, similarly providing an indication of liquid-state miscibility. Analysis of the difference in Hildebrand solubility parameters shown in Table 8.2 also predicts miscibility in the liquid state between each of the diacids and both SDM and BD, as the $\Delta\delta$ was less than 2 MPa^{1/2} for each API: diacid composite. Melting point depression analysis of SDM with the diacids AA, GA and PA suggested deviation from ideal mixing and the excess thermodynamic functions on mixing were computed for each of the SDM: diacid systems. Negative H^E values indicated hydrogen bonding between unlike components, while negative S^E indicated stronger cohesive relative to adhesive interactions on mixing for each of the SDM: diacid systems studied, possibly due to strong carboxyl group dimer formation between the diacids. Most importantly, the thermodynamics of interaction in the liquid mixtures formed between SDM and each of the three diacids were comparable, and did not show any alternation with AA relative to either GA or PA. While the thermodynamics of interaction were determined in the molten state and not at RT, and thus caution must be exercised in terms of quantitatively applying the results to glass solutions formed on comilling at RT, our analysis suggests that the inability of AA to drive the T_g reduction of amorphous SDM on co-milling is not likely due to a significant difference in terms of the thermodynamics of mixing in the glass solution state with amorphous SDM relative to either GA or PA.

The T_g reduction on comilling, as shown in Figure 8.2, suggests that immiscibility in the liquid mixture and by extension in the glass solution formed on comilling explains MAN's inability to reduce the T_g of either API on comilling. However, a similar analysis of the liquid state properties of mixtures of the diacids and SDM does not explain the inability of either AA or SA to reduce T_g on comilling. However, in Figure 8.2 we are comparing glass solutions brought about by melt quenching, in which the API and diacid excipient are in the liquid solution state, molecularly dispersed followed by melt quenching relative to the formation of a glass solution from a top down approach, where the diacid is in the crystalline state and the mill is driving the formation of a glass solution with amorphous API. This analysis suggests that solid-state properties of the crystalline diacids are important in determining the observed T_g reduction on comilling, as shown in Figure 8.2, with resultant consequences for their respective abilities to mitigate amorphisation on comilling. Indeed, the diacids are known to exhibit significant alternation in physical properties in the solid state such as solubility, sublimation enthalpy and melting point (Thalladi, Nüsse et al. 2000). Figure 8.3A highlights the melting point of the

diacids SA, with a carbon chain length of C₄, GA (C₅), AA (C₆) and PA (C₇) and also highlights an apparent correlation with the alternation in the level of T_g reduction on comilling relative to the T_{gs} of the saturated glass solutions formed on co-melt quenching with both SDM and BD composites formed on comilling. Additionally, the solid-state dispersive surface energies of the milled diacids were determined by iGC analysis, after milling for 12 hours in the PBM at RT as shown in Figure 8.3B and interestingly, the γ_s^D values appear to show a similar alternation with carbon chain length.

In an attempt to account for the alternation phenomenon in the physical properties of the dicarboxylic acids with carbon chain length, in particular the systematically higher melting points of the even-chain diacids, Thalladi et al. analysed and compared the crystal structure and packing arrangements of the diacids from single crystal X-ray diffraction data (Thalladi, Nüsse et al. 2000). Analysis of the crystal structure of the diacids reveals the formation of end-to-end infinite hydrogen bonded chains through carboxyl group hydrogen bond dimers as shown in Figure 8.4. The infinite chains interact through inter-chain methylene group hydrophobic interactions, and in the even-chain analogues with C_n ≥ 5, the methylene groups are arranged such that the inter-chain assemblies are offset relative to each other as shown in Figure 8.4A. This offset arrangement crucially reduces steric repulsions between inter-chain carboxyl groups in the even-chain analogues with C_n ≥ 5. In contrast, the authors determined that the odd-chain diacids are geometrically forbidden from attaining such an offset in their inter-chain assemblies. They suggested that the lack of offset in the inter-chain assembly leads to significant inter-chain steric repulsion between the carboxyl groups. In order to reduce the steric inter-chain repulsion, the carboxyl groups **twist out of plane** as shown in the Mercury-generated crystal structure of β-GA shown in Figure 8.4B, highlighting a twist of 61.9° out of plane.

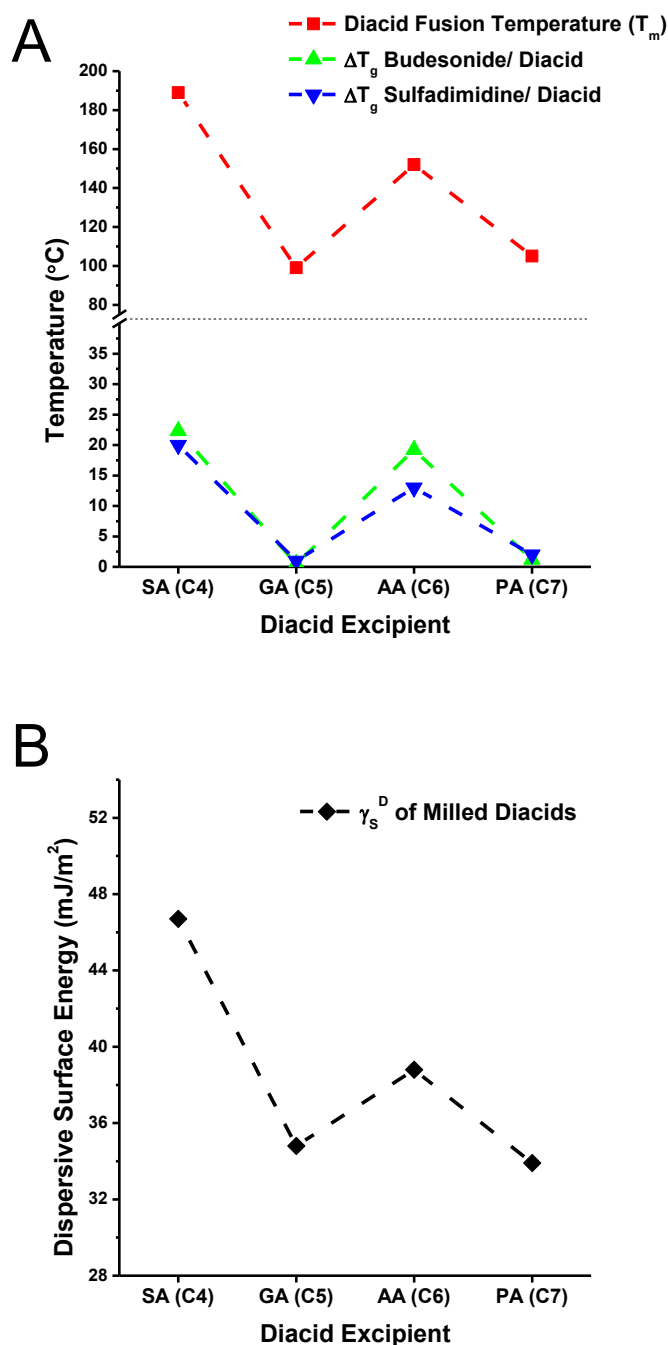


Figure 8.3 A) Alternation in the melting temperature, T_m , of the diacids SA, GA, AA and PA and the alternation in the difference in T_g reduction of 50% w/w amorphous composites formed by mechanical vs thermal activation of each of the diacids with both SDM and BD. B) Dispersive surface energy values determined by iGC analysis of each of the diacids SA, GA, AA and PA after milling in the PBM at RT for 12 hours.

The authors also determined in-silico the hydrogen bonding energies of the ideal and observed conformations of the diacids from C₅ to C₇ (i.e. AA, GA and PA). As shown in Table 8.3, the analysis suggested that the energies of the observed (twisted) conformation of the odd-chain diacids leads to higher energy, less stable

hydrogen bonding in both GA and PA. In contrast, due to the non-twist nature of the observed conformation of AA, the difference in the idealised and observed energies associated with the hydrogen bonding is negligible, indicating lower energy, more stable hydrogen bonding.

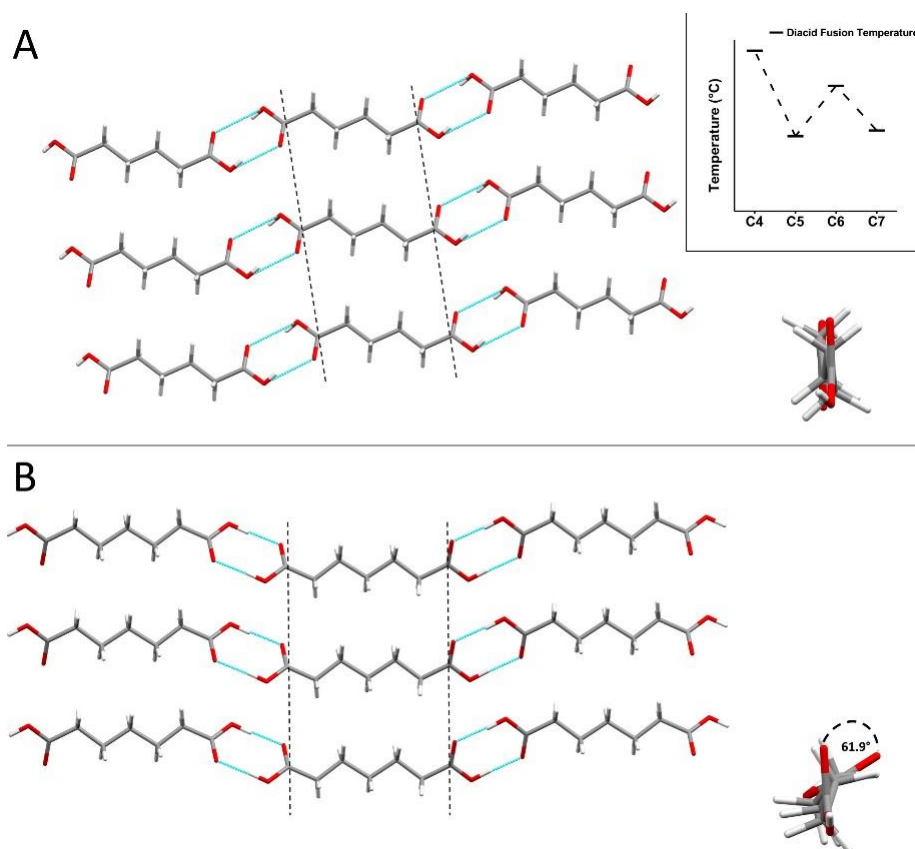


Figure 8.4 A) Layer structure of β -polymorphic adipic acid (even chain - C₆) highlighting the offset between adjacent interchain assemblies with lateral carboxyl group dimer interactions leading to infinite hydrogen bonded chains. Inset shows the lack of intramolecular out-of-plane twisting of carboxyl groups when viewed along the length of the chain. B) Layer structure of β -polymorphic pimelic acid (odd chain - C₇) showing non-offset between adjacent interchain assemblies with lateral carboxyl group dimer interactions leading to infinite hydrogen bonded chains. Inset highlights the torsional intramolecular out-of-plane twisting of carboxyl groups when viewed along the length of the chain. [Images created from the CCDC registry using Mercury software]

While the authors suggested that the offset/ non-offset packing regularities only apply for diacids with $C_n \geq 5$, analysis of the crystal structure of the even-chain C₄ diacid SA, shown in Appendix A-I Figure A-1.17, reveals that the carboxyl groups are not twisted out of plane. As melting represents a molecular dissociation event involving the breaking of the intermolecular-bond framework of the crystalline state, these authors attributed the lower melting point of the odd-chain diacids,

relative to their even-chain counterparts, to the torsional twisting and consequent lower stability of the hydrogen bonding in the solid state. Additionally, the authors also pointed out that in contrast to the alternation in physical properties of the diacids in the solid state, the liquid-state properties of the diacids do not show a similar alternation. This suggests that the alternation phenomenon appears to be specific to the conformational restrictions imposed on the odd-chain/ even-chain diacids in their solid-state crystal structures. Indeed the lack of alternation in the liquid-state properties of the diacids correlates with our analysis of the mixing behaviour of the diacids GA, AA and PA with SDM which exhibited comparable thermodynamics of interaction on mixing in the liquid state.

Table 8.3 Comparison of the COOH torsion angles of the diacids (C₅-C₇) with corresponding differences in the computed energies of the optimised and observed conformations. [Data from reference (Thalladi, Nüsse et al. 2000)]

	C _n	Polymorphic Form	∠ COOH (deg)	ΔE (kJ mol ⁻¹)
Glutaric Acid	5	β	63.0	2.665
Adipic Acid	6	β	0	0.978
Pimelic Acid	7	β	61.9	2.418
Pimelic Acid	7	α	62.7	7.365

Formation of the Driven Molecular Alloys in the Context of the Driven Materials Theory

Milling induced crystalline to amorphous transformations have been suggested by some authors to result from a melting event followed by vitrification from the milling induced liquid state, due to the formation of heat generated within the mill (De Gusseme, Neves et al. 2008, Khan, Ranjan et al. 2016). The correlation between the melting point alternation of the diacids relative to their ability to reduce T_g on comilling (that is that the lower melting point odd-chain diacids, GA and PA, have a greater ability to effect T_g reduction on comilling) could indeed suggest such a mechanism of T_g reduction on comilling, as the lower T_m diacids would provide a lower eutectic melting temperature thus facilitating formation of a melt solution intermediate followed by vitrification with subsequent glass solution formation. However, as shown in Figure 8.2A, comilling BD with GA and PA at CT, where the temperature of the mill was far removed from the eutectic melting temperature, also led to T_g reduction and formation of a saturated glass solution. In addition,

comilling BD with SA and AA led to a **greater level of T_g reduction** on comilling at CT than at RT, suggesting that as the temperature of the mill was reduced (moved away from the eutectic melting temperature) the driving of a glass solution between these two diacids and BD was paradoxically facilitated. Figure 8.5 depicts the transformation of crystalline diacid (e.g. β -GA) on comilling with amorphous API (e.g. amorphous SDM, as shown in Figure 8.2B), in an attempt to drive the formation of a saturated glass solution (and thus reduce the T_g of the API towards T_{mill}). In contrast to the milling induced melting hypothesis, our analysis suggests that the transformation of the crystalline low T_g diacids, as depicted in Figure 8.5, is driven by a mechanical force at a temperature **below the equilibrium eutectic melt temperature**, thus representing an out-of-equilibrium (driven) phase transformation (Descamps and Willart 2016).

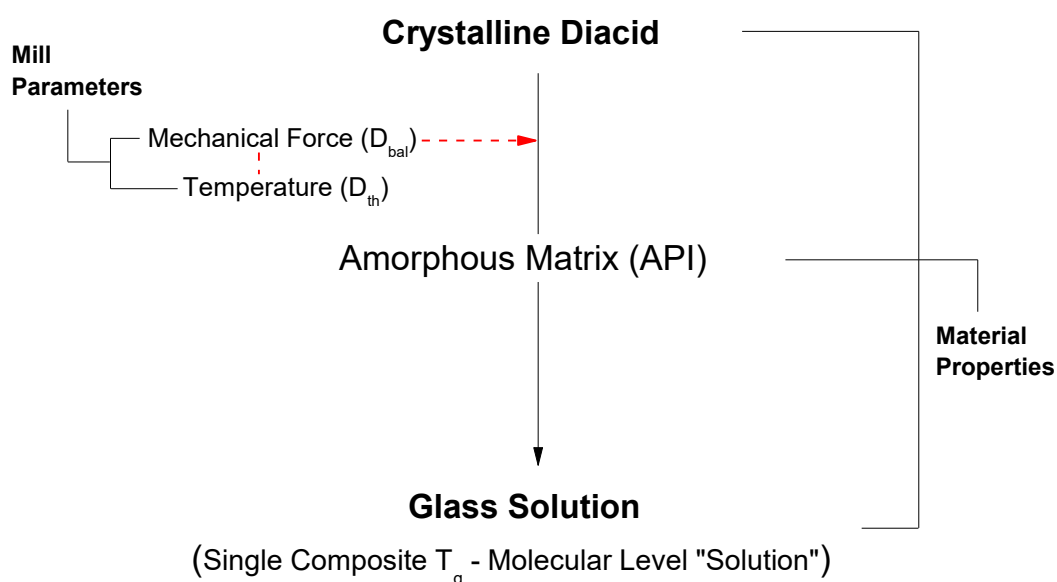


Figure 8.5 Schematic depicting the driven non-equilibrium dissolution of crystalline diacid (e.g. β -GA) into the amorphous matrix of an API (e.g. SDM) with which it is miscible, driven by a mechanical force; leading to the formation of a molecularly dispersed glass solution as evidenced by a single composite T_g (maximally reduced if at or above solubility composition) in a reversing heat flow DSC signal.

Driven transformations in molecular systems have been studied, in particular in the case of single component systems (Willart, Caron et al. 2004, Dujardin, Dudognon et al. 2011). Willart et al. contrasted the unique properties of the amorphous state of α -lactose brought about by mechanical driving relative to that brought about by

quenching from the melt state (Willart, Caron et al. 2004). These authors found that melt quenching a sample of initially crystalline pure α -lactose led to an amorphous glass containing an α/β -anomeric mixture due to mutarotation in the liquid melt. In contrast, milling of crystalline pure α -lactose led an amorphous system containing only α -lactose, indicating that the milling induced transformation had not proceeded via a liquid state intermediate but had proceeded by a direct transformation from the crystalline to amorphous state. In the absence of the formation of a eutectic melt intermediate during comilling with the diacids as depicted in Figure 8.5, it may be suggested that the formation of a reduced T_g glass solution requires that the mechanical driving force disrupts the hydrogen bonded crystal lattice of the diacid **directly** leading to molecular dissociation with subsequent formation of a molecular level glass solution, with spectroscopic and thermodynamic evidence of hydrogen bonding formation, with amorphous API, in turn driving the reduction in the T_g of the amorphous API towards that of the saturated glass solution.

Willart et al. followed the structural and nano-structural evolution of the low T_g material sorbitol ($T_g = 0^\circ\text{C}$) on milling alone in the planetary ball mill at RT and suggested that when the crystallite size was reduced below a critical size limit, a polymorphic transformation to the metastable polymorph occurred (Willart, Lefebvre et al. 2005). Indeed our comilling studies in Chapter 5 suggested that when β -GA was comilled with amorphous SDM above the solubility composition, the GA in excess of the solubility composition underwent a milling induced polymorphic transformation to the metastable α -polymorph, while milling GA alone did not induce any polymorphic transformation. However, in contrast to the polymorphic transformation of the excipient in excess of the solubility composition, we are attempting to account for the relative abilities of the diacid excipients, under the influence of a mechanical driving force, to undergo a direct transformation from the crystalline state to amorphous glass solution consequently driving the T_g of the composite formed towards T_{mill} . Our analysis suggests that the ability of the mechanical force of the milling operation to drive such a direct transformation appears to correlate with the alternation in the solid-state properties of the diacids, which result from the alternation in the strength of hydrogen bonding within their crystal structures, as shown in Table 8.3.

Figure 8.3B shows the dispersive surface energy values for the diacids after milling alone in the PBM for 12 hours at RT. Interestingly, the γ_s^D values of the diacids also

appear to alternate with carbon chain length. However, the surface energy of milled SA, with a value of 46 mJ/m² is close to that of unmilled SDM of 48 mJ/m² and has the highest value of the four diacids studied. Dispersive surface energy has been correlated with the reactivity of solid surfaces (Newman and Zografi 2014). In particular, milling induced increases in the dispersive surface energy have been associated with increased reactivity of solid surfaces on processing (Thielmann, Burnett et al. 2007). Indeed, our analysis of milling induced changes to the solid surface of SDM revealed an increase in the dispersive surface energy on milling from 48 mJ/m² to 56 mJ/m². In spite of the higher surface energy values of both SA and AA, they show a reduced ability to drive T_g reduction of amorphous SDM on comilling. The transformation from crystalline diacid to glass solution, as depicted in Figure 8.5, however represents a bulk phase transformation from the crystalline state to a molecular level glass solution. This suggests that the solid surface energy of the diacids does not correlate with their relative abilities to form a glass solution with amorphous SDM on mechanical driving. However, further work is required to determine the relative importance of the bulk versus surface properties of the diacids with regard to their driven solid-state transformations, in particular measuring and correlating surface acid-base properties with their propensity to drive T_g reduction and glass solution formation with amorphous API in the solid state on comilling.

Analysis of the level of T_g reduction with both SA and AA on comilling with BD at CT (all other milling parameters being maintained at the same level) revealed a greater level of T_g reduction than that observed at RT, as shown in Table 8.2 and Figure 8.2A. Reducing the temperature of milling thus **facilitated** the driving of a glass solution with SA and AA towards the T_g of their respective saturated glass solutions. In addition to the material properties (including the solid-state properties of the crystalline low T_g diacid, miscibility, solubility..) of the system being milled, this observation highlights the importance of the milling parameters, in particular the mill temperature, on the phase transformations of driven alloys formed under non-equilibrium conditions, as depicted in Figure 8.5. The correlation between the influence of milling variables known to affect the mechanical energy input on milling relative to the mill temperature was explored in relation to the driven materials theory as applied to the milling induced crystalline to amorphous transformation of SDM. Consideration of the driven dissolution of the two higher melting point diacids SA and AA into amorphous API, as depicted in Figure 8.5, in the context of the effective temperature on milling, led to a greater level of T_g

reduction on comilling at CT for both SA and AA, indicating a greater level of driven dissolution of these diacids at a lower milling temperature due to an increase in the effective temperature, consistent with the predictions of the driven materials theory, as shown in Equation 8.1.

PHASE SEPARATION FROM THE DRIVEN MOLECULAR ALLOYS

Humidity Accelerated Phase Separation from the Cryomilled Driven Alloys

Mitigation of amorphisation on comilling with the diacids depends not only on the ability of the diacid to reduce the T_g of the API towards T_{mill} on comilling, but also on the crystallisation properties of the API from the reduced T_g composite. The impact of a second excipient component on the crystallisation from amorphous systems has been well documented, in particular for polymeric excipients which tend to impede crystallisation of API from amorphous composites (Wlodarski, Sawicki et al. 2015). Trasi et al compared the effect of high T_g polymers on the stability of amorphous acetaminophen and concluded that, in addition to favourable miscibility and thermodynamics of interaction on mixing, hydrogen bonding was important in terms of the ability of the API to inhibit crystallisation from the amorphous state (Trasi and Taylor 2012). Indeed, Crowley et al. described significant inhibition of crystallisation of indomethacin even with low levels of poly(vinylpyrrolidone) which they ascribed to hydrogen bonding, even when the T_g of amorphous indomethacin was largely unaffected (Crowley and Zografi 2003). Studies have also been conducted on the crystallisation from low molecular weight binary glass solutions. Seefeldt et al. characterised the crystallisation pathways of the carbamazepine-nicotinamide cocrystal from an equimolar glass solution brought about by melt quenching (Seefeldt, Miller et al. 2007). Crystallisation from the amorphous composites formed with the diacids on co-cryomilling under humidity accelerated conditions were compared in terms of their kinetics, as well as monitoring both the crystallographic and spectroscopic properties of both the API and the diacid excipient on crystallisation.

Analysis of the co-cryomilled SDM:GA composite indicated a reduced RH_g as well as RH_c relative to milled amorphous SDM indicating that comilling with GA had indeed resulted in plasticisation of the amorphous API on comilling, consistent with thermal analysis which demonstrated T_g reduction. Similarly SDM:PA resulted in

reduced RH_c relative to SDM milled alone. In contrast to composites formed with GA and PA, the RH_c for the SA composite was not reduced relative to that of SDM milled alone. This was consistent with DSC data in terms of the inability of the mill to drive the formation of a reduced T_g glass solution on comilling SA with amorphous SDM, in contrast to both GA and PA. In addition FTIR evidence suggested the formation of milling induced hydrogen bonding group interactions between amorphous SDM and, in particular, with GA on comilling. Analysis of the crystallisation behaviour from the amorphous composite suggested a concomitant crystallisation of both GA and SDM, as indicated by FTIR peak changes of both GA and SDM on crystallisation, indicating that the excipient was driving the crystallisation of the API from the amorphous state. This suggests the importance of hydrogen bonding formed on comilling in terms of driving crystallisation of the API. Indeed, our thermodynamic analysis of liquid state mixtures indicated an exothermic excess enthalpy on mixing with SDM for each of the diacids, similarly indicating formation of hydrogen bonding on mixing in the liquid state.

A single crystallisation event was observed in the BD:GA co-cryomilled composite compared to PA which exhibited crystallisation over several RH steps, suggesting slower crystallisation kinetics from the BD:PA composite. Additionally, the comilled amorphous composite of BD:SA did not show a crystallisation event in the DVS, indicating a lack of RH_g/T_g reduction on comilling, consistent with DSC analysis. Crystallographic PXRD evidence suggested crystallisation of GA into the thermodynamically stable β -polymorphic form on crystallisation from both SDM and BD composites. In contrast, PA crystallised into the metastable α polymorph. FTIR analysis of the co-cryomilled composites indicated hydrogen bonding group interactions with BD, in particular in the composites formed with GA and PA.

Crystallisation from the co-cryomilled composite with ACV was more complex. Initial crystallisation was confirmed by PXRD analysis which indicated concomitant growth of beta GA and the form V ACV (3:2 hydrate) at 43% RH and 25 °C, indicating that similarly to the BD:GA and SDM:GA amorphous composites, the crystallisation of β -GA was driving crystallisation of ACV. However, due to significant overlap in carbonyl peaks and OH regions associated with both ACV and GA it was difficult to assess changes in peak shifts possibly associated with hydrogen bonding. However, the composite converted to the cocrystal at 80% RH at 25 °C. Indeed, transformation to cocrystal was sensitive to both RH and temperature with transformation to the cocrystal form on increasing the

temperature to 40 °C while maintaining the RH at 43%. In contrast, PA led to crystallisation into the hydrate at 40% RH with crystallisation of PA into the α -polymorph without cocrystal formation.

Mitigation of Amorphisation on Comilling at Room Temperature – Mechanical Rejuvenation from the Reduced T_g Driven Alloys

Similar to the conclusion by Seefeldt et al. (2007) in assessing the importance of hydrogen bonding in the crystallisation pathways of the nicotinamide-carbamazepine cocrystal from the melt-quenched glass solution, humidity accelerated crystallisation studies from the co-cryomilled composites suggested the importance of milling induced hydrogen bonding in terms of the ability of the diacid to drive crystallisation of the API from the milling induced amorphous state. However, in contrast to the humidity accelerated studies, all milling experiments were conducted under dry nitrogen atmosphere and thus humidity could not have accelerated crystallisation from the amorphous composites generated during comilling experiments. Indeed, the very concept of mitigation of amorphisation suggests an apparent paradox – that a mechanical driving force which tends to drive phase transformations to higher energy states could also facilitate crystallisation from the reduced T_g composite formed on comilling. However, our studies indicated that comilling previously milled amorphous BD with GA indeed led to the **regeneration** of crystalline BD. Importantly, the milling operation was operated under controlled dry nitrogen atmosphere both during the milling operation and under subsequent handling. Similarly, previous studies found that comilling previously milled amorphous SDM with GA (in the planetary ball mill) at RT similarly led to the regeneration of crystalline SDM (Curtin, Amharar et al. 2013).

We have emphasised the importance of the T_g of the system being milled relative to the temperature of the mill, in influencing the phase transformations that occur on milling and comilling, as highlighted in Figure 8.1. The T_g represents an important characteristic of an amorphous system, in particular with regard to the stability of the amorphous state towards crystallisation, with molecular mobility below the T_g significantly reduced leading to significantly reduced crystallisation kinetics (Andronis and Zografi 2000). In contrast, above the T_g in the supercooled liquid region, the increased molecular mobility leads to a consequent increase in the nucleation and crystallisation rate (Hilden and Morris 2004). Importantly, the temperature of the mill on comilling at RT ($T_{\text{mill}} = 38\text{ °C}$) was **below** the T_g of the

glass solutions formed with either GA or PA with each of the APIs studied – SDM (44 °C and 46 °C respectively), ACV (48 °C and 54 °C respectively) and BD (45 °C and 42 °C respectively). Indeed, BD comilled with AA led to a composite with a T_g of 67 °C but nonetheless showed some ability to mitigate amorphisation on comilling with BD at RT. This suggests that regeneration of crystalline API on comilling is not simply due to heat generated on milling, as the temperature of maximum nucleation and crystallisation rate lies **above** the T_g in the super-cooled liquid region. In addition to the temperature of the system being below T_g in each of the API: excipient composites studied, the systems were also under the influence of a mechanical drive force, which as shown tends to drive the system to a high energy amorphous/ glass solution state.

Desprez et al. investigated the effect of mechanical energy on the accelerated ageing of a quench cooled sample of amorphous indomethacin (Desprez and Descamps 2006). Importantly, the authors also reported that milling facilitated the crystallisation of the API. Indeed, the crystallisation/ ageing effect of the milling operation was found to depend on the level of mechanical energy input, as determined by the acceleration of the solar disk of the planetary ball mill with crystallisation being favoured at lower RPM values, which is a strong indication that it is the mechanical energy driving crystallisation. Willart et al suggested that the mechanically induced crystallisation (which they termed “mechanical rejuvenation”) of indomethacin was also likely to depend on the characteristics of the material itself and suggested an Arrhenius correlation of the crystallisation rate (r) to the temperature of the system and the activation energy associated with the transformation as shown in Equation 8.2.

$$r(T) \propto \exp\left(\frac{-\Delta E}{k_b T}\right)$$

Equation 8.2

where T represents the temperature, ΔE represents the activation energy and k_b represents Boltzmann’s constant. Equation 8.2 suggests that a system with a lower activation energy barrier should exhibit a higher rate of transformation at a given temperature, and for any given system, the rate of transformation increases with increasing temperature. For amorphous to crystalline transformations, below the glass transition temperature, the crystallisation rate from the amorphous state is

slow over an experimental time scale (Descamps, Aumelas et al. 2015). Willart et al. attributed the observed crystallisation of indomethacin on milling at a temperature below its T_g to a **rescaling of the activation energy**, that is the effect of the mechanical energy on the molecular configuration of the amorphous state paradoxically facilitated nucleation and subsequent crystallisation even though the temperature of the system was below the T_g (Willart and Descamps 2008). The authors suggested that the increased rate of crystallisation was such that the system at real temperature T_{mill} , behaved as though it were at a higher temperature above T_g , in the supercooled liquid region where the nucleation and crystallisation rate is higher; that is at a higher effective temperature on milling. These authors thus utilised the concept of an effective temperature firstly according to Equation 8.1 which applies **specifically** to crystalline to amorphous transformations on milling, analogous to a melting event, by describing an effective temperature displaced relative to the equilibrium melting temperature of the crystalline material being milled (Descamps and Willart 2016). However, they also utilised the concept to account for milling induced amorphous to crystalline transformations in which the effective temperature is displaced relative to the glass transition temperature of the amorphous system being milled (Willart and Descamps 2008).

A similar analysis to that by Willart et al. regarding the milling induced crystallisation of indomethacin could account for the paradoxical milling induced crystallisation observed to occur with the diacids leading to mitigation of amorphisation on comilling at RT. Figure 8.6 depicts the experimentally determined T_g s of the composites formed on comilling amorphous SDM with both GA and PA relative to the temperature of the system. Indeed, similar levels of T_g reduction were also observed on comilling with BD, as shown in Table 8.2.

Although both diacids reduced the T_g **to a similar extent** on comilling, according to the analysis by Willart et al., the mechanical energy imparted to a system milled at a temperature close to the T_g of the system can lead to a milling induced crystallisation from the amorphous state due to a rescaling of the activation energy of crystallisation, as though the system were at a higher (effective) temperature above T_g (Willart and Descamps 2008). Although both GA and PA reduced the T_g of both SDM and BD to similar extents close to T_{mill} at RT, GA consistently led to a greater level of mitigation of amorphisation on comilling in this study and in previous studies. In order to assess the role of the activation energy barrier, as suggested by Willart et al, in effecting milling induced crystallisations from the

reduced T_g composites, the difference in the activation energies of crystallisation from the cryomilled amorphous equimolar composites of GA and PA in SDM was determined by non-isothermal crystallisation kinetics. Kissinger plots indicated a lower activation energy for the GA composite at 260 kJ/mol relative to that determined for the PA composite at 326 kJ/mol. In correlation with Equation 8.2, and in line with the mechanical rejuvenation theory proposed by Willart et al., the lower activation energy barrier of crystallisation for the SDM:GA composite could lead to a higher rate of milling induced crystallisation from the amorphous composite formed on comilling relative to the composite formed with PA, in spite of similar levels of T_g reduction and under the same milling conditions.

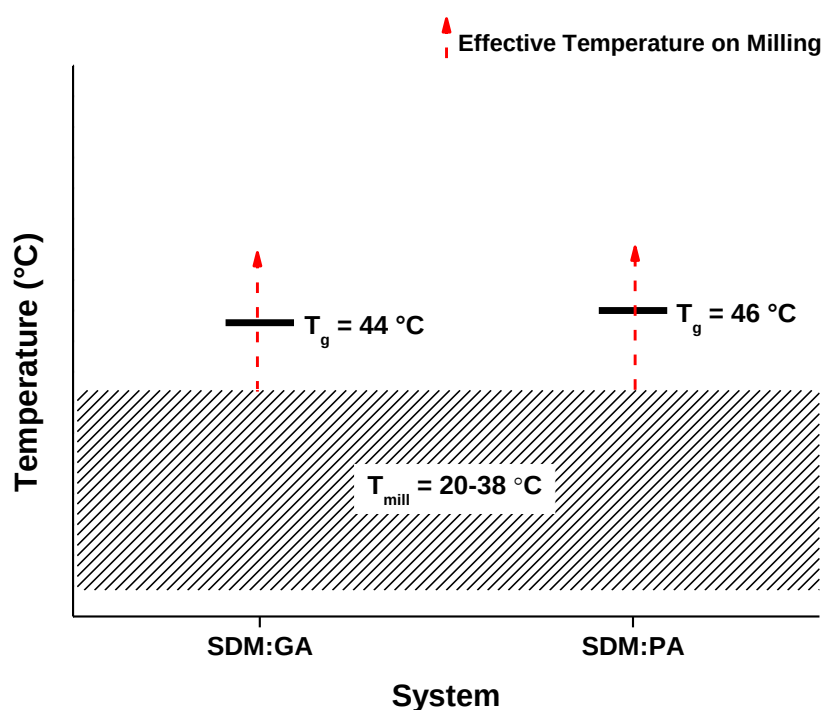


Figure 8.6 Schematic depicting the similarly reduced T_g s of the saturated glass solutions formed on comilling amorphous SDM with both GA and PA relative to the temperature of the mill ($T_{\text{mill}} = 38\text{ °C}$). Due to effect of the mechanical energy on the systems, the crystallisation rate on milling is such that the system behaves as though it were at a higher (unknown) effective temperature above the T_g . In addition to the mechanical energy input, crystallisation rate dependent on the specific properties of the glass solution, i.e. nature of the excipient, hydrogen bonding interaction, activation energy barrier..

This work suggests that the **relative abilities** of the diacids to mitigate amorphisation depends not only on their ability to drive T_g reduction on comilling towards T_{mill} but also on the crystallisation kinetics and the activation energy

barrier of crystallisation from the reduced T_g amorphous composites thus formed. The importance of milling induced hydrogen bonding was explored, which appears to drive concomitant crystallisation of the diacid and API in humidity accelerated studies, and which could also account for the ability of the diacids to drive crystallisation of the amorphous API on comilling. The ability of a disordering mechanical driving force to paradoxically effect crystallisation from the reduced T_g composites, even if the temperature of the system is below T_g , could be related to a rescaling of the activation energy for crystallisation according to the analysis by Willart et al. Importantly, our analysis suggests that both T_g reduction on comilling and subsequent crystallisation from the reduced T_g composite (either humidity or milling accelerated) appear to be influenced to a greater extent by the solid-state properties of the low T_g diacid excipient relative to the solid-state properties of the APIs used in this study. In addition, the driven materials theory and the effective temperature concept provide a rational framework to consider mechanically induced phase transformations, both co-amorphisation and co-crystallisation, in molecular alloy systems.

CO-BLENDING AND CO-COMPACTION RELATIVE TO COMILLING

While previous studies focused on dry mixing salbutamol sulphate alone and in the presence of diacid excipients with glass beads, blending and co-blending studies without any mixing media was conducted, as this is a more common situation in the pharmaceutical industry. Blending led to an increase in the dispersive surface energy of sulfadimidine from 48 mJ/m² to 56 mJ/m² after 24 hours of blending in the Turbula mixer without any glass beads. However, blending did not lead to the amorphisation of SDM as demonstrated by DSC analysis. In addition, co-blending amorphous SDM with GA did not lead to the polymorphic conversion of excess GA above the solubility limit to the metastable α polymorph, as was observed in comilled systems, and there was no evidence by FTIR of hydrogen bonding interaction. These results indicate a level of mechanical energy provided by milling/mixing media is required in order to induce an interaction and form a reduced T_g glass solution by mechanical means, as depicted in Figure 8.5.

In order to investigate the possibility of a compression force inducing crystallisation of amorphous BD: excipient composites formed on co-cryomilling, the composites

formed on co-cryomilling BD with GA, SA and AA were compacted. However, no evidence of crystalline BD was observed on PXRD analysis indicating that under the conditions of this study, crystallisation was not facilitated by application of a compression force.

CONCLUSIONS & FUTURE WORK

- Each of the active pharmaceutical ingredients BD, SDM and form I ACV were found to undergo amorphisation on milling in the VBM at both RT and CT, with T_g s determined to be well above RT of 89 °C, 78 °C and 109 °C respectively. In contrast none of the low T_g excipients SA, GA, AA, PA or MAN underwent amorphisation on milling at either RT or CT. However both MAN and PA underwent polymorphic transformations to metastable polymorphic forms.
- Increasing each of the ballistic milling variables, frequency of vibration, ball to powder mass ratio and ball diameter, were found to have a greater influence on amorphisation of SDM as the temperature of the milling operation was reduced from RT to CT.
- Comilling crystalline BD with GA at RT led to the complete mitigation of amorphisation of BD while comilling with both PA and AA led to the partial mitigation of amorphisation of BD. In contrast, comilling with either SA or MAN led to the amorphisation of BD. Comilling at CT led to the amorphisation of BD in each of the BD: excipient composites.
- Comilling form I ACV with GA led to the formation of a cocrystal, while comilling with PA led to partial mitigation of amorphisation with the regeneration of form I ACV. In contrast, comilling form I ACV with MAN led to the amorphisation of the API at RT. Comilling ACV with each of the excipients at CT led to the amorphisation of the API.
- The experimental solubility of the diacids in amorphous BD was determined as well as the difference in their respective calculated Hildebrand solubility parameters. While the solubility parameter difference between BD and MAN accounted for the inability of MAN to mitigate amorphisation due to a miscibility barrier, neither the Hildebrand solubility parameters nor the

experimental solubility values correlated with the relative abilities of the diacids to mitigate amorphisation of BD on comilling at RT.

- The level of T_g reduction observed on comilling BD with the diacids broadly correlated with their respective abilities to mitigate amorphisation, with SA reducing the T_g of BD to the least extent, followed by AA while both GA and PA reduced the T_g of BD to the greatest extent. Neither SA nor AA were able to reduce the T_g of either BD or SDM on comilling to the T_g of the saturated glass solutions formed on co-melt quenching.
- The miscibility and thermodynamics of interaction in the liquid state between SDM and the diacids did not account for the inability of the even chain C_4 (SA) and C_6 (AA) diacids to reduce the T_g of amorphous SDM on comilling, relative to the T_g of the glass solutions formed on co-melt quenching. We correlated this difference with the solid state properties and melting point alternation of the diacids, itself correlated with the strength of the hydrogen bonding in their respective solid-state crystalline forms.
- We suggested that the driven dissolution of crystalline diacid into amorphous API on comilling was due to an out-of-equilibrium **direct** phase transformation induced mechanically, without an equilibrium-melt intermediate. This was evidenced as both SA and AA led to a greater level of T_g reduction on comilling at CT relative to RT, which correlated with the driven materials theory, which accounts for out-of-equilibrium phase transformations on mechanical driving in terms of the ballistic variables which determine the mechanical energy input, relative to the milling temperature, T_{mill} .
- Spectroscopic evidence suggested the formation of hydrogen bonding group interactions, in particular on comilling with both GA and PA with humidity accelerated crystallisation studies indicating concomitant crystallisation of API and diacid apparently driven by the diacid excipient.

- In contrast to humidity accelerated crystallisation, mitigation of amorphisation on comilling was considered in the context of mechanical rejuvenation which suggests that the mechanical energy of the mill facilitated crystallisation from the reduced T_g composite with the crystalline excipient driving the crystallisation of the API as a result of hydrogen bonding interaction and T_g reduction close to T_{mill} .
- While blending led to an increase in the dispersive surface energy of SDM, no amorphisation was apparent and co-blending amorphous SDM with GA did not lead to any T_g reduction, hydrogen bonding interaction or polymorphic transformation thus suggesting the mechanical force requirement for the formation of a glass solution by mechanical means. Compaction of the reduced T_g amorphous composites formed between BD and the diacids SA, GA and AA did not lead to the crystallisation of BD.

Future Work

- Investigation of the effect of comilling high T_g APIs with low T_g polymers e.g. preliminary studies with poly(ethylene glycol) (PEG) have already been undertaken and have indicated the ability of PEG to mitigate amorphisation on comilling.
- Further analysis of the surface characteristics of high T_g materials, in particular on low energy processing such as blending and low frequency milling.
- Explore the changes to the surface characteristics of low T_g materials which do not amorphise on milling and their correlation with the driven transformation observed on comilling.

- Further investigation of the capacity of the compaction process to mitigate amorphisation of API on co-compaction.
- Further exploration and understanding of phase transformations in single and multi-component systems in the context of the driven materials theory.

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APPENDICES

A-I ADDITIONAL FIGURES

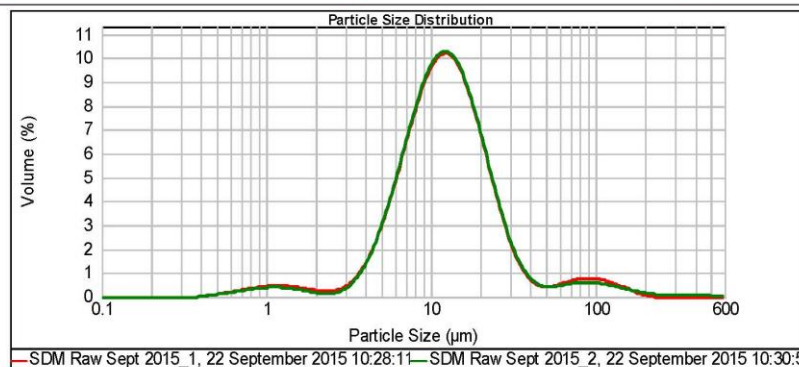


Result Analysis Report

Sample Name: SDM Raw Sept 2015_2	SOP Name: Default SOP_1bar_75vib	Measured: 22 September 2015 10:30:59
Sample Source & type: Sigma Aldrich	Measured by: Kieran	Analysed: 22 September 2015 10:31:05
Sample bulk lot ref: BCBP1062V	Result Source: Measurement	

Particle Name: Default	Accessory Name: Scirocco 2000 (A)	Analysis model: General purpose (fine)	Sensitivity: Normal
Particle RI: 1.520	Absorption: 0.1	Size range: 0.020 to 2000.000 um	Obscuration: 1.32 %
Dispersant Name:	Dispersant RI: 1.000	Weighted Residual: 0.310 %	Result Emulation: Off
Concentration: 0.0003 %Vol	Span : 1.800	Uniformity: 0.901	Result units: Volume
Specific Surface Area: 0.717 m ² /g	Surface Weighted Mean D[3,2]: 8.364 um	Vol. Weighted Mean D[4,3]: 18.669 um	

d(0.1): 5.517 um d(0.5): 12.092 um d(0.9): 27.279 um



Size (um)	Volume In %	Size (um)	Volume In %	Size (um)	Volume In %	Size (um)	Volume In %	Size (um)	Volume In %	Size (um)	Volume In %
0.020	0.00	0.142	0.00	1.002	0.30	7.096	5.48	50.238	0.31	355.656	0.07
0.022	0.00	0.159	0.00	1.125	0.30	7.962	6.36	56.368	0.35	399.052	0.06
0.025	0.00	0.178	0.00	1.262	0.30	8.934	7.06	63.246	0.40	447.744	0.05
0.028	0.00	0.200	0.00	1.416	0.28	10.024	7.55	70.963	0.45	502.377	0.03
0.032	0.00	0.224	0.00	1.589	0.25	11.247	7.74	79.621	0.47	563.677	0.01
0.036	0.00	0.252	0.00	1.783	0.20	12.619	7.74	89.337	0.46	632.456	0.00
0.040	0.00	0.283	0.00	2.000	0.15	14.159	7.63	100.237	0.46	709.627	0.00
0.045	0.00	0.317	0.00	2.244	0.11	15.887	7.20	112.468	0.43	796.214	0.00
0.050	0.00	0.356	0.00	2.518	0.10	17.825	6.52	126.191	0.38	893.367	0.00
0.056	0.00	0.399	0.00	2.825	0.14	20.000	5.62	141.589	0.32	1002.374	0.00
0.063	0.00	0.448	0.02	3.170	0.25	22.440	4.63	158.866	0.26	1124.683	0.00
0.071	0.00	0.502	0.07	3.557	0.47	25.179	3.60	178.250	0.20	1261.915	0.00
0.080	0.00	0.564	0.10	3.991	0.81	28.251	2.65	200.000	0.14	1415.892	0.00
0.089	0.00	0.632	0.14	4.477	1.29	31.696	1.82	224.404	0.10	1588.656	0.00
0.100	0.00	0.710	0.18	5.024	1.93	35.566	1.18	251.785	0.08	1782.502	0.00
0.112	0.00	0.796	0.22	5.637	2.70	39.905	0.73	282.508	0.06	2000.000	0.00
0.126	0.00	0.893	0.26	6.325	3.58	44.774	0.46	316.979	0.06		
0.142	0.00	1.002	0.29	7.096	4.54	50.238	0.34	355.656	0.06		

Operator notes:

Malvern Instruments Ltd.
Malvern, UK

Mastersizer 2000 Ver: 5.22
Serial Number : MAL100114

File name: Adipic Acid Raw Average
Record Number: 292

Figure A-I.1 Laser light diffraction particle size analysis of crystalline unmilled SDM.



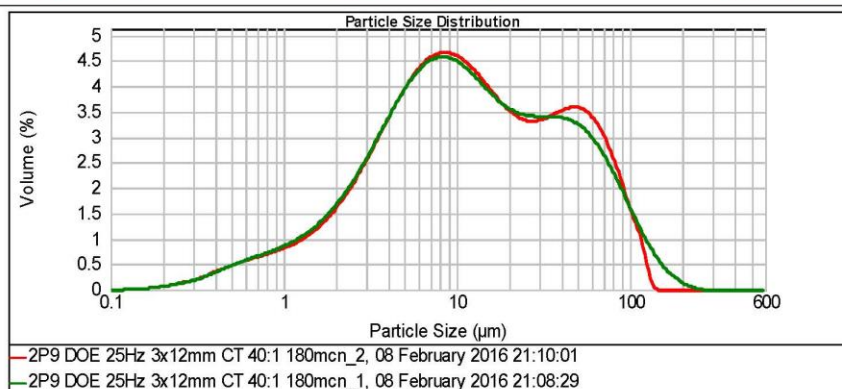
Result Analysis Report

Sample Name: 2P9 DOE 25Hz 3x12mm CT 40:1
SOP Name: Default SOP_1bar_75vib
Measured: 08 February 2016 21:08:29
Sample Source & type: Measured by: Kieran
Analysed: 08 February 2016 21:08:30
Sample bulk lot ref: Result Source: Measurement

Particle Name: Default
Accessory Name: Scirocco 2000 (A)
Analysis model: General purpose (fine)
Sensitivity: Normal
Particle RI: 1.520
Absorption: 0.1
Size range: 0.020 to 2000.000 μm
Obscuration: 2.05 %
Dispersant Name: 1.000
Dispersant RI: 1.000
Weighted Residual: 0.155 %
Result Emulation: Off

Concentration: 0.0003 %Vol
Span : 5.468
Uniformity: 1.66
Result units: Volume
Specific Surface Area: 1.37 m^2/g
Surface Weighted Mean D[3,2]: 4.395 μm
Vol. Weighted Mean D[4,3]: 23.830 μm

d(0.1): 2.027 μm **d(0.5):** 11.336 μm **d(0.9):** 64.018 μm



Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %	Size (μm)	Volume In %
0.020	0.00	0.142	0.01	1.002	0.88	7.096	3.43	50.238	2.40	355.656	0.00
0.022	0.00	0.159	0.02	1.125	0.75	7.962	3.45	56.368	2.26	399.052	0.00
0.025	0.00	0.178	0.04	1.262	0.83	8.934	3.41	63.246	2.08	447.744	0.00
0.028	0.00	0.200	0.06	1.416	0.92	10.024	3.34	70.963	1.86	502.377	0.00
0.032	0.00	0.224	0.08	1.589	1.04	11.247	3.09	79.621	1.61	563.677	0.00
0.036	0.00	0.252	0.10	1.783	1.17	12.619	2.96	88.337	1.34	632.456	0.00
0.040	0.00	0.283	0.13	2.000	1.33	14.159	2.83	100.237	1.07	709.627	0.00
0.045	0.00	0.317	0.17	2.244	1.51	15.887	2.72	112.488	0.81	796.214	0.00
0.050	0.00	0.356	0.23	2.518	1.72	17.825	2.64	126.191	0.58	893.367	0.00
0.056	0.00	0.399	0.28	2.825	1.94	20.000	2.59	141.589	0.39	1002.374	0.00
0.063	0.00	0.448	0.33	3.170	2.17	22.440	2.57	158.866	0.25	1124.683	0.00
0.071	0.00	0.502	0.38	3.557	2.41	25.179	2.56	178.250	0.14	1261.915	0.00
0.080	0.00	0.564	0.43	4.477	2.65	28.251	2.56	200.000	0.06	1415.892	0.00
0.089	0.00	0.632	0.48	5.024	2.88	31.698	2.54	224.404	0.02	1588.656	0.00
0.100	0.00	0.710	0.52	5.637	3.08	35.566	2.54	251.785	0.00	1782.502	0.00
0.112	0.00	0.796	0.57	6.325	3.24	39.905	2.49	282.508	0.00	2000.000	0.00
0.126	0.00	0.893	0.62	7.096	3.36	44.774	2.49	316.979	0.00		
0.142	0.00	1.002				50.238		355.656	0.00		

Operator notes:

Figure A-I.2 Laser light diffraction particle size analysis of SDM milled in the VBM at CT for 60 minutes, subsequently passed through a 180 μm sieve.

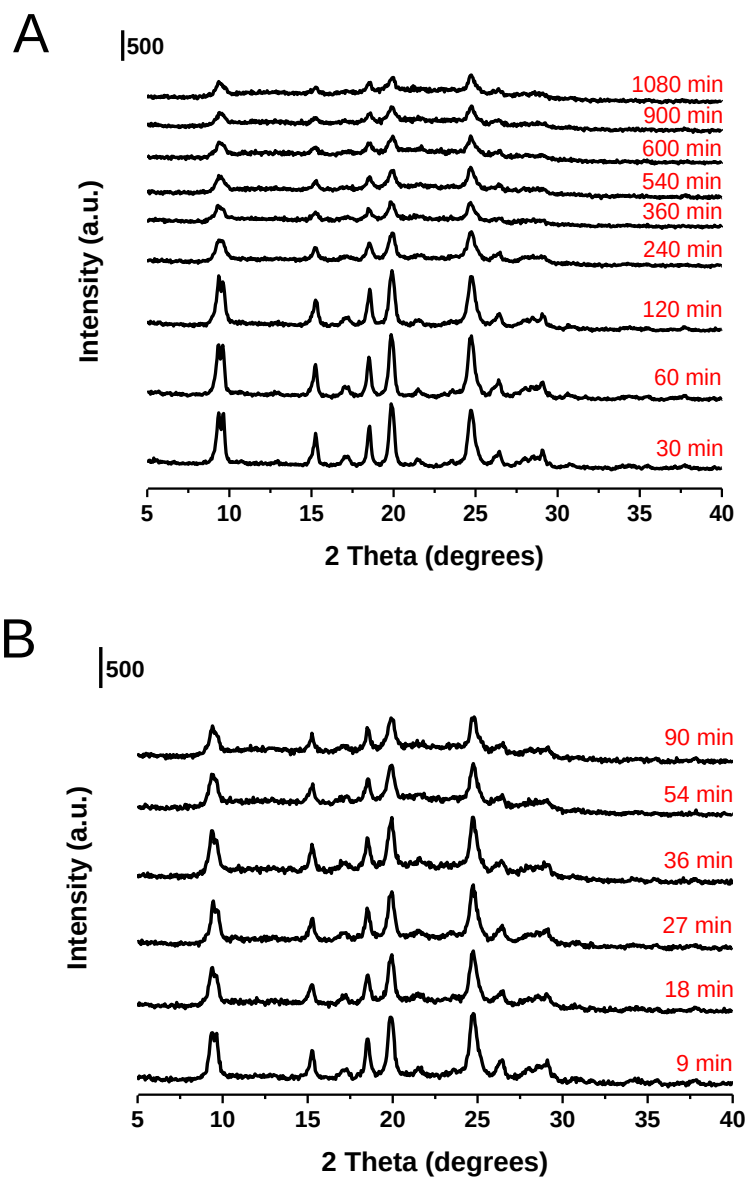


Figure A-I.3 A) PXRD diffractograms of SDM milled in the PBM at RT from 30 minutes to 18 hours. B) PXRD diffractograms of SDM milled in the VBM at RT from 9 minutes to 90 minutes.

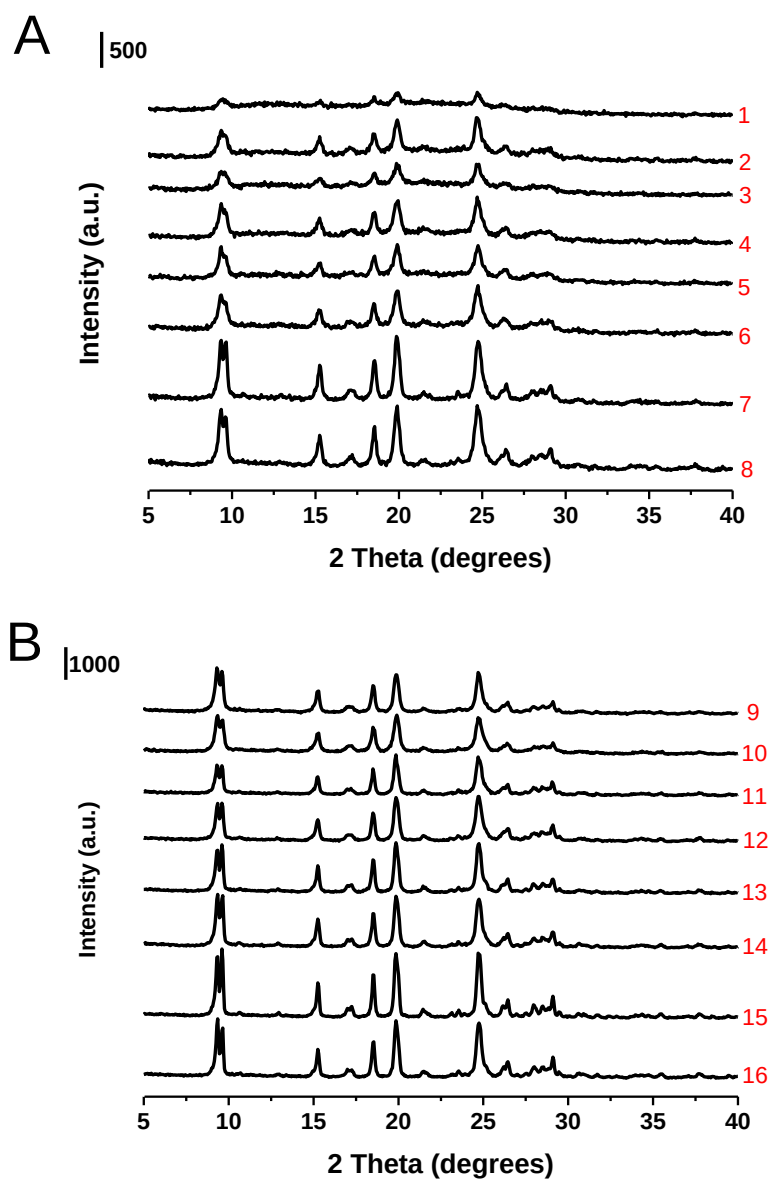


Figure A-I.4 A) PXRD diffractograms of SDM milled according to the DOE design points as described in Chapter 3, Table 3.3.

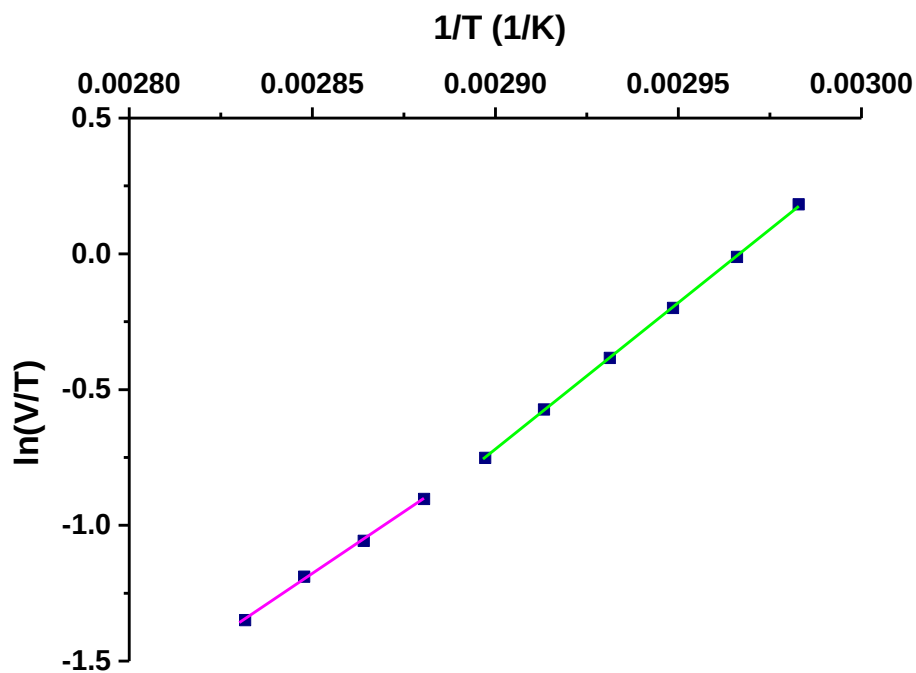


Figure A-I.5 iGC heat of sorption analysis of high frequency milled SDM (25 Hz, DOE design point 2) in the VBM using decane as the probe vapour from 62-80 °C.

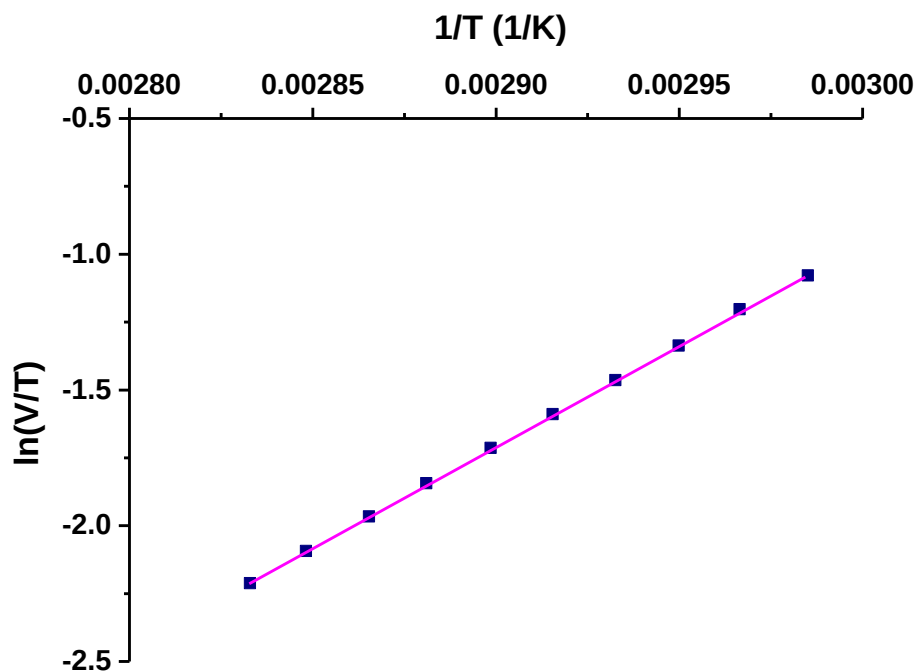


Figure A-I.6 iGC heat of sorption analysis of low frequency milled SDM (15 Hz, DOE design point 14) in the VBM using decane as the probe vapour from 62-80 °C.

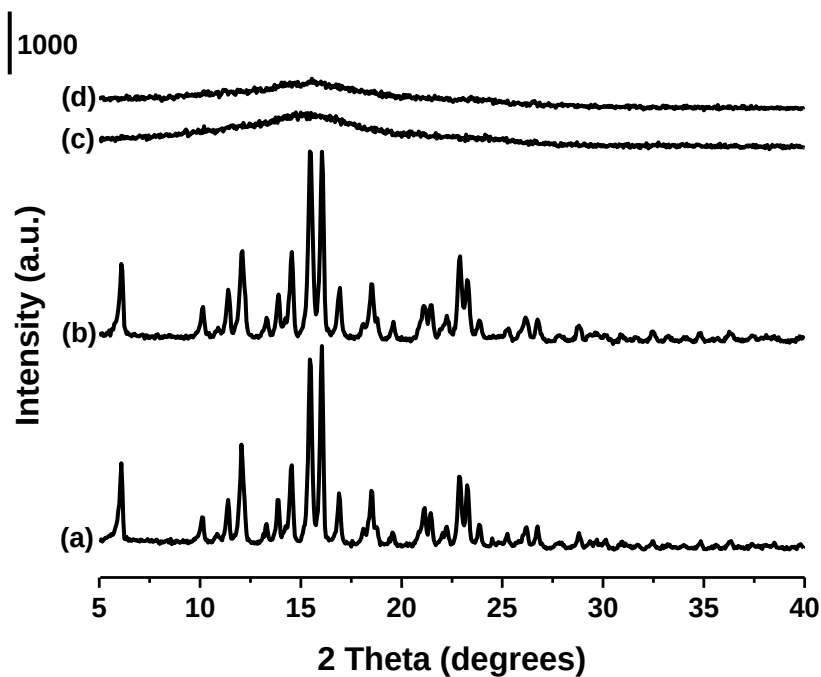


Figure A-I.7 PXR D diffractogram of (a) crystalline BD (b) BD milled in the VBM at RT with a liquid drop of ethanol (c) BD milled in the VBM at RT for 60 minutes and (d) BM milled in the VBM at CT for 45 minutes.

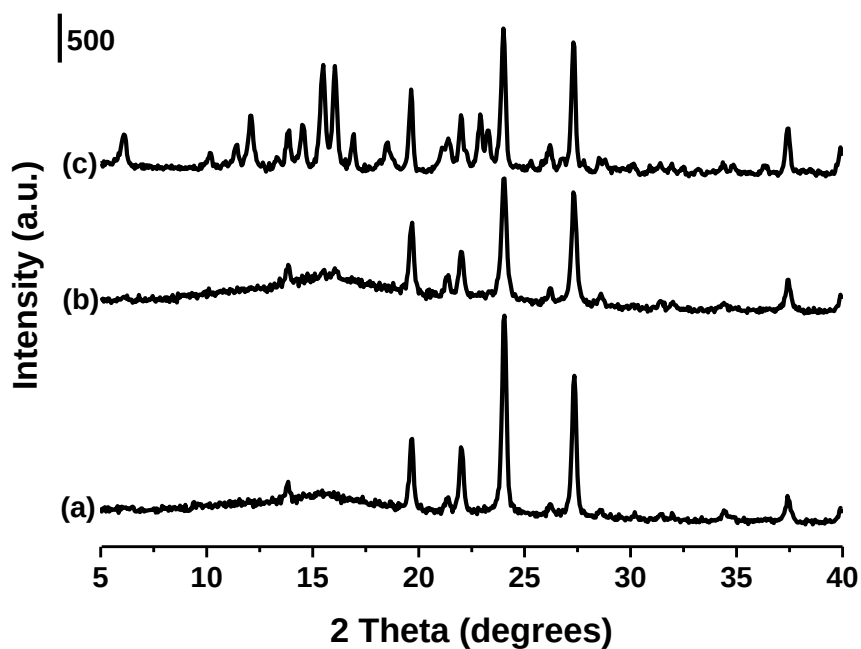


Figure A-I.8 PXR D diffractograms of milled amorphous BD comilled with β -GA in the VBM at RT at 50% w/w for (a) 10 minutes (b) 30 minutes and (c) 60 minutes.

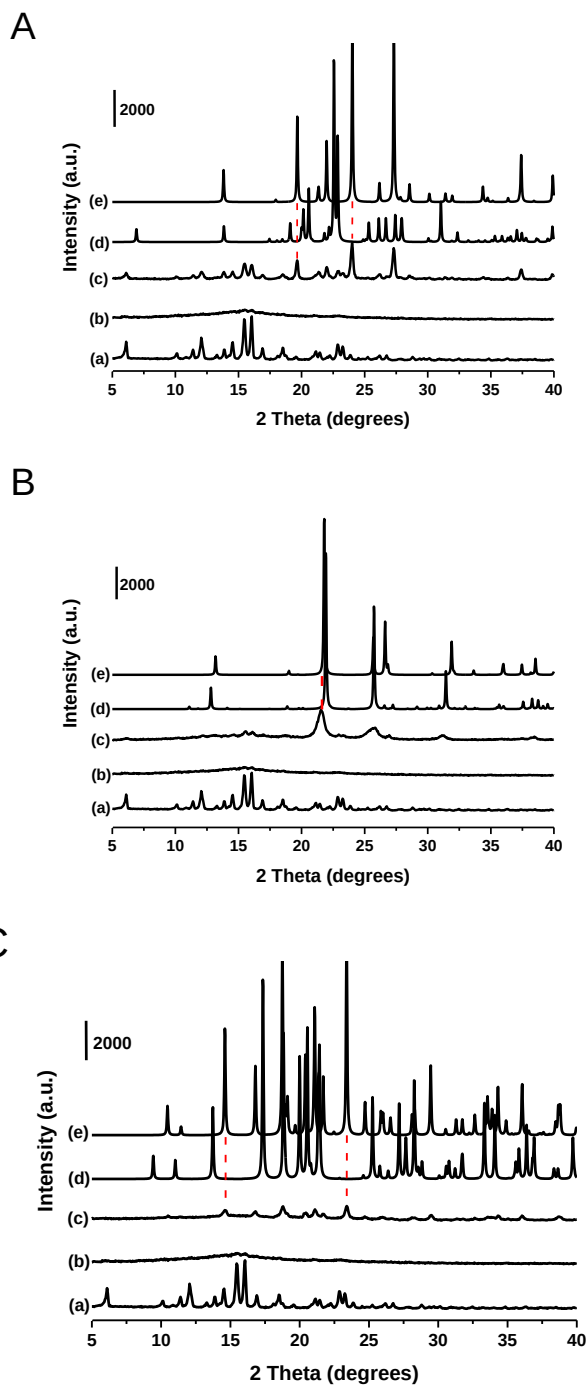


Figure A-1.9 A) PXR D diffractograms of (a) crystalline BD (b) BD milled in the VBM at RT (c) BD comilled with β -GA at 50% w/w in the VBM at RT (d) CCDC generated α -GA and (e) CCDC generated β -GA. B) PXR D diffractograms of (a) crystalline BD (b) BD milled in the VBM at RT (c) BD comilled in the VBM at RT with β -AA at 50% w/w (d) CCDC generated α -AA and (e) CCDC generated β -AA. C) PXR D diffractograms of (a) crystalline BD (b) BD milled in the VBM at RT (c) BD comilled with β -MAN in the VBM at RT (d) CCDC generated α -MAN and (e) CCDC generated β -MAN.

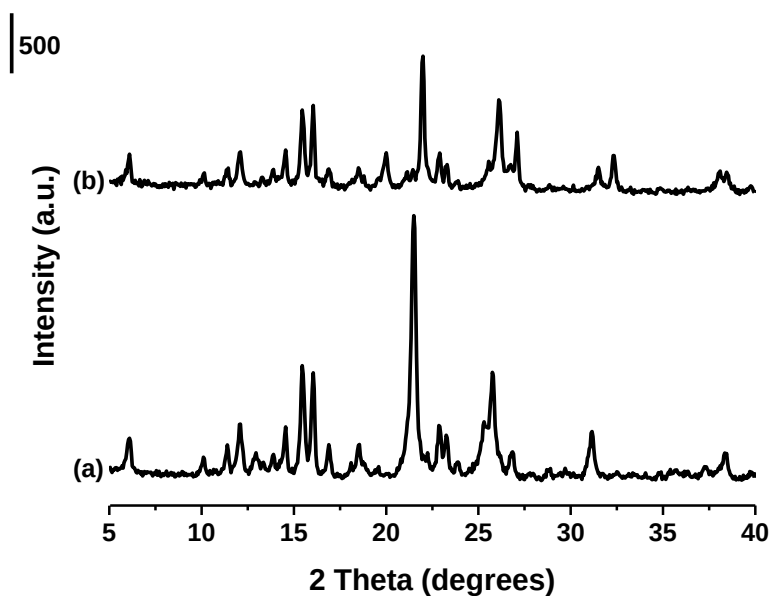


Figure A-I.10 PXRD diffractograms of (a) BD comilled with AA at CT at 50% w/w after DVS analysis and (b) BD comilled with SA at CT at 50% w/w after DVS analysis.

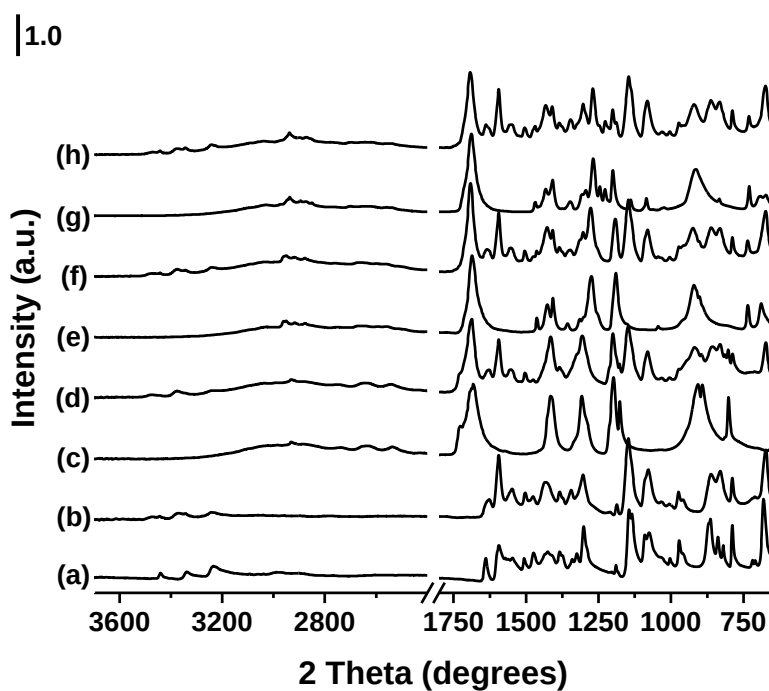


Figure A-I.11 FTIR spectra of (a) crystalline SDM (b) SDM milled in the PBM for 18 hours (mSDM) (c) crystalline SA (d) mSDM comilled with SA at 50% w/w in the VBM at RT for 36 minutes (e) crystalline AA (f) mSDM comilled with AA at 50% w/w in the VBM at RT for 36 minutes (g) milled PA (h) mSDM comilled with PA at 50% w/w in the VBM at RT for 36 minutes.

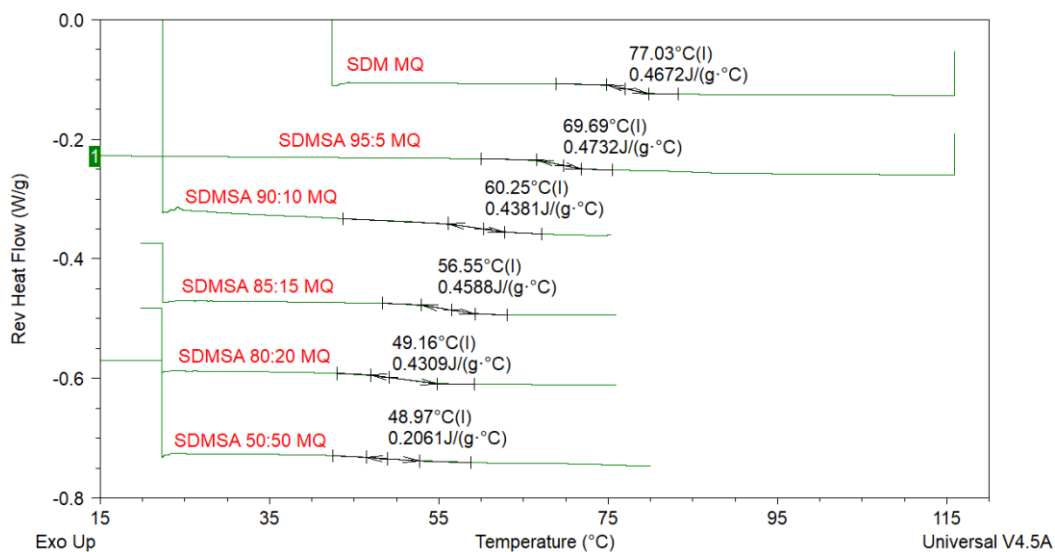


Figure A-I.12 mDSC thermograms showing the reversing heat flow signals of melt quenched SDM and SDMSA melt quench composites in terms of weight fraction from 95:5 to 50:50 SDM:SA.

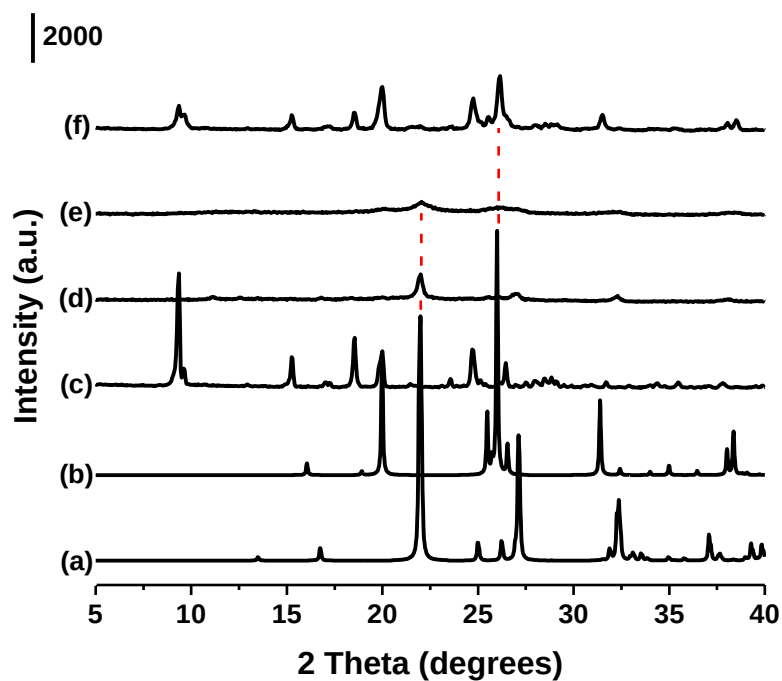


Figure A-I.13 PXRD diffractograms of (a) CCDC generated single crystal structure of α SA (b) CCDC generated single crystal structure of β SA (c) crystalline SDM (d) SDM comilled with SA at 50% w/w for 54 minutes in the VBM at RT and SDM comilled with SA at 50% w/w for 54 minutes in the VBM at CT (e) before and (f) after crystallisation in the DVS.

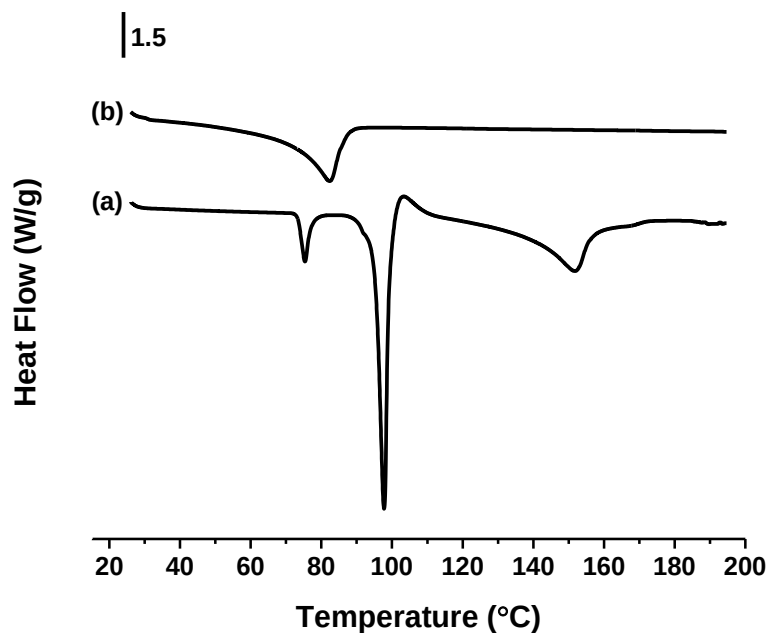


Figure A-I.14 DSC thermograms of (a) physical mixture of form I ACV with crystalline β -GA at 70% w/w (GA in ACV) and (b) the composite formed on co-melt quenching the physical mixture of form I ACV with crystalline β -GA at 70% w/w (GA in ACV).

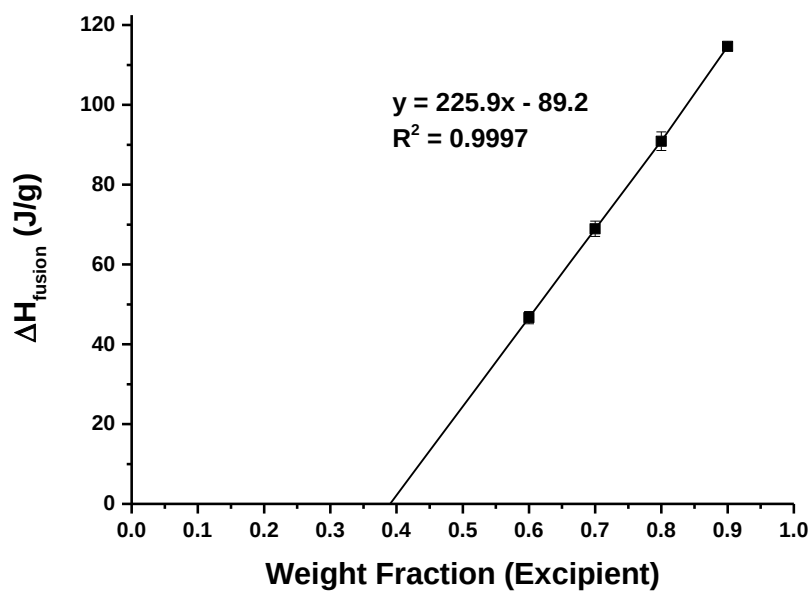


Figure A-I.15 Zero enthalpy extrapolation curve of GA in amorphous ACV determined by extrapolation regression line of the enthalpy of fusion values of melt quench composites from 90% w/w to 60% w/w GA in ACV to the abscissa.

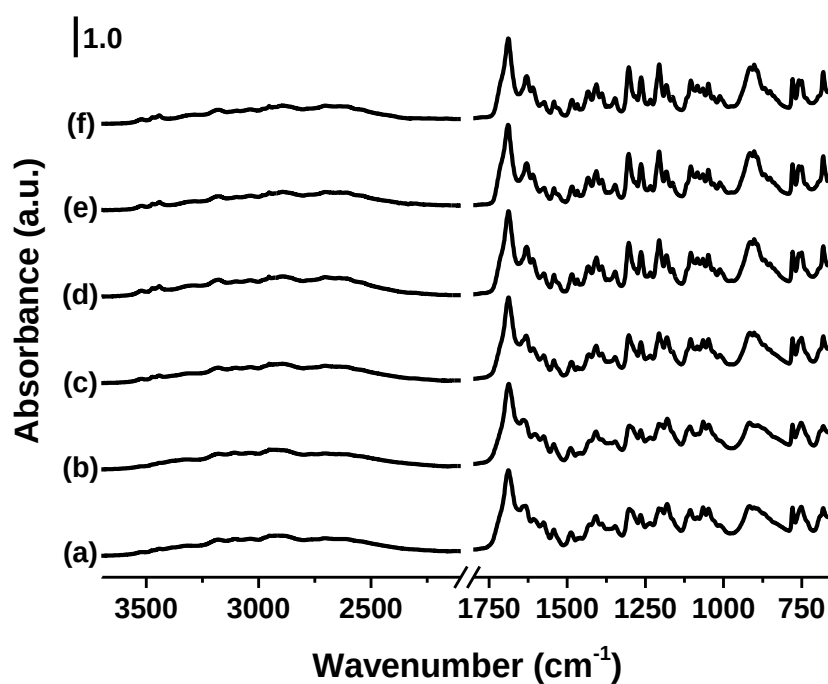


Figure A-I.16 FTIR spectra of Form I ACV comilled with β -GA in the VBM at CT at 25 °C and 43% RH after (a) 0 hr (b) 1hr (c) 2 hr (d) 6hr (e) 9hr and (f) 4days

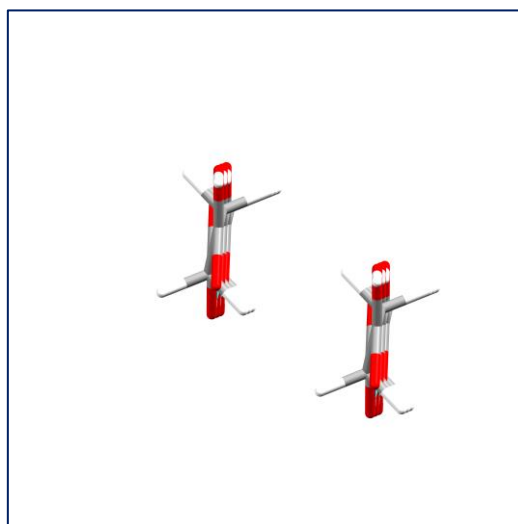


Figure A-I.17 Mercury analysis of the CCDC generated single crystal structure of β -polymorphic AA showing the lack of out-of-plane twisting of the carboxy groups when viewed along the length of the infinite hydrogen-bonded chains.

A-II CHARACTERISATION OF THE SULFADIMIDINE-SUCCINIC ACID COCRYSTAL

Melting point depression analysis of SDM in the presence of increasing concentration of diacid excipient was carried out in order to assess the miscibility and excess thermodynamic functions of interaction on mixing in the liquid state. DSC analysis of physical mixtures of SDM and SA indicated a reduced eutectic melting of SA at 143 °C (relative to the T_m of SA of 188 °C), as shown in Figure A-II.1 (c). However, the eutectic melting endotherm was immediately followed by an exothermic event followed which was subsequently followed by a second endothermic melt at 170 °C.

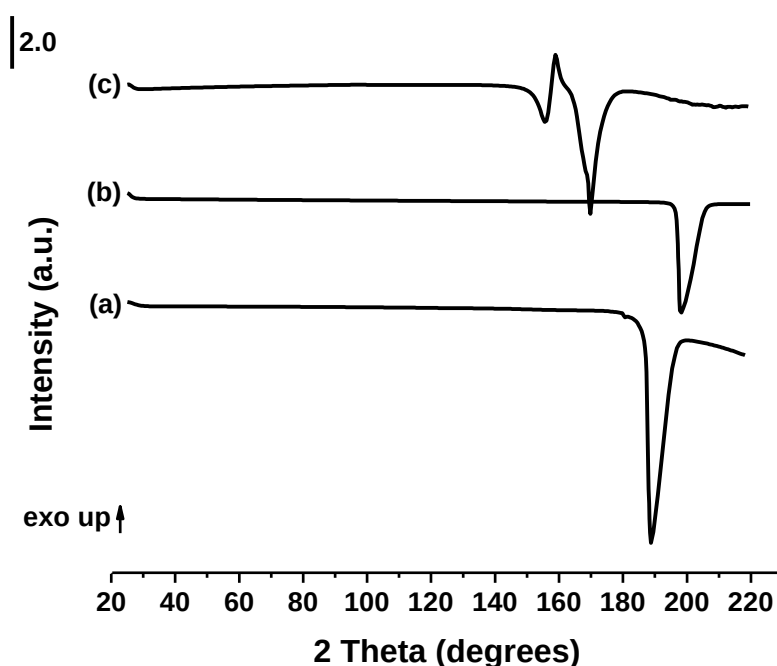


Figure A-II.1 DSC thermograms of (a) crystalline β -SA (b) crystalline SDM and (c) 60% w/w physical mixture of SA in crystalline SDM.

Figure A-II.2 shows the PXRD diffractogram of the physical mixture of SDM with SA heated in the DSC to 162 °C followed immediately by PXRD analysis, indicating the presence of Bragg peaks not associated with either α or β -polymorphic forms of SA or, indeed, crystalline SDM. Figure A-II.3 shows the FTIR spectra of crystalline SDM,

both α and β -polymorphic forms of crystalline SA and the spectrum of the SDM:SA physical mixture heated to 162 °C in the DSC. Unique FTIR spectrum in particular in the regions associated with H-bonding groups an indication of a unique solid-state cocrystal form.

The presence of new Bragg peaks and FTIR spectrum together with the exothermic nature of the peak in DSC analysis suggest the formation of cocrystal system crystallisation from the eutectic melt mixture of SDM and SA. The crystallisation of cocrystal from eutectic melt has previously been shown, for example in the benzophenone/ diphenylamine submerged eutectic which forms a cocrystal on contact at room temperature via the formation of a eutectic melt intermediate.

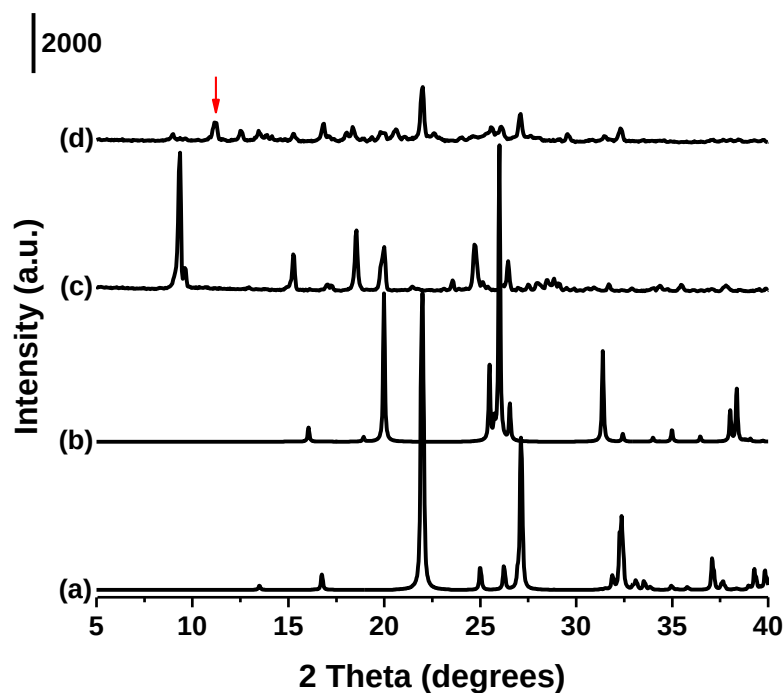


Figure A-II.2 PXRD diffractograms of (a) α -SA generated from the CCDC single crystal structure (b) β -SA generated from the CCDC single crystal structure (c) unmilled SDM (d) physical mixture of SA in SDM heated to 162 °C. Red arrow indicates a new peak not associated with either pure component.

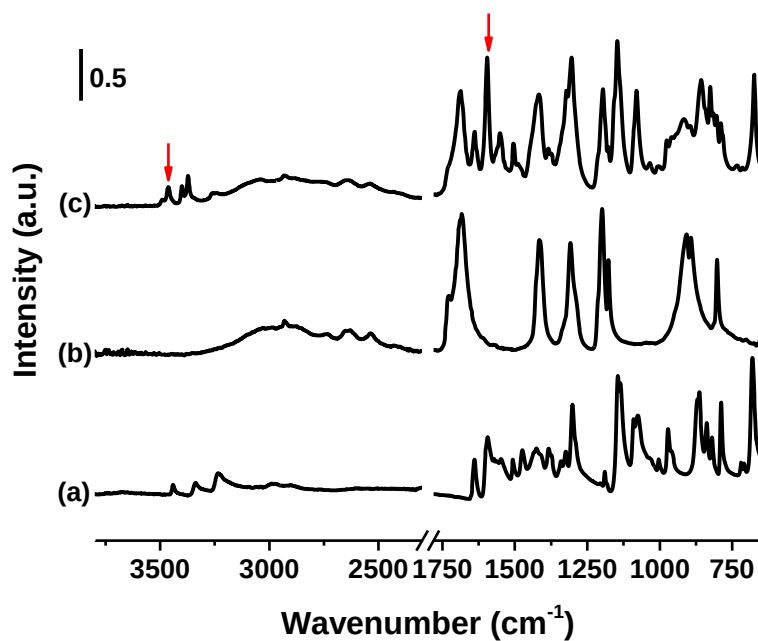


Figure A-II.3 FTIR spectra of (a) unprocessed crystalline SDM (b) unprocessed crystalline β -SA and (c) physical mixture of SA in SDM heated to 162 °C. Red arrows indicate new peaks not associated with either pure component.

A-III CHARACTERISATION OF THE γ -POLYMORPH OF PIMELIC ACID

Figure A-III.1 shows the PXRD diffractogram of the system formed on comilling crystalline BD with β -PA at 50% w/w in the VBM at CT for 60 minutes in addition to the diffractogram of the α polymorph of PA as determined from the single crystal structure from the CCDC.

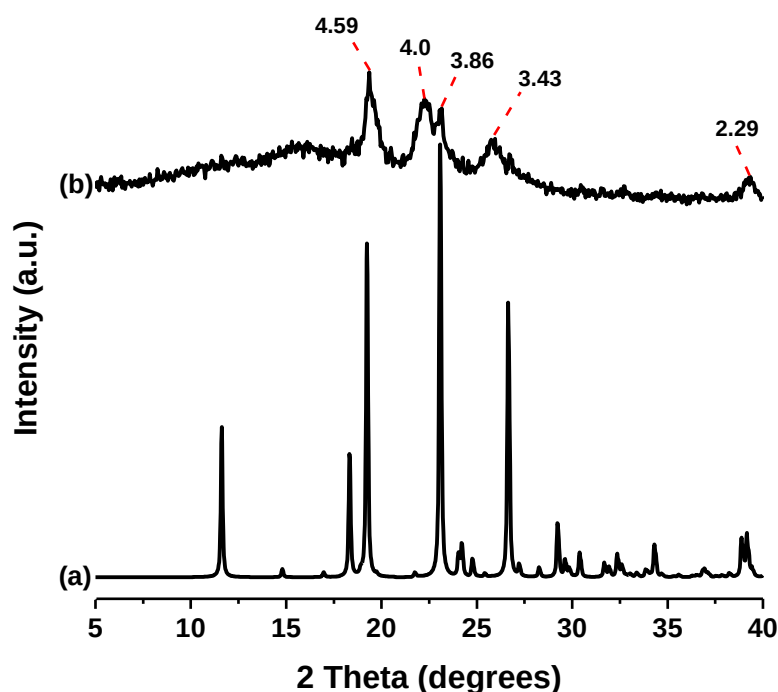


Figure A-III.1 PXRD diffractograms of (a) α -PA generated from the CCDC single crystal structure and (b) BD comilled with PA at 50% w/w at CT for 54 minutes, with the d-spacing of peaks highlighted.

Table A-III.1 shows the d-spacing values the three polymorphic forms of PA, Mod I (γ -PA), Mod II (α -PA) and Mod III (β -PA) as described by Burger et al. (Burger, Henck et al. 1996). Figure A-III.1 (a) shows the corresponding d-spacing values of the peaks associated with PA in excess of the solubility composition of PA in BD. Each of the peaks correspond to peaks associated with the γ polymorph of PA as shown in Table A-III.1, shown in bold. While three of the peaks have d-spacing values similar in both the γ and α polymorphs, two of the peaks are unique to the γ polymorph indicating that PA in excess of the solubility composition in amorphous BD underwent a polymorphic transformation to the γ polymorph on co-cryomilling.

Table A-III.1 d-spacing values of the three polymorphic forms of pimelic acid, as determined by Burger et al. [Data from reference ((Burger, Henck et al. 1996))]

Mod I (γ-polymorph)		Mod II (α-polymorph)		Mod III (β-polymorph)	
<i>d</i> -Value (Å)	I/I _{max} (%)	<i>d</i> -Value (Å)	I/I _{max} (%)	<i>d</i> -Value (Å)	I/I _{max} (%)
7.650	6.53	7.604	14.57	9.411	1.23
7.692	16.99	4.828	7.22	8.491	100
7.609	19.31	4.609	19.49	4.614	4.89
4.818	11.45	4.364	2.2	4.145	1.69
4.596	35.64	3.940	100	4.035	14.64
4.390	0.84	3.625	3.3	3.855	2.05
4.105	6.03	3.386	26.04	3.744	90.48
4.046	100	3.110	4.36	3.224	3.54
3.968	59.97	3.057	2.28	3.199	0.38
3.688	4.05	2.922	2.16	2.831	4.04
3.643	5.20	2.849	2.95	2.53	1.14
3.424	34.68	2.610	12.52	2.394	0.69
3.396	7.58	2.298	3.64	2.364	0.76
3.245	1.62	-	-	-	-
2.783	0.76	-	-	-	-
2.602	2.02	-	-	-	-
2.292	4.94	-	-	-	-

A-IV IGC ANALYSIS CONDITIONS

Table A-IV.1

Material	Process	Mass of Sample (g)	Column Temp. (°C)	Solvent Temp. (°C)	Flow Rate (ccm/min)	Injection Conc. (p/p _o)
Sulfadimidine	Unprocessed	0.25	50	33	10	0.05
	Milled (High Energy)	0.2-0.3	50	33	10	0.05
	Milled (Low Energy)	0.2	50	33	10	0.05
	Blended	0.22	50	33	10	0.05
Mannitol	Unprocessed	0.31	50	33	5	0.05
	Milled	0.34	50	33	5	0.05
Succinic Acid	Milled	0.27	30	33	5	0.05
Glutaric Acid	Milled	0.32	30	33	5	0.05
Adipic Acid	Milled	0.21	30	33	5	0.05
Pimelic Acid	Milled	0.34	30	33	5	0.05

A-V QUANTIFICATION OF THE EXCESS THERMODYNAMIC FUNCTIONS

For the determination of the excess thermodynamic functions of the SDM:GA composite, the predicted (ideal) melting point values of SDM were determined from the Schroeder-van Laar equation as shown in Table A-V.1 and Figure A-V.1. The predicted values were then compared with the experimental melting point values of the SDM:GA physical mixtures as determined by DSC analysis, again highlighted in Table A-V.1 and Figure A-V.1.

Table A-V.1 Predicted (ideal) and experimental melting point values of SDM and the SDM:GA composite respectively, together with the activity coefficients as determined from the modified Schroeder-van Laar equation.

X_{SDM}		$T_{\text{SDM(P)}} \text{ (K)}$	$T_{\text{SDM(E)}} \text{ (K)}$	γ_{SDM}	$\ln(\gamma_{\text{SDM}})$	$\frac{d\ln(\gamma_{\text{SDM}})}{dT} \times 10^{-3}$
Weight Fraction	Mole Fraction					
0.5	0.322	419.5	400.2	0.607	-0.498	8.58
0.6	0.416	430.2	416.9	0.726	-0.32	6.23
0.65	0.469	435.4	425.3	0.79	-0.236	5.06
0.7	0.526	440.5	432.3	0.831	-0.185	4.07
0.75	0.587	445.5	439.2	0.869	-0.141	3.12
0.8	0.655	450.6	446.2	0.909	-0.095	2.14
0.85	0.729	455.6	453.2	0.949	-0.053	1.16
0.9	0.81	460.8	459.7	0.977	-0.023	0.24
0.95	0.9	466	465.8	0.994	-0.006	-0.61

The modified Schroeder-van Laar equation (with the inclusion of the activity coefficient) was then used to determine the activity coefficient for the SDM:GA system across the experimental compositional range. The activity coefficient thus determined was then plotted against the experimental temperature as shown in Figure A-V.2. Curve fitting (using Origin Software Version 9.0) of a second degree polynomial yielded a fit with an R^2 value > 0.999 for the SDM:GA system (R^2 value of 0.995 with SDM:PA and R^2 value of 0.979 with SDM:AA). The equation of the second order polynomial is shown in Figure A-V.2. This equation was then differentiated with respect to temperature in order to obtain a linear equation of T versus $\ln\gamma$, i.e. the derivate of $\ln\gamma$ with respect to T ($d\ln\gamma/dT$), as shown in Table A-V.1, over the experimental composition range which was subsequently used in the determination

of the excess entropy (S^E) and enthalpy (H^E) of interaction in the liquid mixtures as described in Chapter 2, Section 2.4.13.

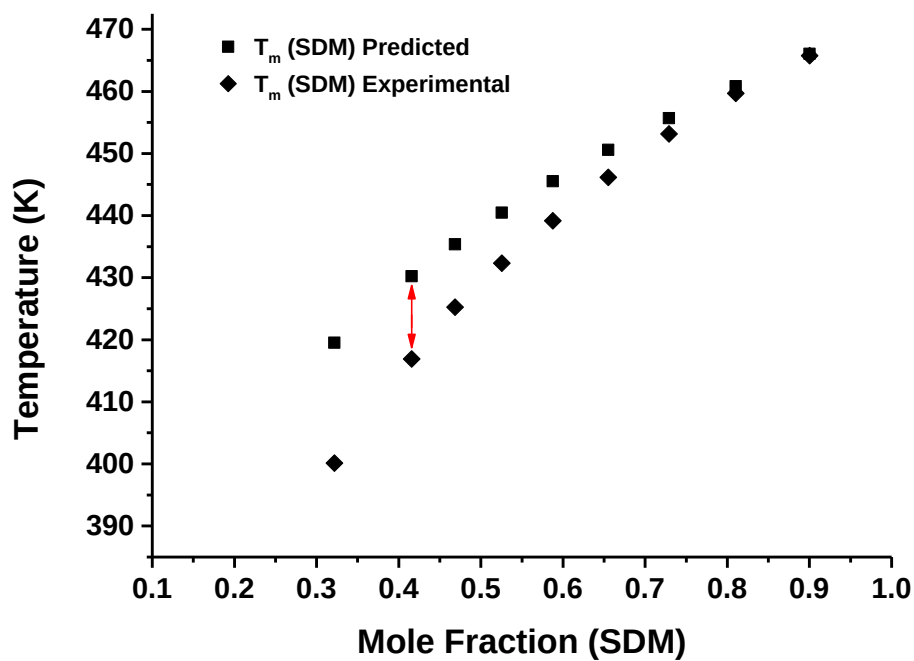


Figure A-V.1 Comparison of the predicated (ideal) melting point values of SDM and the experimentally determined melting point values of the SDM:GA composite indicating deviation from ideality in the SDM:GA mixture.

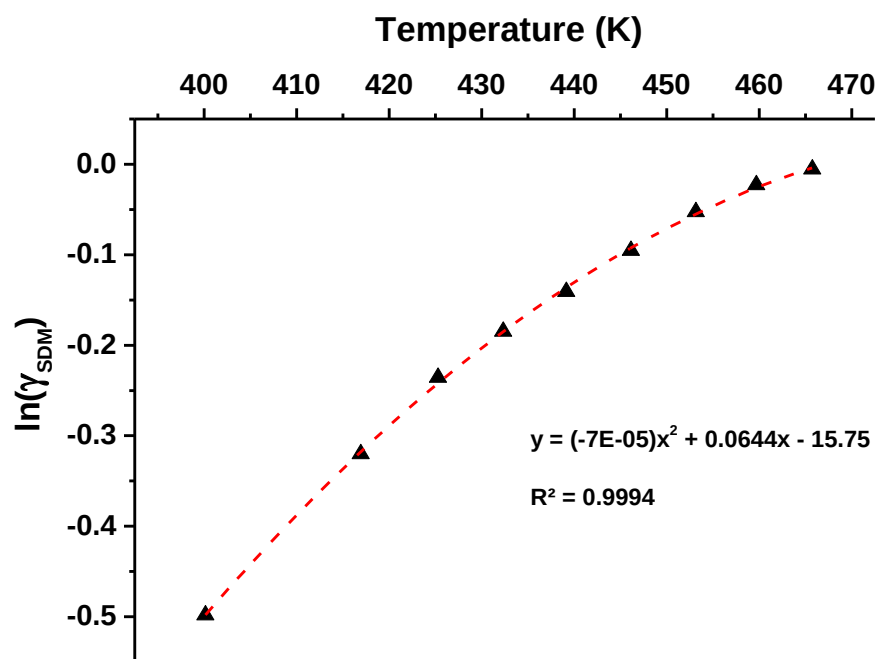


Figure A-V.2 Plot of $\ln(\gamma_{SDM})$ versus the experimental temperature with a second order polynomial fitted using Origin software (Version 9.0).

A-VI CALCULATION OF THE HILDEBRAND SOLUBILITY PARAMETERS

Material	Atom or Group	No. of Atoms or Groups	Δe_i (kJ/mole)	V (cm ³ /mole)	$\Sigma \Delta e_i$ (kJ/mole)	ΣV (cm ³ /mole)	δ (MPa ^{1/2})
Sulfadimidine	CH ₃	2	4.707	33.5	9.414	67	25.7
	-CH=	5	4.309	13.5	21.548	67.5	
	C=	5	4.309	-5.5	21.548	-27.5	
	Ring Closure 5 or More	2	1.046	16	2.092	32	
	Conjugation in Ring for Each Double Bond	6	1.674	-2.2	10.042	-13.2	
	NH ₂	1	12.552	19.2	12.552	19.2	
	NH	1	8.368	4.5	8.368	4.5	
	-N=	2	11.715	5	23.43	10	
	SO ₂ *	1	12.343	23.7	12.343	23.7	
					121.336	183.2	
Budesonide	CH ₃	3	4.707	33.5	14.121	100.5	25.4
	CH ₂	7	4.937	16.1	34.56	112.7	
	CH	6	3.431	-1	20.585	-6	
	C	3	1.464	-19.2	4.393	-57.6	
	-CH=	3	4.31	13.5	12.929	40.5	
	C=	1	4.31	-5.5	4.31	-5.5	
	Ring Closure 5 or More	5	1.046	16	5.23	80	
	Conjugation in Ring for Each Double Bond	2	1.674	-2.2	3.347	-4.4	
	CO	2	17.364	10.8	34.727	21.6	
	O	2	3.347	3.8	6.694	7.6	
	OH	2	29.79	10	59.58	20	
					200.476	309.4	

* From (Martin, Wu et al. 1985)

Material	Atom or Group	No. of Atoms or Groups	Δe_i (kJ/mole)	V (cm ³ /mole)	$\Sigma \Delta e_i$ (kJ/mole)	ΣV (cm ³ /mole)	δ (MPa ^{1/2})
Acyclovir	CH ₂	3	4.93712	16.1	14.81136	48.3	32.7
	-CH=	2	4.30952	13.5	8.619	27	
	C=	3	4.30952	-5.5	12.928	-16.5	
	Ring Closure 5 or More	2	1.046	16	2.092	32	
	Conjugation in Ring for Each Double Bond	3	1.6736	-2.2	5.021	-6.6	
	CO	1	17.3636	10.8	17.364	10.8	
	NH ₂	1	12.552	19.2	12.552	19.2	
	NH	1	8.368	4.5	8.368	4.5	
	N	1	4.184	-9	4.184	-9	
	-N=	2	11.7152	5	23.43	10	
	O	1	3.3472	3.8	3.347	3.8	
	OH	1	29.79008	10	29.79	10	
					142.507	133.5	
Mannitol	CH ₂	2	4.937	16.1	9.874	32.5	38.2
	CH	4	3.431	-1	13.723	-4	
	OH						
	(disubstituted or on adjacent C atoms)	6	21.84	13	131.043	78	
					154.64	106.2	
Succinic Acid	CH ₂	2	4.937	16.1	9.874	32.2	27.0
	COOH	2	27.614	28.5	55.229	57	
					65.103	89.2	
Glutaric Acid	CH ₂	3	4.937	16.1	14.811	48.3	25.8
	COOH	2	27.614	28.5	55.229	57	
					70.04	105.3	
Adipic Acid	CH ₂	4	4.937	16.1	19.785	64.4	24.9
	COOH	2	27.614	28.5	55.229	57	
					79.977	121.4	
Pimelic Acid	CH ₂	5	4.937	16.1	24.686	80.5	24.1
	COOH	2	27.614	28.5	55.229	57	
					79.914	137.5	

