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Utilisation of Thermal Methods for the Screening of Three Component Co-amorphous Systems

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SUMMARY

Indomethacin and piroxicam are known to become amorphous upon rapid cooling after melting. Multiple three-component co-amorphous mixtures have been produced via a melt quench method to evaluate the influence of the third component on stability and physical properties on the co-amorphous mixture of piroxicam and indomethacin. These have then been tested using thermal gravimetric analysis, differential scan calorimetry and hot stage microscopy. Results have confirmed the creation of a three-component co-amorphous system.

INTRODUCTION

Amorphous materials are characterised by short range structural order, although this solid state is characterised by thermodynamic instability (conversion to crystalline) amorphous forms of active pharmaceutical ingredients (APIs) are often preferred over their crystalline counterparts because of their better dissolution rate (Fahlman, 2011).

Amorphous dispersion of amorphous materials is defined as a co-amorphous mixture (Dengale, 2016). A co-amorphous system is primarily identified by one glass transition indicating that the systems are miscible and are interacting. Multiple component co-amorphous systems may allow certain properties to be manipulated giving benefits such as improved dissolution rates, higher glass transition temperatures and increased stability.

This work aims to identify if a three component co-amorphous system can be created reliably using a melt quench method.

MATERIALS AND METHODS

Piroxicam (PXC) and indomethacin (IND) were chosen as preliminary testing showed that the pure compounds formed stable amorphous materials with glass transition temperatures above room temperature.

The third components were also chosen from preliminary tests, two were chosen as they showed a strong tendency to crystallise on cooling (benzamide (BZD), caffeine (CAF)) another two were chosen as they showed a propensity towards amorphicity on cooling (acetaminophen (AC), clotrimazole (CTMZ)). Physical mixtures were prepared in a 1:1:1 molar ratio.

The production of amorphous samples was conducted by melting and cooling within the DSC instrument. The DSC pans were then opened and the sample was removed for analysis. Before analysis, all samples were finely ground using mortar and pestle to ensure a homogenous distribution of components

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and to reduce the possibility of thermal lag within larger particles.

Thermo-gravimetric analysis (TGA) was conducted using the Q5000 IR TGA (TA Instruments, UK) in aluminium pans with sample size 2.0 ± 0.5 mg. Samples were heated from ambient temperature to 300°C at 10°C/min, under nitrogen (25 ml/min).

Hot-stage microscopy (HSM) was conducted using a Mettler Toledo FP90 Central processor with a FP82HT Hot Stage. The heating program used was 10°C/min from 30°C to 300°C. This allowed the visual identification of thermal events (melting, crystallisation, evaporation and degradation). These data were combined with those gathered from TGA to determine the temperature for the DSC experiments.

Differential scanning calorimetry (DSC) was carried out using a Q2000 DSC (TA Instruments, UK) in hermetically sealed Tzero aluminium pans with 2.0 ± 0.5 mg of sample. All samples were heated to 180°C at 10°C/min, cooled at 20°C/min, and then re-heated at 10°C/min to characterise the generated co-amorphous (Table 1).

Table 1. *Temperature data for the thermal events on initial heating, cooling and 2nd heating cycles (DSC).*

Chemicals	Melting point on initial heating (°C)	Thermal events on 2nd heating (°C)	Start of mass loss in TGA (°C)
IND-PXC	140.6	Tg 57.6	186
IND-PXC-AC	130.7	Tg 44.1	187
IND-PXC-CAF	124.0	Tg 43.2, Tc 105.7, Tm 132.0	180
IND-PXC-CTMZ	129.3	Tg 53.3	184
IND-PXC-BZD	105.5	Tg 24.5, Tc (HSM) 90, Tm (HSM) 110	176

[a] Tg – Glass transition, Tc – Crystallisation, Tm – Melting. No events were recorded for crystallisation on cooling for al chemicals.

RESULTS AND DISCUSSION

It was found that the 1:1 molar ratio of IND and PXC formed a stable co-amorphous compound indicated by a single glass transition in the DSC trace. This co-amorphous material has a high glass transition of 57.6^{0}C.

It was found that with the addition of a third component a 3-component co-amorphous mixture could be reliably created using a melt-cool method. The introduction of a third component lowered the glass transition in all case tested (Figure 1).

Glass transition of ternary co-amorphous with CTMZ was higher than the glass transition of the co-amorphous with AC. Nevertheless, AC melting point is higher than the melting of CTMZ. It suggests that the melting temperature of the co-amorphous components is not the main factor influencing the system. Gordon-Taylor equation [2] applied to three component systems will be used to assess influence of mass fraction and molecular size on the stability of the generated co-amorphous system.

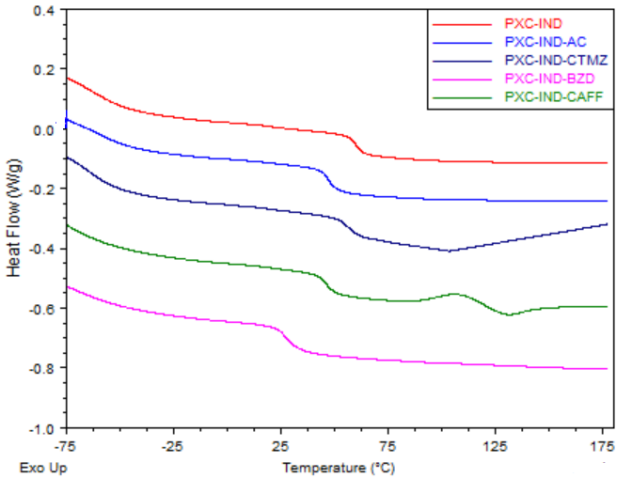

Fig. 1. *DSC thermogram overlay of physical mixtures re-heating after melting and quench cooling.*

CONCLUSIONS

The DSC data have indicated that the combination of piroxicam and indomethacin forms a stable co-amorphous compound with a high glass transition (57.6°C). We have shown that AC, BZD, CAF, and CTMZ can each be added to this mixture and are shown to create stable co-amorphous materials containing three components, although with lower glass transitions. The compounds with higher affinities towards crystallisation can be seen to crystalize upon reheating of the co-amorphous mixture. In the case of BZD, this crystallisation was only detected through HSM. The impact of melting temperature, molecular mass and tendency to

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crystallise on generation and stability of ternary co-amorphous system will be further evaluated.

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REFERENCES

Fahlman, B., 2011, Matherial chemistry, Chapter 2, XI edition, Springer.

Dengale, S., J., Grohganz, H., Rades, T., Löbmann, K., 2016. Recent advances in co-amorphous drug formulations, Advanced Drug Delivery Reviews, 100, 116-125.