W 4259 Quantification of Crystallinity in Amorphous Paracetamol and Solid Dispersions of Paracetamol in Polyvinylpyrrolidone using High Speed Differential Scanning Calorimetry and Attenuated Reflectance-Fourier Transform Infrared Spectroscopy

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Objectives

Recrystallization has been a critical issue for solid dispersion formulation within the pharmaceutical field, particularly as it may lead to unpredictable bioavailability changes on long term storage. However, early recrystallization (where minimal amount of crystalline material may be present) is very difficult to detect by conventional methods.

In this study we are trying to establish the use of High Speed Differential Scanning calorimetry (HSDSC) and Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectroscopy to detect, identify and quantify small levels of crystallinity in amorphous paracetamol (PCM; acetominophen) and solid dispersions of paracetamol-polyvinylpyrrolidone. In addition, validation of the developed methods was performed using conventional approaches.

Methodology

1) Correlation of FTIR-ATR with High Speed DSC

Amorphous paracetamol (PCM; acetominophen) was prepared by quench cooling the molten drug in liquid nitrogen. The product was immediately analysed using high-speed (HS) DSC[1] and FTIR-ATR at 10 defined time points during the first hour, during which early recrystallization took place. HSDSC was used to minimise scan-induced changes in structure, while ATR-FTIR was used to identify the crystalline material. A correlation curve between the two techniques was prepared by using the relative intensity ratio at 797cm^{-1} (crystalline) to 808 cm^{-1} (absence in amorphous) for ATR-FTIR [2], while the enthalpy of crystallisation was used to calculate the crystalline content from HSDSC (we assume negligible enthalpic shift between the two process temperatures) .

$$\%Crystal = \frac{melting\ enthalpy - recrystallization\ enthalpy}{melting\ enthalpy\ of\ pure\ crystal} \times 100\%$$

2) Validation by XRPD and DSC

Hot melt extruded product were intentionally prepared with excess of drug content (55% to 70% PCM PVP K29-32) at 120ºC in order to enable crystal detection for all the available methods.

Further validation was performed using X-ray Powder Diffraction (XRPD). A calibration curve was constructed by physically mixing Paracetamol with PVP K29-32 from 10 to 80% of drug loading. XRPD experiments were performed on prepared samples using a Thermo ARL, Model: Xtra system with Cu X-ray tube (wavelength 1.540Å), voltage 45kV and current 40mA. Measurements were performed at 2Θ 10-30º with 0.01º/step and 0.5 second for every scan step to cover the characteristic peak of Form I Paracetamol. HME samples were then analysed using the same conditions and the crystal content was calculated from the calibration curve.

In addition, validation was also performed via DSC heat capacity (DSC Cp) and melting enthalpy methods (DSC Tm) [2]. Samples were scanned with modulated DSC at 2ºC/minute (±0.318ºC every 60 seconds). The detection limits of XRPD and FTIR-ATR were determined using a physical mixture of low drug loading (1%-5% w/w).

Results and Discussions

1) Correlation of FTIR-ATR with High Speed DSC

The amorphous sample recrystallised extensively over the first hour, as indicated by the reduction in recrystallisation enthalpy in HSDSC (Figure 1). A similar trend was also observed in FTIR-ATR where the intensity of band 808cm^{-1} (indicative of crystalline material) increased (Figure 2). Both HSDSC and the FITR-ATR diagnostic band revealed an exponential growth of crystals from the quench-cooled paracetamol (Figure 3). After circa 50% recrystallisation (based on the FTIR-ATR diagnostic band), the process appeared to slow down and no further changes were seen over a period of 2 hours.

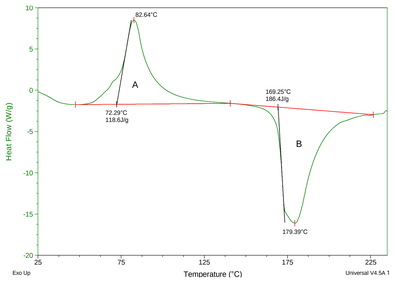

Figure 1: HSDSC profile of Quench-cooled Paracetamol with High Speed DSC

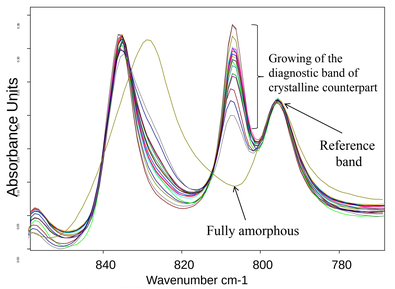

Figure 2: FTIR-ATR spectra of quench-cooled Paracetamol from first 2 hours

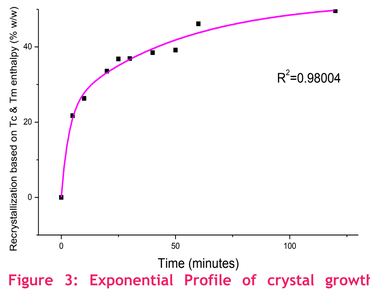

Figure 3: Exponential Profile of crystal growth estimated from HSDSC

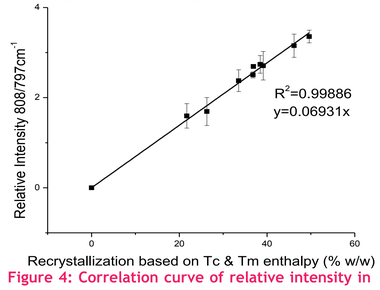

Figure 4: Correlation curve of relative intensity in FTIR-ATR with crystal growth of DSC data

A linear relationship was obtained (R^2=0.9988) between the crystallinity measured using ATR-FTIR and the values obtained using HSDSC (Figure 4). Having validated the measurement using ATR-FTIR, it was noted that the method was able to detect small quantities of crystalline material (down to 1%). Thus, crystal content in the solid dispersion could be obtained from the equation below:

$$Crystal\ content\ (\%) = \frac{Relative\ intenssity\ of\ \frac{808cm^{-1}}{797cm^{-1}}}{0.06931}$$

2) Validation by XRPD and DSC

Good linearity were found for calibration curve of XRPD with R^2= 9898 based on major peaks intensity (data not shown) in physical mixtures. It is worth mentioning that there might be a potential overestimation for this method as crystallinity disruption could be anticipated for physically mixed formulations [4].

Amorphous Paracetamol will undergo recrystallization during the heating process (Figure 1). This raises the issue that heating the HME formulations might lead to a certain extend of recrystallization during the heating run which again could give could give rise to an overestimation of crystal content. On this basis, the heat capacity method might serve as an alternative. With this method, amorphous content was assumed to be linearly proportional to the heat capacity value. The reversing heat capacity signal was used to remove the effects of the endothermic relaxation processes occurring simultaneously.

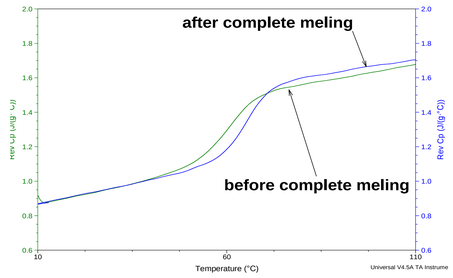

Figure 5: DSC traces of HME 55% PCM PVP K29-32 in heat capacity determination.

The changes in Cp values before and after complete melting were taken to calculate the content of crystalline material (Figure 5).

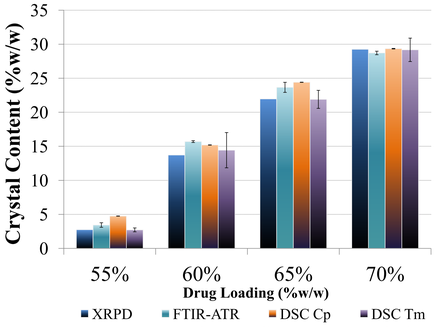

Figure 6: Comparison of crystallinity estimated from different methods

The measured crystallinity by all the four methods (FTIR-ATR, DSC Tm, DSC Cp and XRPD) are presented as a bar chart in Figure 6. The results obtained correlate well with each other with an overall deviation of less than 1.25%w/w.

Detection limits

XRPD was reported to be much less sensitive in comparison to DSC, which has a detection limit of <10% [5]. In the current study, it is found that the sensitivity for XRPD (using facilities available to us) for Form I Paracetamol detection is ≥3%$^{w}/_{w}$ via scanning of low crystal content of Paracetamol in PVP physical mixtures. On the other hand, FTIR is shown to detect down to 1 % of crystal content.

Conclusion

ATR-FTIR and HSDSC of amorphous paracetamol showed high mutual correlation for measuring crystallinity, while ATR-FTIR of the extrudates showed good correlation with XRPD, and DSC data. These studies indicate that crystallinity measurements may be made by all three methods but cross-correlation is very helpful for data validation.

Early detection of crystal in dispersion of HME paracetamol-PVP K29-32 is preferably done by FTIR-ATR method due to the relatively simple and fast analysing step compared to both DSC and XRPD.

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An Investigation into the Recrystallisation Behaviour of Paracetamol (Acetominophen) in Hot Melt Extruded Solid Dispersions

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OBJECTIVES

Solid dispersions have attracted considerable attention recently due to the many benefits of these formulations, including dissolution and bioavailability enhancement of poorly soluble drugs. However, drug recrystallization on storage or manufacture may potentially lead to unpredictable pharmacological effects, hence it is highly pertinent to study this behaviour, in this case using a drug with a poor stability profile due to its low *Tg*.

In this study, we characterize the recrystallization behaviour of paracetamol (PCM; acetominophen) in polyvinylpyrrolidone (PVP) K29-32 prepared by hot melt extrusion (HME) upon storage under high humidity conditions, with a view to exploring the role of PVP in promoting the physical stability of the drug.

METHODOLOGY

The theoretical solubility of the drug in the polymer was estimated by using the interaction parameter obtained from the melting point depression approach at drug-rich compositions [1]. Binary system of the extrudate ranging from 20-60% paracetamol loading was prepared by using co-rotating twin-screw extruder (Thermo Haake MiniLab Micro Compounder twin screw extruder). Extrusion was performed at 120ºC and screw rotation of 100 rpm.

HME 20-50% drug systems were stored under humidity conditions of 0%RH, 22%RH, 33%RH, 53%RH and 75%RH at 25±3ºC. Characterisation of the fresh and aged samples were performed with Modulated Temperature Differential Scanning Calorimetry (MTDSC) (2ºC/minute ±0.212ºC every 40 seconds). Infrared measurements were carried out using a Bruker IFS-60/S Fourier transform infrared spectrometer (FTIR-ATR). The spectra were recorded over a wavenumber range of 500cm^{-1} to 4000cm^{-1} with a resolution of 2 cm^{-1} and 64 scans. Quantification of the degree of recrystallization of drug was measured at the diagnostic wavenumber of 808cm^{-1} [2] daily for the first 14 days and subsequently on a monthly basis.

Powder X-ray diffraction (XRPD) experiments were performed on prepared samples using a Thermo ARL, Model: Xtra system with Cu X-ray tube (wavelength 1.540Å), voltage 45kV and current 40mA. Measurements were performed at 2Θ 10-30º with 0.01º/step and 1 second for every scan step.

Scanning electron microscope (SEM) was used to investigate the surface morphology.

RESULTS AND DISCUSSION

1) Theoretical estimation of solubility

There is a depression of melting temperature seen in the DSC traces of physical mixtures of PCM in PVP K29-32 (Figure 1). Theoretical estimation showed the solubility to be circa 35-45% drug loading at 120ºC (the extrusion temperature; (Table 1).

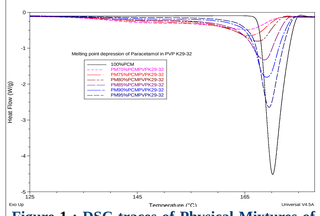

Figure 1 : DSC traces of Physical Mixtures of paracetamol (70-95%w/w) with PVP K29-32

Parameter	Results
Interaction parameter, χ_{12}	-1.652
Solubility range in polymer (%w/w)	35 – 45%

Table 1 : Interaction Parameter and solid solubility of paracetamol (70-95%w/w) in PVP K29-32

2) Fresh extrudate

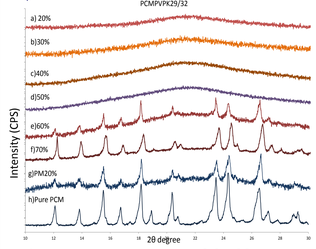

Figure 2: XRPD Spectra of freshly prepare extrudate (20-70%w/w), PM of 20% PCM PVP K29-32 and raw Paracetamol

For freshly prepared formulations, XRPD, FTIR and DSC indicated full amorphicity up to 50% drug loading (Figure 2). SEM showed some crystalline traces (≈40 microns) only in 60% drug systems. Hence, stability studies were performed on 10-50% drug loading formulations.

3) Recrystallization after storage

After 3 months humidity studies (22-75%RH), all the samples displayed halo patterns in XRPD which implied the absence of any detectable crystals in 10-40% drug formulations with the exception of the 50% drug loading formulation. Crystallization was detected using FTIR-ATR (at diagnostic band of 808cm^{-1} (Figure 3)) in 40% drug loading extrudate after storage for 5 days at 75%RH. For HME 50% PCM/PVP K29-32, the crystal band started to appear in FTIR -ATR spectra after 12 hours of storage at 75%RH. The recrystallized form was identified by XRPD as Paracetamol form I (Figure 4).

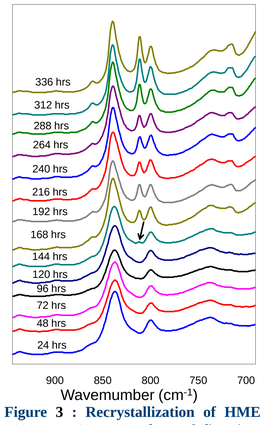

Figure 3 : Recrystallization of HME 40%w/w PCM PVP after a define time point (as labelled) in 75% RH at room temperature

RESULTS AND DISCUSSION

3a) HME 50% PCM-PVP K29/32

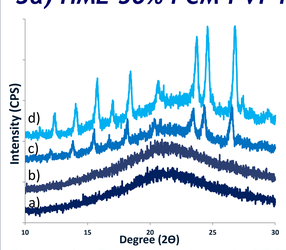

Figure 4: Recrystallization of HME 50%w/w PCM PVP K29-32 after 3 months storage at different humidity a) 19%RH, b) 33%RH, c) 53%RH, d) 75%RH.

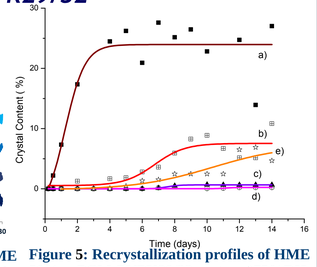

Figure 5: Recrystallization profiles of HME 50% PCM-PVPK29/32 at a)75%RH, b)53%RH, c)33%RH, d)22%RH & e) HME 40%PCM-PVP K29/32 at 75%RH

At the early stage of recrystallization, the rate of crystal growth was in line with the storage humidity whereby higher humidity revealed a higher rate of crystal growth (Figure 4). Under these conditions, the samples possessed higher water content that led to higher molecular mobility that promoted the recrystallization process.

At low humidity conditions i.e. 22%RH and 33%RH, a lag time was observed prior to partial recrystallization. This might be attributed to the nucleation process. After this phase, an exponential growth profiles of crystals were noted. The rate of the growth might be closely dependent on the humidity level as well as the degree of supersaturation (Figure 5). Subsequently, the rate of crystal growth slowed down and a plateau was approached at the end.

Given the higher water uptake of 10-40% systems (>10% water content), these systems are relatively more stable than 50% drug loading formulations (≈9% of water content). Based on the calculated drug solubility in polymer, 35%-45% drug loading is the estimated solubility of Paracetamol in PVP K29-32 at extrusion temperature (Table 1). Thus, 50%w/w Paracetamol extrudate is theoretically in a supersaturated state. The cumulative effect of both water uptake and degree of supersaturation drive the highest rate of recrystallization processes amongst the tested samples.

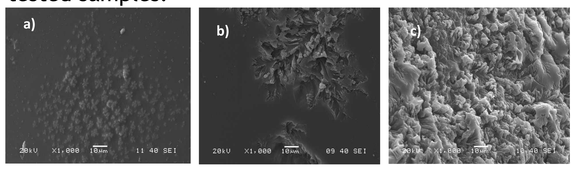

Figure 6 SEM images of extrudates in 25ºC/75%RH a) HME 40%w/w PCMPVP after 48 hours, b) HME50%PCMPVP after 24 hours, c) HME60%PCMPVP after 24 hours

SEM images of HME 50%PCM PVP K29-32 showed a rough surface after 24hours of storage at 75%RH (Figure 6b). Clusters of crystals could also be observed at high magnification of SEM in HME 40% PCM PVP K29-32 after 2days of storage in 75%RH. Smooth surfaces were however observed in formulations with lower drug loading (20% and 30%) implying the absence of crystals (data not shown).

RESULTS AND DISCUSSION

4) Long term storage

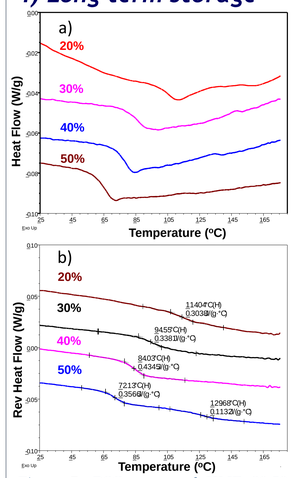

Figure 7: DSC curves of HME 20-50 %w/w PCM PVP K29-32 after 1 year storage at 25ºC/0%RH, a) Total Heat flow versus temperature, b) Reversing heat flow versus temperature

At 25ºC/0%RH, DSC curves of the aged sample (1 year) revealed minor enthalpy changes at circa 150ºC but no obvious melting endotherm was observed (Figure 7a). Similarly, no diagnostic crystalline peaks was detected in FTIR-ATR and XRPD spectra indicating amorphous state of the samples remain.

However, two Tg(s) were noted in 50% drug loading formulations which may be an indication of the separation into two amorphous phases (Figure 7b).

CONCLUSIONS

Amorphous paracetamol is typically a highly unstable API. However, this API showed good physical stability when it was dispersed in PVPK29-32 via HME. These formulations are stable up to a year time in 0%RH at ambient temperature.

The recrystallization of paracetamol was found to be loading and humidity dependent with theoretically supersaturated systems being much more unstable than lower drug content systems

ACKNOWLEDGEMENT

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An Investigation into Drug-Polymer Interactions for Stability Enhancement of Hot Melt Extrusion Systems

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Introduction

Solid dispersion is commenced about a decade ago. However, the range of this produt is still limited available in the market due to the inherent thermodynamic instability of the amorphous state. Recrystallization of these materials leads to unpredictable pharmacological effect and often makes the effort for amorphous production go in vain. Study implied that polyvinylpyrrolidone (PVP) polymer is a potential stabilizer for amorphous solid in long term [1]. However, PVP's hygroscopic properties lowering its capability in stabilizing effect. Thus it is of pertinent for one to study the factors underpin the stability of amorphous solid dispersion. In the current study, PVP based hot melt extrusion (HME) products were studied in various carriers and challenged at high humidity conditions for a better understanding on the process recrystallization. Factors affecting the recrystallization process were then explored.

Methods

Physical mixtures (PM) of paracetamol (40% w/w) and carriers were prepared by simple mixing in mortar and pestle, while solid dispersions (SD) were prepared by hot melt extrusion (HME) at 160°C, 100rpm. Polyvinylpyrrolidone of different molecular weights, MW (PVPK12, K17, K29-32) and polyvinylpyrrolidone-vinylacetate (PVPVA6:4) were used as carriers. Flory-Huggins interaction parameters, χ_{12} were calculated from the melting point depression approach [2]. These values are then correlated to the interaction detected from chemical shift of carbonyl band in Fourier Transform Infrared- Attenuated Total Reflectance (FTIR-ATR).

The samples were placed in controlled humidity conditions (53%RH and 75%RH). Both aged and fresh samples were tested using modulated temperatureat 2°C per minute ±0.212°C 40 seconds Differential Scanning Calorimetry (DSC) to detect the changes of glass transition temperature (Tg). Thermogravimetric analysis (TGA) was employed to determine water content of the annealed samples. Profile of recrystallization were probe by ATR-FTIR by diagnostic band of 808cm^{-1} which represent the crystal content.

1 Drug-polymer interaction

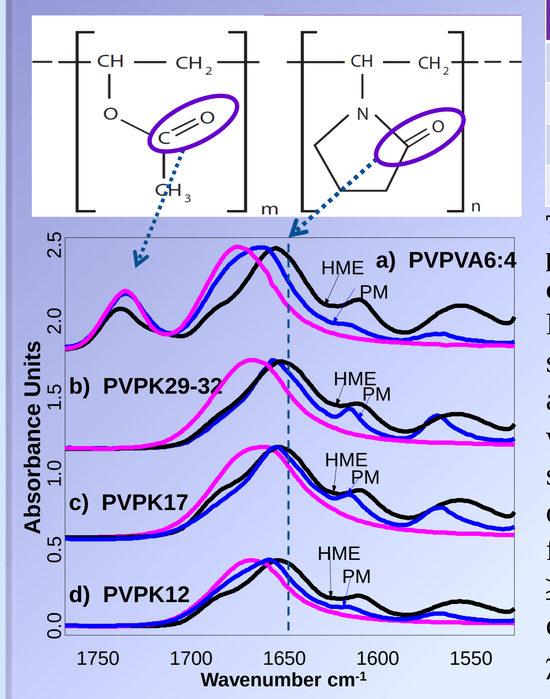

Figure 1: Monomer of PVP and vinyl acetate portion (chemical structure). FTIR-ATR spectra of pure polymers, physical mixture and hot melt extruded of 40% drug loading in different carriers as labelled.

Carriers	Flory-Huggins interaction parameter, χ_{12}
PVPVA 6:4	-0.6095
PVP K29-32	-1.4529
PVP K17	-1.3711
PVP K12	-1.3307

Table 1: interaction parameter for mixture of paracetamol-carries calculated from melting point depression approach

FTIR-ATR spectra showed red-shift of carbonyl stretching at 1653 cm^{-1} for both physical mixture and hot melt extruded samples to lower wavenumber (Figure 1). The extent of the red-shift to lower frequencies determine the density of interaction. Thus, interaction of drug-polymer following the trend of PVP K29-32 >PVP K17 ≥PVP K12 >PVPVA. The trend agreed to the calculated Flory-Huggins interaction parameter, χ_{12} (Table 1).

Carbonyl stretching band from vinyl-acetate (1730cm^{-1}) of PVPVA copolymer did not reveal an apparent shift to lower wavenumber [3]. Hence these portion of the polymer is suspected to have limited role for drug-polymer interaction.

2 Equilibrium Water Content & Changes of glass transition temperature

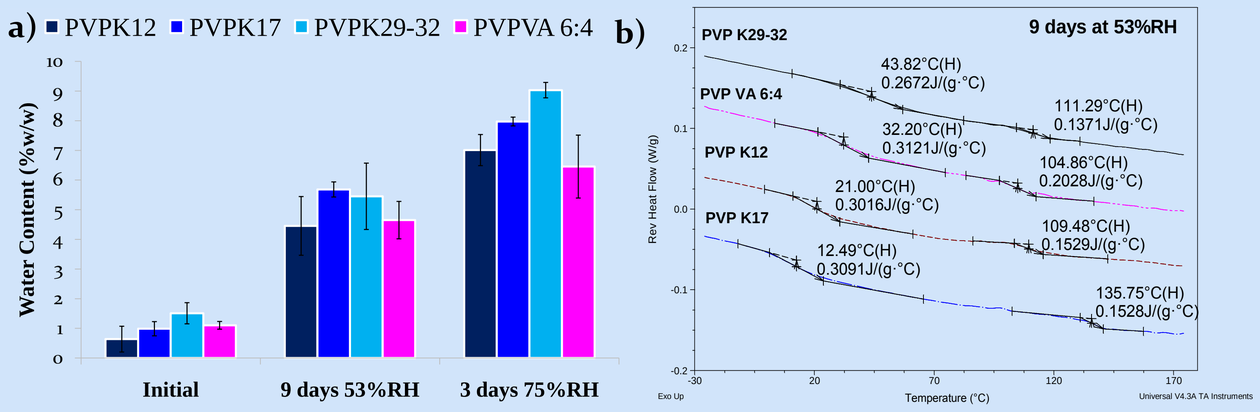

Figure 2: water content at equilibrium (a) and glass transition temperature at day 9 (b) of 40% hot melt extruded paracetamol formulations in different carriers after storage in various humidity conditions

Water uptake of HME formulations exposed at different relative humidity condition were measured with TGA (figure 2a). The highest uptake was observed for HME 40% PCMPVP K29-32, while the lowest was noted for PVPVA 6:4 carrier systems for all the tested range.

From DSC, higher water absorption of the samples revealed lower glass transition temperature (figure 2b). Phase separation occurred in all formulations. There results are related to the plasticization of water in these formulations.

It is worth mentioning that upon extrusion, HME 40% PCM PVPVA6:4 system possessed lowest Tg whereas PVP K29-32 carrier formulation having the highest Tg. The trend was disturbed following the absorption of water. At the end of 1 month, highest Tg was seen in PVPVA 6:4 system followed by PVP K29-32 > PVP K12 > PVP K17. This facet will be evaluated mutually with the recrystallization tendency of these formulations.

3 Recrystallization profiles of HME 40% PCM PVPs carrier system

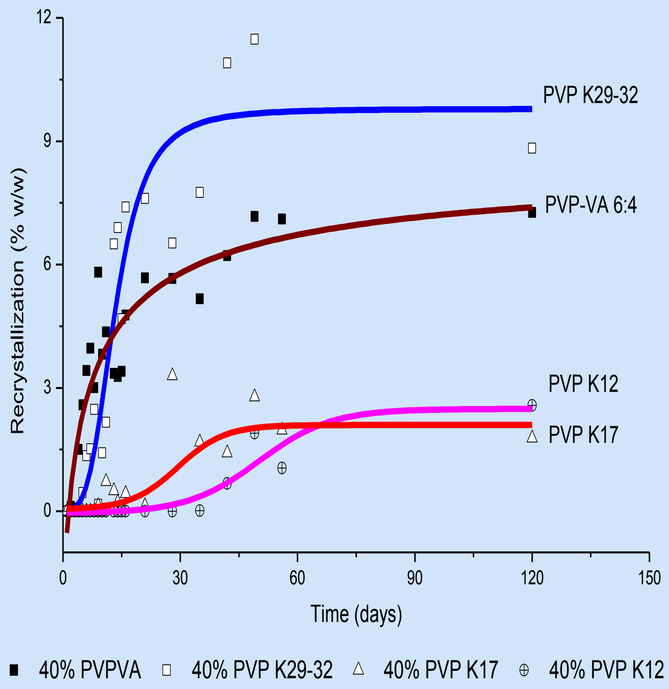

Figure 3: Recrystallization profiles of 40% hot melt extruded paracetamol formulations in different carriers for 2 months storage in 75% relative humidity at 298 K. Crystal content of the aged samples were determined from diagnostic band from FTIR-ATR at 808cm^{-1}.

Recrystallization rate increased significantly in the first 2 weeks for PVPVA 6:4 and PVP K29-32 carrier formulations (figure 3). After this period, subsequent growth rate is reduce. Interestingly, carrier with lower molecular weight i.e. PVP K12 & PVP K17 imply almost no crystal growth at the early stage. Recrystallization only occurred after 3weeks and 1 month in PVP K17 and PVP K12 carrier system respectively.

These behaviors is not parallel to that predicted from Tg and water content. However, with the exception of PVP K29-32 carrier system, they are in accordance to the anticipated Flory-Huggins interaction parameter, χ_{12}.

Therefore, it is suggested that the role of drug-polymer interaction is important in determining early stage of recrystallization. Higher water absorption and lower Tg at initial stage did not offset stabilizing effect of PVP polymer in comparison to the co-polymer PVPVA 6:4 at early stage of crystallization.

For PVP K29-32 carrier system, higher torque value were recorded during processing which is attributed by the higher melt viscosity and the processing condition at temperature below Tg and Tm of the drug and polymer. Thus, suboptimal interaction was predicted for PVP K29-32 system. This explained the lower stability profile of this system in relative to the lower grades PVP (s).

Continuous recrystallization conversely did not reveal the same trend as the early stage of crystallization. This might be attributed to the cumulative effect of interaction and water absorption as presented in figure 2a.

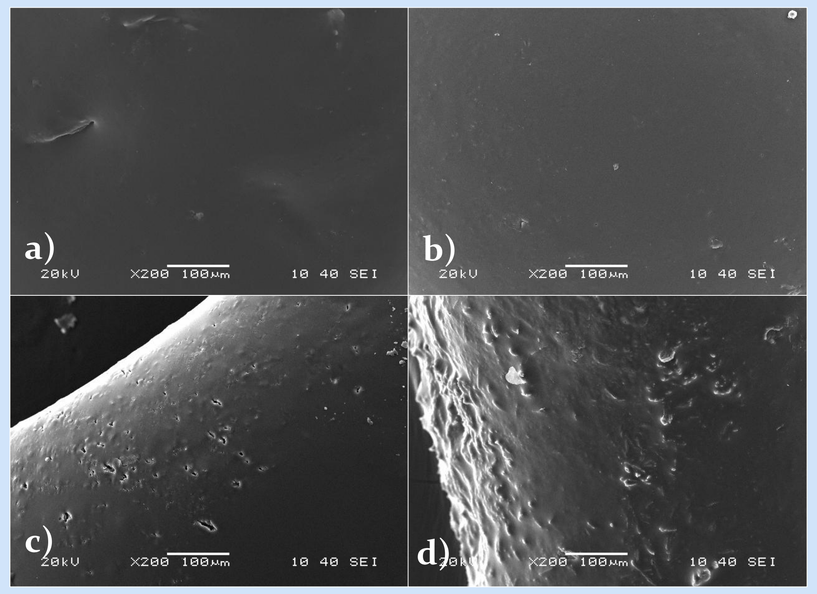

Figure 4: Surface of extrudates after 1 month storage in 75% Relative Humidity for different carrier systems, a) PVP K12, b) PVP K17, c) PVP K29-32 and d) PVPVA 6:4

4 Scanning electron microscope

SEM studies indicated surface roughness of extrudates dependence on extent of recrystallization (Figure 4). The images support FTIR-ATR results regarding the tendency of crystallization. Fresh sample showed smooth surface (data not shown). Roughness of the surface with defined crystal shape were noted clearly in aged PVPVA 6:4 carrier formulations.

To summarize, PVPVA 6:4 carrier system revealed the highest surface roughness followed by PVP K29-32 > PVP K17 >PVP K12 carrier formulations.

Conclusion

A high level of interaction between the paracetamol and PVP appears to be the critical factor in stability of HME PVP based dispersions compared to dispersions in PVPVA6:4 at early stage. This effect superseded the effect of water content and glass transition temperature. Interplay between the cumulative effects of interaction, molecular mobility and processing condition dictate the subsequent extent of the crystallization. Apart from that , processing condition of HME formulations had pertinent repercussion on storage stability of the prepared solid dispersion. It should be borne in mind that, lower MW of PVP polymer allowed higher flowability and mobility of the molten within the extruder and consequently, better drug-polymer interaction. This is one of the key consideration for stability enhancement of solid dispersion.

Acknowledgement

The financial assistance from University of Sains Malaysia is gratefully acknowledged. We would like to thank Richard Storey (Astra Zeneca) for his input and assistance.

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An investigation into using drug-polymer interactions to improve processibility of PVP K29-32 based hot melt extruded solid dispersions

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Introduction

Hot melt extrusion (HME) has attracted considerable attention in the preparation of solid dispersion formulations. In order to successfully extrude a polymer based material, the essential processing criterion is often that the extrusion temperature is higher than the Tg/Tm of the polymer. A high processing temperature is often not favourable as heat induced degradation may occur in many polymer and drug systems. Currently there are few pharmaceutical polymers that are suitable for hot melt extrusion processes as the Tg(s) of many pharmaceutical polymers are too high to be extruded at sensible temperatures. In this study we used model drug molecules as plasticizers to improve the extrudability of the model polymer, PVP.

Materials and Methods

Paracetamol and caffeine were used as model drugs. The stock of Paracetamol (Form I monoclinic polymorph) was from Rhodia Organique, France. Whereas caffeine (98.5%) was obtained from Acros Organics (Geel,. Belgium). Polyvinylpyrrolidone grade of K29/32 with average molecular weight of 58000 was received from International Specialty Products (ISP). Modulated Differential Scanning Calorimetry (MTDSC), Hot Stage Microscopy (HSM), Thermogravimetric Analysis (TGA), Fourier Transform Infrared (FTIR) and X-Ray Powder Diffraction (XRPD) were used for characterisation of the HME products obtained and also the physical mixture counterpart.

Results and Discussion

1 Hot stage Microscopy

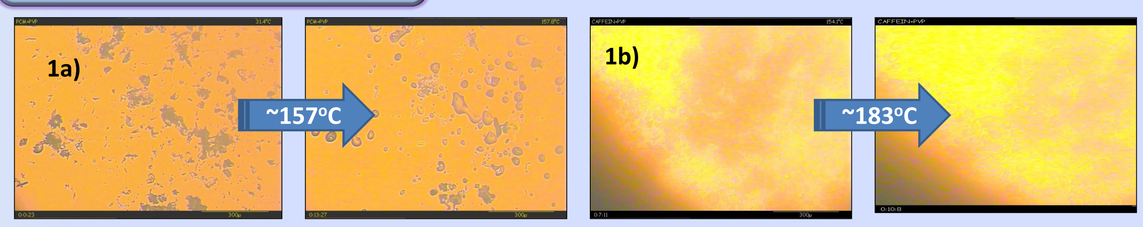

Figure 1a) Physical Mixture of Paracetamol + PVPK29-32, 1b) Physical Mixture of Caffeine + PVPK29-32

Physical mixtures were observed under temperature control of hot stage microscopy with the ramp of 10ºC per minute. The captured HSM screens showed lower melting point temperature of both paracetamol and caffeine in the presence of PVP K29-32 as shown in figures 1a) and 1b).

2 Thermogravimetric Analysis (TGA)

TGA was used to investigate the degradation temperature of raw materials. Then, extrusion of the materials at temperature below the degradation of both polymer and drug was attempted.

The high viscosity of PVP is recognized to have great stability effect on inhibition of recrystallization. However, PVP is classified into class IV hygroscopic material[1], this characteristic could impair its ability on crystal inhibition via mobility enhancement.

TGA results displayed less water content in extrudates as compared to the corresponding physical mixtures. This is ascribed to the hot process in HME that leads to water evaporation during the process. This might maintained PVP's stabilizing ability.

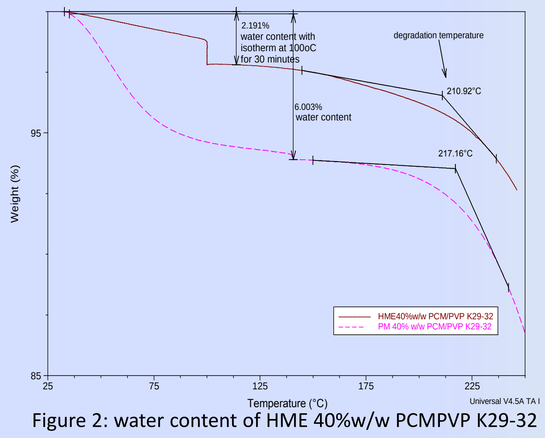

Figure 2: water content of HME 40%w/w PCMPVP K29-32 in comparison with physical mixture determined by TGA

3 MTDSC

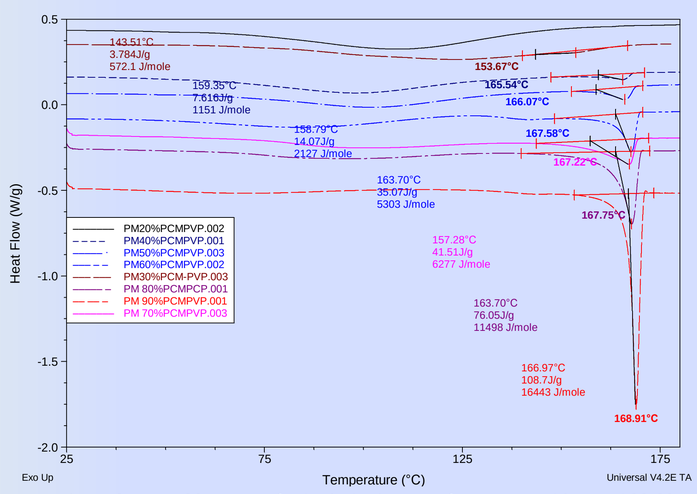

Figure 3a: MTDSC curves of physical mixtures of paracetamol in PVP k29-32 ranging from 20%w/w drug loading to 70%w/w loading.

In addition to HSM, melting point depression could also be quantified from scanning the physical mixture in MTDSC. It is well-known that the melting point depression might be due to the pronounce interaction between the drug and the polymers[2].

Hydrogen bonds between paracetamol and PVP K29-32 played a role. The heat of fusion and onset of the melting decrease accordingly with loading of polymer (figure on the left). With this in mind, physical mixtures were extruded in co-rotating twin screw extruder at a lower temperature, i.e. 120ºC.

Torque value of the extrusion was shown in figure 3b. The reduction in torque vales was due to plasticizing of polymer by the drug. At 60%w/w, when drug is in excess, there is no further reduction in torque .

Scanning of HME extrudates in MTDSC showed single Tg in between the Tg of pure paracetamol and PVP K29-32 respectively. The decreased Tg(s) , in parallel to torque reduction, delineated plasticizing effect of paracetamol toward PVP K29-32. Besides, the measured Tg (s) were lowered than the predicted values from Gordon Taylor equation (figure 3c). This is due to the small molar volume of drug substances that could diffond within the polymer chain and lead to higher free volume and thus lower in glass transition temperature[3]. Entropy associated mixing might also be a possible factor for the ideal deviation[4]. No melting endotherm was detected up to 50%w/w of drug loading.

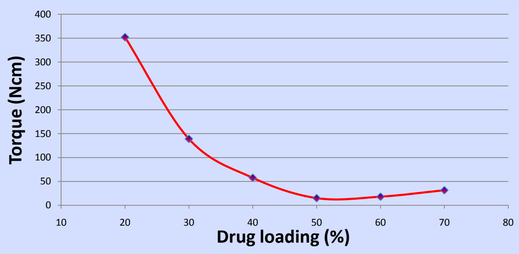

Figure 3b: Torque values of HME Paracetamol in PVP K29-32 with loading from 20%w/w to 70%w/w

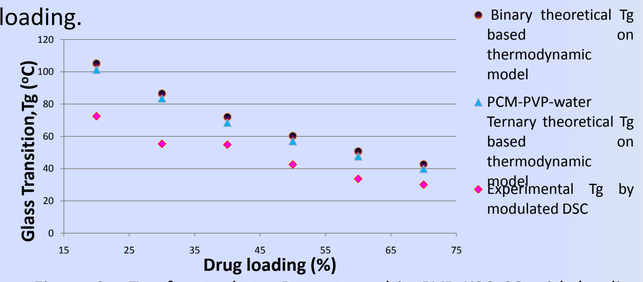

Figure 3c: Tg of extrudates Paracetamol in PVP K29-32 with loading from 20%w/w to 70%w/w versus theoretical values

However, MTDSC of HME 10 % w/w caffeine in PVP K29-32 showed recrystallization bump at around 90ºC, an endothermic transition temperature at ≈150ºC and finally small melting peak at ≈ 210ºC. These observation are in consistent to the conversion of Form I caffeine to Form II crystal , transition of Form II back to Form I at higher temperature .

4 FTIR

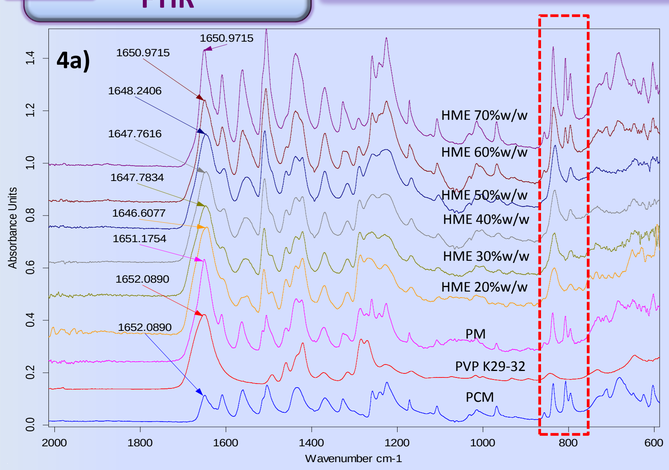

Figure 4a: Infrared spectra of of Paracetamol in PVPK29-32

Paracetamol in PVP K29-32

Physical mixture showed added infrared spectra of the pure components (figure 4a). HME product revealed broadening in infrared bands. This is attributed to the formation of amorphous material within the PVP polymer. Besides, there are shifted bands in carbonyl stretching to lower frequency. This indicated interaction involved for these functional groups. Thus, there is greater interaction of these components in HME as compare to its physical mixtures.

Doublet bands around 800-850cm^{-1} (rectangular doted line) indicating ring puckering of aromatic structure in PCM. The relative intensity of the doublet band increase with drug loading (from 20%w/w to 50%w/w). This indicated ability of PVPK29/32 in maintaining disordering of amorphous PCM .

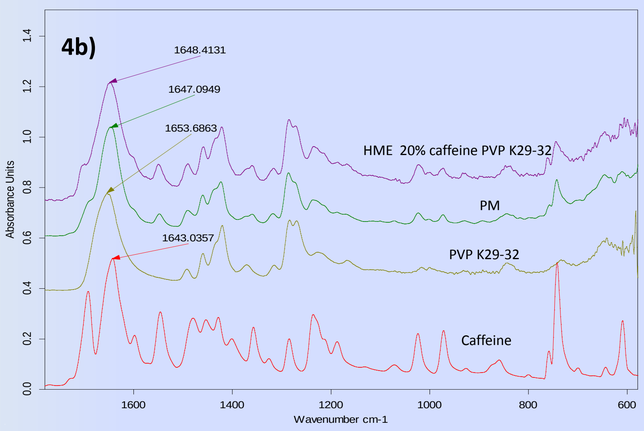

Figure 4b: infrared spectra caffeine in PVPK29-32

Caffeine in PVP K29-32

On the other hand, no apparent shift in carbonyl stretching was seen in HME caffeine with PVP K29-32 as compare to the pure components as well as physical mixtures (figure 4b). This exhibited limited interaction through this functional groups.

At region 3200cm^{-1} to 3500cm^{-1}, intensity of NH stretching reduced in both HME extrudate of caffeine and paracetamol sample relative to corresponding physical mixtures. This is compatible to TGA result in which HME sample possessed less adsorbed water.

5 XRPD

XRPD displayed halo pattern of HME paracetamol in PVP K29-32 up to 50%w/w drug loading (figure 5a). This result is in agreement with FTIR where the characteristic bands started to appear from 60%w/w drug loading.

Direct cooling of the extrudate to room temperature allow the molten material to vitrify without crystallization. It was believed that 50%w/w of loading is the maximum accommodation of PCM to be molecularly dispersed in PVP K29-32 in order to get solid solution. Above this amount, drug exist is in surplus.

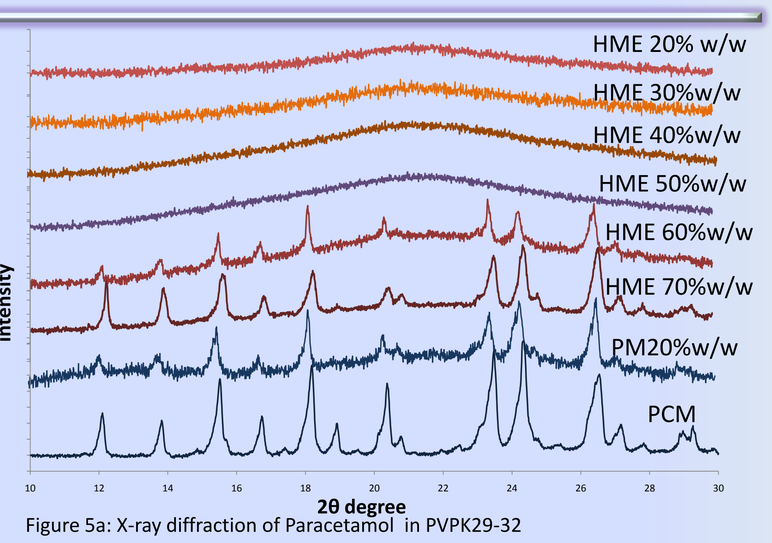

Figure 5a: X-ray diffraction of Paracetamol in PVPK29-32

For the extrudates of caffeine in PVP K29-32, Bragg diffraction peaks of Form I crystal was noted in X-ray powder diffraction (Figure 5b). In contrast with result from MTDSC, HME 10%w/w caffeine in PVP K29-32 revealed halo pattern in which delineated amorphous product. This overestimation could explained the limited sensitivity of X-ray in comparison to modulated DSC. In extrudates, caffeine exist as small crystal in PVP polymers even with low drug loading. Limited interaction of caffeine with PVP is the factor for inability of amorphous production.

It is known that Form I Caffeine is a metastable polymorph, only stable at high temperature, T>140ºC. Since it will transform gradually (months) into Form II at room temperature[5], so the formation of Form I Caffeine by HME process provides another ramification for its stability study.

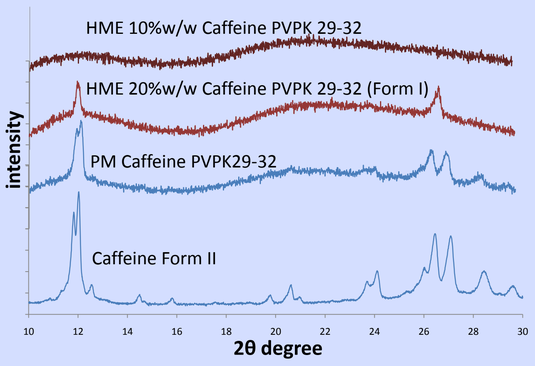

Figure 5b: X-ray diffraction of Caffeine in PVPK29-32

Conclusions

The study suggested that melting point depression of drug in the presence of PVP could be manipulated for improving processibility of PVP in HME formulations. The presence of the drug compound in the extruder promotes softening of PVP and this process facilitates the mixing process of the drug and polymer within the hot barrel of the extruder. After intimate mixing, plasticizing effect of the drug taken place and this lead to higher extrudability of the mixture without degradation of the polymer.

Stronger interaction, e.g. hydrogen bonding, in paracetamol and PVP could contribute to production of solid solution as compare to limited interaction compound such as caffeine that showed crystalline drug even in low drug loading.

Acknowledgements

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Enhanced dissolution of hot melt extruded naproxen-PVPVA 6:4 solid dispersions containing a non-ionic surfactant

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1. Introduction

Solid dispersion technology is often used for formulating poorly water-soluble compounds to enhance dissolution. However, the physical stability of solid dispersions is still poorly understood, which has lead to a very limited number of solid dispersion based products being available commercially. Besides the concern of physical stability upon storage, drug recrystallisation during dissolution has also been noted in our previous studies. Supersaturation of the drug upon exposure to the dissolution media often can leads to drug recrystallisation, which retard drug release from solid dispersion formulations.

In this work, Tween 80, a non-ionic surfactant was incorporated into HME binary dispersion of Naproxen-PVPVA in order to reduce/prevent the drug recrystallisation and enhance drug dissolution.

2. Material and Methods

Naproxen was used as a model of poorly soluble drug and PVPVA 6:4 as a hydrophilic carrier. The solid dispersion of 30 %w/w naproxen in PVPVA 6:4 or PVPVA 6:4 +Tween 80 were prepared by hot melt extrusion (HME) at 150^{o}C. The physical mixtures of Naproxen and PVPVA were prepared by simple mixing using a mortar and pestle.

Fresh extrudates were tested by DSC, XRPD and ATR-FTIR. Dissolution tests of the milled extrudate, with particle size 63-106µm were carried out in 900ml 0.1 M HCl at 37 ^{o}C and 50 rpm. Polarised light microscope (PLM) and real-time ATR-FTIR were used to investigate the onset of drug recrystallisation in milled extrudate particles upon dissolution medium. After 2 minutes of dissolution, the particles suspension within the dissolution bath were collected and the size of the undissolved extrudate particles were measured using a X-ray diffraction particle size analyzer.

3. Results and discussions

a) Production of Amorphous solid dispersion

XRPD showed a halo pattern for all the tested formulations. This is in good agreement with the DSC results indicating that amorphous solid dispersions were obtained (Figure 1).

There are apparent changes in glass transition temperatures of formulations with the addition of Tween 80. The T_g was lowered slightly (8°C) in the formulation with 2% Tween, and significant reduction (28°C) is noted in formulation with 10% Tween 80. The shifts of T_g to a lower temperature may have impact on the physical stability of the formulations upon storage, which is currently under investigation.

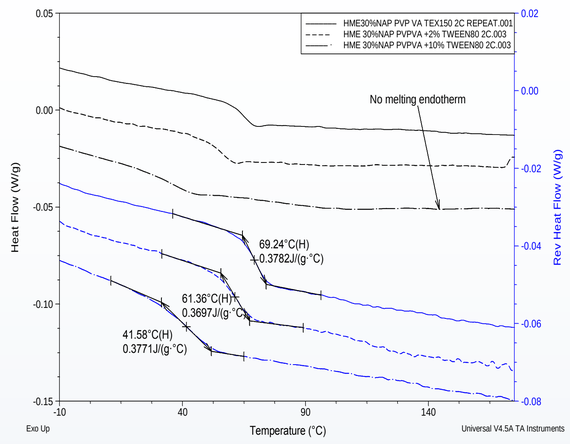

Figure 1: DSC profiles of a) HME 30% NAP PVPVA 6:4, b) HME 30% NAP PVPVA 6:4+2%Tween, c) HME 30% NAP PVPVA 6:4 10%Tween

b) Dissolution behaviour

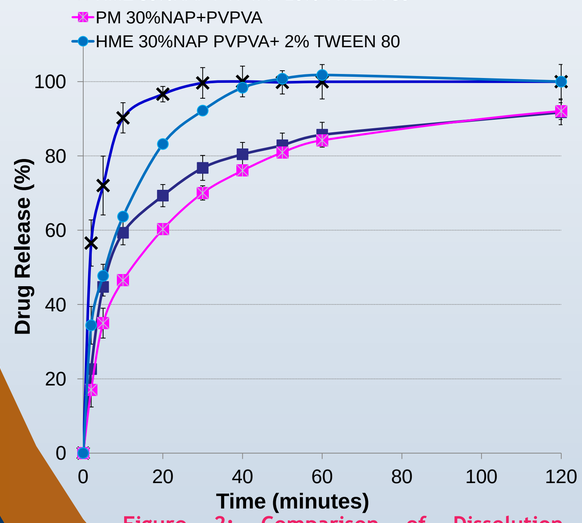

Figure 2: Comparison of Dissolution profiles of different formulations

In the HME formulations, the concentration of the added surfactant did not exceed the CMC of Tween 80 if it completely dissolved in the 900ml media. Therefore it is reasonable to assume that the solubilisation effect of Tween for Naproxen is minimal during dissolution. The solid dispersion with Tween 80 shows a faster dissolution profile than the dispersion without surfactant and the physical mixtures (Figure 2). With increasing the Tween 80 concentration in the formulation, the dissolution rate of the drug can be enhanced dramatically. The underlining mechanism of this enhancement is being further investigated.

c) Drug recrystallization upon exposure to dissolution media

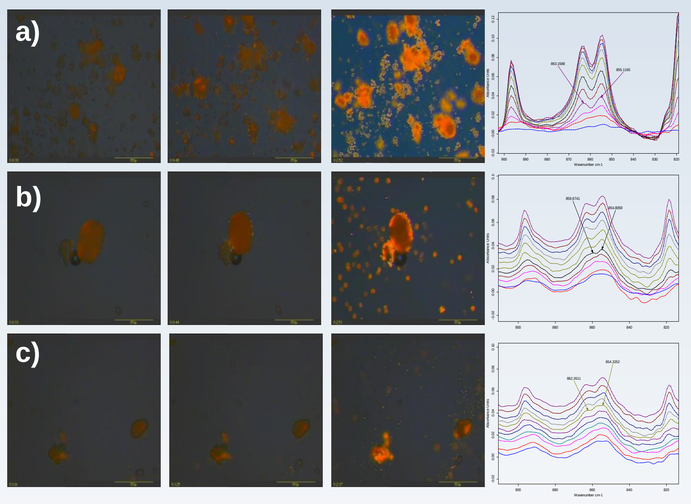

Figure 3: Microscope images and FTIR ATR spectra of (horizontally) a) HME 30% NAP PVPVA 6:4, b) HME 30% NAP PVPVA 6:4+2%Tween, c) HME 30% NAP PVPVA 6:4 10%Tween upon contact to dissolution medium with time

A few milled extrudate particles were exposed to 1-2 drops of dissolution medium, and the dynamic changes were studied using PLM and ATR-FTIR. Crystalline material will show birefringence under polarized light. The extrudates without surfactant reveal birefringence after 45 seconds exposure to the media (Figure 3). Similar behaviour was recorded for the formulations containing 2% Tween. However, the crystallisation onset increased to 85seconds for the formulations with 10% surfactant.

The same trends are observed in the real-time ATR-FTIR results, in which the crystalline peaks (854cm^{-1}, 862cm^{-1}) appear in the spectra when the milled product were exposed to dissolution medium. Each spectra represents a further 15 seconds of exposure to the dissolution medium. Crystalline peaks were revealed after 45seconds of medium exposure for formulations without surfactant. The crystalline peaks were revealed after 60seconds and 90 seconds for formulation with 2% and 10% Tween, respectively. This is in good agreement with the microscopic results. Thus, The significant enhancement in dissolution of the formulations with the addition of Tween 80 could be at least partially attributed to delaying the onset of recrystallisation process.

d) Particle size changes during dissolution

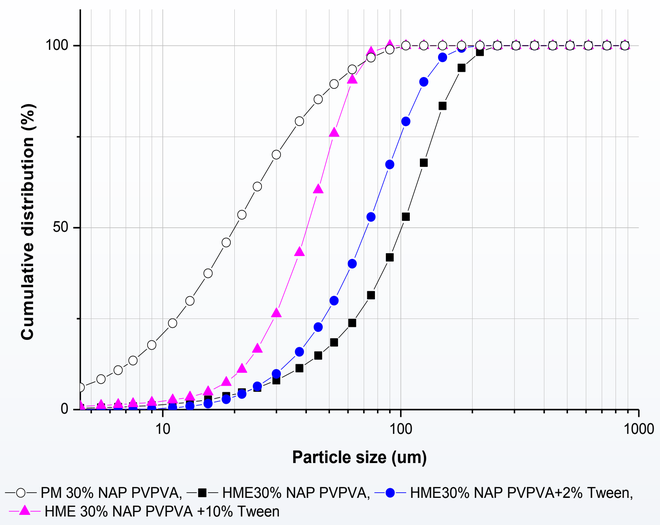

Figure 4: Cumulative curves of particle size analysis of physical mixture and solid dispersions

In order to further confirm that the reduction of drug recrystallisaiotn and improved particle wettaibility are the key mechanisms of the enhanced dissolution of the formulations containing Tween, particle size changes were studied during dissolution. The physical mixes show the smallest particle size, but broadest distribution among all tested samples (Table 1 & Figure 4).

Larger particle size is observed in the HME samples indicating agglomeration upon exposure to dissolution media. With the addition of Tween 80, the particle size during dissolution is reduced suggesting the positive effect on reducing agglomeration with the addition of Tween.

Table 1: Particle size distribution

Formulations	$D_{10\%}$	$D_{50\%}$	$D_{90\%}$	Span
PM 30% NAP PVPVA 6:4	6.31	20.01	54.51	2.41
HME 30% NAP PVPVA 6:4	34.57	101.03	170.1	1.34
HME 30% NAP PVPVA+2%Tw	30.26	72.71	128.78	1.36
HME 30% NAP PVPVA+10%Tw	20.87	40.86	65.01	1.08

Thus, the significant enhancement of dissolution rate in the formulations containing Tween is likely to be mainly a result of improved surface wetting and delayed recrystallisation onset of drug within the formulations. However, the mechanism of Tween delaying the recrystallisation onset of Naproxen in PVPVA is still unclear and under investigation.

4. Conclusion

In this study, the addition of non-ionic surfactant into hot melt extrudate of Naproxen-PVPVA 6:4 is shown to improve the surface wettability and delay the onset of recrystallization in the particles during dissolution. This study demonstrated that the incorporation of surfactants in hot melt extruded drug-polymer dispersion not only ease the processing condition [2] but also enhanced the *in vitro* performance of certain solid dispersion.

Acknowledgement

The financial assistance from University of Sains Malaysia is gratefully acknowledged.

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