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Characterization and stability of ternary solid dispersions with PVP and PHPMA

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ABSTRACT

The effect of adding a third polymer to immiscible binary solid dispersions was investigated. The model actives griseofulvin (GF), progesterone (PG) and phenindione (PD) were selected because they exemplify a key property of many poorly soluble molecules of having at least one hydrogen bonding acceptor moiety while not having any hydrogen bond donating moieties. Ternary solid dispersions of the drug, PVP (polyvinylpyrrolidone) (proton acceptor) and PHPMA (poly[2-hydroxypropyl methacrylate]) (proton acceptor and donor) were prepared by spray drying. Stability results showed that binary solid dispersions (API and PVP) of GF and PVP crystallized quickly while the amorphous form was not possible to prepare for PG and PD. The amorphous form was prolonged upon the incorporation of PHPMA in the solid dispersion (API, PHPMA and PVP). Based on measuring the melting points, the energy of mixing the drug with the polymer was calculated using the Flory–Huggins theory. The results showed that GF had the lowest free energy followed by PG and finally PD which agreed well with the stability results. These results suggest that the addition of a third polymer to immiscible binary solid dispersions can significantly improve the stability of the amorphous form.

1. Introduction

The use of solid dispersions to improve dissolution properties of poorly soluble drugs has been the focus of many studies (Chokshi et al., 2007; Okonogi and Puttipipatkhachorn, 2006; Shibata et al., 2006; Vijaya Kumar and Mishra, 2006; Yamashita et al., 2003). Improved dissolution can be achieved by particle size reduction, increased wettability through mixing with highly soluble carriers, and maintenance of the drug in the amorphous form. However, the main problem with the latter approach is that the amorphous form is thermodynamically unstable (Hilden and Morris, 2004). In certain formulations, the amorphous drug tends to recrystallize on storage, which limits the benefits of this approach. Nevertheless, specific interactions between the drug and the polymer may retard this spontaneous conversion to the crystalline form. One way this has been possible is by tailoring the non-covalent interactions between the drug and excipients, including the formation of hydrogen bonds between an electron acceptor and donor groups on the drug and the polymer (Nair et al., 2001; Tantishaiyakul et al., 1999).

Recently, we have shown that the drug can remain amorphous for significantly long periods (Al-Obaidi and Buckton, 2009). The presence of a third polymer had a minor impact on the stability of the drug in the solid dispersion where the drug could form H-bonds with both polymers. The impact of the third polymer on the amorphous form stability had to be investigated when the drug cannot form H-bonds with the second polymer. We hypothesize that the addition of a third polymer, which can act as a proton donor and acceptor can lead to improved stability of the amorphous form. As such unstable amorphous solid dispersions can be rendered stable upon the incorporation of a third polymer where the third polymer acts as linker. Ternary solid dispersions were prepared by spray-drying homogenous solutions of the drug and the two polymers. Active pharmaceutical ingredients (API) with hydrogen bonding acceptor moieties (carbonyl) were selected. The model drugs are griseofulvin (GF), progesterone (PG) and phenindione (PD) which are hydrogen bond acceptors (Fig. 1, Table 1). The hydrogen bond accepting carrier polymer is polyvinylpyrrolidone (PVP) and the linking polymer that has both hydrogen bond accepting and donating properties is poly[*N*-(2-hydroxypropyl)methacrylate] (PHPMA). The drugs were selected so they could in principle form hydrogen bonds with PHPMA but not with PVP. The PHPMA can also form hydrogen bonds with PVP (Fig. 2). Therefore, the aim of the paper is to study the influence of adding PHPMA to the API/PVP solid dispersion in terms of amorphous form stability. This can be further evaluated using Flory–Huggins theory in order to explain the mixing of the linking polymer (PHPMA) with the API. Flory–Huggins theory has been used recently to explain interactions in solid dispersions based on melting points measurements and we attempt to use the same approach to explain the interactions in the current system that lead

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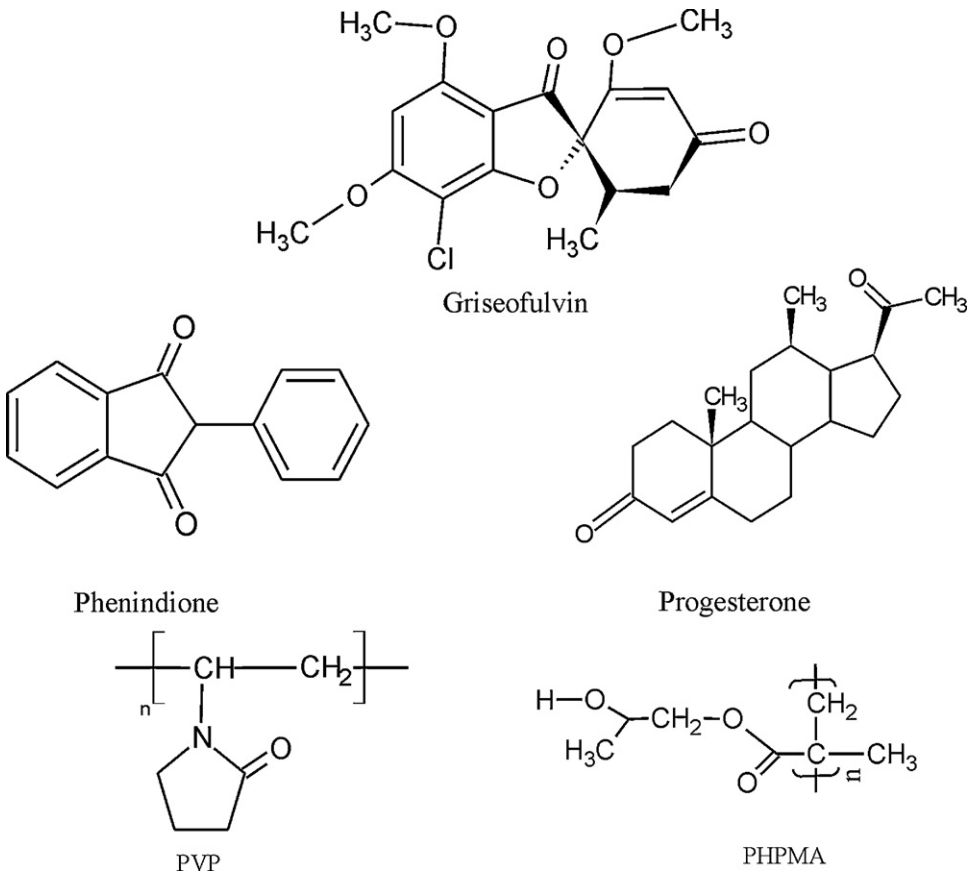

Fig. 1. The chemical structures of the model drugs and polymers used in this study.

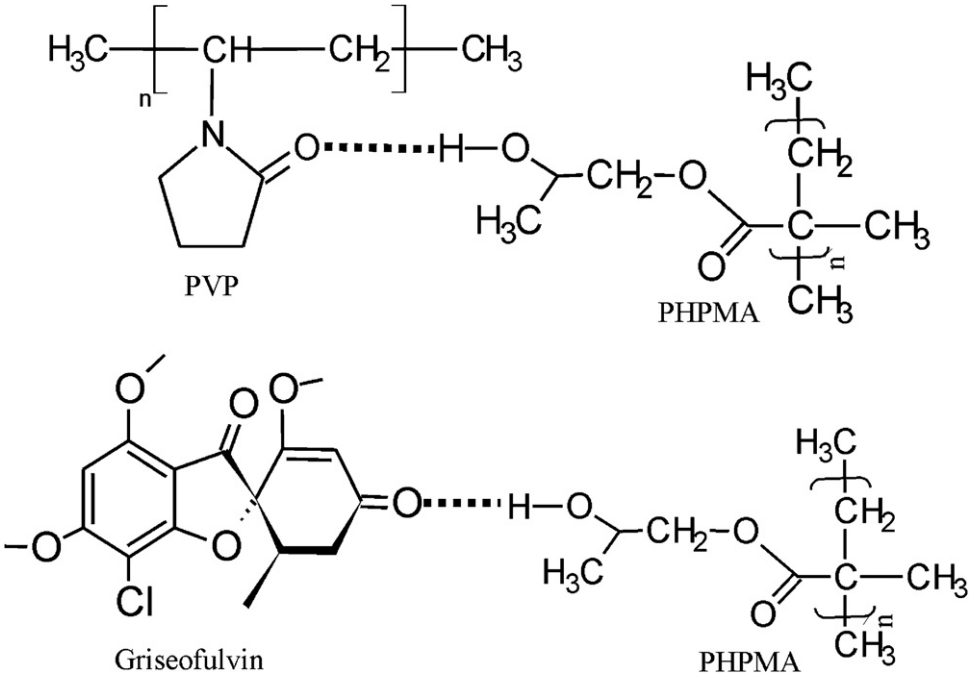

Fig. 2. Schematic showing the possible hydrogen bonding between PHPMA, PVP and griseofulvin. The dotted line indicates the expected hydrogen bond.

Table 1
The physical and chemical properties of the model drugs used in this study.

	Griseofulvin	Progesterone	Phenindione
MW (g/mol)	353	314	222
Aqueous solubility	14.2 μg/ml	10.7 μg/ml	27 μg/ml
Log *P*	2.15	4.036	2.917
T_g (onset)	89 °C	5 °C	8 °C
T_m (onset)	221 °C	129 °C	149 °C
Heat of fusion	114 J/g	83 J/g	118 J/g
Molar volume	255.1 ± 5.0 cm^3	289.7 ± 5.0 cm^3	175.7 ± 3.0 cm^3

to enhanced stability of the amorphous form (Janssens et al., 2010; Li and Chiappetta, 2008; Lin and Huang, 2010; Pajula et al., 2010).

2. Materials and methods

2.1. Materials

Griseofulvin (GF), progesterone (PG), phenindione (PD) and polyvinylpyrrolidone (PVP) (MW = 55,000) were purchased from Sigma and poly[*N*-(2-hydroxypropyl)methacrylate] (PHPMA) (MW = 20,000) was purchased from Fisher. Acetone was purchased from BDH. All chemicals were used directly without further purification.

2.2. Methods

2.2.1. Preparation of griseofulvin solid dispersions

A solid dispersion containing GF/PHPMA/PVP (50%:25%:25%) was prepared. GF (2.5 g) was added to a conical flask (500 ml) containing acetone (185 ml) and was then stirred using a magnetic stirrer for at least 3 min until completely dissolved. Distilled water (85 ml) was then poured directly followed by the addition of PHPMA (1.25 g). The mixture was allowed to dissolve for 30–45 min. Finally, PVP (1.25 g) was added to the mixture and stirred for 5 min until completely dissolved. To prepare the control binary solid dispersions with PVP or PHPMA as the only polymer, GF (2.5 g) was added to a conical flask (500 ml) containing acetone (185 ml) and was then stirred using a magnetic stirrer for at least 3 min followed by distilled water (85 ml). PVP or PHPMA (2.5 g) was added to the mixture and stirred for 5 min. The solutions were spray dried using a Niro Micro Spray Drier (Niro, Soeborg, Denmark) connected to a nitrogen generator (Domnick Hunter, Gateshead, UK). Nitrogen was used as the atomizing gas in the spray drying process. The parameters listed below were used throughout.

- Inlet temperature: 65 °C
- Outlet temperature: 45 °C
- Chamber gas flow: 25 kg/h
- Atomizer gas flow: 2.5 kg/h
- Nozzle diameter: 0.5 mm

2.3. Preparation of progesterone solid dispersions

Solid dispersions containing PG/PHPMA/PVP (40%:30%:30%) and (30%:35%:35%) were prepared. PG (1.5 or 2 g) was added to a conical flask (500 ml) containing acetone (185 ml) and was then stirred using a magnetic stirrer for at least 3 min. Distilled water (85 ml) was then added followed by the addition of PHPMA (1.5 or 1.75 g). The mixture was allowed to dissolve for 30–45 min. Finally, PVP (1.5 or 1.75 g) was added to the mixture and stirred for 5 min. The control binary solid dispersions with PVP (PG/PVP, 40%:60% and 50%:50%) were prepared by adding PG (2 or 2.5 g) to a conical flask (500 ml) containing acetone (185 ml) and was then stirred using a magnetic stirrer for at least 3 min followed by adding distilled water (85 ml). PVP (2.5 or 3 g) was added to the mixture and stirred for 5 min. The solution was spray dried using the same parameters shown above.

2.4. Preparation of phenindione solid dispersions

Solid dispersions containing PD/PHPMA/PVP (15%:42.5%:42.5%), (20%:40%:40%) and (27%:36.5%:36.5%) were prepared. PD (0.75, 1 or 1.35 g) was added to a conical flask (500 ml) containing acetone (185 ml) and was then stirred using a magnetic stirrer for at least 3 min. Distilled water (85 ml) was then added followed by the addition of PHPMA (1.825, 2 or 2.125 g). The mixture was allowed to dissolve for 30–45 min. Finally, PVP (1.825, 2 or 2.125 g) was added to the mixture and stirred for 5 min. The solution was spray dried using the same parameters shown above. Binary mixture with PVP was not prepared as the drug needed higher amounts of the polymers to remain amorphous and as explained below in the results section.

2.5. Preparation of physical mixtures

Different ratios of the API and PHPMA were weighed and mixed using a mortar and pestle. The size of the particles (physical mixtures) was controlled using sieving so that a narrow particle size distribution was chosen (40–90 μm). This step is necessary to conduct DSC studies that were needed for the application of the Flory–Huggins model. Thus, the onsets of the melting peaks obtained from DSC measurements correspond to the interaction between the API and the polymer rather than due to different particles sizes of the physical mixtures.

2.6. Measurement of the glass transition temperatures of solid dispersions

Differential scanning calorimetry (DSC 7, Perkin-Elmer, UK) was used to measure the glass transition temperature of the prepared solid dispersions. Samples (5–10 mg) were accurately weighed into aluminium pans that were hermitically crimped. A heating rate of 10 °C/min was used to measure the T_g of the solid dispersion. Quench cooled API was prepared by melting the API and immediately transfers it into liquid nitrogen. Indium was used as a calibrant which has an onset temperature of 156.6 °C.

2.7. Measurement of the melting temperature and enthalpy of fusion

Samples (5–10 mg) were accurately weighed into aluminium pans and hermitically crimped. A heating rate of 5 °C/min was used to measure the onset of the melting temperature and the enthalpy of fusion. To measure the glass transition temperature, GF samples were heated from 30 °C up to 120 °C using a heating rate of 5 °C/min. For PG and PD samples, the glass transition temperature was determined by holding the samples isothermally at −10 °C for 5 min followed by heating the samples until 120 °C at a heating rate of 5 °C/min.

Melting points measurements were performed in order to calculate the melting point onset and the heat of fusion. For each drug, the physical mixture of the drug and PHPMA was heated starting below the melt onset by 50 °C. To measure the heat of fusion, the area under the peak was calculated and the heat was obtained as the heat to the sample mass in J/g. The physical mixture of GF and PHPMA was heated at 5 °C/min. A series of scanning rates were used (1, 2, 5 and 20 °C/min) to heat the physical mixtures. This was necessary to ensure that melting of the crystalline API occurs regardless of the heating rate. If the scanning rate was fast, then the polymer would not have dissolved the crystalline API totally. This results in the appearance of a larger melting peak that does not reflect

the degree of polymer–API interactions. It was found that heating the physical mixtures using scanning rates of 1, 2 and 5 °C/min resulted in similar mixing (i.e. the melting peak was identical in shape and onset temperature). On the other hand, using scanning rate of 20 °C/min resulted in larger melting peaks that mistakenly reflect poor mixing between the API and the polymer. Therefore, heating rate of 5 °C/min was used to perform the experiments.

The mixing of a big molecule (such as a polymer) with a small molecule (such as an API) cannot be described efficiently using molar ratios. The large size of the polymer means that the volume it occupies is significantly larger than the volume occupied by the API. Hence, the use of the molar ratios may underestimate the mixing process as it underestimates the role of the polymer in the mixing. To begin to solve this problem, the molecular volumes of the drug and the polymer were used. The Flory–Huggins model divides the polymer chain into segments each having the size (volume) of the drug. The ratio between the molecular volumes of the polymer/drug (r) can be used to calculate the total number of polymer chain segments. The molecular volume of the API was calculated using ChemSketch software (ACD labs, Canada). The calculated molecular volume for GF was $255.1 \pm 5.0\,cm^3$, PG ($289.7 \pm 5.0\,cm^3$) and PD ($175.7 \pm 3.0\,cm^3$) while molecular volume of PHPMA was $19{,}870 \pm 4.0\,cm^3$ (Table 1).

2.8. Stability studies

The prepared solid dispersions were immediately stored over a supersaturated KCl salt solution (100 ml) in a desiccator to achieve a relative humidity of 85% at 25 °C. Because of the low T_g of PG and PD solid dispersions, the stability of these solid dispersions was assessed under 0% RH (stored inside dessicator filled with silica gel). The relative humidity was also verified using a digital hygrometer. The samples were regularly checked for crystalline form content.

2.9. X-ray powder diffraction (XRPD)

The X-ray powder diffraction study was performed at ambient temperature with a powder X-ray diffraction apparatus (Philips, Cambridge, UK) using CuKα radiation at 30 mA and 45 kV (scanning rate 0.5°/min), and diffraction angles (2θ) of 5–35°.

2.10. Fourier transforms infrared (FTIR)

A Nicolet Nextus 470 FTIR spectrometer (Thermo Electron Corporation, Massachusetts, USA) equipped with a KBr beam splitter was used to obtain the infrared spectra. IR spectra were obtained using an attenuated total reflectance (ATR) accessory (single reflection bounce diamond crystal; Golden Gate accessory). For each spectrum 96 scans were performed and a resolution of 4 cm was chosen.

3. Results and discussion

3.1. Characterization of the solid dispersions

Spray dried GF showed crystalline peaks as observed by XRPD (Fig. 3). Completely crystalline GF was obtained after 48 h from the time of preparation when stored at ambient conditions. This was confirmed by scanning the raw GF and the area under the peak was calculated for each peak. These were compared with the spray-dried samples to calculate the extent of crystallization. The stability of binary solid dispersions of GF and PVP was studied at room temperature and 85% RH. Because of the hygroscopic nature of amorphous materials (as a consequence of the higher internal volume) (Hilden and Morris, 2004), increased relative humidity would cause increased water uptake. The result would be a reduction

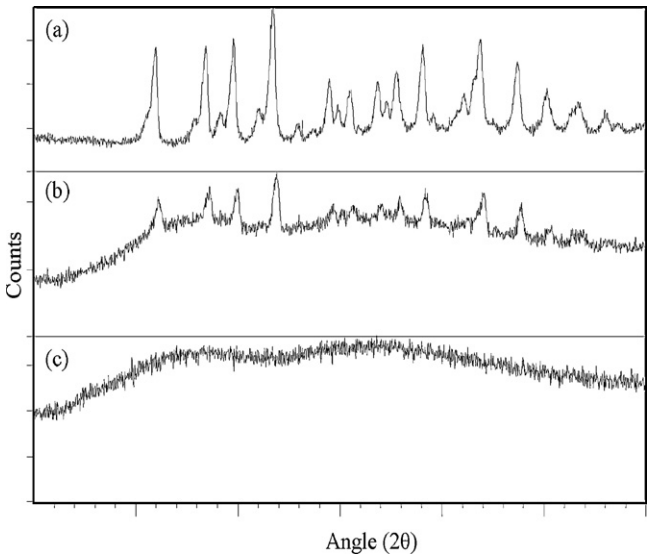

Fig. 3. The X-ray powder diffraction pattern of (a) spray dried griseofulvin after 48 h from day of preparation stored at ambient conditions, (b) griseofulvin: PVP (50%:50%) solid dispersion after 14 days from the day of preparation stored at 85% RH at room temperature and (c) griseofulvin:PHPMA:PVP (50%:25%:25%) solid dispersion after 15 weeks from the day of preparation stored at 85% RH at room temperature.

in the glass transition temperature as well as increased molecular mobility. Ultimately, crystal nuclei are formed which leads to recrystallization (Liu et al., 2006). Our results showed that crystallization started after 5–7 days from the day of preparation for GF/PVP dispersions, which agrees with previous studies (Nair et al., 2001; Vasanthavada et al., 2004).

The instability of GF in the PVP solid dispersion is due to the lack of specific non-covalent interactions between the polymer and GF (Nair et al., 2001). Both the polymer and the drug have hydrogen bond accepting moieties (e.g. carbonyl). To improve the miscibility of GF with PVP, a second polymeric component (PHPMA) was added. PHPMA has both hydrogen acceptor and donor groups hence it was anticipated that PHPMA could form hydrogen bonds with GF and PVP. A key property also being that PHPMA is miscible in PVP (Kuo et al., 2004). Consistent with this expectation, the XRPD results showed that the ternary solid amorphous dispersion remains in the amorphous form for longer than the binary solid dispersion prepared from GF and PVP stored at the same conditions (RH 85% and ambient temperature) (Fig. 3).

To study the effect of incorporating PVP (which cannot form hydrogen bonds with PG) the binary solid dispersion of PG and PVP was then studied. The results showed that the PG/PVP solid dispersion was partially crystalline as distinct peaks in the XRPD scan were observed (Fig. 4). The ratio of PG/PVP was decreased in order to decrease the chance of crystal growth. However, the XRPD scan indicated the presence of crystallinity which showed that preparation of amorphous PG was not possible at ratios of 40% and 50% of this API with PVP.

When PHPMA was added (which can in principle form hydrogen bonds with PG and PVP) to the PG/PVP solid dispersion, an amorphous solid dispersion was obtained. The solid dispersion of PG/PHPMA/PVP (40%:30%:30%) showed that the drug could be made amorphous by the incorporation of 30% PHPMA in the solid dispersion (Fig. 4). The same result was confirmed by increasing the ratio of the polymers in the solid dispersion (35% PHPMA and 35% PVP) which was amorphous. These observations suggest that the hydrogen bond accepting and donating properties PHPMA can participate in solubilising the hydrogen bond accepting PG and PVP.

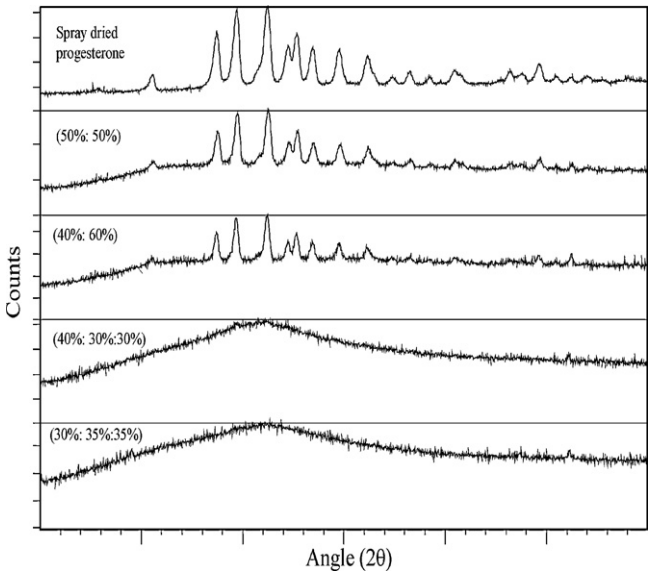

Fig. 4. The X-ray powder diffraction pattern of spray dried progesterone and solid dispersions of (progesterone, PVP) and (progesterone, PHPMA and PVP). The ratios shown indicate the ratio of each component in the dispersion.

When PD was used, considerable crystallinity was detected (XRPD scans, Fig. 5) even when spray dried with PHPMA and PVP. The crystallinity of PD was also evident even when the ratio of the polymers in the solid dispersion was increased to 73% of the solid dispersion. Upon further increasing the ratio of the polymers (PHPMA and PVP) in the solid dispersion (80% of the solid dispersion) it was possible to dissolve the crystalline content of PD and obtain an amorphous solid dispersion which was confirmed by the absence of crystalline peaks. As the preparation of amorphous solid dispersions of PD were only possible at higher ratios of the polymer (80% and 85% of the solid dispersion), comparison with the binary solid dispersion of PD/PVP becomes unnecessary. This is because PVP cannot form hydrogen bonds with PD (since both PD and PVP are hydrogen bond acceptors). Therefore, PHPMA has to be included in the solid dispersion to obtain amorphous PD.

3.2. FTIR studies

FTIR was used to examine the possible formation of hydrogen bonds between the API and the polymer (Jun et al., 2005; Nair et al., 2001; Zahedi and Lee, 2007). FTIR spectra showed that PHPMA has peaks at 1722 and 1710 cm^{-1} (Fig. 6). The first peak is assigned to the free carbonyl group while the second peak refers to the bound carbonyl group to the hydroxyl group of PHPMA (intramolecular hydrogen bonding; Kuo et al., 2004). GF has two peaks in this region, the first peak (1712 cm^{-1}) corresponds to the stretching of the carbonyl group of the benzofuran and the second peak (1662 cm^{-1}) corresponds to the stretching of the carbonyl group of cyclohexene (Nair et al., 2001). PVP has a single peak in this region (1656 cm^{-1}) which represents the stretching of the carbonyl in the amide group. There is a shoulder on the PVP peak which we believe can be due to the hygroscopic nature of PVP, hence it was expected that the polymer can also form a hydrogen bond with water.

The hydrogen bonding potential in GF and PHPMA solid dispersions was then studied. The first peak of GF (which was originally at 1712 cm^{-1}) has broadened and a shoulder could be seen at 1697 cm^{-1}. This represents the shifting of the peak as it is bound to the hydroxyl group of PHPMA. Changes in the second carbonyl group (1662 cm^{-1}) in GF were also observed. The peak which is at 1662 cm^{-1} significantly shifted to 1649 cm^{-1} in the dispersion. This suggested that GF also interacted with PHPMA, presumably by hydrogen bonds. Similar trend in the carbonyl groups peaks of GF could be seen in the ternary solid dispersion. The non-covalent interactions between PHPMA and PVP have previously been studied by FTIR and have been shown to be significant (Kuo et al., 2004). Therefore interactions between PHPMA and PVP are also possible in the ternary solid dispersions that we prepared. The addition of PVP to the solid dispersion was necessary to improve the dissolution and wettability properties of the drug.

The FTIR scan of crystalline PG showed two carbonyl stretches at 1668 and 1707 cm^{-1} (Fig. 7). Evidence for hydrogen bonding between PHPMA and PG was observed from the FTIR spectrum. The peak at 1707 cm^{-1} shifted to 1699 cm^{-1} which may result from a hydrogen bond formed between the carbonyl on the acetyl group in PG with the hydroxyl group on PHPMA. The peak broadened and divided into two separate peaks at higher ratios of PHPMA in the solid dispersion. These two peaks corresponded to the free and hydrogen bonded carbonyl groups. The ratio of the bound carbonyl of PG could be clearly seen to increase (in intensity) in relation to the free carbonyl group. This was consistent with increasing amounts of PG interacting with PHPMA. This trend can be clearly seen in the binary mixture of PG and PHPMA where broadening and shift in the carbonyl peaks can be seen. In the ternary solid dispersion, the second peak at 1668 cm^{-1} could not be analyzed because it overlapped with the carbonyl group of PVP, therefore determination of

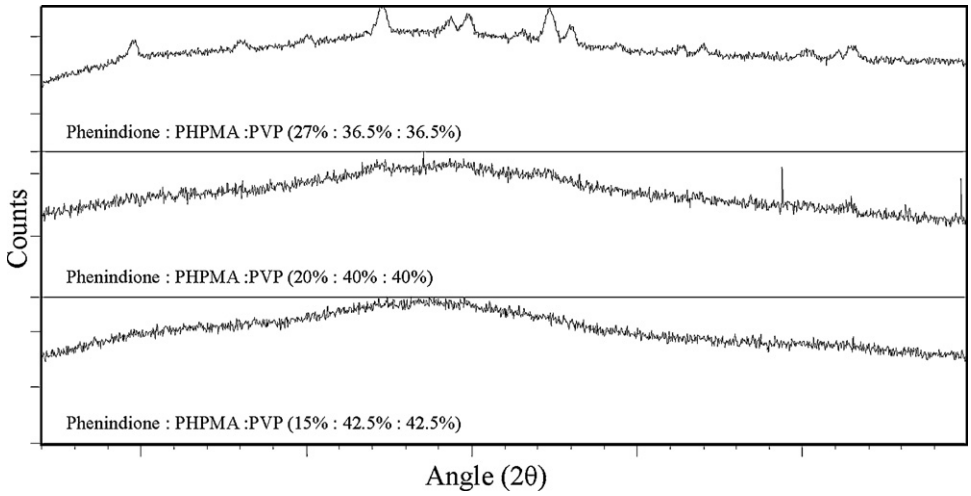

Fig. 5. The X-ray powder diffraction pattern of solid dispersions of (phenindione, PHPMA and PVP). The ratios shown indicate the ratio of each component in the dispersion.

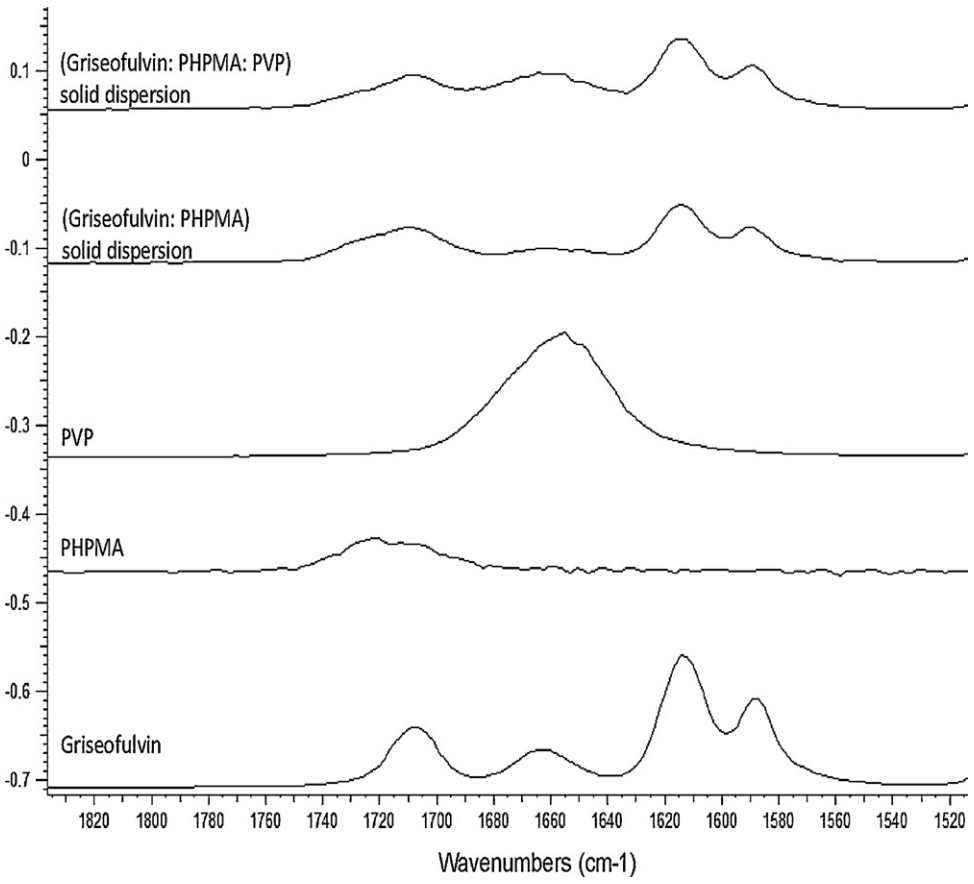

Fig. 6. Fourier transform infrared scans showing the infrared absorption of griseofulvin, PHPMA, PVP and solid dispersions of griseofulvin, PHPMA (50%:50%) and griseofulvin, PHPMA and PVP (50%:25%:25%).

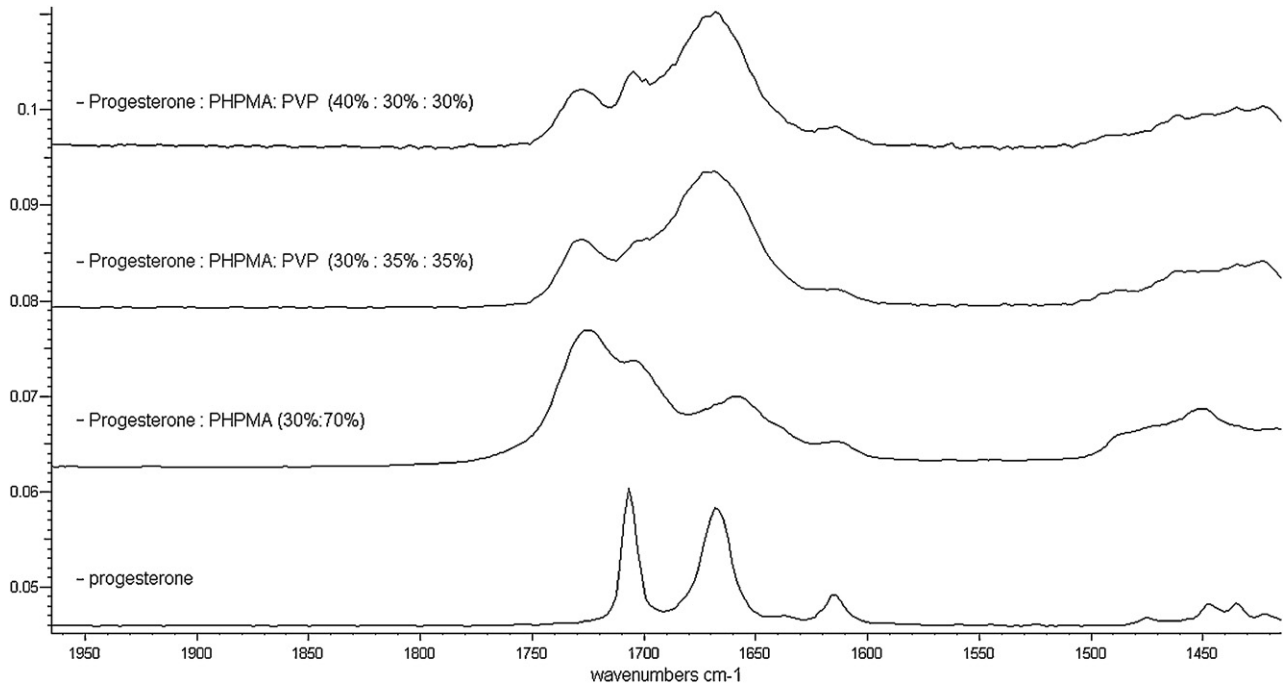

Fig. 7. Fourier transform infrared scans showing the infrared absorption of crystalline progesterone and solid dispersions of progesterone, PHPMA and PVP.

the any possible interaction was not possible using this peak. Peaks in PD mixtures overlapped hence were not considered for possible H-bond formation (data not shown).

3.3. Melting point depression

The measurement of the melting point depression of the drug in the drug/carrier physical mixture was used to calculate the Flory–Huggins interaction parameter. Flory–Huggins model can potentially be used to examine the interactions between different polymers or to explain the interaction between a polymer and a low molecular weight molecule (Jawalkar et al., 2007; Jeong et al., 2006). In our system, PHPMA acts as a bridging solubilising polymer to improve the miscibility of the API within the blend with PVP. Therefore it is hypothesized that the Flory–Huggins model could be used to predict the interactions between each of the three APIs with PHPMA. The purpose was to obtain information about the degree of interaction of the hydrogen bonding accepting API with the hydrogen bond donating polymer (PHPMA). Determining the Flory–Huggins interaction parameter allows us to calculate the free energy of mixing, which can describe how favorable is the mixing of the drug with the polymer.

Upon mixing, drug and polymer molecules come into contact and the number of these contacts is estimated to be a measure of their interaction. To count for these contacts, a value that sums polymer–drug interactions is experimentally determined. This value is known as the Flory–Huggins interaction parameter (χ) and can be calculated by measurement of the drug melting point depression in the drug–polymer physical mixture (Fried, 2003). When heating the physical mixture above the T_g of the polymer, the polymer will be in the rubbery state hence it can act as a solvent for the drug (Marsac et al., 2009). The drug will be dissolved to a certain extent depending on its affinity towards the polymer. The crystalline drug will turn into its amorphous form as the polymer continues to dissolve it. Once the melting point of the drug is reached, the crystalline part of the drug, which has not been dissolved by the polymer, melts and a melting peak can be seen at lower temperatures (melting point depression). An ideal solvent (polymer) will dissolve the drug totally and no melting peak will be detected.

The DSC results showed that the melting point onset decreased with increasing the polymer fraction in the mixture (Fig. 8). The melting point decreased from 219 °C for crystalline GF to 194 °C for the physical mixture containing 90% (v/v) PHPMA. For PG, a shift in the melting point onset was also observed. The melting point decreased from 129 °C for crystalline PG to 118 °C for the physical mixture containing about 90% (v/v) PHPMA. For PD, the melting point decreased very slightly with the incorporation of PHPMA in the solid dispersion.

A similar approach was used where the interaction between nifedipine and felodipine with PVP was predicted (Marsac et al., 2006). Using the same methodology, the interaction parameters were calculated using the measured melting points and were found to be: 0.40 for GF, 0.77 for PG and 1.08 for PD. Based on the measured melting point depression and the calculated Flory–Huggins parameters, the energy of mixing was calculated. The results indicated that the three model APIs had a negative free energy of mixing (Fig. 9). Negative free energy indicates that the mixing of the API is associated with a net decrease in the energy of the mixture formed. In other words, the interaction between the API and the polymer results in a more stable state. This is a key factor to determine if the API is miscible with the polymer. GF showed the lowest free energy of mixing. PG had a lower free energy of mixing than PD at lower ratios of PHPMA; however at higher ratios PD showed a lower free energy of mixing. A minimum could be seen for each of the three APIs, which represents the maximum miscibility of the API with the

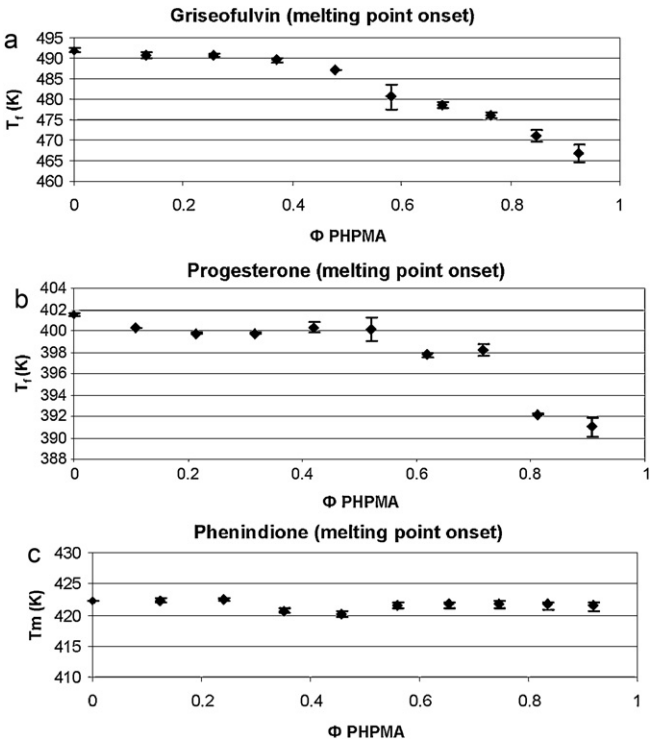

Fig. 8. The melting points of griseofulvin (a), progesterone (b) and phenindione (c) in the physical mixture with PHPMA.

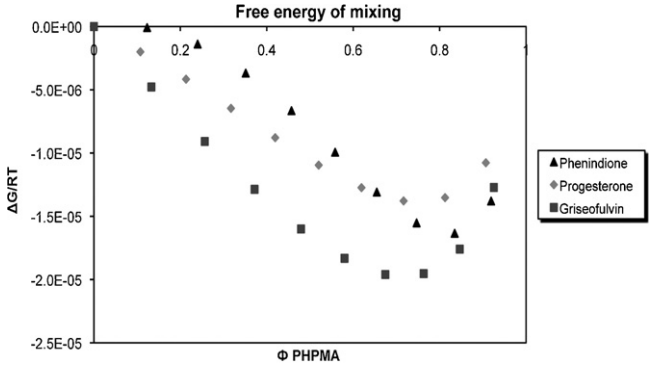

Fig. 9. The calculated free energy of mixing for the three model drugs using Flory–Huggins theory.

polymer. GF had a minimum at about 65% (v/v) of PHPMA while PG showed a minimum at 70% of the polymer. PD showed a minimum at about 85% (v/v) of PHPMA. These results correlate with the stability data and thus conclude that the order of hydrogen bonding and miscibility of each of the APIs with PHPMA is GF > PG > PD. Because of the degradation of PVP when heated, the free energy of mixing PVP with API could not be obtained. Since PHPMA is the bridging polymer, interaction with the API is the key step for increased stability of the amorphous form. This is because it is already known that PHPMA is miscible with PVP. Hence, free energy of mixing sequence (GF > PG > PD) with PHPMA can adequately describe the stability of the ternary solid dispersion including PVP.

4. Conclusions

The use of tailored ternary solid dispersions may be utilized to prolong the presence of the amorphous form of hydrophobic APIs. The stability of the amorphous drug in immiscible binary solid dispersion can be significantly improved via the incorporation of a

bridging polymer, which can form H-bonds with the API, and the second polymer. The interaction between the API and the polymer can be studied using Flory–Huggins model, which could well explain these interactions.

Conflict of interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2011.06.052.

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