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RESEARCH ARTICLE

Lyophilization monophase solution technique for preparation of amorphous flutamide dispersions

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Abstract

Flutamide (FLT) is a poorly soluble anticancer drug. Therefore, lyophilized dispersions (LDs) of FLT with polyvinylpyrrolidone (PVP) K30, polyethylene glycol (PEG) 6000, and pluronic F127 were prepared via lyophilization monophase solution technique with the aim of increasing its dissolution rate. FLT showed an A_L-type phase solubility diagrams with PVP and PEG, whereas A_N-type diagram was obtained with pluronic. The amount of residual tertiary butyl alcohol, determined by gas chromatography, was 0.015–0.021% w/w. Differential scanning calorimetry and X-ray diffractometry revealed that FLT–polymer 1:1 LDs were partially amorphous, whereas the 1:3 and 1:5 LDs were completely amorphous. After 6 months storage, polymers under study inhibited FLT recrystallization maintaining its amorphous form. The particle size of FLT–polymer LDs was between 0.81 and 2.13 μm, with a high surface area (268.43–510.82 m^2/g) and porosity (354.01–676.23 e^{-3} mL/g). Also, the poor flow properties of FLT could be improved but to a limited extent. FLT dissolution was significantly enhanced with the fastest dissolution that was achieved using pluronic. After 30 min, about 66.52%, 78.23%, and 81.64% of FLT was dissolved from 1:5 FLT–PVP, PEG, and pluronic LDs, respectively, compared with only 13.45% of FLT. These data suggest that these polymers might be useful adjuncts in preparation and stabilization of amorphous immediate-release FLT LDs.

Keywords: Lyophilization monophase solution, amorphous dispersions, particle size, surface area and porosity, physical stability

Introduction

Many approaches have been developed to improve the solubility and enhance the dissolution rate and oral bioavailability of poorly soluble drugs, for example, salt formation, solid dispersion, inclusion complex, microemulsion, and micronization. Among the many methods available to improve bioavailability, formulation of amorphous solid dispersions and solid solutions has gained enormous attention (Sekiguchi and Obi, 1961; Goldberg et al., 1965).

An amorphous solid often exhibits a higher solubility than a crystalline solid. Countless studies have illustrated the advantages of formulating drugs in the amorphous form for the enhancement of dissolution and bioavailability of poorly soluble drugs (Yu, 2001). Polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) are commonly used carriers in the formulation of solid dispersions. The molecular size of both polymers favors the formation of interstitial solid solutions (Van den Mooter et al., 1998). Additionally, water-soluble amphiphilic surfactant–polymers have been widely used to prevent drug precipitation and increase the aqueous solubility of poorly water-soluble drugs (Rouchotas et al., 2000).

Flutamide (FLT) is the only one of the nonsteroidal antiandrogens presently recommended for monotherapy of prostatic carcinoma. However, its poor water solubility can give rise for both formulation problems and low or variable bioavailability (Zhong et al., 2000). In our previous study, FLT complexes with cyclodextrins have been prepared via lyophilization monophase solution technique with the dissolution rate of FLT that was significantly enhanced (Elgindy et al., 2010). On the other hand, few investigations aimed to improve FLT

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dissolution properties by formulation of solid dispersions via solvent evaporation method (Adel et al., 1997). However, due to their toxicity, the use of solvents is unacceptable and impractical because the amount of residual solvent present after drying has to be below the detection limits (Kushida et al., 2002). Moreover, during removal of solvents, phase separation, for example, crystallization of the lipophilic drug is commonly encountered (Martínez-Ohárriz et al., 1999).

Therefore, lyophilization monophase solution technique was developed as a suitable alternative procedure that could overcome the above-mentioned demerits of the conventional solvent method. In this technique, TBA/water cosolvent system was used to dissolve both the hydrophobic drug and hydrophilic carrier simultaneously (Teagarden and Baker, 2002; Van Drooge et al., 2004; Wang et al., 2006).

Although the use of solid dispersions has been reported frequently in the pharmaceutical literature, only few solid dispersion systems are used commercially. The main reason for this discrepancy is the possible physical instability of these structures that can be metastable. Conversion from the amorphous (metastable) to the crystalline state during storage inevitably results in decreased solubility and dissolution rate. However, the presence of a hydrophilic polymer is often adequate to prevent recrystallization (Leuner and Dressman, 2000).

Therefore, the present study was undertaken to prepare physically stable amorphous FLT dispersions with hydrophilic polymers (PVP K30, PEG 6000, and pluronic F127) via lyophilization monophase solution technique. The aim was also extended to evaluate the influence of these hydrophilic polymers on the flow properties of FLT and also on various physicochemical properties of FLT lyophilized dispersions (LDs) that may contribute to enhancement of the drug dissolution, for example, particle size, surface area, and porosity.

Materials and methods

Materials

FLT was kindly donated by Archimica (Origgio, Italy). Polyvinyl pyrrolidone (PVP K30), PEG 6000, and pluronic F127 were supplied by Pharaonia Pharmaceuticals (Alexandria, Egypt). Tertiary butyl alcohol (TBA) was purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals were of analytical grade and used without further purification.

HPLC assay for FLT

FLT was quantified using a reverse phase HPLC method Umrethia et al., (2005). HPLC analysis was carried out with a Perkin Elmer series 200 chromatograph (Perkin Elmer, Boston, MA) using a Spheri-5, RP-18, 220 × 4.6 mm, 5 μm column (Perkin Elmer), and a UV detector. An isocratic solvent system consisting of 75:25 (v/v) methanol–water was used at a flow rate of 1 mL/min, an injection volume of 20 μL, and the peaks were detected at 304 nm. Under these experimental conditions, the total run time was ~6 min and the retention time was 3.5 min. Calibration curves (peak area versus drug concentration) were linear (R^2 > 0.999) over the FLT concentration range of 0.6–60 μg/mL.

Phase solubility study

Aqueous solubility of FLT in presence of PVP K30, PEG 6000, or pluronic F127 was carried out according to the method described by Higuchi and Connors (1965). An excess amount of FLT was added to 10 mL of aqueous solutions containing increasing concentrations of the hydrophilic polymer (0%, 1%, 5%, 10%, 15%, and 20% w/v) in screw-capped vials. The suspensions were shaken in a thermostatically controlled water bath (GFL, type 1083, Gmbh & Co., Burgwedel, Germany) at 37 ± 0.5°C for 24 h. After equilibrium has been attained, aliquots were withdrawn, filtered through 0.45-μm membrane filter, suitably diluted, and analyzed for FLT using HPLC at 304 nm. Each experiment was carried out in triplicate. The solubilization efficiency of polymers was calculated as the ratio of FLT aqueous solubility at the highest polymer concentration used (20% w/v) and FLT intrinsic solubility in pure water.

Preparation of FLT–polymer LDs

FLT–polymer LDs in 1:1, 1:3 and 1:5 w/w ratios were prepared by dissolving the calculated amount of hydrophilic polymer in 5 mL water and then mixed with FLT/TBA solution (300 mg/5 mL) in 50 mL vials. Immediately after mixing, the vials were frozen at –80°C for 4 h followed by placing them in a Cryodos-50 lyophilizer (Telstar Cryodos, Spain) with a condenser temperature of –70°C. Lyophilization was performed at a pressure of 40 mbar and a shelf temperature of –40°C for 1 day followed by a secondary drying at 25°C for another day. After removing the samples from the freeze-drier, they were placed in a desiccator over P_2O_5 at 4°C until testing.

The corresponding physical mixtures (PMs) were prepared by homogeneous blending of accurately weighed amounts of the drug and polymer in a mortar and stored at room temperature in hermetically sealed bottles until use.

Characterization of FLT LDs

Residual TBA determination

The amount of residual TBA in LDs was determined using AutoSystem XL gas chromatograph (GC) with RX5 column cross bond 5% diphenyl–95% dimethyl polysiloxane 30 m, 0.32 m ID with a film thickness of 0.25 μm (Perkin Elmer). A known weight of the lyophilized sample was immediately dispersed in 2 mL distilled water and GC quantificated the concentration of TBA in 1 μL of the vapor. The injection temperature was 200°C at a rate of 10°C/min. A flame ionization detector operating at 150°C yielded quantitative data. Control experiments showed that the peak areas were not affected by presence of the drug or carriers. Calibration curves of pure TBA/water mixtures were used for all experiments.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) thermograms of pure materials, PMs, and LDs were recorded by DSC 6 differential scanning calorimeter (Perkin Elmer). Samples (2–4 mg) were placed in sealed aluminum pans and heated at 10°C/min under a nitrogen atmosphere (flow rate 20 mL/min) in the 30–400°C range. An empty aluminum pan was used as a reference. The equipment was periodically calibrated with indium. The heat of fusion of crystallized drug in the LD was calculated from the peak area of the melting endotherm. The heat of fusion of pure crystalline drug was determined in a separate experiment. The ratio of these fusion energies was used to calculate the percent crystallinity of drug in the LDs and PMs using the following equation:

$$\%\ \text{Crystallinity} = 100 \times \frac{\Delta H_s}{\Delta H_c \times C}$$

where ΔH_s and ΔH_c are enthalpies of fusion of the sample and pure drug, respectively, and C is the weight fraction of drug in the mixture assuming that the pure drug was 100% crystalline (Rawlinson et al., 2007).

Physical stability

To determine the physical stability of LDs, samples were placed in a climate chamber of 20°C and 45% relative humidity (RH). After 6 months, the % crystallinity of FLT in the samples was determined by means of DSC.

Powder X-ray diffractometry

The X-ray diffractograms (XRDs) of pure materials and LDs were carried out using XRD-7000 (Shimadzu, Japan) where Cu–Kα1 radiation was selected by a Ni monochromator. The scanning rate employed was 2°/min over a diffraction angle of 2θ and range of 5°–60°, operated at a voltage of 30 kV and a current of 30 mA, the scan step size was 0.018 (2θ). The analysis was carried out at room temperature under ambient conditions.

Fourier transform infrared spectroscopy

The Fourier transform infrared spectroscopy (FT-IR) spectra of pure materials, PMs, and LDs were recorded using a Spectrum RXI FT-IR spectrophotometer (Perkin Elmer) according to the KBr disk technique and IR measurements were performed in transmission in the scanning range of 4000–500 cm^{-1} at ambient temperature.

Scanning electron microscopy

The surface morphology of drug and LDs were examined by means of a JEM-100S scanning electron microscope (SEM) (Joel, Japan). Double-sided adhesive tape was placed on an aluminum specimen holder upon which a small amount of powdered samples was deposited. The particles were coated with approximately 10–20 nm gold for 20 sec using a sputter coater. Scans were performed at an acceleration voltage of 10 kV.

Particle size analysis

The particle size of pure drug and LDs was determined using model 1064 liquid laser diffraction particle size analyzer (Cilas, France). A suitable amount of sample was transferred to the dispersion medium of 0.1 N HCl. The medium was agitated at 100 rpm. Particle size was expressed as the equivalent number diameter.

Surface area and porosity analysis

Specific surface area and porosity of pure drug and LDs were measured using the NOVA 1000 series surface area analyzer (Quantachrome, Melbourne, FL). A known weight of powder was added to a 12 mm Quantachrome bulb sample cell and degassed for 3 h prior to analysis. A five-point nitrogen adsorption isotherm at 77 K was measured and the sample was then analyzed by the NOVA-enhanced data reduction software via the Brunauer, Emmett, and Teller (BET) theory of surface area (Kirk et al., 2007).

Flow properties

Flow properties of pure drug and LDs were evaluated by determining the angle of repose. Static angle of repose was measured according to the fixed funnel and free standing cone method (Goddeeris and Van den Mooter, 2008). The samples were carefully poured through the funnel until the apex of the conical pile formed just reaches the tip of the funnel. The circumference of the pile formed was drawn, the mean diameter ($2R$) was determined, and the tangent of the angle of repose was given by the following equation:

$$\tan\theta = H/R$$

where θ is the repose angle and $H = 2$ cm.

In vitro *dissolution study*

FLT dissolution behavior was evaluated using the USP XXIV dissolution rate apparatus II (Pharmatest, Germany) at a stirring rate of 100 ± 2 rpm. Powder samples containing 60 mg of pure FLT or its equivalent amount of LDs or PMs were placed in 900 mL of dissolution fluid (0.1 N HCl, pH 1.2) at 37 ± 0.5°C for 2 h. At predetermined time intervals, 5 mL samples were withdrawn and immediately replaced with an equal volume of pre-warmed dissolution medium. All samples were run in triplicate, filtered through 0.45-μm membrane filter, and the amount of dissolved FLT was analyzed by HPLC at 304 nm. The percentage cumulative amount of drug dissolved was plotted against time.

Results and discussion

Phase solubility study

Solubility experiments showed that the concentration of FLT in water at 37°C increased linearly as a function of PVP K30 or PEG 6000 concentration. According to the phase solubility diagram classification introduced by Higuchi and Connors (1965), the solubility diagrams of

FLT and the hydrophilic polymers (i.e. PVP K30 or PEG 6000) at 37°C correspond to A_L-type profiles (Figure 1A). The obtained results indicate that 20% w/v PVP and PEG solutions provided for a 3.63 and 3.71 solubilization efficiency, respectively.

The linear relationship indicated the possible formation of weakly soluble complexes and/or cosolvent effect of the carrier (Paradkar et al., 2004; Ahuja et al., 2007). Hydrophilic carriers are known to interact with drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds. In addition, the enhanced solubility may also be attributed to a reduction of interfacial tension of water and polarity (Van den Mooter et al., 1998).

The solubility of FLT in presence of different concentrations of pluronic F127 in water illustrated that the phase solubility diagram followed A_N-type (Figure 1B). An initial linear increase in drug solubility was observed with the increase in pluronic concentration up to 5% w/v. Further increase in the polymer concentration showed an almost a plateau region, which may be associated with an alteration in the effective nature of the solvent in the presence of large concentrations of pluronic (increased viscosity) (Higuchi and Connors, 1965). Results from the current study show that pluronic F127 has a significant solubilizing effect on the solubility of the drug corresponding to a solubilization efficiency of 45.76, which is attributable to the micellar solubilization of drug where the arrangement of ethylene oxide (EO) and propylene oxide (PO) blocks pluronic results in an amphiphilic structure, which has the properties of self-assemble into micelles in aqueous solution (Kabanov et al., 2002).

Characterization of FLT LDs

Residual TBA determination

The controlling of residual TBA was needed though TBA is a low toxic organic solvent and has little detriment to human body. Although not listed in the ICH guidelines for residual solvents, TBA is likely to fall in the category of a class 3 solvent based on its similarity of LD_{50} toxicity data for other class 3 solvents with a maximum daily dose of 50 mg of TBA. Therefore, the low level of TBA in the lyophilized cakes should not be harmful to both animal and human. It is reported that during the secondary drying not all TBA will evaporate from the freeze-concentrated fraction (Teagarden and Baker, 2002).

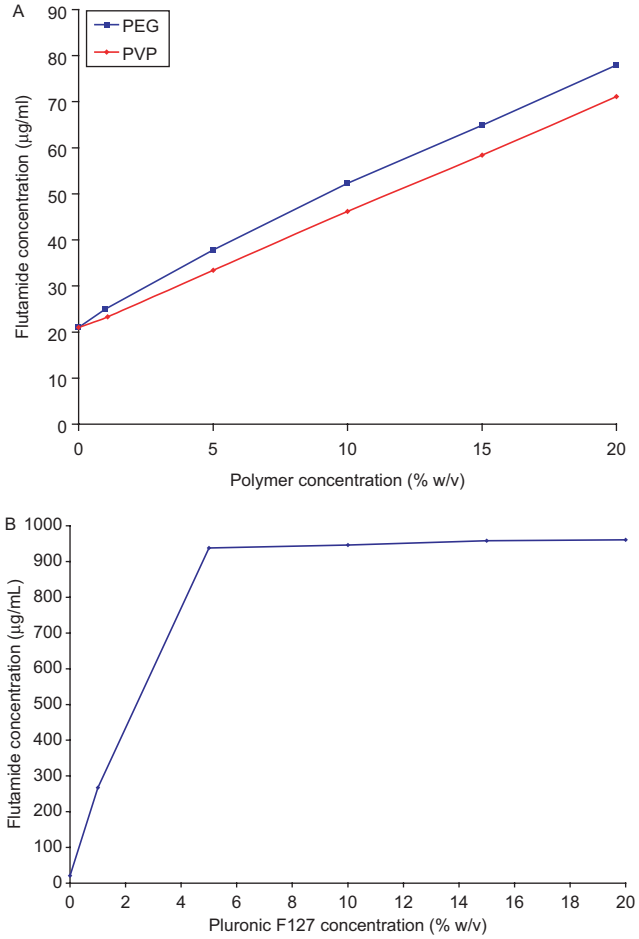

Figure 1. (A) Phase solubility diagram of flutamide in aqueous solutions of PVP K30 and PEG 6000 at 37°C. (B) Phase solubility diagram of flutamide in aqueous solutions of pluronic F127 at 37°C.

GC confirmed that there are 0.015%, 0.021%, and 0.019% w/w residual TBA in the 1:1 FLT–PVP, FLT–PEG, and FLT–pluronic LDs, respectively, which were much lower than the toxic level. The low level of TBA in the LDs results from its ability to form high surface area crystals and from the fact that the intermolecular forces among TBA molecules are not as strong as those of water. This allows TBA to sublime more completely and easily than water (Van Drooge et al., 2004).

Differential scanning calorimetry

The thermograms of pure components and different FLT–polymer binary systems are shown in Figure 2A–2C. The DSC thermogram of FLT was typical of a crystalline substance with a sharp endothermic peak at 113.21°C corresponding to its melting point that was in accordance with a previous report (Adel et al., 1997).

Thermograms of 1:1 FLT–polymer LDs demonstrated two endothermic peaks (Figure 2). The first peak is very close to the polymer melting temperature, whereas the second peak corresponds to FLT melting shifted to a lower temperature and broadened loosing its sharp distinctive appearance. Consequently, the % drug crystallinity was dramatically dropped to 54.40%, 0.23%, and 24.06% for FLT–PVP, FLT–PEG, and FLT–pluronic LDs, respectively.

Figure 2 demonstrated that the endothermal profile of the drug was totally disappeared in the 1:3 and 1:5 LDs of FLT with all polymers under investigation since the thermograms showed only one peak corresponding to the melting point of polymer revealing total drug amorphization and presence of a marked solid state interaction between drug and polymer (Zerrouk et al., 2004).

Physical stability

Thermodynamically, solid solutions are unstable compared with solid dispersions because in the former the drug exists in a high-energy amorphous form that is prone to precipitation or crystallization under environmental stress during processing and storage (Leuner and Dressman, 2000). Therefore, a stability study was performed on the prepared FLT LDs. The results of the stability study of LDs stored at 20°C and 45% RH for 6 months revealed that the thermograms of 1:1 FLT–PVP, FLT–PEG, and FLT–pluronic LDs showed no significant increase in % drug crystallinity after 6 months storage (data not shown). Similarly, the thermograms of 1:3 and 1:5 LDs showed a great stability under storage conditions where no peaks corresponding to FLT melting were detected. Thus, the hydrophilic polymers used in the LD preparation completely inhibited drug recrystallization and maintained its amorphous form.

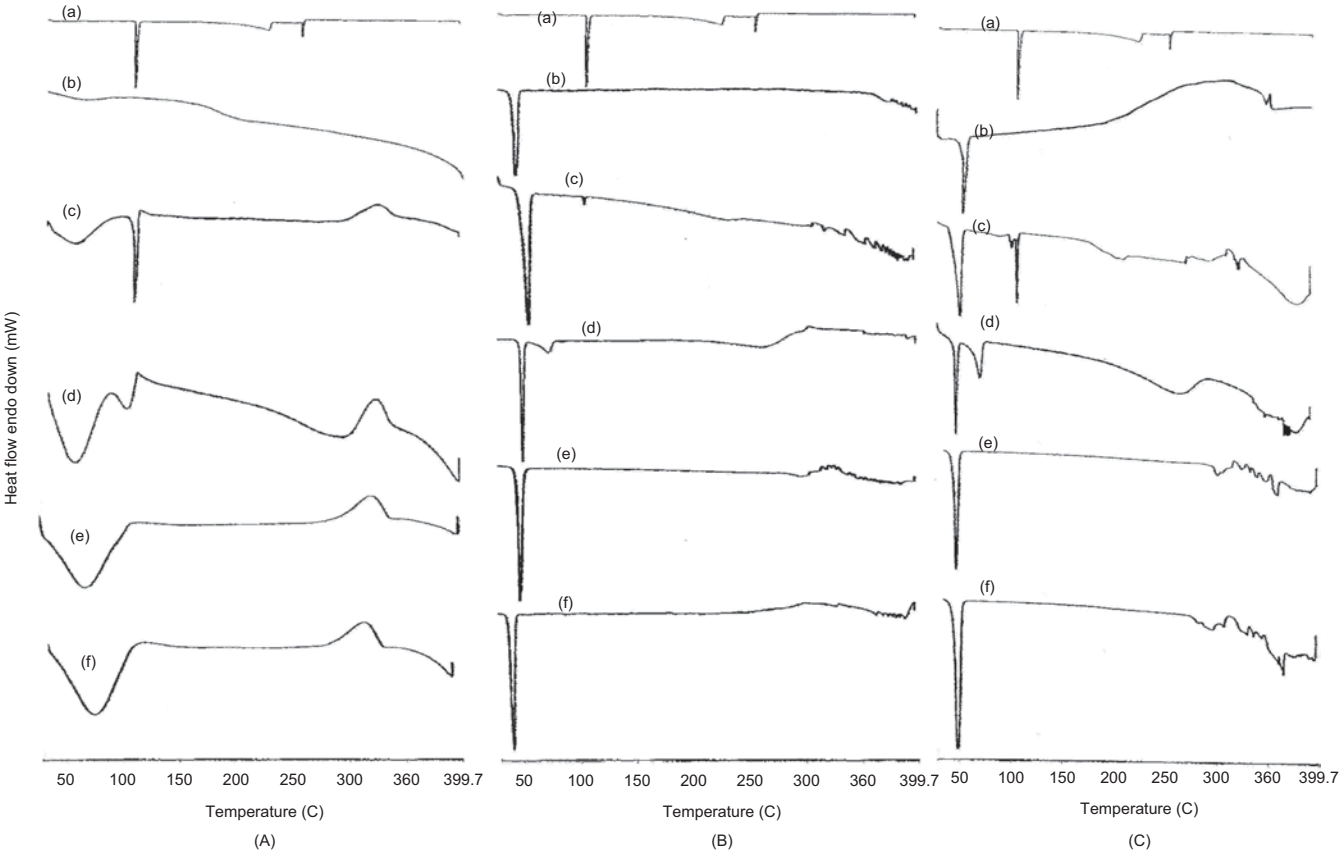

Figure 2. (A) DSC thermograms of pure flutamide (FLT) (a), PVP K30 (b), FLT–PVP 1:1 PM (c), FLTPVP 1:1 LD (d), FLT–PVP 1:3 LD (e), and FLT–PVP 1:5 LD (f). (B) DSC thermograms of pure FLT (a), PEG 6000 (b), FLT–PEG 1:1 PM (c), FLT–PEG 1:1 LD (d), FLT–PEG 1:3 LD (e), and FLT–PEG 1:5 LD (f). (C) DSC thermograms of pure FLT (a), pluronic F127 (b), FLT–pluronic 1:1 PM (c), FLT–pluronic 1:1 LD (d), FLT–pluronic 1:3 LD (e), and FLT–pluronic 1:5 LD (f).

Powder X-ray diffractometry

XRD analysis was performed to confirm the results of the DSC study. XRDs revealed that FLT is a crystalline compound showing a very strong sharp diffraction peak at 2θ of 8.726°, although other peaks are present at a lower intensity (Figure 3).

The diffraction patterns of 1:1 and 1:3 FLT LDs with PVP, PEG, and pluronic compared with that of both pure drug and polymers were shown in Figure 3A–3C. All the principal peaks from FLT and polymer were present in their respective 1:1 LDs although the peak of FLT was of very low intensity and slightly shifted to a lower value. Total disappearance of the FLT diffractive peak was observed in the 1:3 FLT LDs. This confirmed the drug transformation from the crystalline to the amorphous form. This result was in a good agreement with the work done by Yamashita et al. (2003) and Karavas et al. (2007). They confirmed that tacrolimus existed in an amorphous state in its LDs with PVP and PEG.

These results confirmed that the partial or complete loss of drug crystallinity was not merely a thermal artifact caused during the DSC heating cycle and so conversion to an amorphous form was strongly suggested.

Fourier transform infrared spectroscopy

The FT-IR spectra of FLT LDs with PVP, PEG, and pluronic compared with that of their PMs and pure drug are shown in Figure 4A–4C, respectively. The characteristic peak of FLT at 3360 cm^{-1} corresponding to its amino group was detected in 1:1 FLT–polymer LDs but shifted toward a lower wave numbers, although all characteristic peaks of FLT are present in the PMs in their original positions. Furthermore, the carbonyl stretching peak at 1718 cm^{-1} of FLT and the vibrational band of C=C bond at 1580 cm^{-1} were shifted to lower values as the PVP, PEG, or pluronic content increased. This result indicated a change in the environment of carbonyl group of the drug as a consequence of the interaction with the polymers under study. The major shift in carbonyl stretching peak indicated that the drug crystalline form may be altered during LD formation.

Scanning electron microscopy

The morphologies of pure FLT and 1:5 FLT–polymer LDs were investigated by SEM analysis (Figure 5). Pure FLT image showed crystalline drug of plate-like crystals, although no crystals were detectable in the micrographs of FLT LDs with PVP, PEG, and pluronic did not show drug crystals suggesting that the drug is present in amorphous form.

Particle size analysis

It is known that in glass, solid solutions, and amorphous dispersions the particle size is reduced to a minimum level. After carrier dissolution, the drug is molecularly dispersed in the dissolution medium resulting in an enhanced dissolution rate. Literature lacks sufficient data about the influence of hydrophilic polymers on the particle size of drug solid dispersions. Therefore, our study gave a special emphasis to particle size of FLT LDs and consequently on their surface area and porosity. The particle size measurements of the pure drug and LDs are listed in Table 1. The average particle size of FLT crystals was 2.96 µm. It was observed that lyophilization technique reduced the particle size of the drug in its LDs. The particle size of the prepared FLT LDs ranged from 0.81 to 2.13 µm for 1:5 FLT–PVP and 1:5 FLT–pluronic LDs, respectively.

Upon using PVP, the size of the LD particles was directly affected by drug proportion in the dispersion. By decreasing the drug proportion in LDs, the particle size gradually becomes smaller. These results were in a good agreement with the work done by Karavas et al. (2007); they observed that the particle size in felodipine–PVP LD increased as the drug proportion in the PVP matrix increased.

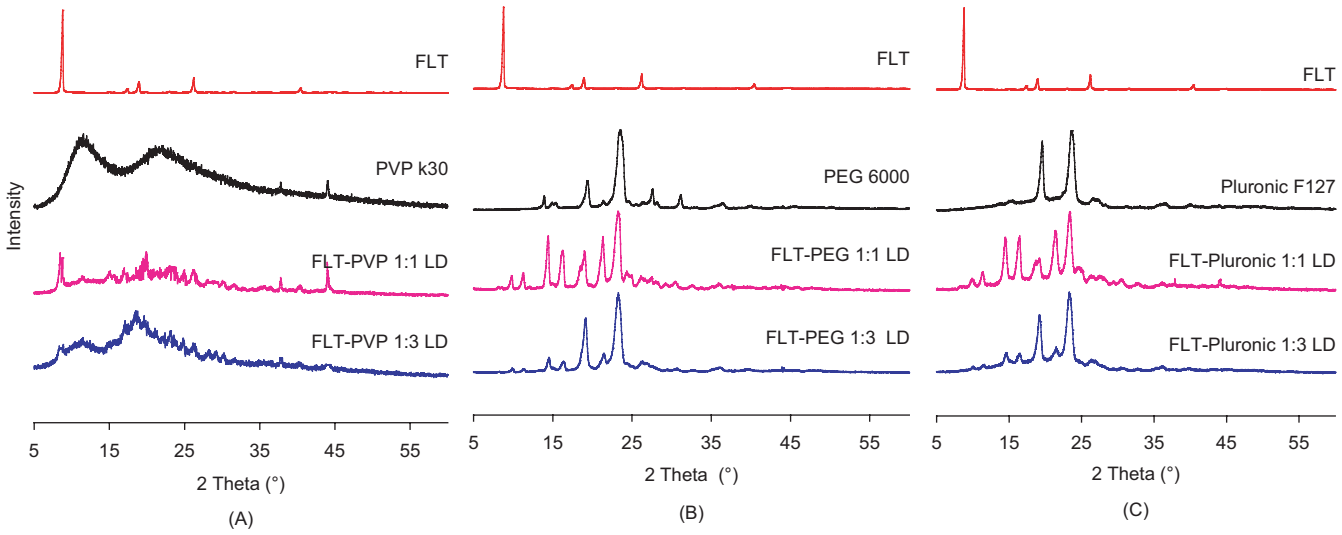

Figure 3. (A) X-ray diffractograms of FLT–PVP lyophilized dispersions. (B) X-ray diffractograms of FLT–PEG lyophilized dispersions. (C) X-ray diffractograms of FLT–pluronic lyophilized dispersions.

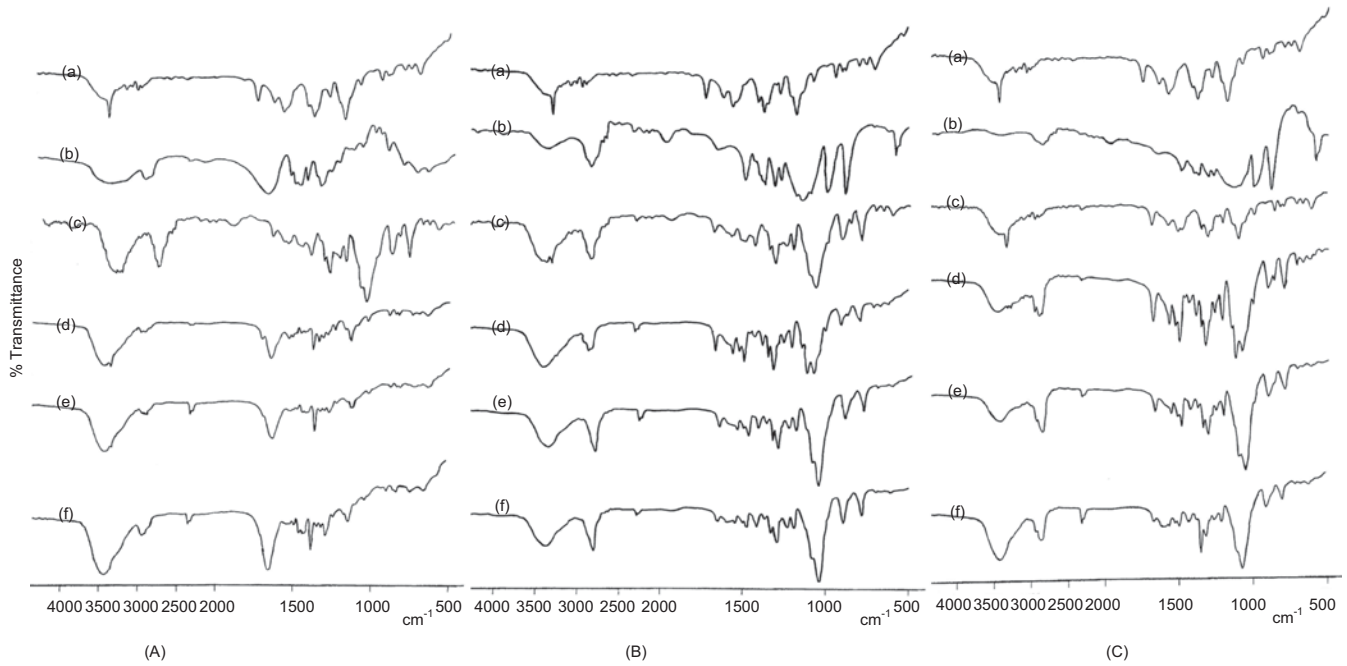

Figure 4. (A) FT-IR transmission spectra of pure flutamide (FLT) (a), PVP K30 (b), FLT–PVP 1:1 PM (c), FLT–PVP 1:1 LD (d), FLT–PVP 1:3 LD (e), and FLT–PVP 1:5 LD (f). (B) FT-IR transmission spectra of pure FLT (a), PEG 6000 (b), FLT–PEG 1:1 PM (c), FLT–PEG 1:1 LD (d), FLT–PEG 1:3 LD (e), and FLT–PEG 1:5 LD (f). (C) FT-IR transmission spectra of pure FLT (a), pluronic F127 (b), FLT–pluronic 1:1 PM (c), FLT–pluronic 1:1 LD (d), FLT–pluronic 1:3 LD (e), and FLT–pluronic 1:5 LD (f).

On the other hand, in case of using PEG and pluronic as carriers, increasing the polymer proportion in LDs resulted in increased average particle size. The largest particle size (2.13 μm) was observed in case of 1:5 FLT–pluronic lyophilized system, which may be due to the micelle forming ability of pluronic.

Surface area and porosity analysis

An important factor that influences the dissolution rate is the available surface area of the active pharmaceutical ingredient (API). The surface area per unit powder mass was calculated from the fit of nitrogen adsorption data to the BET equation. The determined specific surface area and total pore volume of pure FLT and LDs are listed in Table 1. The specific surface area of FLT crystals was 233.42 m^2/g with a total pore volume of 339.64 e^{-3} mL/g. The utilized lyophilization technique using PVP, PEG, and pluronic increased the specific surface area and total pore volume of the drug. Specific surface area ranged between 268.43 and 510.82 m^2/g, whereas the total pore volume was in the range of 354.01–676.23 e^{-3} mL/g for 1:5 FLT–pluronic and FLT–PVP LDs, respectively. Such a high surface area indicated that the lyophilized powder particles were highly porous. Their highly porous structures may be attributed to the channels created as the solvent was removed during the sublimation process in the lyophilization cycle. These results were in agreement with the work done by Williams III et al. (2003).

Flow properties

The soft and tacky properties of solid dispersion powders result in poor flowability and mixing property, which may complicate the operations and render poor reproducibility of physicochemical properties of final products (Sun et al., 2008).

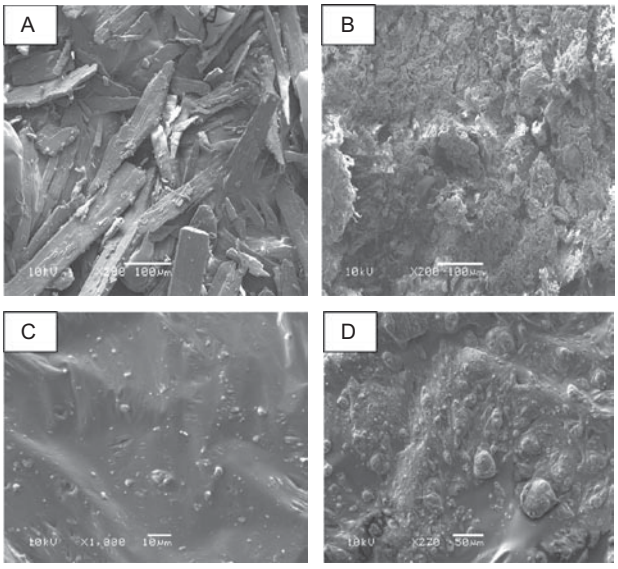

Figure 5. Scanning electron micrographs of selected 1:5 flutamide (FLT)–polymer LDs: pure FLT (A), FLT–PVP K30 (B), FLT–PEG 6000 (C), and FLT–pluronic F127 (D).

Therefore, the flow properties of pure FLT and LDs were evaluated by measuring the angle of repose (Table 1). FLT showed a poor flow property as indicated by the high value of angle of repose (57.23°), although the FLT–polymer LDs may be categorized as fair flowing to cohesive powders with an angle of repose value between

Table 1. Physicochemical properties of flutamide (FLT) and its lyophilized dispersions (values are mean ± SD, $n = 3$).

Formula	Particle size (μm)	Specific surface area (m^2/g)	Total pore volume (e^{-3} mL/g)	Angle of repose (θ)
FLT	2.96 ± (0.03)	233.42 ± (5.06)	339.64 ± (4.71)	57.23 ± (2.24)
FLT–PVP 1:1	0.91 ± (0.10)	406.34 ± (4.12)	587.65 ± (5.09)	53.87 ± (4.09)
FLT–PVP 1:3	0.86 ± (0.02)	449.03 ± (7.60)	627.22 ± (8.14)	54.21 ± (4.44)
FLT–PVP 1:5	0.81 ± (0.05)	510.82 ± (6.83)	676.23 ± (7.76)	56.21 ± (6.26)
FLT–PEG 1:1	0.95 ± (0.04)	478.73 ± (8.64)	691.64 ± (6.15)	51.78 ± (3.70)
FLT–PEG 1:3	1.00 ± (0.08)	456.21 ± (7.73)	677.34 ± (6.41)	52.64 ± (5.74)
FLT–PEG 1:5	1.33 ± (0.06)	432.34 ± (4.10)	654.93 ± (5.73)	52.87 ± (4.76)
FLT–Pluronic 1:1	1.00 ± (0.03)	295.47 ± (4.90)	380.63 ± (4.90)	47.73 ± (3.90)
FLT–Pluronic 1:3	1.03 ± (0.02)	275.24 ± (7.54)	374.50 ± (9.37)	44.71 ± (6.74)
FLT–Pluronic 1:5	2.13 ± (0.10)	268.43 ± (5.12)	354.01 ± (6.76)	40.36 ± (2.76)

Table 2. Dissolution parameters of flutamide (FLT), physical mixtures, and lyophilized dispersions in 0.1 N HCl at 37°C (values are mean ± SD, $n = 3$).

Formula	$\%DE_{60}$ [a]	RDR_5 [b]	PD_{30} [c]	$T_{25\%}$ [d]
FLT	10.83 ± (0.42)	1	13.45 ± (0.50)	120 ± (2.11)
FLT–PVP 1:1 PM	16.29 ± (0.61)	4.52 ± (0.34)	17.81 ± (2.99)	119 ± (2.17)
FLT–PVP 1:1 LD	34.43 ± (1.00)	14.09 ± (0.25)	36.54 ± (1.82)	5 ± (0.30)
FLT–PVP 1:3 LD	50.74 ± (0.58)	17.12 ± (0.37)	55.23 ± (2.80)	4 ± (0.02)
FLT–PVP 1:5 LD	62.87 ± (0.39)	28.46 ± (0.20)	66.52 ± (3.28)	2 ± (0.46)
FLT–PEG 1:1 PM	16.60 ± (3.27)	4.13 ± (0.56)	18.05 ± (1.66)	110 ± (3.06)
FLT–PEG 1:1 LD	44.72 ± (0.39)	19.31 ± (1.03)	48.56 ± (0.58)	4 ± (0.06)
FLT–PEG 1:3 LD	56.60 ± (2.31)	26.25 ± (0.20)	59.64 ± (4.58)	3 ± (0.38)
FLT–PEG 1:5 LD	72.21 ± (0.53)	23.71 ± (0.68)	78.23 ± (0.95)	2 ± (0.18)
FLT–Pluronic 1:1 PM	17.59 ± (3.24)	5.15 ± (0.02)	18.96 ± (1.39)	64 ± (2.81)
FLT–Pluronic 1:1 LD	46.19 ± (2.09)	20.47 ± (1.20)	49.57 ± (3.78)	3 ± (0.05)
FLT–Pluronic 1:3 LD	59.29 ± (1.63)	25.23 ± (0.93)	62.07 ± (2.05)	2 ± (0.01)
FLT–Pluronic 1:5 LD	76.98 ± (3.65)	38.05 ± (2.84)	81.64 ± (3.88)	1 ± (0.02)

[a]Area under the dissolution curve up to 60 min.
[b]Ratio of FLT dissolved from lyophilized dispersion to that of drug alone at 5 min.
[c]Percentage of FLT dissolved at 30 min.
[d]Time (min) required to dissolve 25% of FLT.

40.36° and 56.21° corresponding to FLT–pluronic 1:5 and FLT–PVP 1:5 LDs, respectively. The technique and polymers used improved the flow property of the drug but to a limited extent. The relatively high value of angle of repose indicated the roughness of the particle surface that may hinder the flow of the drug particles. As the roughness of the surface increased, the points of contact and so the friction between particles increased that resisted the flow of the particles relative to each other. The poor flow of the LDs could also be attributed to the nature of the LDs that are usually soft and tacky (Sun et al., 2008).

In vitro *dissolution study*

The dissolution profiles of FLT from its LDs with the hydrophilic polymers under study, and their corresponding PMs are presented in Figure 6A–6C, respectively. For their evaluation, four parameters, dissolution efficiency calculated after 60 min ($\%DE_{60}$), percentage of dissolved drug after 30 min (PD_{30}), relative dissolution rate after 5 min (RDR_5), and time required to dissolve 25% of drug ($T_{25\%}$) were measured for all products studied (Table 2). The dissolution rate of pure FLT was very slow that after 120 min about 19% of the drug was dissolved. This poor dissolution behavior of the drug could be explained on the basis of its low aqueous solubility, poor wettability, and/or agglomeration.

Figure 6A showed clearly that the FLT–PVP PM showed only a slight increase in dissolution rate, with a relative dissolution rate at 5 min (RDR_5) of 4.52. The enhanced dissolution rate of FLT LDs compared with PM may be attributed to increasing the drug solubility and wettability in case of 1:1 FLT–PVP LD and it may be owing to the changes in the solid state during the formation of dispersion such as the formation of high-energy amorphous phase in case of 1:3 and 1:5 FLT–PVP LDs. The RDR_5 was 14.09, 17.12, and 28.46 for 1:1, 1:3, and 1:5 FLT–PVP LDs, respectively, compared with that of pure drug. In addition, there was a good correlation between the particle size and drug dissolution rate from FLT–PVP LDs. Increasing PVP ratio from 1:1 to 1:3 and 1:5 resulted in a gradual decrease in particle size from 0.91 to 0.86 and 0.81 μm, respectively, with a consequent increase in the surface area and porosity. These findings suggested that the particle size reduction may contribute to the dissolution enhancing mechanism of PVP.

Similar results were obtained with FLT–PEG 6000 binary systems (Figure 6B). The percentage FLT dissolved at 30 min (PD_{30}) was 48.56%, 59.64%, and 78.23%

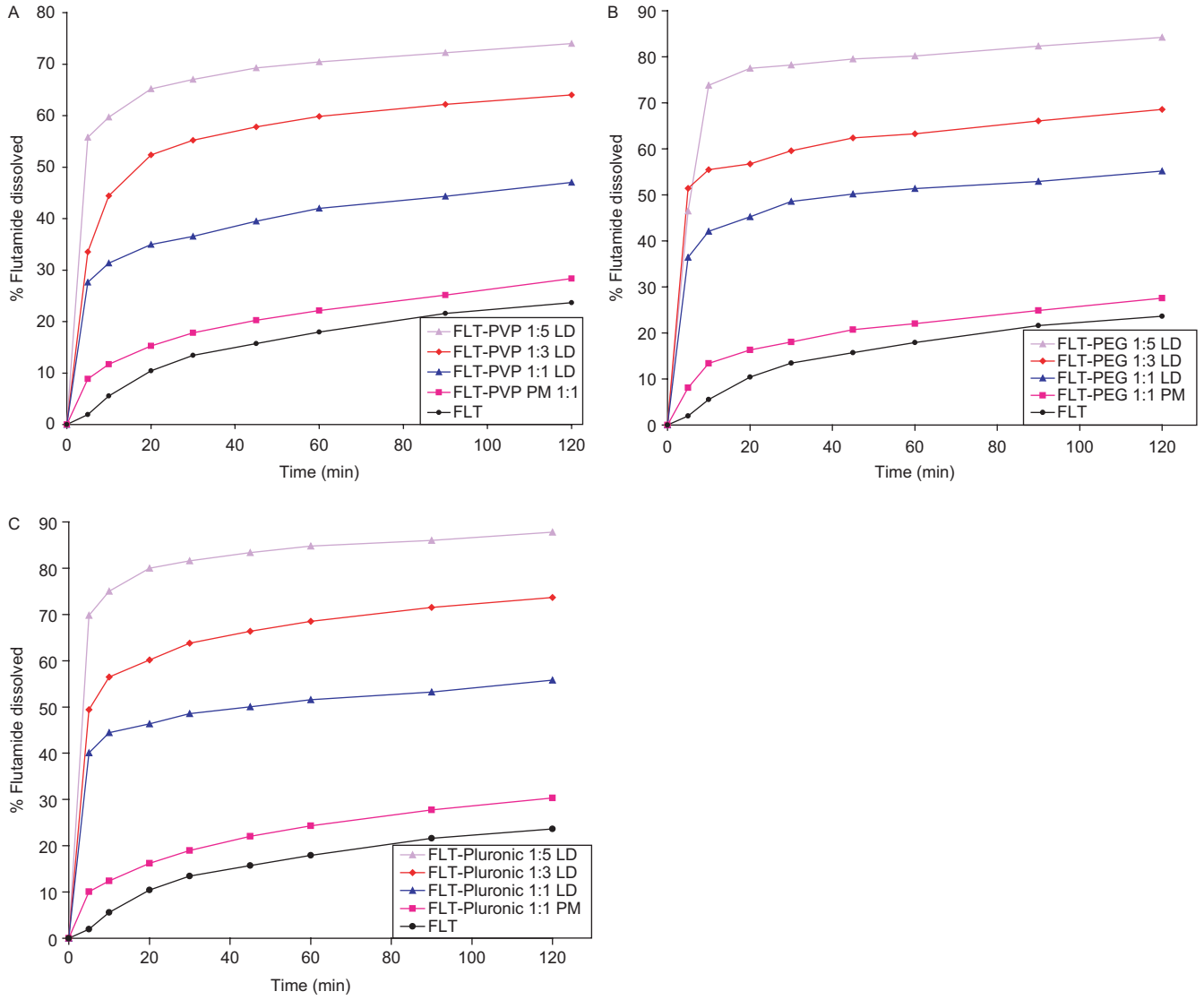

Figure 6. (A) Dissolution profile of flutamide (FLT) from different FLT–PVP systems in 0.1 N HCl at 37°C. (B) Dissolution profile of flutamide from different FLT–PEG systems in 0.1 N HCl at 37°C. (C) Dissolution profile of flutamide from different FLT–pluronic systems in 0.1 N HCl at 37°C.

from 1:1, 1:3, and 1:5 FLT–PEG LDs, respectively, compared with PD_{30} of 13.45% for the pure drug. A direct correlation between the increase of polymer content and dissolution enhancement was observed. This phenomenon could be ascribed to the solubilizing effect of PEG in addition to the drug amorphization in case of 1:3 and 1:5 FLT–PEG LDs. It was noticed that the FLT dissolution rate from FLT–PEG binary systems was higher than from FLT–PVP binary systems. The dissolution enhancing effect of PEG is probably attributable to the formation of regions of high concentration of dissolved polymer at the surface of drug crystals in which the drug can solubilize and subsequently diffuse and dilute in the bulk of solution. On the other hand, when PVP comes in contact with the dissolution medium it dissolves rapidly forming a viscous layer around the LD particles that might be considered as a diffusion barrier for drug release thus retarding to a certain extent the drug dissolution (Cirri et al., 2004).

The lyophilized FLT–pluronic F127 dispersions exhibited the highest dissolution rate of FLT (Figure 6C). This could be explained on the basis of the markedly high-solubilizing effect of pluronic and the improved wetting of the drug. When this LD comes in contact with the dissolution medium, the polymer particles will be hydrated rapidly into polymer solution solubilizing the adjacent drug particles and subsequently releasing the drug into the medium (Chen et al., 2004). Table 2 showed that increasing pluronic content from 1:1 to 1:3 and 1:5 FLT–pluronic LDs reduced the time required to dissolve 25% of drug ($T_{25\%}$) from 3 to 2 and 1 min, respectively, compared with 64 min for the 1:1 FLT–pluronic PM and 120 min for pure drug. In the 1:3 and 1:5 LDs, the enhancement in drug dissolution rate may be strongly attributed to amorphous nature of the drug, which can be beneficial since dissolution of an amorphous drug does not require energy to break up the crystalline lattice (Hancock and Zografi, 1997).

Conclusions

From the previous results, we can conclude that at 1:1 FLT–polymer ratio, lyophilized solid dispersions of FLT are obtained in which FLT transformed from crystalline to partially amorphous form. Upon using 1:3 and 1:5 FLT–polymer ratios, lyophilized solid solutions could be formed where FLT was completely molecularly dispersed and drug has no crystal structure, that is, completely amorphous. Our study revealed that in lyophilized solid solutions, the improvement in dissolution rate may be mainly due to the high-energy amorphous nature of FLT. Other parameters such as micellar solubilization, reduced particle size, and increased surface area and porosity were found to contribute to the enhanced dissolution of FLT. Also, the polymers could improve the poor flow properties of FLT but to a limited extent. Furthermore, it was observed that the hydrophilic polymers under study could stabilize the amorphous FLT preventing its recrystallization after storage. Therefore, these polymers may offer a useful tool in terms of improving the low oral bioavailability of FLT by lyophilization monophase solution technology.

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Declaration of interest

The authors report no declarations of interest.

References

Adel MS, Geneidi AS, Ali Shoukri R, Saad I. (1997). *In vitro* evaluation of flutamide-carrier systems. Part 1: Preparation and evaluation of flutamide systems with polyvinyl pyrrolidone and polyethylene glycol 4000 and 6000. Pharmazie 52:373–375.

Ahuja N, Katare OP, Singh B. (2007). Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur J Pharm Biopharm 65:26–38.

Chen Y, Zhang GG, Neilly J, Marsh K, Mawhinney D, Sanzgiri YD. (2004). Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68. Int J Pharm 286:69–80.

Cirri M, Mura P, Rabasco AM, Ginés JM, Moyano JR, Gònzalez-Rodrìguez ML. (2004). Characterization of ibuproxam binary and ternary dispersions with hydrophilic carriers. Drug Dev Ind Pharm 30:65–74.

Elgindy N, Elkhodairy K, Molokhia A, Elzoghby A. (2010). Lyophilization monophase solution technique for improvement of the physicochemical properties of an anticancer drug, flutamide. Eur J Pharm Biopharm 74:397–405.

Goddeeris C, Van den Mooter G. (2008). Free flowing solid dispersions of the anti-HIV drug UC 781 with Poloxamer 407 and a maximum amount of TPGS 1000: investigating the relationship between physicochemical characteristics and dissolution behaviour. Eur J Pharm Sci 35:104–113.

Goldberg AH, Gibaldi M, Kanig JL. (1965). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. I. Theoretical considerations and discussion of the literature. J Pharm Sci 54:1145–1148.

Hancock BC, Zografi G. (1997). Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci 86:1–12.

Higuchi T, Connors KA. (1965). Phase solubility techniques. Adv Anal Chem Instrum 4:117–212.

Kabanov AV, Batrakova EV, Alakhov VY. (2002). Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. J Control Release 82:189–212.

Karavas E, Georgarakis E, Sigalas MP, Avgoustakis K, Bikiaris D. (2007). Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug–polymer interactions. Eur J Pharm Biopharm 66:334–347.

Kirk AO, Josh DE, Bo C, Brian DS, Thomas EM, Keith PJ, Robert OW. (2007). Novel ultra-rapid freezing particle engineering process for enhancement of dissolution rates of poorly water-soluble drugs. Eur J Pharm Biopharm 65:57–67.

Kushida I, Ichikawa M, Asakawa N. (2002). Improvement of dissolution and oral absorption of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity by preparing solid dispersion. J Pharm Sci 91:258–266.

Leuner C, Dressman J. (2000). Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 50:47–60.

Martínez-Ohárriz MC, Martín C, Goñi MM, Rodríguez-Espinosa C, Tros-Ilarduya MC, Zornoza A. (1999). Influence of polyethylene glycol 4000 on the polymorphic forms of diflunisal. Eur J Pharm Sci 8:127–132.

Paradkar A, Ambike AA, Jadhav BK, Mahadik KR. (2004). Characterization of curcumin–PVP solid dispersion obtained by spray drying. Int J Pharm 271:281–286.

Rawlinson CF, Williams AC, Timmins P, Grimsey I. (2007). Polymer-mediated disruption of drug crystallinity. Int J Pharm 336:42–48.

Rouchotas C, Cassidy OE, Rowley G. (2000). Comparison of surface modification and solid dispersion techniques for drug dissolution. Int J Pharm 195:1–6.

Sekiguchi K, Obi N. (1961). Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull 9:866–872.

Sun N, Wei X, Wu B, Chen J, Lu Y, Wu W. (2008). Enhanced dissolution of silymarin/polyvinylpyrrolidone solid dispersion pellets prepared by a one-step fluid-bed coating technique. Powder Technol 182:72–80.

Teagarden DL, Baker DS. (2002). Practical aspects of lyophilization using non-aqueous co-solvent systems. Eur J Pharm Sci 15:115–133.

Umrethia ML, Ghosh PK, Majithiya RJ, Murthy RSR. (2005). A new reverse phase high performance liquid chromatographic method for determination of flutamide in liposomes, rat blood plasma and tablet dosage forms. Ars Pharm, 46:109–124.

Van den Mooter G, Augustijns P, Blaton N, Kinget R. (1998). Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int J Pharm 164:67–80.

Van Drooge DJ, Hinrichs WL, Frijlink HW. (2004). Incorporation of lipophilic drugs in sugar glasses by lyophilization using a mixture of water and tertiary butyl alcohol as solvent. J Pharm Sci 93:713–725.

Wang Z, Deng Y, Sun S, Zhang X. (2006). Preparation of hydrophobic drugs cyclodextrin complex by lyophilization monophase solution. Drug Dev Ind Pharm 32:73–83.

Williams III RO, Johnson KP, Hu J. (2003). Spray freezing into liquid (SFL) particle engineering technology to enhance dissolution of poorly water soluble drugs: organic solvent versus organic/aqueous cosolvent systems. Eur J Pharm Sci 20:295–303.

Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R, Higaki K, Kimura T. (2003). Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int J Pharm 267:79–91.

Yu L. (2001). Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv Drug Deliv Rev 48:27–42.

Zerrouk N, Mennini N, Maestrelli F, Chemtob C, Mura P. (2004). Comparison of the effect of chitosan and polyvinylpyrrolidone on dissolution properties and analgesic effect of naproxen. Eur J Pharm Biopharm 57:93–99.

Zhong Z, Bruce S, Glen k, James D, Leonard IW. (2000). Hydroxypropyl-β-cyclodextrin–flutamide inclusion complex. I. Formulation, physical characterization and absorption studies using the Caco-2 *in vitro* model. J Pharm Pharmaceut Sci 3:220–227.