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Tailoring the Release Rates of Fluconazole Using Solid Dispersions in Polymer Blends

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Formulations of the drug Fluconazole with different release characteristics were prepared by dispersing the active pharmaceutical ingredient (API) in various polymeric carriers, and especially in polymer blends. Fluconazole was tested as a model drug with low solubility in water. First solid dispersions in pure polymers were studied. Use of pure polyvinylpyrrolidone (PVP) as carrier even for high drug load (30 wt%) resulted in rapid release. The drug release rates decreased by increasing the API content. The dissolution rate enhancement was attributed to drug amorphization, particle size reduction, and possible improvement of the drug wetting characteristics. Hydroxypropyl methylcellulose (HPMC) gave solid dispersions, from which the release rates of the drug varied from immediate to sustaining. As the drug amount increased, the rates became higher. Similar behavior also was found when Chitosan was used as carrier, with much more controlled rates close to those for sustained release. These differences were mainly attributed to the limited solubility and swelling of HPMC and Chitosan in aquatic media. To study the effectiveness of polymer blends in adjusting the release rates of the drug, solid dispersions in PVP/HPMC and PVP/Chitosan miscible blends were studied. The release rates of Fluconazole were adequately adjusted by differentiating the weight ratio of the polymers in the blends. PVP/HPMC blends with high PVP content can be used for immediate release formulations but PVP/Chitosan blends are inappropriate for such formulations and can only be used for controlled release.

Keywords fluconazole; solid dispersion; PVP; HPMC; chitosan; dissolution rates; miscible blends

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INTRODUCTION

The development of effective formulations of antifungals is hindered considerably by the fact that these are only poorly soluble in water. Fluconazole is an important representative of the wide spectrum triazole antifungal medicinal active ingredients. Figure 1 shows the chemical structure of the substance. It is mainly administered orally. It is used in the treatment of oropharyngeal, esophageal, and vulvovaginal candiasis and in the treatment of other serious systemic candidal infections. Fluconazole also is used in the treatment of meningitis caused by *Cryptococcus neoformans* (Ayub et al., 2007; Porta, Chang, & Storpirtis, 2005). In order for Fluconazole to be used as an effective systemic antimycotic, its dissolution rate must be enhanced since it shows very limited solubility in water. It has been reported that decreasing particle size or the use of detergents or disintegrants is ineffective when dissolution rate of Fluconazole is to be increased (Fekete et al., 2005). To achieve higher dissolution rates of the drug, solid dispersions might be an alternative (Leuner & Dressman, 2000).

Solid dispersions are dosage forms whereby the drug is dispersed in a biologically inert matrix, like a polymer (Ford, 1986). They can be used to increase the dissolution rate of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound surface as well as increasing the interfacial area available for drug dissolution. Molecular dispersion represents the ideal case (Craig, 2002;

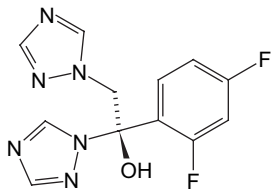


FIGURE 1. Chemical structure of Fluconazole.

Hörter & Dressman, 2001). Solid dispersions can be prepared by the solvent method, which involves dissolving the components in a mutual volatile solvent and subsequent solvent evaporation. Solid dispersions also can be formed by the hot-melt method, which involves heating mixtures of the drug and the carrier to the molten state and then cooling it to the solid state. Finally, solid dispersions can be produced following the melt-solvent method (Craig, 2002; Ford, 1986; Matsumoto & Zografi, 1999; Serajudin, 1999).

The most used polymers for solid dispersions are amorphous polymer carriers like polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) as well as semicrystalline polymers like poly(ethylene glycol) PEG (Craig, 1995; Kanaze et al., 2006; Karavas et al., 2006a; Matsumoto & Zografi, 1999; Tantishaiyakul et al., 1999; Van den Mooter et al., 2001; Verheyen, 2002). PVP is a water-soluble tertiary amine and a strong Lewis base. It exhibits biocompatibility and, thus, it is used in many applications in pharmaceutical technology. It is a strong proton acceptor and, due to the presence of polar groups, can easily exhibit hydrogen bond interactions with proton donors, including other polymers or small molecules. Interactions with PVP in respective solid dispersions may prevent the crystallization of drugs, resulting in enhanced drug dissolution rates (Kanaze et al., 2006; Karavas, Ktistis, Xenakis, & Georgarakis, 2006a; Matsumoto & Zografi, 1999; Tantishaiyakul et al., 1999; Van den Mooter et al., 2001).

Hydroxypropyl methylcellulose (HPMC) has been used extensively as a drug carrier and for the enhancement of the dissolution behavior of poorly water-soluble drugs as well. It is not dissolved in water easily, and first it swells on contact with aqueous solutions creating a hydrocolloid gel mass on its external surface. This mass gradually dissolves with time. Compared with PVP solid dispersions, systems based on HPMC have a slower drug release rate (Mitchell, Reynolds, & Dasbach, 2003; Okimoto et al., 1997).

Polymer blends may offer the advantage to adjust the release rates of drugs in the respective solid dispersions (Karavas, Georgarakis, & Bikiaris, 2006b; Koo et al., 2003; Nyamweya & Hoag, 2000; Karavas, Georgarakis, & Bikiaris, 2006c). Chitosan has found a vast number of applications in recent years and it is considered one of the most significant materials from the point of view of potential applications. This is attributed to the high nitrogen content (6.89%) and the fact that it is a completely biodegradable polymer that is also biocompatible, non-toxic, and has a high adsorption capability. Furthermore, it can easily form films or fully miscible blends with other polymers having multiple applications, since it is soluble in weak acids such as acetic acid. In contrast to most natural polysaccharides, like cellulose, starch, dextrin, and so forth, which exhibit a weak acidic or neutral behavior, Chitosan shows a weak basic character.

In this work, five series of solid dispersions of Fluconazole were prepared following the solvent evaporation method. Three different types of polymeric carriers were used, namely PVP, Chitosan, HPMC, and also polymer blends comprised of PVP/HPMC or PVP/Chitosan. The aim of the present work was to investigate the possible increase in dissolution rates of Fluconazole from solid dispersions in the above mentioned polymers as well as from their blends. This task has a specific practical importance due to the demand for the development of respective formulations for immediate release of Fluconazole.

EXPERIMENT

Materials

Fluconazole was purchased from Dr Reddy's (Andra Pradesh, India) as a white crystalline powder with assay 99.8% (limits 99.0–101.0%), slightly soluble in water and freely soluble in methanol. Poly(vinyl pyrrolidone) (PVP) type Kollidon K30 with a molecular weight (Mw) of 50,000–55,000 was obtained from BASF (Ludwigshafen, Germany), T_g = 167°C (DSC), moisture content 1.95% (TGA) and bulk density 0.410 g/cm^3. HPMC type Methocel K4M was obtained from Colorcon Italy with a T_g = 202°C (DSC) and moisture content 2.1% (TGA). Chitosan with a low molecular weight, 75–85% deacetylated, dilute in aqueous acid (pH < 6.5) and viscosity 20–200 cP, (1 wt% in 1% acetic acid, Brookfield) was supplied from Aldrich chemicals. Ethanol absolute was obtained from Merck. All the other materials and reagents were of analytical grade of purity.

Preparation of Solid Dispersions in Neat Polymers

The solid dispersions were prepared following the solvent evaporation method. In the case of solid dispersions of PVP, volumes of two solutions, one of the drug (5 wt%), and one of the polymer (5 wt%), in ethanol were mixed and the mixtures were sonicated for 10 min. The final solutions were poured in petri plates and maintained in a vacuum oven for 24 h at 25°C. After evaporation of the solvent, the solid dispersions were stored at 25°C in a desiccator. The solid dispersions had Fluco/PVP weight ratios 10/90, 20/80, 30/70, and 40/60 w/w. Solid dispersions of HPMC and chitosan with similar drug quantities were prepared in a similar manner. Chitosan was dissolved in water containing 2v/v% acetic acid, while HPMC—in order to dissolve first—remained in water for 7 days to swell; complete dissolution was achieved by gently heating at 60°C for 1 h. At these solutions a very dilute aquatic drug solution was added

and mixed. The final solutions were poured in petri plates and maintained in a vacuum oven for 48 h at 25°C.

Preparation of Solid Dispersions in Miscible Polymer Blends

Miscible blends of PVP/HPMC and PVP/Chitosan were prepared as described in our previous work by solvent evaporation method in the entire composition range (Karavas, Georgarakis, & Bikiaris, 2006d). For PVP/HPMC blends, PVP and HPMC were dissolved in pure water; for PVP/Chitosan blends, first Chitosan was dissolved in an acetic acid solution 2 wt%. The solutions were mixed at different amounts preparing PVP/HPMC and PVP/Chitosan blends with concentrations 10/90, 20/80, 30/70, 40/60, 50/50, 60/40, 70/30, 80/20, and 90/10 w/w. Water was removed from the solutions at room temperature and the blends were received as cast films for further studies. From these blends weight ratios 90/10, 80/20, and 50/50 w/w were chosen for the preparation of Fluconazole solid dispersions by mixing the proper amounts of the polymers' solution and a very dilute aquatic solution of Fluconazole in ethanol. The drug content at these dispersions was 10 and 40 wt%. The solutions, after mixing, were sonicated for 15 min and poured in petri plates. In order to remove the solvent, the mixtures were maintained in a vacuum oven at 40°C for 48 h. After complete removal of the solvent, the solid dispersions were stored at 25°C in a desiccator over silica gel.

Differential Scanning Calorimetry (DSC)

DSC studies of the prepared samples were conducted using a Perkin Elmer Pyris 1 DSC equipped with Intracooler 2P cooling accessory. Samples of 5mg were placed in standard aluminium pans. Heating scans at 20°C/min or 100°C/min were applied with a nitrogen purge of 20 ml/min in all drug solid dispersions. Fast-heating rates should be preferred in order to prevent changes during scanning. In the case of studied miscible blends heating rates of 20°C/min were used.

Dynamic Mechanical Analysis (DMA)

The dynamic mechanical properties of the blends were measured with a Perkin Elmer analyzer (Diamond DMA). The bending (dual cantilever) method was used with a frequency of 1 Hz, in the temperature range from 25°C to 220°C. The heating rate was 3°C/min. The testing was performed using rectangular bars measuring approximately 50 × 10 × 2 mm. The exact dimensions of each sample were measured before the scan.

Wide-angle X-ray Diffractometry (WAXD)

WAXD study of the samples after storage for ten days as well as after six months was performed over the range 2 θ from 5 to 60°, at steps of 0.05°C. A Philips PW1710 powder diffractometer, with CuK_{α} Nickel-filtered radiation was used.

Scanning Electron Microscopy (SEM)

The morphology of the samples was examined by a scanning electron microscopy system (SEM) Jeol (JMS 840). The films were covered with carbon coating in order to increase conductivity of the electron beam.

Fourier Transformed-Infrared Spectroscopy (FT-IR)

FTIR spectra were obtained using a Perkin-Elmer FTIR spectrometer, model Spectrum One. A small amount of each material was mixed with KBr (1 wt% drug content) and compressed to tablets. The IR spectra of these tablets were obtained in absorbance mode and in the spectral region of 450 to 4000 cm^{-1} using a resolution of 4 cm^{-1} and 64 co-added scans.

Dissolution Testing

A dissolution apparatus I of USP (baskets) type DISTEK 2100C was used. An appropriate amount of each system, equivalent to 100 mg of Fluconazole was filled into a hard gelatin capsule. Powder with particle size distribution of 50–250 mesh was used. The empty capsules were pretested concerning their disintegration time in the dissolution medium. Their effect on the obtained dissolution rate was found to be negligible. The capsules were placed into the baskets before the initiation of the dissolution testing which was performed at 37 ± –0.5ºC and 100 rpm, using 900 mL HCl 0.1 N as a dissolution medium. Samples were collected using an automatic sampler type Distek Evolution 4300, filtered by nylon filters (Wattmann 0.45 μm) and analyzed immediately after sampling, according to an appropriately HPLC method. Each test was performed in triplicate while the RSD was found to be less than 3%.

The analyses were performed using an HPLC system (Varian, Palo Alto, CA, USA) consisting of two high-pressure solvent delivery pumps (Model 2510), a static high-pressure mixer (Model 2584), a variable wavelength UV-Vis detector (Model 2550), a manual injector with a 20 μl loop (Rheodyne, Cotati, CA, USA), and an integrator (Model 4290). Separation was performed on a Macherey Nagel Nucleosil C18 analytical column (5 μm particle size, 250 × 4.6 mm I.D.), proceeded by a guard column (20 × 4.6 mm I.D.) dry packed with pellicular ODS material (37–53 μm).

The mobile phase used was tris(hydroxymethyl)aminomethane phosphate (25 mM, pH 7):acetonitrile (75:25, v/v), and the analytes were detected at 260 nm. The flow rate of the mobile phase was 1 ml/min and the column temperature was 30°C.

RESULTS AND DISCUSSION

Dissolution Enhancement Using Neat Polymers as Drug Carriers

As was reported in the introduction, the aim of this work was mainly to evaluate the use of polymer blends as drug

carriers. First, the solid dispersions of Fluconazole, which also was used as a model drug, in the pure polymers were studied. Prior to studying the physicochemical characteristics of Fluconazole in its formulations and the respective dissolution profiles, the thermal behavior and solid structure of the pure drug was examined. Figure 2, shows the DSC heating scan of crystalline and amorphous Fluconazole prepared by quenching in liquid nitrogen, at a heating rate 20°C/min. From this DSC trace it is concluded that the drug has a melting temperature (T_m) of 141°C while after amorphization its glass transition temperature (T_g) is recorded at about 35°C. Also a cold-crystallization occurred during heating, the peak temperature being T_{cc} = 104.8°C, while the onset of the cold-crystallization was at about 85°C, which is much higher than the T_g. Though this finding refers to a heating rate of 20°C/min, it is important from a practical point of view, since it means that the amorphous Fluconazole should not be anticipated to crystallize during storage at room temperature, or at least that its crystallization rates would be slow. The DSC trace of the dug sample as received from the supplier showed high crystallinity. This also was confirmed by the WAXD pattern of the as-received drug sample as it showed sharp peaks, which prove a fine crystal structure and the high purity of the sample (see Figure 3). The SEM micrographs of the pure drug powder showed a mean particle size of about 30 μm.

Approximately 80% of all pharmaceutical drug formulations are in the solid dosage form. Thus, in pharmaceutical applications the size, shape, and physical state of the solid particles are important because they can affect the bioavailability of drug particles. Since the bioavailability of orally applied drugs depends on the rate of dissolution and absorption, methods to increase the rate of dissolution are often necessary to reach significant blood levels. The dissolution rate is directly proportional to the surface area of the drug (Noyes-Whitney equation) and a suitable way to increase the rate of dissolution

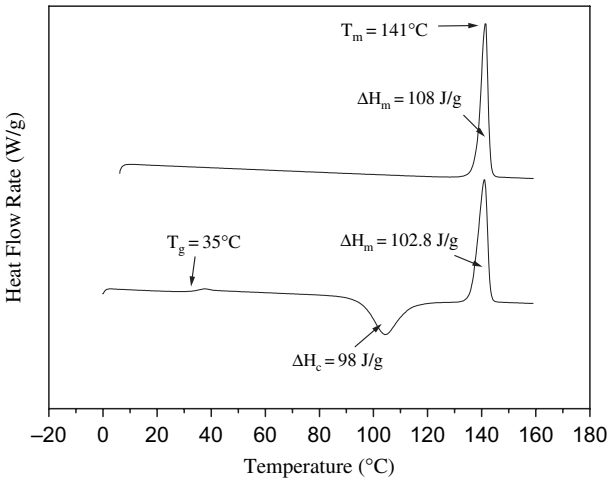


FIGURE 2. DSC trace for amorphous Fluconazole. Heating rate 20°C/min.

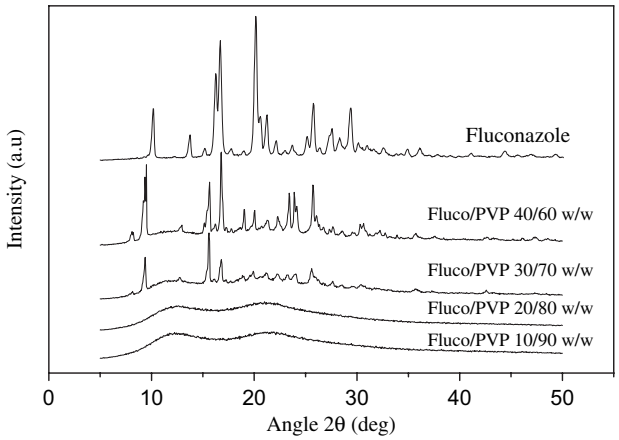


FIGURE 3. WAXD patterns for PVP/Fluco solid dispersions.

is the reduction of the particle size. Micronization to particle sizes of about 3–5 μm is often a successful strategy for enhancing the dissolution rate. In order to evaluate the change in release rates of Fluconazole caused by dispersing the drug in polymer matrices, first a series of solid dispersions of the drug in PVP were prepared, as described in the experimental section. The solid state of Fluco/PVP solid dispersions was studied by WAXD. As can be seen in Figure 3 solid dispersions with 20% drug or less did not show crystalline reflections, thus it should be supposed that the drug was amorphous. This was in contrast to what was observed in the WAXD patterns for the respective physical mixtures, where crystalline drug reflections were recorded. It must be mentioned that WAXD is a sensitive technique for detecting crystalline content in solid dispersions (Bikiaris et al., 2005). Furthermore, in the patterns for the solid dispersions with 30 or 40% drug, its crystalline peaks were observed, indicating that an over-saturated solid dispersion was prepared. The most interesting feature was that most of these peaks, if not all, were located at different positions compared to those for the as-received pure Fluconazole sample. It seems that a second polymorph of the drug appeared. It is known that Fluconazole shows different polymorphic forms (Gu & Jiang, 1995). This is usual for pharmaceutical substances and the polymorphic forms appear often, depending on the preparation method for the solid dispersions formations (solvent evaporation or melt mixing) (Papageorgiou et al., 2006). Probably the crystallization of Fluconazole from an ethanol solution, where PVP also was present, leads to the formation of the second crystal modification.

The results from the DSC study of the samples were in agreement with those from WAXD. The DSC traces for the solid dispersions with 20 or 10 wt% drugs did not show any melting peak, as one can see in Figure 4. Also, the glass transition temperatures for these solid dispersions were between those for the pure drug (35°C) and the pure polymer (167°C) and shifted to lower values with increasing the drug content. These T_gs were recorded at 129 and 112°C for solid dispersions

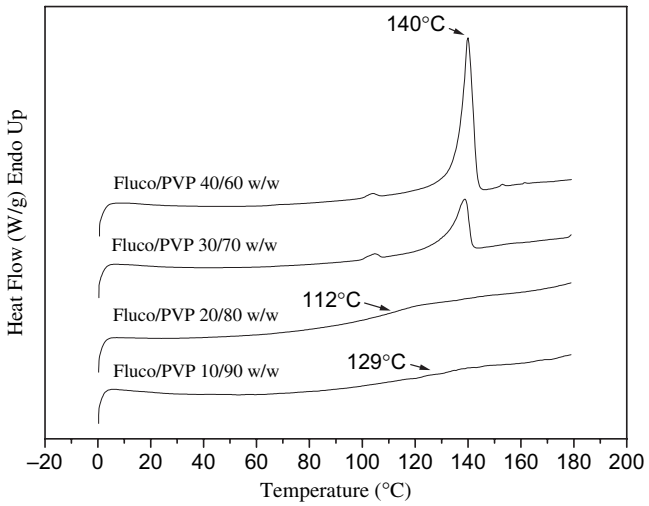
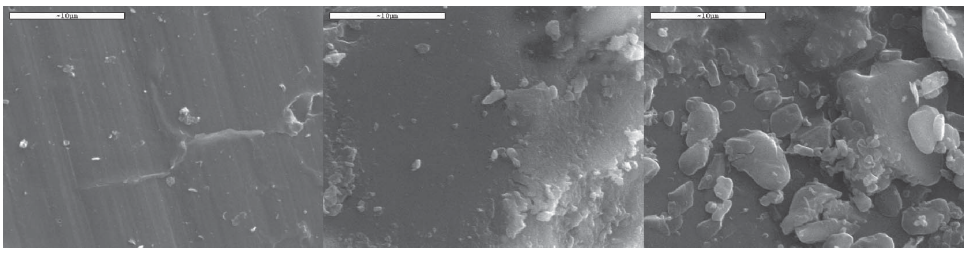


FIGURE 4. DSC traces for Fluco/PVP solid dispersions.

containing 10 and 20 wt% Fluconazole, respectively. This is an indication of a molecular dispersion and that miscibility of the drug and the polymer in the amorphous phase has been achieved, which is very usual in similar solid dispersions (Gupta & Bansal, 2005; Gupta, Thilagavathi, Chakraborti, & Bansal, 2005; Kaushal, Gupta, & Bansal, 2004). This was confirmed by the SEM microphotographs for the Fluco/PVP 10/90 w/w solid dispersion (Figure 5A), which revealed only a smooth surface. Since these formulations are completely amorphous, the drug particles' size could not be determined. For higher drug content, the melting peak of the drug was obvious in the respective DSC traces. The melting peak temperature at 140°C was approximating that for the pure drug (141°C). It seems that the two polymorphs of Fluconazole melt at almost the same temperature. In these formulations few drug particles are detectable with SEM analysis. As can be seen in Figure 5B particles with size of less than 1 μm are obvious in the sample containing 30 wt% Fluconazole, while the particle size increased up to 5 μm for the solid dispersion containing 40 wt% drug (Figure 5C).

The release of Fluconazole from these solid dispersions was studied in comparison to the pure drug (Figure 6). It is obvious that the release rates from the solid dispersions in PVP were remarkably increased compared to the pure drug. However, as can be seen, they decreased with increasing the drug load. This behavior is reasonable since for low drug content amorphization of Fluconazole, fine dispersion and particle size reduction was achieved. In such amorphous dispersions it is claimed that the drug is dispersed in molecular level or in the form of nanodispersions (Kanaze et al., 2006; Karavas et al., 2007). In both these cases the drug particles were less than 1 μm in diameter (as was already proved by SEM analysis), which is essential to enhance the dissolution rate of a poorly water soluble drug (Serajudin, 1999). PVP seems to be an ideal matrix for preparing drug dispersions in amorphous form since it is an amorphous material itself. However as can be seen in Figure 6 amorphization is not the only factor that affected the dissolution rate of the drug. It is important to note that even in the case of the Fluco/PVP 40/60 w/w solid dispersion, more than 90% of the drug was released in 60 min; for the dispersion containing 30 wt% drug, the release took about the same time to complete. At these dispersions a part of the drug amount is crystalline, but in the form of very small crystal particles, less than 5 μm, increasing the available surface for dissolution (Leuner & Dressman, 2000). Thus, the particle size reduction also was important for dissolution rate enhancement (Hu, Johnston, & Williams, 2004). Finally, this behavior might be the result of an improved wetting due to the presence of the polymer (Vaughn et al. 2006, Pandit, Strykowski, McNally, & Wallbillig, 1985; Wong, Kellaway, & Murdan, 2006).

Apart from PVP, two additional polymers were used as drug carriers containing appropriate reactive groups, namely HPMC and chitosan. They contain hydroxyl and amino groups, respectively, which can form hydrogen bonds with the functional groups of Fluconazole leading to amorphization of the drug in the dispersions, as in the case of PVP. HPMC also has been used as an effective carrier to prepare solid dispersions intending to increase the dissolution rates of other parmaceutical substances like Felodipine, another poorly water soluble drug (Karavas et al., 2001). The effectiveness of HPMC as carrier for immediate or controlled release drug formulations depends on its molecular weight (Mitchell et al., 2003; Okimoto et al., 1997). The WAXD patterns of these HPMC based formulations showed that most of the drug was rather amorphous, especially for low drug content (Figure 7A). The



A B C

FIGURE 5. SEM microphotographs for the Fluco/PVP solid dispersions containing different drug content (A) 10 wt%, (B) 30 wt%, and (C) 40 wt%.

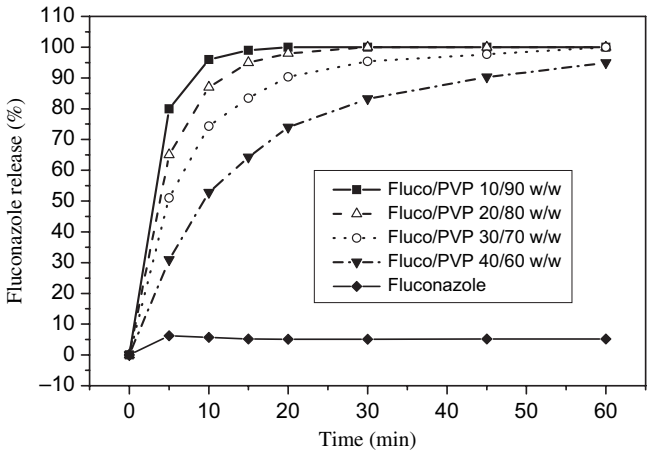


FIGURE 6. Fluconazole release profile from Fluco/PVP solid dispersions.

WAXD study showed successful amorphization of the drug. For the Fluco/HPMC 40/60 w/w solid dispersion some peaks corresponding to reflections of Fluconazole crystals were observed. Some very weak peaks were recorded in the Fluco/HPMC 30/70 w/w pattern (Figure 7A). Similar to what was observed in the cases of solid dispersions in PVP, the peaks' positions show formation of another polymorphic form of the drug. However, it seems that HPMC is a more appropriate carrier to prepare dispersions with higher amorphisation. In agreement with the WAXD observations the DSC data proved that only a very small drug portion remained in the crystalline state, and most of the drug was amorphous. The DSC traces showed a very small melting peak for the solid dispersion containing 30 wt% drug (Figure 7B). This increased in heat of fusion for the 40/60 w/w sample.

Fourier transform infrared spectroscopy (FTIR) is a versatile technique for studying specific interactions between reactive groups in drug/polymer solid dispersions. Consequently, in the prepared Fluco/HPMC solid dispersions, it is expected that intermolecular hydrogen bonding between the hydroxyl groups of HPMC and the hydroxyl or fluoride groups of Fluconazole might be created. To gain a deeper understanding of the hydrogen-bonding interactions in Fluco/HPMC dispersions, their FTIR spectra were studied. From all spectrum areas, two regions that the hydroxyl groups of both materials were absorbed are of great importance. These are recorded in the range 3000–3700 cm^{-1} (Figure 8A) and at 900–1300 cm^{-1}, respectively (Figure 8b).

In the HPMC spectrum, the characteristic peaks appear at 3050–3750 cm^{-1} (Figure 8A), which are attributed to the –O-H bond stretching, while the triple peak in the so-called fingerprint spectrum area of >C-O- appears at 960–1230 cm^{-1} (Figure 8B). A broad band at 3442cm^{-1} denotes the superposition of stretching for two types of hydroxyl groups in HPMC: (1) Free hydroxyl groups, at 3585 cm^{-1} and (2) self-association of hydroxyl groups through intermolecular and intramolecular hydrogen bonding at 3444 cm^{-1} that is not easily observed due to the peak broadness. On the other hand Fluconazole's hydroxyl groups absorbed at 3185 and 2292 cm^{-1} and at 1104 and 1143 cm^{-1}. The intensity and the position of these characteristic peaks of both polymers permit us to interpret rather easily the influence of interactions between these groups. From the FTIR spectra of the prepared solid dispersions it can be seen that as the amount of Fluconazole increases the hydroxyl band of HPMC moves to different wavenumbers. Thus the peaks at 1122 and 1064 cm^{-1} are moved to 1118 and 1060 cm^{-1} respectively. However the most intense shifts are in the area of wavenumbers 3100–3600 cm^{-1}. The peak of pure HPMC at 3445 cm^{-1} is moved to 3470 and 3491 cm^{-1} in the solid dispersions containing 30 and 10 wt% Fluconazole (Figure 8a). These differences are strong indications that hydrogen bonds are formed between the Fluconazole and HPMC, which are

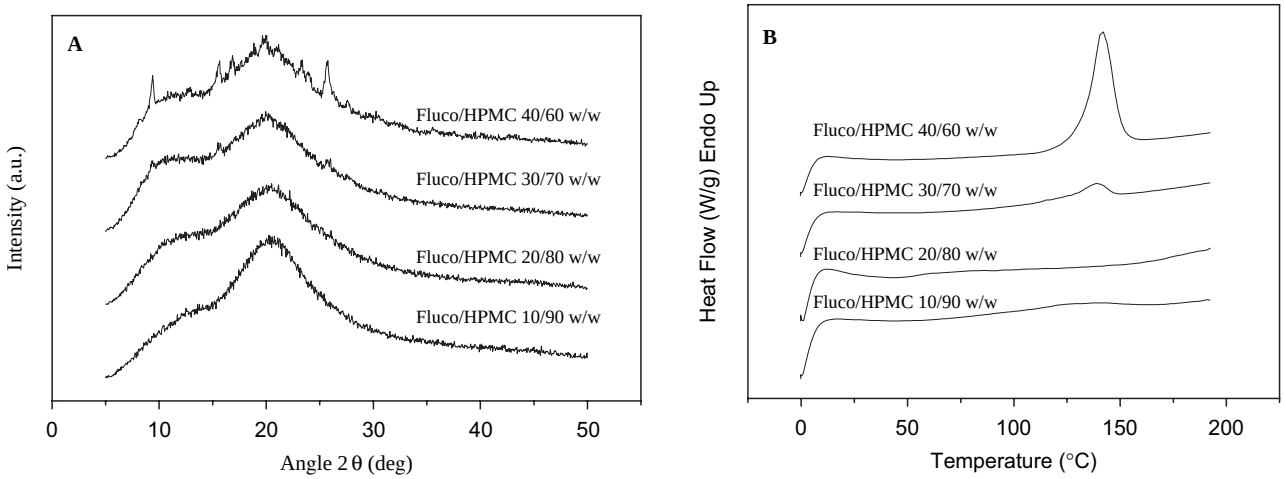


FIGURE 7. (A) WAXD patterns and (B) DSC traces for Fluco/HPMC solid dispersions.

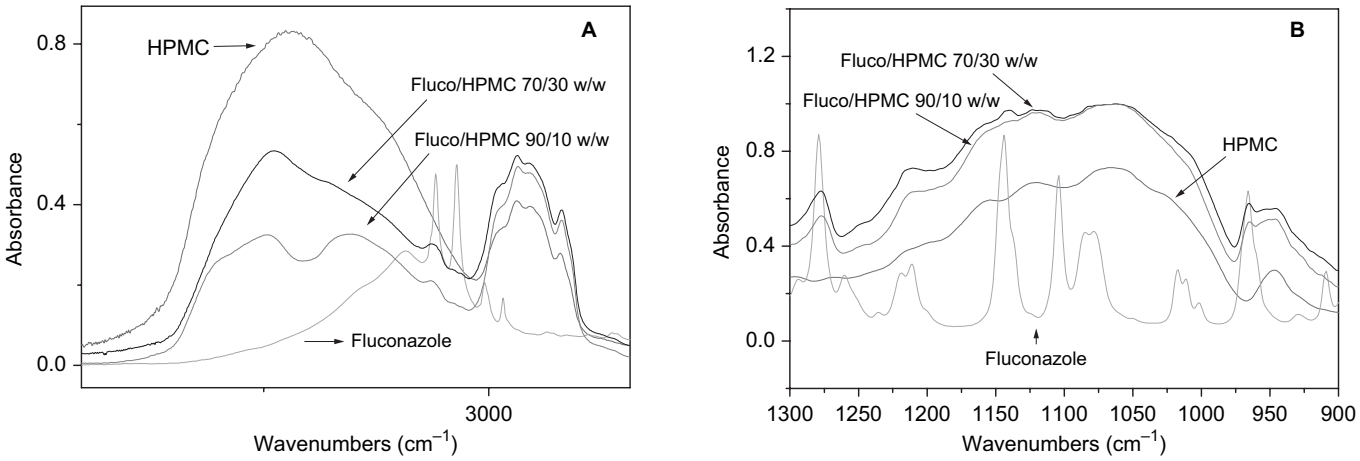


FIGURE 8. FTIR spectra of Fluconazole, HPMC, and their solid dispersions: A) in the range 3100–3600 cm^{-1} and B) in the range 900–1300 cm^{-1}.

responsible for the amorphization and the finer drug dispersion into the polymer matrix of the particular formulations.

What is important in the case of such formulations is the modification in the release rates of the dispersed drug. The respective tests showed an increase in the Fluconazole release rates from Fluco/HPMC solid dispersions comparing to the pure drug, probably as a result of the amorphization and particle size reduction (Figure 9). However, the release rates of Fluconazole increased with increasing the drug load, in contrast to what was found for the solid dispersions in PVP. Furthermore, the release rates were slower than those from dispersions in PVP.

It is well known that HPMC is dissolved very slowly in water and, in fact, first it swells in aquatic media resulting in rather slow release rates. For this reason, in the dispersions with the highest drug content, a large portion of the drug is dispersed in the surface of the HPMC particles. This drug amount is immediately released, and as can be seen only from the solid dispersion containing 40 wt% Fluconazole, 100% release was achieved at a time shorter than 40 min. At this formulation almost half of the tablet used for dissolution tests is made from drug, which dissolves almost immediately due to the high amorphization and particle size reduction of the drug. Thus, the tablet disintegrates rapidly. SEM micrographs of the respective samples (data not shown) proved a behavior similar to that already discussed for Fluco/PVP solid dispersions and shown in Figure 5. Thus in such high drug load the release rate is not controlled by diffusion, but rather by matrix disintegration. The release rates of Fluconazole from the Fluco/HPMC 40/60 formulation were high compared to those from Fluco/PUP solid dispersions, because more effective amorphization of the drug was achieved in the case of Fluco/HPMC 40/60 formulation. As can be seen from the WAXD patterns, the peak intensity for the drug is much higher in the case of solid dispersions in PVP (Figures 7A and 3). As the amount of the drug becomes lower, the release rate is obviously controlled by a drug diffusion process resulting in retardation, especially from the formulations containing 10 and 20 wt% Fluconazole. In these solid dispersions the drug also is amorphous, but the matrix cannot disintegrate rapidly and thus it diffuses through the formed gel layer.

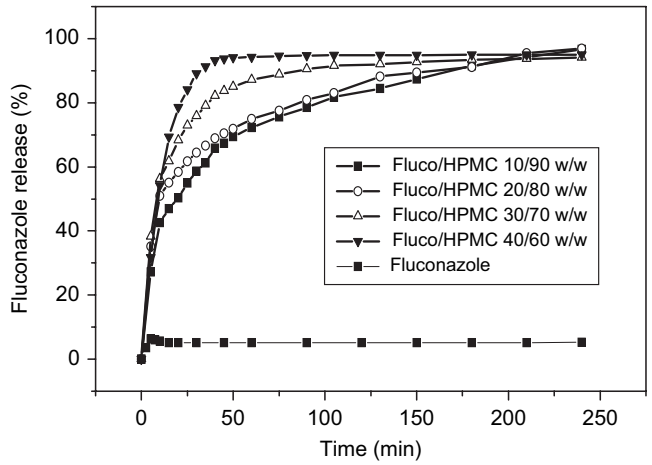


FIGURE 9. Fluconazole release profile from Fluco/HPMC solid dispersions.

The release behavior of Fluco/Chitosan solid dispersions is different from those of the Fluco/PVP and Fluco/HPMC formulations. As can be seen from Figure 10 the release rate is very low and even after 25 h only a portion of the whole drug amount was released from the dispersions containing up to 30 wt% Fluconazole. Only for the sample containing 40 wt% of Fluconazole the drug release is complete. This behavior must be attributed to the nature of the particular polymer. It is well known that Chitosan is soluble only in acidic conditions (pH < 5) and in contact with water it is only hydrated and slightly swells. In fact, even in acidic conditions the tablets of Fluco/Chitosan solid dispersions used for dissolution studies swelled and were very slowly dissolved. Thus, in these formulations the release rate is completely controlled from the drug

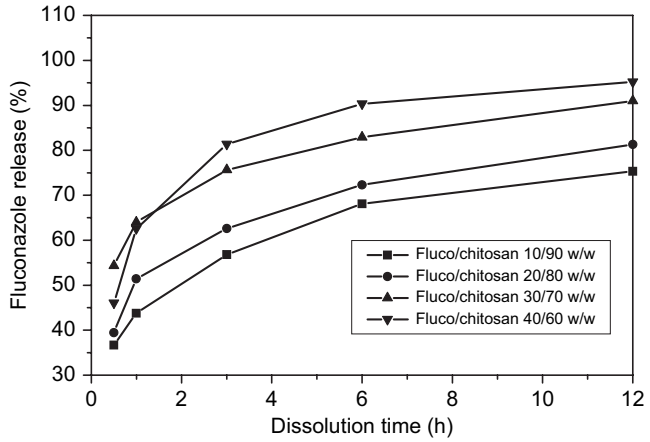


FIGURE 10. Fluconazole release profile from Fluco/Chitosan solid dispersions.

diffusion. As the amount of drug lowers the diffusion is more difficult and the release rate becomes lower. In order to exclude any effect caused by the physical state of the drug into chitosan matrix and the particle size distribution on the dissolution rate, the particular formulations were further studied with WAXD and DSC. From the WAXD patterns and DSC thermograms it was verified that the physical state of Fluconazole in these formulations is similar to that reported for HPMC (data not shown). The drug at low content is completely amorphous and only at concentrations 30 and 40 wt% is some crystallinity detected. Thus the physical state could not explain such a dissolution profile and the particular rates should be attributed to the chitosan matrix.

Dissolution Enhancement by Using Miscible Polymer Blends as Drug Carriers

From the above study it was found that even though HPMC and Chitosan are effective carriers for drug amorphization and preparation of fine dispersed drug formulations, both are inappropriate as carriers for immediate release. However, it is well known that the physicochemical properties of a polymeric matrix can be modified by mixing with others and creating miscible blends. From our previous studies it was found that PVP can create fully miscible blends with HPMC and Chitosan due to the interactions taking place between the reactive groups of the polymers. (Karavas et al., 2006b). Polymer blending provides a relatively facile means of combining the separate desirable properties of different polymers into a single new matrix. Thus, miscible blends were used for adjusting the drug release rates of several drugs (Edlund & Albertsson, 2000; Lyu, Sparer, Hobot, & Dang, 2005; Tomkins, Konotopoulou, & Amsden, 2005). It was proved that PVP can enhance the dissolution rate of Fluconazole but more drastically in the case of a low drug content. In contrast for matrices like HPMC or Chitosan, the reverse phenomenon is observed with the drug release rates to be higher from solid dispersions containing higher drug loading. Thus, in the present study PVP/HPMC and PVP/chitosan miscible blends were used as carriers in an attempt to prepare solid dispersions from which the dissolution rates of Fluconazole could be modified, compared with those from respective dispersions in the neat polymers (HPMC or Chitosan) alone. Preparation and characterization of these miscible polymer blends were described in our previous paper and is out of the scope of the present study. Thus only some limited data are presented.

In general, for binary polymer blends a single composition dependent T_g intermediate of those for the pure components is considered to be a proof for miscibility (Bikiaris et al., 2004; Papageorgiou & Bikiaris, 2006). In Figure 11 the DMA studies of PVP/HPMC (Figure 11A) and DSC thermograms of PVP/Chitosan blends (Figure 11B) are presented, proving that both polymer pairs are completely miscible in the entire composition area. The DMA study in PVP/HPMC blends showed that

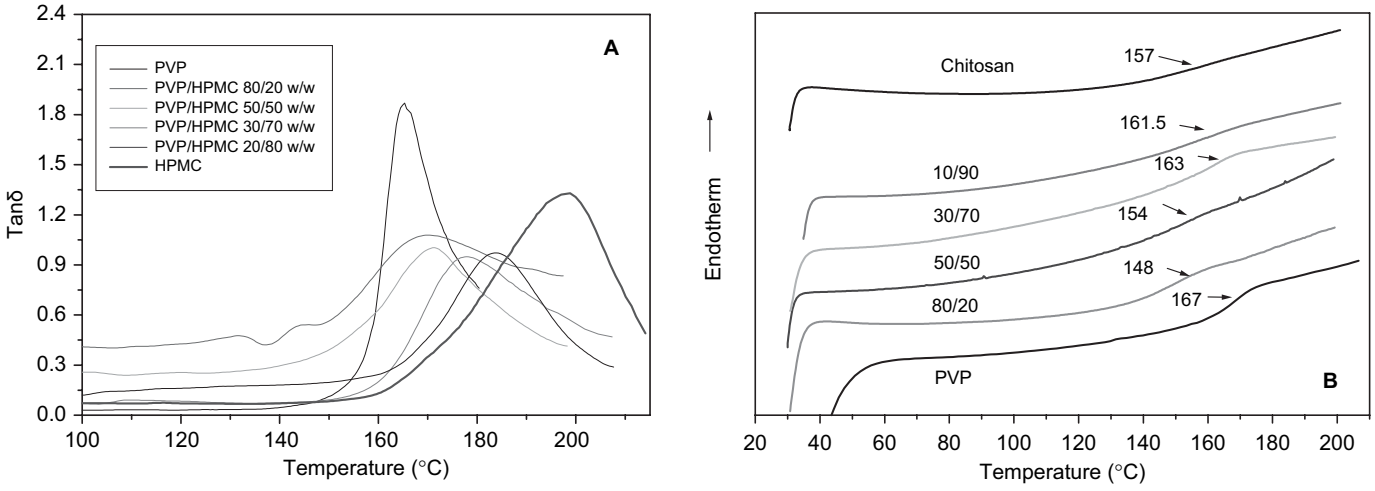


FIGURE 11. (A) DMA traces for the PVP/HPMC miscible blends showing the variation of T_g (Tanδ) with the composition; (B) DSC thermograms of PVP Chitosan blends.

the T_g values for the blends, in the whole range of composition, were intermediate of those for the pure polymers and varied with blend composition, indicating that the two polymers are miscible. Similarly, single composition dependent T_g also was found for each of the PVP/Chitosan blends, indicating that these blends are miscible over the entire composition range as the result of the strong interactions between the carbonyl group of PVP and the amino groups of Chitosan (Karavas et al., 2006b).

From each series of PVP/HPMC or PVP/Chitosan miscible blends three cases were tested for their efficiency as drug carriers with the weight ratios being 90/10, 80/20, and 50/50 w/w, respectively. Using the discussed blends solid dispersions having drug content 10 or 40 wt% were prepared. For all the solid dispersions containing 10 wt% drug the DSC showed no sign for melting of crystalline Fluconazole. In accordance to the DSC observations, the WAXD patterns did not show any drug crystal reflections (Figure 12). These observations show the effectiveness of the carries also in the form of blends to obtain

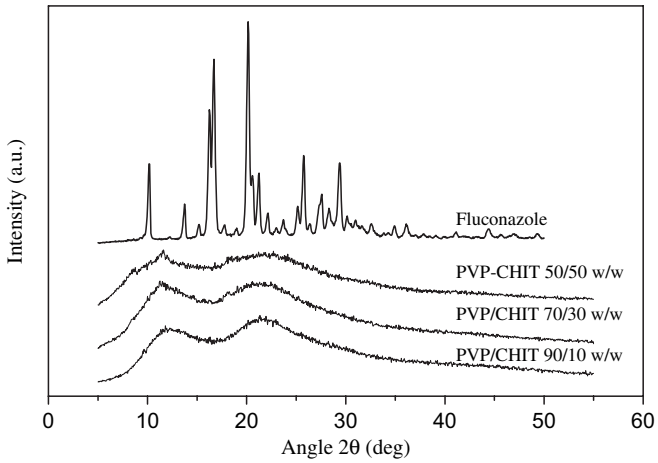


FIGURE 12. WAXD patterns for solid dispersions of Fluconazole in PVP/Chitosan blends. Drug content 10 wt%.

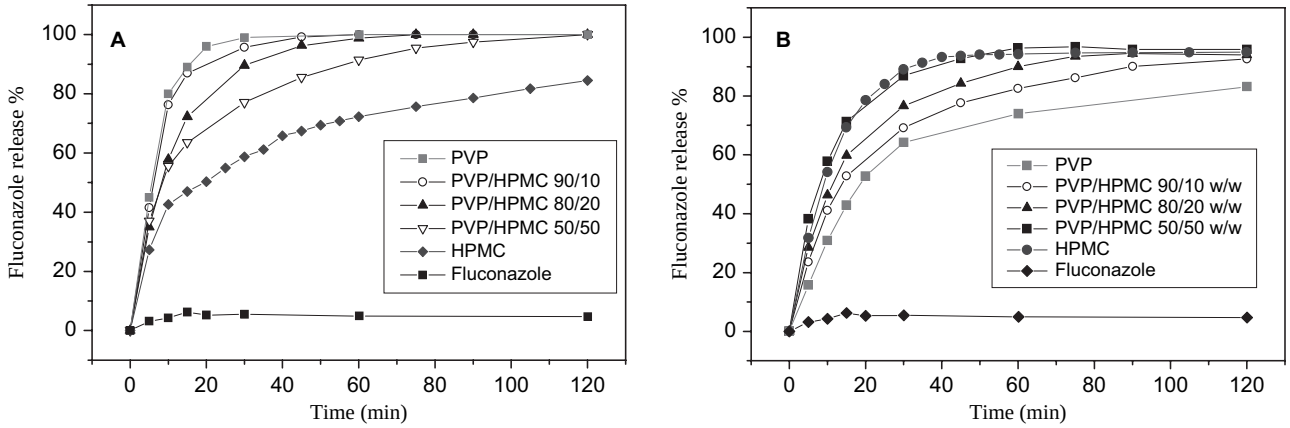


FIGURE 13. Fluconazole release profile from its solid dispersions in PVP/HPMC miscible blends with compositions 90/10, 80/20, and 50/50 w/w containing (A) 10 wt% Fluconazole and (B) 40 wt% Fluconazole.

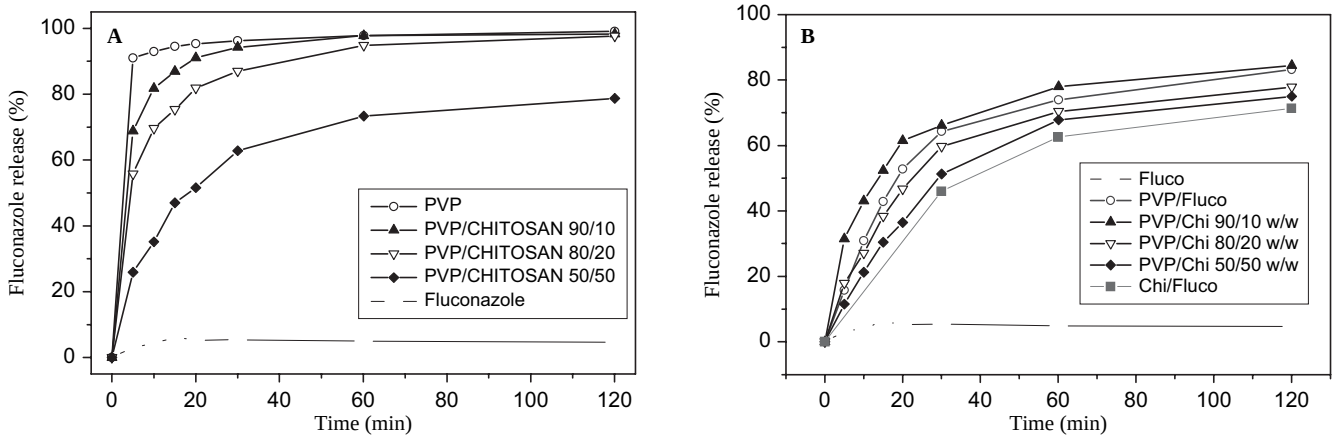


FIGURE 14. Fluconazole release profile from its solid dispersions in PVP/Chitosan miscible blends with compositions 90/10, 80/20, and 50/50 w/w containing (A) 10 wt% Fluconazole and (B) 40 wt% Fluconazole.

amorphous dispersions. However, when the drug load was 40 wt%, in all WAXD patterns the characteristic peaks of drug were detected indicating that a small portion of the drug was in the crystalline state. It seems that the behavior of Fluconazole in dispersions in the blends is almost identical to when the neat polymers were used as carriers. Also, the SEM microphotographs revealed fine dispersion of the drug in the carrier, as was already reported for neat polymers.

The dissolution rate measurements showed that the release profile of the drug from the PVP matrix was modified by blending PVP with HPMC. In the case that 10 wt% of Fluconazole was used it can be seen in Figure 13A that the release rates were retarded with increasing HPMC weight ratio. Only in the blend containing 10 wt% HPMC the release rate is almost identical with the corresponding neat PVP. However, in the blends that Fluconazole was used at 40 wt% loading it can be seen that the release rate became lower by increasing the PVP content (Figure 13B). Furthermore, the dissolution of Fluconazole was drastically enhanced for the blend containing equal amounts of each polymer (PVP/HPMC 50/50 w/w). For the other blends the release rate is slightly lower. From these dissolution profiles it can be concluded that the release of Fluconazole can be controlled by using different PVP/HPMC blend ratios. The benefit is the high dissolution rate achieved for drug loading 40 wt%. This could not be achieved with the use of PVP alone.

The release rate of Fluconazole from dispersions in PVP/Chitosan blends is for both of the tested drug amounts (10 and 40 wt%), dependent on the Chitosan content in the blend. As can be seen in Figure 14, by increasing the chitosan content in the blend the release rate became lower. Thus the enhancement that was achieved in the case of dispersions in PVP/HPMC blends could not be reached in these formulations. This is similar to what was observed in the case of solid dispersions in pure Chitosan compared with those in pure PVP or pure HPMC. Chitosan can only swell and the resulting dissolution rates through such polymer layers are slow. Thus, it can be said that these blends are appropriate to control the release rate of the drug, but not for a significant dissolution enhancement.

CONCLUSION

Solid dispersions of the poorly water-soluble drug Fluconazole using polyvinylpyrrolidone or its blends with hydroxypropylmethylcellulose or chitosan were tested. Fluconazole was used as a model drug. In most cases the drug was found to be amorphous with an exception for a high drug load in the samples; also the release profile was improved. The results proved that tailoring the dissolution rates of poorly soluble drugs could be achieved using such polymer blends based on PVP. Thus, a variety of carriers is offered, suitable for the preparation of immediate or controlled release formulations.

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