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Research Article

Evaluation of Griseofulvin Binary and Ternary Solid Dispersions with HPMCAS

Hisham Al-Obaidi[1,2] and Graham Buckton[1]

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Abstract. The stability and dissolution properties of griseofulvin binary and ternary solid dispersions were evaluated. Solid dispersions of griseofulvin and hydroxypropyl methylcellulose acetate succinate (HPMCAS) were prepared using the spray drying method. A third polymer, poly[*N*-(2-hydroxypropyl) methacrylate] (PHPMA), was incorporated to investigate its effect on the interaction of griseofulvin with HPMCAS. In this case, HPMCAS can form H bonds with griseofulvin directly; the addition of PHPMA to the solid dispersion may enhance the stability of the amorphous griseofulvin due to greater interaction with griseofulvin. The X-ray powder diffraction results showed that griseofulvin (binary and ternary solid dispersions) remained amorphous for more than 19 months stored at 85% RH compared with the spray-dried griseofulvin which crystallized totally within 24 h at ambient conditions. The Fourier transform infrared scan showed that griseofulvin carbonyl group formed hydrogen bonds with the hydroxyl group in the HPMCAS, which could explain the extended stability of the drug. Further broadening in the peak could be seen when PHPMA was added to the solid dispersion, which indicates stronger interaction. The glass transition temperatures increased in the ternary solid dispersions regardless of HPMCAS grade. The dissolution rate of the drug in the solid dispersion (both binary and ternary) has significantly increased when compared with the dissolution profile of the spray-dried griseofulvin. These results reveal significant stability of the amorphous form due to the hydrogen bond formation with the polymer. The addition of the third polymer improved the stability but had a minor impact on dissolution.

KEY WORDS: amorphous solid dispersion; dissolution rate; hydrogen bonding; PHPMA; spray drying HPMCAS.

INTRODUCTION

Poor aqueous solubility of hydrophobic drugs remains a challenge for oral drug delivery (1–3). The low solubility often results in a low fraction of the administered dose being absorbed, which results in low bioavailability. A classical example on such drugs is griseofulvin, which is an antifungal drug being classified by the British Pharmacopeia as practically insoluble in water. Griseofulvin is also classified as class II drug according to its solubility and absorption profile (low solubility with good absorption through the gut) (4).

One of the promising methods to increase the dissolution rate is the use of amorphous solid dispersions (5–8). Solid dispersions are mixtures of the drug and the polymer (ideally molecular dispersions). The amorphous nature of these preparations dictates their higher dissolution profile as the amorphous form has a higher degree of disorder (higher free energy). Hence, no additional energy is required to break up the crystalline lattice (such as the case for the crystalline form). The dispersion of the drug molecules into the polymer matrix is another factor which increases the dissolution rate of the drug. In this case, when the drug is molecularly dispersed into a hydrophilic polymer, the wetting properties of the drug are greatly improved (9).

However, the tendency of the amorphous form to recrystallize on storage limits its use. In a recent study, we could significantly extend the stability of the amorphous form by preparing a solid dispersion of griseofulvin with two other polymers (ternary solid dispersion). Griseofulvin could form hydrogen bonds with one of the polymers, poly [*N*-(2-hydroxypropyl)methacrylate] (PHPMA), but not with polyvinylpyrrolidone (PVP). PHPMA acted as a linker molecule between griseofulvin and PVP; thus, a miscible mixture could be prepared. It was concluded that adding the third component can significantly extend the amorphous form of the drug when added to non-interacting drug/polymer mixture (10,11).

In this paper, we aim to use the same principle but using an interacting ternary system, i.e., griseofulvin can form hydrogen bonds with both polymers. The difference between binary and ternary solid dispersions in terms of stability and dissolution rate enhancement is the focus of this work. The first polymer is PHPMA and the second polymer is hydroxypropyl methylcellulose acetate succinate (HPMCAS; Fig. 1). Three different grades of HPMCAS are commercially available (H, L, and M) that differ in acetyl and succinoyl group content. These differences were used to compare the extent of interaction with the drug (in terms of hydrogen bond formation) (Table I).

Our hypothesis is based on the formation of a heterogeneous system of the polymers where thermodynamic stability

[1] The School of Pharmacy, University of London, 29-39 Brunswick Square, London, WC1N 1AX, UK.
[2] To whom correspondence should be addressed. (e-mail: hisham.al-obaidi@pharmacy.ac.uk)

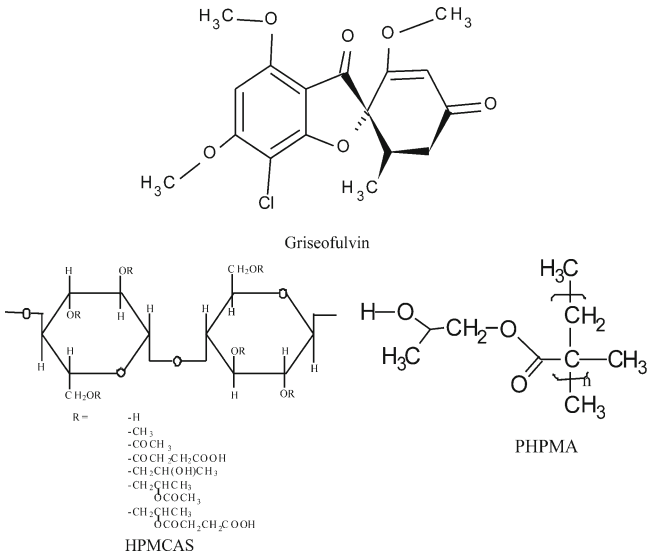

Fig. 1. Chemical structures of GF, HPMCAS, and PHPMA

is achieved by interaction of the polymers with each other in addition to the interaction with the drug. Another factor for stability is the kinetic retardation of drug molecular mobility due to the high viscosity of the polymer system.

MATERIALS AND METHODS

Materials

Griseofulvin was purchased from Sigma (Poole, Dorset, UK), and HPMCAS was obtained from Shin-Etsu chemical (Tokyo, Japan). PHPMA (MW=20,000) was obtained from Fisher (Loughborough, Leicestershire, UK). Acetone was purchased from BDH (Lutterworth, Leicestershire, UK). All chemicals were used directly without further purification.

Preparation of the Solid Dispersions

To prepare the binary solid dispersion, a mixture of griseofulvin (GF)/HPMCAS (50:50%) was prepared by adding 2.5 g GF 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 added and the solution stirred for at least 3 min. This was followed by the addition of HPMCAS (2.5 g). The mixture was stirred for 30–45 min until a clear solution was obtained.

The ternary solid dispersion of GF/PHPMA/HPMCAS (50:25:25%) was prepared by dissolving 2.5 g of GF into 185 mL acetone, and it was allowed to dissolve for at least 3 min followed by the addition of 85 mL distilled water, and the mixture was stirred for an extra 3 min. This was followed by the addition of 1.25 g HPMCAS which was dissolved in 30–45 min. Finally, PHPMA (1.25 g) was added to the solution and allowed to dissolve for 30–45 min.

The solution was then spray-dried using Niro SD-Micro spray dryer (Niro, Soeborg, Denmark) connected directly to a nitrogen generator (Domnick Hunter, Gateshead, UK). The spray drying parameters used in the experiment were inlet temperature (65°C), outlet temperature (45°C), system gas flow (25 kg/h), and atomizer gas flow 2.5 kg/h.

Measurement of the Glass Transition Temperatures of Solid Dispersions

Differential scanning calorimetry (DSC 7, Perkin-Elmer, Waltham, Massachusetts, USA) was used to measure the glass transition temperature of the prepared solid dispersions. Samples (5–10 mg) were accurately weighed into aluminum pans that were hermitically crimped. A heating rate of 10°C/min was used to measure the T_g of the solid dispersion. The heating range was from 30°C to 180°C. Indium was used as a calibrant which has an onset temperature of 156.6°C.

X-ray Powder Diffraction

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°. The samples were stored in a desiccator containing an excess amount of KCl to achieve a relative humidity of 85% at room temperature. The relative humidity inside the desiccator was checked regularly using a digital hygrometer.

Fourier Transform Infrared

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

Saturation Solubility Studies

An excess amount of the drug was added to 100 mL phosphate buffer (potassium dihydrogen orthophosphate and sodium hydroxide, pH 6.8), and the mixture was stirred at 100 rpm for 24 h using a Pharma Test dissolution apparatus (Pharma Test, Hainburg, Germany). The solution was then passed through a 0.22-μm filter and diluted with phosphate buffer (pH 6.8) in 50-mL volumetric flasks. The absorbance was measured using a Cary 3E UV–Visible Spectrophotometer (Varian, Palo Alto, CA, USA). The obtained value was

Table I. Acetyl and Succinoyl Group Contents of Different Grades of HPMCAS

	Grade	Acetyl (%)	Succinoyl (%)
HPMCAS	(L)	8	15
	(M)	9	11
	(H)	12	6

Data were taken from supplier (Shin-etsu, Japan)

then converted to concentration values to calculate the saturation solubility. The solubility experiments were carried out at 37°C.

Dissolution Test

The dissolution experiments were carried out using a USP II dissolution apparatus (Pharma Test) which was connected to a UV–Vis spectrophotometer (Cecil CE 2020, Cecil Instruments, Cambridge, UK) to analyze the samples. The samples (solid dispersions and spray-dried GF) were filled inside gelatin capsules (to achieve 3.33 μg/mL GF in the final dissolution media). Phosphate buffer (pH 6.8) was used as the dissolution medium (900 mL in each dissolution vessel) at 37°C with the paddles rotated at 100 rpm. Samples were taken at 10- to 20-min intervals from each of the vessels and filtered through 0.45-μm disposable filter units. The absorbance of the samples was measured at 295 nm.

RESULTS AND DISCUSSION

Characterization of Solid Dispersions

Spray-dried GF was studied using X-ray powder diffraction (XRPD) to determine the physical nature of the drug. The results showed that sharp peaks could be observed, indicating the presence of the crystalline form (Fig. 2). In fact, the corresponding area under the curve (if compared with the crystalline form) showed almost total crystallinity.

Most of amorphous materials tend to recrystallize on storage (12). If the drug is bound to the polymer, then crystallization of the drug could be prevented. We have

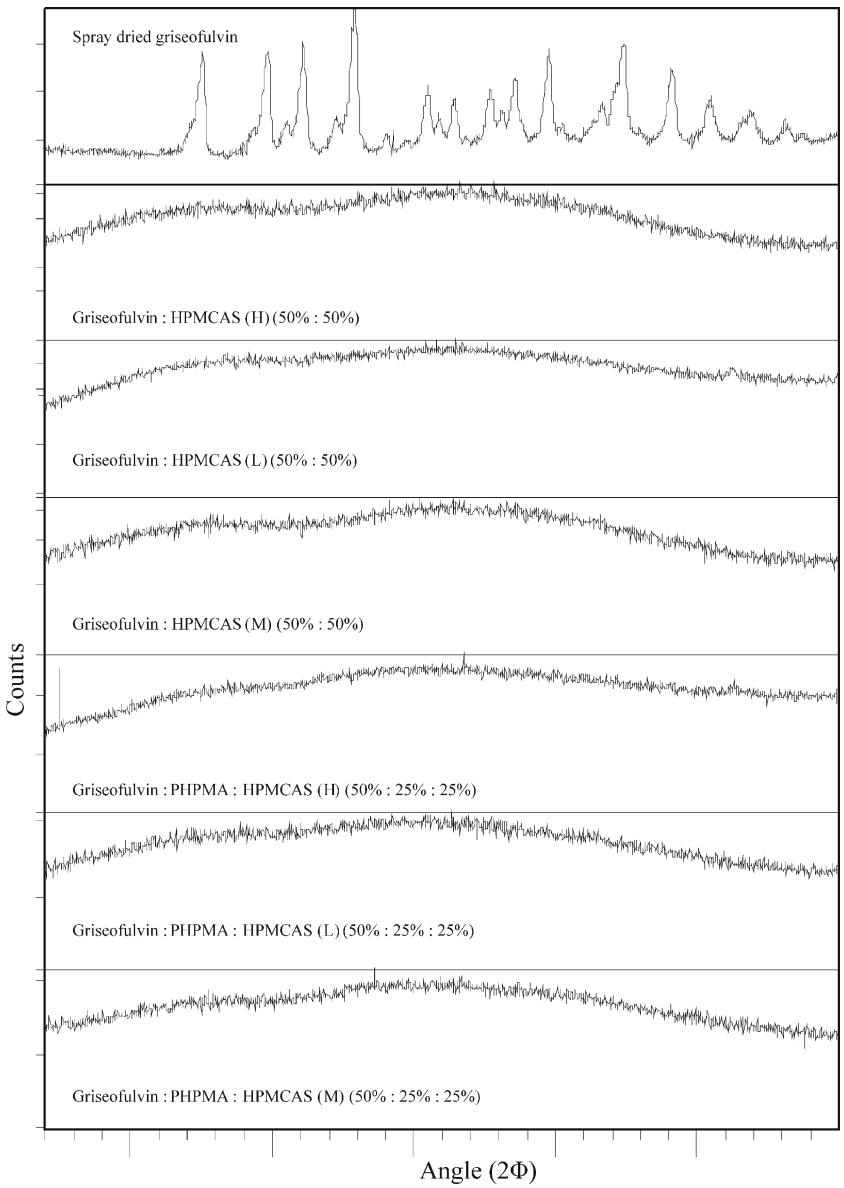

Fig. 2. X-ray powder diffraction pattern of solid dispersion of GF, HPMCAS, and PHPMA stored at 85% RH and at room temperature after 16 months from day of preparation

showed that the introduction of a linker polymer (PHPMA) can increase the stability of the solid dispersion of GF and PVP where the polymer and the drug cannot form hydrogen bonds (10,11). In this study, we endeavor to understand the role of the linking molecule (PHPMA) and whether the linking molecule extends the stability of the amorphous form of the drug and HPMCAS (to which GF can form hydrogen bonds). To test this hypothesis, the stability of spray-dried solid dispersions of GF and HPMCAS was studied (samples stored under high relative humidity and temperature) using XRPD. These conditions involved elevated relative humidity (85% RH). These conditions lead to increased molecular mobility of the drug molecules; thus, nucleation is initiated and subsequently crystal growth progresses.

The stability results showed that GF remained amorphous for more than 16 months when spray-dried with HPMCAS (Fig. 2). The solid dispersions which contained PHPMA showed similar amorphous form within the same time period. Remaining the drug in the amorphous form indicates that there is a specific interaction between GF and the polymers. The significant improvement in the stability of the amorphous form provides evidence that the amorphous form can be rendered stable. No significant differences were found between the stability of the drug in the binary and the ternary solid dispersion after 19 months (duration of the study) as the drug remained amorphous in both cases.

Table II. Glass Transition Temperatures of Griseofulvin, HPMCAS, and PHPMA Solid Dispersions

	T_g onset (°C)
HPMCAS (H)	117.9±0.9
HPMCAS (L)	118.8±1.4
HPMCAS (M)	117.3±0.8
Griseofulvin/HPMCAS (H) (50:50%)	81.1±0.3
Griseofulvin/HPMCAS (L) (50:50%)	81.2±0.3
Griseofulvin/HPMCAS (M) (50:50%)	82.5±0.2
Griseofulvin/PHPMA/HPMCAS (H) (50:25:25%)	82.7±0.6
Griseofulvin/PHPMA/HPMCAS (L) (50:25:25%)	84.2±0.9
Griseofulvin/PHPMA/HPMCAS (M) (50:25:25%)	83.4±1.4

FTIR Analysis of Hydrogen Bonding

To examine the possibility of hydrogen bond formation, an FTIR study was undertaken. As shown in Fig. 3, GF has two peaks; the first peak (1,712 cm^{-1}) corresponds to the stretching of carbonyl group of the benzofuran, and the second peak (1,662 cm^{-1}) corresponds to the stretching of the carbonyl group of cyclohexene (13). On the other hand, HPMCAS has carbonyl group stretching at 1,739 cm^{-1}. FTIR spectra showed that PHPMA has a peak at 1,722 cm^{-1} and another at 1,710 cm^{-1}. The first peak refers to the free carbonyl group, while the second peak refers to the bound carbonyl group to the hydroxyl group of PHPMA (intramolecular hydrogen bonding) (14).

The FTIR results showed that there is a broadening of the GF carbonyl peak at 1,662 cm^{-1} in the binary solid dispersion with HPMCAS (L) (Fig. 3). The FTIR scans of HPMCAS (H) and (M) were identical to that HPMCAS (L) (as well as to the solid dispersions); thus, we only show the results for HPMCAS (L). The broadened peaks indicated that the drug has formed hydrogen bonds, resulting in the shift of the peak toward lower frequency (1,650 cm^{-1}). The broadening also refers to the distribution of free and bound carbonyl groups of GF. Solid dispersions of HPMCAS (L)/GF were compared with the ternary solid dispersions containing PHPMA by FTIR to confirm the above finding of hydrogen bond formation. When PHPMA was incorporated, this broadening was increased and a shoulder could be observed. This suggests that stretching of the carbonyl group is divided into two peaks; the first corresponds to the

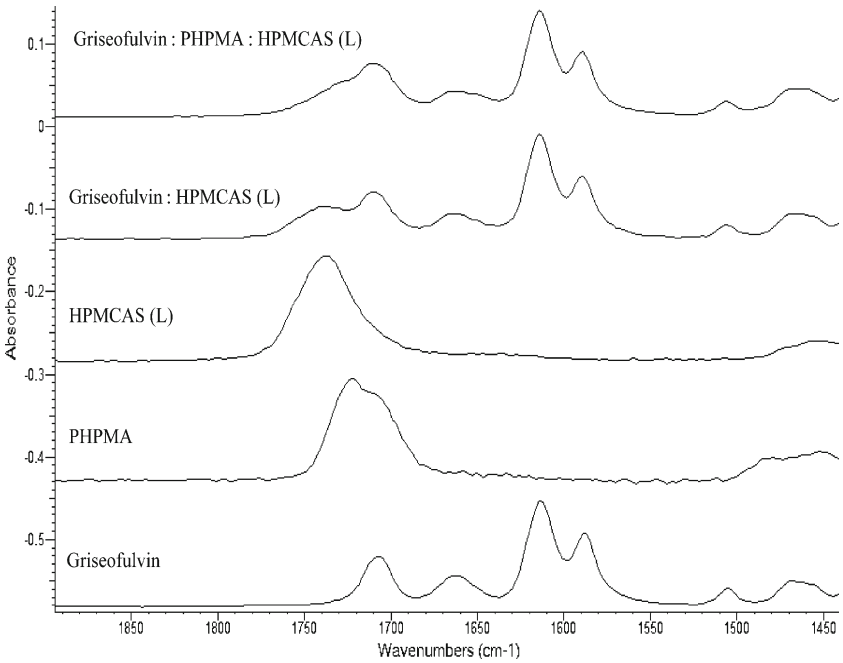

Fig. 3. Fourier transform infrared spectra showing the infrared absorption of GF, HPMCAS (L), and PHPMA and their solid dispersions

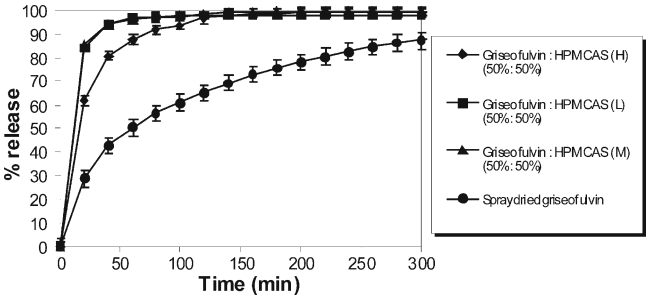

Fig. 4. Dissolution profiles of spray-dried GF and binary solid dispersions in phosphate buffer (pH 6.8) at 100 rpm and kept at 37°C (n=3)

free carbonyl group and the second to the bound group (to hydroxyl group on PHPMA and HPMCAS). Ultimately, these results suggest that the incorporation of PHPMA in the solid dispersion enhanced the hydrogen bonding with the drug.

Glass Transition Temperature of the Solid Dispersion

The formation of a miscible one-phase solid dispersion could be determined using the glass transition temperature of the mixture (T_g). If a single T_g is obtained, then this indicates that one phase of the drug and the polymer was formed (15). The glass transition temperature of amorphous GF prepared by quenching in liquid nitrogen was found to be 89°C, while the T_g for PHPMA was 78°C. The glass transition temperature for the binary solid dispersion of GF and the polymer (HPMCAS) was measured, and the results showed that a single T_g was obtained. The ternary solid dispersion also (with PHPMA) showed single T_g.

The T_g of the binary mixture GF/ HPMCAS (Table II) (solid dispersion) was found to be 81–82°C. In the ternary solid dispersion (GF/HPMCAS/PHPMA), the T_g increased to 83–84°C. The increase in T_g indicated that HPMCAS and the drug are interacting with PHPMA. This small change in T_g could be attributed to the non-ideal mixing of the polymer with the drug. This leads to negative deviation from the expected values (16). In addition, the T_g values for the solid dispersions were similar before and after storage for 19 months (only one T_g could be detected), indicating the absence of phase separation. This coincides with the XRPD results where the drug remained amorphous in the solid dispersions. As shown in Table II, the glass transition temperature was found to vary slightly among the different HPMCAS grades and, accordingly, their solid dispersions. These results suggest that the effect of PHPMA on the glass transition temperature of the ternary solid dispersion is independent of the HPMCAS grade.

Dissolution Studies

To ensure that sink conditions have been achieved, the saturated solubility of GF was measured into phosphate buffer (pH 6.8). The results showed that the saturation solubility of GF was 14.2 μg/mL, which coincided reasonably with previous studies (17,18). To carry on the dissolution experiments, 3.33 μg/mL GF was used, which equals to 23.5% of the saturated solubility. Lower concentrations were not possible for use due to practical reasons such as the UV absorbance detection and balance weighing limits.

The dissolution profile of the prepared solid dispersions was studied. The dissolution studies were carried out in phosphate buffer at pH 6.8. The particle size of the spray-dried GF was found similar to the solid dispersion particles according to scanning electron microscopy results (1 to 5 μm; scanning electron microscopy images, data not shown). Therefore, any improvement in the dissolution of the solid dispersions is because of the properties of the solid dispersion rather than the small size of the particles. Freshly spray-dried GF was used for dissolution experiments to ensure that amorphous GF is used (Fig. 4).

The results showed that slow dissolution rate of the drug is obtained from spray-dried GF. Complete dissolution of the drug took place in more than 6 h. This is because of the hydrophobic nature of the drug which slows down the dissolution process. The dissolution rate of GF from HPMCAS solid dispersions was studied. The results showed higher dissolution rate of drug from the solid dispersions. About 90% of GF was dissolved within the first 15 min of the experiment. The difference in the dissolution rate between the pure drug (spray-dried) and the solid dispersion is due to the hydrophilic nature of the polymer as well as the existence of the drug in the amorphous form. It was found that GF undergoes fast crystallization when exposed to humidity (dynamic vapor sorption and hot stage microscopy, data not shown). On the contrary, in the solid dispersion, GF remains in the amorphous form. Thus, the dissolution of the drug is greatly improved because of its amorphous nature. A similar dissolution profile was obtained for ternary solid dispersions containing PHPMA, which means that the dissolution process is dominated by the dissolution of HPMCAS since the addition of PHPMA did not alter the dissolution process. The dissolution of the drug was similar to solid dispersions containing the different grades of HPMCAS. The hydrophilic nature of the polymers is expected to be the main reason for the improved dissolution (Fig. 5).

CONCLUSIONS

Binary solid dispersions of GF and HPMCAS were prepared by spray drying. The drug remained in the amorphous form for extended periods even when exposed to high relative humidity. When PHPMA was added to the solid dispersion, the stability of the amorphous form was

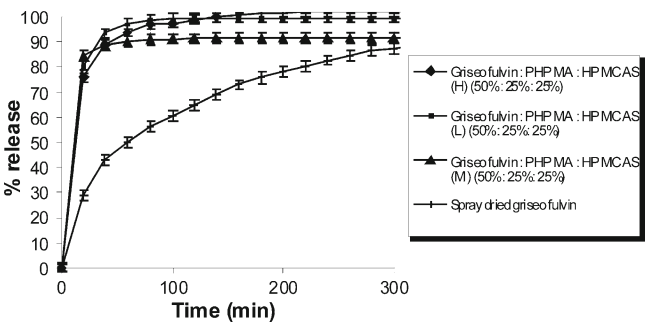

Fig. 5. Dissolution profiles of spray-dried GF and ternary solid dispersions in phosphate buffer (pH 6.8) at 100 rpm and kept at 37°C (n=3)

found to be similar to the binary solid dispersion during the duration of study (19 months). The possibility of formation of hydrogen bonds between the drug and the polymer was studied, and the results suggest that hydrogen bonding occurred in both cases. The T_g of the ternary solid dispersion was measured and found higher than the binary solid dispersion, which indicated that PHPMA is interacting with GF and HPMCAS. Also, it was found that one T_g is present for the solid dispersions (binary and ternary), which shows that one phase of the solid dispersion was formed (i.e., there is no phase separation). Improvement in the dissolution rate of the solid dispersions was obtained as a result of the amorphous nature of GF as well as due to molecular interaction with the hydrophilic polymer (HPMCAS). In conclusion, amorphous solid dispersions were proven to be stable for long periods. Ternary solid dispersions (two polymers and one drug) were comparable to binary solid dispersions (polymer and one drug) in terms of stability and dissolution profile.

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