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Physicochemical Characterization and Dissolution Study of Solid Dispersions of Furosemide with Polyethylene Glycol 6000 and Polyvinylpyrrolidone K30

e-mail: raka_77us@yahoo.com

Rakesh P. Patel[1], Dhaval J. Patel, Dipen B. Bhimani, and Jayvadan K. Patel

Department of Pharmaceutics, S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat vidyanagar, Kherva, Mehsana-Gozaria Highway, PIN-382 711, Gujarat, India.

ABSTRACT

Solid dispersions traditionally have been used as effective methods to improve the dissolution properties and bioavailability of poorly water-soluble drugs. The aim of the present study was to improve the solubility and dissolution rate of a poorly water-soluble drug, furosemide, by a solid dispersion technique. Solid dispersions were prepared using polyethylene glycol 6000 (PEG 6000) and polyvinylpyrrolidone K30 (PVP K30) in different drug-to-carrier ratios. Dispersions with PEG 6000 were prepared by fusion-cooling and solvent evaporation, while dispersions containing PVP K30 were prepared by solvent evaporation technique. These new formulations were characterized in the liquid state by phase solubility studies and in the solid state by differential scanning calorimetry, powder X-ray diffraction, and FTIR spectroscopy. The aqueous solubility of furosemide was favored by the presence of both polymers. Solid state characterizations indicated that furosemide was present as an amorphous material and entrapped in polymer matrix. In contrast to the very slow dissolution rate of pure furosemide, the dispersion of the drug in the polymers considerably enhanced the dissolution rate. Solid dispersion prepared with PEG showed the most improvement in wettability and dissolution rate of furosemide. Even physical mixtures of furosemide prepared with both polymers also showed better dissolution profiles as compared with that of pure furosemide. Tablets prepared using solid dispersions showed significant improvement in the release profile of furosemide as compared with conventional tablets prepared using furosemide without PEG or PVP.

INTRODUCTION

The therapeutic efficacy of a drug product intended to be administered by the oral route depends first of all on its absorption by the gastro-intestinal tract. It is well established that dissolution is frequently the rate-limiting step in the gastrointestinal absorption of a drug from a solid dosage form. The relationship between solution rate and absorption is particularly distinct when considering drugs of low aqueous solubility. Poorly soluble drugs have been shown to be unpredictable and are slowly absorbed as compared with drugs with higher solubility. Several methods that have been employed to improve the solubility of poorly water soluble drugs include increasing the particle surface area available for dissolution by milling (*1*), improving the wettability with surfactants or doped crystals (*2*), decreasing crystallinity by preparing a solid dispersion (*3*), use of inclusion compounds such as cyclodextrin derivatives (4), use of polymorphic forms or solvated compounds (*5*), and use of salt forms.

Solid dispersions (SDs) represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term "solid dispersion" refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the melting, solvent, or melting solvent methods (*6*).

A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs (*7*).

The mechanisms for the enhancement of the dissolution rate of SDs have been proposed by several investigators. A molecular dispersion of drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process, and there is an improvement in drug solubility and wettability due to the surrounding hydrophilic carriers (*8*). Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution.

The method of preparation and the type of the carrier used are important influences on the properties of such solid dispersions (*9*). The methods used to prepare SDs include the melting method, the solvent method, and the solvent wetting method (*10*).

[1]*Corresponding author.*

Among the carriers used in the formation of solid dispersions, polyethylene glycol and polyvinylpyrrolidone are the most commonly used. Both polymers show excellent water solubility and vary significantly in molecular weight, ranging from 200 to >300,000 for polyethylene glycol and from 10,000 to 700,000 for polyvinylpyrrolidone. The molecular size of both polymers favors the formation of interstitial solid solutions (*11*).

Both polymers are often employed as vehicles due to their low toxicity, low melting point, rapid solidification rate, high aqueous solubility, availability in various molecular weights, economic cost, and physiological tolerance. These and other properties make them very suitable vehicles in the formulation of dosage forms (*12*–*14*).

Many methods are available for determining the physical nature of an SD. Solid dispersions can be characterized in the solid state by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and so forth (*11*, *15*, *16*).

Furosemide (FUR) is a potent loop diuretic, chemically designated as 4-chloro-2-(2-furylmethylamino)-5-sulfamoyl-benzoic acid. It is a white to slightly yellow, odorless, crystalline powder, practically insoluble in water (10 µg/mL), sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids (*17*). The rate of absorption and the extent of bioavailability for such an insoluble hydrophobic drug are controlled by the rate of dissolution in the gastrointestinal fluids. Improvement of aqueous solubility in such a case is a valuable aim to improve therapeutic efficacy. Hence, attempts are being made to increase the rate of dissolution of such poorly water soluble hydrophobic drugs, to increase their effectiveness and simultaneously reduce their doses and hence their toxic effects.

The present study was planned to improve the aqueous solubility and dissolution rate of FUR by preparing the SD with polyethylene glycol 6000 (PEG 6000) and polyvinylpyrrolidone (PVP K30) employing various methods such as solvent evaporation, melting, and physical mixing. The study further aimed to characterize the interaction of FUR with PEG 6000 and PVP K30 by using FTIR, DSC, and PXRD techniques.

MATERIALS AND METHODS

Materials

The samples of FUR, PEG 6000, and PVP K30 (average molecular weights of 6000 and 50,000, respectively) were generous gifts from Maan Pharmaceuticals Ltd. (Mehsana, India) and were used without further purification. Directly compressible lactose, colloidal silicon dioxide, and magnesium stearate were procured from S.D. Fine-Chem Ltd., Mumbai. All chemicals and solvents used in this study were of analytical reagent grade. Freshly distilled water was used throughout the work.

Phase-Solubility Study

Phase-solubility studies were performed according to the method reported by Higuchi and Connors (*18*). FUR, in amounts that exceeded its solubility, were transferred to screw-capped vials containing 25 mL aqueous PEG 6000 or PVP K30 solutions of different concentrations (0, 1, 5, and 10%). The contents were stirred on an electromagnetic stirrer (Remi, India) at 25 °C and 37 °C for 72 h and 300 rpm. This duration was previously tested to be sufficient to reach equilibrium, after which no improvement in solubility was observed. After reaching equilibrium, samples were filtered through a 0.22-µm membrane filter, suitably diluted with 0.1 N NaOH, and analyzed for drug content at the λ_{max} of 274 nm (*17*) using a spectrophotometer (Shimazdu-1601, UV–vis spectrophotometer, Shimadzu Corp, Kyoto, Japan). All assays were performed in triplicate.

Preparation of Solid Dispersion and Physical Mixture

Solid Dispersions Prepared by Solvent Evaporation

SDs of FUR in PEG 6000 or PVP K30 containing different weight ratios (1:1, 1:5, 1:10 and denoted as SEPEG or SEPVP 1/1, 1/5, 1/10, respectively) were prepared by the solvent method (*19*) as follows.

To a solution of FUR in ethanol (10 mg/25 mL), an appropriate amount of PEG 6000 or PVP K30 was added. The solvent was evaporated under reduced pressure at 40 °C, and the resulting residue was dried under vacuum for 3 h, stored in a desiccator at least overnight, ground in a mortar, and passed through a #100 sieve.

Solid Dispersions Prepared by Melting of the Carrier

Four SD preparations containing different weight ratios of FUR in PEG 6000 (1:1, 1:5, 1:10 and denoted as MEPEG 1/1, 1/5, 1/10, respectively) were prepared by the melting method (*20*). FUR was added to the melted PEG 6000 at 75 °C, and the resulting homogeneous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in a desiccator for 24 h. Subsequently, the dispersion was ground in a mortar and sieved through a #100 sieve.

Physical Mixtures

Physical mixtures (PMs) having the same weight ratios, as described in the previous two methods, were prepared by thoroughly mixing appropriate amounts of FUR and PEG 6000 or PVP K30 in a mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through a #120 sieve and denoted as PMPVP or PMPEG, respectively.

Characterization of Solid Dispersion

Infrared (IR) Spectroscopic Analysis

FTIR spectra of moisture-free powdered samples of FUR and its PMs and SDs with PEG 6000 and PVP K30 were obtained using a spectrophotometer (FTIR-8300,

Shimadzu Co., Kyoto, Japan) by potassium bromide (KBr) pellet method. The scanning range was 750–4000 cm^{-1}, and the resolution was 1 cm^{-1}.

Powder X-ray Diffraction (PXRD) Analysis

The physical state of FUR in the various preparations was evaluated by powder X-ray diffraction study. Powder X-ray diffraction patterns of all samples were determined using a Phillips PW 3710 scanner, IW 1830 generator with a CuK α anode at 40 kV and 30 mA, and a scan rate of 1° min^{-1} from 2θ range 1 to 40°.

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of all powdered samples were recorded using Shimadzu DSC-60 with TDA trend line software. All samples were weighed (8–10 mg) and heated at a scanning rate of 10 °C/min under dry nitrogen flow (100 mL/min) between 50 and 300 °C. Aluminum pans and lids were used for all samples. Pure water and indium as primary standard were used to calibrate the DSC temperature scale and enthalpic response.

Wettability and Dissolution Studies

A wettability study was performed using open tubes containing FUR and its PMs and SDs with PEG 6000 and PVP K30; these were placed with their lower capillary ends dipped into colored water (0.01% eosin in water). The upward migration of the colored front was registered as a function of time (*21*).

Dissolution studies of FUR in powder form and its PMs and SDs with PEG 6000 and PVP K30 were performed to evaluate in vitro drug release profile. Dissolution studies were performed using USP Apparatus 2 with 500 mL dissolution medium (demineralized water containing 0.25% [w/v] of sodium lauryl sulfate [SLS]) at 37 ± 0.5 °C and 50 rpm for 4 h. Samples of pure FUR and PMs and SDs equivalent to 20 mg of the drug were added to the dissolution medium. At fixed time intervals, 5-mL aliquots were withdrawn, filtered through a 0.22-µm membrane filter, suitably diluted, and assayed for FUR content by measuring the absorbance at 274 nm using a spectrophotometer. Equal volume of fresh medium prewarmed at the same temperature was replaced in the dissolution medium after each sampling to maintain constant volume throughout the test. Each test was performed in triplicate, and release curves were plotted using calculated mean values of cumulative drug release. Similarity factor (f_2) and mean dissolution time (MDT) values were calculated to compare the extent of improvement in the dissolution rate of FUR from different samples. Preliminary tests demonstrated that there was no change in the λ_{max} of FUR due to the presence of PEG 6000 or PVP K30 dissolved in the dissolution medium.

Formulation Studies

Formulation excipients were selected on the basis of preliminary tests, which demonstrated no interference of these excipients with the λ_{max} of FUR. Tablets containing 20 mg of FUR were made by direct compression using different formulation excipients such as directly compressible lactose, colloidal silicon dioxide, and magnesium stearate. Tablets containing SDs equivalent to 20 mg FUR were made similarly. The blend was compressed on an eight-station single rotary machine (Cadmach, India) using round-shaped, flat punches to obtain tablets of 3–6 kg/cm^2 hardness and 3.8–4.0 mm thickness. For the assay, three tablets were crushed, and a blend equivalent to 10 mg of FUR was weighed and dissolved in dissolution medium. The release profile of drug from tablets was studied in triplicate using the same dissolution media, conditions, and procedure as described for in vitro dissolution studies.

Statistical Analysis

A model-independent mathematical approach proposed by Moore and Flanner (*22*) for calculating a similarity factor f_2 was used for comparing dissolution profiles of different samples. The similarity factor f_2 is a measure of similarity in the percentage dissolution between two dissolution curves and is defined by following equation:

$$f_2 = 50 \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \times 100\right\} \quad [1]$$

where n is the number of withdrawal points, R_t is the percentage dissolved of reference at the time point t, T_t is the percentage dissolved of test at the time point t, and W_t is optional weight at time t (for the entire study, the value of W_t is assumed to be 1).

A value of 100% for the similarity factor (f_2) suggests that the test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, while lower f_2 values imply an increase in dissimilarity between release profiles (*22*).

MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate (*23*). It is an accurate expression for drug release rate. A higher MDT value indicates a greater drug retarding ability (*24*). To understand the extent of improvement in dissolution rate of FUR from its PMs and SDs with PEG and PVP, the obtained dissolution data of all samples were fitted into the equation

$$\mathrm{MDT}_{\text{in vitro}} = \frac{\sum_{i=1}^{n} t_{\text{mid}}\Delta M}{\sum_{i=1}^{n} \Delta M} \quad [2]$$

where i is the dissolution sample number, n is the number of dissolution times, t_{mid} is time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of FUR dissolved (µg) between times t_i and t_{i-1}.

RESULTS AND DISCUSSION

Phase-Solubility Study

The solubility of FUR in water at 25 °C is 10 µg/mL; therefore, FUR can be considered to be a water-insoluble drug. The phase solubility curve of FUR in the presence of PEG and PVP at 25 and 37 °C is shown in Figures 1A and 1B. (For ease in discussion, hereafter, PEG 6000 and PVP K30 are abbreviated as PEG and PVP, respectively). From this curve, it can be seen that the apparent solubility of FUR increased with increasing temperature and carrier concentrations. At the highest polymer concentration (10% w/w), the solubility increased approximately 27-fold and 23-fold for PEG and PVP, respectively, at 37 °C. The same tendency was observed at 25 °C.

An indication of the process of transfer of FUR from pure water to aqueous solution of PEG or PVP was obtained from the values of Gibbs free energy change (*25*). The Gibbs free energy of transfer ($\Delta G_{tr}°$) of FUR from pure water to aqueous solutions of SDs was calculated using the following equation:

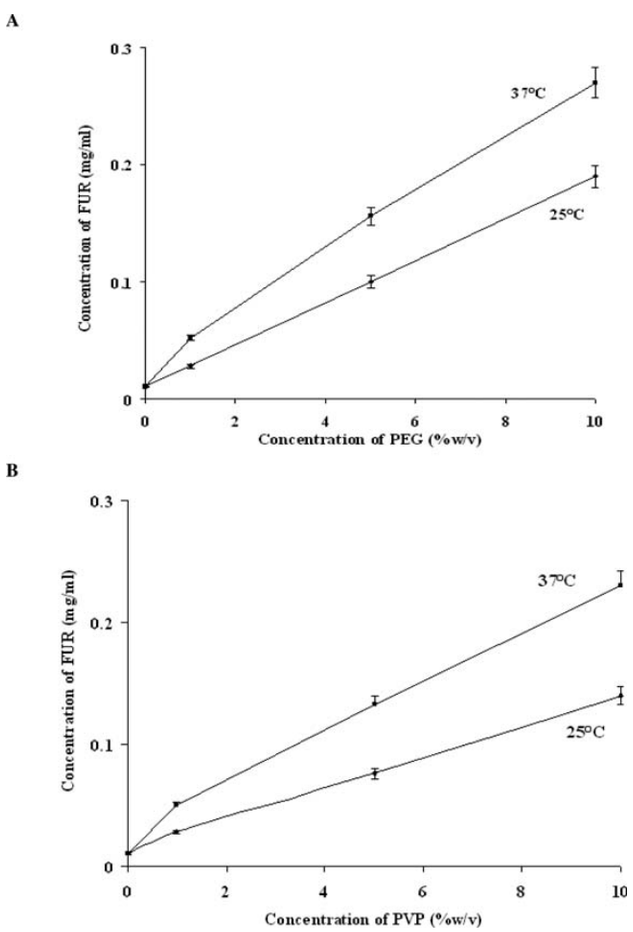

Figure 1. Solubility of FUR (g/100 mL) in aqueous solutions of (A) PEG 6000 and (B) PVP K30 in water at 25 and 37 °C (n=3).

Table 1. Thermodynamic Parameters for Solubilization Process of FUR in Aqueous Solutions of PEG 6000 and PVP K30 at 25 and 37 °C

Polymer concentration (%w/v)	PEG 6000			PVP K30		
	$\Delta G_t°$ (KJ/mol)		$\Delta H_t°$	$\Delta G_t°$ (KJ/mol)		$\Delta H_t°$
	25 °C	37 °C		25 °C	37 °C	
1	–2.7	–4.2	–22.7	–2.6	–4.1	–29.4
5	–5.2	–7.0	–29.3	–5.2	–6.7	–33.6
10	–7.6	–8.5	–36.4	–6.8	–8.1	–38.9
Ka (m^{-1})	884.0	1240.0		631.1	1042.1	

$$\Delta G_{tr}^{\circ} = -2.303RT\log\left(\frac{S_c}{S_o}\right) \quad [3]$$

where S_c/S_o is the ratio of molar solubility of FUR in aqueous solution of PEG or PVP to that of pure water.

The enthalpy of transfer ($\Delta H_t°$) can be calculated from a modification of the van't Hoff equation:

$$\Delta H_t^{\circ} = -R\frac{d\ln(S_c/S_o)}{d(1/T)} \quad [4]$$

The obtained values of $\Delta G_{tr}°$, $\Delta H_t°$, and apparent stability constants (K_a) are shown in Table 1. The $\Delta G_{tr}°$ values show whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solution. Negative $\Delta G_{tr}°$ values indicate favorable conditions. $\Delta G_{tr}°$ and $\Delta H_t°$ values were all negative for both polymers at various concentrations, indicating the spontaneous nature of FUR solubilization, and decreased with an increase in PEG or PVP concentration, demonstrating that the reaction became more favorable as the concentration of PEG or PVP increased. These values also indicated that the extent of improvement in solubility was more with PEG as compared with PVP.

Characterization of SDs

Fourier Transform Infrared (FTIR) Spectroscopic Analysis

FTIR has been used to assess the interaction between carrier and guest molecules in the solid state. In the SD preparations, there is a peak band shift in the absorption spectrum of the guest. However, some of the changes are very subtle requiring careful interpretation of the spectrum.

The FTIR spectra of all samples are shown in Figure 2. The spectrum of pure FUR presented characteristic peaks at 3340 cm^{-1} (NH_2 stretching vibration of Ar-$NHCH_2$), 3260 cm^{-1} (stretching vibration of SO_2NH_2), 1665 cm^{-1} (bending vibration of amino group), 1560 cm^{-1} (asymmetric stretching vibration of the carboxyl group), and 1318 cm^{-1} (asymmetric stretching vibration of the

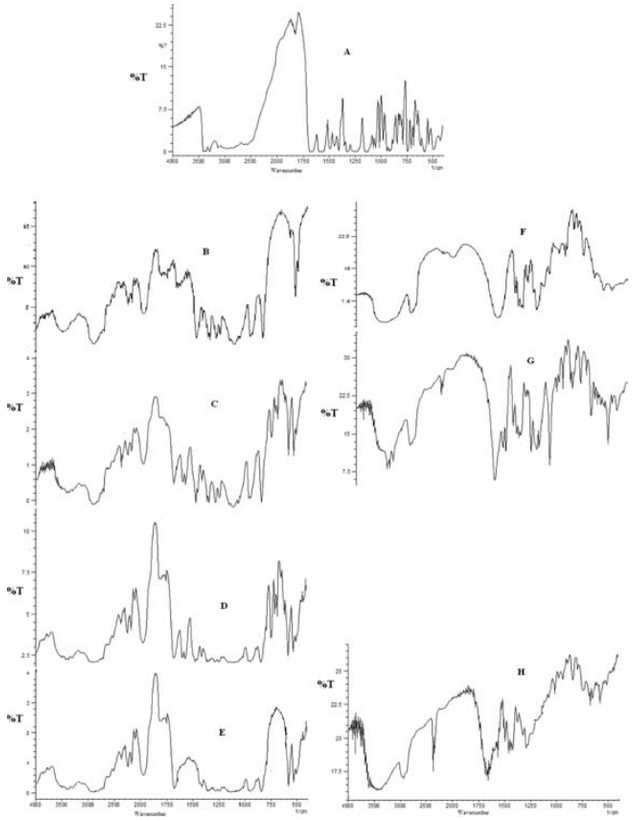

Figure 2. FTIR spectra of (A) FUR, (B) PEG 6000, (C) PMPEG 1/10, (D) MEPEG 1/10, (E) SEPEG 1/10, (F) PVP K30, (G) PMPVP 1/10, and (H) SEPVP 1/10.

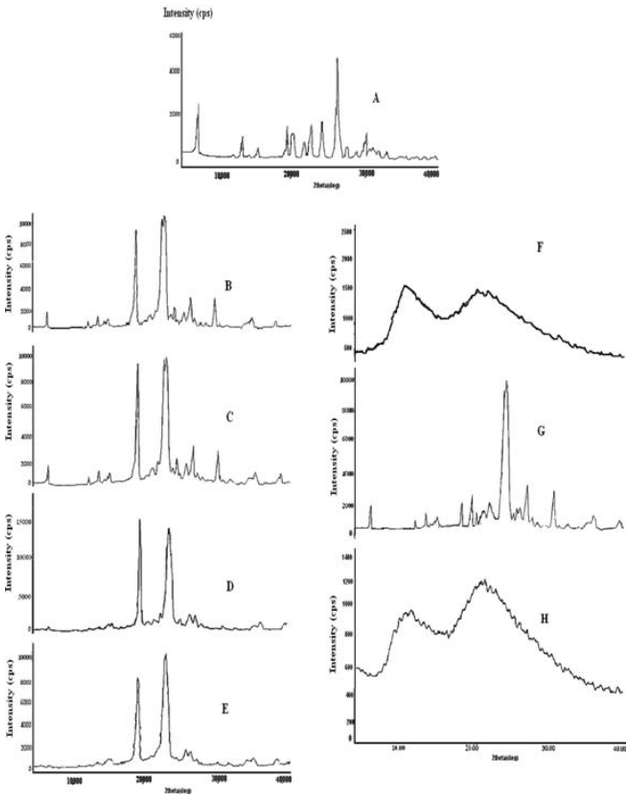

Figure 3. Powder X-ray Diffractograms of (A) FUR, (B) PEG 6000, (C) PMPEG 1/10, (D) MEPEG 1/10, (E) SEPEG 1/10, (F) PVP K30, (G) PMPVP 1/10, and (H) SEPVP 1/10.

sulfonyl group). Important vibrations detected in the spectrum of PEG are the C–H stretching at 2890 cm^{-1} and the C–O (ether) stretching at 1125 cm^{-1}. The spectrum of PVP showed important bands at 2925 cm^{-1} (C–H stretch) and 1652 cm^{-1} (C=O). A very broad band was also visible at 3300 cm^{-1}, which was attributed to the presence of water confirming the broad endotherm detected in the DSC experiments.

The spectra of PMPEG 1/10 and PMPVP 1/10 can be simply regarded as the superposition of those of FUR and PEG or PVP. No difference was seen in the position of the absorption bands of FUR and PEG or PVP.

In the spectra of SEPEG 1/10, MEPEG 1/10, and SEPVP 1/10, the characteristic peaks of PEG or PVP were present at almost the same positions, whereas peaks due to FUR were absent indicating trapping of FUR inside the PEG or PVP matrix. Moreover, all the spectra showed no peaks other than those assigned to FUR, PEG, and PVP, which indicates the absence of any well-defined chemical interactions. Although hydrogen bonding between the hydrogen atom of the OH of the drug and oxygen atom in PEG or PVP could be expected, this was not demonstrated.

Powder X-ray Diffraction (PXRD) Studies

Powder X-ray diffractograms of FUR, PEG, PVP, their PMs and SDs are shown in Figure 3. The presence of numerous distinct peaks in the PXRD spectrum indicate that FUR was present as a crystalline material with major characteristic diffraction peaks appearing at a diffraction angle of 2θ at 5.95, 11.98, 14.11, 18.05, 18.90, 20.36, 21.28, 22.82, 24.73, 27.48, and 29.17. PEG also exhibited a distinct pattern with diffraction peaks at 2θ at 15.00, 18.75, 23.15, 26.60, and 29.35, but the spectrum of PVP was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound.

The diffraction patterns of all the samples of SDs show peaks due to PEG or similar to PVP and an absence of major diffraction peaks corresponding to FUR, with most of the diffraction indicating FUR was present as amorphous material inside the PEG or PVP matrix. Moreover, no peaks other than those that could be assigned to pure FUR and PEG or PVP were detected in the SEPEG 1/10, MEPEG 1/10, and SEPVP 1/10, indicating no chemical interaction in the solid state between the two entities. In the case of physical mixing, diffractograms of PMPEG 1/10 showed more resemblance to PEG, whereas diffractograms of PMPVP 1/10 showed resemblance to FUR due to presence of free drug.

Differential Scanning Calorimetry (DSC) Studies

DSC enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic

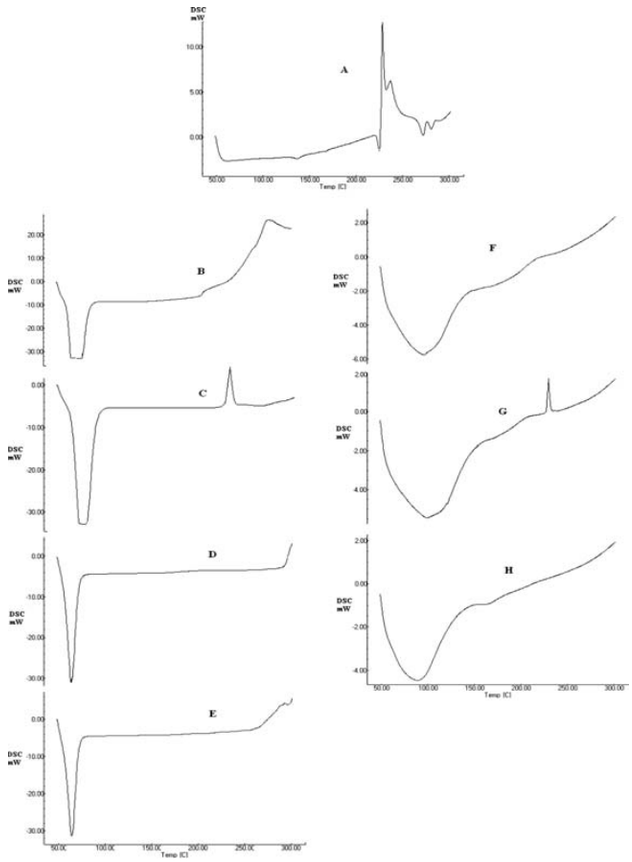

Figure 4. DSC thermograms of FUR (A), PEG 6000 (B), PMPEG 1/10 (C), MEPEG 1/10 (D), SEPEG 1/10(E), PVP K30 (F), PMPVP 1/10 (G), and SEPVP 1/10 (H).

or exothermic phase transformations). The thermal behavior of the prepared solid dispersions of FUR with PEG and PVP was studied by DSC.

The DSC thermograms for pure FUR, PEG, PVP, their PMs and SDs are shown in Figure 4. The FUR showed a melting peak at 225 °C with an enthalpy of fusion (ΔH) of 302.22 mJ/g (*26*). The DSC scan of PVP showed a broad endotherm ranging from 80 to 120 °C due to the presence of residual moisture in PVP, whereas PEG showed a single sharp endotherm at 58 °C due to melting.

DSC thermograms of PMPEG 1/10 and PMPVP 1/10 showed the melting peak of the drug at 225 °C, a sharp endothermic peak at 58 °C due to melting of PEG, and the broad endotherm due to the presence of water ranging from 90 to 110 °C in PVP.

The DSC scans of SEPEG 1/10 and MEPEG 1/10 showed only one peak at 58 °C due to melting point of PEG, and the scan of SEPVP 1/10 showed one peak at 90–110 °C due to loss of water from PVP. All samples of SDs showed complete absence of drug peak at 225 °C. This complete absence of the FUR peak indicates that FUR is amorphous or is in a solid solution inside the PEG and PVP matrix. This type of interaction was also observed in the FTIR and PXRD studies.

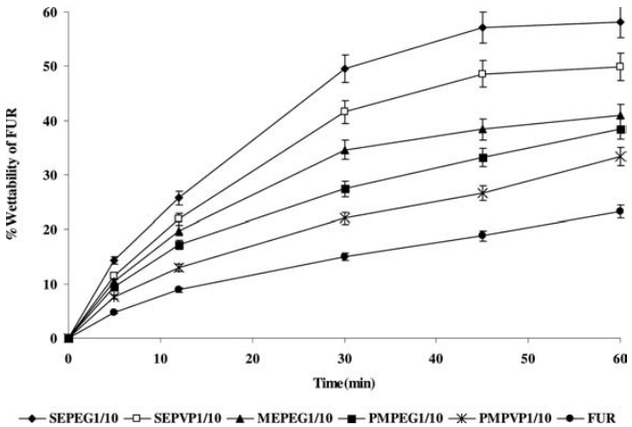

Figure 5. Wettability study of pure FUR, its PMs and SDs with PEG 6000 and PVP K30 in water (n=3).

Wettability and Dissolution Studies

The wettability of FUR was significantly improved by preparing its solid dispersions with PEG and PVP (Figure 5). The greatest improvement of wettability in water was observed with SEPEG 1/10 and SEPVP 1/10 (58.7% and 49.9%, respectively after 60 min). A significant improvement in the wettability of FUR was also observed in PMPEG 1/10 and PMPVP 1/10 as compared with pure FUR (20%) after 60 min.

It is generally accepted that dissolution media are not completely representative of gastrointestinal (GI) conditions, yet it is proposed in guidelines that a good method will employ a dissolution medium that is physiologically meaningful or closely mimics in vivo conditions (*27*). It has been suggested that including surface-active agents in dissolution media is important for poorly soluble compounds, because the lack of a surface tension lowering agent would result in poorer wetting and in vitro dissolution rates that are not representative of in vivo rates (*28*). The FDA has permitted the use of surfactants in media for conducting dissolution studies of poorly soluble compounds (*29*).

Dissolution of pure FUR and all other prepared systems (SDs and PMs) were carried out in demineralized water containing 0.25% (w/v) SLS. $DP_{30\ min}$ values (percent drug dissolved within 30 min), $t_{50\%}$ (time to dissolve 50% drug), and mean dissolution time (MDT) values for different samples are reported in Table 2. In vitro dissolution profiles of pure FUR, its PM and SDs with PEG and PVP over a period of 4 h are shown in Figure 6.

From data presented in Table 2 and Figure 6, it is evident that the dissolution rate of pure FUR is very low ($DP_{30\ min}$ 7.6%, $t_{50\%}$ >> 4 h, and MDT of 58.3 min at 4 h). SDs of FUR with PEG and PVP significantly enhance the dissolution rate of FUR (80–95%, respectively) within 4 h as compared with PM as well as pure FUR. PMs with PEG and PVP also improved the dissolution rate of FUR. The highest improvement was obtained in SDs prepared with

Table 2. Percent Drug Dissolved within 30 min ($DP_{30\ min}$), Time to Dissolve 50% Drug ($t_{50\%}$), and Mean Dissolution Time (MDT) from Pure FUR, its PMs and SDs

Sample	$DP_{30\ min}$	$T_{50\%}$(min)	MDT(min)
FUR	7.5	>240	58.4
PMPEG (1/10)	26.0	113.1	45.7
MEPEG (1/10)	59.7	18.2	33.7
SEPEG (1/10)	68.2	16.0	20.2
PMPVP (1/10)	22.5	170.0	43.6
SEPVP (1/10)	63.7	18.8	21.6

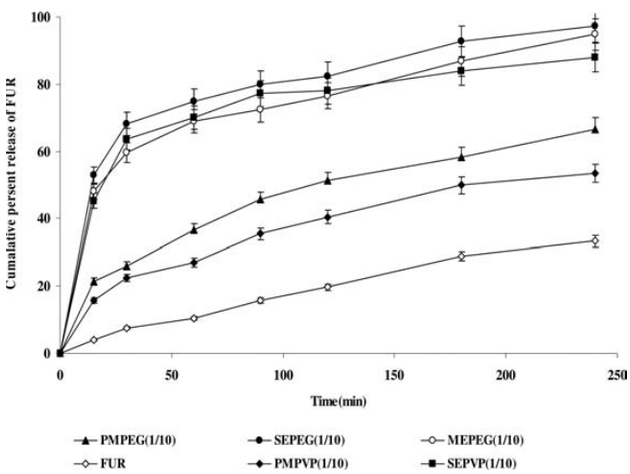

Figure 6. In vitro dissolution profiles of pure FUR, its PMs and SDs with PEG 6000 and PVP K30 (n=3).

PEG by solvent evaporation techniques. SEPEG 1/10 (97%) has a higher dissolution rate as compared with SEPVP 1/10 (88%) at the end of 4 hrs.

The obtained values of MDT for all samples are presented in Table 2. The MDT of pure FUR is very high (58.3 min). This value decreased to a greater extent after preparing its SDs and PM with PEG and PVP. SEPEG 1/10 showed the lowest MDT (20.2 min). MDT values of SDs prepared with PEG were lower than that with PVP. The same relationship was also observed with PM prepared with PEG and PVP also.

Comparisons between the release profiles of FUR from different samples were made by similarity factor f_2. Calculated f_2 values are presented in Table 3a and 3b. From this table, it is evident that the release profile of FUR from all the samples (i.e., SDs and PMs of PEG and PVP) and from pure FUR was dissimilar since f_2 values for all these comparisons were less than 50. Release profiles of FUR from SEPEG and MEPEG at different concentrations

Table 3a. Similarity Factor (f_2) for Release Profiles of FUR from SDs and PMs with PEG 6000

Sample	FUR	PMPEG (1/10)	MEPEG (1/10)	SEPEG (1/10)
FUR	---	41.5	26.0	23.9
PMPEG(1/10)	---	---	40.3	36.2
MEPEG(1/10)	---	---	---	66.1

Table 3b. Similarity Factor (f_2) for Release Profiles of FUR from SDs and PMs with PVP K30

Sample	FUR	PMPVP (1/10)	SEPVP (1/10)
FUR	---	45.2	26.1
PMPVP (1/10)	---	---	34.5

were similar. Release of FUR from SDs with PEG and PVP were also significantly different from PMs with PEG and PVP at different concentration levels.

Formulation Studies

The physical properties of all samples were studied to judge tabletting ability. In general, compressibility index values up to 15% and an angle of repose between 25 and 30 results in good to excellent flow properties (*30*). Percentage compressibility and the angle of repose of samples are shown in Table 4. These values indicate good compressibility and flow properties, making these samples suitable for tabletting.

Release profiles of FUR from conventional tablets containing FUR (without PEG or PVP) and tablets containing SDs and PMs of FUR with PEG or PVP are

Table 4. Physical Properties of SDs and PMs of FUR with PEG 6000 and PVP K30

	Sample					
Physical Property	FUR	PMPEG (1/10)	MEPEG (1/10)	SEPEG (1/10)	PMPVP (1/10)	SEPVP (1/10)
% Compressibility	10.11	12.84	12.04	14.92	12.07	13.69
Angle of repose	21.22°	25.74°	24.29°	27.35°	26.35°	26.12°
Hardness (kg/cm^2)	4.0	4.2	4.0	4.8	4.0	4.5
Friability (%)	1.0	0.9	0.6	0.6	0.8	0.7
Diameter (mm)	7.6	7.8	7.7	7.7	7.8	7.7
Thickness (mm)	3.8	3.8	3.7	3.8	3.8	3.7

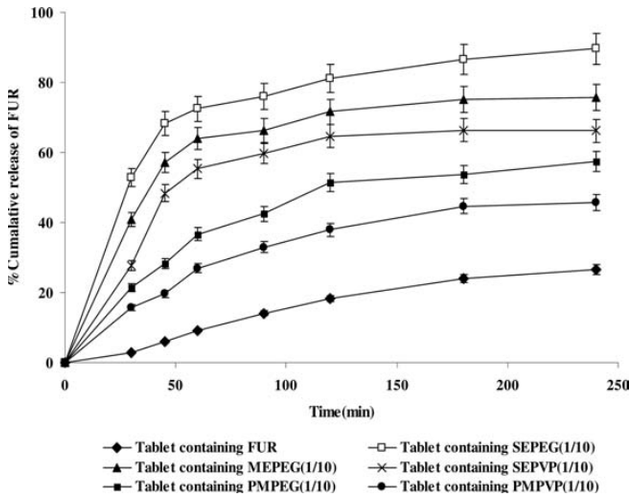

Figure 7. Release profiles of FUR from tablets containing pure FUR, its PMs and SDs with PEG 6000 and PVP K30 (n=3).

shown in Figure 7. Release of FUR from tablets containing SDs with PVP or PEG was faster and greater as compared with conventional tablets containing FUR. This confirmed the advantage of improved aqueous solubility of FUR in its SD form, which can be formulated as tablets with better dissolution characteristics.

DP_{30min}, $t_{50\%}$, and MDT values for release of FUR from tablets prepared using different samples are shown in Table 5. DP_{30min} values were higher for tablets prepared using SDs and PMs as compared with those of conventional tablets containing only FUR (2.9), whereas $t_{50\%}$ and MDT values of FUR from tablets containing SDs and PMs were significantly lower than those of conventional tablets containing only FUR and no PEG or PVP (76.0 min and >4 h, respectively).

CONCLUSION

The solid dispersions of FUR with PEG 6000 and PVP K30 were prepared in different weight ratios using methods like solvent evaporation, melting, and physical mixing.

Table 5. DP_{30min}, $t_{50\%}$, and MDT Values for Release of FUR from Tablets Prepared Using Different Samples

Samples	$DP_{30\ min}$	$t_{50\%}$ (min)	MDT (min)
FUR	2.9	>240.0	76.0
PMPEG (1/10)	15.7	113.8	53.7
MEPEG (1/10)	27.8	38.1	41.3
SEPEG (1/10)	52.8	32.2	32.1
PMPVP (1/10)	19.4	195.3	55.2
SEPVP (1/10)	40.9	48.4	39.7

Solubility studies show a solubilizing effect of both polymers on FUR at different temperatures. The negative values of the Gibbs free energy and enthalpy of transfer for FUR from water to an aqueous solution of both polymers indicate the spontaneity of the transfer. FTIR, DSC, and X-ray diffraction spectroscopic studies indicate that in solid dispersions, drug was present as amorphous form inside the polymeric matrix. The highest improvement in solubility and in vitro drug release was observed in solid dispersions prepared with PEG by the solvent evaporation method. Solid dispersions and physical mixtures prepared using PEG showed more improvement in solubility and in vitro drug release than those prepared using PVP. The solubility and in vitro drug release from the physical mixture, when compared to that of the solid dispersion, was improved to a lesser degree.

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