Original Article

Influence of some hydrophilic polymers on dissolution characteristics of furosemide through solid dispersion: An unsatisfied attempt for immediate release formulation

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Abstract

Background: The objective of the present investigation was to enhance dissolution characteristics of water insoluble drug, furosemide (FRMD), by solid dispersion in various hydrophilic carriers. **Materials and Methods:** The solid dispersions were prepared by solvent evaporation technique using urea and Hydroxy Propyl Methyl Cellulose (HPMC E50 LV). Physical mixtures of drug with above-mentioned polymers were also prepared. Phase solubility studies were performed for drug in the presence of excipients in different ratios. The formulations were evaluated for drug content, in vitro dissolution, Fourier transform infrared (FT-IR) and differential scanning calorimetry (DSC). Similarity factor (f2) was calculated for comparison between dissolution of pure drug and drug–polymer physical mixtures with solid dispersions. **Results:** Phase solubility studies indicated linear increase in the drug solubility with increase in carrier concentration. In vitro release studies revealed that dissolution characteristic of FRMD was improved by solid dispersion technique. All the preparations of FRMD exhibited significant improvement in its dissolution profiles. Solid dispersion of FRMD with HPMC E50 LV exhibited the highest rate and extent of dissolution. Optimized batches of solid dispersions of both the carriers were characterized by FT-IR and DSC analysis, which indicated absence of major interactions between FRMD and carriers. **Conclusion:** Solid dispersion technique is one of the finest techniques to improve dissolution of poorly soluble drugs.

Key words: Dissolution, differential scanning calorimetry, furosemide, Fourier transform infrared, solid dispersion, solubility

INTRODUCTION

Oral route is the most prominent and popular route for administration of drugs for systemic use because of ease of administration and patient compliance compared to other routes.[1] But for many drugs it can be an inefficient route of administration, especially for poorly soluble drugs. For drugs which have poor aqueous solubility, dissolution is the rate limiting step for its bioavailability.[2] Majority of newly discovered drugs are poorly water soluble.[3] Solid dispersion is one of the approaches to improve drug dissolution and hence bioavailability. Many approaches have been used to prepare solid dispersions, such as melting (fusion), solvent evaporation, melting-solvent method, hot-melt extrusion, supercritical fluid process, lyophilization technique, melt agglomeration process, and spray drying.[4-11]

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Furosemide (FRMD) is 5-(aminosulfonyl)-4-chloro-

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2-[(2-fuanyl-methyl) amino] benzoic acid. FRMD has narrow absorption window. It is potent high ceiling (loop) diuretic, mainly used in the treatment of edema of hepatic, cardiac, pulmonary and renal failure and in chronic hypertension.[12,13] This drug has been classified as a class IV drug as per the Biopharmaceutical Classification System (BCS).[2,3,14] Preparation of solid dispersion of FRMD is a very challenging task because it decomposes on and above its melting point. Few attempts to enhance the solubility and/or dissolution of FRMD have been made in the literature by solvent evaporation, spray drying and kneading methods using carrier like Polyvinyl Pyrollidone (PVP), superdisintegrants like sodium starch glycolate, cross-povidone and cross-caramallose and eudragits, etc.[15-20] In the present study, attempts have been made to improve dissolution rate of FRMD using crystalline carrier urea and hydrophilic polymer HPMC E50 LV.

MATERIALS AND METHODS

FRMD was a gift sample from Nectar Pharma (Mumbai, India). Urea was procured from Ranbaxy Fine Chemicals Ltd. (New Delhi, India). HPMC was purchased from Loba Chemicals, Mumbai, India, and ethanol was procured from Merck Specialties Pvt. Ltd. (Mumbai, India). All other chemicals used were of analytical grade.

Phase solubility studies

Phase solubility studies were carried out as described by Higuchi and Connors.[21] An excess amount of FRMD was added to the aqueous solutions of each carrier in simulated gastric fluid (SGF, USP XXIII) containing increasing concentrations of the individual carrier (i.e., 0.5%, 1.0%, 2.5%, and 5.0% w/v). Excess of FRMD was added in the above flasks containing 25 ml solutions of different concentrations of carriers in SGF, pH 1.2, without enzymes. The flasks were sealed and shaken in an environmental shaker at 25°C for 24 hours. The samples were filtered with Whatman filter paper (0.12 μm) and analyzed spectrophotometrically for the dissolved drug at 274 nm. Gibb's free energy of transfer (ΔG^{o}_{tr}) of FRMD from pure media to solution of carrier was calculated using the equation

$$\Delta G^{\circ}_{tr} = -2.303\ RT \log\left(\frac{S_O}{S_S}\right) \quad \text{.....(1)}$$

where S_0/S_s is the ratio of the solubility of FRMD in buffer solution of polymer to that of the pure buffer media, R is gas constant in KJ/degree/ mole and T is absolute temperature in °C.

Preparation of solid dispersion

The solid dispersions with urea were prepared by solvent evaporation technique in which FRMD and urea were dissolved in methanol and the solvent was allowed to evaporate until a constant weight was obtained, by keeping in an oven at 50°C. Each solid dispersion batch was prepared in triplicate employing drug to carrier ratios of 1:1 and 1:5. The solid dispersions were subsequently desiccated under vacuum for 24 hours and sieved (10#). The physical mixtures of drug and urea were also prepared by blending them and triturating for 10 minutes followed by sieving (10#). The solid dispersions with Hydroxy Propyl Methyl Cellulose (HPMC E50 LV) were prepared by modified solvent evaporation technique in which FRMD was dissolved in methanol up to its saturation solubility.[22] The polymer was suspended in sufficient amount of water (up to wet mass of polymer). The drug solution was poured at once into polymer suspension. The entire solvent was evaporated in an oven at 60–70°C. Each solid dispersion batch was prepared in triplicate employing drug to carrier ratios of 1:1 and 1:2. The dispersions were subsequently desiccated under vacuum for 24 hours and sieved (10#). The physical mixtures of drug and HPMC were prepared by blending them and triturating for 10 minutes followed with sieving (10#).

Determination of drug content

Drug content was determined by dissolving accurately weighed quantity of formulation in 0.1 N NaOH. [19] Then, appropriate dilutions were made and samples were measured spectrophotometrically at 271 nm and the drug content was calculated.

In vitro dissolution studies

Drug release studies were performed in triplicate on a dissolution test apparatus at 37 ± 0.5°C employing USP apparatus I in 900 ml of SGF (USP XXIII, pH 1.2) for 1 hour.[23] The rotational speed of the basket was set at 100 rpm. Dissolution studies were performed on pure drug (10 mg) and the solid dispersions containing an equivalent amount of the drug. Aliquots (5 ml each) were withdrawn at predetermined time intervals for 1 hour and sink condition was maintained. The samples were analyzed spectrophotometrically (model no. UV 1700 PC, Shimadzu Corporation, Tokyo, Japan) at 274 nm.

Data analysis

Sampling time corresponding to the amount of drug released in that time (e.g., $DP_{20\ min}$) was computed. Similarity factor f_2 was calculated for comparison of *in vitro* dissolution of solid dispersions with pure drug and physical mixtures. A model-independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor f_2 was used to compare dissolution profiles of different samples.[24] The f_2 value was calculated using the following equation:

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

Where,

R_t = % drug dissolved at each time point from reference,

T_t = % drug dissolved at each time point from test product, and

n = number of observations.

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.[24]

Characterization of solid dispersion of furosemide

Fourier transform infrared spectroscopy analysis

Fourier transform infrared (FT-IR) spectroscopy study was carried out to check the possible interaction between the drug and hydrophilic carriers in prepared formulations. Powdered samples of FRMD, carriers and their preparations were characterized with an FT-IR spectrophotometer (Shimadzu 8400, Japan), using potassium bromide (KBr) pellet method. The scanning range was between 4000 and 400 cm^{-1}.

Differential scanning calorimetry analysis

Differential scanning calorimetry (DSC) spectra of pure FRMD, carriers and all the preparations were recorded using Differential Scanning Calorimeter (Shimadzu, DSC 60 TSW 60, Japan). Accurately weighed samples were crimped in aluminum pans and heated from 30 to 250°C, at a heating rate of 10°C/minute in air atmosphere. Empty sealed aluminum pan was used as reference.

RESULTS AND DISCUSSION

Phase solubility studies

Solubility of FRMD in SGF, pH 1.2, without enzymes was observed to be 17.89 µg/ml, indicating that FRMD is poorly soluble in SGF, pH 1.2, without enzymes. Various parameters computed from the phase solubility studies [Table 1] revealed linear increases in drug solubility with increased carrier levels, with R^2 values of 0.9995 and 0.9993 for urea and HPMC E50 LV as carriers, respectively. Hydrophilic carriers are known to interact with drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds. Table 1 depicts various parameters obtained from phase solubility studies. Value of slope obtained for both the carries (urea and HPMC E50 LV) was less than 1.0, indicating quick increase in solubility of FRMD.

Further, as shown in Table 2, the Gibb's free energy values, ΔG^o_{tr}, were negative, indicating spontaneous solubilization process of FRMD in both the carriers (urea and HPMC E50 LV).

Drug content determination

The drug content values calculated using linear equation in the solid dispersion prepared from urea and HPMC E50 LV are summarized in Table 3. In all the ratios of drug: polymer, the drug content was more than 99%.

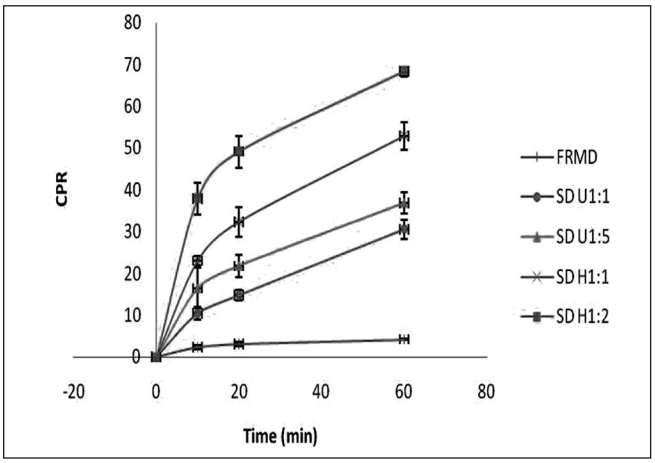

Figure 1: A comparative dissolution profile of pure drug and all the solid dispersions

Table 1: Solubility parameters of furosemide

Carrier	Slope	R^2
Urea	2.706×10^{-4}	0.9995
HPMC E50 LV	24.58×10^{-4}	0.9993

Table 2: Values of Gibb's free energy

Concentration of carrier (% w/v)	ΔGotr (KJ/mole) for water soluble carriers	
	Urea	HPMC E50 LV
0.5	−284.95	−266.31
1	−191.9	−365.74
2.5	−224.50	−691.14

Table 3: Drug content data

Formulations*	% Drug content ± SD**
SD U1:1	99.91 ± 1.71
SD U1:5	99.89 ± 2.77
SD H1:1	99.49 ± 2.83
SD H1:2	99.14 ± 2.42

*SD U is solid dispersion of drug in urea; SD H is solid dispersion of drug in HPMC E50 LV, **The trials were in triplicate

Table 4: Dissolution data of formulations with Hydroxy Propyl Methyl Cellulose E50 LV

Time (minutes)	FRMD	PM H1:1	PM H1:2	SD H1:1	SD H1:2
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
10	2.36 ± 0.44	5.86 ± 0.97	14.34 ± 1.64	23.03 ± 1.04	37.91 ± 3.79
20	3.13 ± 0.53	8.08 ± 1.09	17.59 ± 1.71	32.33 ± 3.65	49.11 ± 3.83
30	3.58 ± 0.73	9.38 ± 1.39	20.36 ± 1.77	41.03 ± 2.33	55.71 ± 4.46
40	3.74 ± 0.79	10.22 ± 1.76	22.27 ± 1.99	44.69 ± 3.17	63.78 ± 4.34
50	4.04 ± 0.87	11.35 ± 1.69	24.86 ± 2.15	48.20 ± 3.21	71.97 ± 4.24
60	4.20 ± 0.93	12.54 ± 0.77	27.37 ± 2.11	52.85 ± 3.29	79.34 ± 1.15

PM = physical mixture; SD = solid dispersion, FRMD = furosemide

Table 5: Dissolution data of formulations with urea

Time (minutes)	FRMD	PM U1:1	PM U1:5	SD U1:1	SD U1:5
0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
10	2.36 ± 0.43	2.44 ± 1.51	3.49 ± 1.38	10.44 ± 1.59	16.47 ± 4.84
20	3.13 ± 0.53	4.12 ± 1.31	5.45 ± 1.24	14.77 ± 1.15	21.82 ± 2.61
30	3.58 ± 1.37	5.03 ± 1.45	6.35 ± 1.33	18.73 ± 4.38	25.93 ± 2.37
40	3.74 ± 1.13	5.76 ± 1.36	7.17 ± 1.26	22.76 ± 3.11	29.66 ± 3.26
50	4.04 ± 1.21	6.41 ± 2.23	8.12 ± 1.53	26.86 ± 4.22	33.10 ± 2.30
60	4.20 ± 0.15	7.15 ± 0.39	8.89 ± 0.25	30.51 ± 2.30	36.84 ± 2.49

Table 6: f_2 Value data for comparison between dissolution of pure drug and solid dispersions

Comparison between FRMD and SD	SD U1:1	SD U1:5	SD H1:1	SD H1:2
f_2 Value	37.98	30.19	20.87	13.38

Table 7: f_2 Value data for comparison between dissolution of physical mixtures and solid dispersions

Comparison between PM and SD	SD U1:1	SD U1:5	SD H1:1	SD H1:2
f_2 value	40.51	33.92	25.73	22.60

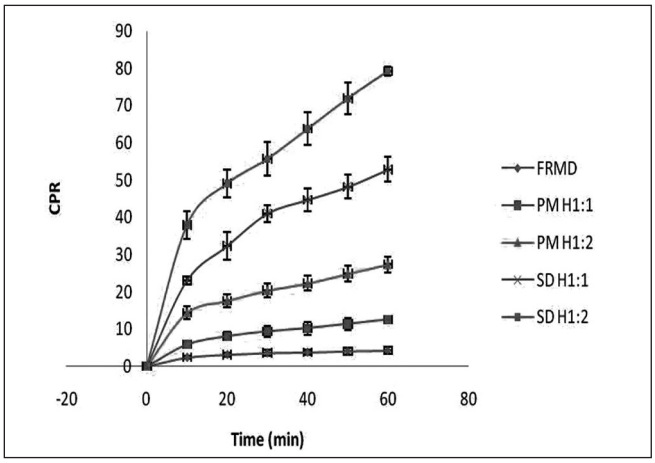

Figure 2: Drug release profiles of physical mixtures and solid dispersions prepared from HPMC E50 LV

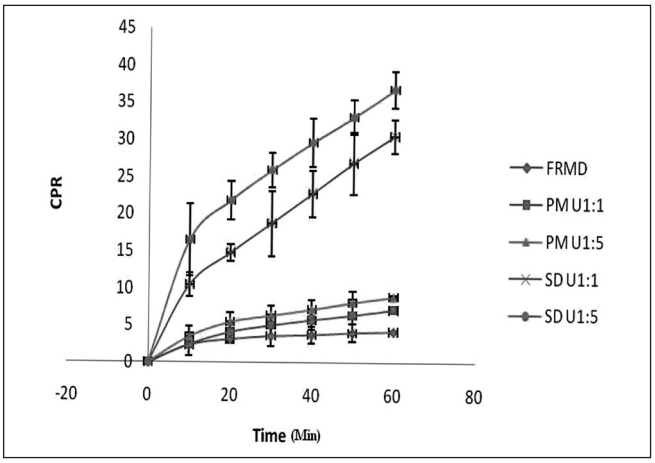

Figure 3: Drug release profiles of physical mixtures and solid dispersions prepared from urea

In vitro dissolution study

The results from dissolution study revealed an improvement in dissolution rate of FRMD by solid dispersion formulated from both the carriers (urea and HPMC E50 LV). The cumulative amount of drug dissolved from pure drug and dispersions was studied. The results of dissolution parameters are shown in Figure 1. The value of cumulative drug release was significantly enhanced from the pure

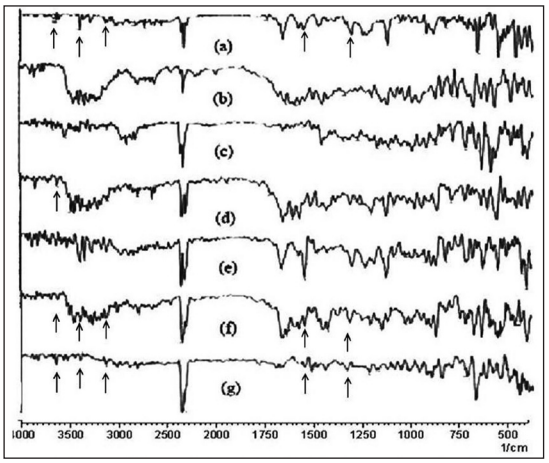

Figure 4: FT-IR spectra of (a) pure drug, (b) urea, (c) HPMC E50 LV, (d) physical mixture of drug with urea, (e) physical mixture of drug with HPMC E50 LV, (f) solid dispersion of drug with urea, (g) solid dispersion of drug with HPMC E50 LV

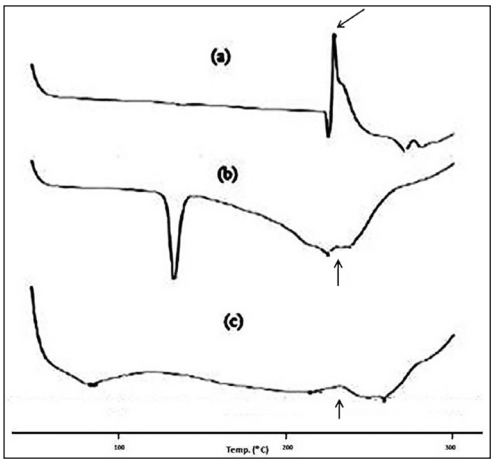

Figure 5: DSC thermograms of (a) pure drug, (b) solid dispersion from urea, (c) solid dispersion from HPMC E50 LV

drug to solid dispersion. Cumulative drug release from solid dispersions indicated the achievement of higher dissolution rate.

Table 4 and Figure 2 show the *in vitro* drug release profile of FRMD, its physical mixture and formulations using HPMC E50 LV as a carrier. As the drug to carrier ratio was increased, the dissolution also improved. It might be due to a complex formation between the drug and polymer.[23] Physical mixture also improved the dissolution rate of drug.

Table 5 and Figure 3 show *in vitro* drug release profile of FRMD, its physical mixture and formulations using urea as a carrier. As the drug to carrier ratio was increased, the dissolution also improved. It might be due to a complex formation between the drug and polymer.[23] Physical mixture also improved the dissolution rate of drug.

The probable reason for the dissolution rate enhancement with both the carriers used might be particle size reduction, improved wettability and complexation of FRMD by hydrophilic carrier.[23]

Data analysis

Tables 6 and 7 show f_2 values for *in vitro* dissolution of pure drug and solid dispersions, and of physical mixture and solid dispersion, respectively.

In all the cases, f_2 values are found to be less than 50, which is a sign of dissimilarity between dissolution profiles. It explains a significant improvement in dissolution profile of solid dispersions when compared to pure drug as well as physical mixtures.

Characterization of solid dispersion of furosemide

Fourier transform infrared studies

FT-IR analysis was carried out to assess any possible interaction between drug and hydrophilic carriers. Figure 4 shows the FT-IR spectra of drug, carriers and the solid dispersions with the carriers. The spectrum of pure FRMD [Figure 4a] shows the characteristic peaks at 3647.51 cm^{-1} (O–H stretch), 3286.81 cm^{-1} (N–H stretch), 3147.05 cm^{-1} (C–H stretch), 1568.18 cm^{-1} (C=O stretch), 1672.34 cm^{-1} (N–H bending), and 1263.44 cm^{-1} (S=O asymmetric stretch).

FT-IR spectra of solid dispersions prepared from urea and HPMC [Figure 4f and g, respectively] showed no substantial shifting of the position of functional groups. The peaks indicated no major interactions between FRMD and carriers.

Differential scanning calorimetry

Figure 5 shows the DSC curves of pure drug and solid dispersions of drug with both the carriers. The DSC thermogram of FRMD alone shows a characteristic, sharp exothermic peak at 229.8°C, which is associated with melting point of the drug and indicates the crystalline nature of the drug; the degradation product shows an endothermic peak at 272.4°C.[25] The endothermic peak corresponding to the melting point of FRMD is broader in the solid dispersions prepared with urea (at 246.24°C) and HPMC E50 LV (at 262.50°C), indicating a change in crystalline structure of FRMD to amorphous state in solid dispersion.[19] The disappearance of endothermic peaks associated with degradation product of FRMD is also an indication of change in crystalline structure of FRMD in solid dispersion.[19]

CONCLUSION

The solid dispersion of FRMD was prepared with urea and HPMC E50 LV by solvent evaporation technique. *In*

vitro drug release profiles from solid dispersions were better than that of the physical mixtures and pure drug. FT-IR analysis indicated no major interaction among FRMD and carriers. Results of DSC study revealed decrease in drug crystallinity in prepared solid dispersions. The maximum drug release achieved from solid dispersion was 79% (with HPMC E50 LV), though it is not acceptable as per the regulatory guidelines for IR dosage form (i.e., at least 85% drug release in the first 15 minutes as per SUPAC IR). So, it requires further trials in solid dispersion techniques and polymers to bring the dissolution profile in the range of IR dosage forms. But solid dispersion technique improved the dissolution profile of drug from 4% (FRMD) to 79% (SU H1:2) within 1 hour. Thus, solid dispersion by solvent evaporation technique can be used to improve the dissolution of even very poorly soluble drug of class IV like FRMD.

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