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Research Article

Development and Characterization of Solid Dispersion for Dissolution Improvement of Furosemide by Cogrinding Method

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Abstract

Purpose: The purpose of this study was to prepare and characterize solid dispersion formulation of furosemide to enhance dissolution rate.

Methods: Solid dispersions with different drug: carrier ratios were prepared by cogrinding method using crospovidone and microcrystalline cellulose as carrier. The physical state and interactions between the drug and carrier were characterized by Fourier transform infrared spectroscopic (FT-IR) and X ray diffraction (XRD).

Results: Solid dispersions (especially with drug: Carrier ratio of 1:2) showed a higher dissolution rate than their respective physical mixture and pure furosemide. Dissolution rate in pH 5.8 was also higher than pH 1.2. The XRD analysis showed that crystalline form was changed to the amorphous state in the solid dispersions. FT-IR analysis did not show any physicochemical interactions in the solid dispersion formulations. Release kinetic of formulations were fitted best to the Weibull and Wagner log probability (linear kinetic) as well as suggested 2 and Gompertz (non-linear kinetic) models.

Conclusion: The dissolution properties of furosemide were improved with the use of hydrophilic carriers in solid dispersions due to change in the crystalline form of the drug and more intimate contact between drug and carriers which was dependent on the type and ratio of carrier as well as dissolution medium pH.

Introduction

Oral drug delivery is the simplest and easiest way of drugs administering, because of the greater stability, smaller bulk, and easy production. Nearly 40% of new discovered chemical are poorly water soluble. Dissolution is the rate limiting step for the poorly water soluble drugs. Poor solubility results in low bioavailability, increase in the dose, large inter and intra subject variation and large variations in blood drug concentrations depending on fed and fasted conditions. Enhancement of solubility and dissolution rate is an important step in drug development. For better absorption and quick onset of action, dissolution rate enhancement is critical.[1-4] To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization, solubilization, salt formation, use of surfactant, use of cosolvent, complexation with polymers, use of prodrug and drug derivatization, pH alteration and others.[5-10] Among various approaches, the solid dispersion (SD) technique is a promising and most successful method in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economical and advantageous. A solid dispersion can be defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a melting (fusion), solvent, or melting-solvent method. The increased dissolution rates from solid dispersions are mostly attributed to the reduction of particle size of the drug within the dispersions and increased wettability.[11-14] Solid dispersion has advantages like, increase in the dissolution with absorption enhancement and therapeutic efficacy of dosage form, obtaining a homogeneous distribution of a small quantity of drug in a solid state, stabilization of unstable drugs, formulation of sustained release product of soluble drugs by using poorly soluble and insoluble carriers and increase in the rate and extent of the absorption of the drug. Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound surface, as well as particle size reduction and increasing the interfacial area available for drug dissolution.[15-20] Various hydrophilic carriers such as polyethylene glycols, polyvinylpyrrolidone, gelucires, poloxamers, sugars, urea,

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HPMC and gums have been investigated for improving the dissolution rate and bioavailability of poorly water soluble drugs.[21-27]

Furosemide is practically insoluble in water (Class-II of Biopharmaceutical classification system, BCS). The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs.[28-30] The objective of the present investigation was to formulate FUR solid dispersion to enhance its dissolution rate.

Materials and Methods

Materials

Furosemide was purchased from Jinaram Mandel Factory (India). Microcrystalline cellulose (Avicel PH-101) was obtained from Blanver Company (Korea). Crospovidone was supplied by BASF Company (Germany). HCl, NaOH and KH_2PO_4 were obtained from Merck Company (Germany).

Preparation of physical mixture

The physical mixtures were prepared by weighing the calculated amounts of FUR and carriers and then mixing them in a glass mortar by trituration. The resultant physical mixtures were passed through 40-mesh sieve and stored in desiccator until used for further studies.

Preparation of solid dispersions

Solid dispersions of FUR with crospovidone and microcrystalline cellulose were prepared by the cogrinding method. Accurately weighed quantities (10 g) of FUR and the respective dispersion carrier were transferred into a Ball Mill (Fritsch, Germany). The mixtures were then rotate (rpm=360) at room temperature for 3 hrs.

Characterization of formulations

Fourier Transform Infrared (FT-IR) spectroscopic analysis

FT-IR spectra of moisture free powdered samples of FUR and its physical mixtures and solid dispersion with crospovidone and Avicel (1:2 drug: carrier) were obtained using a spectrophotometer (Bomem, USA) by potassium bromide (KBr, 150 bar) pellet method. The scanning range was 450–4000 cm^{-1}, and the resolution was 1 cm^{-1}.

X-Ray diffraction (XRD) studies

The X-ray diffraction patterns were determined for pure drug, carriers, physical mixtures and solid dispersions. X-ray diffractograms were obtained using the X-ray diffractometer (Siemens, Germany) and Cu-kα radiation (λ=1.54). Diffractograms were run at scanning speed of 2º/min and a chart speed of 0.6º/min.

Particle size analyzing

The particle size and size distribution of the prepared solid dispersions were determined using the laser diffraction particle size analyzer (Shimadzu, Japan) equipped with the Wing software (version 2101). The mean diameter and size distribution of the resulted homogeneous suspension were assessed. Each value resulted from triplicate determinations.

In vitro release study

In vitro dissolution study was performed in a paddle type dissolution apparatus (USP Type II). A fixed amount of each batch of formulation and pure FUR powder, containing 20 mg equivalent of FUR were used for dissolution study purpose. Simulated Gastric Fluid (SGF) without pepsin and Phosphate buffered saline (PBS), pH 5.8, was used as dissolution media, where 900 mL of it was taken in each dissolution vessel at a temperature of 37±0.5 °C and a paddle speed of 100 rpm. The dissolution test was carried out for 60 min and 5 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 30, 45 and 60 min. The dissolution samples were then analyzed spectrophotometrically by UV-VIS spectrophotometer (SHIMADZU, Japan) at 234 nm in pH 1.2 (linear in the range of 1-5 µg/mL, R^2= 0.9997) and at 272 nm in pH 5.8 (linear in the range of 2.5-20 µg/mL, R^2= 0.9997).

Release kinetic analysis

The release data obtained from *in vitro* dissolution studies were fitted to ten linear and seven non-linear kinetic equations to find out the mechanism of drug release (Table 1).[31,32] The precision and prediction power of the modes were evaluated by calculation of mean percent error (MPE) for each set as well as overall mean percent error (OMPE) for all set using following equations.[33]

$$MPE = \frac{100 \times \sum \frac{|Fcal - Fobs|}{Fobs}}{N}$$

$$OMPE = \frac{\sum_1^{14} MPE}{14}$$

Where, 14 is the number of formulations.

Where Fobs and Fcal are the measured and calculated fraction of the drug released in each sampling time, and N is the number of sampling times.[5,34]

Dissolution profile of different formulations were compared using calculation of mean percent dissolution (MPD) and time needed to release 30% of incorporated drug (t30%) in pH 1.2 and 5.8.

MPD was calculated according to following equation.[35]

$$MPD = \frac{\sum_{i=1}^{n} D\%}{n}$$

Where D is the percent of drug dissolved at different sampling times.

Table 1. Mean squared correlation coefficients (MRSQ), mean percent error (MPE) and percent of total number of error (NE) of the kinetic models used for analysis of drug release data.

Models	Equation	MRSQ	MPE	NE<5	NE<10	NE<12
Zero	$F = K_0 t$	0.898	18.333	16.667	14.286	46.429
First	$\ln(1-F) = -k_f t$	0.962	51.415	25.000	25.000	36.905
Higuchi	$F = k_H \sqrt{t}$	0.943	12.346	29.762	29.762	64.286
Pepas	$\ln F = \ln k_p + p \ln t$	0.959	15.325	16.667	16.667	42.857
Hixon–Crowell	$1-\sqrt[3]{1-F} = k_{\frac{1}{3}} t$	0.960	49.488	1.190	1.190	13.095
Square root of mass	$1-\sqrt{1-F} = k_{\frac{1}{2}} t$	0.947	14.459	23.810	23.810	52.381
Three seconds root of mass	$1-\sqrt[3]{(1-F)^2} = k_{\frac{2}{3}} t$	0.931	16.271	19.048	19.048	50.000
Weibull	$\ln[-\ln(1-F)] = \beta \ln t_d + \beta \ln t$	0.970	5.308	64.286	64.286	88.095
Wagner Linear	$Z = Z_0 + qt$	0.919	15.432	25.000	25.000	63.095
Wagner Log probability	$Z = Z_0' + q' \ln t$	0.962	7.638	41.667	41.667	85.714
Gompertz	$F = e^{\left(-a \times e^{-b \log t}\right)}$	0.971	8.028	42.857	42.857	71.429
Skrdla (homogen)	$F = 1 - e^{\left(ate^{-bt^2} - 1\right)}$	0.925	10.447	33.333	33.333	63.095
Skrdla (hetrogen)	$F = 1 - e^{\left(\frac{-a}{t\left(e^{bt^2}-1\right)}\right)}$	0.869	25.368	13.095	13.095	42.857
Logistic	$F = e^{\left(\frac{a+b\log t}{1+e^{(a+b\log t)}}\right)}$	0.979	9.657	45.238	45.238	73.810
Reciprocal powered time (suggested 1)*	$\left(\frac{1}{F}-1\right) = \frac{m}{t^b}$	0.939	17.076	16.667	16.667	51.190
Suggested 2*	$n<1$ $\quad 1-\left(1-F\right)^{1-n} = kt$	0.979	8.411	52.381	67.857	71.429
Suggested 3*	$n>1$ $\quad \frac{1}{(1-F)^{n'-1}} - 1 = (n'-1)k_{n'-1}t$	0.968	22.406	53.571	66.667	67.857

F denotes fraction of drug released up to time t. k_0, k_f, k_H, p, k_P, $k_{1/3}$, $k_{1/2}$, $k_{2/3}$, t_d, β, Z_0, Z_0', q, q', a and b are parameters of the models. Z and Z' are probits of fraction of drug released at any time. Z_0 and Z_0' are the values of Z and Z' when t=0 and t=1 respectively.
*See reference 31

Results and Discussion

Characterization of the solid dispersions

Particle size analysis

The particle size analysis results showed that mean particle size of ground powders were decreased significantly ($p<0.05$) compared to the pure drug (Figure 1).

The ground powders had a reduced geometric diameter and as a result higher surface area than that of pure FUR. According to the Noyes–Whitney equation, the amount

of solute dissolved per unit time, dM/dt, is related to the surface area of the solute.

$$\frac{dM}{dt} = \frac{DS}{h}(C_S - C)$$

Where D is the diffusion coefficient of the solute in solution, h stands for the thickness of the diffusion layer, C_s and C are the solubility and the concentration of the solute in the solution, respectively.[20,36]

Therefore, one of the reasons of higher dissolution rate of the solid dispersions comparing to pure FUR maybe be explained by particle size reduction during solid dispersion process.

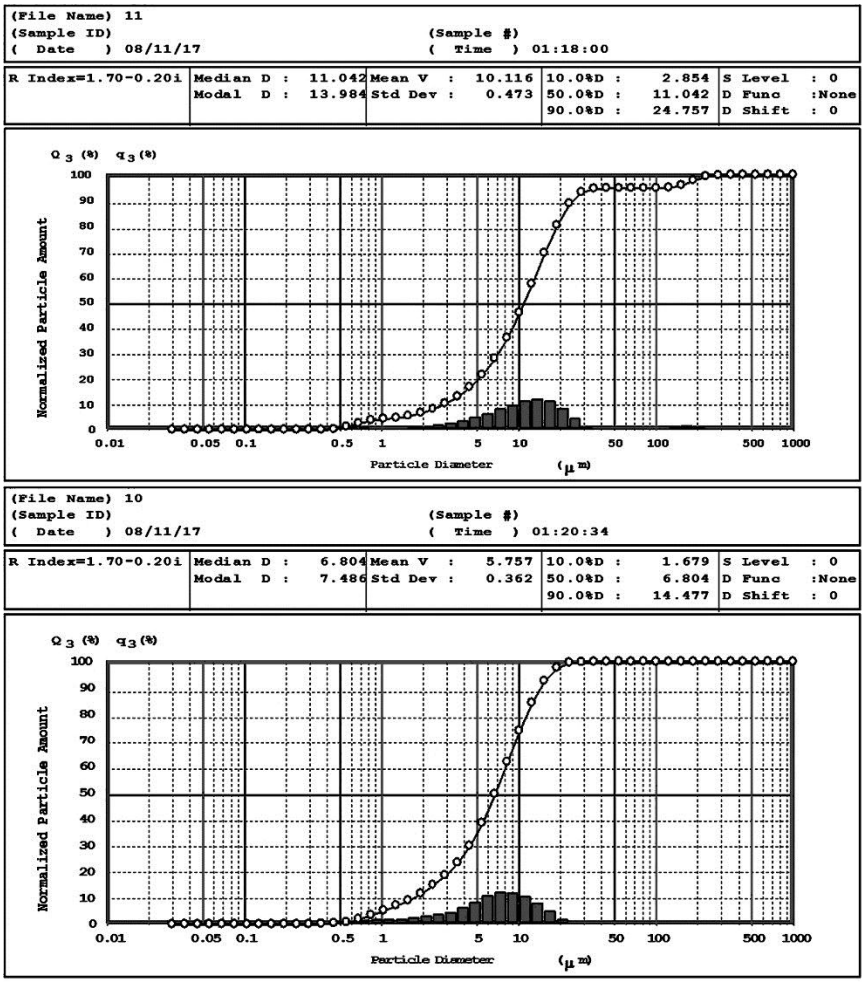

Figure 1. Particle size distribution of pure (Top) and treated powder (Below) of Furosemide

X-Ray diffraction studies

XRD diffractograms revealed that pure FUR showed distinctive peaks in 2θ=18, 18.9, 24.7 and 28.6 which indicate the crystalline nature of pure FUR. However, in treated FUR powder, the height and number of peaks were decreased, indicating the reduced crystallinity of the treated FUR powder. Comparing height of the peaks in the physical mixtures of both carriers demonstrated the reduction in magnitude of peaks due to the dilution effect of the carriers. Reduction in the height of the peaks and absence of some major peaks were seen in XRD patterns of the solid dispersions represented a decrease in FUR crystallinity in these preparations (Figure 2). The results confirmed the transformation of crystalline polymorph of FUR into its amorphous polymorph in the form of solid dispersion.

Fourier Transform Infrared Spectroscopy

In order to find out the possible intermolecular interactions between the FUR and carriers, FTIR studies were conducted. The FT-IR peaks of pure and treated FUR as well as carriers, physical mixture (drug: carrier 1:2) and solid dispersion (drug: carrier 1:2) are presented in Figure 3. There are three absorption peaks in 3340, 3260 and 16650 cm^{-1} which are related to the amino group, as well as 1560 and 1318 cm^{-1} which belong to carboxyl and sulphonyl groups, respectively. Lack of any new peaks in the solid dispersions and also no differences in the positions of the absorption bands, indicate the absence of significant interactions between FUR and carriers during cogrinding.

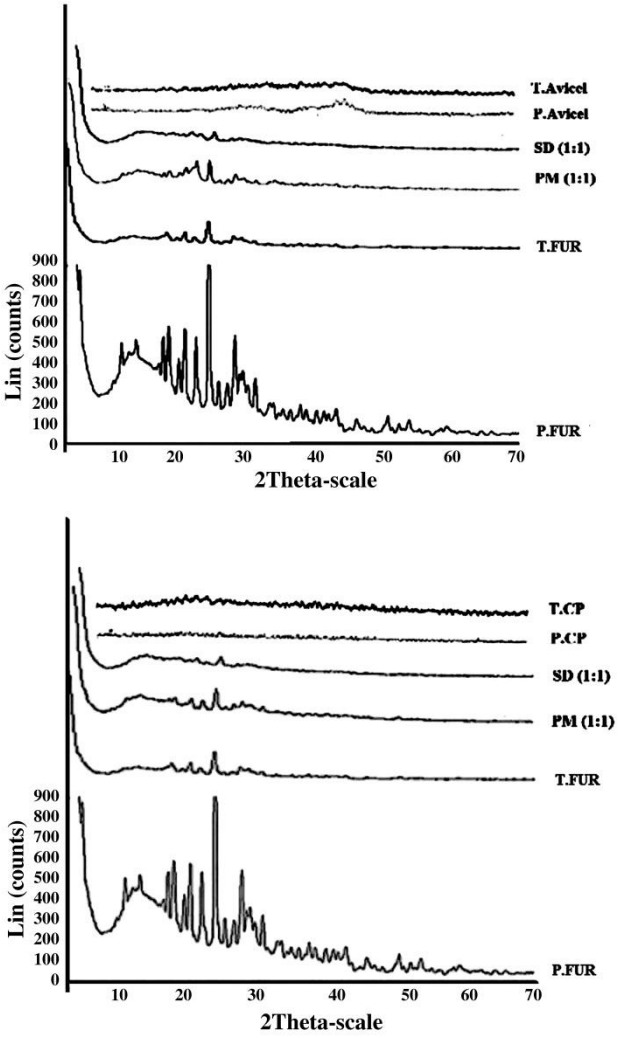

Figure 2. Powder X-Ray Diffraction patterns of pure FUR (P.FUR), treated FUR (T.FUR), physical mixtures (PM) 1:2, solid dispersions (SD) 1:2, pure Avicel (P.Avicel) and treated Avicel (T.Avicel), pure Crospovidone (P.CP) and treated Avicel (T.CP).

In vitro drug release

Dissolution profiles of physical mixtures, solid dispersions, pure and treated FUR powders prepared with various drug: carrier ratios of both carriers at pH 1.2 and 5.8 are presented in Figure 4 and 5. Dissolution rate of all formulations in pH 5.8 is considerably faster than pH 1.2 in the presence or absence of carriers. This could be due to the better solubility of the FUR, a weak acid, because of a greater ionization at higher pH values. In addition, as a result of lower particle size in treated powder compared with pure FUR (10.12 µm and 5.76 µm respectively), dissolution rate was also higher than pure FUR powder in both pHs. On the other hand, the physical mixtures of both carriers exhibited noticeably faster dissolution rates than the pure and treated FUR, which may be is due to high hydrophilicity of the carriers. Hydrophilic polymers caused aggregation reduction, wettability improvement and local solubilization in the diffusion layer and thereby increasing in the dissolution rate. Although, a direct relationship between the amount of carrier and FUR dissolution rate could not be established from the dissolution profiles of the different physical mixtures, but dissolution rate of all physical mixtures were much higher than the pure FUR. The solid dispersions of FUR and both carriers with different drug to polymer ratios showed the higher drug release rate when compared to the respective physical mixtures and pure drug.

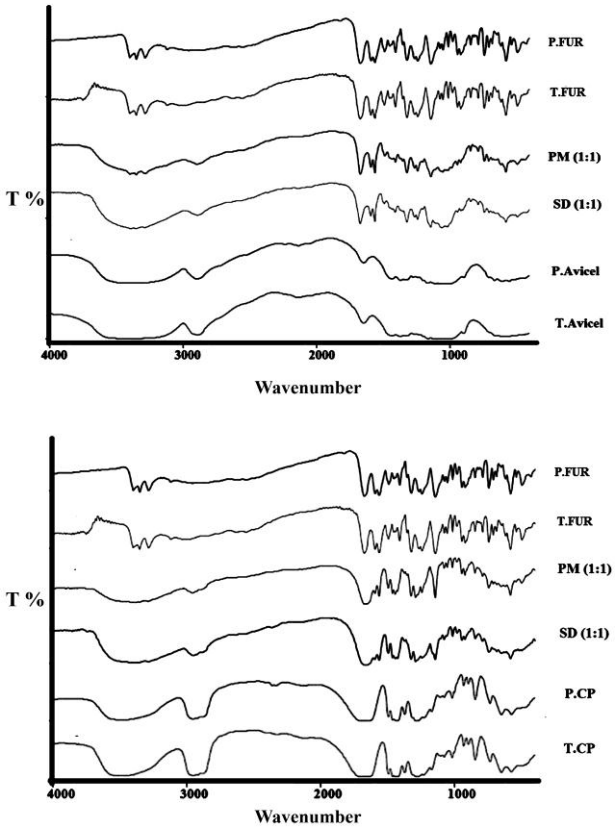

Figure 3. Powder FT-IR patterns of pure FUR (P.FUR), treated FUR (T.FUR), physical mixtures (PM) 1:2, solid dispersions (SD) 1:2, pure Avicel (P.Avicel) and treated Avicel (T.Avicel), pure Crospovidone (P.CP) and treated Avicel (T.CP).

Table 2 illustrates the time needed to release 30% of incorporated drug and the mean percent dissolution of pure FUR, treated FUR, physical mixtures and solid dispersions. Dissolution rate is considered faster, if the value of $t_{30\%}$ is lower and MPD value is higher. Similarly, these model independent parameters also verified that the drug is released faster from the solid dispersions. The improved drug release rate could be attributed to the drug crystallinity reduction in the FUR loaded solid dispersions prepared by Avicel and Crospovidone. It is generally well known that a drug in a solid dispersions system every so often exists in an amorphous form. The amorphous form of a drug has a higher thermodynamic activity than its crystalline form, leading to rapid dissolution of the drug. Furthermore, the reduced particle size and accordingly elevated surface area could enhance the dissolution rate of FUR in the solid dispersions. In addition to latter evidences, increasing drug wettability and solubility as well as deaggregation of the drug particles brought about by the polymers could be the reasons for enhanced drug release rate from the solid dispersions.[5,20,37]

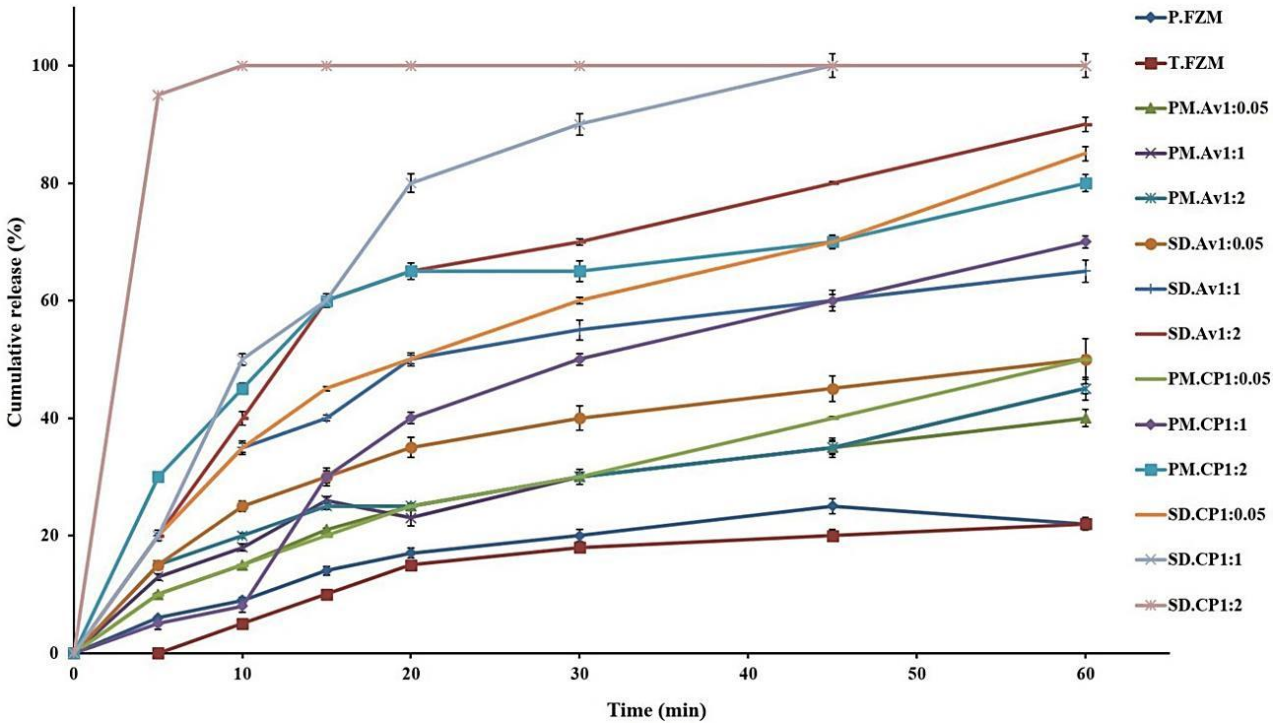

Figure 4. Dissolution profiles of pure FUR (P.FUR), treated FUR (T.FUR) physical mixtures (PM) 1:2 and solid dispersions (SD) 1:1 containing Avicel (AV) and Crospovidone (CP) in pH 1.2. (mean ± SD, n=3)

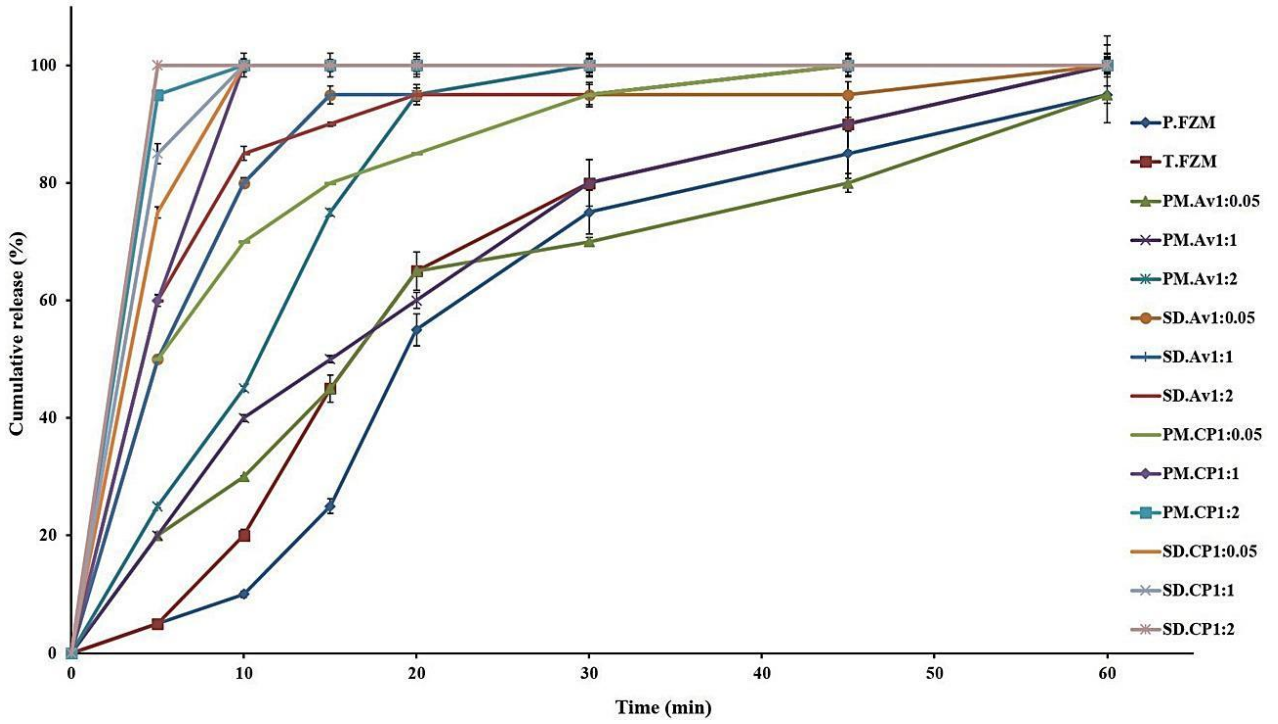

Figure 5. Dissolution profiles of pure FUR (P.FUR), treated FUR (TFUR) physical mixtures (PM) and solid dispersions (SD) containing Avicel (AV) and Crospovidone (CP) in pH 5.8. (mean ± SD, n=3).

Drug release rate was enhanced as a consequence of increasing carrier concentration, while solid dispersions showed the maximum release rate at the drug: carrier ratio of 1:1 and 1:2 (Table 2 as well as Figure 4 and 5). However, solid dispersions with drug: carrier ratio of 1:1 are economically the best formulation to enhance dissolution rate of FUR.

Table 2. Mean percent dissolution (MPD) and time needed to release 30% of incorporated drug (t30%) of Furosemide formulations in pH 1.2 and 5.8

Formulation		pH 1.2		pH 5.8	
		MPD	$t_{30\%}$	MPD	$t_{30\%}$
Pure Furosemide		12.27	84.5	50.33	10.8
Treated Furosemide		16.49	62.2	60.52	7
Avicel	**PM 1:0.5**	17.02	44.8	54.19	9.6
	PM 1:1	20.78	39	56.52	6.8
	PM 1:2	26.52	26.6	63.67	5.4
	SD 1:0.5	30.90	21.2	-	4.2
	SD 1:1	44.81	6	-	3
	SD 1:2	68.18	3	53.65	2
Crospovidone	**PM 1:0.5**	24.97	27.4	59.39	6.2
	PM 1:1	39.75	17.2	63.73	2.2
	PM 1:2	67.24	3.2	98.48	1
	SD 1:0.5	48.43	13.8	73.94	2
	SD 1:1	78.43	2.2	85.11	1.2
	SD 1:2	89.95	1.8	98.88	0.8

Release kinetics

To clarify the mechanism of release, the *in vitro* release data were fitted in to 10 linear and 7 non-linear kinetic models (Table 1). The accuracy and prediction ability of the models were compared by calculation of mean squared correlation coefficients (MRSQ) and mean percent error (MPR). Considering the RSQ and mean percent error values, release data of the all formulations were fitted best to the Weibull and Wagner log probability models from linear kinetics as well as Gompertz and suggested 2 models from nonlinear kinetic models.

Conclusion

Bioavailability of poorly water soluble drugs could be improved as a result of release rate enhancement. Thus, the present study was aimed to enhance the dissolution rate of FUR by means of cogrinding method using Crospovidone and microcrystalline cellulose as hydrophilic carriers. The results showed that both carriers enhanced dissolution rate in solid dispersion formulations in all three ratios and also physical mixture of Crospovidone in drug: carrier ratio of 1:2 compared with drug powder at both dissolution medium (pH 1.2 and 5.8). Drug: carrier ratio, type of polymer and pH can carry out a major role to control the dissolution rate from the solid dispersion. The best economical drug: carrier ratio of both carriers was 1:1. The solid state studies confirmed that solid dispersion of FUR with both carriers can decrease crystallinity or increase amorphousness of the drug. In conclusion, solid dispersion can be beneficially applied to enhance the dissolution rate of the poorly water-soluble drugs. Overall, the increased dissolution rate of solid dispersions can be described by the several factors including the increased surface area and creation of amorphous polymorph of the drug.

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Conflict of Interest

The authors report no conflicts of interest.

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