

Enhancement of solubility and dissolution rate of fenofibrate using β -Cyclodextrin

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Introduction

Poorly water-soluble drugs often require high doses to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. Therefore, there is a great interest to develop efficient, reliable, economical, and scalable method to increase the oral bioavailability of poorly water-soluble drugs.^[1,2]

To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization, solubilization, salt formation, and complexation with polymers, changing in physical forms (amorphous), use of prodrugs

ABSTRACT

Aim: The aim of the present research work, fenofibrate a BCS class II antihyperlipidemic drug belongs to fibrate class was formulated as solid dispersions using various hydrophilic carriers to enhance the solubility, dissolution rate, and oral bioavailability. **Methodology:** Various techniques such as physical method, kneading technique, solvent evaporation method, and fusion method were used to prepare solid dispersions of fenofibrate. Solid-state characterization of solid dispersions is done by differential scanning calorimetry and Fourier-transform infrared spectrometry. The solid dispersions can be evaluated by *in-vitro* dissolution studies. The solid oral dosage form (Tablets) with fenofibrate solid dispersions was prepared by direct compression method. Different evaluation parameters were performed, which include hardness, friability, weight variation, and disintegration dissolution, % drug content in the solid dispersions, and the fabricated formulations. **Results and Conclusion:** The pre-compression and post-compression parameters were studied and the results were given. All the results were in the acceptable limit. The rate of dissolution was excellently increased that tablets which were formulated from solid dispersions with disintegrating agents and excipients. Moreover, formulations showed their highest release (99.26%) for the tablets formed by solid dispersion 1:1.5 (fenofibrate:HP β -Cyclodextrin) with Ludiflash (15 mg) disintegrating agent.

Keywords: Fenofibrate, solubility, β -Cyclodextrin

and drug derivatization, pH alteration, addition of surfactants, micelles, microemulsions, nanoemulsions, nanosuspensions, solid-lipid nanoparticle, and solid dispersion which is considered one of the most successful strategies to improve the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous.^[3]

Definition of solid dispersion

Solid dispersion technology is a science of dispersing one or more active ingredients in the inert matrix in the solid stage to achieve the altered solid state properties, increased dissolution rate, enhanced release of drugs, the sustained release of drugs, and improved solubility and the stability.^[4]

Advantages of solid dispersion

The reasons for solid dispersion or advantages of solid dispersions are as follows:
Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased

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dissolution rate is attained. Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here, the carriers play the major role to improve the wettability of the particles. Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties. In solid dispersions, drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus, presenting drugs in an amorphous form increases the solubility of the particles.^[4]

Disadvantages of solid dispersions

Some problems limiting the commercial application of solid dispersion which involved, there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress), the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern because it may increase drug mobility and promote drug crystallization. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth, or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage.^[4]

Mechanisms to increase dissolution rate

The formulations of solid dispersions result into a reduction in particle size, this leads to an enhanced dissolution rate because an increase in the surface area. When the carrier material dissolves, it has a solubilization effect on the drug. Reduced lattice energy due to the formation of metastable dispersions results in a faster dissolution rate. Carrier used has an enhancing effect on wettability and dispersibility of the drug, thereby markedly improving the dissolution rate.^[5,6]

The classification of solid dispersions

- a. On the basis of molecular arrangement, solid dispersions are classified into eutectic mixtures, amorphous precipitations in crystalline matrix, solid solutions, and glass suspensions and glass solutions
- b. On the basis of carrier employed, solid dispersions are classified into first-generation, second-generation, third-generation, and fourth-generation solid dispersions.

Methods of preparation of solid dispersion^[7,8]

1. Melting or fusion method
2. Solvent evaporation method
3. Melt evaporation method
4. Kneading method
5. Co-grinding method
6. Method of melt extrusion
7. Melt agglomeration process
8. Co-precipitation method (co-evaporates)
9. Spray drying method
10. Gel entrapment technique

11. Super critical fluid technology
12. Dropping solution method
13. Lyophilization technique
14. Electrospinning.

Materials and Methods

Materials

Fenofibrate the active pharmaceutical ingredient was obtained from Ajanta Pharma, Aurangabad, Potato Starch, PVP K-30, Mannitol, Magnesium Stearate, and Talc were obtained from Dipa Chemical Industries, Aurangabad and Ludiflash were obtained from Signet Chemical Corp. Mumbai.

Methods: Preformulation studies

The following preformulation studies were performed for drug and polymers;

- Determination of melting point
- Solubility studies
- Drug-excipient compatibility studies.
 - Fourier-transform infrared (FT-IR)
 - Differential scanning calorimetry (DSC)

Determination of melting point

Melting point of the drug was determined by taking a small amount of drug in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted.^[9]

Solubility studies

Solubility of fenofibrate was carried out in different buffers. Saturated solutions were prepared by adding the excess drug to the vehicles and shaking on the shaker for 24 h at 25°C under constant vibration. Filtered samples (1 ml) were diluted appropriately with a suitable buffer and solubility of fenofibrate was determined spectrophotometrically at suitable nm.^[10]

Drug-polymer compatibility studies

This study was done to check whether any compatibility related problems are associated with drug and the excipients used for the formulation. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, and easy to administer and safe.

FT-IR studies

FT-IR studies were employed to ascertain the compatibility between fenofibrate and the selected polymers. The pure drug and drug with excipients were scanned separately. Potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of fenofibrate was compared with FT-IR spectrum of fenofibrate with polymer. Disappearance of fenofibrate peaks or shifting of peak in any of the spectra was studied.^[9]

DSC study

DSC analysis of pure drug, and optimized formulation was performed with Shimadzu DSC 60 thermal analyzer at the heating flow rates of 5°C per min between 0 and 450°C under static air using aluminum pans.^[11,12]

Preparation of solid dispersions of fenofibrate

Physical mixture method

Fenofibrate and HP β -Cyclodextrin were accurately weighed, pulverized, and then mixed thoroughly by light titration for 5 min in a glass mortar until a homogenous mixture was obtained.^[13]

Kneading technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for a particular time. The kneaded mixture is then dried and passed through a sieve if necessary and finally obtained product was stored into desiccators.^[14]

Solvent evaporation method

In solvent evaporation method, the drug and carriers were mixed in 1:0.25, 1:0.5, 1:0.75, 1:1, 1:1.25, and 1:1.5 ratios in methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverized and passed through sieve # 100. And now the obtained product was collected and stored in desiccators.^[15]

Melting (or) fusion method

Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion, the mixture is heated at or above the melting point of all the components. It is then cooled to acquire a congealed mass. It is crushed and sieved.^[16] Formulation of solid dispersion by various methods is shown in Table 1.

Evaluation of Solid Dispersions

Prepared polymer-drug conjugates were evaluated by:

Estimation of drug content

A quantity, which was equivalent to 10 mg of drug, was accurately weighed and transferred to 100 ml volumetric flask. Then the volume was made up with 0.1 N HCl buffer and shaken for 10 min to ensure complete solubility of the drug. Then the solution was filtered. The same concentration of the standard solution was prepared by dissolving 10 mg of standard drug in 0.1 N HCl buffer. For both the sample and standard solutions, absorbance was measured at 273 nm for fenofibrate in ultraviolet (UV)-visible spectrophotometer.^[17]

Entrapment efficacy

Entrapment efficiency of the solid dispersions was an important characteristic to assess the quantity of material entrapped inside solid dispersions before the study of behavior of this entrapped drug in physical and biological systems since the effects observed experimentally are usually dose related. Solid dispersions formulation of a drug can only be developed if the encapsulation efficiency of therapeutic doses can be delivered with a reasonable amount of drug since the lipids in higher doses may be toxic and also result in non-

linear (saturable) pharmacokinetics of formulation. An optimized loading procedure would achieve trapping efficiencies of 90% and more. This obviates the need for removal of non-entrapped material because loading doses of 10% or less of free drug can usually be tolerated. Procedures such as dialysis and passage through the exclusion column for removal of non-entrapped material are often time-consuming, tedious, costly, and recovery of non-entrapped material is usually difficult.^[18]

Entrapment efficacy was calculated by the following formula:

$$\% \text{Entrapment efficiency} = \frac{\text{Drug content} \times 100}{\text{Drug added in each formulation}}$$

In-vitro dissolution study

Dissolution rate of fenofibrate from all formulations was performed using the dissolution testing apparatus (paddle). The dissolution fluid was 900 ml of 0.1N HCl, a speed of 50 rpm, and a temperature of 37 \pm 0.5°C was used in each test. Samples of dissolution medium (5 ml) were withdrawn at different time intervals (5, 10, 20, 30, 45, 60, 75, and 90 min), suitably diluted and assayed for fenofibrate by measuring the absorbance at 273 nm using UV spectrophotometer.^[19,20]

Formulation of Fenofibrate Immediate Release Tablets

Equivalent weight of fenofibrate was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table. All the ingredients were passed through # 60 mesh sieve separately. The drug and mannitol were mixed by adding a small portion of each at a time and blending it to get a uniform mixture and kept aside. Then, the other ingredients were mixed in geometrical order and passed through a coarse sieve (#44 mesh) and the tablets were compressed. Compression force of the machine was adjusted to obtain the hardness in the range of 3–4 kg/cm² for all batches. The weight of the tablets was kept constant for all formulations F1–F6 (250 mg). Formulation composition of Fenofibrate immediate-release tablets is shown in Table 2.

Evaluation of Tablets

Hardness test

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. The hardness of the tablets was determined using Pfizer Hardness Tester. It is expressed in kg/cm². Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.^[21]

Friability test

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight or a sample of 20 tablets are dedusted in a drum for

a fixed time (100 revolutions) and weighed again. Percentage friability was calculated from the loss in weight as given in the equation. The weight loss should not be more than 1%.^[21]

$$\text{Friability} = [(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \times 100$$

Weight variation test

The USP weight variation test is run by weighing 20 tablets individually, calculating the average weight of the sample, and comparing individual weights with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed. In all the formulations, the tablet weight was more than 130 mg and <324 mg, hence a 7.5% maximum difference allowed.^[22]

Thickness and diameter

Tablet thickness and diameter can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier Caliper. The thickness and diameter are measured by placing tablet between two arms of the Vernier Caliper.^[22]

Drug content uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 25 mg was weighed accurately and dissolved in 100 ml of 0.1 N HCl. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No. 41 filter paper. Then, dilute the solution to obtain 10 μ g solution. The absorbance of the diluted solutions was measured at 273 nm.^[23]

In-vitro disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of six glass tubes which are three inches long, open at the top, and held against a 10 mesh screen at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 L beaker containing pH 0.1N HCl buffer solution at $37^\circ\text{C} \pm 1^\circ\text{C}$ such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.^[24,25]

In vitro dissolution studies

In vitro dissolution study is performed using USP Type II Apparatus (Paddle type) at 50 rpm. 0.1N HCl buffer 900 ml is used as a dissolution medium which is maintained at $37 \pm 0.5^\circ\text{C}$. Aliquots of dissolution medium (10 ml) are withdrawn at specific time intervals and filter. An equal amount of fresh dissolution medium is replaced immediately following the withdrawal of test sample. The percentage of drug released at various intervals is calculated using beer-lamberts law by measuring the absorbance at 273 nm.^[26]

Results and Discussion

Preformulation studies

The following preformulation studies were performed for drug and polymers;

1. Determination of melting point
The melting point of fenofibrate was found to be 82°C which was determined by capillary method.
2. Solubility
Solubility of fenofibrate was carried out at 25°C using 0.1 N HCl, 6.8 phosphate buffer, and purified water.

Discussion

From the above-conducted solubility studies in various buffers, we can say that 0.1 N HCl solutions have more solubility when compared to other buffer solutions. The result of solubility data of fenofibrate is shown in Table 3.

3. Drug-excipient compatibility studies
Drug and excipient compatibility was confirmed by comparing the spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

Discussion

Form the drug excipient compatibility studies, we observe that there are no interactions between the pure drug (fenofibrate) and optimized formulation (fenofibrate: excipients) which indicates there are no physical changes.

- The IR spectrum of fenofibrate exhibited a peak at 2990 cm^{-1} due to C-H stretching and at 1649 cm^{-1} due to C=C stretching, and 748 cm^{-1} due to C-Cl stretching, 1363 cm^{-1} due to the OH stretching
- The IR spectrum of a physical mixture of drug and excipient showed peaks at 2983 cm^{-1} due to C-H stretching, and 1649 cm^{-1} due to C=C stretching, and 763 cm^{-1} due to C-Cl stretching, 1411 cm^{-1} due to the OH stretching
- This shows that there was no interaction between fenofibrate and optimized formulation. The results are shown in Figures 1 and 2.

DSC study

DSC thermogram of the optimized solid dispersion (10 mg sample) was recorded using automatic thermal analyzer.

Discussion

DSC shows that no drug-excipient interaction, as the original exotherm of the drug was clearly evident in the physical mixture. The thermograms are shown in Figures 3 and 4, respectively. Figure 3 indicates that the melting of drug has taken place at 82.7°C . It is matching with the literature value $80\text{--}84^\circ\text{C}$. Figure 4 indicates that the melting point of the blend is 81.8°C . This indicates that there is no interaction between drug and excipients. These results are further supported by the results of FT-IR studies. The results are shown in Figures 3 and 4.

Table 1: Formulation of solid dispersion by various methods

Method	Physical mixture method			Kneading method			Solvent evaporation method			Fusion method		
Formulation code	PF1	PF2	PF3	KF1	KF2	KF3	SF1	SF2	SF3	FF1	FF2	FF3
Drug: Polymer ratio	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5

Table 2: Formulation of Fenofibrate immediate-release tablets

Ingredients	F1	F2	F3	F4	F5	F6
Complex equivalent to 60 mg of fenofibrate	150	150	150	150	150	150
Potato starch (mg)	5	10	15	-	-	-
Ludiflash (mg)	-	-	-	5	10	15
PVP K-30 (mg)	10	10	10	10	10	10
Mannitol (mg)	81	76	71	81	76	71
Magnesium stearate (mg)	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2
Total (mg)	250	250	250	250	250	250

Table 3: Solubility data of fenofibrate

Medium	Solubility (mg/ml)
Water	0.126
0.1 N HCl	0.236
6.8 PH buffer	0.162

Evaluation of solid dispersions

Prepared polymer-drug conjugates were evaluated by

Estimation of drug content

By comparing results of all the formulations (PF1-PF3), (KF1-KF3), (SF1-SF3), and (FF1-FF3), formulation SF3 containing fenofibrate:HP β -Cyclodextrin (1:1.5) shows higher drug content 92.9%. Drug content values are shown in Table 4.

Entrapment efficiency

By comparing results of all the formulations (PF1-PF3), (KF1-KF3), (SF1-SF3), and (FF1-FF3), formulation SF3 containing fenofibrate:HP β -Cyclodextrin (1:1.5) shows higher entrapment efficiency 94.43%. Entrapment efficiency values are shown in Table 5.

Discussion (physical mixture method): *In vitro* drug release of fenofibrate solid dispersions with HP β -cyclodextrin in various ratios was observed which shows at the end of 90 min, the formulation PF1 releases 82.21, formulation PF2 releases 86.42, and PF3 releases 89.94%.

Discussion (kneading method): *In vitro* drug release of fenofibrate solid dispersions with HP- β cyclodextrin in various ratios was observed which shows at the end of 90 min, the formulation KF1 releases 78.92, formulation KF2 releases 80.46, and formulation KF3 releases 82.21%.

Discussion (solvent evaporation method): *In vitro* drug release of fenofibrate solid dispersions with HP- β cyclodextrin in various ratios were observed which shows at the end of 90 min the formulation SF1

releases 92.46, formulation SF2 releases 95.29, and formulation SF3 releases 98.56% of drug at the end of 90 mints.

Discussion (fusion method): *In vitro* drug release of fenofibrate solid dispersions with HP- β cyclodextrin in various ratios was observed which shows at the end of 90 min the formulation FF1 releases 79.86, formulation FF2 releases 82.06, and formulation FF3 releases 85.29%.

By comparing results of all the formulations (PF1-PF3), (KF1-KF3), (SF1-SF3), and (FF1-FF3) formulation SF3 containing fenofibrate:HP β -Cyclodextrin (1:1.5) shows higher drug release 98.56% at the end of 90 min. Finally by comparing results of content uniformity, entrapment efficacy, *in vitro* drug release studies for all formulations (PF1-PF3), (KF1-KF3), (SF1-SF3), and (FF1-FF3), formulation SF3 containing fenofibrate:HP β -Cyclodextrin (1:1.5) shows the better result, hence, it was selected as the best formulation among all the formulations. % drug release for various solid dispersion formulations is shown in Table 6.

Phase-II

Evaluation of Tablets

Evaluation of post compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters such as weight variation, hardness, friability, tablet thickness, and drug content and results are shown in Table 7.

Discussion

- Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.7–4.1 kg/cm²
- All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight
- Friability values were found to be <1% in all the formulations F1–F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

Drug content uniformity of formulations

The prepared formulations were analyzed for drug content and the data are reported in Table 8. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Discussion

The drug content values for all the formulations (F1–F6) were found to be in the range of 95.29–99.62%; formulation F6 shows higher drug content uniformity 99.62%.

Table 4: Drug content uniformity for solid dispersion

Method	Physical mixture method			Kneading method			Solvent evaporation method			Fusion method		
	PF1	PF2	PF3	KF1	KF2	KF3	SF1	SF2	SF3	FF1	FF2	FF3
%Drug Content	75.3	80.12	83.6	54.64	66.21	74.82	62.2	79.19	92.9	68.2	72.6	79.4
Discussion	% drug content was in the range of 75.3–83.6%, formulation PF3 shows higher drug content 83.6%			% drug content was in the range of 54.64–74.82%, formulation KF3 shows higher drug content 74.82%			% drug content was in the range of 62.2–92.9%, formulation SF3 shows higher drug content 92.9%			% drug content was in the range of 68.6–79.4%, FF3 shows higher drug content 79.4%		

Table 5: Entrapment efficiency of solid dispersions by physical mixture method

Method	Physical mixture method			Kneading method			Solvent evaporation method			Fusion method		
	PF1	PF2	PF3	KF1	KF2	KF3	SF1	SF2	SF3	FF1	FF2	FF3
% Entrapment efficiency	75.4	82.5	80.3	68.21	72.85	75.3	79.59	88.75	94.43	54.9	62.9	78.21
Discussion	The entrapment efficacy was found to be in the range of 75.4–82.5%. Formulation PF2 shows higher entrapment efficiency 82.5%			The entrapment efficacy was found to be in the range of 68.21–75.36%. Formulation KF3 shows higher entrapment efficiency 75.36%			The entrapment efficacy was found to be in the range of 79.59–94.43%. Formulation SF3 shows higher entrapment efficiency 94.43%			The entrapment efficacy was found to be in the range of 54.9–78.21%. Formulation FF shows higher entrapment efficiency 78.21%		

Table 6: *In vitro* dissolution studies (*in vitro* drug release studies of solid dispersions)

Method	Physical mixture method			Kneading method			Solvent evaporation method			Fusion method		
	PF1	PF2	PF3	KF1	KF2	KF3	SF1	SF2	SF3	FF1	FF2	FF3
Time (min)	% Drug release											
0	0	0	0	0	0	0	0	0	0	0	0	0
5	10.42	19.46	24.26	12.48	17.29	22.68	18.26	26.48	30.52	12.84	19.26	28.69
15	26.82	28.32	39.69	32.78	35.12	37.26	36.61	48.21	51.22	28.86	32.26	41.12
30	34.26	44.28	47.22	39.92	39.98	41.22	55.02	57.26	60.26	42.21	45.29	53.27
45	52.98	55.21	55.25	47.36	49.82	52.82	61.33	62.82	74.82	51.26	52.02	64.86
60	64.82	69.71	72.84	56.28	58.22	61.21	70.26	76.21	81.86	63.81	64.39	63.71
75	73.92	78.46	81.92	64.27	68.64	70.29	84.20	88.65	92.78	70.46	76.29	79.58
90	82.21	86.42	89.94	78.92	80.46	82.21	92.46	95.29	98.56	79.86	82.06	85.29

Table 7: Evaluation of post-compression parameters

Formulation	Wt variation (mg) (mean \pm SD)	Thickness (mm) (mean \pm SD)	Hardness (kg/cm ²) (mean \pm SD)	Friability (%) (mean \pm SD)	Disintegrating time (s) (mean \pm SD)
F1	251.6 \pm 0.04	3.4 \pm 0.01	3.9 \pm 0.01	0.65 \pm 0.02	32.08 \pm 0.08
F2	249.2 \pm 0.03	3.2 \pm 0.01	3.7 \pm 0.01	0.59 \pm 0.08	34.29 \pm 0.02
F3	249.8 \pm 0.02	3.5 \pm 0.02	4.1 \pm 0.06	0.48 \pm 0.06	32.12 \pm 0.07
F4	249.2 \pm 0.06	3.6 \pm 0.06	3.9 \pm 0.02	0.52 \pm 0.02	34.26 \pm 0.05
F5	251.2 \pm 0.02	3.2 \pm 0.02	3.8 \pm 0.08	0.46 \pm 0.08	36.21 \pm 0.02
F6	249.02 \pm 0.08	3.4 \pm 0.06	3.7 \pm 0.04	0.52 \pm 0.02	26.28 \pm 0.04

Table 8: Drug content uniformity of formulations F1–F6

Tablet formulation	% of drug content
F1	96.59
F2	98.02
F3	98.26
F4	95.29
F5	97.65
F6	99.62

Table 9: % Cumulative drug release of formulations F1–F6

Time (min)	F1	F2	F3	F4	F5	F6
00	0	0	0	0	0	0
05	30.81	36.77	38.65	30.26	36.86	42.86
10	46.29	50.28	54.17	48.32	56.21	61.86
15	60.8	66.48	71.31	66.82	69.86	78.62
20	72.25	81.85	83.46	89.26	84.84	85.21
30	89.87	93.17	95.12	92.86	94.86	99.26

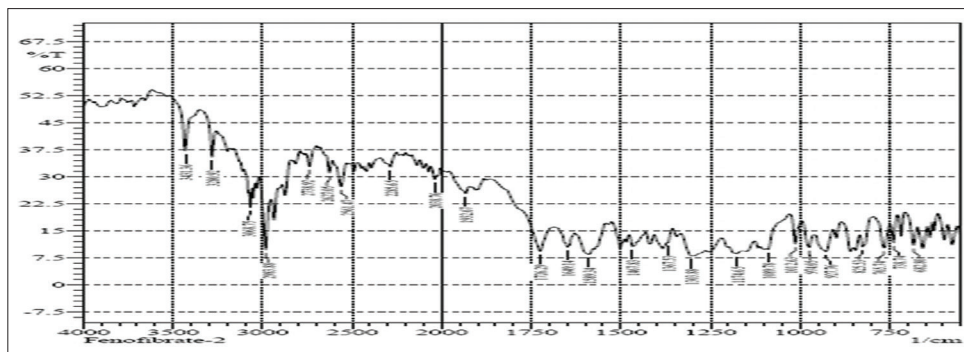


Figure 1: Infrared spectrum of pure Fenofibrate

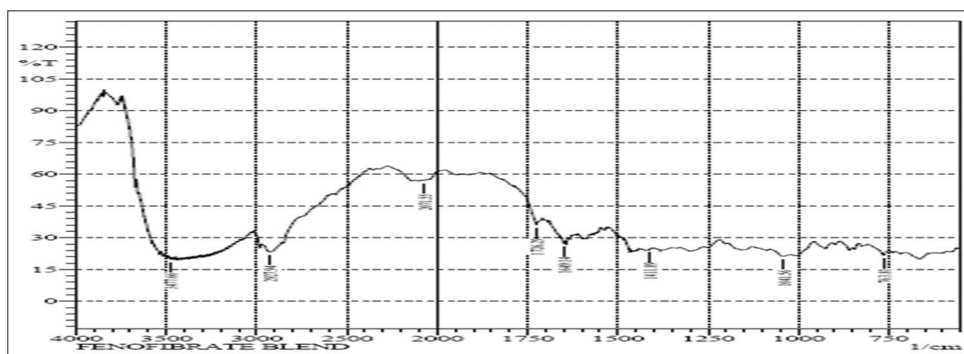


Figure 2: Infrared spectrum of physical mixture of drug and excipient blend

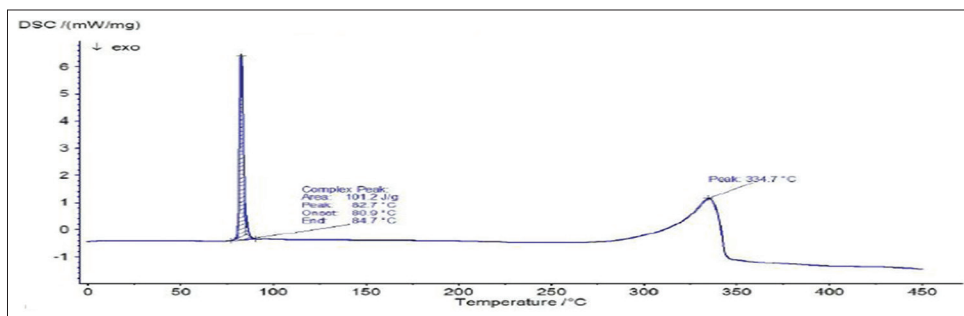


Figure 3: Differential scanning calorimetry thermogram of fenofibrate

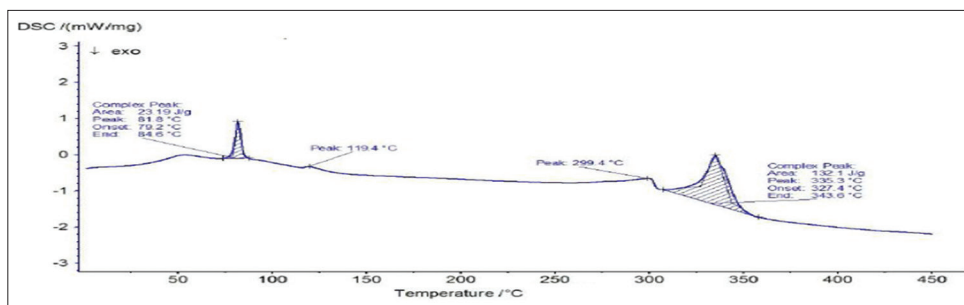


Figure 4: Differential scanning calorimetry thermogram of solid dispersion of drug: excipient blend

Dissolution studies of the tablets

The prepared tablets were subjected to dissolution studies to know the amount drug release.

Discussion

The complete comparative study of 250 mg various tablets for the equivalent weight of fenofibrate 60 mg various tablets formulated by

pure fenofibrate with excipients and solid dispersion with excipients. The rate of dissolution was excellently increased that tablets which were formulated from solid dispersions with disintegrating agents and excipients. Moreover, formulations showed their highest release (99.26%) for the tablets formed by solid dispersion 1:1.5 (fenofibrate:HP β -Cyclodextrin) with Ludiflash (15 mg) disintegrating agent. In this study, it was shown that the incorporation of disintegrants (Ludiflash) in solid dispersion tablets containing a high drug load can strongly enhance the dissolution rate of the highly lipophilic drug fenofibrate. % Cumulative drug release of tablet formulations F1–F6 is shown in Table 9.

Conclusions

HP β -cyclodextrin was used in the preparation of solid dispersions by the physical mixture method, kneading method, solvent evaporation, and fusion method. Formulation (SF3) containing fenofibrate + HP β -cyclodextrin (1:1.5) shows better results by the solvent evaporation method at the end of 90 min with drug release of 98.56%, hence, it was selected as the best formulation. In this study, it was found that the addition of a disintegrating agent to formulations containing solid dispersions is a suitable technology to improve the dissolution behavior of poorly water-soluble drugs when the drug load is high. Moreover, formulations showed their highest release (99.26%) for the tablets formed by solid dispersion 1:1.5 (fenofibrate:HP β -Cyclodextrin) with Ludiflash (15 mg) disintegrating agent.

References

- Vimalson DC, Parimalakrishnan S, Jegathanan NS, Anbazhagan S. Solid dispersion technique to enhance the solubility and dissolution of febusostat an BCS class II drug. *Int J Appl Pharm* 2019;11:241-6.
- Chouhan M, Gupta D, Choukse R, Maheshwari RK. Formulation and evaluation fast dissolving tablets of lovastatin using solid dispersion method. *J Drug Deliv Ther* 2019;9:29-31.
- Sabritri B, Snehamayee M. Recent approaches of solid dispersion: A new concept toward oral bioavailability. *Asian J Pharm Clin Res* 2018;11:72-8.
- Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS. Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs and application to anticancer drugs. *Pharmaceutics* 2019;11:132.
- Chaturvedi M, Kumar M, Pathak K, Bhatt S, Saini V. Surface solid dispersion and solid dispersion of meloxicam: Comparison and product development. *Adv Pharm Bull* 2017;7:569-77.
- Uddin MZ, Chowdhury JA, Hasan I, Reza MS. Enhancement of dissolution profile of poorly water soluble loratadine by solid dispersion technique. *Dhaka Univ J Pharm Sci* 2016;15:195-201.
- Kumar GY, Naveen G, Babu JA, Krishna KG, Reddy KG. A review on solid dispersion and its application. *World J Pharm Res* 2019;8:340-54.
- Cid AG, Simonazzi A, Palma SD, Bermúdez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. *Ther Deliv* 2019;10:363-82.
- Qingyun Z, Liquan O, Guowei Z, Ping C, Zhenggen L, Wei D, *et al.* Preparation and characterization of PEG4000 palmitate/PEG8000 palmitate-solid dispersion containing the poorly water-soluble drug andrographolide. *Adv Polym Technol* 2020;2020:1-7.
- Raj AL, Kumar YS. Preparation and evaluation of solid dispersion of nebigolol using solvent evaporation method. *Int J Pharm Sci Drug Res* 2018;10:322-8.
- Xi Z, Zhang W, Fei Y, Cui M, Xie L, Chen L, *et al.* Evaluation of the solid dispersion system engineered from mesoporous silica and polymers for the poorly water soluble drug indomethacin: *In vitro* and *in vivo*. *Pharmaceutics* 2020;12:144.
- Jung BA, Dong-Hyun K, Sang-Eun L, Yong-Chul P, Jeong-Sook P. Improvement of the dissolution rate and bioavailability of fenofibrate by the supercritical anti-solvent process. *Int J Pharm* 2019;564:263-72.
- Prasanthi D, Guvva J, Lakshmi AK. Solid dispersions of fenofibrate: Comparison of natural and synthetic carriers. *Pharm Innov J* 2019;8:42-50.
- Mohmeed O, Anil M, Ramkrishna D. Formulation and *in vitro* evaluation of immediate release tablets of fenofibrate solid dispersions by different techniques. *Int J Pharm Res* 2015;4:468-77.
- Vimalson DC, Parimalakrishnan S, Jegathanan NS, Anbazhagan S. Enhancement of solubility and dissolution characteristics of fenofibrate by solid dispersion technique. *Int Res J Pharm* 2018;9:145-50.
- Rampal A, Singh M, Mahajan S, Bedi N. Formulation and characterization of HPMC and HPMCAS based solid dispersions of fenofibrate: A comparative study. *Int J Appl Pharm* 2019;11:41-8.
- Usmanova LS, Ziganshin MA, Rakipov IT, Lyadov NM, Klimovitskii AE, Mukhametzyanov TA, *et al.* Microspherical particles of solid dispersion of polyvinylpyrrolidone K29-32 for inhalation administration. *BioMed Res Int* 2018;2018:1-12.
- Sapkal SB, Adhao VS, Thenge RR, Darakhe RA, Shinde SA, Shrikhande VN. Formulation and characterization of solid dispersion of etoricoxib using natural polymers. *Turk J Pharm Sci* 2020;17:7-19.
- Wen T, Niu B, Wu Q, Zhou Y, Pan X, Quan G, *et al.* Fenofibrate solid dispersion processed by hot-melt extrusion: Elevated bioavailability and its cell transport mechanism. *Curr Drug Deliv* 2019;16:538-47.
- Viswanadh K, Devala RG, Vidyadhara S, Venkata BR, Ramesh BJ, Siva PS. Solubility and dissolution rate enhancement of telmisartan by solid dispersion and pelletization techniques using soluplus as carrier. *Int J Appl Pharm* 2020;12:50-8.
- Brahmaiah B, Nama S, Nuthakki S, Kiran KV, Pasumarthi P. Enhancement of dissolution rate of fenofibrate by using various solid dispersion techniques. *World J Pharm Pharm Sci* 2014;3:914-32.
- Tamboli JA, Mohite SK. Immediate release solid dispersion tablet of azilsartan: Formulation strategy to enhance oral bioavailability. *Int J Appl Pharm* 2020;12:126-34.
- Ghosh MK, Wahed MI, Ali MA, Barman RK. Formulation and characterization of fenofibrate loaded solid dispersion with enhanced dissolution profile. *Pharmacol Pharm* 2019;10:343-55.
- Kaur B, Dua JS, Prasad DN. Development and characterization of fenofibrate tablet by comparing two different solubility and dissolution enhancement methods. *Asian J Pharm Res Dev* 2018;6:32-40.
- Prasanthi D, Prakash C, Aishwarya KL. Solid dispersions of fenofibrate by dropping method. *Int J Pharm Sci Res* 2019;10:4995-5001.
- Patel TB, Patel LD, Patel T, Makwana S, Patel T. Enhancement of dissolution of fenofibrate by solid dispersion technique. *Int J Res Pharm Sci* 2010;1:127-32.