ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Heightening the solubility of poorly soluble fenofibrate by Solid Dispersion Technique

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Article History:

Received on: 15.09.2019
Revised on: 20.12.2019
Accepted on: 29.12.2019

Keywords:

Fenofibrate,
solid dispersions,
PEG 4000,
PEG 6000,
PEG 8000,
Urea,
β-cyclodextrin,
Fusion technique

ABSTRACT

The intention of the current study was to boost the solubility of Fenofibrate by solid dispersion technique which is an efficient technique in improving the solubility and hence the dissolution rate of poorly soluble drugs in the form of eutectic mixtures by producing fine dispersion when in contact with gastrointestinal fluid and also the technique offers the choices of carriers to be combined with drug conveniently to improve the solubility to a considerable extent. Fenofibrate a BCS class II Antihyperlipidemic drug belongs to fibrate class and it is a lipid-lowering drug used in the treatment of hyperlipidemia. Fenofibrate is insoluble in water and hence shows poor dissolution in gastric fluid with reduced absorption characteristics. In order to improve the solubility, dissolution rate, gastrointestinal absorption and oral bioavailability, it was decided to prepare fenofibrate solid dispersion and evaluated. They were prepared using poly ethylene glycol 4000, 6000, 8000 and β-cyclodextrin by fusion technique and optimized solid dispersion was also lyophilized. Physical characterization of solid inclusion complex of fenofibrate was studied and showed that there were no drug excipients interactions. Dissolution studies showed a momentous rise in a dissolution of Fenofibrate when dispersed in polymers. Inturn aqueous solubility was enlarged linearly as a function of the concentration of β- Cyclodextrin.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i1.1873

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INTRODUCTION

The drug's solubility and permeability behavior of a drug plays a main in producing appreciable bioavailability when administered orally. Almost 40% of drugs available in the current field are poorly soluble. The drug development industry faces a lot of challenges in augmenting the oral bioavailability of such drugs. The basic scenario what the current industry follow is to alter the formulation approaches to improve the solubility of the drugs and release rate. As part of it, the first and foremost approach is micronizing the drug particle size to improve the dissolution rate-limited gastrointestinal absorption.

However, in most of the similar cases, it was created that drug's micronization produced poor wettability of the particles due to their aggregation and agglomeration when in contact with water. Though micellar solubilization and salt formation have been

considered as promising techniques to escalate dissolution rate-limited oral absorption and bioavailability of poorly water-soluble drugs, there survives some practical boundaries for these techniques. The hands-on method, which was later identified to overcome the above limitations as solid dispersion that comprises the formation of a eutectic mixture of drugs with soluble carriers by fusion of their physical mixtures. This is simply defined as a dispersion of drug in a matrix of hydrophilic carriers.

Fenofibrate an Antihyperlipidemic BCS class II drug have low water solubility and high permeability (Jamzad and Fassihi, 2006; Noyes and Whitney, 1897; Drooge *et al.*, 2006). Here solubility is the rate-limiting step if it is increased, then bioavailability of the drug also increases. When the dug dispersed in solid dispersion that contains soluble carrier on exposure to water/gastrointestinal fluid, the carrier dissolves first along with the drug releases in the form of colloidal dispersion that creates an enormous increase in surface area and hence yields better dissolution rate (Timpe, 2010). In addition, there exists a saturation of dissolved drug at part immediately in the gastrointestinal tract fluid, and the remaining drug precipitates in its submicron level as colloidal particles or oily globules.

The technique of solid dispersion was initially established by Sekiguchi and Obi (Hancock and Zografi, 1997; Hörter and Dressman, 1997). They proved the eutectic mixture of drug sulfathiazole with a physiologically inert and highly soluble carrier say, for example, urea produced better dissolution rate and hence oral absorption (Dhirendra *et al.*, 2009). The solid dispersion as an eutectic mixture in water/gastrointestinal fluid produces fine dispersion of the drug proving sooner dissolution of the soluble matrix. On the other hand, the technique of solid dispersion also provides a wide variety of processing techniques and excipients choices that makes the researchers/drug development industry to feel convenience when processing poorly water-soluble drugs.

The oral bioavailability of a drug's fenofibrate might undoubtedly depend on its solubility and/or dissolution rate, and also undergo dissolution rate-limited onset time (Wen *et al.*, 2019). Finofibrate Solid dispersion were prepared by using polyethylene glycol and ß cyclodextrin further. This complex was found to be the best with improved solubility and dissolution rate since it possesses hydrophilic carriers which are responsible for improved wettability, reduced drug crystallinity (Kamalakkannan *et al.*, 2010).

MATERIALS AND METHODS

Materials

Fenofibrate was kindly gifted by BMR chemicals, Hyderabad. Pottassium dihydrogen phosphate, Urea, sodium hydroxide, PEG 4000, PEG 6000, PEG 8000 and Cyclodextrin were obtained from Qualichem lab, Hyderabad.

Calibration Curve of Fenofibrate

Fenofibrate equivalent to 100 mg of the solid dispersion was taken into a 100ml volumetric flask and dissolved in 10ml methanol. The volume was made up to 100ml with pH 6.8 phosphate buffer. This stock solution was further diluted to get the concentrations ranging from 2 to 10μg/ml. They were assayed by the U.V. spectrophotometer at 287nm for drug content. It was measured using a calibration curve of fenofibrate pure drug.

Formulation Development

Preparation of solid dispersions by fusion technique

Drug fenofibrate and excipients such as PEG 4000, PEG 6000, PEG 8000, UREA and ß-cyclodextrin at the ratios of 1:5, 1:10 & 1:15 (Table 1) were individually weighed. The carriers were taken individually on an aluminum pan of a hot plate and molten at a temperature of about 60°C with constant stirring, Then the drug fenofibrate was added with the molten carrier mass as per the ratios mentioned above and constantly stirred to obtain homogeneity. The mixture was continued with heating to get a clear homogeneous melt. After that, the pan was taken out of the hot plate and cooled at room temperature. After cooling and solidification, the solid dispersion was separated and sieved through sieve number 40. The homogeneous dispersion of the drug equivalent of 10mg was taken and used for further studies (Tran *et al.*, 2019).

Lyophilisation of selected solid dispersion

The selected solid dispersion was lyophilized by initially dissolving solid dispersion in a small quantity of Chloroform. This chloroform solution of solid dispersion was quickly hardened by moving it with a Pasteur pipette into the inner surface of a cold flask, which was rotating at -50°C in a methanol bath. After attaining a firm layer of depth, the flask was fused with the vacuum adapter of the lyophilizer. At a pressure of 8-10 mmHg, the solvent was sublimed and condensed onto a condenser, which was at -60°C. After removing the solvent completely, there appeared the light, fluffy and porous residue of the lyophilized powder. The lyophilized preparation was stored at room temperature in a desicca-

Table 1: Composition of Fenofibrate solid dispersion

S.No.	Code	Composition	Ratio(Drug: Polymer)
1	F1	Fenofibrate: PEG4000	1:5
2	F2	Fenofibrate: PEG4000	1:10
3	F3	Fenofibrate: PEG4000	1:15
4	F4	Fenofibrate: PEG6000	1:5
5	F5	Fenofibrate: PEG6000	1:10
6	F6	Fenofibrate: PEG6000	1:15
7	F7	Fenofibrate: PEG8000	1:5
8	F8	Fenofibrate: PEG8000	1:10
9	F9	Fenofibrate: PEG8000	1:15
10	F10	Fenofibrate: Urea	1:5
11	F11	Fenofibrate: Urea	1:10
12	F12	Fenofibrate: Urea	1:15
13	F13	Fenofibrate:β-Cyclodextrin	1:5
14	F14	Fenofibrate: β-Cyclodextrin	1:10
15	F15	Fenofibrate:β-Cyclodextrin	1:15

Table 2: FTIR results

	Wave numbers (cm^{-1})			
S.No	physical mixture	fenofibrate	Wave no.range	Functional group
1	1511.677	1509.233	1400-1600	Aromatic
2	1716.791	1716.791	1670-1820	Carbonyl
3	2956.648	2959.344	2970-2950	Methyl
4	1603.255	1601.490	1600	Amine

tor (Singh *et al.*, 2017).

FT-IR studies

Fenofibrate and excipient's compatibility was tested before making solid dispersions using physical mixtures of both drug and excipients by FTIR Spectroscopy. FTIR spectrophotometer (Brucker) was used to test the compatibility by potassium bromide pellet technique against a scanning range of 4400 to 400 cm^{-1}.

DSC studies

DSC thermogram was recorded out using Hitachi Japan-DSC-6200 for the selected solid dispersion by taking a 10mg sample of solid dispersion. The samples were taken in sealed aluminium pans and scanned under an atmosphere of nitrogen between 0 –450°C at a constant heating run rate of 7°C/h.

InVitro Dissolution Studies

In-vitro dissolution rate of Fenofibrate solid dispersion of varying carrier combinations were tested by using an eight-stage dissolution rate testing apparatus with paddle stirrer LAB INDIA 2000. Fenofibrate equivalent of 10mg was taken in a 900ml pH 6.8 phosphate buffer as dissolution medium, which was maintained at 37 $\pm$ 0.5°C and the paddle was rotated at 50 rpm. The run time was 90 min and samples of 5 ml were collected at every 15 min interval throughout the run time. After filtering the sample through the Whatman filter paper, the absorbance was measured at 287 nm (He *et al.*, 2010).

RESULTS AND DISCUSSION

Analytical Method

The calibration graph of Fenofibrate in pH 6.8 phosphate buffer displayed decent linearity, having a r^2 value of 0.998, suggesting that it obeys the "Beer-Lambert" law (Figure 1).

In-vitro Dissolution Studies

The dissolution tests of solid dispersions containing various grades of PEG and β- Cyclodextrin displayed a substantial increase in dissolution rate in phosphate buffer pH 6.8. Almost all the solid dispersions of fenofibrate showed a better dissolution profile comparatively with Fenofibrate alone. The comparative dissolution profile revealed that the rate of dissolution was higher with the dispersions pre-

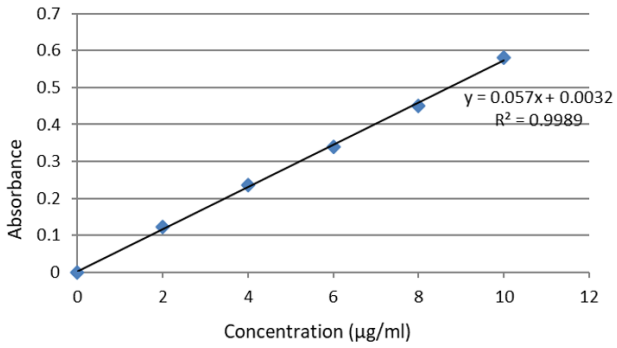

Figure 1: Standard Plot of Fenofibrate

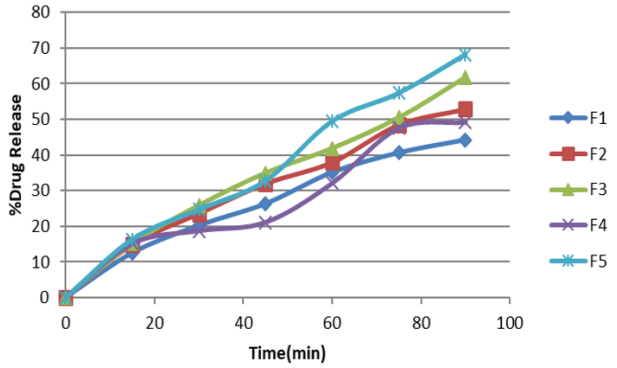

Figure 2: Dissolution Profile of Fenofibrate solid dispersions from F1-F5

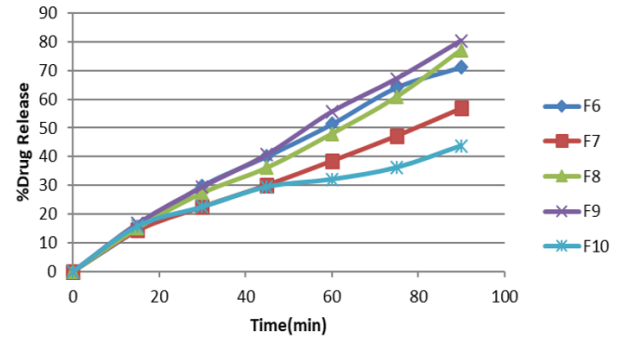

Figure 3: Dissolution Profile of Fenofibrate solid dispersions from F5-F10

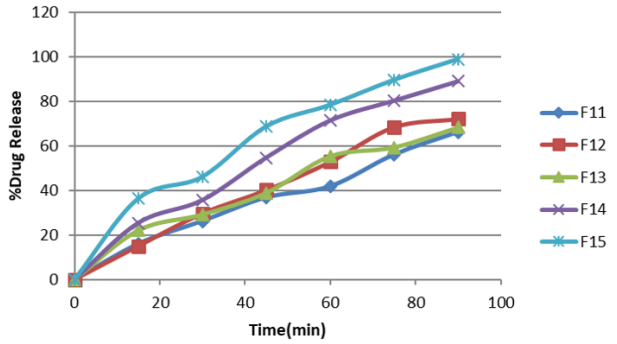

Figure 4: Dissolution Profiles of Fenofibrate solid dispersions from F11-F15

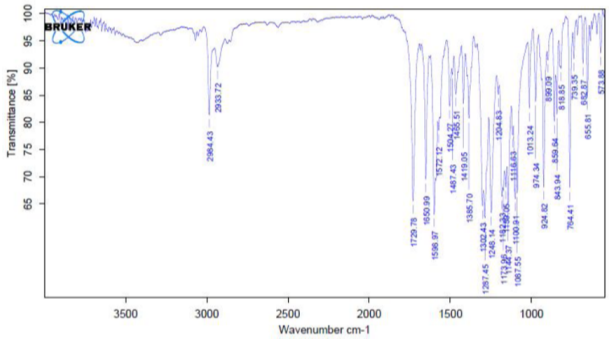

Figure 5: FTIR spectrum of fenofibrate

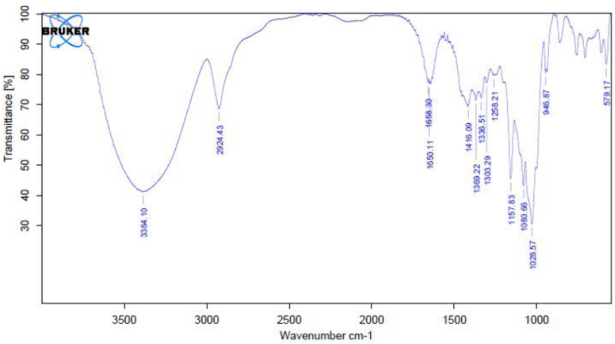

Figure 6: FTIR spectrum of solid dispersion of fenofibrate with β-cyclodextrin (F15)

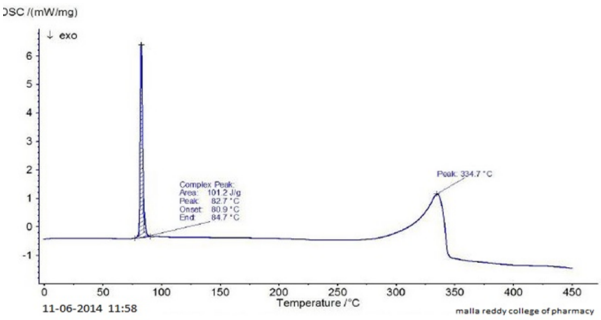

Figure 7: DSC thermogram of fenofibrate

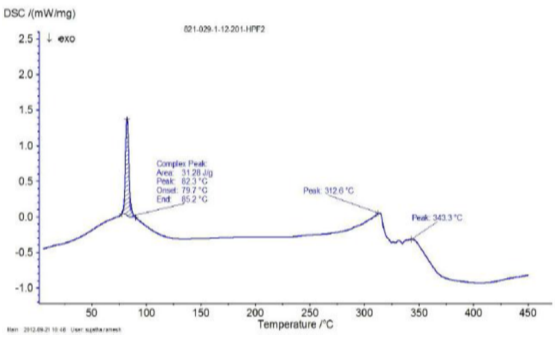

Figure 8: DSC thermogram of 1:15 solid dispersion of fenofibrate: β-cyclodextrin

pared with β- Cyclodextrin when compared to various grades of PEG and urea as carriers. The dispersion readied with 15 parts of carrier concentration was found to show a better dissolution rate. That means there was direct proportionality of the dissolution rate with the amount of carrier contained in the solid dispersions. It was found to be the common result for all the carriers (Figures 2 and 3 & Figure 4).

The dissolution result of F15 that 1:15 ratio of drug and β- Cyclodextrin was found to show a drastic increase in dissolution rate when compared to other formulations. This might be due to the fact that a positive increase in wettability in the presence of β- Cyclodextrin, highly hydrophilic nature of β-Cyclodextrin and also due to the possibility of a reduction in drug crystallinity in the presence of β-Cyclodextrin. Lyophilized solid dispersion of F15 had shown a significant increase in dissolution rate when compared to plain solid dispersions. It was found to produce 95.82% of drug dissolution in 60 minutes.

The freezing process principally determines the physical personae of the dried solid product. Primary drying embodies the preliminary onset of the drying course from the top. The secondary drying course initiates when the ice has been totally removed from that area. Thus, simultaneous primary and secondary drying could have occurred. The volume of the starting material was maintained constant while the resultant product was fluffy and porous. Hence surface free energy increased due to a rise in surface area that resulted in an e calation in the dissolution percentage.

FT-IR Studies

There were no drug-carrier interactions when it was compared to the characteristic absorption bands of drug alone and drug carrier mixture. FTIR spectrum of drug-carrier interaction studies are presented in Figure 5 & Figure 6. It was found that fenofibrate was compatible with carriers used since there were no extra peaks observed in the physical mixture when compared to the spectrum of drug alone (Figure 5 & Figure 6;Table 2).

Differential Scanning Calorimentry (DSC)

DSC thermograms of Fenofibrate and its solid inclusion complex with β- Cyclodextrin F15 were shown in Figure 7 & Figure 8. DSC thermogram of fenofibrate unveiled a sharp exothermic peak at 82.3°C analogous to its melting point. In the DSC thermograms of β-cyclodextrin inclusion complexes, this peak was shifted slightly to a lower temperature, i.e., 82.°C. The corresponding melting point depressions and enthalpy of fusion are shown in Figure 8. A slight depression in the melting point of fenofibrate in solid dispersions designates an interaction of fenofibrate with β- Cyclodextrin. But it was very much negligible depression found.

CONCLUSIONS

The present investigation disclosed that the dissolution rate of Fenofibrate could be heightened to an excessive level by solid dispersion. Fifteen solid dispersions were successfully prepared using various polymers such as PEG 4000, 6000, 8000, urea and β cyclodextrin by fusion technique. Amongst them, the formulation prepared using β cyclodextrin at higher carrier concentration was found to be the best since it produced greater solubility and dissolution (98%) when compared to the other solid dispersions. The aqueous solubility of Fenofibrate was improved linearly as a function of the concentration of the β Cyclodextrin. The lyophilized form produced a drastic increase in the dissolution rate. FTIR studies and DSC studies revealed that their where no drug-polymer, polymer-polymer interaction. Thus Cyclodextrin complexation could be employed for heightening the solubility and dissolution percentage of poorly soluble drug Fenofibrate.

ACKNOWLEDGEMENT

I acknowledge King Khalid University, K.S.A and Malla Reddy Group of Institutions, Hyderabad for constant support during the project.

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