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Research Article

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Formulation and evaluation of solid dispersions of fenofibrate for dissolution rate enhancement

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ABSTRACT

Fenofibrate is a lipid lowering drug used in the treatment of hyperlipidemia, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid and to enhance its dissolution rate solid dispersions is designed and evaluated. Solid dispersions of Fenofibrate were prepared by using various ratio of different carrier like PEG-400,6000, MCC, pregelatinized starch, cremophor, etc., (formulations from F1 to F9 and one reproducibility batch F10 were formulated). Then prepared solid dispersions were evaluated for invitro dissolution, DSC, and also stability studies were conducted. Solid dispersion with PEG were formulated in different ratio. The differential scanning calorimetry demonstrated that enhanced dissolution of Fenofibrate from solid dispersion might be due to a decrease in the crystallinity of Fenofibrate in carrier in solid dispersion preparation. PEG, MCC, pregelatinized starch has increased the solubility and bioavailability of Fenofibrate significantly.

Key Words: Solid dispersion, dissolution enhancement, PEG-400,6000, MCC, pregelatinized starch,, Fenofibrate.

INTRODUCTION

Poorly water-soluble drugs often require high doses in order 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. Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states [1,2]. Several methods have been employed to improve the solubility of poorly water soluble drugs. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi [3]. Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were codissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion [4]. In conclusion, physical mixtures, solid dispersions and lyophilized solid dispersions increase dissolution of Fenofibrate. solid dispersions of PEG-400,600, MCC, pregelatinized starch increases the rate and extent of dissolution of Fenofibrate. The results of this study clearly suggest that solid dispersions is ideal for poorly water soluble drugs and aging has an adverse effect on the dissolution.Fenofibrate has been used for many years to lower

cholesterol levels and its pharmacokinetic profile is well understood [5,6]. Originally launched in 1975, it is currently on the compound is practically insoluble in water [7,8] and has high lipophilicity (log P = 5.24) [5]. Thus the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract. Attempts to increase the oral bioavailability of the drug have therefore chiefly centered on particle size reduction. Increasing the rate and extent of dissolution of fenofibrate by micronization has been shown to lead directly to an increased oral bioavailability, which in turn enables dosage reduction .Recently, ''suprabioavailable'' tablets have been developed combining the classic micronization process with a specific microcoating technology, through which micronized drug particles are coated onto hydrophilic polyvinylpyrrolidone (PVP) cores .In this study, solvent evaporation is employed for the formulation of solid dispersion . Fenofibrate was chosen as a water-insoluble model drug . PEG-400,600, MCC, pregelatinized starch were employed as a carrier material for formulation of solid dispersion with model drug. Differential scanning calorimetry (DSC) were performed to determine the physicochemical properties of the solid dispersions in comparison with the plain drug.

EXPERIMENTAL SECTION

Apparatus and chemicals

Fenofibrate (99% purity) was obtained from Aurobindo pharmaceuticals, India. MCC, pregelatinized starch was obtained from Kemphasol, Bombay. PEG 6000 was purchased from Merck. Other excipients used were of analytical grade.

Preparation of solid dispersion of Fenofibrate:

Solvent Evaporation method using fluid-bed coating technique:-

The Fenofibrate was dispersed in hydrophilic polymers like PEG 6000.Surfactants like PEG 400 or Miglyol or Cremophore EL are used to disperse Fenofibrate in polymer.Then this dispersion was dissolved using IPA & DCM solvents. The solid solution of Fenofibrate and polymer was coated onto inert bed of Sugar spheres or Lactose monohydrate or Celpheres using Fluid-bed coater granulater.Therefore solvent will be evaporated leaving a Fenofibrate-polymer coat around the inert carrier. The dry mass obtained will be in granular form which was passed through 30 mesh (ACTM No. 30) and composition of solid dispersion were tabulated in table 1.

Table 1: Composition of Solid dispersion

		Ingredients(mg/tablet)									
S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Fenofibrate	120	120	120	120	120	120	120	120	120	120
2	PEG 6000	156	-	156	156	156	156	156	120	120	120
3	Cremophore EL	67	-	-	-	-	-	-	-	-	-
4	Miglyol 812	-	120	-	-	-	-	-	-	-	-
5	PEG 400	-	-	30	30	30	30	30	24	24	24
6	DCM	1150	158	310	310	310	310	310	310	310	310
7	IPA	682	300	200	200	200	200	200	200	200	200
8	Sugar spheres	300	-	-	-	-	-	-	-	-	-
9	Lactose monohydrate	-	384	-	300	300	300	300	366	366	366
10	Celpheres	-	-	300	-	-	-	-	-	-	-
Extra Granular											
1	Pharmatose 200M	-	-	-	-	344	-	-	-	-	-
2	Pregelatinized Starch (Lycatab)	-	-	-	-	-	134	134	134	134	135
3	Ac-di-sol (CCS)	-	-	-	-	-	100	50	100	50	51
4	MCC pH 102	-	-	-	-	-	130	180	106	156	156
5	Aerosil 200	-	-	-	-	-	10	10	10	10	12
6	Magnesium stearate	-	-	-	14	20	20	20	20	20	18
Total				-	650	1000	1000	1000	1000	1000	1002
Ratio of Fenofibrate- polymer		1:1.3	-	1:1.3	1:1.3	1:1.3	1:1.3	1:1.3	1:1	1:1	1:1

Differential scanning calorimetry (DSC) analysis

Thermal properties of Fenofibrate, polymer and solid dispersion were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3 to 5 mg of product was placed in perforated aluminum sealed 50-µl pans, and the heat runs for each sample was set from 40°C to 250°C at 10°C/min, under an inert environment using nitrogen.The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔHfusion).

Dissolution studies

Dissolution studies were performed in phosphate buffer (pH 7.2, 900 ml) at 37 ± 0.5 °C, using USP apparatus II (Paddles) ; [Electro lab USP] with a paddle rotating at 75 rpm.The samples equivalent to 120 mg fenofibrate, were subjected to dissolution. At fixed time intervals, samples (5 ml) were withdrawn and equal amount of fresh dissolution medium was added. Withdrawn samples were filtered through 0.45 µm membrane filter, and spectrophotometrically assayed for drug content at 287.4 nm wavelengths using a UV-VIS spectrophotometer (SHIMADZU Corporation, Japan).

Stability studies

Stability studies were carried out by keeping the samples in screw cap vials in stability chambers at 25 ± 2°C and 60 ± 5 % relative humidity (RH). Samples were drawn regularly and analysed for drug content and dissolution studies until 6 months. All the data obtained from the stability study were analyzed for significant differences by one-way analysis of variance (ANOVA) using a Student-Newman-Keuls test for all pair wise comparisons in this study. The statistical analysis was conducted using MedCalc software version 9.6.4.0.

RESULTS AND DISCUSSION

Various Fenofibrate solid dispersions were prepared using PEG-400,6000, MCC, pregelatinized starch in combination and individually, as carriers by solvent evaporation technique to increase the solubility as well as dissolution of poorly aqueous soluble drug Fenofibrate.

The DSC thermograms of pure fenofibrate and fenofibrate solid dispersion using PEG 6000 are shown in Fig. 1.

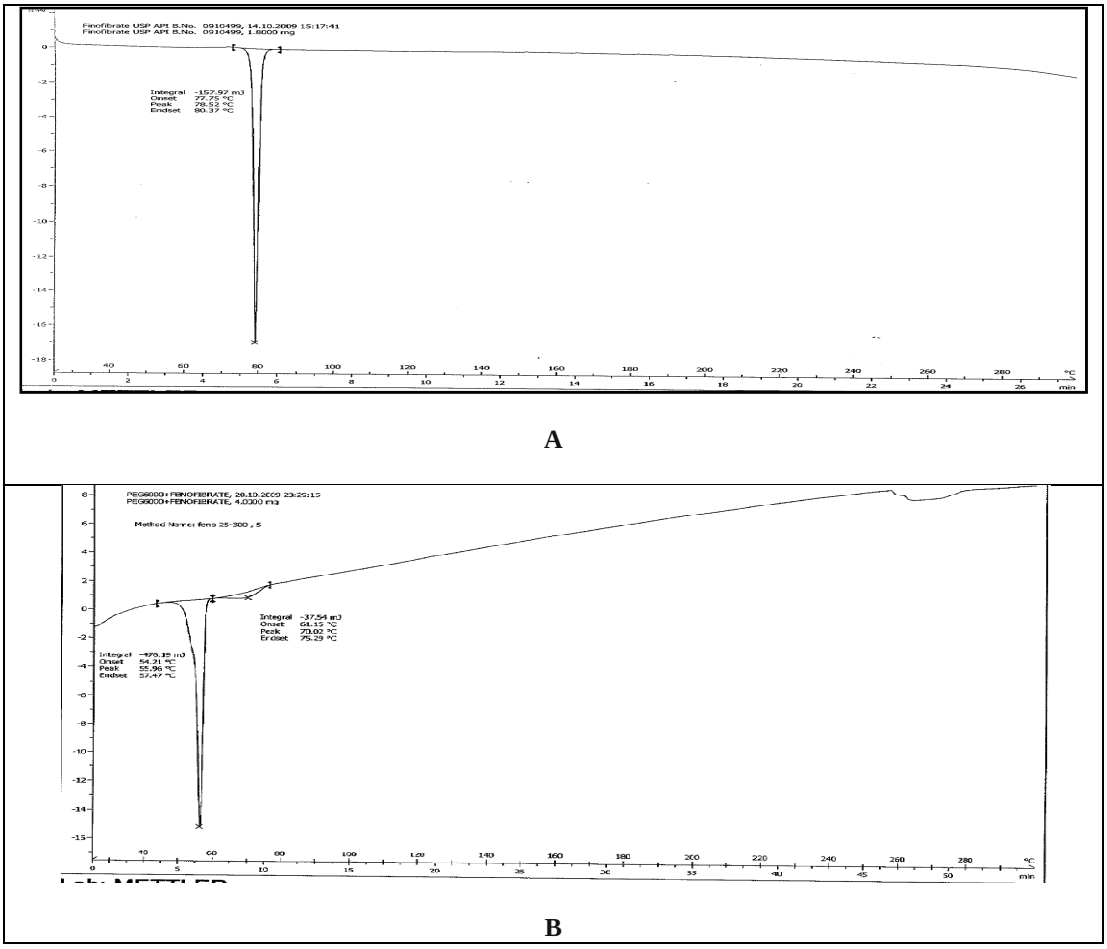

Fig 1 A : Pure Fenofibrate ,Fig 1 b :Mixture Of Fenofibrate& PEG 6000

The *in vitro* dissolution profiles of the drug (Fenofibrate), various solid dispersions using PEG 6000 and others in combination and individually with their respective physical mixtures in phosphate buffer (pH=7.2) for 60 minutes are shown in Figs. 2.All of the physical mixture and solid dispersion samples showed improved dissolution of Fenofibrate over that of pure Fenofibrate. The improved dissolution of Fenofibrate is mainly attributed to increased wettability and accordingly solubility due to the higher level of hydrophilicity by the use of polymeric carriers. Again, all of the solid dispersion samples revealed more improved Fenofibrate dissolution than their respective physical mixture samples. This observation indicated that the increased dissolution of Fenofibrate from Fenofibrate solid dispersion due to presence of drug in amorphous state as compared the physical mixtures and pure drug, where drug is present in crystalline state [9].In case of various ibuprofen solid dispersions, the dissolution of Fenofibrate solid dispersions as better than that of prepared Fenofibrate solid dispersions using these polymers as carriers individually and this Was increased with the increase of polymer ratio in the solid dispersion.

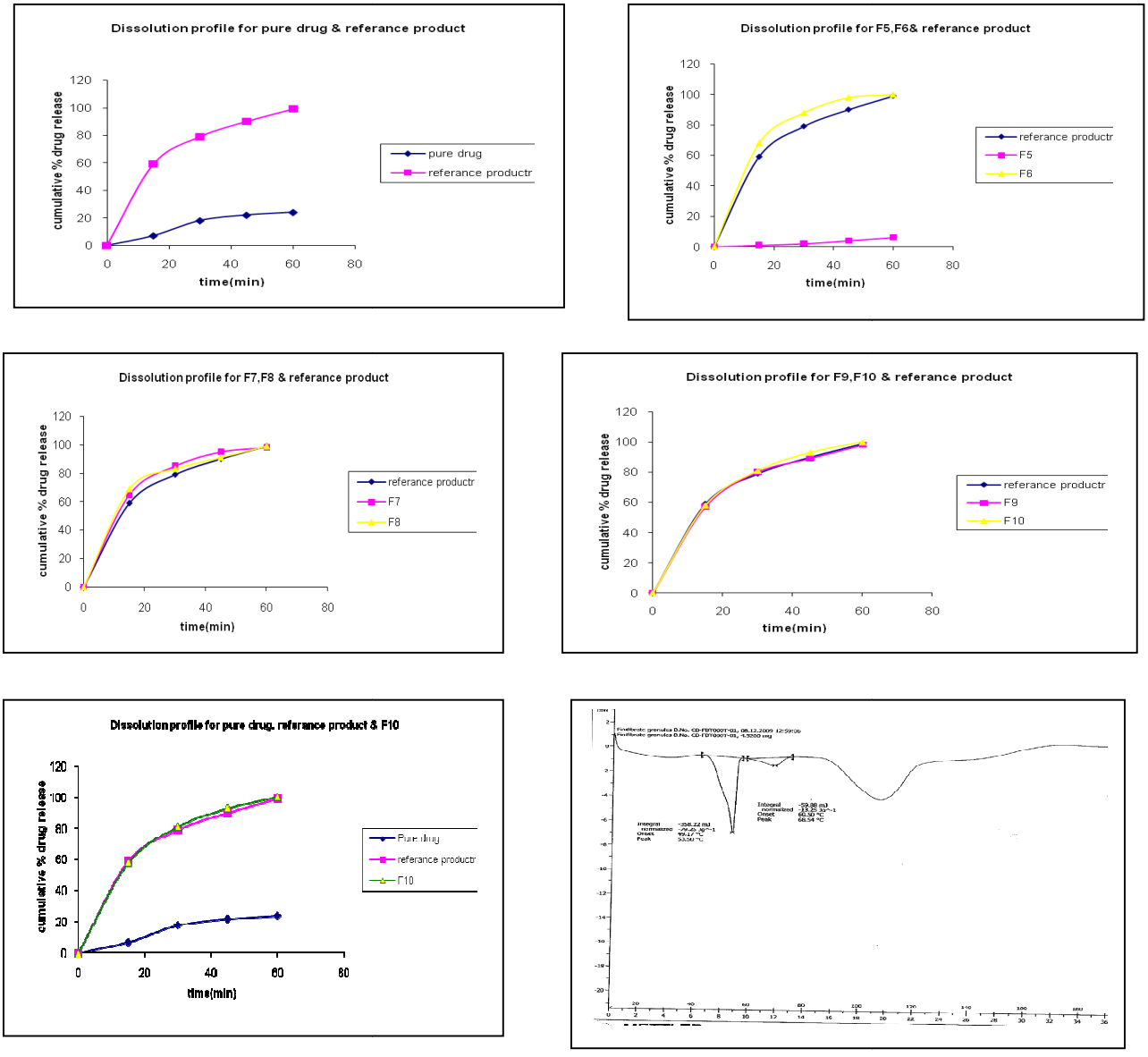

Fig 2 : dissolution profiles of drug (Fenofibrate), various solid dispersions

The stability study for various Fenofibrate solid dispersions using PEG 6000 and others combination (F10)Was carried out for a period of 6 months at 25 ± 2°C and 60 ± 5 % relative humidity (RH). No significant differences (*p*

< 0.05) in drug content and percent drug dissolved in 60 minutes (Q60 min) in those solid dispersions Were observed throughout the study (Table 2). These observations of the stability study of various Fenofibrate solid dispersions indicated no change in the state of solid dispersion during the study period indicating stable enough.

Table 2 : Stability data for F10

S.NO	% Fenofibrate release (60 min)	%Assay	Related substances (total impurity)
Initial	99	100.2	0.05
40/75, 1M	97	99.4	0.59
40/75, 2M	98	98.5	0.52
40/75, 3M	96	99.2	0.45

CONCLUSION

Fenofibrate solid dispersions were prepared by solvent evaporation technique. The DSC studies indicated the transformation of crystalline Fenofibrate (in pure drug) to amorphous Fenofibrate (in Fenofibrate solid dispersions) by the solid dispersion technology. The *invitro* dissolution Studies showed a remarkable improvement in drug dissolution of these new Fenofibrate solid dispersions than those of ibuprofen solid dispersions individually. The *invitro* dissolution of ibuprofen from these solid dispersions was found to follow Hixson-Crowell model. Stability studies revealed that these solid dispersions were stable enough throughout the study period. This study concluded that the improved Drug dissolution of these newly prepared Fenofibrate solid dispersions using PEG 6000-PVPK 30 Combination carrier may be attributed to the improved Wettability, and decreased drug crystallinity, which can be modulated by appropriate level of hydrophilic carriers.

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