DESIGN, FORMULATION DEVELOPMENT AND SOLUBILITY ENHANCEMENT OF FENOFIBRATE, A WATER INSOLUBLE DRUG BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Fenofibrate is a lipid lowering agent used in the treatment of hyperlipidemia. In order to improve the solubility and oral absorption of Fenofibrate in gastric fluid and to enhance its dissolution rate solid dispersion technique by solvent evaporation method has been designed and evaluated. Poloxamer 188, Poloxamer 407, Polyethylene glycol (PEG) 6000, Polyvinyl Pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC) and Mannitol have been used as the hydrophilic polymers which were employed as carriers for formulation of solid dispersion with model drug in ratio of (Drug: Cariers) 1:1, 1:3, 1:5, 1:7 and 1:10. The pure drug and solid dispersions with all their ratio were characterized using FTIR techniques. The effect of solvent evaporation methods preparing of solid dispersion on dissolution behavior was investigated. Dissolution studies indicated a significant increase in dissolution of Fenofibrate when dispersed in carriers. In all the cases solid dispersions showed improved dissolution of Fenofibrate compared to that of pure drug. It was observed that higher concentration of carriers in preparing solid dispersion showed higher release of Fenofibrate. Solid dispersion prepared with Poloxamer 188 showed fastest and maximum release (93.74%) among all formulations and solid dispersions with PVP, HPMC, Poloxamer 407, PEG 6000, Mannitol showed 88.21%, 88.14%, 82.87%, 76.50% and 65.77% release respectively in 1:10 ratio within 1 hour whereas pure Fenofibrate showed only 23.60% release. The release of drug was plotted in Zero order, First order, Korsmeyer and Higuchi release pattern. The correlation coefficients values of the trend lines of the graphs showed that the formulations best fit in Higuchian release pattern.

KEY WORDS: Solid dispersion, Fenofibrate, Solvent evaporation method, Dissolution.

INTRODUCTION

Fenofibrate is biopharmaceutics classification system (BCS) class II drug [1] which has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood[2,3]. Originally launched in 1975, it is currently on the compound is practically insoluble in water[4,5] and has high lipophilicity[2] (logP=5.24). Thus the dissolution rate of Fenofibrate is expected to limit its absorption from the gastrointestinal tract. Attempts to increase the oral bio-availability 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 bio-availability, which in turn enables dosage reduction[2]. 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[5].

The enhancement of oral bioavailability of poorly water soluble and water insoluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wet ability.

In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later, termed solid dispersion, involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical

mixtures. It is suggested that the drug was present in a eutectic mixture in a microcrystalline state[6,7]. Later, Goldberg demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high[8].

Drug substances are seldom administered alone, but rather as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical function. The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in fabricating the product. An important physical-chemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility[9,10].

Poor water solubility is the major drawback for the various types of drugs and many approaches have been introduced for the solubility enhancement of such drugs. Solid dispersion is one of the techniques adopted for the formulation of such drugs and various methods are used for the preparation of solid dispersion like kneading method, solvent evaporation method, supercritical method, fusion method. Recently various type of carriers like surfactants, disintegrants included in the solid dispersion formulations, named as third generation solid dispersion have also been discussed in this review. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. The review also encompasses the criteria of solvent selection, challenges in formulation of solid dispersion dosage forms, future prospects and various types of marketed preparations[11].

MATERIALS AND METHODS

Drugs and Chemicals

Fenofibrate (Nexchem Pharmaceutical Co. Ltd., China) was a gift from The White Horse Pharmaceuticals Ltd. Poloxamer 188, Poloxamer 407, Mannitol, Lactose, Starch, Avicel pH

102, Purifie Talc and Sodium Starch Glycollate were procured from BASF, Germany. PEG 6000 and PVP were purchased from Loba Chemicals, India. HPMC 6cps (Samsung, Korea), Magnesium stearate (Cabot Sanmar Limited, India), Methanol (Merck, Germany), Ethanol (Merck, Germany) and powdered Sodium lauryl sulphate (Merck, Germany) were procured from local vendors and purified water from our own University Research Laboratory.

Instruments and Equipments

UV-VIS Spectrophotometer (UV-1601, Shimadzu, Japan), FT-IR (IRAFINITY-1 CE, Shimadzu, Japan), Tablet dissolution tester USP XIII (TDT-06T, Electrolab, India), Electronic Balance (AY120, Shimadzu, Japan), Water Bath (Shimadzu, Japan), Sonicator (Power Sonic 505, Hwashin Technology Co., Korea), pH Meter (pH 211 Microprocessor, Hanna Instruments, Germany), Vortex Mixer (VM-2000, Dig system laboratory Instrument Inc, Taiwan), Hair Dryer (Miyako Super 1200W, China), Oven (Precision Scientific Co. Bangladesh).

Preparation of Standard Curve for Fenofibrate

To prepare a standard curve for Fenofibrate, stock solution of 25 μg/ml was prepared in 0.75% Sodium Lauryl Sulfate solution of distilled water and the serial dilution of different concentrations were analyzed by UV spectrophotometer at 291 nm. Absorbance values were plotted against drug concentration and standard curve of Fenofibrate was produced.

Preparation of Solid Dispersion

A solid dispersion is the dispersion of one or more active ingredients in an inert carrier at solid-state prepared by melting (fusion), solvent or the melting-solvent method, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states[12]. The method of preparation of solid dispersions[13,14,15] was based on the solvent evaporation method. In the solvent evaporation method of preparation, Fenofibrate, the drug solution was prepared by using drug (40 mg), solvent (Ethanol: Methanol, 4:5) and polymer (PEG 6000, PVP, Poloxomer 188, Poloxomer 407, HPMC 6cps and Mannitol. The polymers have been used as carriers with Fenofibrate in various (Drug:Carrier) ratio such as, 1:1. 1:3, 1:5, 1:7 and 1:10 and finally the solvent was evaporated by a dryer at 50-60°C. The solid dispersions were withdrawn from vials, crushed in mortar and pestle then passed through sieve (first 40 mesh and the 80 mesh). Then the resulted samples were weighed and transferred in fresh vials with proper labeling. After preparation solid dispersions were kept in the dessicator.

In vitro Dissolution Study of Solid Dispersion

The release rate of fenofibrate from solid dispersion were carried out in dissolution test apparatus Paddle type II (Electrolab, India) at rotation speed of 75 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 40 mg of the Fenofibrate in 900 ml 0.75% sodium lauryl sulfate (SLS) in distilled water as dissolution media and the temperature was maintained at $37^{o}C\pm0.5^{o}C$. At different interval (5-60 min) samples were collected (US FDA Dissolution Methods) and assayed by UV spectrophotometer. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Characterization of Drug & Solid Dispersion by FT-IR Study

Fourier Transform- Infra Red spectroscopy (FT-IR) spectra of pure Fenofibrate and prepared solid dispersions were recorded on Shimadzu FT-IR. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. The powdered sample was intimately mixed with dry powdered potassium bromide. The mixture was then compressed into transparent disc under high pressure using special dies. The disc was placed in IR spectrophotometer using sample holder and spectrum was recorded. Each spectrum was derived from single average scans collected in the region 400-4000 cm^{-1} at spectral resolution of $4cm^{-1}$ and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu. In this study, potassium bromide disc method was employed.

RESULT AND DISCUSSION

In Vitro **Dissolution Study of solid dispersion**

The present study was aimed to observe release pattern of drug from the solid dispersion by using different carriers which generally change the nature of the insoluble drug to amorphous form and help to enhance the rate of drug release. The complete comparative study of pure Fenofibrate and prepared formulations of solid dispersions were observed where the rate of dissolution was found increased in all the solid dispersions compared to pure Fenofibrate. Solid dispersions with all the carrier used showed their highest release (65.77% to 93.74%) in the maximum drug-carrier ratio of 1:10 (Figure 1). Solid dispersions prepared with Poloxamer 188 showed fastest and the maximum release (93.74%) among all (Figure 2) and then formulations with PVP, HPMC, Poloxamer 407, Mannitol showed their release enhancement (82.87%, 76.50%, 88.14%, 88.21% and 65.77% respectively). This is to be noted that micronized pure Fenofibrate showed its release of only 23.60% after 60 minutes of dissolution study.
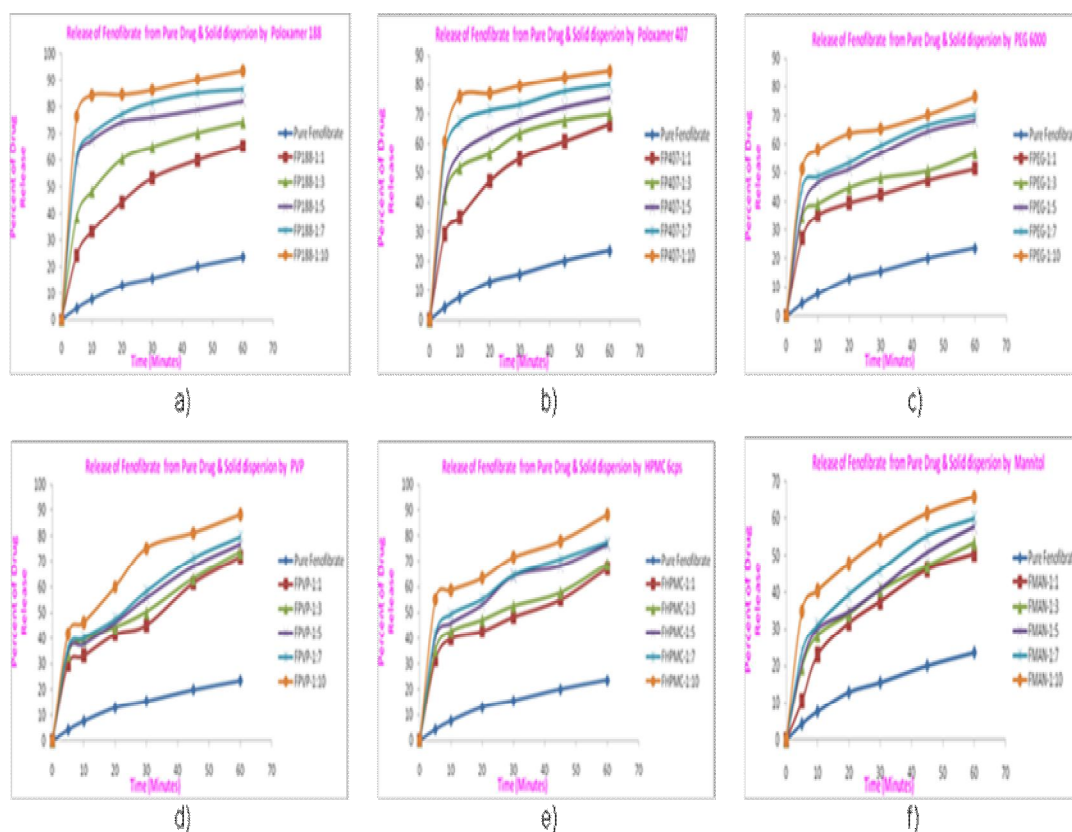
Figure 1: Zero order release kinetics of pure Fenofibrate and solid dispersion with carriers a) Poloxamer 188, b) Poloxamer 407, c) PEG 6000, d) PVP, e) HPMC 6 cps and f) Mannitol
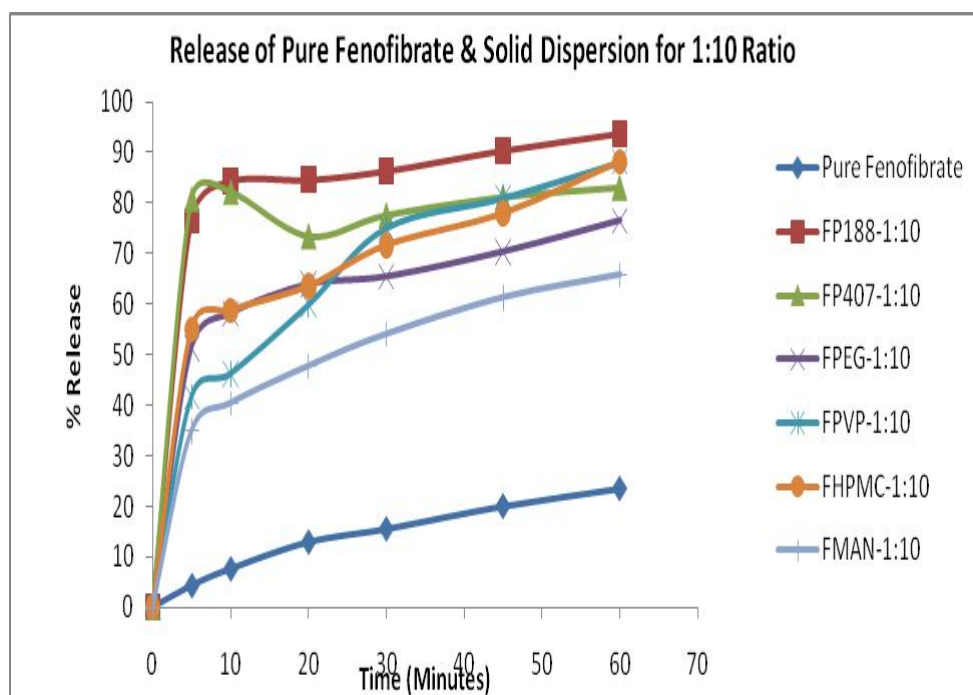

Figure 2: Comparative study of Fenofibrate solid dispersions with all the carriers for 1:10 Ratio (Zero Order)

All of the carriers used for solid dispersions successfully increased the release profile of Fenofibrate while Mannitol has given comparatively lower release than others. The efficacy of these carriers on drug release was also evaluated with different solvent such as methanol, water and 0.75% SLS in Distilled water in terms of *in vitro* drug dissolution. The variables affecting drug dissolution were dispersion property, hydrophilic polymer loading and physicochemical property of the drug molecule.

All of the formulations of solid dispersion successfully made their enhancement of release profile which proved that the carriers were exclusively able to change the drug in the micro label and finally crystal Fenofibrate drug was formed to the amorphous state. That is why solubility enhancement occurred which was the great promise of this study. Moreover it has been observed that when the ratio of the carriers were increased the solubility and the drug release were respectively increased.

Release kinetics Solid Dispersion

The release kinetics study of Zero Odrer, First Order, Krosmeyer[16] and Higuchi[13] were done and showed in Figure 1, 3, 4 and 5 respectively.
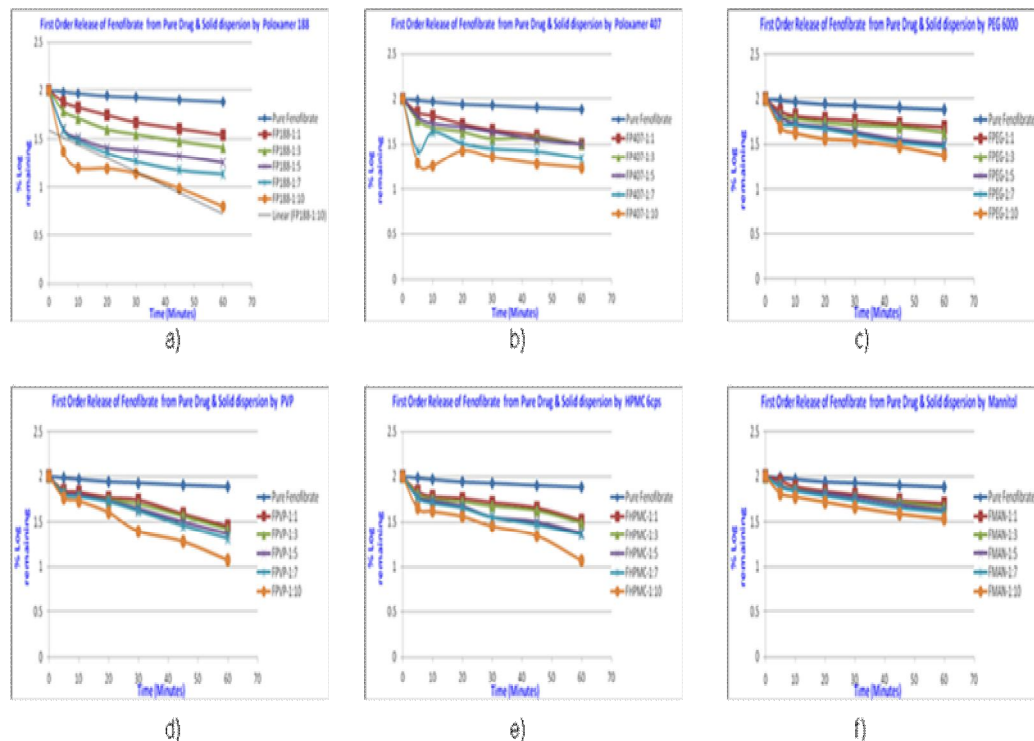

Figure 3: First order release kinetics of pure Fenofibrate and solid dispersion with carriers a) Poloxamer 188, b) Poloxamer 407, c) PEG 6000, d) PVP, e) HPMC 6 cps and f) Mannitol
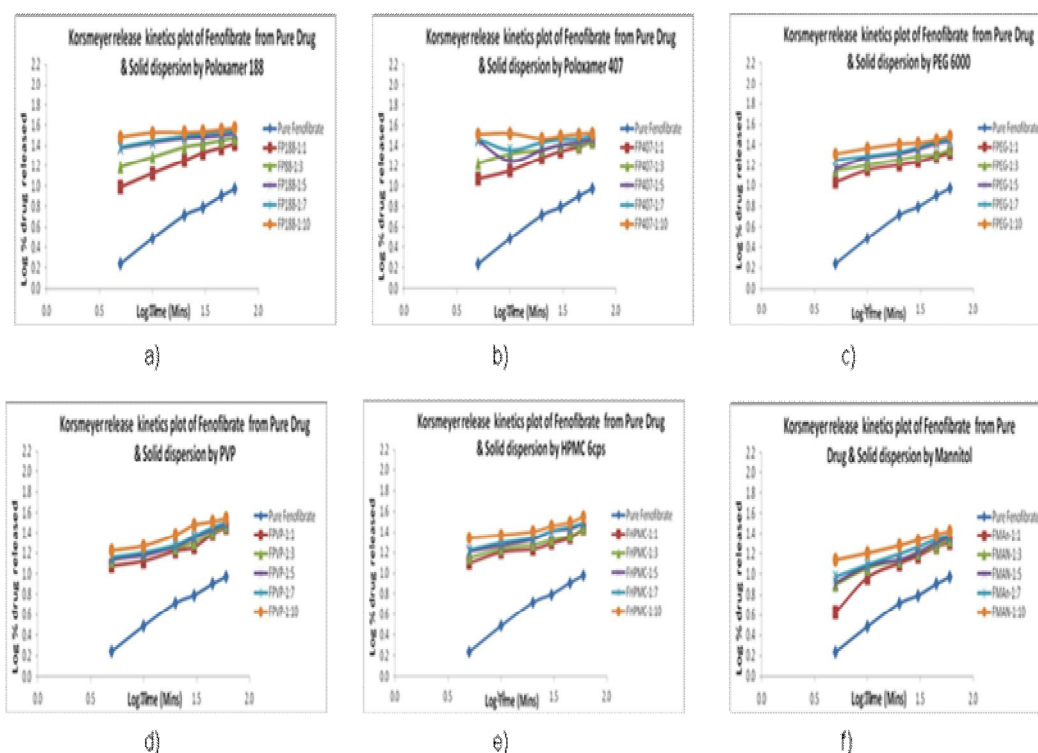
Figure 4: Korsmeyer release kinetics of pure Fenofibrate and solid dispersion with carriers a) Poloxamer 188, b) Poloxamer 407, c) PEG 6000, d) PVP, e) HPMC 6 cps and f) Mannitol
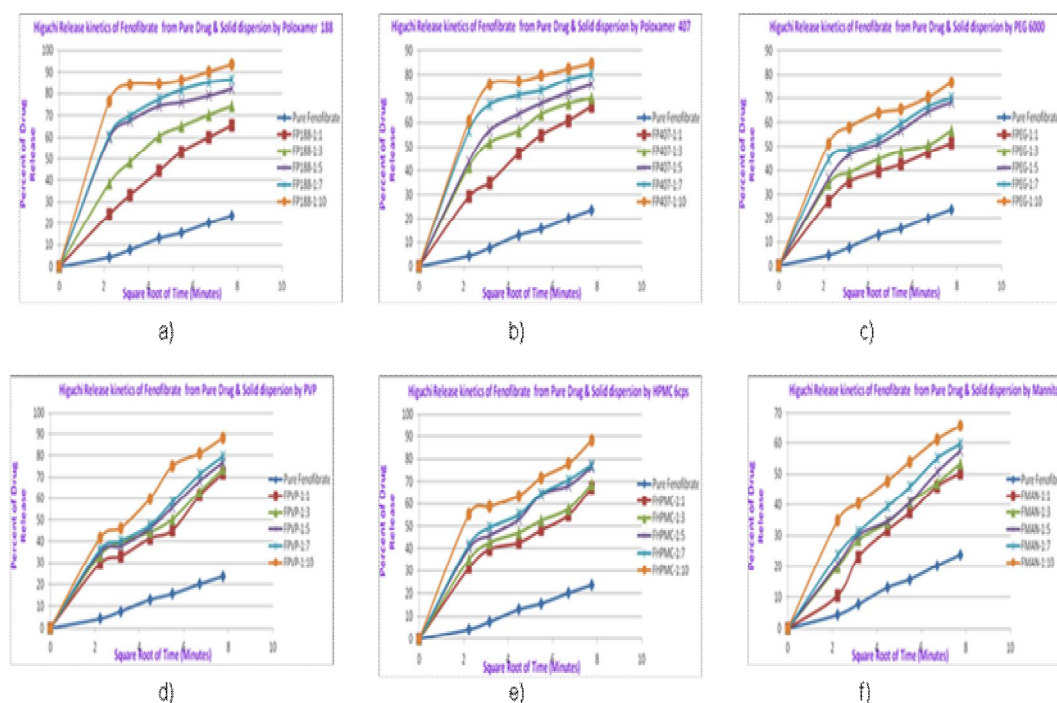

Figure 5: Higuchi release kinetics of pure Fenofibrate and solid dispersion with carriers a) Poloxamer 188, b) Poloxamer 407, c) PEG 6000, d) PVP, e) HPMC 6 cps and f) Mannitol

Two Distinct Processes of Dissolution of This Study

The solid dispersion has exposed to aqueous media and the carrier dissolved in the aqueous medium, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high.

The enhancing efficacy of the dissolution rates was also pronounced in cases with hydrophilic surfactants Sodium Lauryl Sulfate (SLS) used as dissolution medium (0.75% SLS in distilled water). It is well known SLS in the SDs could play a key role as solubilizers and wetting agents for poorly water soluble drugs. Finally it can be concluded that dissolution rate of Fenofibrate was increased by the Solid Dispersion Technique which is due to the wettability and spreadability of the precipitated drug by reducing aggregations in the readily soluble state.

Interpretation of release rate constants and Correlation coefficient (R^2) values for different release kinetics of Fenofibrate and Formulation by Solid dispersion

Maximum formulations (20 out of 31) displayed highest fitting with Higuchi release pattern and some formulation (12 out 31) also displayed with Korsmeyer release pattern for Solid Dispersion. On the other hand one formulation (FMAN 1:3) was fitted for both Higuchi and Korsmeyer release pattern. In these cases lowest fitting with zero order kinetic model of drug release (Table 1).

The pure Fenofibrate (R^2=0.991) and solid dispersion formulation FP188-1:1 (R^2=0.994), FP188-1:3 (R^2=0.983), FP188-1:5 (R^2=0.974), FP188-1:7 (R^2=0.978), FP188-1:10 (R^2=0.914), FP407-1:1 (R^2=0.994), FP407-1:3 (R^2=0.949), FPEG-1:1 (R^2= 0.979, FPEG-1:3 (R^2=0.988), FPEG-1:5 (R^2=0.984), FPEG-1:7 (R^2=0.972), FPEG -1:10 (R^2=0.979), FHPMC-1:1 (R^2=0.946), FHPMC-1:5 (R^2=0.980), FHPMC-1:7 R^2=(0.988), FHPMC-1:10 R^2=(0.930), FMAN-1:3 (R^2=0.982), FMAN-1:7 (R^2= 0.994), FMAN-1:10 (R^2=0.998) were best fitted of Higuchian kinetics release pattern. On the other hand solid dispersion formulation FP407-1:5 (R^2=0.845), FP407-1:7 (R^2=0.740), FP407-1:10 (R^2=0.704), FPVP-1:1 (R^2=0.969), FPVP -1:3 (R^2=0.955), FPVP -1:5 (R^2=0.970), FPVP -1:7 (R^2=0.969), FPVP -1:10 (R^2=0.9058), FHPMC-1:3 (R^2=0.9013), FMAN-1:1 (R^2=0.984), FMAN-1:5 (R^2=0.985) were fitted for Korsmeyer model. Moreover, It was found that only one formulation FMAN-1:3 (R^2=0.982) that fitted for both Korsmeyer and Higuchi model.

Table 1: Interpretation of release rate constants and correlation coefficient (R^2) values for different release kinetics

Formulation	Zero Order		First Order		Korsmeyer		Higuchi	
	R^2	K_0	R^2	K_1	R^2	n	R^2	K_H
Pure Fenofibrate	0.950	0.376	0.965	-0.001	0.988	3.169	**0.991**	0.675
FP188-1:1	0.827	0.941	0.928	-0.007	0.982	8.448	**0.994**	0.404
FP188-1:3	0.670	0.953	0.839	-0.008	0.902	9.100	**0.983**	0.263
FP188-1:5	0.459	0.880	0.671	-0.009	0.733	9.150	**0.974**	0.123
FP188-1:7	0.489	0.963	0.743	-0.011	0.768	9.895	**0.978**	0.142
FP188-1:10	0.375	0.914	0.688	-0.014	0.643	9.855	**0.914**	0.070
FP407-1:1	0.790	0.920	0.923	-0.007	0.966	8.378	**0.994**	0.350
FP407-1:3	0.600	0.850	0.697	-0.006	0.851	8.334	**0.949**	0.185
FP407-1:5	0.590	0.913	0.832	-0.006	**0.845**	8.993	0.137	0.073
FP407-1:7	0.469	0.867	0.477	-0.007	**0.740**	8.969	0.233	0.056
FP407-1:10	0.429	0.891	0.286	-0.006	**0.704**	9.403	0.001	0.002
FPEG-1:1	0.667	0.639	0.766	-0.004	0.894	6.094	**0.979**	0.242
FPEG-1:3	0.607	0.664	0.726	-0.004	0.848	6.459	**0.988**	0.190
FPEG-1:5	0.676	0.860	0.832	-0.006	0.899	8.165	**0.984**	0.242
FPEG-1:7	0.615	0.835	0.791	-0.007	0.851	8.089	**0.972**	0.176
FPEG-1:10	0.531	0.845	0.729	-0.007	0.787	8.475	**0.979**	0.148
FPVP-1:1	0.867	0.981	0.951	-0.007	**0.969**	8.540	0.930	0.351
FPVP-1:3	0.815	0.967	0.934	-0.008	**0.955**	8.621	0.939	0.302
FPVP-1:5	0.835	1.048	0.958	-0.009	**0.970**	9.297	0.948	0.328
FPVP-1:7	0.831	1.086	0.961	-0.010	**0.969**	9.656	0.951	0.326
FPVP-1:10	0.740	1.209	0.966	-0.014	**0.9058**	11.03	0.974	0.323
FHPMC-1:1	0.763	0.842	0.884	-0.006	0.933	7.668	**0.946**	0.274
FHPMC-1:3	0.717	0.844	0.861	-0.006	**0.9013**	7.839	0.965	0.246
FHPMC-1:5	0.722	0.977	0.895	-0.008	0.925	9.098	**0.980**	0.260
FHPMC-1:7	0.700	0.976	0.888	-0.009	0.912	9.159	**0.988**	0.246
FHPMC-1:10	0.630	1.026	0.886	-0.012	0.853	9.831	**0.930**	0.183
FMAN-1:1	0.885	0.786	0.940	-0.004	**0.985**	6.828	0.947	0.599
FMAN-1:3	0.835	0.749	0.914	-0.004	**0.982**	6.687	**0.982**	0.392
FMAN-1:5	0.857	0.809	0.937	-0.005	**0.984**	7.142	0.982	0.392
FMAN-1:7	0.831	0.846	0.924	-0.006	0.982	7.572	**0.998**	0.374
FMAN-1:10	0.717	0.846	0.859	-0.006	0.924	7.909	**0.994**	0.259

Fourier Transformed Infrared Spectroscopy (FT-IR) Study

Fourier transformed spectroscopy is widely used because of its rapid providing of high resolution spectra with samples in the nanogram range. Structural changes and lack of crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not[17]. State of drug molecule with the different hydrophilic polymers and surfactants was determined using FTIR.

Figure 6 shows the IR spectra of pure Fenofibrate drug and prepared formulations by solid dispersions. The identical peaks of the IR-spectra of Fenofibrate and solid dispersions are same, and there is no shift of peaks after adsorption of drug onto polymer and surface of the surfactants; indicating that there is no change in chemical structure of drug after preparing it into melt granules. The major peaks of Fenofibrate are observed at 3439, 3040, 2983.88, 1728.22, 1651.07, 1588.09, 1587.42, 1384.89, 1301.95, 1296.52, 1273.94, 1247.94, 1203.58, 1180.44, 1172.72, 1159.22, 1101.35, 1087.85, 1012.63, 974.05, 925.83, 860.25, 842.89, 763.81, and 655.80 cm^{-1} . It has observed that there were a great difference in the percent of transmittance for different carriers with different ratio used in the formulations of solid dispersions which were found in the study.
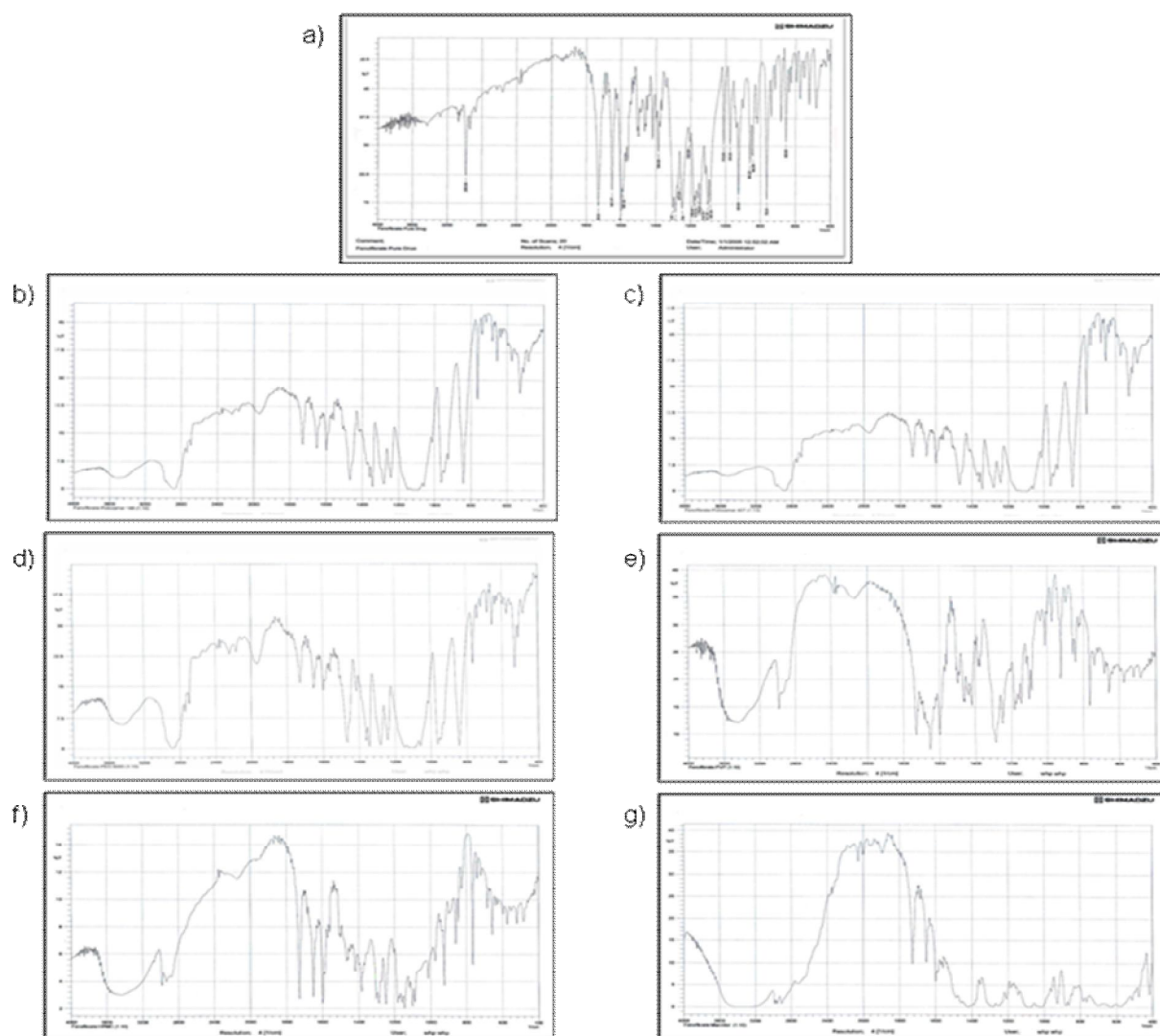

Figure 6: Infrared spectrum of a) pure Fenofibrate b) Fenofibrate:Poloxamer 188 (1:10), c) Fenofibrate : Poloxamer 407 (1:10), d) Fenofibrate : PEG 6000 (1:10), e) Fenofibrate : PVP (1:10), f) Fenofibrate : HPMC 6 cps (1:10) and g) Fenofibrate : Mannitol (1:10)

The spectra of pure drug shows characteristic peaks at 3040 to cm-1 due to alkyl groups, at 3439 cm^{-1} due to phenol and at 1651 cm^{-1} due to carbonyl group. FT-IR spectra of solid dispersion showed broadening of the peak at 3300 cm^{-1} to 2900 cm^{-1} which may be due to carbonyl group of the carriers. Hence we can say that significant interaction between drug and carriers have taken place and the band spectrum which were found from pure Fenofibrate have significantly stretched in the band spectrum which were found from the formulation of solid dispersion by IR scanning. It also clearly observed that the peaks of Fenofibrate in the region of 2000 cm^{-1} to   400 cm^{-1} have disappeared in solid dispersion indicating possible Vander Waal interaction between drug and polymer[18].

CONCLUSION

After performing dissolution study, Fenofibrate release profiles were analyzed on the basis of various mathematical models such as zero order kinetic model, Higuchi release pattern and Korsmeyer release pattern. The overall experiment has revealed the effect of polymer on the release kinetics of Fenofibrate from different solid dispersion. The following features are quite notable from the above study

1. Maximum formulations (20 out of 31) displayed highest fitting with Higuchi release pattern and some formulation (12 out 31) also displayed with Krosmeyer release pattern for solid dispersion. And one formulation (FMAN: 3) was fitted for both Higuchi and Krosmeyer release pattern. In these cases lowest fitting with zero order kinetic model of drug release.

2. Increase in the amount of carriers (polymers) in solid dispersion displayed a common phenomenon that the drug release rate and extent were exclusively increased in all in case of all formulation and their maximum concentrations.

3. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility. The study encompasses the criteria of solvent selection, challenges in formulation of solid dispersion dosage forms, future prospects and various types of marketed preparations containing poor soluble and water insoluble drug.

It is assumed that more extensive *in vitro-in vivo* correlation study on similar formulations deemed necessary to establish a successful formulation from biopharmaceutical view point. Further study would be carried out for finding out the possibilities of formulations containing Fenofibrate having the lipid lowering activity which is used to reduce cholesterol and

triclygerides in the blood and treatment of hyperlipidemia. Further research is also required for the better implementation of solid dispersion technology as this is an eminent technique for the solubility enhancement of poorly soluble drugs.

ACKNOWLEDGEMENT

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