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Enhancement of Dissolution Rate of Fenofibrate by Using Solid Dispersion Techniques

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ABSTRACT
The aim of the present research work, Fenofibrate a BCS class II Antilipidemic drug belongs to fibrate class was formulated as solid dispersions by using various solid dispersion techniques to enhance the solubility, dissolution rate and oral bioavailability. Solid dispersion technique by HP β-cyclodextrin has been used to improve the dissolution properties and bioavailability of poorly water- soluble drugs. Solid dispersions of Fenofibrate were prepared with polymers in different ratios of drug and carrier physical mixture, kneading method, solvent evaporation and fusion method. Results of prepared solid dispersions of Fenofibrate by physical mixture method, kneading method, solvent evaporation and fusion method were discussed which includes solubility, drug content uniformity, entrapment efficiency and in vitro dissolution studies. Formulation (SF3) containing Fenofibrate + HP β-cyclodextrin (1:1.5) shows better results by solvent evaporation method at the end of 90 min with drug release of 98.56%. In this study, it was found that the solid dispersions is a suitable technology to improve the dissolution behavior of poorly water soluble drugs when the drug load is high.

Key words: Fenofibrate, Hydroxyl Propyl B-Cyclodextrin, Solid Dispersion, Ludiflash, Solvent Evaporation.

I. INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability.[1]The enhancement of oral bioavailability of poorly water soluble and water insoluble drugs remains one of the most challenging aspects of drug development.[2]

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration.[3]Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more re-producible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy.[4] Therefore, there is a great interest to develop efficient, reliable, economical, and scalable method to increase the oral bioavailability of poorly water-soluble drugs.[5]

To improve the dissolution and bioavailability of poorly water-soluble drugs, researchers have employed various techniques such as micronization, solubilisation, salt formation, complexation with polymers, changing in physical forms (amorphous), use of prodrugs 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.[6,7]

MATERIALS AND METHODS

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.

Preformulation Studies[8-11]

Determination of melting point

Melting point of the drug was determined by taking 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.

Solubility studies:

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

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 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**.**

Differential scanning calorimetry (DSC) Study

DSC analysis of pure drug, and optimized formulation was performed with Shimadzu DSC 60 thermal analyser at the heating flow rates of 5°C per min between 0-450°C under static air using aluminium pans.

Preparation of Solid Dispersions of Fenofibrate[8-11]

Physical mixture method

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

Table 1: Formulation for physical mixture method

Formulation code	Drug : polymer ratio (Fenofibrate: HP β-Cyclodextrin)
PF1	1:0.5
PF2	1:1
PF3	1:1.5

Kneading Technique

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

Table 2: Formulation for kneading technique

Formulation code	Drug : polymer ratio (Fenofibrate: HP β-Cyclodextrin)
KF1	1:0.5
KF2	1:1
KF3	1:1.5

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 pulverised and passed

through sieve # 100. And now the obtained product was collected and stored in desiccators.

Table 3: Formulation for solvent evaporation method

Formulation code	Drug : polymer ratio (Fenofibrate: HP β-Cyclodextrin)
SF1	1:0.5
SF2	1:1
SF3	1:1.5

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.

Table 4: Formulation for fusion method

Formulation code	Drug : polymer ratio (Fenofibrate: HP β-Cyclodextrin)
FF1	1:0.5
FF2	1:1
FF3	1:1.5

Evaluation of Solid Dispersions[12,13]

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. Same concentration of 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 UV-Visible spectrophotometer.

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 behaviour 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 exclusion column, for removal of non-entrapped material are often time consuming, tedious, costly and recovery of non-entrapped material is usually difficult.

Entrapment efficacy was calculated by following formula:

%Entrapment efficiency= Drug content ×100/Drug added in each formulation

In-Vitro dissolution study

Dissolution rate of Fenofibrate from all formulations was performed using dissolution testing apparatus (paddle). The dissolution fluid was 900ml of 0.1N HCl, a speed of 50 rpm and a temperature of 37±0.5°C was used in each test. Samples of dissolution medium (5ml) were

withdrawn at different time intervals (5,10,20,30,45,60,75 and 90min), suitably diluted and assayed for Fenofibrate by measuring the absorbance at 273nm by using U.V. spectrophotometer.

II. RESULTS AND DISCUSSION

Preformulation Studies

The following preformulation studies were performed for drug and polymers;

Determination of melting point

The melting point of Fenofibrate was found to be 82^{o}C which was determined by capillary method.

Solubility

From the solubility studies in various buffers we can say that 0.1 N HCl solutions has more solubility when compared to other buffer solutions.

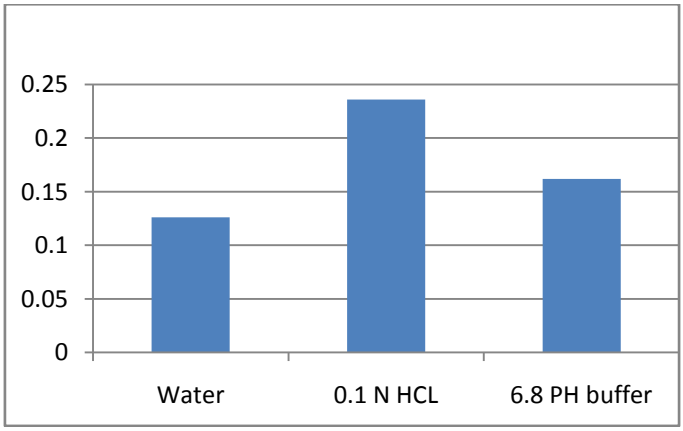


Fig 1:Solubility studies of Fenofibrate

1) Drug–excipient compatibility studies

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

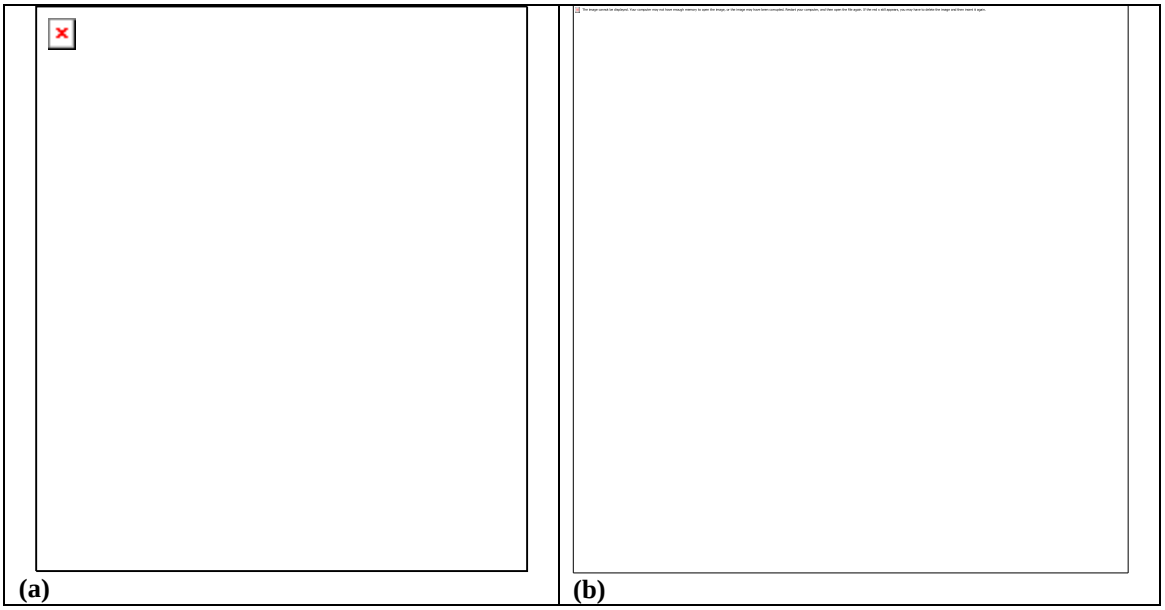
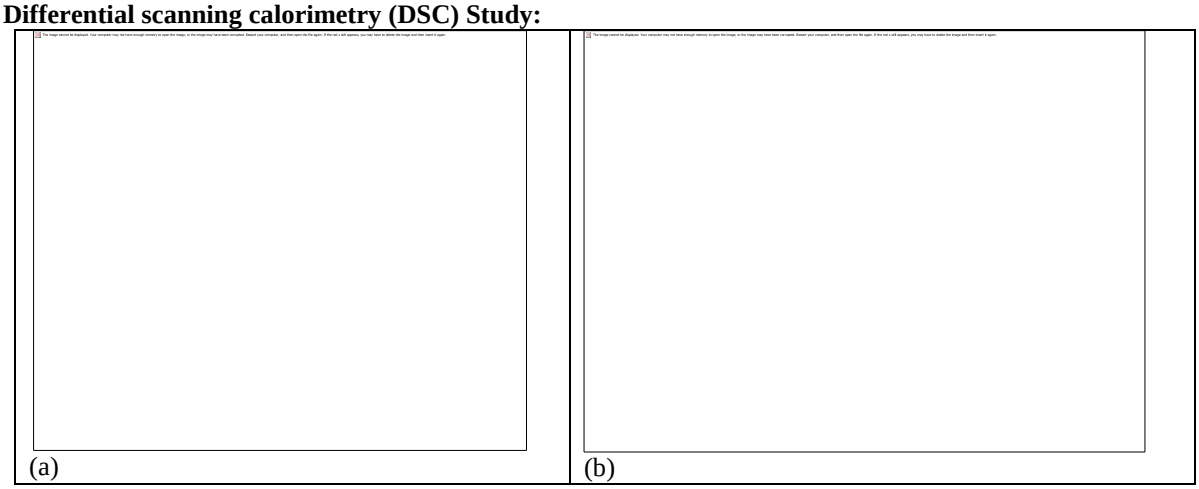


Fig 2: a) IR spectrum of pure Fenofibrateb) IR spectrum of physical mixture of drug and excipient blend

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.

Differential scanning calorimetry (DSC) Study:



(a) (b)

Fig.3:(a) **DSC thermo gram of Fenofibrate (b) DSC thermo gram of Solid dispersion of Drug: Excipient Blend**

DSC shows that no drug-excipient interaction, as the original exotherm of the drug was clearly evident in the physical mixture.

Evaluation of Solid Dispersions

Prepared polymer drug conjugates were evaluated by

Estimation of Drug Content

Physical mixture method

Table 5: Drug content uniformity for solid dispersions by physical mixture

Form. Code	%Drug Content
PF1	75.3
PF2	80.12
PF3	83.6

% drug content values of all the formulation (PF1-PF3) was in the range of 75.3-83.6%, formulation PF3 shows higher drug content 83.6%.

Kneading method

Table 6: Drug content uniformity for solid dispersions by kneading method

Form. Code	%Drug Content
KF1	54.64
KF2	66.21
KF3	74.82

% drug content values of all the formulation (KF1-KF3) were in the range of 54.64 – 74.82%, formulation KF3 shows higher drug content 74.82%.

Solvent evaporation method

Table 7: Drug content uniformity for solid dispersions by solvent evaporation method

Form. Code	%Drug Content
SF1	62.2
SF2	79.19
SF3	92.9

% drug content values of all the formulation (SF1-SF3) were in the range of 62.2 - 92.9%, formulation SF3 shows higher drug content 92.9%.

Fusion method

Table 8: Drug content uniformity for solid dispersions by Fusion method

Form. Code	%Drug Content
FF1	68.2
FF2	72.6
FF3	79.4

% drug content values of all the formulation (FF1-FF3) were in the range of 68.6 – 79.4%, FF3 shows higher drug content 79.4%.
By comparing results of all the formulations (PF1-PF3) (KF1-KF3) (SF1-SF3) & (FF1-FF3), formulation SF3 containing Fenofibrate: HP β-Cyclodextrin (1:1.5) shows higher drug content 92.9%.

Entrapment Efficiency

Physical mixture method

Table 9: Entrapment efficiency of solid dispersions by physical mixture method

Form. Code	% Entrapment Efficiency
PF1	75.4
PF2	82.5
PF3	80.3

The entrapment efficacy of the formulated solid dispersions was found to be in the range of 75.4-82.5%. Formulation PF2 shows higher entrapment efficiency 82.5%.

Kneading method

Table 10: Entrapment efficiency of solid dispersions by kneading method

Form. Code	% Entrapment Efficiency
KF1	68.21
KF2	72.85
KF3	75.3

Discussion: The entrapment efficacy of the formulated solid dispersions was found to be in the range of 68.21-75.36%. Formulation KF3 shows higher entrapment efficiency 75.36%.

Solvent evaporation method

Table 11: Entrapment efficiency of solid dispersions by solvent evaporation

Form. Code	Entrapment Efficiency
SF1	79.59
SF2	88.75
SF3	94.43

The entrapment efficacy of the formulated solid dispersions was found to be in the range of 79.59- 94.43%. Formulation SF3 shows higher entrapment efficiency 94.43%.

Fusion method

Table 12: Entrapment efficiency of solid dispersions by Fusion method

Form. Code	Entrapment Efficiency
FF1	54.9
FF2	62.9
FF3	78.21

The entrapment efficacy of the formulated solid dispersions was found to be in the range of 54.9- 78.21%. Formulation FF shows higher entrapment efficiency 78.21%.

By comparing results of all the formulations (PF1-PF3) (KF1-KF3) (SF1-SF3) & (FF1-FF3), formulation SF3 containing Fenofibrate: HP β-Cyclodextrin (1:1.5) shows higher entrapment efficiency 94.43%.

In-Vitro dissolution studies (In-Vitro Drug Release Studies Of Solid Dispersions)

Physical mixture method (PF1-PF3)

In-Vitro drug release of Fenofibrate solid dispersions with HP β-Cyclodextrin in various ratios were observed which shows at the end of 90 mins, the formulation PF1 releases 82.21, formulation PF2 releases 86.42, PF3 releases 89.94%.

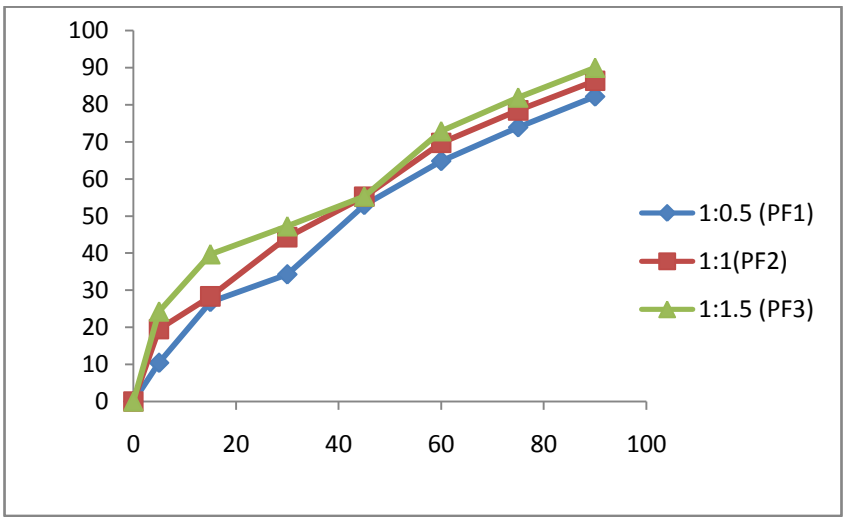


Fig 4: In-Vitro drug release profile for drug: HP β-Cyclodextrin (PF1-PF3)

Kneading 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 mins, the formulation KF1 releases 78.92, formulation KF2 releases 80.46, formulation KF3 releases 82.21%

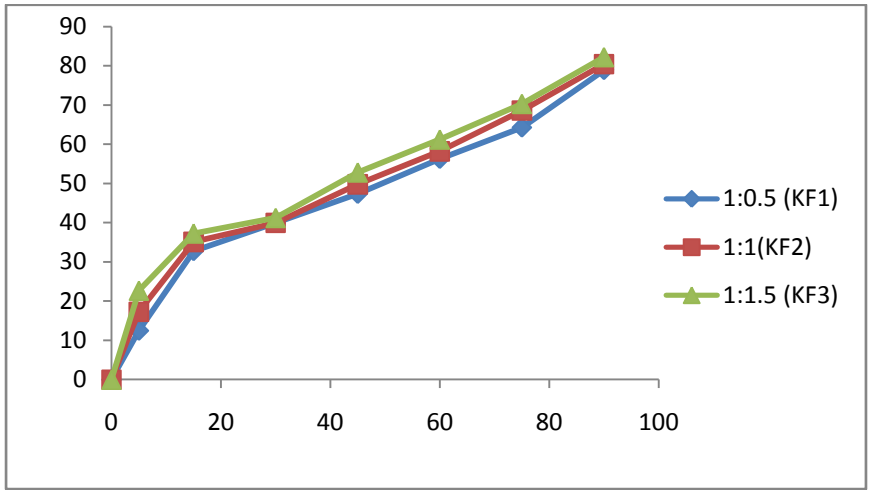


Fig 5: In-Vitro drug release profile for drug: HP β-Cyclodextrin (KF1-KF3)9

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 mins the formulation SF1 releases 92.46, formulation SF2 releases 95.29, formulation SF3 releases 98.56% of drug at the end of 90 mints.

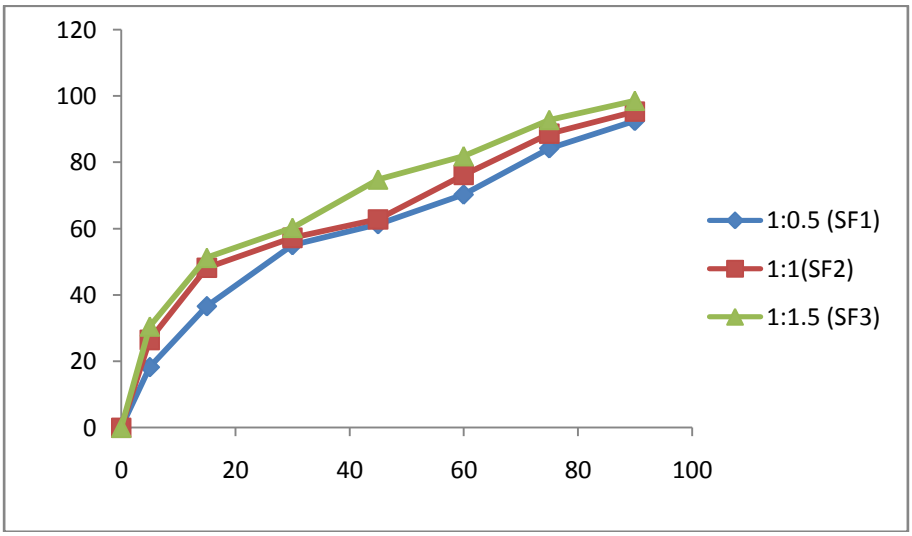


Fig 6: In-Vitro drug release profile for drug: HP β-Cyclodextrin (SF1-SF3)

Fusion 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 mins the formulation FF1 releases 79.86; formulation FF2 releases 82.06, formulation FF3 releases85.29%.

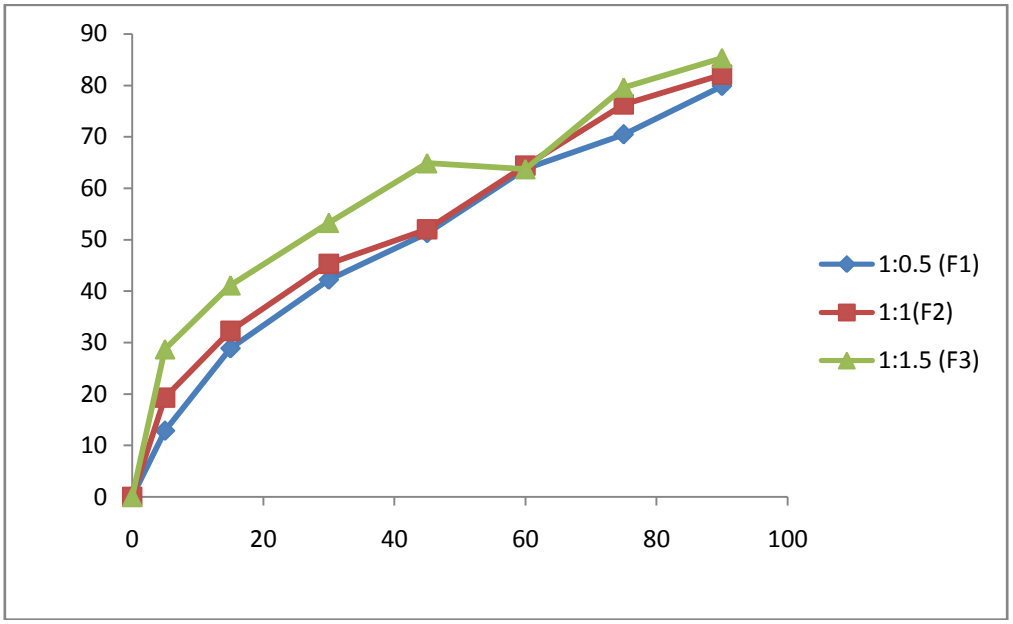


Fig 7: In-Vitro drug release profile for drug: HP β-Cyclodextrin (FF1-FF3)

By comparing results of all the formulations (PF1-PF3) (KF1-KF3) (SF1-SF3) & (FF1-FF3) formulation SF3 containing Fenofibrate: HP β-Cyclodextrin (1:1.5) shows higher drug release 98.56% at the end of 90 mins.

III. CONCLUSIONS

HP β-cyclodextrin was used in the preparation of solid dispersions by physical mixture mehod, kneading method, solvent evaporation and Fusion method. By observing the dissolution studies,the dissolution rate of Fenofibrate can be enhanced to a great extent by the solvent evaporation method for fenofibrate with HP β-cyclodextrin (1:1.5).

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