

Design and Development of Fenofibrate Solid Dispersions for Solubility Enhancement

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Abstract

This research work designed to overcome the problems associated with poorly aqueous soluble drug. Fenofibrate (FENO) being BCS Class II drug shows low solubility but permeability is high. Compatibility of the drug and polymer studies was done by FTIR. Physical mixtures (PM) of the drug and polymer HPMCAS were prepared by trituration method. Fenofibrate solid dispersions (SD) were prepared by common solvent technique ascribed feasibility in laboratory scale. Physical state of formulations was characterized by powder XRD, TGA. Solubility of pure drug (FENO), Physical mixture and SD found to be 0.3, 0.78±0.15 to 1.15±0.28 and 2.17±0.37 to 3.25±0.14 mg/ml respectively. Percentage yield and percentage drug content were determined and found within satisfactory range. The maximum cumulative percentage of drug release from pure drug (FENO), Physical mixture and SD found to be 34.5%, 72.1 and 97.2% respectively at 60 minutes. Microscopy (SEM) study was found that the prepared solid dispersion has porous morphology. The present study establishes the increased bioavailability of the optimized batch when compared with the pure FENO. There was significant (50%) increase in absorption of Fenofibrate observed from the *in vitro* everted gut sac model. SD of FENO was developed successfully. The solubility of FENO was ameliorated significantly while compared with API (pure FENO). This research work found formulation of SD preferable technique to enhance solubility and enhance dissolution of lipophilic drugs.

Keywords: Bioavailability, HPMCAS, Poor aqueous solubility, physical mixture, solid dispersion.

INTRODUCTION

Solid dosage form prevail the most popular dosage form due to ease of production, patient compliance and have good stability although many APIs are hydrophobic in nature. Drug characteristics like poor water solubility, poor membrane permeability are crucial factors among other factors for drug absorption from gastrointestinal tract.^[1] This creates a challenge for optimization of a dosage formula and acts as a driving force to think about alternative formulation techniques to cross confront. Solubility is one of the most important criteria to be considered by formulation scientists while formulating any delivery system as it is essential to get the required systemic concentration of a drug for achieving the desired therapeutic effect.^[2]

Fenofibrate (FENO) is a peroxisome proliferator-activated- α (PPAR α) receptor agonist used as a hypolipidemic drug, effective in the management of various forms of dyslipidemia.^[3, 4, 5] As a PPAR α , it regulates gene/protein interactions which are associated in various pathological processes like regulation of β -oxidation of fatty acids, oxidative stress, inflammation and even cancer progression and tumorigenesis.^[6] As a result of PPAR α activation of gene transcription and translation which leads to peroxisomes filled with hydrogen peroxide, reactive oxygen species and hydroxyl radicals act as participant in lipolysis.^[7] This active pharmaceutical compound is clinically efficacious against elevated triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) serum levels at the same time amplifies the level of essential cholesterol, e.g. high-density lipoprotein (HDL) in serum.^[8] The half-life of the drug is 20 hours and is metabolized by hepatic cytochrome P (CYP)-450 3A4 isoenzymes.

Being BCS class II drug Fenofibrate possesses high permeability while showing poor aqueous solubility. Solubility is the rate limiting step for this class of drugs. Bioavailability of drugs comes under class II of Biopharmaceutical Classification System can be ameliorated by improving solubility thereby drug dissolution. Decrease in particle size results in an increase in surface area. Enhanced surface area may expedite solubility and bioavailability of active pharmaceutical ingredients.^[9] Converting crystalline drugs into an amorphous state by disintegration of the crystal lattice may prove a vital approach to enhance drug solubility as it is in the higher energy state.^[10, 11, 12]

Nowadays, Solid dispersion (SD) emerged as a novel technique for delivery of drugs to overcome the barriers to drug absorption. In this technique, one or more active ingredients dispersed in a hydrophilic carrier/polymer in a solid-state which can be prepared by various methods i.e. kneading, fusion, common solvent, gel entrapment, spray drying, lyophilization method etc. Among various methods for the preparation of solid dispersions, the common solvent or solvent evaporation method is found to be the most successful one due to ease of preparation, reproducibility of the manufacturing process and simple equipments are required with respect to many other production methods.^[13, 14, 15]

In this approach, drug and polymer dissolved in a common solvent and then the solvent is evaporated completely, which results in co-precipitation of dissolved substances from the solution. When, such co-precipitate exposed to water leads to form a colloidal dispersion.^[16, 17] Thermal degradation of drug or carrier can be avoided which makes this method precedence over other manufacturing processes of solid dispersion.

MATERIALS AND METHODS

Materials:

Fenofibrate/C₂₀H₂₁ClO₄/2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester was obtained from Aurobindo Pharma Ltd. Hypromellose Acetate Succinate/ C₁₀H₂₂O₉ (HPMCAS) was obtained from Wockhardt Limited. Methanol (CH₃OH) was of analytical grade. Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Sodium chloride purchased from Merck Pvt. Ltd., Spectrochem Pvt. Ltd. and Thomas Bakers (Chemicals) Pvt. Ltd. respectively.

Methods:

Physical mixing: Physical mixtures (PM) of C₂₀H₂₁ClO₄ were prepared (Table 1) by triturating the drug with the polymer/carrier. In first step required quantity of Hypromellose Acetate Succinate (C₁₀H₂₂O₉) was triturated with the help of mortar and pestle. Then Fenofibrate was added gradually and triturated enough to ensure proper mixing of the drug and the carrier. Then the prepared physical mixtures were pulverized and stored in desiccators under vacuum until further use.

Common solvent method: SDs of FENO were prepared by common solvent technique according to Table 1. C₁₀H₂₂O₉ used as polymer to formulate solid dispersions. Methanol used as a solvent to dissolve both polymer and the drug as both are soluble in this volatile solvent. Then the mixtures were treated with an elevated temperature nearly up to 50°C to evaporate the solvent and get dry mass. Vigorous continuous stirring was done to ensure uniform distribution of drug within the carrier. The resulting mass then cooled to room temperature, pulverized, passed through sieve and stored in desiccators under vacuum until further use.^[18, 19]

Table 1: Composition of formulation batches of Fenofibrate Physical mixtures and Solid dispersions

Physical mixture		Common solvent method	
Formulations code	Drug : Polymer (w/w)	Formulations code	Drug : Polymer (w/w)
FPM 1	1:1	FSD 1	1:1
FPM 2	1:2	FSD 2	1:2
FPM 3	1:3	FSD 3	1:3
FPM 4	1:4	FSD 4	1:4

FPM 5	1:5	FSD 5	1:5
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Solubility studies: Solubility studies were carried out by using orbital shaker. Screw capped bottles containing excess of pure drug PMs and prepared SDs shaken mechanically for 24 hours at room temperature.^[20, 21] The resulting samples were filtered through 0.45 µm Whatman filter paper. Filtrates were diluted suitably and absorbencies were determined at 286 nm by UV-Vis spectrophotometer model 2202, Systronics.

Drug-excipient compatibility study: Before approaching formulation trials it is essential to do drug excipient compatibility study to confirm there is no interaction between drug and excipient proposed for formulation of trial batches. It can be determined by Fourier Transform Infra Red spectrophotometer (FTIR).^[22] Drug and excipient mixed in the ratio of 1:1 (w/w) used to exaggerate the drug-excipient interactions which will be easier to examine.^[23]

Yield: Yield percentage was calculated by the equation below by using final mass of the product with respect to total theoretical mass of drug and polymer^[24] while sensitive electronic balance by Wensar was used:

$$\% \text{ Yield} = \frac{\text{Mass of the product}}{\text{Theoretical mass}} * 100$$

Theoretical mass

(Polymer+ drug)

Determination of drug content: Weighed quantities of sample (physical mixtures/solid dispersions) were dissolved in 10 ml of methanol kept in 10 ml volumetric flask.^[25, 26] The resulting mixture was diluted suitably and absorbance was measured at λ_{max} 286 nm.

Percentage of drug content was calculated by following equation after appropriate dilutions:

$$\% \text{ Drug content} = (\text{Mact/Mt}) * 100$$

Where, Mact = Actual amount of drug in solid dispersion

Mt = Theoretical amount of drug in solid dispersion

Powder X-ray diffraction: X-ray diffraction study used for qualitative study of the material. Sharper diffraction peaks indicate more crystalline powder^[27]. Crystallinity of drug PM and SD were determined by using X-Ray Diffractometer (AXRD Benchtop Powder Diffraction System). Samples were loaded in the diffractometer and scanned over a range of 2θ values from 10° to 80° at a scan rate of $0.025^\circ/\text{sec}$.

Thermogravimetric analysis: Thermal stability of FENO and optimized solid dispersion was determined by using Thermogravimetric analyser^[28] STA 449 F5 Jupiter by NETZSCH-Geratebau GmbH. Auto sampler was attached to analyse the decomposition stage and thermal stability of FENO and solid dispersion. Alumina crucible was used for analysis. Heating range of 25°C to 500°C with an accelerated heating rate of 10.0 k/min was maintained.

In-vitro drug release ^[29, 30]: Drug release profile of solid dispersions were determined by dissolution rate test apparatus USP Type II by Veego. Phosphate buffer 7.4 used as dissolution media and temperature was maintained at $37 \pm 0.1^\circ\text{C}$ to simulate body temperature. Samples were placed in baskets containing 900 ml of dissolution medium. At predetermined time intervals samples were collected and maintenance of sink condition was taken care of by adding fresh dissolution media of equivalent quantity. Samples were filtered through $0.45\mu\text{m}$ whatsmen filter paper, diluted suitably with dissolution media and were analyzed for amount of drug dissolved by using UV-Vis spectrophotometer, Systronics at 286 nm.

Scanning Electron Microscopy: Surface morphology of prepared solid dispersion can be determined by SEM. Scanning Electron Microscope can determine shape and porosity of the drug under study.^[31] Optimized solid dispersion sample was mounted on a carbon film and sputtered with gold and analyzed under the microscope at high resolution and responses are recorded for further study.

Stability study: Accelerated stability study carried out at exaggerated storage condition to determine the effect of environment on product quality. Temperature and humidity maintained at $40\pm 2^{\circ}\text{C}$ and $75\pm 5\%$ RH respectively for six months.^[32, 33] Samples were kept in closed vials for analysis at later stage for assay and in-vitro drug release.

IN VITRO DRUG ABSORPTION STUDY (EVERTED SAC MODIFICATION METHOD):

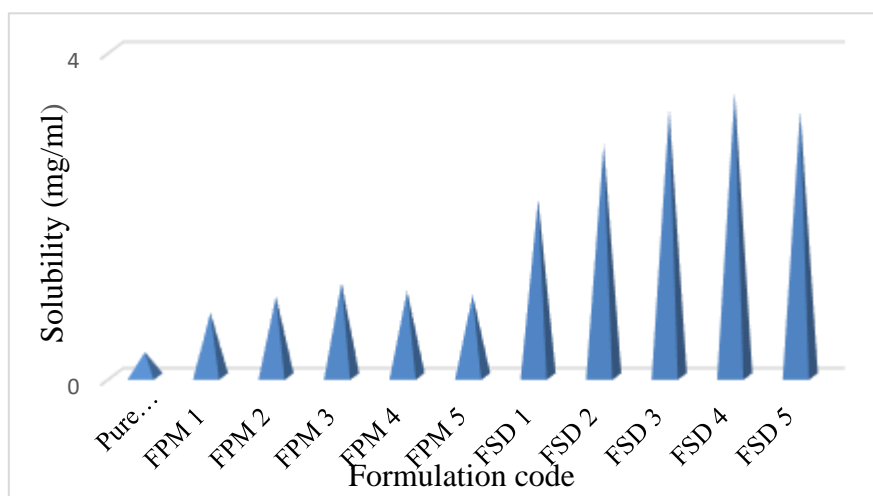
Intestinal drug absorption studies were performed by everted gut sac method^[34, 35] with some moderations. The freshly excised goat intestine was amassed from the local market from the provincial slaughter house instantly after slaughtering the goat. This was shifted to the laboratory in ice-cold normal saline. Approximately 12 cm of small intestine was abstracted from the collected tissue by separating each end. The abstracted intestinal segments were immediately treated with ice-cold normal saline to wash it from intestinal materials and clear away the mesenterium present underneath, blood and any other materials which is not required for the study. By entering a glass rod carefully through the length of the intestine, the intestinal segment can be everted over the glass rod. At this condition sterilised thread was used to tie both ends of the tissue. This tissue filled with the test and standard drug solutions. Phosphate buffer pH 7.4 was used as medium and constantly stirred with a magnetic stirrer at 50 rotations per minute. Oxygenation was maintained by constant aeration. Temperature was maintained at $37^{\circ}\text{C}\pm 0.5^{\circ}\text{C}$. 20 mg of pure drug and optimized solid dispersion containing equivalent quantity of drug were taken for this study and carried out for 2 hours. 3 ml of sample from the sac were withdrawn at predetermined time intervals. Similar volume of fresh media was added to maintain sink condition. The concentration of the drug that crossed the intestinal surface was analysed by using UV Spectrometer at 286 nm.

RESULTS AND DISCUSSION

Physical mixtures and solid dispersions of FENO were prepared by simple trituration and common solvent method respectively according to Table 1. The prepared batches were evaluated for solubility, percentage yield, drug content, crystallinity, *in-vitro* drug release, morphology, stability and *in vitro* drug absorption study.

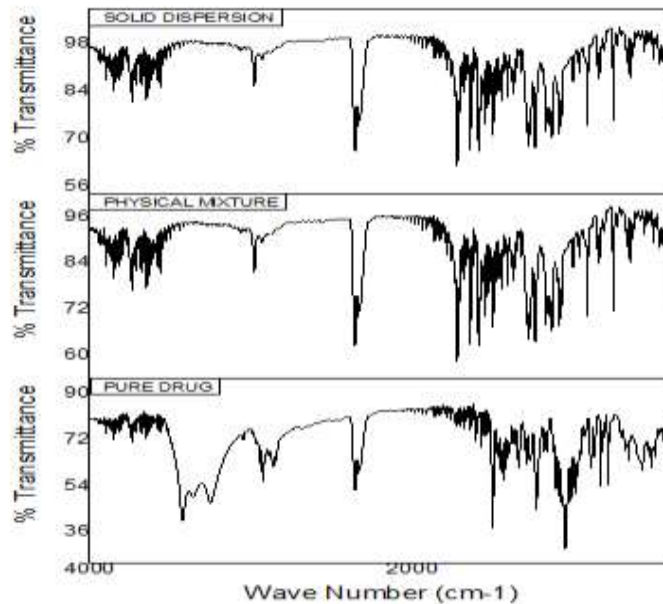
Solubility studies: Effect of polymeric insertion of FENO on water solubility of the drug can be determined by the method discussed above and results are depicted in Figure 1. Solubility of pure drug was found to be 0.3 mg/ml whereas for physical mixer solubility ranges from 0.78 ± 0.15 to 1.15 ± 0.28 mg/ml and prepared solid dispersions showed improved solubility to many folds which ranges from 2.17 ± 0.37 mg/ml to 3.25 ± 0.14 mg/ml.

Figure 1: Solubility of pure FENO, FPMs and FSDs



FTIR spectroscopy: The extent of interactions between drug and matrix was measured by FTIR spectroscopy (IRPrestige-21, Shimadzu). Samples (Fenofibrate/mixture of drug and HPMCAS/prepared solid dispersion) were mixed with potassium bromide and compressed into pellets. Spectra are recorded and analysed for any interactions. FTIR offers quantitative and qualitative analysis for different samples. FTIR is an effective analytical instrument for detecting functional group and characterizing covalent bonds in a molecule by producing an infrared absorption spectrum. It detects the interactions between drug and carrier in the solid phase leading to spectral variations due to alteration in bonds showing different vibration frequencies. The FT-IR spectrum of pure drug (FENO) shows characteristics peaks at 3439 cm^{-1} due to phenol, at 1504 cm^{-1} due to C-O stretching, at 3087 cm^{-1} due to C-H stretching, at 674 cm^{-1} due to benzene ring, at 1625 cm^{-1} due to carbonyl group. The IR spectra of mixture showed that there is no significant interaction has taken place between the drug and carrier. Optimized formulation also didn't show any significant change in spectra. FTIR spectra of pure drug, PM and optimized SD is represented in the Figure 2.

Figure 2: Comparative FTIR spectra of Pure drug (FENO), Drug + HPMCAS (PM) and Optimized SD



Yield: Yield percentage was found satisfactory and in the range of 97 – 98.7 % for various batches of physical mixtures (FPMs) and 96.2 to 98.5% for common solvent method (FSDs). Values for percentage of yield by both the methods are depicted in the Table 2.

Table 2: Percentage yield of various batches of Physical mixtures and Solid dispersions

Formulation Code	% Yield	Formulation Code	% Yield
FPM 1	98.5	FSD 1	98.1
FPM 2	97	FSD 2	96.2
FPM 3	98	FSD 3	97
FPM 4	97.7	FSD 4	97.3
FPM 5	98.7	FSD 5	98.5

Determination of drug content: drug content was determined by the method mentioned earlier by using UV spectrophotometer (Model 2202, Systronics) at λ_{max} 286 nm. Percentage drug content was summarized in Table no. 3. Drug contents were found to be within the acceptable range. For physical mixture drug content percentage was in the range of 98.5-100.5 % and for various batches of common solvent method range was 98.4-100.3 %.

Table 3: Percentage drug content of various batches of Physical mixtures and Solid dispersions

Formulation Code	% Drug content	Formulation Code	% Drug content
FPM 1	100.5	FSD 1	99.8
FPM 2	98.5	FSD 2	98.9
FPM 3	99.7	FSD 3	100.3
FPM 4	100.2	FSD 4	99.3
FPM 5	99.5	FSD 5	98.4

Figure 3: Percentage yield and DC for various batches of Physical mixture (FPMs)

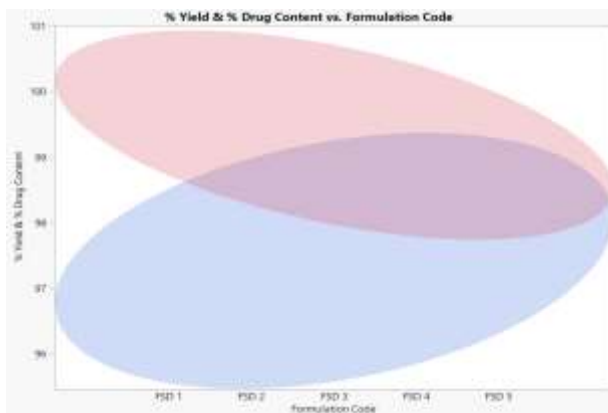
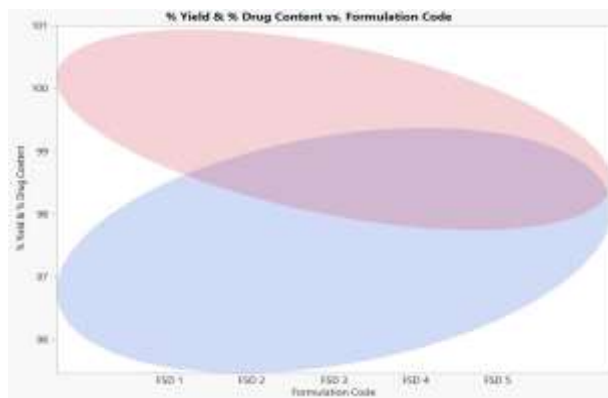
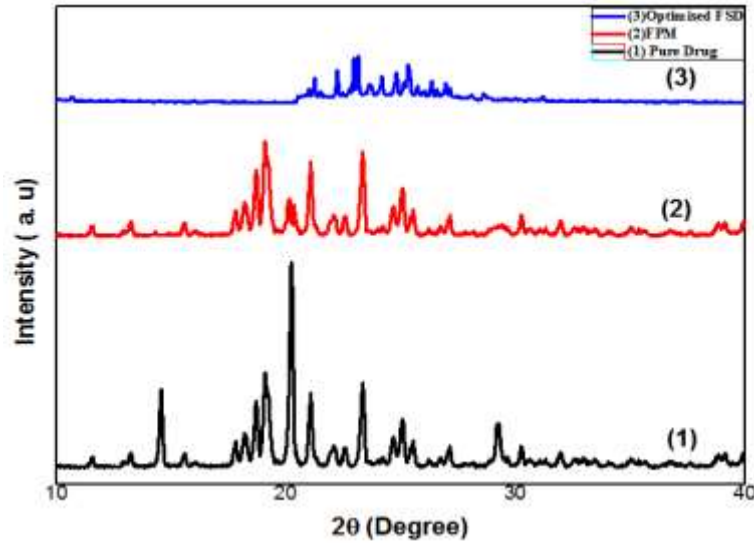


Figure 4: Percentage yield and DC for various batches of solid dispersions (FSDs)



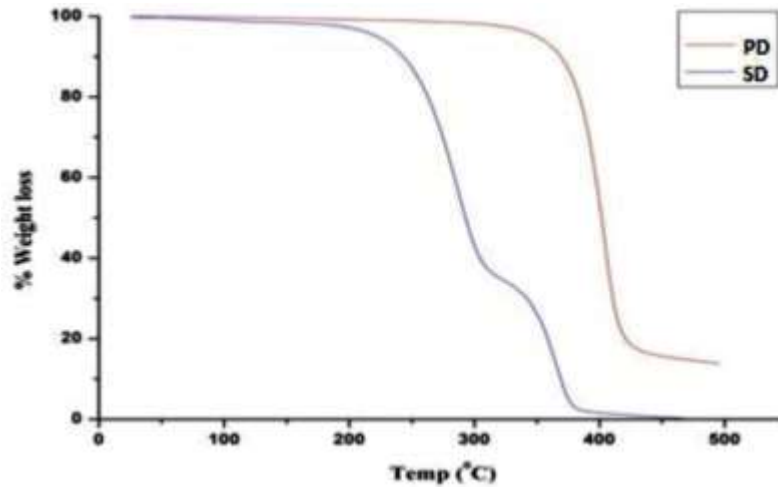
Powder X-ray diffraction: Comparative X-ray diffraction patterns of pure drug, FPM and optimized SD batch were presented in Figure 5. As a crystalline compound pure drug (FENO) showed sharp distinct characteristics peak at 2θ diffraction angles for 14.669°, 18.714°, 19.128°, 20.258°, 21.082°, 23.341°, 25.066°, 29.255°. The XRD pattern of FPM showed curtailed number of peaks and reduced intense peaks than the pure drug. The diffraction patterns of physical mixture were quiet similar to that of pure drug which suggest simple mixing of the drug and carrier. In case of optimized batch the XRD pattern showed absence of these distinct peaks confirming the conversion of drug from crystalline to amorphous form.

Figure 5: Comparative XRD diffractograms of pure drug (Feno), FPM and optimized SD batch



Thermogravimetric analysis: TGA study was done to analyze the stability of the solid state. To interpret data percentage weight loss was plotted against temperature and represented in Figure 6. For pure drug major weight loss occurred nearly 380°C. Solid dispersion showed weight loss in two steps: First weight loss was nearly 220°C and second loss was around 340°C.

Figure 6: Comparative TGA graph of Pure drug (PD) and optimized solid dispersion



In-vitro drug release: Drug release profile of solid dispersions determined by dissolution rate test apparatus USP Type II. The cumulative percentage of drug release from API (Fenofibrate), PMs and SDs with respect to time are represented in the Figure 7 and Figure 8. Cumulative % drug releases for FPMs at 60 minutes were varying from 62.4-72.1 %. From Figure 7 it was observed that the drug release percentages for all the physical mixtures were elevated while comparing with pure FENO. For FSDs, % drug release was from 87.4-97.2 % for various formulation batches at 60 minutes. The Figure 8 reveals that all the FSDs had higher drug release percentages than the pure FENO. The dissolution profile of both formulation batches (physical mixture and solid dispersion) having higher % of drug release as compared with pure drug and unveil in Figure 9. The comparative dissolution profile graph (Figure 9) evident that the solid dispersion (FSD 1) was able to release maximum drug that is 97.2% at 60 minutes.

Figure 7: Comparative dissolution profile of pure drug (FENO) and FPMs

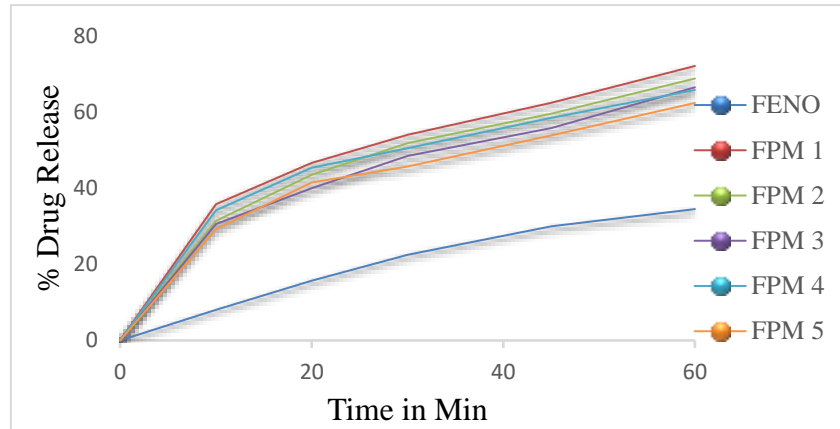


Figure 8: Comparative dissolution profile of pure drug (FENO) and SDs

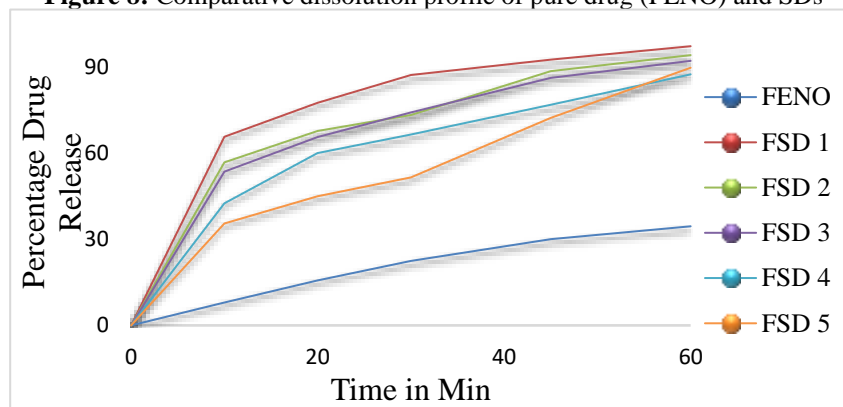
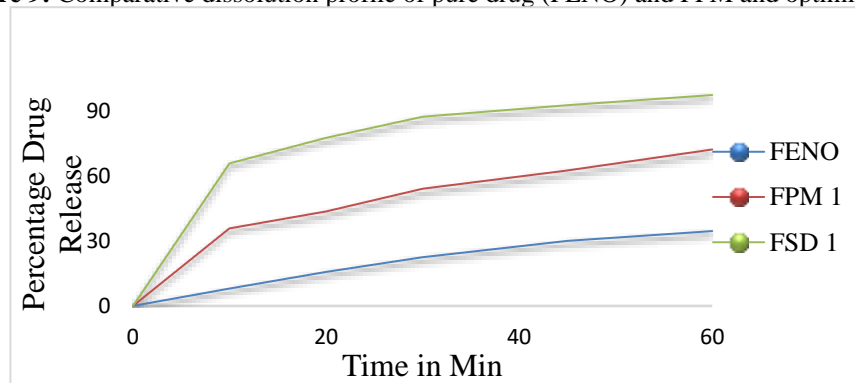
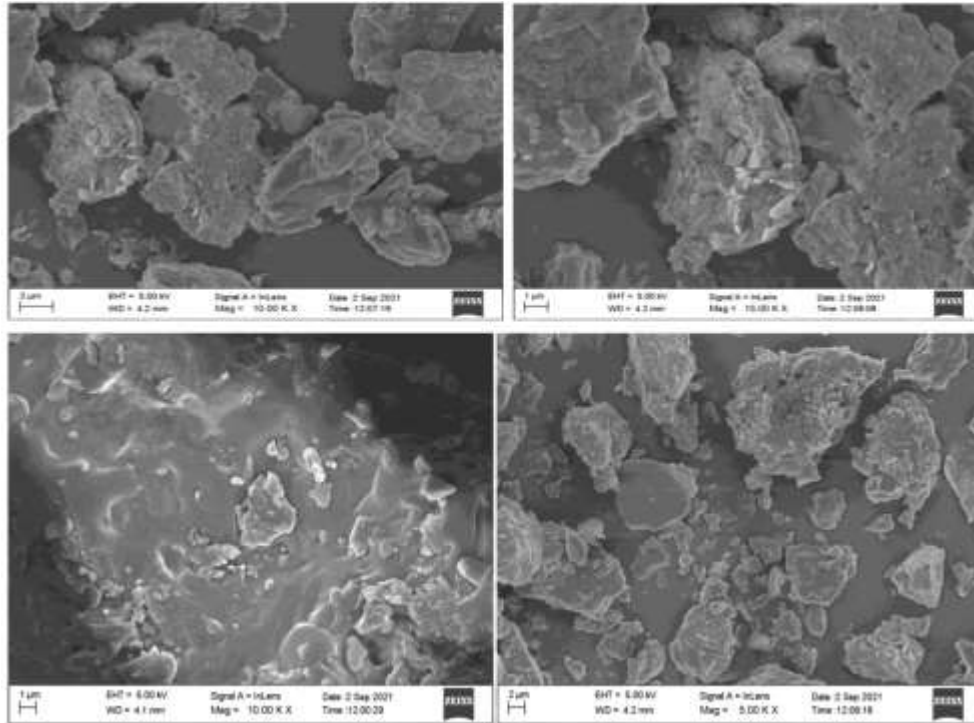


Figure 9: Comparative dissolution profile of pure drug (FENO) and FPM and optimized SD



Scanning Electron Microscopy: Analysis of microscopic characterization of optimized SD (FSD 3) was carried out by an extremely potent optical light, microscopy developed by the Zeiss company (SIGMA VP-FESEM) with a resolving capacity of 1.3 nm and 5 axes motorized stage: X=125 mm, Y= 125 mm).

Figure 10: SEM images of optimized SD batch



From the SEM images Figure 10 it was clear that the optimized solid dispersion has irregular blocky particles with porous morphology.

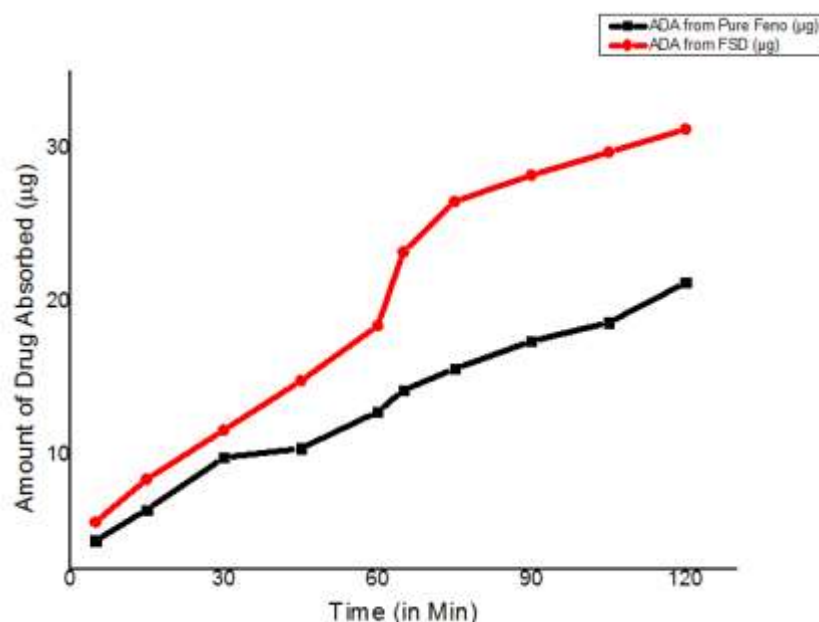
IN VITRO DRUG ABSORPTION STUDY BY EVERTED GUT SAC MODIFICATION METHOD:

The inverted intestinal sac model has proven its significance in studying the in vitro drug absorption and comparison for different formulation factors involved in drug absorption. Aforementioned drug absorption study expected to prove significance of solid dispersion formulation over the pure API (FENO) at the intestinal absorption sites.^[36, 37]

The absorption data confirmed better absorption of drug from optimized FSD 3 in intestinal area as compared to pure FENO. The intestinal absorption of drug from optimized formulation and pure drug was presented in Figure 11. Drug absorption from optimized SD and standard sample were 31.2 µg and 21.2 µg respectively. Result ascertains that intestinal absorption of FENO elevated about 50% higher from SD in comparison to pure FENO. Intestinal permeation is ameliorating due to improvement rate of dissolution of FENO by formulation of SD.

HPMCAS has the ability to enhance solubility of the FENO. Solid dispersions formulated from the drug and polymer was in close contact. Intestinal fluid/buffer solution hydrates the polymer when SD formulations approaches the fluid/buffer which causes swelling of the polymer and ultimately solubilize the adjacent drug particles.

Figure 11: Comparison of In-vitro drug absorption between pure FENO and optimized solid dispersion formulation using everted gut sac method



CONCLUSION

Fenofibrate being poorly aqueous soluble, its dissolution hampers which consequently affects bioavailability of the drug. Low bioavailability limits its therapeutic effects. Poor solubility can delay absorption rate and onset of action. The factors that influence the improvement of solubility may be due to rapid solubilization of the carrier, and/or transformation of the drug from crystallinity to amorphous state. In this research study solid dispersions of FENO were prepared by using HPMCAS as polymer. HPMCAS which is used in the formulation of solid dispersion while come in contact with intestinal fluid swell and dissolve immediately, there by helps dissolving adjacent drug particles. Solid dispersion can be proved as an effective technology to improve bioavailability of Fenofibrate and equally advantageous strategy for other pharmaceutically active compounds which have low aqueous solubility.

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