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Design and Development of Fenofibrate Solid for Solubility Enhancement

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Abstract

This research work is designed to overcome the problems associated with the poorly aqueous soluble drug. Fenofibrate (FENO) being a BCS Class II drug shows low solubility with high permeability. Compatibility of the drug and polymer studies was done by FTIR. Physical mixtures (PM) of the drug and polymer HPMCAS were prepared by the trituration method. Fenofibrate solid dispersions (SD) were prepared by a common solvent technique ascribed to feasibility on a laboratory scale. The physical state of formulations was characterized by powder XRD and TGA. Solubility of a pure drug (FENO), Physical mixture, and SD were 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 a satisfactory range. The maximum cumulative percentage of drug release from the pure drug (FENO), Physical mixture, and SD was found to be 34.5%, 72.1 and 97.2% respectively at 60 minutes. A microscopy (SEM) study 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 a 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 the formulation of SD preferable technique to enhance solubility and enhance dissolution of lipophilic drugs.

Keywords: Design, Development, Fenofibrate, Solid Dispersions, Solubility, Hydroxyl propyl methyl cellulose.

Introduction

The solid dosage form prevails as the most popular dosage form due to ease of production, patient compliance, and good stability although many APIs are hydrophobic. Drug characteristics like poor water solubility and poor membrane permeability are crucial factors among other factors for drug absorption from the 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 with 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 a 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 amplify the level of essential cholesterols, 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 the Biopharmaceutical Classification System and 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 disseverance of the crystal lattice may prove a vital approach to enhance drug solubility as it is in the higher energy state (10-12).

Nowadays, solid dispersion (SD) emerged as a novel technique for the delivery of drugs to overcome the barriers to drug absorption (13). In this technique, one or more active ingredients are 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 (14). 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 types of equipment required concerning many other production methods (15).

In this approach, drug and polymer are 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 is exposed to water leads to form a colloidal dispersion (16). Thermal degradation of drug or carrier can be avoided which makes this method precedence over other manufacturing processes of solid dispersion (17).

Materials and Methods:

Materials

Fenofibrate/$C_{20}H_{21}ClO_4$/2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester was obtained from Aurobindo Pharma Ltd. Hypromellose Acetate Succinate/ $C_{10}H_{22}O_9$ (HPMCAS) was obtained from Wockhardt Limited. Methanol (CH_3OH) was of analytical grade. Disodium hydrogen phosphate, Potassium dihydrogen phosphate, and Sodium chloride were purchased from Merck Pvt. Ltd., Spectrochem Pvt. Ltd. and Thomas Bakers (Chemicals) Pvt. Ltd. respectively.

Methods

Physical mixing

Physical mixtures (PM) of Fenofibrate were prepared by triturating the drug with the polymer/carrier. In the first step required quantity of Hypromellose Acetate Succinate ($C_{10}H_{22}O_{9)}$ was triturated with the help of a 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 (Table 1). $C_{10}H_{22}O_9$ is

used as a polymer to formulate solid dispersions. Methanol is 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 of nearly up to 50^0C 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 a 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

Solubility studies

Solubility studies were carried out by using an orbital shaker. Screw capped bottles containing an 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 a 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

The percentage yield was calculated by the equation below by using a final mass of the product with respect to the total theoretical mass of drug and polymer while sensitive electronic balance by Wensar was used **(**24)

Determination of drug content

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

The percentage of drug content was calculated by the following equation after appropriate dilutions

% Drug content = (Mact/Mt) X 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 was used for a qualitative study of the material. Sharper diffraction peaks indicate more crystalline powder. The 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 2^0 values from 10^0 to 80^0C at a scan rate of 0.025^0/sec(27).

Thermogravimetric analysis

Thermal stability of FENO and optimized solid dispersion was determined by using the Thermogravimetric analyzer STA 449 F5 Jupiter by NETZSCH-Geratebau GmbH. The auto sampler was attached to analyze the decomposition stage and thermal stability of FENO and solid dispersion. Alumina crucible was used for analysis. A heating range of 25^0C to 500^0C with an accelerated heating rate of 10.0 k/min was maintained (28).

In-vitro drug release

The drug release profile of solid dispersions was determined by dissolution rate test apparatus USP Type II by Veego. Phosphate buffer 7.4 was used as dissolution media and temperature was maintained at 37±0.1^{0}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 0.45µm Whatman filter paper, diluted suitably with dissolution media, and were analyzed for the amount of drug dissolved by using UV-Vis spectrophotometer, Systronics at 286 nm(29**,** 30).

Scanning electron microscopy

Surface morphology of prepared solid dispersion can be determined by SEM. Scanning Electron Microscope can determine the shape and porosity of the drug under study. An 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 (31).

Stability study: Accelerated stability study was carried out under exaggerated storage conditions to determine the effect of the environment on product quality. Temperature and humidity were maintained at 40±2°C and 75±5% RH respectively for six months. Samples were kept in closed vials for analysis at a later stage for assay and in-vitro drug release (32, 33).

In vitro drug absorption study

Everted sac modification method:

Intestinal drug absorption studies were performed by everted gut sac method 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 the 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 are 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, the sterilized thread was used to tie both ends of the tissue. This tissue is filled with the test and standard drug solutions. Phosphate buffer p^H 7.4 was used as a medium and constantly stirred with a magnetic stirrer at 50 rotations per minute. Oxygenation was maintained by constant aeration. The temperature was maintained at 37^0C±0.5^0C. 20 mg of pure drug and optimized solid dispersion containing an 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. A similar volume of fresh media was added to maintain sink condition. The concentration of the drug that crossed the intestinal surface was analyzed by using a UV Spectrometer at 286 nm (34, 35).

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

The effect of polymeric insertion of FENO on the water solubility of the drug can be determined by the method discussed above and the results are depicted in Figure 1. Solubility of the 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.

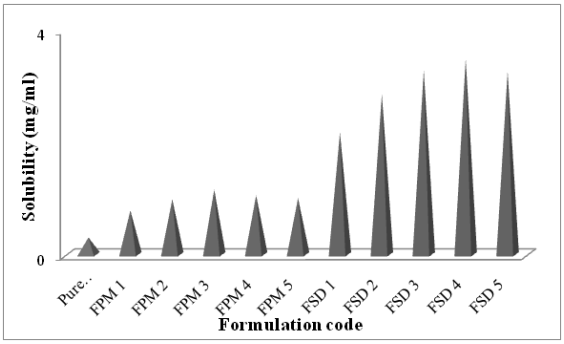

Figure 1: Solubility of pure FENO, FPMs, and FSDs

FT-IR 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 analyzed for any interactions. FTIR offers quantitative and qualitative analysis for different samples. FTIR is an effective analytical instrument for detecting functional groups 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 the pure drug (FENO) shows characteristic 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 a carbonyl group. The IR spectra of the mixture showed that there is no significant interaction had taken place between the drug and carrier. The optimized formulation also didn't show any significant change in spectra. FTIR spectra of pure drug, PM, and optimized SD are represented in Figure 2.

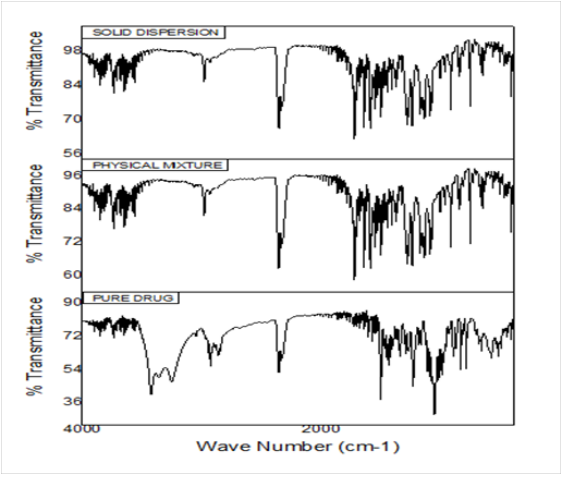

Figure 2: Comparative FT-IR spectra of Pure drug (FENO), Drug + HPMCAS (PM) and Optimized SD

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 the common solvent method (FSDs). Values for the percentage of yield by both methods are depicted in Table 2.

Table No 2: Percentage yield 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

Determination of drug content

Drug content was determined by the method mentioned earlier by using a UV spectrophotometer (Model 2202, Systronics) at λ_{max} 286 nm. Percentage of drug content was summarized in Table 3 and Figure 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 % (Figure 4).

Table 3: Percentage of drug content 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

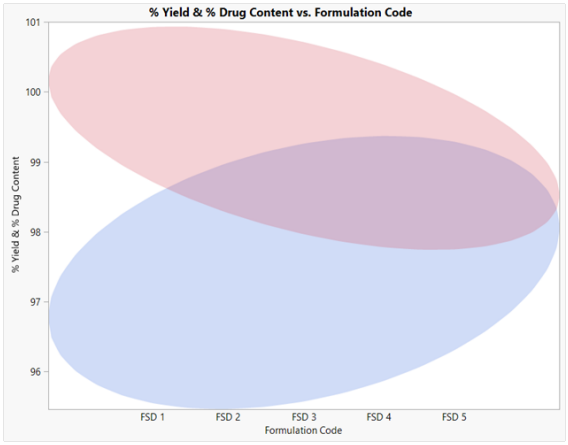

Figure 3: Percentage yield and DC for various batches of Physical mixture (FPMs)

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 a sharp distinct characteristics peak at 2θ diffraction angles

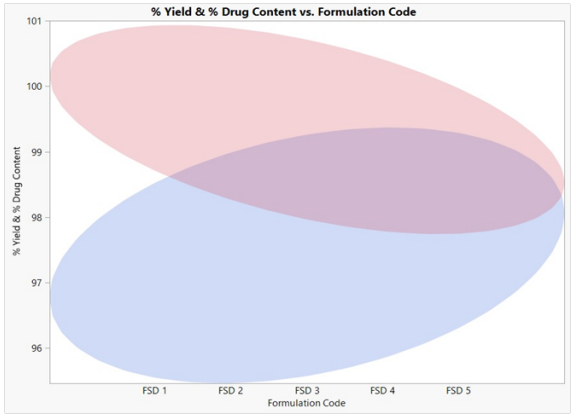

Figure 4: Percentage yield and DC for various batches of solid dispersions (FSDs)

for 14.669^0, 18.714^0, 19.128^0, 20.258^0, 21.082^0, 23.341^0, 25.066^0, 29.255^0. The XRD pattern of FPM showed the curtailed number of peaks and reduced intense peaks than the pure drug. The diffraction patterns of the physical mixture were quite similar to that of pure drug which suggests simple mixing of the drug and carrier. In the case of the optimized batch, the XRD pattern showed the absence of these distinct peaks confirming the conversion of the drug from crystalline to amorphous form.

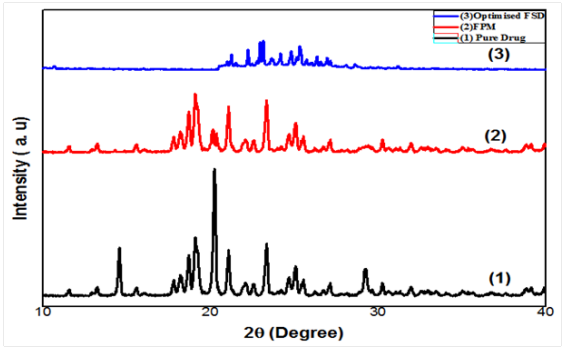

Figure 5: Comparative XRD diffractograms of pure drug (Feno), FPM and optimized SD batch

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

drugs, major weight loss occurred at nearly 380^{0}C. Solid dispersion showed weight loss in two steps: First weight loss was nearly 220^{0}C and the second loss was around 340^{0}C.

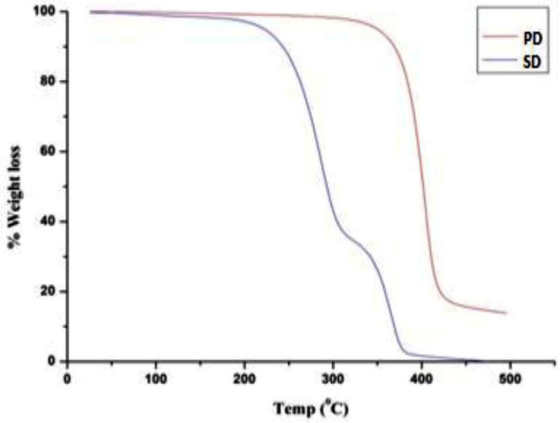

Figure 6: Comparative TGA graph of Pure drug (PD) and optimized solid dispersion

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 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 compared with pure FENO. For FSDs, % drug release was from 87.4-97.2 % for various formulation batches at 60 minutes. 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 a higher % of drug release as compared with pure drug and unveil in Figure 9. The comparative dissolution profile graph evident that the solid dispersion (FSD 3) was able to release maximum drug that is 97.2% at 60 minute.

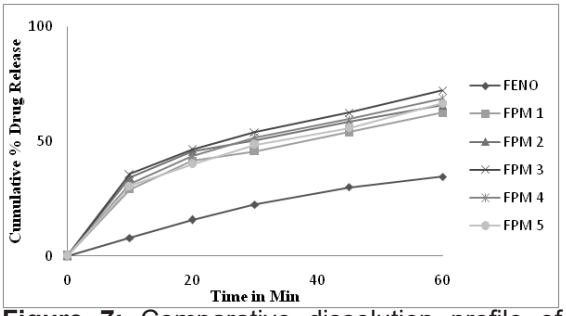

Figure 7: Comparative dissolution profile of pure drug (FENO) and FPMs

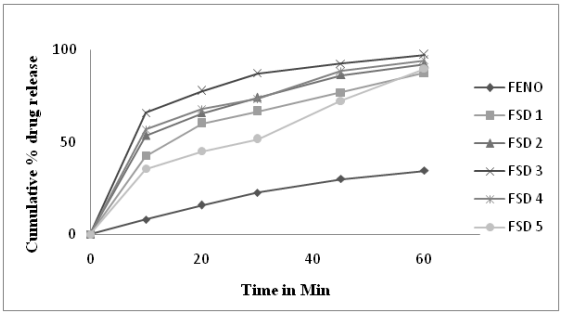

Figure 8: Comparative dissolution profile of pure drug (FENO) and SDs

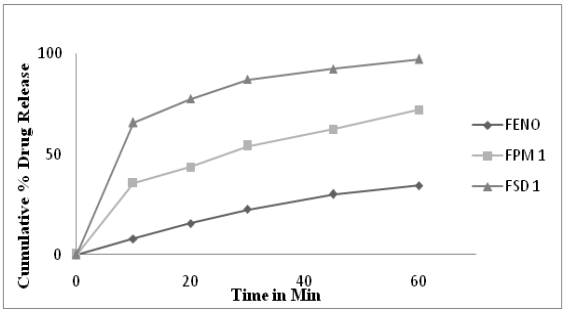

Figure 9: Comparative dissolution profile of pure drug (FENO) and FPM and optimized SD

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-FE-SEM) with a resolving capacity of 1.3 nm and 5 axes motorized stage: X=125 mm, Y= 125 mm). From the SEM images in Figure 10, it was clear that the optimized solid dispersion has irregular

blocky particles with porous morphology.

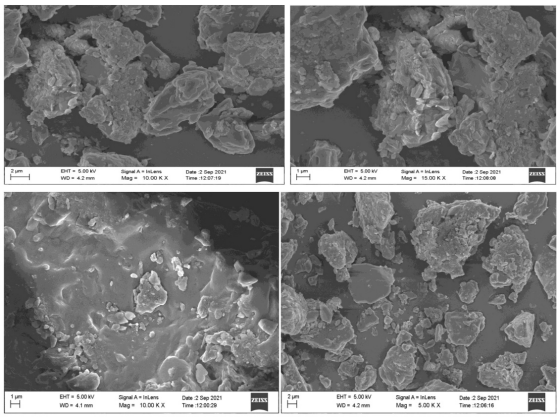

Figure 10: SEM images of optimized SD batch

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. The aforementioned drug absorption study is expected to prove the significance of solid dispersion formulation over the pure API (FENO) at the intestinal absorption sites (36, 37).

The absorption data confirmed better absorption of the drug from optimized FSD 3 in the intestinal area as compared to pure FENO. The intestinal absorption of the drug from the optimized formulation and pure drug was presented in Figure 11. Drug absorption from optimized SD and standard samples were 31.2 µg and 21.2 µg respectively. The result ascertains that intestinal absorption of FENO elevated about 50% higher from SD in comparison to pure FENO. Intestinal permeation is ameliorating due to the improvement rate of dissolution of FENO by formulation of SD. HPMCAS can enhance the solubility of the FENO. Solid dispersions formulated from the drug and polymer were in close contact. Intestinal fluid/buffer solution hydrates the polymer when SD formulations approach the fluid/buffer which causes swelling of the polymer and ultimately solubilizes the adjacent drug particles.

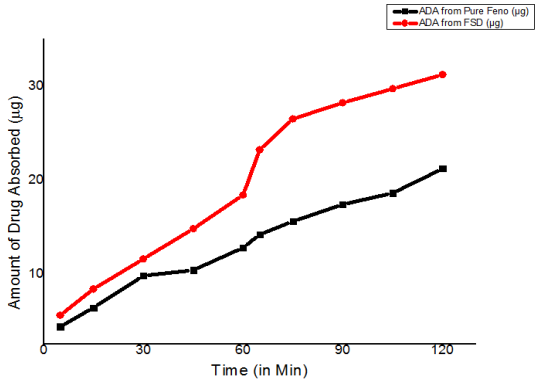

Figure 11: Comparison of In-vitro drug absorption between pure FENO and optimized solid dispersion formulation using everted gut sac method

Conclusion

Fenofibrate being poorly aqueous soluble, its dissolution hampers which consequently affects the bioavailability of the drug. Low bioavailability limits its therapeutic effects. Poor solubility can delay the absorption rate and the 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 an amorphous state. In this research study, solid dispersions of FENO were prepared by using HPMCAS as a polymer. HPMCAS which is used in the formulation of solid dispersion while coming in contact with intestinal fluid swell and dissolves immediately thereby helping to dissolve adjacent drug particles. Solid dispersion can be proved as an effective technique to improve the bioavailability of Fenofibrate and an equally advantageous strategy for other pharmaceutically active compounds which have low aqueous solubility.

Conflict of interests

There is no conflict of interest.

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