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RESEARCH PAPER

DEVELOPMENT AND CHARACTERIZATION OF FENOFIBRATE SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) FOR BIOAVAILABILITY ENHANCEMENT

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Fenofibrate is lipid regulating agent, which is insoluble in aqueous solution and bioavailability after oral administration is low. The objective of present work was to develop a self-microemulsifying drug delivery system (SMEDDS) to enhance the oral bioavailability of poorly water soluble fenofibrate. SMEDDS is a mixture of oil, surfactant, and cosurfactant, which are emulsified in aqueous medium under gentle digestive motility in the gastrointestinal tract. Psuedoternary phase diagrams were constructed to identify the efficient self-emulsifying region. A SMEDDS were further evalauted for its percentage transmittance, emulsification time, drug content, phase separation, globule size, zeta potential, pH, refractive index, X-ray diffraction, Differential scanning calorimetry and in vitro dissolution studies. Optimized formulation was also compared with marketed product in male sprague dawley rats. The pharmacokinetic study exhibited 1.87 fold increase in the oral bioavailability of fenofibrate SMEDDS compared with the marketed product.

Key words: SMEDDS, Fenofibrate, Pharmacokinetic study, Globule size, *In vitro* release studies.

INTRODUCTION

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα). Through activation of PPARα fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII, which leads to a reduction in very low and low density fractions (VLDL and LDL) containing apoprotein B and an increase in the high density lipoprotein fraction (HDL) containing apoprotein AI and AII. Fenofibrate is BCS class-II drug with a log P value of 5.3. Fenofibrate is a lipophilic drug with a low aqueous solubility. Thus, the low oral bioavailability of fenofibrate is due to its solubiliy and dissolution limitations. (Amidon *et al* 1995; Horter and Dressman, 2011).

The oral route has been traditionally preferred for prolonged use. However, oral delivery of poorly soluble drugs creates critical problems during their formulation. Approximately, 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra and intersubject variability and a lack of dose proportionality (Gursoy and Benita, 2004; Abdalla *et al* 2008). Several recent techniques have been used for their solubilization including micronization, complexation, solid dispersion, cyclodextrins, nanoparticles and co-precipitation (Pabreja and Dua, 2001; Dahiya and Tayde, 2013; Prusty, 2014). Recently, much attention has been paid to lipid based formulations with

particular emphasis on self-emulsifying drug delivery systems (SEEDS) to improve the oral bioavailability of lipophilic drugs (Stegemann *et al* 2007; Sugimoto *et al* 1998; Nazzal *et al* 2002). Self-emulsifying drug delivery systems (SEEDS) is the mixture of oil and surfactants, ideally isotropic contaning co-solvents, which emulsify spontaneously to produce fine oil-in-water (*o/w*) emulsions or microemulsions upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids (Gershanik and Benita, 2000; Tang *et al* 2008; Craig *et al* 1995). SEDDS are generally encapsulated either in hard or soft gelatin capsules. Lipid formulations however may interact with the capsule resulting in either brittleness or softness of the shell (Shah *et al* 2012).

The main objective of this study was to formulate an *o/w* microemulsion system of fenofibrate for oral administration. Fenofibrate is available in various doses (45 mg, 54 mg, 100 mg, 145 mg, 160 mg and 200 mg). For our study, we selected 54 mg as working dose to limit the total formulation volume. According to a solubility study and pseudoternary phase diagrams, the formulation composed of various vehicles in different ratios were investigated and droplet size, stability after dilution, pH, percentage transmittance, refractive index, X-ray diffraction, drug content, differential scanning calorimetry and *in vitro* dissolution studies were performed for the optimized formulation. In addition, different formulations were compared by the evaluation of the pharmacokinetics.

MATERIALS

Chemicals and reagents

Fenofibrate was a generous gift from Cadila Healthcare Ltd. (Ahmedabad, India). PEG 400 (polyethylene glycol 400), Tween 80 (polyoxyethylene sorbitan monooleate), Tween 20 (polyoxyethylene sorbitan monolaurate), Span 80 (sorbitan monooleate), Propylene Glycol (PG), Glycerol were obtained from Merck Chemicals (Mumbai, India). Acrysol EL135 (polyoxyl 35 castor oil) were obtained from Corel Pharma (Gujarat, India). Capmul MCM (glycerol mono-dicaprilate) and Capmul PG 8 (propylene glycol monocaprylate) were gifted from Abitec Corporation (USA). Olive oil and Cottonseed oil were obtained from S. D. fine chem (Mumbai, India). Solutol HS 15 (macrogol 15 hydroxystearate) and Kolliphore RH 40(polyoxyl 40 hydrogenated castor oil) were also donated from BASF (Mumabai, India). Labrafil M 1944 CS (oleoyl macragol-6 glycerides) was received as a gift sample from Gattefosse (Mumbai, India). Empty hard gelatin capsule shells were generously donated by Associated capsules Pvt. Limited, (Mumbai, India). Acetonitrile and methanol used in the present study were of high performance liquid chromatography(HPLC) grade. Double distilled water was used throughout the study. All other chemicals were reagent grade.

Animals

Male Sprague Dawley rats (weighing approximately 250±30 g) were used for the pharmacokinetic study. The animals were maintained at temperature (25±2°C), humidity (60±5%) and were supplied food, water and libitum. The animal requirement was approved by the institute animal ethical committee (IAEC) and all experiments were conducted as per the norms of the committee for the purpose of supervision of experiments on animals, India.

METHODS

Solubility study

The solubility of Fenofibrate in various oils, surfactants, and co-surfactants was determined by supersaturation method. An excess amount of Fenofibrate was added into each vial containing 2 ml of selected vehicle. After sealing, the mixture was vortexed using a cyclomixer for 10 min in order to facilitate proper mixing of drug with the vehicles. Then, the formed suspensions were shaken for 24 h in a mechanical shaker (Remi, India) maintained at 37±1°C. After reaching equilibrium, the mixtures were centrifuged at 5000 rpm for 5 min to remove undissolved fenofibrate, followed by filtration through a 0.45 μm millipore membrane filter. The concentration of Fenofibrate was quantified by UV spectrophotometrically (UV-1601, Shimadzu Corporation, Japan) (Shah *et al* 1994).

Psuedo ternary phase diagram

Pseudo ternary phase diagrams of oil, surfactant/Co-surfactant (S_{mix}) and water were developed using the water titration method. On basis of the solubility studies oil, surfactants and co-surfactants were grouped in different combinations for phase studies. Distilled water was used as an aqueous phase for the preparation of Microemulsions. For each phase diagram at a specific ratio of Surfactant and co-surfactant (S_{mix}) were mixed in different ratios (1:1, 1:2, 2:1), a transparent and homogenous

mixture of oil and Smix was formed by vortexing for 5 min. The resultant mixture titrated with distilled water dropwise and observed for transparency and flowability. The concentration of water at which gel formation, turbidity to transparency and tranparency to turbidity transitions occurred was noted. Phase diagrams were plotted using Chemix 3.5 software (Patel and Vavia, 2007).

Preparation of liquid self emulsifying drug delivery system (SMEDDS)

The phase diagrams were constructed at different Km values and the Km value at which high microemulsion region obtained was selected for formulation of Liquid SMEDDS. Formulations were prepared using Labrafil M 1944 CS as oil, Solutol HS 15 as surfactant and Tween 80 as cosurfactant.

In all the formulations, the level of Fenofibrate was kept constant (i.e. 54 mg) Briefly, oil, surfactant and cosurfactant were accurately weighed into glass vials according to their ratios. The amount of SMEDDS should be such that it should solubilizes the drug (single dose) completely. Then, the components were mixed by gentle stirring and vortex mixing, and heated at 60°C in waterbath till Fenofibrate dissolved completely. Then, the mixture was sealed in glass vial and stored at room temperature until used.

Evaluation of liquid self emulsifying drug delivery system (SMEDDS)

Thermodynamic stability studies

Thermodynamic stability study of prepared SMEDDS was determined by carrying Emulsification time, Robustness to Dilution, centrifugation test and freeze thaw cycle.

Emulsification time

Self-emulsifying formulations can be graded for self-emulsification time, dispersibility and appearance as shown in **Table 1**. One milliliter of preconcentrate of SMEDDS was added in to 250 ml of distilled water & contents were stirred using magnetic stirrer at approx 100 rpm and the time required for the formation of emulsion, appearance & dispersibility is noted (Shen and Zhong, 2006).

Table 1. Visual assessment criteria for self emulsification

Grade	Time for self-emulsification	Appearance	Dispersibility
I	within 1 min	Clear or slightly bluish	Rapid emulsification
II	within 2 min	Slightly less clear, bluish white	Rapid emulsification
III	within 3 min	Bright white, similar in appearance to milk	Rapid emulsification
IV	longer than 3 min	Dull, grayish white emulsion, slightly oily appearance	Slow to emulsify
V	longer than 3 min	Large oil droplets present on the surface	Poor or minimal emulsification

Robustness to dilution

Robustness to dilution was studied by diluting the SMEDDS up to 250 times with various dissolution media *viz.* distilled water, 0.1 N HCl and phosphate buffer (pH 6.8). The diluted SMEDDS were stored for 24 h and observed for any signs of phase separation or drug precipitation.

Centrifugation test and freeze thaw cycle

Passed SMEDDS were centrifuged at 3500 rpm for 30 min using digital centrifuge (Remi motors limited). If SMEDDS did not show any phase separation were taken for freeze thaw stress test.

The emulsions were subjected to freeze thawing cycles which include freezing at 4°C and 45°C for 24 h up to 7days. The formulations were then observed for phase separation or precipitation of drug. The formulations which were stable at these temperatures, was selected for further study.

% Transmittance

Liquid SMEDDS was diluted to 250 ml distilled water and observed for any turbidity and % transmittance was measured at 650 nm using UV-vis spectrophotometer (Shimadzu-1800, Japan) against distilled water as a blank.

Electroconductance

Type of emulsion whether *o/w* or *w/o,* can be determined by measure of conductance. For the conductivity measurements, liquid SMEDDS was diluted to 250 ml with a 0.01 N aqueous solution of sodium chloride instead of distilled water.

Percent electroconductance was measured using conductivity meter (CM 200, Welltronix, India).

Globule size, PDI and zeta potential

Liquid SMEDDS was diluted to 100 times with distilled water and globule size, PDI and zetapotential were determined using Dynamic Light Scattering (also known as PCS- Photon Correlation Spectroscopy) with a Zetasizer Nano ZS 90 (Malvern Instruments, U.K.).

Determination of drug content

Drug content was estimated by extracting Fenofibrate from SMEDDS. In brief SMEDDS was dissolved in sufficient quantity of methanol. Solution was sonicated for 10-15 min for extraction of the fenofibrate in methanol and filtered through 0.45 μm millipore membrane filter. The sample was analysed at 286 nm on high performance liquid chromatography (HPLC -Agilent, 1200 series).

Stability studies

Optimized formulation were put into empty hard gelatin capsules (size 0) and subjected to stability studies in to accelerated condition 40±2°C and 75±5% RH up to 6 months. They were withdrawn at specified intervals for analysis over at period of 3 and 6 months for accelerated conditions Drug content of the capsules was analyzed using a previously developed and validated stability-indicating HPLC method. Globule size and dissolution parameter were also studied. (Sahoo *et al* 2014).

In vitro dissolution study

In vitro dissolution study of SMEDDS filled in empty hard gelatin capsules (size 0), Plain fenofibrate drug and marketed product (capsule) were carried out using USP Type-II dissolution test apparatus in 900 ml 0.1 N HCl at 37±0.5°C with 75 rpm speed.

Sample of 5 ml were withdrawn at regular time interval of 5, 10, 15, 30 and 60 min and filtered through 0.45 μm millipore membrane filter. An equal volum of respective dissolution medium was added to maintain the volume constant. The sample was analysed at 286 nm on high performance liquid chromatography (HPLC-Agilent, 1200 series). All measurements were done in triplicate from three independent samples.

Formulation of solid self emulsifying drug delivery system (S-SMEDDS)

Solid Self emulsifying drug delivery systems (S-SMEDDS) were prepared by mixing Fenofibrate liquid SMEDDS with PEG 6000 in 1:1 proportion. In breif Liquid SMEDDS was added dropwise over PEG 6000 contained in glass beaker. After each addition, mixture was homogenized using glass rod to ensure uniform distribution of formulation. Prepared Solid self emulsifying drug delivery system (S-SMEDDS) containing Fenofibrate were evaluated for FTIR, DSC and XRD studies.

FTIR study

FTIR spectrum was recorded for Fenofibrate and Prepared S-SMEDDS using Shimadzu FTIR 8300 spectrophotometer in the region of 4000 to 400 cm^{-1}. Samples were mixed with Potassium bromide (200-400 mg) and compressed in to discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The compressed discs was placed in the light path and spectrum was obtained. After running the spectra, significant peaks relating to major functional groups were identified, sectra of subsequent sample of the same compund were compared with the original.

Differential scanning calorimetry

DSC is very useful in investigation of thermal properties of S-SMEDDS providing both qualitative & quantitative information about the physicochemical state of drug inside S-SMEDDS. Differential Scanning Calorimetry instrument equipped with an intracooler (TA Instruments, SDT-2960, USA). Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder samples was hermetically kept in the aluminium pan and heated at constant rate 10°C/min, over a temperature range of 50°C to 300°C inert atmosphere was maintained by purging nitrogen at the flow rate of 100 ml/min.

Powder X-Ray diffraction studies

XRD patterns of pure fenofibrate and Fenofibrate S-SMEDDS of were obtained using a powder X-ray diffractometer (X'pert, MPD, Philips, Holland). The samples were studied by placing a thin layer of powder in conventional cavity mounts. The scanning rate was 5°/min and diffraction angle (2θ) was 0 to 40°C.

Pharmacokinetic study

The rats were deprived of food but had free access to water 24 h before the day of the experiment. Comparative of pharmacokinetic

parameters of Fenofibrate following oral administration of fenofibrate SMEDDS (test formulation) and marketed product (reference product) were studied in male Sprague Dawley rats. Two group (n = 6) were administered required amount of test and reference formulation were filled in the empty mini hard gelatin capsules with help of funnel provided with Torpac® kit one day prior dosing. Each rat from respective group was administered with single test and reference capsule at the dose 3 mg API per rat using oral gavage needle which contains capsule holding cup.

Approximately 0.20 ml of blood was collected at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24 and 48 h post dose from each rat via retro orbital plexus under light isoflurane anesthesia. Blood samples were placed on ice before collection of plasma. All samples were centrifuged at 5000 rpm for 5 minutes at 4±2°C within 60 minutes of scheduled time to obtain plasma. The plasma samples were stored below -20°C until bioanalysis. Fenofibric acid is the active metabolite after oral administration of fenofibrate. So, fenofibrate would be metabolized *in vivo* to the main active metabolite fenofibric acid by plasma and tissue esterases. In this study, fenofibric acid was analysed using fit for purpose RP-HPLC method.

Pharmacokinetic parameter

Pharmacokinetic parameters for Fenofibric acid were calculated using the non-compartmental analysis tool of the Phoenix WinNonlin software (Version 6.3). The area under the plasma concentration-time curve (AUC_{last}) was calculated by the linear trapezoidal rule from time zero to the time of last quantifiable concentration. The AUC_{inf} were obtained by adding AUC_{last} and the extrapolated area determined by C_{last}/K_{el}, provided there is a well-defined elimination phase. Peak plasma concentration (C_{max}) and time for the peak plasma concentration (T_{max}) were the observed values. The elimination rate constant (K_{el}) were calculated by log-linear regression of concentration data during the elimination phase with a correlation coefficient of >0.8 and the terminal half-life ($t_{1/2}$) were calculated as $0.693/K_{el}$ and were reported if found appropriate. The relative bioavailability of test formulation with respect to reference formulation was calculated and reported. The test to reference exposure ratio was also calculated and reported.

RESULT AND DISCUSSION

Solubility study

One important consideration when formulating a self-emulsifying formulation is avoiding precipitation of the drug. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported in **Figure 1** and **Figure 2**. Labrafil M 1944 CS showed the highest solubilization capacity for Fenofibrate. Thus, for our study we selected Labrafil M 1944 CS as oil, Solutol HS 15 and Tween 80 as surfactant and cosurfactant, respectively.

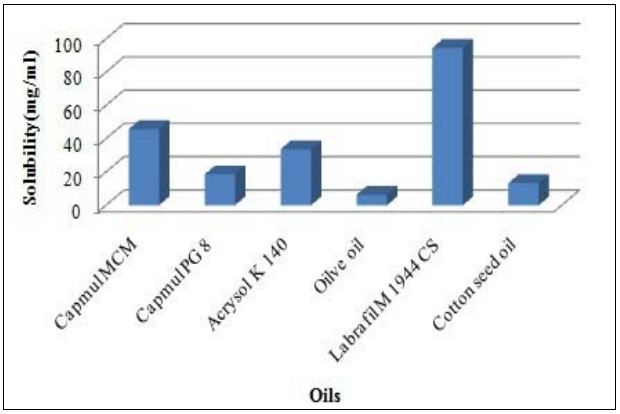

Fig. 1. Solubility in oils

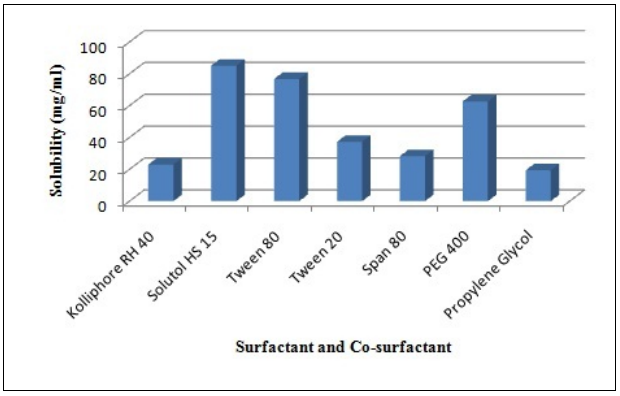

Fig. 2. Solubility in surfactant and co-surfactant

Construction of psuedo ternary phase diagram

A series of SMEDDS were prepared and their self emulsifying properties were observed visually. Psuedoternary phase diagrams were constructed in the absence of fenofibrate to identify the self emulsifying regions and to optimize the concentration of oil, surfactants and cosurfatctant in the SMEDDS formulation. In the present study Labrafil M 1944 CS was tested for phase behavior studies with Solutol HS 15 and

Tween 80 as S_{mix} ratio of 1:1, 2:1, 3:1 (% *w/w*). As shown ternary plot in **Figure 3**. the maximum self emulsifying region found at S/Cos mixture ratio of 3:1 (% *w/w*).

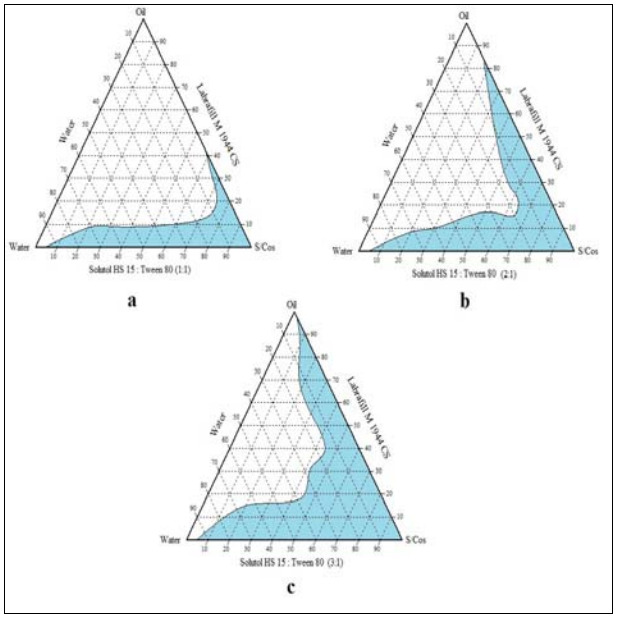

Fig. 3. Phase diagram prepared with the following components:oil-Labrafil M 1944CS, surfactant-Solutol HS 15 and cosurfactant-Tween 80. S_{mix} ratio of a is 1:1, b is 2:1, and c is 3:1

Based on above results, a three component SMEDDS formulation was established containing 22.89% Labrafil M 1944 CS as an oil (on the basis of the solubility study), required target amount of fenofibrate 54 mg, 51.50% Solutol HS 15 as surfactant, and 17.17% Tween 80 as cosurfactant (on the basis of Phase diagrams).

Evaluation of liquid self emulsifying drug delivery systems (SMEDDS)

Thermodynamic stability studies

Physical stability of SMEDDS was essential to its performance, which can be affected by precipitation of the drug. In addition, the formulation having poor physical stability can affects the formulation performance and it also leads to phase separation or cracking. Hence thermodynamic stability studies were performed by performing robustness to dilution, emulsification time, centrifugation test and freeze thaw cycle.

Emulsification time

In SMEDDS, the primary means of self-emulsification assessment is visual estimation. The *in vitro* performance of SMEDDS was visually assessed using the grading system and it was found that, SMEDDS rapidly formed microemulsion within 1 min which was clear and slightly bluish in appearance as per grade A.

Robustness to dilution

After diluting Liquid SMEDDS up to 250 times with various dissolution media *viz.* Distilled water, 0.1 N HCl and phosphate buffer (pH 6.8) and storing for 24 h, it was observed that there was no any signs of phase separation or drug precipitation.

Centrifugation test and freeze thaw cycle

It was observed that, SMEDDS passed the robustness to dilution test hence, further exposed to centrifugation test. SMEDDS did not show any phase separation or cracking after centrifugation test formulation was taken for freeze thaw stress test. There is no cracking, phase separation or precipitation after freeze thaw stress test which showed SMEDDS of good stability.

% Transmittance

% Transmittance of reconstituted liquid SMEDDS was found to be 98.04±1.26% (mean±SD, n = 3). These results indicate the high clarity of microemulsion. This may be due to smaller globule size and zeta potential of formulation. Higher globule size may reduce the transparency of microemulsion and thereby decrease the value of % Transmittance.

Electroconductance

The type of emulsion was confirmed by using electroconductivity test. Electroconductance of reconstituted liquid SMEDDS was found to be 98.47±0.51 μs/cm (mean±SD, n=3). which indicate that the continuous phase was water, which signified the formation of *o/w* micro emulsion.

Globule size, PDI and zeta potential

The globule size of microemulsion is a crucial factor in self emulsification performance because it determines the rate and extent of drug release as well as absorption. The charge of oil globules of SMEDDS is another property that should be assessed for increased absorption.

An ideal SMEDDS should be widely distributed with globule size less than 200 nm. Results of Globule size with PDI and Zeta potential are shown on **Figure 4** and **Figure 5** respectively.

		Size (d.nm):	% Intensity	Width (d.n...
Z-Average (d.nm): 27.84	Peak 1:	24.66	83.6	8.294
PdI: 0.369	Peak 2:	728.4	11.6	272.5
Intercept: 0.749	Peak 3:	4714	4.8	784.2
Result quality : Good				

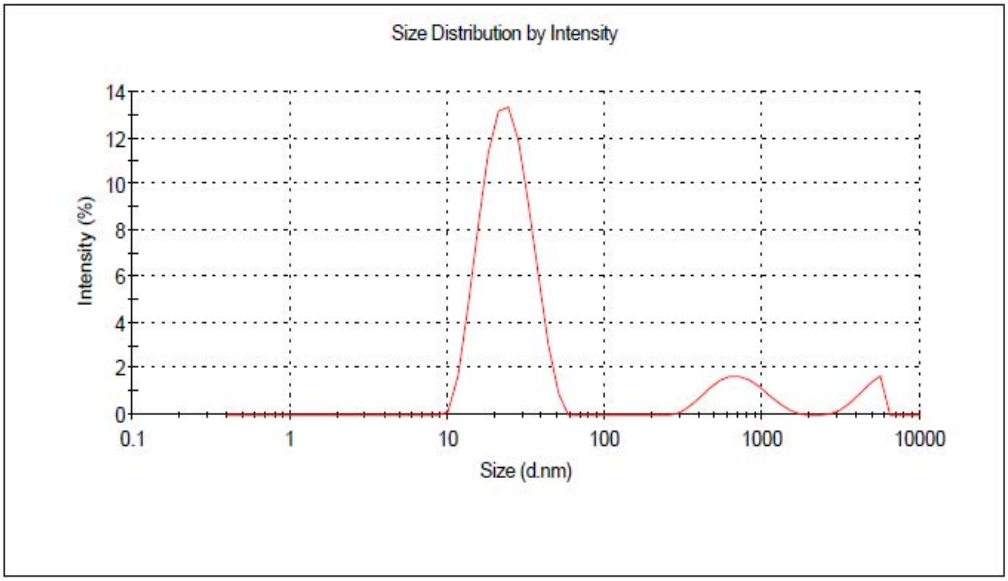

Fig. 4. Globule size of fenofibrate SMEDDS

		Mean (mV)	Area (%)	Width (mV)
Zeta Potential (mV): -9.16	Peak 1:	-9.16	100.0	6.09
Zeta Deviation (mV): 6.09	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.0122	Peak 3:	0.00	0.0	0.00
Result quality : Good				

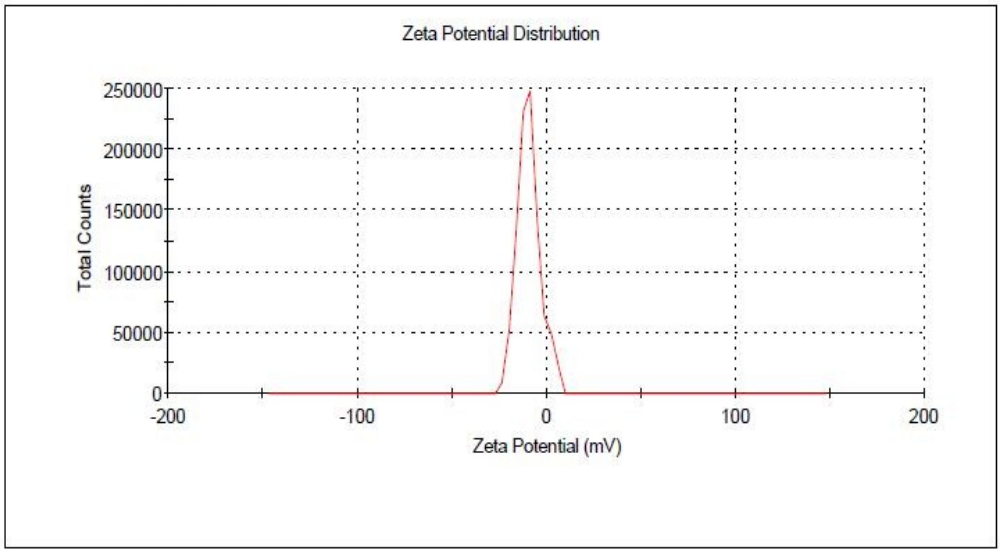

Fig. 5. Zeta Potential of fenofibrate SMEDDS

An optimized SMEDDS formulation gave smallest globule size Globule size was found to be 27.84 nm with polydispersity index 0.369. The charge in SMEDDS was negative due to free fatty acids; zeta potential of optimized formulation was found to be -9.16±6.09 mV. In general, zeta

potential value of ±30 mV is sufficient for the stability of microemulsion.

Determination of drug content

The drug content of optimized formulation was found to be 101.5±1.36 % (mean±SD, n=3).

Stability studies

The developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. **Table 2** gives the results of the evaluation test conducted on stability sample.

Table 2. Stability study data at accelerated condition 40±2°C and 75±5% RH

Parameter	Initial	3 months	6 months
Assay (%)	101.53±1.32*	99.10±2.14	96.8±1.12
Dissolution(%drug release)	101.30±2.49	100.50±2.74	95.60±2.61
Globule Size (nm)	27.84±2.15	21.2±1.89	25.4±1.78

**The values are expressed as mean ± SD (n=3)*

The formulation was found to be stable for accelerated condition 40±2°C and 75±5% RH up to 6 months. There was no significant change in the drug content, dissoluton or globule size of the resultant emulsion. It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. Furthermore, the formulation was found to show no phase separation, drug precipitation. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules.

In vitro dissolution study

Figure 6 showed cumulative percent drug release of fenofibrate SMEDDS and plain fenofibrate and marketed product in 0.1 N HCl. As shown in **Table 3** drug released from SMEDDS was found to be significantly higher as compared to plain fenofibrate drug and marketed preparation. More than 70% drug released from fenofibrate SMEDDS in 30 min which is faster than marketed product. This could be attributed due to solubilization of drug in SMEDDS preparation, which is major concern in BCS class-II drugs. Pure Fenofibrate showed less than 20 % release at Q point (60 min).

Table 3. *In vitro* dissolution data

Product	% Cumulative drug release
Fenofibrate SMEDDS	99.60±1.25*
Plain drug	12.40±2.16
Marketed product	79.59±2.64

**The values are expressed as mean ± SD (n=3)*

FTIR study

Figure 7 and **Figure 8** showed FTIR spectrum of fenofibrate and fenofibrate S-SMEDDS respectively. The compatibility of drug and

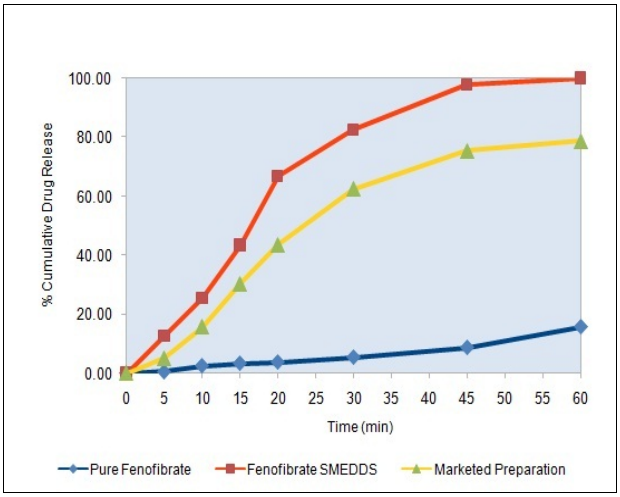

Fig. 6. % Cumulative drug release of fenofibrate SMEDDS, pure fenofibrate and marketed product in 0.1 N HCl

excipients used in the S-SMEDDS were characterized by their FTIR spectra. The FTIR spectrum of pure fenofibrate has four characteristic peaks at 2997 cm^{-1}, 1746 cm^{-1}, 1658 cm^{-1} and 1597 cm^{-1} for O-H stretching vibration, C-H vibration, ester stretching vibration and lactone carbonyl functional group respectively. Appearance of all these peaks and absence of any new peaks in the S-SMEDDS formulation indicate no chemical interaction between the drug and excipients.

Differential scanning calorimetry

DSC was used to assess the thermal behavior of the Pure drug (Fenofibrate) and its S-SMEDDS prepared. In Figure 9, DSC thermogram of Fenofibrate shows a single sharp characteristic endothermic peak (Tpeak = 84.39°C) corresponding to its melting, indicating its crystalline nature and a single peak indicates that the drug sample is free from impurities. However, the characteristic endothermic peak

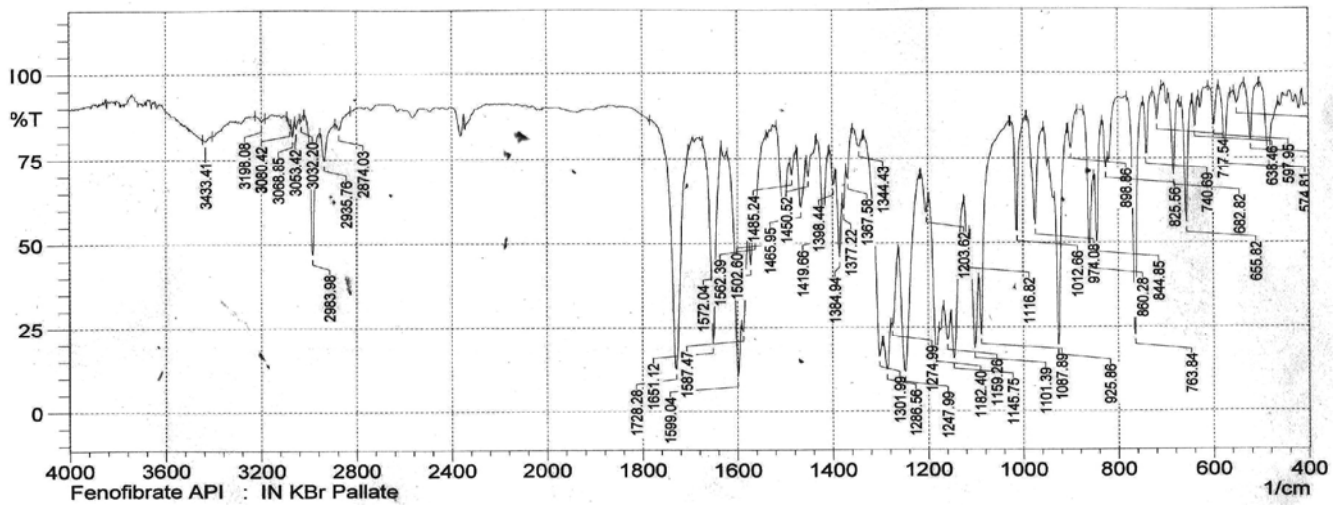

Fig. 7. FTIR Spectra of pure fenofibrate

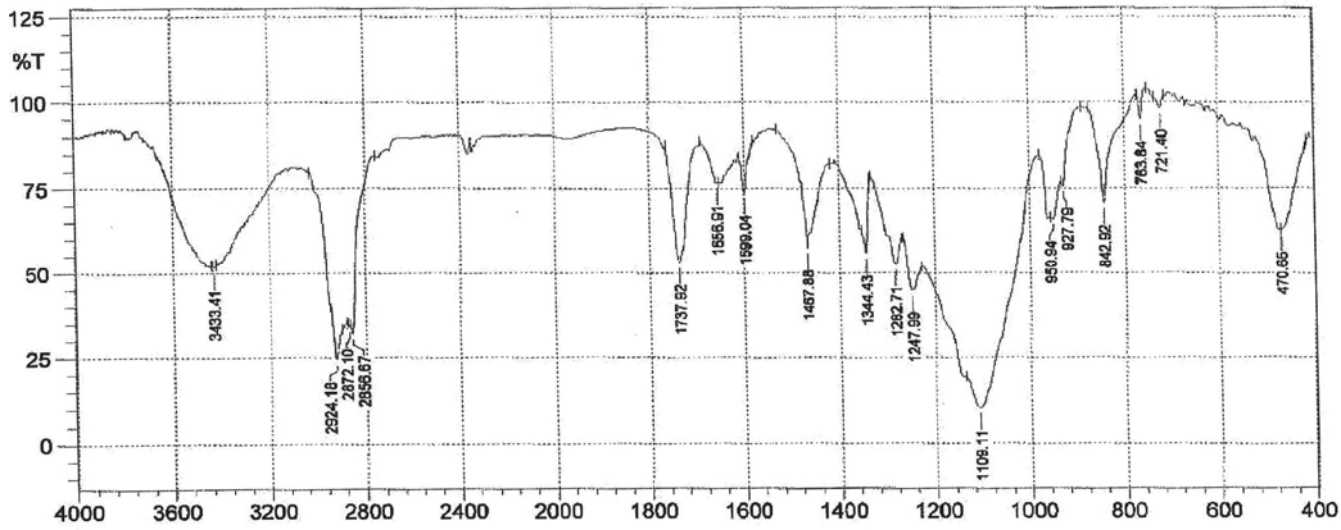

Fig. 8. FTIR Spectra of Fenofibrate S-SMEDDS

corresponding to drug melting was broadened and shifted toward lower temperature with reduced intensity in the S-SMEDDS formulation. This could be attributed to change of crystalline nature of drug in the S-SMEDDS (solubilization of Fenofibrate in SMEDDS).

Powder X-Ray diffraction studies

XRD patterns of pure fenofibrate and fenofibrate S-SMEDDS is shown in **Figure 10**. The diffraction pattern of Fenofibrate revealed several sharp high intensity peaks at diffraction angles (2θ) at 14.3°,16.1°, and 22.2° suggesting that the drug existed as crystalline material. The XRD pattern of Fenofibrate S-SMEDDS showed considerable reduction in the peak intensity compared with characteristic peaks of pure fenofibrate. This diminished peak suggests fenofibrate in S-SMEDDS contained mostly in amorphous form. This marked reduction in peak intensities provides an explanation for the significant increase in the dissolution rates and hence bioavailbility by S-SMEDDS formulation.

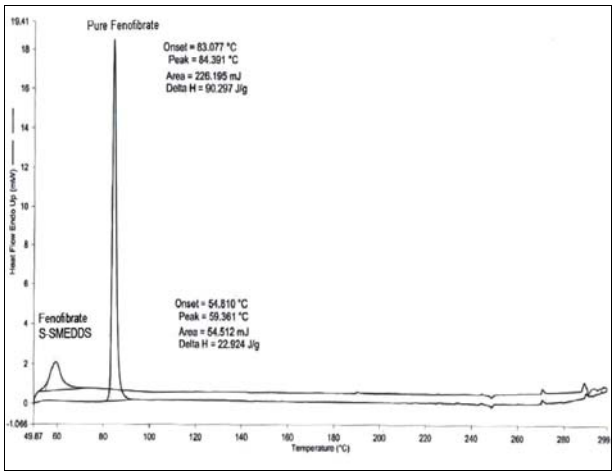

Fig. 9. DSC thermogram of pure fenofibrate and fenofibrate S-SMEDDS

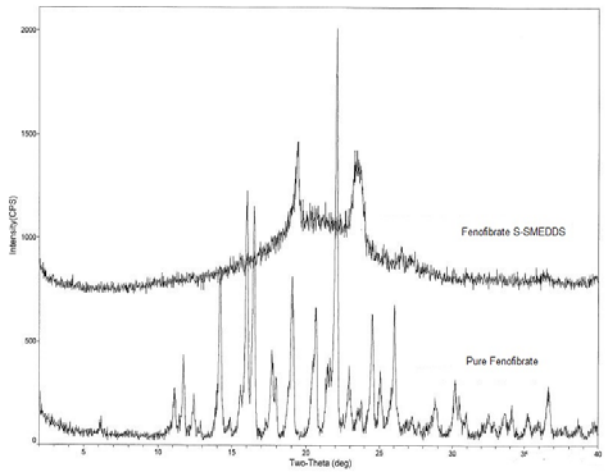

Fig. 10. XRD spectra of pure fenofibrate and fenofibrate S-SMEDDS

Pharmacokinetic study

The comparative plasma concentration versus time profiles for both test (fenofibrate SMEDDS) and reference formulation (marketed product) are presented in **Figure 11**. The mean (mean ± SD; n = 6) pharmacokinetic parameters of fenofibric acid following oral administration of test and reference Formulation in Sprague Dawley rats are given in **Table 4**.

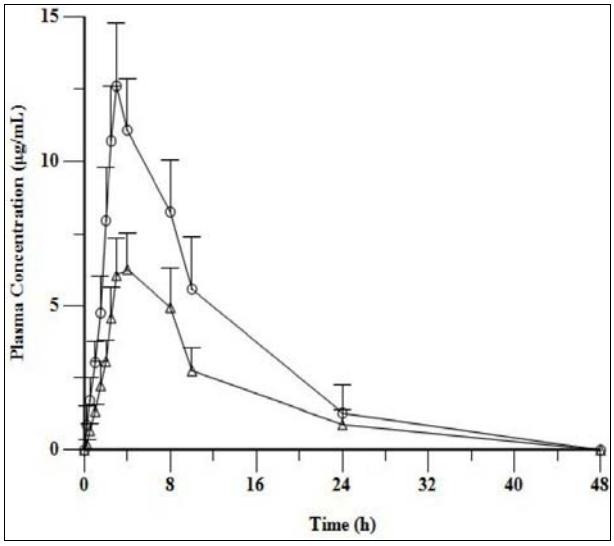

Fig. 11. Mean plasma concentration-time profiles of fenofibric acid in male Sprague Dawley rats

Table 4. Pharmacokinetic parameters of fenofibric acid following oral administration of test and reference formulation in Sprague Dawley rats

Treatment/Group	T_{max} (h)	C_{max} (µg/ml)	AUC_{last} (µg*h/ml)	T/R ratio	F[a]
Test formulation (SMEDDS)	3.17±0.408	13.3±1.49	129±28.2	1.87	18
Reference formulation (Marketed product)	4.33±1.86	7.11±0.762	68.9±10.5	NA	NA

[a]*Nominal doses and AUC_{last} of test and reference were used to calculate relative bioavailability(F); T/R: Test to reference ratio was calculated by AUC_{last} of test/AUC_{last} of reference; NA: not applicable*

Following oral administration of test formulation (SMEDDS) filled capsules in male Sprague Dawley rats, the mean time to reach maximum plasma concentration (T_{max}) was found to be 3.17 h. The plasma exposures (C_{max} and AUC_{last}) were found to be 13.3 µg/ml and 129 µg*h/ml, respectively. Following oral administration of reference formulation the mean time to reach maximum plasma concentration (T_{max}) was found 4.33 h. The plasma exposures (C_{max} and AUC_{last}) were found 7.11 µg/ml and 68.9 µg*h/ml. The test to reference (T/R) ratio was found 1.87, suggesting higher exposure of test compared to reference formulation.

CONCLUSION

In this study, fenofibrate SMEDDS of were prepared and evaluated for their *in vitro* and *in vivo* behavior. Prepared liquid SMEDDS was thermodynamically stable with good self emulsification efficiency and having globule size in nanometric range which may be physiologically stable. The optimized formulation consisting of fenofibrate (54 mg), Labrafil M 1944 CS (22.89% *w/w*), Solutol HS 15 (51.50% *w/w*) and Tween 80 (17.17% *w/w*) exhibited faster release profiles with a rapid rate of emulsification. The optimized SMEDDS formulation of fenofibrate showed a significant increase in oral absorption compared to the marketed product. The exposure (C_{max} and AUC_{last}) of developed SMEDDS was found to be comparatively higher (1.87 fold) than reference marketed product indicating better rate and extent of absorption than reference formulation. Thus, SMEDDS can be regarded as a novel and commercially feasible alternative to current fenofibrate formulations. However, further studies in the higher animals and human beings need to be performed before this formulation can be commercially exploited.

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