

SOLUBILITY ENHANCEMENT OF FENOFIBRATE, A BCS CLASS II DRUG, BY SELF EMULSIFYING DRUG DELIVERY SYSTEMS

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ABSTRACT

The present work was aimed at the enhancement of solubility of Fenofibrate a BCS class II drug by Self Emulsifying Drug Delivery systems (SEDDS). The solubility of Fenofibrate in various excipients was determined. The excipients were screened for maximum solubility and compatibility. SEDDS formulations of Fenofibrate were developed using different Oils, Surfactants and Co-Surfactant combinations. Pseudoternary phase diagrams were drawn using Triplot software and by applying Pseudoternary phase diagrams, microemulsification area was evaluated.

Formulations were screened based on visual observations and phase diagrams. Seven formulations were selected for further evaluations like stability, effect of dilution, freeze-thawing, emulsion droplet size and zeta potential. Among the seven formulations three were optimized and In-Vitro dissolution was performed. The dissolution rate of SEDDS was compared with plain Fenofibrate (API). The study confirmed that the solubility and dissolution rate of Fenofibrate were remarkably increased when compared to that of plain drug. Hence SEDDS formulations can be a potential alternative to traditional oral drug delivery systems of Fenofibrate to improve its bioavailability

KEY WORDS: Fenofibrate, surfactants, co-surfactants, lipid vehicles, SEDDS, Pseudoternary phase diagrams.

INTRODUCTION

An increasing number of recently discovered drug substances exhibit poor water solubility and hence low absorption after oral administration. Approximately 35-40% of all new chemical entities discovered suffer from poor aqueous solubility. The properties of new chemical entities (NCE) shifted towards higher molecular weight and increasing lipophilicity, resulting in decreased aqueous solubility. Due to poor aqueous solubility, many drug candidates become unsuccessful to reach the market in spite of exhibiting potential pharmacodynamic activity. Further, poorly water soluble drugs are administered at much higher individual doses than actually desired to achieve necessary plasma levels.

The therapeutic efficacy and bioavailability of any drug depends upon the solubility of drug. Solubility of drug is one of the important parameter to attain the desired concentration of drug in systemic circulation for the pharmacological response. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation.

Various solubility enhancement techniques are investigated such as particle size reduction¹, pH adjustment², co-solvency³, complexation⁴, solid dispersions⁵, SEDDS⁶ etc. However each technique has its own advantages and limits. Among all these techniques SEDDS appear to be potential method for the solubility enhancement due to its ease of formulation and evaluation.

SEDDS are well known for their potential to enhance the solubility of hydrophobic drugs and consists of isotropic mixtures of an oily vehicle, surfactants, co-surfactants and thickening agents. SEDDS require very less energy to emulsify, and so they undergo spontaneous emulsification in the lumen of gut up on dilution in aqueous phase under the gentle agitation provided by the gastrointestinal motility. The microemulsions so formed are easily absorbed from the gastrointestinal tract through the villi as chylomicrons. Selection of suitable SEDDS depends on (1) solubility of Fenofibrate in various excipients (2) area of self-emulsifying region in the phase diagram (3) time required for self-emulsification (4) droplet size distribution of emulsion (5) thermodynamic stability of emulsions^{7,8}.

Fenofibrate is a lipid-regulating agent and is chemically a fibric acid derivative. Fenofibrate is a Biopharmaceutics Classification System (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 solubility and dissolution limitations. The absorption of Fenofibrate is increased by the presence of food in the gastro intestinal tract. Hence SEDDS seemed to be an option for enhancement of solubility of Fenofibrate.

Fenofibrate is available in various doses (45 mg, 54 mg, 100 mg, 145 mg, 160 mg, and 200 mg). For our study we selected 50 mg as the working dose to limit the total formulation volume. The main objective of the study was to enhance the solubility of Fenofibrate by formulating an optimal SEDDS formulation and to evaluate various *in-vitro* characteristics.

MATERIALS AND METHODS

Materials

Fenofibrate was obtained as a gift sample from Hetero Labs (Hyderabad, India). The following material were donated by Gattefosse (Mumbai, India) - Labrafac Lipophile 1349, Labrafac PG, Peceol, Labrasol, Cremophor RH 40, Transcutol HP, Capryol 90, Lauroglycol 90, Plurol Oleique. Tween 80, PEG 400, and castor oil was bought from Merck (Mumbai, India). Methanol, Acetonitrile, water, and potassium bromide used in the present study were bought from Merck (Mumbai, India) and were of HPLC grade. Deionized water was prepared by Milli-Q purification system from Millipore pvt India. Empty hard gelatin capsule shells were generously donated by Associated capsules Pvt Ltd., India

Methods

Solubility studies

Solubility of Fenofibrate in various lipid vehicles and surfactants were determined by super saturation method. The supersaturated solutions of Fenofibrate in various excipients was prepared by taking 1 gram of excipients in a cap vial, to that excess of Fenofibrate (500 mg) was added. The resultant mixture was immediately cyclomixed on a vortex mixer for 5 minutes. The supersaturated solution was then left for equilibration at room temperature in rotary shaker at a speed of 100 rpm for 72 hours¹¹.

The supersaturated solutions were then centrifuged at a speed of 3000 rpm for 15 minutes to separate the undissolved drug from the supernatant liquid. Aliquots of supernatant liquid were withdrawn using a micropipette and diluted accordingly. The concentration of drug in solution was determined by HPLC.

HPLC analysis

The concentration of Fenofibrate in the samples was determined by HPLC analysis. The HPLC analysis system consisted of Shimadzu HPLC (Tokyo, Japan). The chromatographic conditions maintained were

Column - Phenomenex Luna C-18

Column temperature - Room temperature

Flow rate - 1ml/min

Mobile phase - Acetonitrile : water (70:30) pH-2.5

Retention time - 20 ± 0.5 min

Type of flow - Isocratic

UV wavelength - 286 nm

Pseudoternary Phase Diagrams

Pseudoternary phase diagrams of oil, surfactant/ co-surfactant (S/CoS), and water were plotted using the water titration method. The mixtures of oil and S/CoS at fixed ratios were diluted with water in a drop wise manner. For each phase diagram at a specific ratio of S/CoS (ie, 1:1, 2:1, 3:1, and 4:1 wt/wt), a transparent and homogenous mixture of oil and S/CoS was formed by vortexing for 5 minutes. Then each mixture was titrated with water and visually observed for phase clarity and flowability. The concentration of water at which gel formation, turbidity-to-transparency and transparency-to-turbidity transitions occurred was noted. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. Phase diagrams were then constructed using Tri plot V 4.1.2 software^{10,11}.

Preparation of SEDDS Formulations

A series of SEDDS were prepared using Cremophor RH 40 as surfactant, Labrasol and Transcutol HP as co-surfactant and Labrafac Lipophile WL 1349 as the oil (Table-1). In all the formulations, the concentration of Fenofibrate was kept constant (i.e, 5% wt/wt of the total formulation weight). Accurately weighed Fenofibrate was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by vortex mixing for 5 min, until Fenofibrate was perfectly dissolved. The mixture was stored at room temperature until further use.

Emulsification time and stability studies of formulations

Evaluation of self-emulsifying properties of SEDDS formulations was performed by visual assessment. The formulations were categorized on time of emulsification, clarity and stability. The 0.1 ml of preconcentrate of SEDDS was added into 250 ml of distilled water and the contents were stirred using magnetic stirrer at ~ 100 rpm and the time required for the formation of emulsion is noted¹¹.

The resulting mixture was evaluated for precipitation and phase separation at various time intervals (2, 4, 6, 8, 12, 24 hours). The formulations were then categorized as

Grade I: Rapidly forming emulsion having a clear or bluish appearance.

Grade II: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade III: Fine milky emulsion that formed within 2 minutes.

Grade IV: Dull, grayish white emulsion and slow to emulsify

Effect of Dilution

Formulations were diluted with excess of water, 0.1 N HCl and phosphate buffer (pH 6.8) and was stored for 24 hours. No precipitation or phase separation was found which indicate that all the formulations were stable on dilution.

Freeze thawing

Freeze thawing was performed to evaluate the thermodynamic stability of the formulations. The emulsions were subjected to 4 Freeze-Thawing cycles which include freezing at -20°C for 4 hours and thawing at +25°C for 4 hours. Each cycle followed by centrifugation at 3000 rpm for 15 min. The formulations were observed for phase separation and drug precipitation. The

formulations which were thermodynamically stable were only selected for studies.

Emulsion droplet size analysis

0.1ml of each formulation was diluted in 250 ml of water and stirred gently; the resulting solution was subjected to size analysis using Malvern Mastersizer with a particle size measurement range of 0.02 to 2000 μ m. All studies were repeated in triplicate.

In Vitro Dissolution Studies

The *in-vitro* drug release test was performed in 900 ml of HCl media at pH 1.2 using US Pharmacopeia dissolution apparatus II. The bath temperature was maintained at $37 \pm 0.5^\circ\text{C}$; the paddle speed was maintained at 50 rpm. The SEDDS formulations were filled into hard gelatin capsules (0 sizes) and used for drug release studies; results were compared with those of plain Fenofibrate. At regular intervals of time, a 5-mL sample of medium was taken out and subjected to drug analysis using UV spectroscopy. The removed volume was replaced each time with 5 ml of fresh medium.

RESULTS AND DISCUSSIONS**Solubility studies**

The excipients used in the SEDDS should show maximum solubility for the drug to ensure maximum solubilization of the drug and to prevent precipitation of the drug in gut lumen. The solubility results of the Fenofibrate in various lipid vehicles, surfactants and co-surfactants are reported in the figures 1, 2 and 3

The maximum solubility of Fenofibrate in oils was found to be maximum in Labrafac Lipophile WL 1349 and in surfactants the highest solubility was found in Labrasol and in co-surfactants the highest solubility was in Transcutol HP.

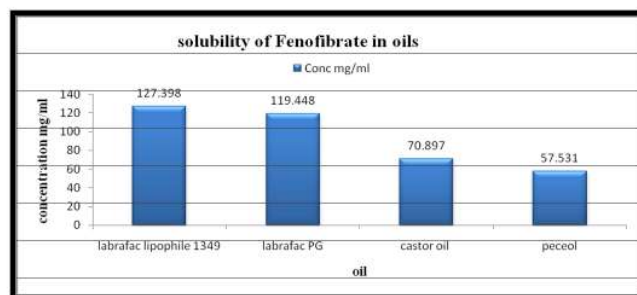


Figure 1: solubility of Fenofibrate in oils

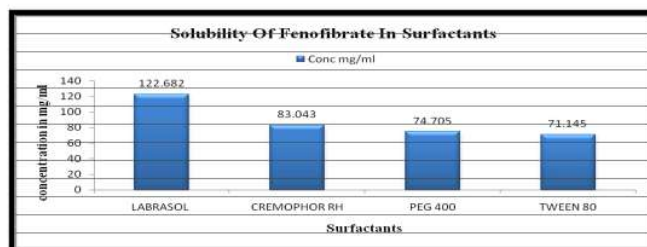


Figure 2: solubility of Fenofibrate in surfactants

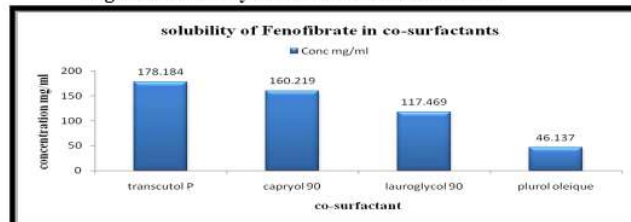


Figure 3: solubility of Fenofibrate in co-surfactants

Screening and compatibility studies of excipients

Excipients were selected in such a way the excipients showed maximum solubility for Fenofibrate. The drug excipient compatibility studies were also performed by comparing the IR spectrums of plain Fenofibrate and Fenofibrate plus excipient. Only

those excipients were selected which showed no significant shifts in the characteristic peaks ($3192, 2984, 1730, 1693, 683 \text{ cm}^{-1}$) of Fenofibrate. The excipients include Labrafac Lipophile WL 1349, Labrasol, Transcutol HP, and Cremophor RH 40. The IR spectrum of drug and excipients are shown in figure 4

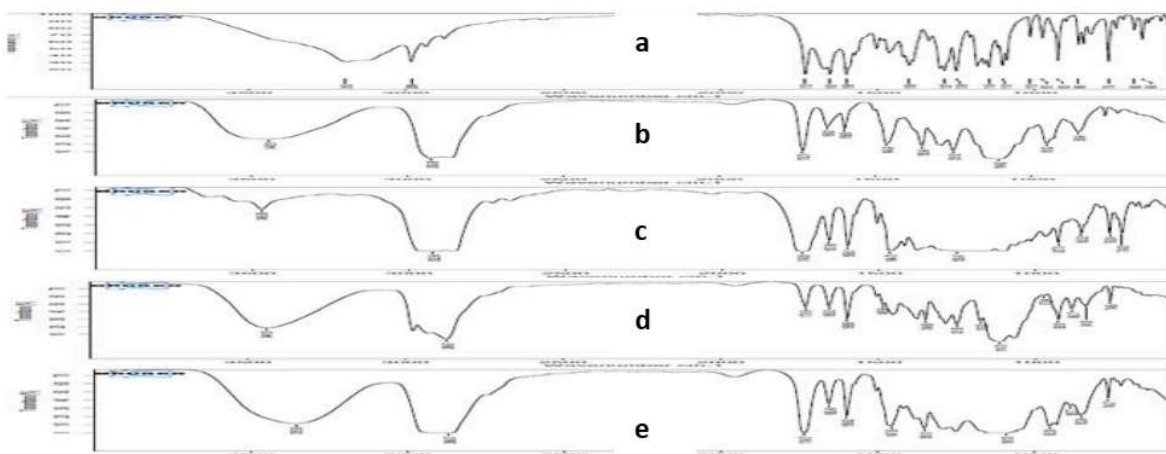


Figure 4: IR spectrums of plain Fenofibrate (a) and Fenofibrate in Labrasol (b), Labrafac Lipophile WL 1349 (c), Transcutol HP (d) and Cremophor RH 40 (e).

Preparation of formulations

From the solubility and IR spectroscopy studies, the formulations were formulated for the further studies. The formulations and their compositions are given in table-1.

Table -1: Table showing various formulations and their compositions selected

S.NO.	Formulation Name	Surfactant	Co-surfactant	Surfactant – cosurfactant ratio (S:Co)	Oil
1	LLCL11	Cremophor RH 40	Labrasol	1:1	Labrafac Lipophile WL 1349
2	LLCL12	Cremophor RH 40	Labrasol	2:1	Labrafac Lipophile WL 1349
3	LLCL13	Cremophor RH 40	Labrasol	3:1	Labrafac Lipophile WL 1349
4	LLCL14	Cremophor RH 40	Labrasol	4:1	Labrafac Lipophile WL 1349
5	LLCT11	Cremophor RH 40	Transcutol HP	1:1	Labrafac Lipophile WL 1349
6	LLCT12	Cremophor RH 40	Transcutol HP	2:1	Labrafac Lipophile WL 1349
7	LLCT13	Cremophor RH 40	Transcutol HP	3:1	Labrafac Lipophile WL 1349
8	LLCT14	Cremophor RH 40	Transcutol HP	4:1	Labrafac Lipophile WL 1349

Pseudoternary Phase Diagrams

SEDDS should undergo spontaneous emulsification with only gentle agitation, upon their introduction into aqueous media. Surfactant and cosurfactant get preferentially adsorbed at the oil-water interface. This decreases the free energy required for the emulsion formation and consequently improves the thermodynamic stability of the microemulsion. Therefore, the selection of oil surfactant and co-surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion.

In the present study pseudo ternary phase diagrams were constructed against oil, water and surfactant/ co-surfactant using water titration methods. The results are shown in the figures 5 and 6.

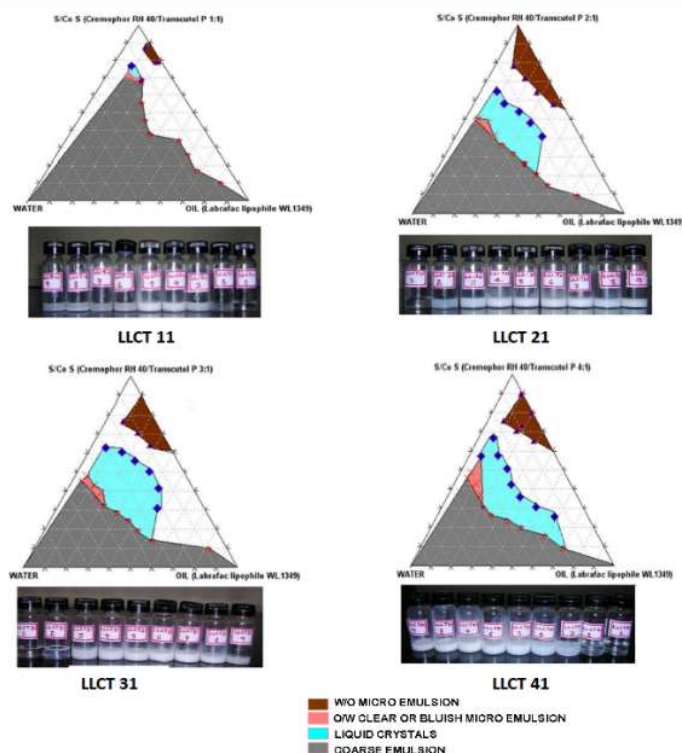


FIGURE 5: pseudo ternary phase diagrams of formulation LLCT at different surfactant/co-surfactant ratios (1:1, 2:1, 3:1, 4:1). The light orange color indicates the micro emulsion region.

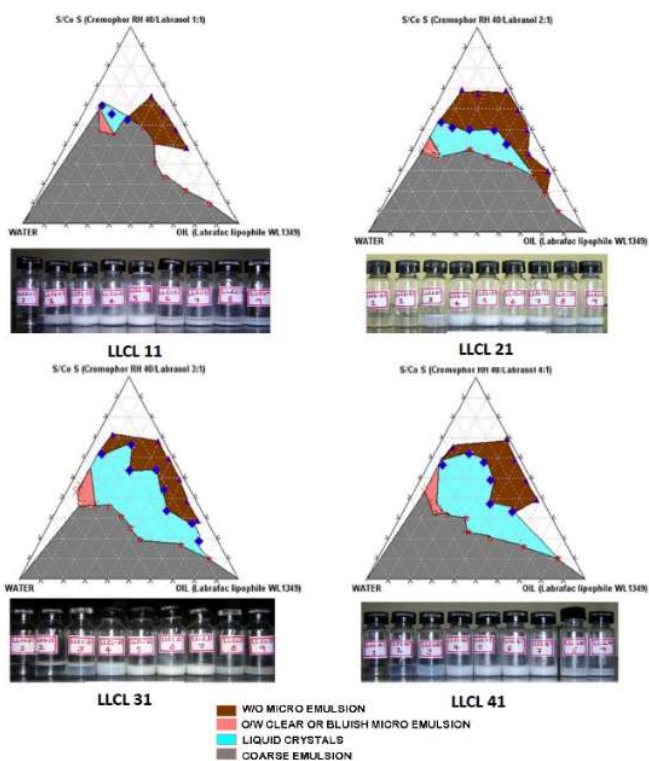


FIGURE 6: pseudo ternary phase diagrams of formulation LLCL at different surfactant/co-surfactant ratios (1:1, 2:1, 3:1, 4:1). The light orange color indicates the micro emulsion region.

From the phase diagrams it is clear that the formulations LLCT21-2, LLCT31-2, LLCT41-2, LLCL21-2, LLCL31-2, LLCL31-3 and LLCL41-2 were selected for further studies since they show formation of transparent or bluish transparent emulsions with thermodynamic stability. They are also stable and showed no sign of precipitation or phase separation on dilution or freeze-thawing.

Table2: table showing the characterization of selected SEDDS formulations

S. No.	Formulation Name	Grade	Self-emulsification time (sec)	Stability	Effect of dilution	Freeze-thawing	Z-Average (r.nm)	Zeta Potential (mV)
1	LLCT21-2	I	45.66±2.13	Pass	Pass	Pass	16.93	-12.6
2	LLCT31-2	I	51.33±1.70	Pass	Pass	Pass	1334	-6.97
3	LLCT41-2	I	50.45±2.15	Pass	Pass	Pass	127	-17.6
4	LLCL21-2	I	42.76±1.08	Pass	Pass	Pass	258.3	-16.0
5	LLCL31-2	I	46.33±2.52	Pass	Pass	Pass	20.05	-17.7
6	LLCL31-3	I	52.66±3.52	Pass	Pass	Pass	134	-12.6
7	LLCL41-2	I	51.66±1.42	Pass	Pass	Pass	27.50	-12.5

Droplet size analysis

The droplet size distribution (Z-average) of various formulations and their Zeta Potential is given in Table2. The compositions LLCL21-2, LLCT21-2 and LLCT41-2 were finally selected based on their size, zeta-potential and visual observation as potential SEDDS formulations of Fenofibrate.

In-Vitro Dissolution Studies

Dissolution studies of above formulations were performed and the drug release from SEDDS was compared with plain drug (API). The results are shown in the figure7. The results shows that the formulation all of the SEDDS formulations showed an improved drug release of above 70% and that the plain showed a drug release of 0.296% at the end of 90 minutes.

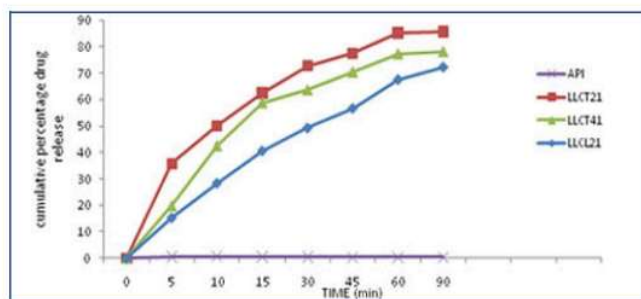


Figure 7: Comparative results of drug release from plain Fenofibrate and SEDDS formulations.

CONCLUSION

An optimized SEDDS formulations consisting of Fenofibrate, Labrafac Lipophile WL1389, Labrasol, Transcutol HP and Cremophor RH 40 were successfully developed. The developed formulations showed an increased solubility, dissolution rate and bioavailability of Fenofibrate. Further the formulations were found to be thermodynamically stable, for dilution, freeze-thawing and

centrifugation. None of the formulations showed drug precipitation or phase separation. The dissolution profiles of all the 3 formulations selected showed a drug release of greater than 70% in 90 minutes. Among all the formulations LLCT 21-2 showed a maximum drug release of 85.6% in 90 minutes. Thus our study confirmed that the SEDDS formulations can be potentially used as an alternative to the traditional oral formulations for the poorly soluble drugs like Fenofibrate to improve its solubility and dissolution.

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