Research Article

FORMULATION AND EVALUATION OF SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM FOR LIPOPHILLIC DRUG

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ABSTRACT

Fenofibrate is a BCS Class II drug with a high dose number. Thus, it can be assumed that the low oral bioavailability of fenofibrate is due to its solubility and dissolution limitations. The objective of the present study was to develop and characterize self-emulsifying drug delivery system (SEDDS) of Fenofibrate and formulate and evaluate Solid self emulsifying drug delivery system for filling into hard gelatin capsules. Solubility of Fenofibrate was evaluated in various careers that included oils, surfactants, and cosurfactants. Pseudoternary phase diagrams were constructed to identify the self-microemulsification region. Eight self-microemulsifying formulations were prepared using mixtures of oils such as Soyabean oil and Olive oil, surfactants, and cosurfactants in various proportions. The self emulsification properties, droplet size, and zeta potential of these formulations were studied upon dilution with water and drug diffusion studies were carried out. The liquid SEDDS formulation was converted into free flowing powder by adsorbing onto a solid carrier. The dissolution characteristics of solid intermediates of SEDDS filled into hard gelatin capsules was investigated and compared with marketed formulation to ascertain the impact on self-emulsifying properties. The results indicated the rate and extent of drug dissolution for solid intermediates was significantly higher than commercial tablet formulation. The results from this study demonstrate the potential use of SEDDS as a means of improving solubility, dissolution, and concomitantly the bioavailability.

Keywords: Fenofibrate, self emulsifying drug delivery system (SEDDS), Solid Self emulsifying drug delivery system.

INTRODUCTION

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. 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.[1]

SEEDS or self-emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively one or more hydrophilic solvents and co-solvents/ surfactants. Upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or micro emulsions. However, SEDDS are usually limited to liquid dosage forms because many excipients used in SEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SEDDS have been extensively exploited in recent years as they are frequently more effective alternatives to conventional liquid SEDDS.[1]

Fenofibrate is a lipid-regulating agent that has chemical, pharmacological, and clinical similarities to the other fibrate drugs, such as clofibrate and gemfibrozil. Fenofibrate is Biopharmaceutical Classification System (BCS) Class II drug with a high dose number. Thus, it can be assumed that the low oral bioavailability of fenofibrate is due to its solubility and dissolution limitations. Furthermore, it is reported that absorption of fenofibrate is increased by ~35% when it is administered with food rather than in a fasting state. Thus, formulating a lipid-based system of fenofibrate can be viewed as an option for improving its oral bioavailability. Fenofibrate is available in various doses (54 mg, 67 mg, 100 mg, 160 mg, and 200 mg).[2]

The main objectives of the study were to develop and evaluate an optimal SEDDS formulation containing fenofibrate and also formulate and evaluate Solid-SEDDS.

MATERIALS AND METHODS

Materials

Fenofibrate was obtained as a gift sample from Glenmark Pharmaceuticals Ltd (Mumbai, India). Peanut oil (Gemini groundnut oil), Soyabean oil (Fortune Soyabean oil), Olive oil (Loba chemie Pvt. Ltd), Sesame oil (Tiloni Sesame oil), as a lipid vehicle, Tween-80 and Span 80 from Merck Specialities Pvt. Ltd, Mumbai, Polyethylene glycol-400 (Rankem India Pvt. Ltd) obtained as gift sample, Empty hard gelatin capsule shells were generously donated by microlabs Ltd. Banglore.

Methods

1) Solubility Studies

The solubility of Fenofibrate in individual components and mixture of components was determined by adding of 2.0 ml of each of the selected vehicles to screw capped vial containing an excess of fenofibrate (500 mg). The vials capped tightly and content was heated to 40^{0}C to fascillitate Solubilization. Then the vials containing

fenofibrate and other excipients were shaken in mechanical shaker for 48 hours to reach in the equilibrium. After 48 hrs, the each vial was centrifuged at 3000-4000 rpm for 10 minutes and after that excess of fenofibrate in vials was discarded by filtration using a whatman filter paper (#35). Aliquot (1.0 ml) of sample was taken and diluted with dichloromethane to the concentration suitable for the determination of solubility. Analysis of drug was carried out with double beam UV-Visible spectrophotometer at 300 nm.[2]

2) Plot of pseudo ternary phase diagrams

10g of sample having olive oil or Soyabean oil (%w/w) and surfactant/cosolvent (%w/w) were prepared by using 50, 60, 70, 80 %w/w of lipids and with the remaining concentration of surfactant (tween-80 %w/w)/cosolvent (PEG-400 %w/w) in the ratio 1:1, 2:1, 3:1, 4:1 and 5:1 respectively. The mixture of lipids and surfactant/cosolvent at certain weight ratios were diluted with water (drop wise) by vortexing on magnetic stirrer till transparent to turbidity occurs. The volume used for titration was recorded and it was converted into %w/w according to density of water 0.9971g/cm^3. Ternary phase diagram were plotted with the help of CHEMIX School 3_51 software. [2]

3) Formulation of SEDDS

A series of SEDDS formulations were prepared (Table 1) using Tween 80 and PEG 400 as the S/CoS combination and Olive oil or Soyabean oil as the oil. Accurately weighed fenofibrate was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing and were heated at 40ºC on a magnetic stirrer, until fenofibrate was perfectly dissolved. The mixture was stored at room temperature until further use.

Table 1: Composition of Soyabean oil – SEDDS

Components (%w/w)	S1	S2	S3	S4	O1	O2	O3	O4
Fenofibrate(g)	11.5	11.5	11.5	11.5	13.0	13.0	13.0	13.0
Oil	50	60	70	80	50	60	70	80
Tween 80	41.6	34.0	25.0	16.6	41.6	34.0	25.0	16.6
PEG 400	8.4	6.6	5	3.3	8.4	6.6	5	3.3

Evaluation of self-emulsifying drug delivery systems

1) Thermodynamic stability studies (Freeze-thawing cycle)[3]

Freeze thawing was employed to evaluate the stability of formulations. The formulations were subjected to 3-4 freeze-thaw cycles, which included freezing at 4°C for 24 hours followed by thawing at 40°C for 24 hours. Centrifugation was performed at 3000 rpm for 5 minutes. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.

2) Self-emulsification efficiency test (dispersibility test)[3]

The efficiency of self-emulsification of microemulsion was assessed by using a standard USP XXII dissolution apparatus type II. 1.0 milliliter of each formulation was added to 500 ml of water at 37 ± 0.5°C. The in vitro performance of the formulations was visually assessed using the following grading system.

3) Drug content of SEDDS [3]

An accurately 0.1 ml of each formulation of SEDDS equivalent to 10mg of fenofibrate was placed in a 100 ml of volumetric flask and diluted to the mark with dichloromethane and after making further dilutions it was analyzed spectrophotometically at 300 nm, using a spectrophotometer (Model UV/Vis-2300).

4) Emulsion globule size analysis[4]

Each formulation were diluted 100 times in a beaker with distilled water and gently mixed by stirring on magnetic stirrer at 50 rpm for 5 minutes. The resultant emulsion was then subjected to particle size analysis using a photon correlation spectrometer

5) *In vitro* drug diffusion studies[5]

Each 1ml of the formulations were placed on diffusion cell by placing dialyzing membrane on it in 1.2 pH buffer containing 1% Tween 80 as dialyzing medium. 1ml of aliquot was taken after each 1 hr interval for 12 hrs and volume was made up to 10 ml and then it was analyzed spectrophotometrically at 300 nm.

Solidification of SEDDS

Solidification of SEDDS was carried out with 2:1 proportion of Colloidal silicon dioxide (Aerosil) as solid carriers and microcrystalline cellulose (MCC) to make a free flowing powder.

Table 2: Formulation of S-SEDDS

Name of in ingredients	Qty. Required
Liquid SEDDS	10ml
Colloidal silicon dioxide	3.33g
microcrystalline cellulose (MCC)	6.4. g

Evaluation of solid-self emulsifying drug delivery system

1) *In vitro* dissolution studies[4]

The release of solidified SEDDS and tablet was studied by dissolution apparatus USP XXII (Elecrolab Inc.), type II (peddle) in 1.2 pH as dissolution medium at 50 rpm of rotating speed and 37±0.5°C in which 500mg of SEDDS was filled in a capsules. The concentration of fenofibrate was determined by UV-spectrophotometer at 300 nm by standard calibration plot. The release profiles of SEDDS were compared with the available marketed products. Dissolution profiles of each dosage form were compared with its marketed products (Tablet≈120mg).

2) Zeta potential determination[4]

This is used to identify the charge of the droplets. 1:250 dilutions were made of formulation for the determination of zeta potential with the help of photon correlation spectroscopy (Zetasizer).

3) Powder Characteristics[6]

All the solidified powders are evaluated for bulk density, tapped density, angle of repose, Hausners ratio and Carr's consolidation index.

4) Drug loading in Solid-SEDDS[6]

Drug loading is the important criteria to determine the drug content which was loaded in Solid-SEDDS after solidification. Drug content in Solid-SEDDS was determined by UV spectrophotometrically as procedure prescribed in the determination of drug content.

RESULTS AND DISCUSSION

1) Solubility studies

Results from solubility studies are reported in Figure 1. As seen from the figure, Tween 80 and PEG 400 showed the highest solubilization capacity for fenofibrate, followed by Olive oil and Soyabean oil. Thus, for our study we selected Olive oil and Soyabean oil as oils and Tween 80 and PEG 400 as surfactant and cosurfactant, respectively.

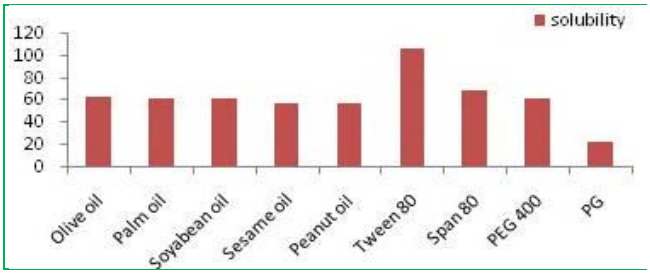

Figure 1: Solubility of fenofibrate in various components PEG 400- Polyethylene glycol 400, PG- Propylene glycol

2) Plot of Pseudoternary Phase Diagrams

In the present study both Olive oil and Soyabean oil were tested for phase behavior studies with Tween 80 and PEG 400 as the S/CoS mixture. As seen from the ternary plot, Olive oil gave a wider microemulsion region than did Soyabean at all S/CoS ratios. Thus, Olive oil was selected as the preferred vehicle for the optimized formulation. The microemulsion existence area increased as the S/CoS ratio increased. Thus, an S/CoS ratio 5:1 was selected for the formulation study.

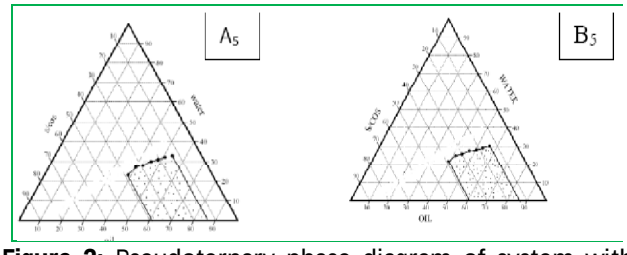

Figure 2: Pseudoternary phase diagram of system with the following components: oil (A) = Soyabean oil, (B) = Olive oil, surfactant = Tween 80, and cosurfactant = polyethylene glycol 400. S/CoS ratio A_5 and B_5 is 5:1. S/CoS indicates surfactant/cosurfactant.

3) Thermodynamic stability studies (Freeze-thawing cycle)

Thermodynamic stability study (Table 3) was performed to evaluate the precipitation of the drug in the excipients mixture. It was found that all the SEDDS formulations were physically stable and there was no precipitation of drug into lipid matrix and form a single homogeneous phase except S4 batch of Soyabean oil-SEDDS.

Table 3: Thermodynamic stability studies of Fenofibrate-SEDDS

Soyabean oil - SEDDS	After centrifuge	Olive oil - SEDDS	After centrifuge
S1	No phase separation	O1	No phase separation
S2	No phase separation	O2	No phase separation
S3	No phase separation	O3	No phase separation
S4	Phase separation	O4	No phase separation

4) Dispersibility test

From table no.4, dispersibility of formulation increases with decreasing the proportion of oils with simultaneously increasing the ration of S/CoS results in reduction of interfacial tension between oil globules and aqueous phase. The batch S1 has good dispersibility than the batch S2 and S3. The batch O1, O2 and O3 have good dispersibility than the batch O4. Amongst the SEDDS prepared with Soyabean oil and Olive oil, Olive oil-SEDDS have good dispersibility.

Table 4: Dispersibility test of Fenofibrate-SEDDS

Soyabean oil - SEDDS	Visual Observation	Olive oil - SEDDS	Visual Observation
S1	B	O1	B
S2	C	O2	C
S3	C	O3	C
S4	-	O4	D

5) Drug content analysis

Table 5, indicates that the quantity of drug content of each formulation is more than 92.66% to the amount of drug loading. Therefore, it can be might be told that the entire drug is well uniformly distributed and there is no precipitation in the each formulation of Soyabean oil as well as Olive oil.

Table 5: Drug content of Soyabean oil-SEDDS as well as Olive oil-SEDDS

Soyabean oil - SEDDS	Drug content (%)	Olive oil - SEDDS	Drug content (%)
S1	101.11±0.513	O1	103.18±0.932
S2	97.96±1.103	O2	98.56±0.776
S3	94.88±0.459	O3	97.53±0.409
S4	-	O4	94.66±1.381

Mean ± S.D. *n=3*

6) *In vitro* drug diffusion Studies

From the table 6, it shows that in Soyabean oil-SEDDS, S1 (86.64 %) shows drug diffusion than S2 and S3. In case of Olive oil-SEDDS, O1 (92.374 %) drug diffusion than O2, O3 and O4. From the above results it indicates that, as the concentration of oil increases and surfactant concentration decreases drug diffusion decreases.

Table 6: % Drug Diffused from Soyabean oil-SEDDS

	% Drug diffused						
Time (Hrs)	**S1**	**S2**	**S3**	**O1**	**O2**	**O3**	**O4**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	6.695	5.950	5.578	6.695	6.323	5.826	5.739
2	21.068	20.823	18.979	26.353	26.230	23.600	24.731
3	27.790	27.790	26.817	35.089	34.846	32.291	31.938
4	41.065	40.824	37.212	43.955	43.027	41.823	37.368
5	53.476	52.761	49.424	56.336	50.259	49.305	46.564
6	70.031	66.399	63.097	69.995	60.443	59.618	59.146
8	70.075	69.725	69.259	72.759	69.609	69.550	69.445
10	75.910	75.518	71.558	81.948	78.069	74.837	71.258
12	86.640	76.362	74.786	92.374	90.044	83.226	78.543

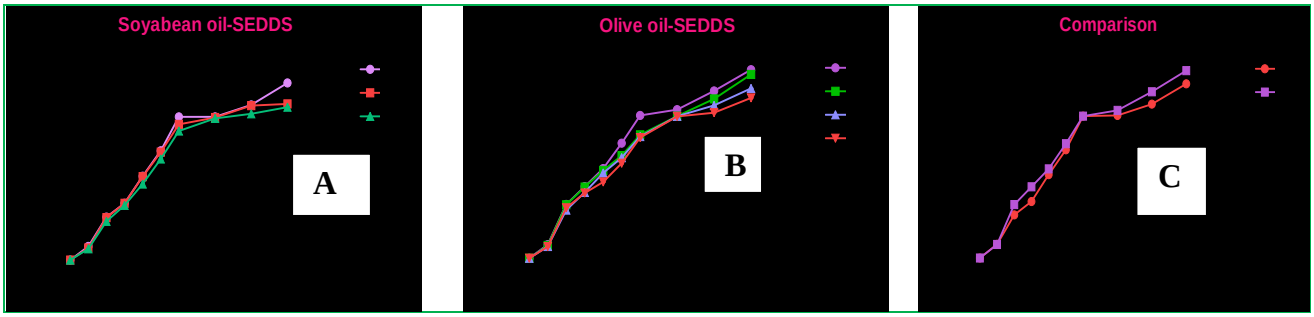

Figure 3: Comparative % Drug diffusion of (A) Soyabean oil-SEDDS (B) Olive oil-SEDDS (C) Comparison between S1 of Soyabean oil-SEDDS and O1 of olive oil-SEDDS

7) Globule size analysis

From table 7, O2 batch of Olive oil-SEDDS shows less droplet size than Soyabean oil- SEDDS.

Table 7: Globule size of Fenofibrate-SEDDS

Formulation	Globule size (d.nm)
O1	342.5
O2	301.7
S1	363.2

Evaluation of solid-sedds

1) Drug loading in S-SEDDS

Table 8, indicates Drug Loading in Solid –SEDDS, it shows that in Soyabean oil Formulation, S1 shows more drug loading than S2 and S3 and in case of olive oil formulation; O1 shows more drug loading than O2, O3 and O4. When comparing Soyabean oil and Olive oil formulation, O1 shows more drug loading than S1.

2) *In vitro* drug release comparison of S-SEDDS with the marketed Fenofibrate tablet

Table no. 9, S1 batch shows 93.77% release, O1 batch shows 95.83% and marketed formulation F1 shows 64.37% release. From the results it is clear that using Self emulsifying system, solubility of Fenofibrate was increased even the release is also enhanced as compared to marketed formulation.

Table 8: % drug loading in Solid-SEDDS

Formulation	Drug loading (%)
S1	62.49
S2	60.21
S3	60.13
O1	65.10
O2	63.29
O3	61.49
O4	59.87

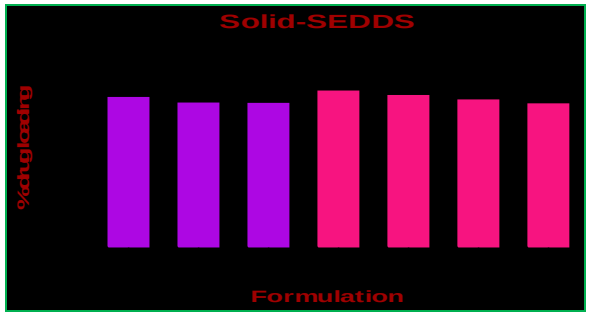

Figure 4: Comparing drug loading in Solid formulation

Table 9: Percentage (%) release (average) of Fenofibrate Soyabean/Olive oil S-SEDDS

Time (min)	S1	S2	S3	O1	O2	O3	O4	F_1
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
5	25.175	26.292	26.739	33.666	35.68	28.973	30.090	13.006
15	53.588	54.921	54.033	63.587	64.14	53.699	52.588	23.600
30	66.768	65.331	64.558	68.314	66.77	65.110	64.005	27.857
45	74.852	73.204	73.424	79.466	77.93	73.204	72.325	37.656
60	88.630	86.992	83.168	88.630	87.97	86.118	84.479	51.230
75	97.685	94.752	90.082	98.618	96.86	94.535	91.494	64.378
90	93.779	90.539	86.759	95.831	94.05	94.859	88.271	63.340

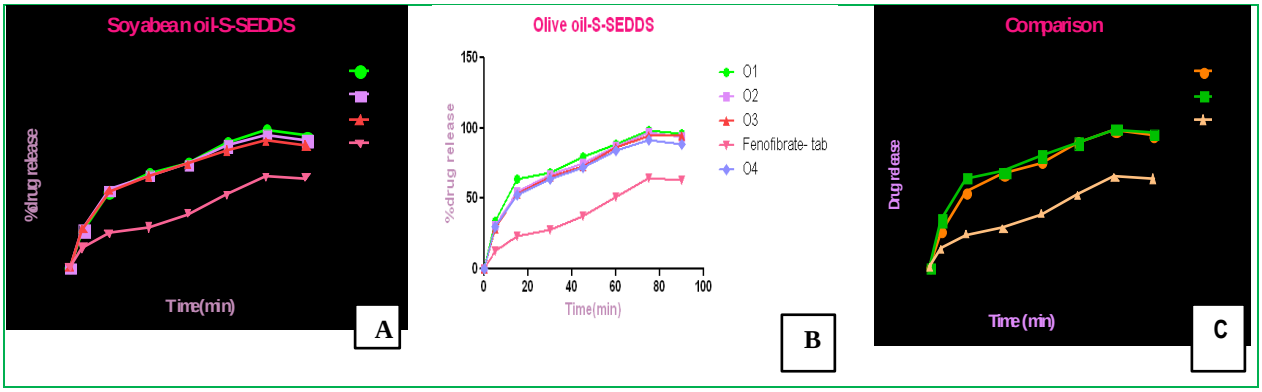

Figure 5: Comparative release pattern of (A) Soyabean oil S-SEDDS (B) Olive oil S-SEDDS with Fenofibrate tablet (C) Comparison between S1 of Soyabean oil-SEDDS and O1 of olive oil-SEDDS with marketed Fenofibrate tab

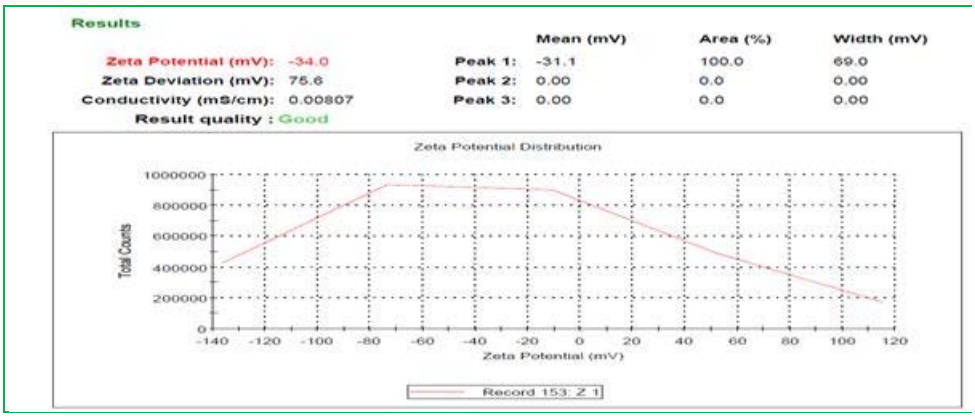

Figure 6: zeta potential of O1 of olive oil S-SEDDS (For Olive oil-S-SEDDS: Sample no.O1)

3) Zeta Potential Determination

Figure 6, shows that zeta potential of O1 of olive oil S-SEDDS is -34.0 mv which indicates that the droplet of SEDDS having negative charge, which indicates that system is stable.[17]

CONCLUSION

These current results demonstrated that SEDDS and S-SEDDS containing 50% w/w olive oil, 41.6%w/w tween80 and 8.4% w/w polyethylene glycol was successfully developed with an increased solubility, increased dissolution rate of a poorly water-soluble drug, fenofibrate. A result from stability studies confirms the stability of the developed formulation. Thus, the study confirms that the SEDDS for Fenofibrate can be used as a possible alternative to traditional oral formulations of fenofibrate with improved solubility and drug release.

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