**RESEARCH ARTICLE**

# Formulation and Evaluation of the Fenofibrate Spray-dried Emulsion Tablets

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**ABSTRACT**

The present research work deals with the development of a self-micro emulsifying drug delivery system (SMEDDS) of Fenofibrate (FF) followed by spray drying to form solid SMEDDS and tablets with enhanced solubility and dissolution. FF is BCS class II drug with low bioavailability and low aqueous solubility. The solubility of the FF can be improved by formulating SMEDDS. Liquid SMEDDS were developed by adding the drug in oleic acid, Tween 80, and Transcutol HP to get a clear solution. In the spray drying method, dextran was used to form the granules. Further, direct compression method was used to manufacture the tablets. The spray-dried product containing solid SMEDDS of FF showed nearly 30-fold solubility enhancement in distilled water in comparison to pure FF. The optimized formulation containing solid SMEDDS of FF (F9) showed an increased dissolution rate (100% drug release at 60 minutes) in comparison to conventional tablets. The optimized batch showed excellent stability at the accelerated condition for the period of 3 months. The current research work demonstrates spray drying as a potential approach to transfer the liquid SMEDSS to a solid SMEDDS with an enhanced solubility and dissolution rate.

**Keywords:** SMEDDS, Bioavailability, Solubility, Fenofibrate, Dissolution, Spray drying.

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## INTRODUCTION

Lipid-based drug carriers greatly impact the solubility, dissolution, and bioavailability of the drug molecule from the GIT by reducing the variation of systemic exposure. Self-micro emulsifying drug delivery system (SMEDDS) are lipidic formulations have been more thoroughly described from a physiological perspective. For these formulations, bile and lipolytic agents combine to generate a solubilized phase and the drug release takes place from lipidic phase upon digestion. When a well-designed lipidic dosage form gets diluted with the surrounding aqueous media, a drug can be transported from the molecular dispersion to the mixed micellar system.[1] This technology's key characteristic is its capacity to produce small O/W microemulsions upon dilution with the aqueous phase. The digestive motility of the stomach and intestine provides the agitation required to form the emulsion. In addition to solubilization, the fat present in the formulation's inclusion of fat enhances bioavailability by influencing drug absorption.[2,3]

Fenofibrate (FF) is a lipid-lowering agent belonging to BCS class II, which is having lower solubility and higher permeability.[4,5] The limited oral bioavailability of FF can therefore be attributed to its solubility and dissolving restrictions. To get beyond these restrictions, researchers have experimented with various techniques such as cyclodextrin complexation, micronization, and solid dispersion.[6-8] The pharmaceutical applications of FF are limited due to poor water solubility and bioavailability.[9] The interest in research of SMEDDS has tremendously increased in recent years. Xiumin, Li, *et al.* developed SMEDDS with the aim of increasing the bioavailability of the FF.[10] Kanaujia *et al.* developed SEDDS to enhance the dissolution of FF.[11] Manohari *et al.* formulated the SEDDS of FF to improve the dissolution and bioavailability by utilizing a blend of oil surfactant and co-surfactant.[12] Shah and Serajuddin optimized SEDDS by using a solidifying and emulsifying agent for lipids.[13]

In addition to having several benefits including low manufacturing costs, simple process controls, high stability and repeatability, greater patient compliance, and improved solubility and bioavailability, S-SEDDS can be used to create nanoparticles, microspheres, free flowing powders etc.[14,15] Therefore, it is advised to create or convert L-SMEDDS into a solid state to achieve the combined benefits of SMEDDS as well as solid dosage forms. Spray drying is a widely used method to manufacture S-SMEDDS from L-SMEDDS. It has the potential to form a dry microemulsion containing submicron particles i.e., microspheres, microparticles etc. This technique

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has received considerable interest recently from researchers as a method for solidifying liquid SMEDDSs. Due to its excellent scalability, the spray drying method is used in the industrial setting to convert liquid SMEDDS.[16] During this spray drying technique, the solvent's evaporation occurs rapidly, leading to an increase in viscosity that finally traps the oil globules with drug molecules onto the carrier matrix.[17]

As far as we know, only a little study has been done on the formulation of fenofibrate SMEDDS to convert it into solid SMEDDS using the spray drying method. This study's primary goal was to develop SMEDDS that could be transformed into solid SMEDDS using a spray drying process. These spay-dried solids then formed tablet dosage forms to enhance patient compliance and better stability of the final product.

## MATERIALS AND METHODS

### Materials

Fenofibrate (FF) was obtained from Wockhardt Ltd, Aurangabad, India. Kolliphor RH 40, Cremophore RH 40, PEG 400, PEG 300, Oleic acid, Tween 80, and Transcutol HP were purchased from BASF, Mumbai. Maltodextrin was purchased from Nutrichem products, Mumbai. MCC was procured from Maple Biotech Pvt ltd, Pune.

### Methods

#### Solubility Profile of FF

The solubility of FF was determined in oils, surfactants, and co-surfactants. About 500 mg of the drug fenofibrate was mixed in the vehicle and vortexing was done for about 5 minutes. This mixture was shaken at 25°C for 3 days in a shaking water bath. Centrifugation was done for the resulting liquid at 12,000 rpm for 20 minutes to separate the non-dissolved drug. The supernatant portion of the liquid supernatant was removed and dilutions were done with diluted with acetonitrile, and its absorbance was measured by UV analysis at 286 nm.[10]

#### Surfactant Emulsification Study

This study was performed to select the surfactant. Oil and surfactant were mixed at ratios from 1:9 to 9:1 with constant stirring to get a homogeneous mixture of the component. The distilled water was mixed with the oil and surfactant mixture before being visually inspected. As a result of the observation of the spontaneity of emulsification, the ratio of oil to surfactant was chosen.[10]

#### Co-surfactant Emulsification Study

This study was performed to select the oil phase with varying ratios of surfactant and co-surfactants (1:1, 1:2, 2:1). The water titration method was used to titrate the oil and S-mix combinations, and the endpoints at which emulsification was seen were reported. The quantity of water required to form the emulsion was noted.[10]

#### Pseudo-ternary Phase Diagram

This phase diagram was constructed by water titration method, the S-mix (surfactant and co-surfactant-1:1, 1:2, 2:1) and oil ratios were utilized to produce the pseudo-ternary phase diagram (Figure 1). Three variable oil, S-mix, and water were used to plot the ternary phase diagram and zone showing microemulsion was identified.

#### Formulation of L-SMEDDS

50 mg of FF was dispersed in different volume ratios of oleic acid (oil), Tween 80 (surfactant), and Transcutol HP (co-surfactant). The final mixture was stirred with a magnetic stirrer to get a clear solution. Further, the sign of turbidity or phase separation was examined.[11] The formula composition is presented in Table 1.

#### Characterization of optimized formulation of FF-loaded L-SMEDDS

*pH and Density*

The pH of the liquid SMEDDS was determined using calibrated pH meter (Lab India PICO$^{+}$). Density is mass per unit volume of L-SMEDDS. It was determined by using a density measurement bottle.

*Viscosity*

A Brookfield viscometer was used to measure the viscosity of SMEDDS's. Spindle 7 was lowered perpendicularly into the sample after the formulation had been deposited in the sample container. The ideal speed was maintained for the spindle's rotation. At room temperature, the formulation's viscosity was measured with an angular velocity that was gradually increased from 0.5 to 20 rpm.

*Zeta Potential, Globule Size*

The Malvern zeta sizer ZS 90 was used to determine the microemulsion's zeta potential and globule size. The SMEDDS was diluted at 1:10 ratio using double distilled water and samples were analyzed.

*% Transmittance*

The % transmittance of L-SMEDDS formulation was identified by measuring the absorbances at 638.2 nm using UV-spectroscopy.

**Table 1:** The formula for optimization trials

| *Formula* | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* |
|---|---|---|---|---|---|---|
| Fenofibrate (FF) | 50 | 50 | 50 | 50 | 50 | 50 |
| Oleic acid (Oil Phase) | 86 | 86 | 86 | 43 | 43 | 43 |
| Tween 80 (Surfactant) | 57 | 28.5 | 57 | 28.5 | 57 | 57 |
| Transcutol HP (Co-surfactant) | 28.5 | 57 | 57 | 57 | 28.5 | 57 |
| Total weight (mg) | 218.5 | 218.5 | 250 | 178.5 | 178.5 | 207 |

*Self-micro-emulsifying Time*

It was tested by adding liquid SMEDDS while stirring at 50 rpm with USP dissolution apparatus II in pH 6.8 buffer and the time of dispersion was recorded.[1]

*Cloud Point Measurement*

L-SMEDDS was kept in a water bath and the temperature was allowed to rise gradually. The mixture was diluted at ratio of 1:250 with distilled water. The temperature at which clouds suddenly became visible was noted and considered as a cloud point.[1]

*Conductivity Measurement*

A conductivity meter was used to measure the liquid SMEDDS's conductivity. The electro-conductivity of the micro-emulsion was assessed using a conductivity measuring test, which reveals whether it is an o/w or w/o kind of micro-emulsion.[1]

*Centrifugation*

To test phase separation in the formulation using the centrifugation method, liquid SMEDDS formulation was introduced to a centrifuge device (Bio Lab BLD-165). SMEDDS were centrifuged in liquid form for 30 minutes at 3500 rpm.

*Formulation of Solid SMEDDS by Spray Drying Technique*

Pre-sieved dextran (1.0 gm) was added slowly in water (100 *mL*) and dissolved under continuous stirring on the magnetic stirrer. To this dextran solution, optimized SMEDDS formulation was added slowly and mixed properly for 15 minutes at room temperature using a magnetic stirrer. The resulting suspension formulation was spray-dried with a 0.7 mm diameter nozzle. The following parameters were set during spray drying. Inlet temperature: 100°C, outlet temperature: 78–82°C, aspiration: 85%, drying airflow: 500 NL/h and feeding rate of the suspension: 5 *mL*/min[16].

**Characterization of S-SMEDDS**

*Drug Content*

About 100 mL of methanol was used to dissolve the solid SMEDDS. To determine the amount of drug in the solid SMEDDS, the solution was filtered using Whatman filter paper. The filtrates were analyzed at 286 nm using UV-spectroscopy.

*Scanning Electron Microscopy (SEM)*

The surface morphology and characteristics of the S-SMEDDS were observed using SEM. At a distance of 8.6–8.7 mm the SEM was used with a 1.0 kV accelerating voltage

*X-ray Powder Diffraction (XRD)*

The amorphous or crystalline nature of the S-SMEDDS and pure FF was determined by using Philips PAN analytical expert Shimadzu XRD-7000 (Japan).

*DSC Analysis*

DSC study of pure FF and spray-dried S-SMEDDS of FF was performed using DSC (Hitachi 9020). Approximately 1–3 mg of FF and S-SMEDDS samples were placed on a heated aluminium pan at a nitrogen flow rate of 50 *mL*/min at a heating temperature of 10°C/min. Thermal analysis of data was then conducted with a DSC thermogram.

*Saturation Solubility of Pure FF and S-SMEDDS of FF*

The saturation solubility of the pure FF and S-SMEDDS of FF was determined in distilled water (DW). An excess amount of pure FF drug and S-SMEDDS of FF was added to 10 mL of DW and the solution was stirred for the period of 24 hours at a temperature of 37°C. The samples were withdrawn and filtered using membrane filter to get a clear solution. The samples were analyzed using UV-spectroscopy at 286 nm. The saturation solubilities of the both pure FF and S-SMEDDS of FF was determined and compared.[18]

*Angle of Repose*

Granular material was poured to create a pile with a circular base to measure the angle of repose. For additional computations, the pile's height and the base's radius are measured.

$$\text{Tan}(\theta) = h/r$$

*Bulk Density (BD)*

The BD of the spray-dried S-SMEDDS was estimated by pouring a predetermined weight sample in glass cylinder and volume occupied by the sample was noted down. The following formula was used to determine the BD

$$\text{BD} = \text{Powder weight/Bulk volume}$$

*Tapped Density (TD)*

Tapping the measuring cylinder-prepared granules determined TD until constant volume is achieved. TD was determined by using formula

$$\text{TD} = \text{Wt. of powder/Tapped volume.}$$

*Carr's Index (CI)*

The following formula was used to calculate the CI to get an idea about the compressibility of the powder sample.

$$\text{CI} = \text{TD} - \text{BD/TD}$$

**Table 2:** Formula composition of tablets containing FF-loaded S-SMEDDS

| *Name of Excipients* | *Qty (mg/tab)* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* | *F7* | *F8* | *F9* |
| S-SMEDD eq. to 100 mg of FF | 170 | 170 | 170 | 170 | 170 | 170 | 170 | 170 | 170 |
| MCC | 75 | 73.75 | 72.5 | 71.25 | 70 | 68.75 | 67.5 | 66.25 | 65 |
| Croscarmellose sodium | 1.25 | 2.5 | 3.75 | 5 | 6.25 | 7.5 | 8.75 | 10 | 11.25 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Mg stearate | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| Total Weight | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

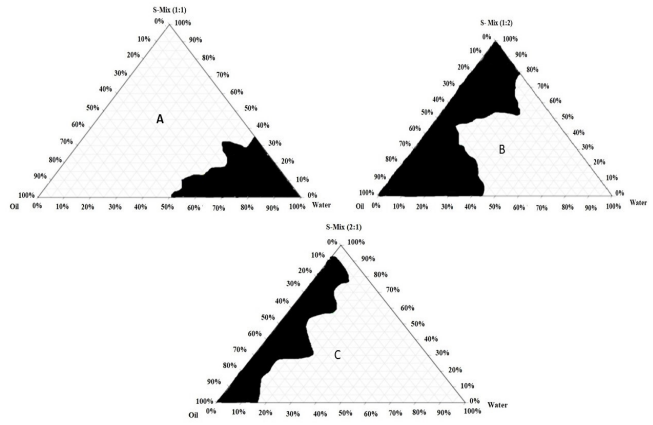


**Figure 1:** Pseudoternary Phase Diagram A) S-Mix (1:1), B) S-Mix (1:2), C) S-Mix (2:1).

*Hausner's Ratio (HR)*

HR was used to determine the flowability of the S-SMEDDS. It is calculated by using the following formula

$$HR = TD/BD$$

*Formulation of Tablets from Solid SMEDDS*

The direct compression method was utilized to form the tablets. The complex (S-SMEDDS) equivalent to 100 mg of the medication was combined with immediately compressible diluents in a plastic container. The initial mixture in the plastic container was combined with croscarmellose sodium, magnesium stearate, and talc and sifted through # 60. The mixture was then blended and the tablets were compressed using 8 mm punches. The compression was carried out on a Cadmach 16-station tablet compression machine[19]. The formula composition is presented in Table 2.

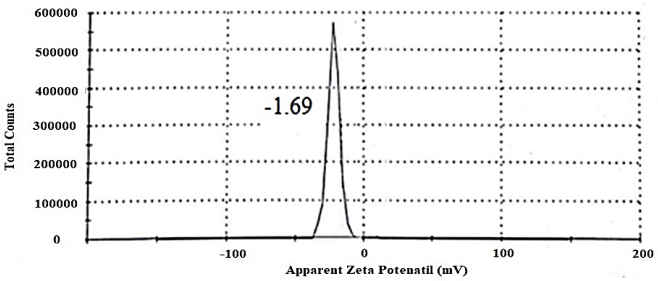


**Figure 2:** Zeta potential of optimised formulation (F3) showing excellent stability.

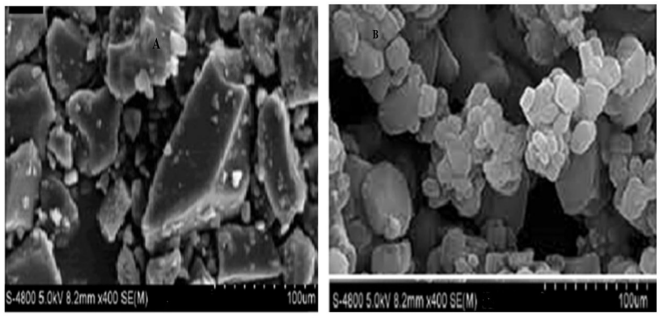


**Figure 3:** SEM images of A) Pure FF API and; B) FF-loaded S-SMEDDS.

## Characterisation of Tablets[19]

*Thickness*

The thickness was measured using a digital vernier caliper on 10 rando*mL*y selected tablets and thickness was determined with standard deviation.

*Hardness*

The hardness of the tablets was determined using Stokes Monsanto hardness tester on 10 rando*mL*y selected tablets. The average, as well as the standard deviation, was calculated.

*Friability*

This test was done on an automatic friabilator. For this test, 20 tablets were randomly selected from various batches, and the test was run for 100 rotations. The weight of the dedusted tablets was recorded, and the mean of three assessments for friability was calculated. Typically, tablets were regarded as appropriate when there was a weight loss of less than 1%.

*Content Uniformity (CU)*

In accordance with USP, CU of the tablets was determined on 10 tablets. The tablets were crushed and soaked in pH of 1.2 buffer for 24 hours. The suspension was filtered through a 0.45-micron filter to get clear solution and samples were analyzed using UV spectrophotometer at 286 nm wavelength.

*Weight Variation*

The weights of 20 tablets were recorded in mg and the standard deviation was determined.

*Disintegration Test (DT)*

The DT of the manufactured tablets was carried out in disintegration test apparatus containing 900 *mL* of DW (37 ± 0.5°C). The disintegration time was noted when no visible residue of the tablet left in the DT apparatus. The time was noted in seconds.

*In-vitro Dissolution Studies*

Type II dissolution test apparatus was used to determine the drug release in 900 *mL* pH 6.8 PBS buffer (37 ± 0.5°C; 25 rpm). The samples (5 *mL*) were withdrawn at a predetermined time interval and same volume of buffer was added to maintain the sink condition. The samples were analyzed using UV spectrophotometer at 286 nm wavelength and drug release was determined at each time point.

*Stability Study*

The F9 formulation was loaded for accelerated stability study based on their acceptable disintegration time, hardness, thickness, weight variation, dissolution, and content uniformity. For the selected formulation, the formulation was loaded at 40ºC/75% RH for 3 months. After every month, the samples were analyzed results were noted down.

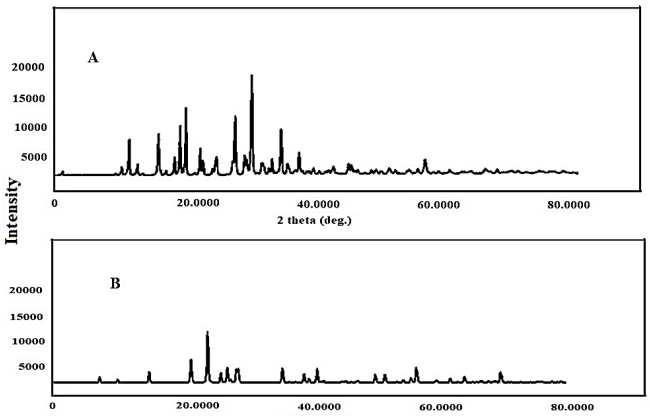


**Figure 4:** X-RD graph for pure FF (A) and S-SMEDDS of FF (B).

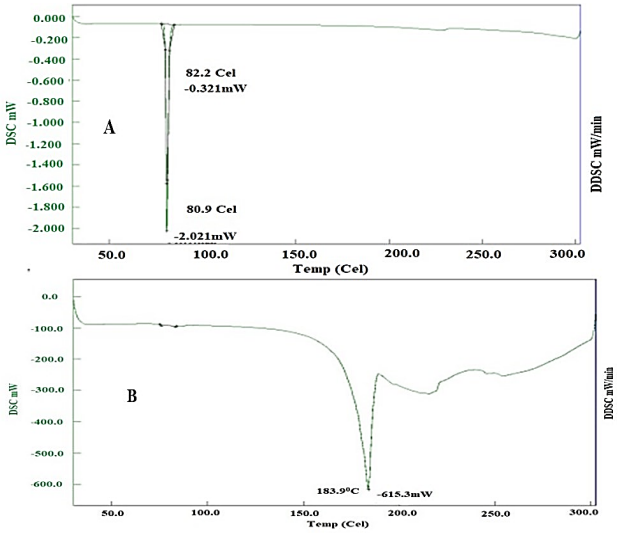


**Figure 5:** DSC thermogram of pure FF (A) and FF-loaded S-SMEDDS (B).

**Table 3:** solubility of FF in different oils, surfactants, and co-surfactants

| *S. No.* | *Medium* | *Solubility (mg/mL)* |
|---|---|---|
| Oils | | |
| 1 | Castor Oil | 0.35 ± 0.20 |
| 2 | Oleic Oil | 1.34 ± 0.22 |
| 3 | Virgin Coconut Oil | 0.41 ± 0.65 |
| 4 | Isopropyl Myristate Oil | 1.14 ± 0.03 |
| 5 | Soybean Oil | 0.75 ± 0.66 |
| Surfactants | | |
| 6 | Tween 60 | 2.92 ± 0.21 |
| 7 | Tween 80 | 3.54 ± 0.43 |
| 8 | Span 80 | 1.65 ± 0.65 |
| Co-surfactants | | |
| 9 | PEG 400 | 0.42 ± 0.65 |
| 10 | PEG 300 | 0.35 ± 0.12 |
| 11 | Transcutol HP | 0.92 ± 0.15 |
| 12 | Span 20 | 0.17 ± 0.76 |
| 13 | PEG 400 | 0.56 ± 0.22 |

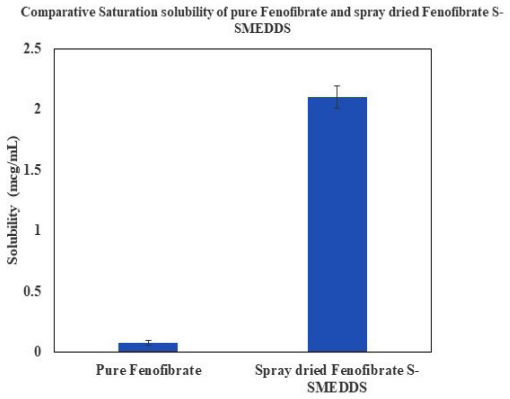


**Figure 6:** Saturation solubility of the pure FF and FF-loaded S-SMEDDS

## RESULTS AND DISCUSSION

### Solubility Study of FF

The solubility profile of the FF was determined in oils, surfactants and co-surfactants using the super saturation method. Oleic oil demonstrated the maximum solubility of 1.34 ± 0.22 mg/*mL* among all the studied oils. Among all surfactants tested, FF showed the highest solubility in tween 80 (3.54 ± 0.43 mg/*mL*) while among co-surfactants, transcutol HP showed the highest solubility of 0.92 ± 0.15 mg/*mL*. The solubility profile of FF is represented in Table 3. An acceptable region of the o/w type of microemulsion is produced by a s-mix with a 1:1 ratio of the concentration of surfactant and co-surfactant, according to the findings of the pseudo ternary phase diagram.

### Physicochemical Characterization of L-SMEDDS

The developed L-SMEDDS of FF was evaluated for various physicochemical properties. The comparative physicochemical parameters are compiled in Table 4. Considering all the observed results, formulation F3 was found to be optimised formulation with excellent and acceptable physicochemical properties. Oleic acid, Tween 80, and transcutol HP at 43:28.5:28.5 ratio was found to be optimized to form the stable microemulsion. The pH of liquid FF SMEDDS (Optimised batch F3) was found to be 7.6, with a viscosity of 420 cps and density of 0.719 g/mL. The liquid SMEDDS of FF had a zeta potential of -1.69 mV (Figure 2) with a globule size of 250 microns, which suggested good microemulsion quality and stability as well as rapid emulsification. The ideal range of zeta potential as per official documents ranges between -30 mV to +30 mV.[20]

Using a UV-spectrophotometer, the transmittance of the SMEDDS formulation was evaluated at 638.2 nm. The %T value was found to be nearly 92% which indicates good transparency. It was found that the time required for emulsification of liquid FF SMEDDS was 1.34 ± 0.12 minutes. The cloud point of liquid SMEDDS was found to be 66.9°C, indicating that the microemulsion is stable at room temperature. The conductivity of SMEDDS formulation was reported 23.3 ± 0.01 µS/cm. It was determined from the electro-

**Table 4:** Physicochemical properties of the FF liquid SMEDDS

| *Batch* | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* |
|---|---|---|---|---|---|---|
| pH | 6.8 | 6.2 | 7.6 | 6 | 6.3 | 6.6 |
| Density (g/mL) | 0.457 | 0.521 | 0.719 | 0.309 | 0.35 | 0.32 |
| Viscosity (cps) | 180 | 188 | 420 | 168 | 175 | 165 |
| Globule size (micron) | ND | ND | 250 | ND | ND | ND |
| Zeta Potential | -1.8 | -1.4 | -1.69 | -1.7 | -1.82 | -1.95 |
| % T | 62 | 58 | 92 | 52 | 67 | 71 |
| Emulsification time (min) | 2.25 ± 0.20 | 2.71 ± 0.17 | 1.34 ± 0.12 | 4.20 ± 0.20 | 4.50 ± 0.25 | 5.11 ± 0.20 |
| Cloud point (°C) | 32 | 35 | 66.9 | 31 | 33 | 29 |
| Conductivity (µS/cm) | 19.24 ± 0.07 | 17.71 ± 0.15 | 23.3 ± 0.01 | 15.24 ± 0.20 | 11.71 ± 0.20 | 11.21 ± 0.25 |
| Centrifugation test (Phase separation) | Yes | Yes | No | Yes | Yes | Yes |

**Table 5:** Physicho chemical characterization of tablets

| *Formulation* | *Thickness (mm)* | *Hardness (N)* | *Uniformity of weight* | *Friability %* | *Total FF content* | *DT (Sec)* |
|---|---|---|---|---|---|---|
| F1 | 2.7 ± 0.08 | 54 ± 0.67 | 0.70 ± 0.14 | 0.69 ± 0.32 | 95.06 ± 0.32 | 177 |
| F2 | 3.4 ± 0.06 | 44 ± 0.13 | 0.73 ± 0.23 | 0.64 ± 0.34 | 92.06 ± 1.4 | 158 |
| F3 | 3.6 ± 0.04 | 65 ± 0.65 | 0.72 ± 0.17 | 0.67 ± 0.22 | 98.7 ± 0.1.4 | 155 |
| F4 | 3.0 ± 0.06 | 66 ± 0.32 | 0.78 ± 0.15 | 0.61 ± 0.22 | 95.76 ± 0.55 | 136 |
| F5 | 3.1 ± 0.09 | 73 ± 0.67 | 0.74 ± 0.17 | 0.60 ± 0.35 | 98.06 ± 1.2 | 126 |
| F6 | 3.2 ± 0.06 | 54 ± 0.12 | 0.69 ± 0.14 | 0.63 ± 0.30 | 94.06 ± 1.4 | 110 |
| F7 | 3.5 ± 0.02 | 59 ± 0.22 | 0.71 ± 0.20 | 0.68 ± 0.14 | 95.66 ± 0.13 | 95 |
| F8 | 4.5 ± 0.08 | 42 ± 0.52 | 0.74 ± 0.10 | 0.69 ± 0.65 | 92.6 ± 0.12 | 85 |
| F9 | 2.5 ± 0.09 | 59 ± 0.32 | 0.71 ± 0.15 | 0.66 ± 0.55 | 95.06 ± 0.32 | 71 |

**Table 6:** Cumulative % drug release

| *Time (min)* | *Batch* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *F1* | *F2* | *F3* | *F4* | *F5* | *F6* | *F7* | *F8* | *F9* | *Conv tab* |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 17.2 | 18.27 | 20.47 | 22.27 | 25.25 | 30.12 | 34.11 | 49.11 | 65.71 | 10.25 |
| 20 | 20.22 | 22.71 | 25.51 | 26.11 | 28.51 | 35.42 | 38.39 | 45.26 | 72.67 | 15.24 |
| 30 | 22.27 | 24.46 | 27.18 | 30.12 | 35.34 | 39.67 | 43.27 | 50.12 | 80.25 | 19.27 |
| 40 | 25.9 | 28.89 | 32.34 | 35.45 | 37.21 | 42.28 | 46.19 | 65.25 | 89.09 | 22.25 |
| 50 | 30.12 | 32.51 | 35.44 | 39.98 | 42.34 | 45.51 | 50.09 | 72.89 | 92.28 | 27.41 |
| 60 | 32.41 | 35.44 | 38.51 | 42.27 | 48.11 | 50.71 | 54.34 | 86.11 | 100 | 30.12 |
| 70 | 35.44 | 39.11 | 43.21 | 47.23 | 52.21 | 54.28 | 60.56 | 94.28 | …. | 32.45 |
| 80 | 42.9 | 44.47 | 52.21 | 55.11 | 59.51 | 62.13 | 65.21 | 100 | …. | 36.52 |
| 90 | 48.54 | 52.51 | 55.71 | 60.24 | 64.11 | 67.09 | 74.65 | …. | …. | 42.11 |
| 100 | 50.55 | 55.7 | 59.56 | 63.11 | 67.67 | 72.81 | 85.9 | …. | …. | 45.9 |

conductivity investigation that the system was an O/W type of microemulsion. It was determined that no phase separation in the formulation had been seen during the centrifugation test. Overall, the developed L-SMEDDS was found to have desirable physicochemical properties.

**Evaluation of S-SMEDDS**

*Drug Content*

According to the technique adopted, the FF content of S-SMEDDS was examined and found to be 98.80 %, which complies with the acceptance criteria of 96-110 %w/w S-SMEDDS.

*SEM*

The morphological characteristics as well as structural elucidation of the pure FF and prepared fenofibrate loaded SEM validated SMEDDS. As seen in the image, the surface particles of the optimized fenofibrate-loaded SMEDDS were smooth and had mixed structures, round-shaped, oval, and rectangle-shaped. Figure 3 shows an SEM image of FF API (3A) and FF-loaded S-SMEDDS (3B).

**Table 7:** Stability studies of Dry emulsion tablet (F9 formulation) stored at 40ºC/75% RH

| *S. no.* | *Parameters (F9)* | *40ºC/75%RH* | | | |
|---|---|---|---|---|---|
| | | *Initial* | *1M* | *2M* | *3M* |
| 1 | Disintegration time in water (sec) | 71 | 75 | 70 | 73 |
| 2 | Hardness(N) | 59 ± 0.32 | 57 ± 0.12 | 62 ± 0.37 | 61 ± 0.29 |
| 3 | Thickness (mm) | 2.5 ± 0.09 | 2.5 ± 0.07 | 2.4 ± 0.06 | 2.5 ± 0.08 |
| 4 | Weight variation(mg) | 0.71 ± 0.15 | 0.69 ± 0.13 | 0.72 ± 0.25 | 0.70 ± 0.13 |
| 5 | Assay (%) | 98.8 ± 0.15 | 97.6 ± 0.11 | 96.5 ± 0.25 | 97.6 ± 0.24 |
| 6 | DR at 60 min (%) | 100 | 98.5 | 99.0 | 97.21 |

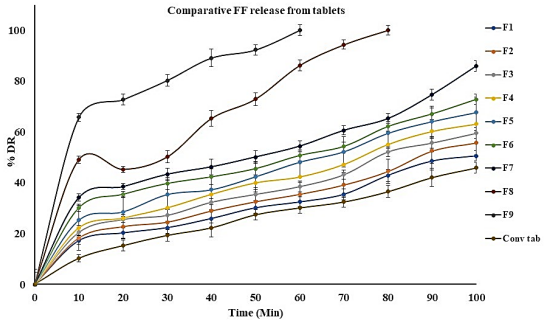


**Figure 7:** Comparative cumulative % drug release from tablets manufactured with S-SMEDDS and conventional tablet

*X-Ray Diffraction*

The substance may be crystalline or amorphous, which can be investigated by X-ray diffraction study. The pure FF was found to be crystalline in nature because X-ray diffraction pattern of FF exhibited multiple strong, high-intensity peaks at diffraction angles (θ) at 14.3°, 16.1°, and 22.2°. There was a small reduction in the intensity of the FF-loaded S-SMEDDS compared to peaks of pure FF. This reduction in the peak is an indication that FF in SMEDDS is in an amorphous form. This notable decrease in peak intensities explains why the FF SMEDDS formulation's increased bioavailability and dissolving rates were so substantial. Figure 4 shows the XRD images.

*DSC*

The thermal analysis of pure FF exhibited a sharp endothermic peak at 80.9°C corelating to the melting point of FF (Figure 5A). The spray-dried S-SMEDDS of FF reveal an endothermic peak at 183.9°C (Figure 5B). The slight change in the endothermic peak demonstrated the proper encapsulation of FF in SMEDDS.

*Saturation Solubility of Pure FF and S-SMEDDS of FF*

FF is a highly lipophilic drug (log *p*=5.24) but having very less aqueous solubility. It belongs to BCS class II and hence shows very poor absorption from GIT leading to poor bioavailability. The saturation solubility of the pure FF and S-SMEDDS of FF was determined in distilled water. As expected, pure FF showed solubility of only 0.0707 µg/mL but the drastic enhancement in the solubility of FF was observed with S-SMEDDS of FF (2.1 µg/mL). The comparative solubility profile of both formulations is presented in Figure 6. Nearly 30-fold solubility enhancement was observed with spray-dried solid SMEDDS of FF. This significant enhancement in solubility might be due to the formation of the amorphous nature of the spray-dried powder containing S-SMEDDS.[21]

*Granule Flow Properties*

The angle of repose of the S-SMEDDS was found to be 0.425 g/mL while TD was 0.716 g/mL. The angle of repose was found to be 26º while CI was found to be < 10; hence, the granules had excellent flow properties. The HR was found to be between 1.00–1.11; hence, the granules have excellent flow properties[22]. Overall, the flow properties of the granules obtained by the spray drying method were found to be excellent, a prime requirement for manufacturing tablet dosage form by direct compression method. Considering all these excellent flow properties, the direct compression method was adopted to develop the tablets containing S-SMEDDS of FF.

*Evaluation of Tablets Containing S-SMEDDS of FF*

The developed tablets were characterized for different parameters. Table 5 depicts the results of parameters evaluated for T-SMEDDS of EZE. The average weight of tablets did not deviate more than 5% w/w and none of the tablets deviated by 10% w/w of average weight, indicating compliance with weight variation test. The produced tablets were found to be hard enough (42-66 N). The average DT of 6 tablets was ranged from 71 to 177 sec showing the ability of CCS as super disintegrants in spontaneity to disperse the tablet in a dissolution medium. T-SMEDDS of FF passes the friability test (< 1%). All physical parameters were found to be within an acceptable range.

*In-vitro Dissolution Study*

A dissolution study in pH 6.8 PBS buffer showed that tablets containing S-SMEDDS had a rapid drug release profile compared to the conventional tablet. The F9 formulation showed a very fast dissolution profile in comparison to other batches. The rapid dissolution profile was due to the presence of S-SMEDDS, FF as well as the presence of CCS. CCS being an excellent super disintegrating agent helped to burst the tablet immediately when it comes in contact with the release media. In addition, S-SMEDDS incorporated in the tablet played a crucial role in solubilizing the FF in pH 6.8 PBS buffer. Due to increased solubility, FF was rapidly released in the buffer. The comparative dissolution profile of the tablets is presented in Table 6 and Figure 7.

*Stability Study*

The formulation F9 was tested for stability studies for 3 months at 40ºC/75% RH condition. There was no significant change noticed during stability studies over 3 months. The results showed the excellent stability of the developed formulation (Table 7).

## CONCLUSION

The present study represents the successful development of dry emulsion tablets using L-SMEDDS with improved solubility and dissolution characteristics. For the conversion of liquid SMEDDS to solid SMEDDS, the spray drying method was found to be an excellent approach to form the amorphous material with enhanced solubility and dissolution rate. The tablets containing S-SMEDDS of FF showed a rapid dissolution compared to tablets manufactured by a conventional method. The optimized formulation of the tablet was stable for 3 months. The current research work demonstrates spray drying as a potential approach to convert the liquid SMEDSS to a solid form with an enhanced solubility and dissolution rate.

## CONFLICT OF INTEREST

Authors do not report any conflict of interest with respect to this research work.

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