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Formulation and Evaluation of Self-Emulsifying Drug Delivery System

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ABSTRACT

The aim of the present study was to formulate and evaluate self - emulsifying drug delivery system of Fenofibrate and Glimepiride. For screening purposes, the solubility of glimepiride and fenofibrate in various oils (Lipids), surfactants and co-surfactants were determined to select a suitable combination of these ingredients. Flow and compressive strength have been shown to depend on the carrier and drying process. Emulsification efficiency was determined and pseudo-ternary phase diagrams were constructed. Formulated S-SNEDDS, prepared by spray drying using Aerosil® 200 as a hydrophobic carrier, provides nanoemulsions with small particle sizes and drug release when subjected to different stresses such as depressed thermodynamic conditions and forever freeze-thaw. In vitro dissolution studies have shown that L-SNEDDS and S-SNEDDS are more effective than crude glimepiride. SEM showed that crystalline glimepiride was present in a transitional amorphous state in SNEDDS formulations prepared with Aerosil® 200 as a vehicle. For the formulation of fenofibrate SNEDDS, Capmul MCM as oil, Cremophor RH 40 as surfactant and Transcutol-P as co-surfactant were used as pre-test. Global size (GS), zeta potential (ZP), polydispersity index (PDI), and 15-minute fenofibrate release. A batch containing 0.471 ml of Capmul MCM oil, and 1.608 ml of Cremophor RH 40: Transcutol-P (3:1) was selected as the best formulation of SNEDDS. The optimized process was subjected to in vitro dissolution for evaluation of drug release compared to the commercial product. The stability study of the refined product was carried out at room temperature and 40°C and 75% relative humidity. The optimum concentration was found to be stable, with more than 90% of the solution dissolved in 15 minutes. The ideal goal can be achieved as soon as possible by establishing a standardized procedure while reducing the number of tests for fenofibrate formulation development.

INTRODUCTION

Oral delivery of many proteins and therapeutic peptides is limited. Due to the limitations of the enzymatic and absorption membranes of the digestive tract, strategies are being sought to address these issues. In the last few years, SEDDS has attracted attention as a potential vehicle for oral peptide and protein delivery. [1] Emulsions are used as drug carriers in pharmaceutical formulations, but they can increase the oral bioavailability of drugs through poor absorption. [2] An important strategy to improve the stability of oral APIs is the use of lipid-based delivery systems. According to the literature, the terminology of lipid-based technologies is highly controversial. Particle size is not important in the determination of microemulsions and nanoemulsions (SMEDDS and SNEDDS). If the droplet size of the emulsion is in the nanoscale range, the term SNEDDS should be used. SEDDS is an oil and surfactant-based formulation that emulsifies rapidly in water and releases slowly. [3] The chemical structure and physical properties of SEDDS are important determinants of application and tolerance. Therefore, these changes should be created in advance of the special education period.[4] Self-emulsification is affected by the surfactant concentration, the quality and structure of the oil/surfactant pair, the oil/surfactant ratio, and the physiological parameters at which self-emulsification occurs, including pH and temperature. SEDDS differs from oral pharmaceuticals because enzymatic digestion changes the additives in the sample. [5] Gastric and pancreatic lipases hydrolyze lipids in the oil phase of SEDDS in the GIT, releasing additional amphiphilic lipid digestion products. Bile lipids are rapidly secreted in the bile and release the digested lipids. The difference in lipid digestion is not related to the lipolysis process in the digestive tract. These parameters include pancreatic and gastric lipase secretions, the pH difference between the intestines and stomach, the pH of lipase activity, and bile secretion, which allows lipolysis products to dissolve the micelles. [6,7] SEDDS has also been developed for many years for oral administration of hydrophilic macromolecular drugs such as pDHA, peptides, proteins and polysaccharides. Due to the hydrophobic ion pairing (HIP) with the coagent charge, which is lipophilic in nature, the combination can be incorporated into the lipophilic phase of SEDDS. Drug release is deliberately varied according to the solubility of the compound in the SEDDS pre-concentrate and release matrix using adjuvants at the required HIP ratio.[8] An increasing number of newly discovered drugs are less soluble in water, thus appearing to be less absorbed. Technology Catalysts International reported in 2002 that approximately 35-40% of new chemical plants found contaminated water.[9]

Materials and methods Drugs and chemicals

Fenofibrate, Glimepiride, Capmul MCM oil, Labrasol, Cremophor RH 40, Transcutol-P, Lauroglycol ^{R} FCC, TWEEN 80, Ethanol, Oleic acid, Sunflower oil, PEG 400, Span 60 etc.

Solubility Study of Glimepride

In order to select the best oils, surfactants and co-surfactants for the production of SNEDDS, the solubility of glimepiride in the raw material oil (castor oil, sesame oil, coconut oil, peanut oil, sunflower oil, eucalyptus oil, cottonseed oil) is investigated. seed oil, oleic acid, sunflower oil, Labrafac®, olive oil, Labrafil® 1944CS, Capmul® MCM, Labrafil® M2125, soybean oil, Capryol® 90, Lauroglycol® FCC, Maisine® 35-1, Miglyol® 812N, Mustard oil, Triacetin®, and Cithrol® GMS), Surfactants (PEG 400, PEG 200, PEG 600, PEG 800, PG, Tween 80, Tween 20, Tween 60, Span 20, Span 60, Span 80, Echoline Phosphid, [% 1] in water w/v: ethanol blend (50:50 v/v)], soybean phosphatidylcholine [1% w/v in water: ethanol blend (50:50 v/v)] and Labrasol®) and co-surfactant substances (Transcutol ® P, ethanol), respectively. Dispense 100 mg of crude glimepiride into clean 5 mL glass bottles, take 1 mL of each oil, surfactant and co-surfactant and vortex for 2 minutes to mix glimepiride and vehicle (CM 101 CYCLO MIXER, REMI, India). Cap the bottle and shake in a 37 ± 0.2 °C water bath for 48 hours. After equilibration, all samples were centrifuged at 10,000 rpm for 15 minutes to remove undissolved glimepiride from the saturated solution. Measure the supernatant and dilute appropriately with ethanol and estimate the glimepiride concentration by HPLC at 228 nm.

Solubility study of Fenofibrate

Excipients were evaluated by determining the balance of fenofibrate in various oils, surfactants, and co-surfactants. Add excess fenofibrate to 2 ml vehicle. Mix the two ingredients in the bottle for 5 minutes using a vacuum cleaner. The mixture in the vial is shaken using a temperature-controlled rotary shaker for 48 hours at 25 ± 1.0 °C. Centrifuge the mixture at 5000 RPM for 15 minutes using a laboratory centrifuge. The supernatant was separated and fenofibrate was extracted in methanol. Surfactants with emulsifying ability are selected by measuring and comparing the percentage of differences between different surfactants and selected oils, to explain the basis for selecting the nanoemulsion treatment from the pseudo-ternary phase diagram. Oils are selected based on their ability to dissolve fenofibrate. Add an equal amount of surfactant to the selected oil. Heat the mixture slowly at

45-50°C to homogenize the product. Dilute the isotropic mixture with 250 mL of distilled water to obtain a good emulsion. The time it takes to form a Mini emulsion is called the dispersion and closure time. Relative turbidity of the final emulsion was observed. Mix the selected surfactant with the co-surfactant. 1:1 S mixed mix. Then, an equal amount of the selected oil is added to the mixture (50:50) and the mixture becomes homogeneous with the help of heat (4550°C). Dilute this isotropic mixture with 250 mL of distilled water to obtain a good emulsion. How long the emulsion takes to produce and how easily it is produced is recorded by recording the number of alcohol inversions required to produce a homogeneous emulsion. Relative turbidity of the final emulsion was observed. Fenofibrate concentration estimated by HPLC at 248 nm.

Construction of ternary phase diagram of Glimepiride

Selected oils, surfactants and co-surfactants were mixed in different proportions and a triple phase diagram was drawn to achieve a self-limiting and stable self-emulsifying effect. To assess the self-emulsifying power, the self-emulsifying power of the prepared emulsion was verified by visual inspection with minor changes. The triple-phase diagram was created by considering factors such as milk preference, phase separation, clarity, and combination of water and chemical precipitation. Place the prepared SNEDDS (200 µL) in a beaker filled with 500 mL distilled water and maintain it at 37 ± 0.2 °C with continuous stirring at 100 rpm using a magnetic stirrer. Relative turbidity of the final emulsion was observed. The stability of the emulsion was confirmed by visual inspection, such as temporary emulsification, precipitation, chemical, phase separation, and disintegration of the emulsion when stored at room temperature (48 hours). A formulation is considered unstable when there is no emulsion formation or when an emulsion is formed and the droplets immediately combine with phase separation and precipitation. The nanoemulsion region is selected from the pseudoternary phase diagram. The results showed that Lauroglycol® FCC, Tween-80 and ethanol were used in different ratios such as 1:1 (F1-4), 1:2 (F10-18) and 2:1 (F19-21) to show the largest nanoemulsion. area. It has also been shown that increasing Lauroglycol® FCC over 40% results in an increase in droplet size and PDI while increasing the percentage of surfactant and co-surfactant results in a slight decrease in size of 60% and PDI.

Construction of ternary phase diagram of fenofibrate

The so-called triple phase diagram is based on the type of mixture or separation process that occurs when the Capmul MCM oil-surfactant/co-surfactant mixture is continuously titrated with water at ambient temperature. To make mixed body surfactants/cosurfactants with HLB values 8.1, 9.4, 10.1, 9, prepare various weight ratio mixtures of selected surfactants/cosurfactants in a ratio of 1:1, 2:1 and 3:1.6, 11.4 and 12.3, respectively. Capmul MCM oil and the surfactant/cosurfactant mixture from each HLB value were separately weighed in glass beakers and a special oil of sufficient weight for the 0.25:4.75-4.5:0.5 surfactant/cosurfactant mixture. Mix and vortex. Each mixture was slowly titrated dropwise with distilled water using a pipette. After each addition of water, the system was vortexed for 10-20 seconds and the final mixture was vortexed for 2-3 minutes at room temperature. The first visual impression of the mixed effect is classified as a motor. Microscopic examination of the final mixture was performed to determine the type of emulsion obtained using water-soluble dyes (e.g. Congo red and methylene blue). Details of visual inspection and microscopic analysis of the mixture were recorded. Keep the mixture at room temperature for 24 hours to equilibrate. After reaching equilibrium, record the last observations. The oil peak in the phase triangle represents Capmul MCM oil, the S/Cos peak represents surfactant/co-surfactant and the remainder represents the water phase.

Preparation of solid SNEDDS of Glimepiride

Different parts of S-SNEDDS are made using a dryer. Suspend hydrophobic carriers (1 g) such as A-200, SFP, SXDP, MCC PH 102 and MS in 100 mL of ethanol, respectively. Similarly, dissolve the hydrophilic carriers (1 g) PVA, Na-CMC, and HPBCD in 100 mL of water, respectively. Each dispersion was spray dried from a 0.7 mm diameter nozzle, a peristaltic pump flow of 16 mL/min, spray air pressure of 4 Kg/cm2, vacuum pressure of -25 mbar, and inlet temperature. Turn off the ignition temperature at 70 °C (for ethanol dispersions) and 100 °C (for aqueous dispersions) and the ignition temperature at 35 and 50 °C, respectively.

Preparation of SNEDDS of Fenofibrate

Pour the appropriate amount of fenofibrate into a glass beaker and add the desired oil, surfactant, and co-surfactant. Mix the mixture by gentle mixing and vortexing on a magnetic

stirrer at 200 rpm at 40 ºC until fenofibrate dissolves. Store the mixture in an airtight container at room temperature until next use.

Evaluation Parameters of Glimepiride Emulsion droplet size and zeta potential analysis

Particle size, PDI and zeta potential of SNEDDS were determined by photon correlation spectroscopy (PCS) using Malvern zeta sizer nano ZS90 (Malvern Instruments Ltd., UK). Data with 50 mV laser at 90° angle in disposable polystyrene cell at 25°C. L-SNEDDS/S-SNEDDS samples (100 µL) were diluted with 100 mL of double distilled water. Each run has 12 sub-runs at 2 minutes. All studies were repeated in triplicate and average data were recorded.

Transmission electron microscopy (TEM)

TEM studies were carried out to examine the droplet morphology of the selected S-SNEDDS formulations. The model used for testing is H-7500, Hitachi, Japan. The program is complete. The ideal formulation of SNEDDS (100 µL) was diluted with 10 mL of double distilled water. For negative staining of the sample, place a drop of emulsion on the carbon-coated copper grid to leave a thin film and use filter paper to remove excess solution. After 10 minutes, drip 2% w/v phosphotungstic acid (PTA) solution on the copper plate for approximately 1 minute, then drain excess liquid. Allow the plate to dry and examine the sample by TEM.

Scanning electron microscopy (SEM) of S-SNEDDS

Surface morphologies of intact glimepiride, A-200, physical mixing, and S-SNEDDS were observed by scanning electron microscopy (SEM) as standard. In short, take 12mm diameter double-sided conductive tape and stick it on a metal stud. The sample is then fixed on top. The data station used is the Supra 35VP (Oberkochen, Zeiss, Germany) with an acceleration voltage of 1.00 kV.

In vitro dissolution studies

Use 500 mL of simulated gastric juice (SGF) (pH 1.2) maintained at 37 ± 0.5 °C at a mixing speed of 50 ± 4 rpm. Glimepiride, S-SNEDDS powder and L-SNEDDS raw materials were weighed and packaged into "0" size hard gelatine capsules and stored in baskets to act as a mix. Samples (5 mL) were drawn after 5, 10, 15, 30, 45 and 60 minutes using a 0.2 µm filter

membrane. The filtrate was then centrifuged at 10,000 rpm for 15 minutes. Supernatants were collected and analyzed for glimepiride using HPLC at 228 nm. This study was completed six times and the mean data (± s.d.) noted down.

Evaluation parameters of fenofibrate Refractive Index and %Transmittance

Add to the self-nano emulsifier drug delivery system (SNEDDS) 250 ml of filtered water at room temperature with continuous stirring (50-60 rpm) in a magnetic machine. Measure the index of the design using an Abbe refractometer and the percentage of 694 nm in the UV-Vis spectrophotometer using a blank.

Measurement of Globule Size, Polydispersity Index (PDI) and Zeta Potential

The particle size, polydispersity index (PDI) and zeta potential of SNEDDS were determined using Zetasizer Nano ZS (Malvern Instruments, UK) based on the principle of laser light diffraction. The light source is a HeNe gas laser with an intensity of 4 mW. Observe the light scattering at a 90° angle at 25°C. Add SNEDDS (after appropriate dilution) to the cell sample and place it in the sample holder and measure using the software of the same instrument.

Drug Content

Fenofibrate was extracted from the pre-weighted SNEDDS by dissolving it in 25 ml of methanol. Separate the methanol extract and analyze the fenofibrate content in the methanol extract HPLC method with fenofibrate standard methanol solution as a control.

Effect of Dilution and Aqueous Phase Composition

The effect of SNEDDS on dilution strength and aqueous phase composition was evaluated using an optimized fenofibrate SNEDDS composition. Disperse fenofibrate SNEDDS in 250 mL of aqueous phase (distilled water) with gentle mixing. Store the resulting nanoemulsions at 25 ± 2 °C and measure drug precipitation, phase separation and mass change within 24 hours.

Measurement of Viscosity of Fenofibrate SNEDDS

The viscosity of SNEDDS containing fenofibrate was measured at 25°C using a Brookfield viscometer. Measured using an S-61 rotor at 30 rpm before and after dilution with water (250 ml).

Measurement of pH Fenofibrate SNEDDS

The pH of SNEDDS comprising Fenofibrate was measured by using a pH meter (Lab India) at controlled room temperature. It was measured before and after dilution with water (250 ml).

Self-Emulsification and Precipitation Assessment

The self-emulsifying properties of the SNEDDS formulations were evaluated by visual assessment as previously described. The difference is classified according to the emulsification rate, the clarity, and stability of the resulting emulsion. Visual tests were performed by adding preconcentrate (SNEDDS) dropwise to 250 mL distilled water. This is done in a beaker at room temperature with gentle magnetic stirring at 50-100 rpm. The precipitate was evaluated by visual inspection of the final emulsion after 24 hours. Processes are classified as clear (clear or clear, with a blue tint), opaque (cloudy), stable (no precipitation after 24 hours), or unstable (showing precipitation within 24 hours).

Centrifugation and Freeze–Thaw Cycle

SNEDDS containing Fenofibrate was diluted with 250 ml and 900 ml distilled water and centrifuged at 5000 rpm for 30 minutes. Additionally, they were subjected to freeze–thaw cycle with storage at -20°C for 24 hours followed by another 24 hours at 40°C. Nano emulsions were visually observed for phase separation and precipitation, whereas their physical stability was assessed by measuring globule size before and after centrifugation and freeze–thaw cycle**.**

In-Vitro Drug Release Study

In vitro, drug release studies were conducted for the formulation, product and active ingredient using the USP Type II dissolution tester (Electrolab TDT-06P, India). The dissolution medium (900 mL water) was held at 37 ± 0.5 °C and rotated at 50 rpm. Periodically (10, 15, 20, 30, 45, 60 min) aliquots were collected and replaced with fresh dissolution medium. The part is after filtering by HPLC analysis of fenofibrate content at 0. 45µ PVDF filter paper, 248nm.

Stability Study of Fenofibrate SNEDDS

The physical and chemical stability of fenofibrate SNEDDS was evaluated according to ICH guidelines at 25 ± 3 °C / 60 ± 5% (room temperature). Fenofibrate SNEDDS is stored in a glass bottle for 6 months. Samples were taken at 0, 1, 3, and 6 months and evaluated for physical changes, bead size, zeta potential, drug content, and in vitro drug release.

Results and Discussion Solubility Study of Glimepiride

The solubility of glimepiride in oil, surfactants, co-surfactants, oil mixture and surfactant mixture was determined. The results are shown in Table 1. Among selected oils, glimepiride has the highest solubility in Lauroglycol® FCC (14.46 ± 2.18 µg/mL) Among surfactants, glimepiride has the highest solubility in Tween-80 (212.92 ± 1.48 µg/mL), and among co-surfactants, raw material glimepiride has the highest solubility in ethanol (10.75 ± µg/ml). Hence these excipients were sort listed for the preparation of SNEEDS of Glimepiride.

Table 1. Solubility of glimepiride in various vehicles (each value represents the mean ± SD, n = 3).

Vehicle	Solubility of raw glimepiride (µg/mL)	Vehicle	Solubility of raw glimepiride (µg/mL)
Water	6 ± 1.16		
Oil		**Surfactants**	
Oleic acid	7.21± 1.15	**Tween 80**	**212.92 ± 1.48**
Sunflower oil	1.11 ± 0.09	PEG 200	19.44 ± 1.15
Olive oil	11.07 ± 3.33	PEG 400	10.85± 0.19
Labrafil M® 1944 CS	7.13 ± 2.8	PEG 600	11.76 ± 3.18
Labrafac® CC	2.44 ± 0.18	PEG 800	38.81 ± 1.56
Castor oil	1.38 ± 0.17	PG	11.78 ± 3.47
Sesame oil	1.11 ± 0.02	Span 20	9.54 ± 1.16
Peanut oil	2.87 ± 0.45	Span 40	9.81 ± 2.12
Eucalyptus oil	2.33 ± 0.76	Span 60	11.81 ± 2.87
Cottonseed oil	6.82± 1.34	Span 80	13.66 ± 1.16
Mustard oil	0.6 ± 2.54	Transcutol® P	18.21 ± 1.22
Capmul® MCM	5.6 ± 1.18	**Ethanol**	**10.75 ± 0.18**
Labrafiil® M 2125 CS	6.8± 0.18	Soya PC	07.01± 2.12
Soyabean oil	4.4± 2.14	Egg PC	13.13± 3.22

Maisine® 35-1	3.66 ± 0.95		
Lauroglycol® FCC	**14.46 ± 2.18**		
Triacetin	1.85 ± 1.26		
Miglyol® 812 N	4.11 ± 2.23		
Surfactants Capryol™ 90	18.8 ± 3.22		
Cithrol GMC	3.17± 2.43		
Labrasol®	18.23±1.24		
Tween 20	4.64 ± 1.41		
Tween 60	8.72 ± 1.67		

Solubility study of Fenofibrate

The carrier should have good drug solubility, which is important for SNEDDS production. The solubility results of fenofibrate in various vehicles are shown in Table 2. Fenofibrate has excellent solubility in Capmul MCM oil (caprylic/capric glyceryl) compared to other lipid vehicles. Fenofibrate has excellent solubility in Cremophor RH 40 (polyoxyethylene 40 hydrogenated castor oil) and Transcutol-P compared to other surfactants and co-surfactants. Capmul MCM oil was chosen as the oil, Cremophor RH 40 as the surfactant, and Transcutol-P as the co-surfactant for the approved SNEDDS formulation to improve drug loading.

Table 2: Solubility of Fenofibrate.

Material	**Average (mg/ml) ± SD**
	Fenofibrate
Castor Oil	72.18 ± 0.15
Labrafac PG	58.85 ± 0.14
Oleic Acid	21.43 ± 0.11
Capmul MCM Oil	178.93 ± 0.38
Light Liquid Paraffin	25.70 ± 0.12
Tween-80	74.80 ± 0.20
Span-20	47.22 ± 0.24
Labrafac Lipophile WL 1349	63.89 ± 0.22
Cremophor EL	61.48 ± 0.18
Labrasol	119.93 ± 0.46
Capmul GMO-50	36.29 ± 0.14
Captex 355	25.19 ± 0.08
PEG-400	36.39 ± 0.11
Propylene Glycol	34.17 ± 0.11

Transcutol-P	177.11 ± 0.43
Cremophor RH 40	112.85 ± 0.31

Ternary phase diagram of Glimepiride

Different compositions of SEDDS were produced and their self-emulsifying properties were observed. The produced emulsions were determined as SNEDDS, SMEDDS and normal emulsions according to turbidity measurements and visual acuity. A triple-phase diagram was created in the presence of glimepiride to determine the area of self-emulsification and to optimize the oil, surfactant and co-surfactant in the formulation. Component concentrations are expressed as volume/vol% (%v/v) in the triple phase diagram. The results showed that Lauroglycol® FCC, Tween-80 and ethanol were used in different ratios such as 1:1 (F1-3), 1:2 (F10-12) and 2:1 (F1921) to widen the biggest shows. Nanoemulsion area and minimum emulsification time (less than 1 minute).

Ternary Phase diagram of fenofibrate

A pseudo-triple phase image was generated in the presence of fenofibrate to obtain an appropriate balance of oil, water, surfactant, and co-surfactant. After adding SNEDDS to the aqueous medium, a good oil-water emulsion can be formed by stress alone. The S/CoS mix can form any type of dispersion, including conventional w/w and w/w emulsions, w/w and w/w microemulsions. Large regions of transparent isocratic solutions (o/w microemulsions/nanoemulsions) were formed along the oil-S/CoS axis in the oil-rich region. Minimum amount of Cremophor RH 40 / Transcutol-P (3:1) in HLB 12 Produced in 11.05% isocratic system (fenofibrate). The smaller the S/CoS ratio in the microemulsion/nanoemulsion system, the higher the solubility of S/CoS, the better the oil and S/CoS HLB ratio, and the higher the frozen product stability. Cremophor RH 40/TranscutolP (3:1) was chosen as the best S/Cos according to its solubility ability.

Evaluation parameters of Glimepiride Droplet size and polydispersity index (PDI) of L-SNEDDS of Glimepiride

The selected L-SNEDDS formulations (F1-3, 10-12 and 19-21) were subjected for droplet size and polydispersity index analysis. It was observed that formulations containing Smix in the ratio of 1:1 revealed very good droplet size having a z-average less than 100 nm along with PDI less than 0.5. The other formulations (F10-13 and 19-21) have also shown droplet

size in nanometer range with greater PDI values (Table 4). It was also observed that increasing the amount of Lauroglycol® FCC above 30% (300 µL) caused increase in droplet size as well as PDI, whereas, increase in surfactant and co-surfactant percentage above 70 revealed in decrease in droplet size and PDI. The increasing order of droplet size and PDI was:

F1< F10< F19< F2< F11< F20< F3< F12< F21

Formulation "F1" showed least droplet size and PDI, hence, it was selected as the best batch and study was continued further on "F1".

Table 3. Composition of selected batches of glimepiride loaded L-SNEDDS (% w/w) and evaluation parameters.

Formulation code	S/CS (Smix) (%w/w)	Oil/Smix (%w/w)	Mean droplet size(nm)	PDI	Cloud point (°C)	Appearance separation after 48h centrifugation	Phase	Phase separation after
F1		10:90	117.91	0.436	93.16	TP*		
F2	1:1	20:80	262.45	0.561	93.54	TL**		
F3		30:70	346.66	0.662	91.18	TL		
F10		10:90	152.41	0.448	96.54	TP		
F11	1:2	20:80	276.34	0.566	91.48	TL	No	No
F12		30:70	564.16	0.680	88.18	TL		
F19		10:90	167.22	0.467	99.16	TP		
F20	2:1	20:80	294.36	0.654	87.38	TL		
F21		30:70	528.88	0.718	81.16	TL		

TP* - Transparent; TL**- Translucent

Droplet size and PDI analysis of solid-SNEDDS (S-SNEDDS) of Glimepiride

L-SNEDDS is prepared by spray drying (SD) using a variety of hydrophobic and hydrophilic carriers. The mean diameter and PDI of the S-SNEDDS and L-SNEDDS formulations are listed in Table 4. The best L-SNEDDS have a small average size of 117.91 nm and a very good PDI 0.436. It is noted that the average size and PDI are highly dependent on the machining process and the supporting material. Spray-dried S-SNEDDS powder showed rapid dispersion (within 30 s) when diluted in water. It is important to note that hydrophobic support is more effective than hydrophilic support. Lactose, magnesium stearate, Na-CMC

and HPβ-CD were investigated for size reduction. Only Aerosil® 200 has a diameter close to L-SNEDDS. The average droplet diameter of S-SNEDDS prepared by using various solid carriers was:

Aerosil®200 < SXDP < SFP < MCC PH102 < HPβ-CD < Na-CMC < MS< Lactose

Table 4 Droplet size and PDI of various carriers.

Formulations/S-SNEDS prepared using different carriers	**Droplet size (nm)**	**Polydispersity Indices (PDI)**
L-SNEDDS	117.91 ± 1.18	0.436 ± 0.06
Aerosil® 200	126.18 ± 3.38	0.456 ± 0.09
SXDP	144.19 ± 2.31	0.56 ± 0.012
SFP	181.18 ± 1.16	0.59 ± 0.021
MCC PH102	266.67 ± 1.46	0.66 ± 0.028
HPβ-CD	387.26 ± 3.23	0.42 ± 0.001
Na-CMC	418.16 ± 1.34	0.51 ± 0.02
MS	486.18 ± 9.69	0.42 ± 0.021
Lactose	566.18 ± 9.69	0.65 ± 0.034

Dissolution studies of S-SNEDDS powder (Aerosil) of Glimepiride

In vitro dissolution studies showed nearly overlapping drug release data for S-SNEDDS powder and L-SNEDDS (P>0.05). All formulations exhibited rapid drug release (>90%) within 10 minutes and almost complete drug release within 15 minutes. In contrast, the drug showed a maximum release of only 48% over a 60-minute period. Therefore, when compared with the raw material glimepiride, the separation of the preparation increased by about 2.08 times. In addition, the physical interaction between SNEDDS and the hydrophobic surface of the Aerosil® 200 silica particles is also responsible for preventing drug separation during the initiation period. Overall, statistical analysis of separation behaviour by calculating similarity (f2) from the comparison curve showed 70.21 for S-SNEDDS powder and L-SNEDDS, respectively. In both cases, f2 values >50 indicate similar drug release data for liquid and solid SNEDDS formulations, the two formulations having product available.

Zeta Potential of Glimepiride

The zeta potential of S-SNEDDS [Aerosil®] was found to be -18.16 mV.

TEM analysis of Glimepiride

The TEM image clearly shows the spherical droplets of S-SNEDDS at a scale of 200 nm (0.2 µm). These images confirm that the droplets are not agglomerated, clear and nanoscale spherical, and correlate with photon correlation spectroscopy results for droplet size analysis.

Scanning Electron Microscopy (SEM) of Glimepiride

Scanning electron micrographs of Glimepiride, Aerosil® 200 powder and their SNEDDS formulation {Glimepirid-S-SNEDDS powder [Aerosil®] are shown in Figure 13. Glimepiride appears as flat, knife-edged flat-topped rectangular crystals with sharp, irregular edges. Due to its amorphous structure, Aerosil® 200 exhibits a poor quality with no visible crystallinity. SSNEDDS appeared as a rough surface with porosity and poor pore size, indicating that liquid SNEDDS was absorbed or coated in the pores of Aerosil® 200.

Evaluation of Fenofibrate:

(a) Refractive Index and Turbidimetric Evaluation

The results of the refractive index and % transmittance of batches T1 to T9 are shown in Table 5. The refractive index and percent transmittance data proved the transparency of the system.

Table 5: Refractive Index and %Transmittance of various SNEDDS formulations

Batches	Refractive Index	% Transmittance
	Water (250 ml)	Water (250 ml)
T1	1.373	91.36
T2	1.359	97.43
T3	1.352	97.86
T4	1.369	92.75
T5	1.338	100.0
T6	1.347	98.14
T7	1.362	93.52
T8	1.339	99.31
T9	1.342	98.92

(b) Measurement of Globule Size, Polydispersity Index, and Zeta Potential

The globule size distribution behind the self-nanoemulsion is important to evaluate the self-nanoemulsion system. Smaller drops have a larger surface area to deliver the drug. Dimensional analysis, standard deviation, and zeta potential data are shown in Table 6.

Table 6: Droplet size analysis, Polydispersity Index, and Zeta Potential data of SNEDDS formulation

Batches	Globule Size (nm)	Polydispersity Index	Zeta Potential (mV)
T1	357.0	0.428	-15.12
T2	64.1	0.283	-16.40
T3	55.8	0.221	-17.12
T4	332.0	0.427	-15.68
T5	20.7	0.189	-27.96
T6	44.0	0.233	-17.60
T7	307.0	0.426	-15.96
T8	26.6	0.195	-24.28
T9	29.2	0.191	-21.12

In general, the increased electrostatic repulsion of the microemulsion/nanoemulsion droplets prevents the microemulsion/nanoemulsion droplets from coalescing. Conversely, a decrease in electrostatic repulsion leads to phase separation. Fenofibrate SNEDDS (T5) diluted in distilled water has a zeta potential of -27.96 mV. Many studies have shown that the zeta potential plays an important role in the stability of microemulsions/nanoemulsions.

(c) Drug Content

The drug content of SNEDDS formulation can be found by methanolic extract of SNEDDS was analyzed by HPLC at 248nm for Fenofibrate. Drug content of various formulations shown in Table 7 (n=3).

Table 7: Drug content in various SNEDDS formulations (Fenofibrate)

Batches	% Drug Content			Average	Standard Deviation
	I	II	III		
T1	99.1	98.3	99.3	98.9	0.53
T2	98.3	98.6	98.9	98.6	0.30
T3	99.4	100.2	99.1	99.6	0.57
T4	99.8	99.1	100.4	99.8	0.65
T5	100.2	101.1	100.5	100.6	0.46
T6	99.2	100.4	99.5	99.7	0.62
T7	101.4	99.8	100.6	100.6	0.80
T8	99.6	100.7	99.9	100.1	0.57
T9	100.3	99.1	100.9	100.1	0.92

(d) Effect of Dilution and Aqueous Phase Composition on SNEDDS

The effect of dilution and aqueous phase composition on SNEDDS are shown in Table 8. Data was shown for various SNEDDS formulation at 25 ± 2°C for 24 hour.

Table 8: Effect of dilution and aqueous phase composition on SNEDDS formulation			
Batches	**Medium**	**Drug Precipitation**	**Phase Separation**
T1	Distil water	Not found	Not found
T2	Distil water	Not found	Not found
T3	Distil water	Not found	Not found
T4	Distil water	Not found	Not found
T5	Distil water	Not found	Not found
T6	Distil water	Not found	Not found
T7	Distil water	Not found	Not found
T8	Distil water	Not found	Not found
T9	Distil water	Not found	Not found

Ability of nanoemulsion to be diluted without any phase separation and drug precipitation is essential for its use as a drug delivery system. The results indicated that SNEDDS can be diluted up to 1,000-fold without any phase separation or drug precipitation and remained stable over a period of 24 hr. Aqueous phase composition also did not affect physical stability of resulting nanoemulsion. These results were in contrast with phospholipids-based microemulsion systems described in literature that became turbid leading to phase separation after dilution. This suggested that Cremophor RH 40 and Transcutol-P system could reside at the interface for sufficiently longer period despite larger dilutions, producing stable microemulsion/nanoemulsion. In addition, drug was not precipitated even after large dilution of up to 24 hours, thus confirming solvent capacity of nanoemulsion.

(e) Measurement of Viscosity and pH of SNEDDS

The viscosity of SNEDDS was measured by using Brookfield viscometer at 25°C temperature. Spindle S-61 was selected for the measurement of viscosity of various SNEDDS formulations. Viscosity measurement was done at 30 rpm before and after dilution with water. pH of SNEDDS formulations was measured by using pH meter at room temperature. pH of SNEDDS formulations was also measured before and after dilution with distil water. Viscosity and pH data of SNEDDS formulation was shown in Table 9.

Table 9: Viscosity and pH of various SNEDDS formulations				
Batches	Viscosity (CP)		pH	
	Dilution		Dilution	
	Before	After	Before	After
T1	97.8	1.04	7.731	6.423
T2	114.9	1.01	7.681	6.466
T3	105.6	1.08	7.659	6.531
T4	106.0	1.04	7.186	6.505
T5	109.4	1.02	7.710	6.496
T6	107.3	1.03	7.522	6.481
T7	104.5	1.05	7.539	6.493
T8	117.0	1.02	7.485	6.512
T9	115.0	1.05	7.565	6.501

Viscosity data has shown that the viscosity of the formulation before dilution was much better than after dilution of the formulation. Data has shown that the viscosity of formulation after dilution was near to viscosity of water.

(f) Self-Emulsification and Precipitation Assessment

The results of self Nano emulsification and precipitation studies are shown in Table 10.

Table 10: Self-emulsification and Precipitation of various SNEDDS formulations			
Batches	Dispersion Time (second)	Clarity	Precipitation
T1	70	Translucent to clear	Stable
T2	55	clear	Stable
T3	55	clear	Stable
T4	58	Translucent to clear	Stable
T5	40	clear	Stable
T6	50	clear	Stable
T7	62	Translucent to clear	Stable
T8	43	clear	Stable
T9	42	clear	Stable

Formulation T5 and T9 showed less dispersion time, and clear and stable nanoemulsion.

(g) Centrifugation and Freeze– Thaw Cycle

The effect of centrifugation and freeze–thaw cycling on phase separation of nanoemulsion and precipitation of drug is shown in Table 11. Both accelerated tests were done to determine the stability of nanoemulsion under stress conditions.

Table 11: Centrifugation and Freeze-Thaw Cycle data of various SNEDDS formulations

Batches	Centrifugation		Freeze-thaw cycle	
	Phase separation	Drug precipitation	Phase separation	Drug precipitation
T1	No	Slight	No	Slight
T2	No	No	No	No
T3	No	No	No	No
T4	No	No	No	No
T5	No	No	No	No
T6	No	No	No	No
T7	No	No	No	No
T8	No	No	No	No
T9	No	No	No	No

A rapid test was performed on equipment that did not show precipitate, and the phase separation was found to be stable after centrifugation. Similarly, materials that survive freeze-thaw cycles have been shown to regenerate from decomposition and precipitates exhibit some nanoemulsion stability under stress pressure after exposure to freeze-thaw cycles.

(h) In Vitro Drug Release Study

A higher drug release was observed from the SNEDDS series T5 compared to fenofibrate generic powder and commercial drug formulation. This will demonstrate how fast the SNEDDS formulation occurs in the spontaneous formation of nanoemulsions with small droplet sizes allowing the rapid release of the drug into the aqueous phase, fenofibrate drug

powder and commercial drug formulations. Therefore, greater availability of dissolved fenofibrate from SNEDDS formulations will lead to greater absorption and greater oral bioavailability.

Table 12: Comparison of drug release profile of various SNEDDS formulations with pure drug and marketed formulation (Fenofibrate)

Batches	% Drug Release (Fenofibrate) (Mean ± SD)						
	Time (Minutes)						
	0	10	15	20	30	45	60
T1	0±0	88.6±1.9	91.8±2.1	96.0±1.1	98.4±0.4	99.4±0.2	99.5±0.2
T2	0±0	90.7±2.1	93.9±1.8	96.7±0.5	98.7±0.3	99.2±0.4	99.7±0.2
T3	0±0	90.3±1.1	93.1±1.5	95.8±1.1	98.4±0.4	99.4±0.2	99.6±0.2
T4	0±0	90.6±1.8	93.8±1.3	97.1±1.5	98.7±0.9	99.3±1.1	99.5±0.5
T5	0±0	92.6±1.5	96.7±1.2	99.5±1.1	100.1±0.2	99.8±0.1	99.6±0.3
T6	0±0	91.2±2.0	94.1±2.0	96.9±1.4	98.9±0.6	99.5±0.5	99.7±0.3
T7	0±0	90.1±2.0	93.5±1.8	96.7±0.6	98.3±0.7	98.9±0.6	99.2±0.4
T8	0±0	91.2±2.0	94.5±1.1	96.9±1.4	98.9±0.6	99.5±0.5	99.7±0.3
T9	0±0	91.2±1.7	95.0±1.2	97.5±1.2	98.9±0.4	99.2±0.2	99.5±0.3
Pure drug	0±0	7.3± 0.7	17.6±0.8	19.1±0.5	27.4±1.1	38.7±0.4	48.2±0.5
Fenostat	0±0	14.1±0.2	22.8±0.7	23.2±0.8	32.4±0.5	47.5±1.4	59.3±1.4

Stability study of Fenofibrate SNEDDS optimized batch (OP1)

The stability study of the optimized batch (OP1) was done at two different storage conditions:

1. Room temperature
2. Accelerated condition (40°C & 75% RH)

The stability chamber is used for accelerated conditions. Particle size, zeta potential, drug content, and drug release of fenofibrate were varied over time for 15 minutes to determine the stability of the drug in the sample at different locations.

Results of Globule size and Zeta potential at storage conditions

The globule size and zeta potential of the optimized stack (OP1) were measured periodically by Zetasizer. globule size and Zeta potential were measured after 1, 3 and 6 months. The results are summarized in Table 13 and Table 14.

Table 13: Globule size of the optimized batch at storage conditions				
Storage Conditions	**Average of Globule Size (nm)**			
	Initial	**1 Month**	**3 Month**	**6 Month**
Room Temperature	78.3	79.2	82.1	82.5
Accelerated Conditions	78.3	79.8	83.3	83.9

Table 14: Zeta Potential of optimized batch at storage conditions				
Storage Conditions	**Zeta Potential (mV)**			
	Initial	**1 Month**	**3 Month**	**6 Month**
Room Temperature	-23.13	-22.38	-22.24	-21.79
Accelerated Conditions	-23.13	-22.45	-22.92	-21.47

Drug content determination at storage conditions

Drug content was measured by the HPLC method. Table 15 represents the results of chemical drug stability during the storage conditions. It was summarized that there was no significant change in drug amount during 6 months. The optimized batch (OP1) was found stable chemically.

Table 15: Drug content of optimized batch at storage conditions				
Storage Conditions	**% Assay (±) SD (For Fenofibrate)**			
	Initial	**1 Month**	**3 Month**	**6 Month**
Room Temperature	100.2 ± 0.46	100.1 ± 0.27	99.7 ± 0.52	99.4 ± 0.38
Accelerated Conditions	100.2 ± 0.46	100.0 ± 0.58	99.4 ± 0.65	99.1 ± 0.62

Drug release at 15 minutes for Fenofibrate determination at storage conditions

Drug release at 15 minutes for Fenofibrate was carried out. Table 16 represents the results of chemical drug stability during the storage conditions. It was assured that there was more than 90% drug dissolution was achieved in 15 minutes during 6 months. The optimized batch (OP1) was found stable chemically.

Table 16: Drug release at 15 minutes for Fenofibrate for an optimized batch at storage conditions				
Storage Condition	**% Drug release at 15 minutes for Fenofibrate (±) SD**			
	Initial	**1 Month**	**3 Month**	**6 Month**
Room Temperature	96.2 ± 1.2	97.4 ± 1.7	97.7 ± 2.4	96.4 ± 1.9
Accelerated Condition	96.2 ± 1.2	97.1 ± 1.6	96.9 ± 2.1	96.1 ± 2.5

Comparison of in vitro drug release between optimized batch (OP1), pure drug powder, and marketed product

The Fenofibrate release of the optimized batch (OP1) was correlate with pure drug powder and marketed capsule product. The marketed product was FENOSTAT of Ordain Health Care Global Pvt Ltd. which is a conventional capsule formulation.

Table 17: Comparison of Fenofibrate release profile of batch OP1 with pure drug and marketed formulation							
Batches	**% Drug Release (Mean ± SD)**						
	Time (Minutes)						
	0	**10**	**15**	**20**	**30**	**45**	**60**
OP1	0±0	92.1±1.5	96.2±1.2	99.7±1.1	100.1±0.2	99.6±0.1	99.7±0.3
Pure drug	0±0	7.3± 0.7	17.6±0.8	19.1±0.5	27.4±1.1	38.7±0.4	48.2±0.5
Fenostat	0±0	14.1±0.2	22.8±0.7	23.2±0.8	32.4±0.5	47.5±1.4	59.3±1.4

Table 18: Dissolution Efficiency (DE) for optimized batch (OP1) and marketed formulation (Fenostat)				
Time points (min)	**% Drug Release (Mean)**			
	Fenofibrate			
	OP1	**Area**	**Fenostat**	**Area**
0	0.0	460.5	0.0	70.5
10	92.1	470.8	14.1	92.3
15	96.2	489.8	22.8	115.0
20	99.7	999.0	23.2	278.0
30	100.1	1497.8	32.4	599.3
45	99.6	1494.8	47.5	801.0
60	99.7	-	59.3	-
	DE	**90.21**	**DE**	**32.60**

Better drug release was observed for the improved formulation (OP1) compared to pure drug powder and commercial drug (Fig. 20). This will show that optimization of SNEDDS leads to the emergence of small spherical nanoemulsions that allow the drug to dissolve rapidly in the water phase compared to pure drug powder and sample work. Similarity characteristics (F2) and separation efficiency were calculated for the effective batch (OP1) and the commercial model (Fenostat) (Tables 18 and 19). The F2 value of the fenofibrate optimization is 10.64. The results of the F2 value show that there is a difference between the optimization and the production model.

The commercial formulation of fenofibrate has a dissociation factor of 32.60. The combined activity of fenofibrate is 90.21. Therefore, it can be concluded that the optimization is best for the production model. Therefore, a higher concentration of dissolved fenofibrate from SNEDDS formulations will result in greater absorption and higher oral bioavailability.

CONCLUSION

SNEDDS are isotropic mixtures of oils, surfactants and sometimes co-surfactants or co-solvents. Homogeneous, transparent (or at least translucent), isotropic and thermodynamically stable dispersions in an aqueous medium will cause stress. SNEDDS is ideal for dose formulation for poorly soluble drugs. SNEDDS of glimepiride was performed with Lauroglycol FCC, Tween 80 and ethanol as components. Additionally, optimization of L-SNEDDS was achieved using a drying process to produce solid SNEDDS (S-SNEDDS) using both hydrophilic and hydrophobic support materials. Then, the microparticle was examined in detail with biopharmaceutical and stability studies. Flow and compressive strength have been shown to depend on the carrier and drying process. Formulated S-SNEDDS, prepared by spray drying using Aerosil® 200 as a hydrophobic carrier, provides nanoemulsions with small particle sizes and drug release when subjected to different stresses such as depressed thermodynamic conditions and forever freeze-thaw. In vitro dissolution studies have shown that L-SNEDDS and S-SNEDDS are more effective than crude glimepiride. SEM showed that crystalline glimepiride was present in a transitional amorphous state in SNEDDS formulations prepared with Aerosil® 200 as a vehicle. Therefore, the results of the present study confirm the successful selection of the treatment modality for L-SNEDDS and estimate the magnitude of S-SNEDDS formation using spray drying. Fenofibrate is a BCS class II drug with poor solubility and high permeability. For the formulation of fenofibrate SNEDDS, Capmul MCM as oil, Cremophor RH 40 as surfactant

and Transcutol-P as co-surfactant were used as pre-test. Global size (GS), zeta potential (ZP), polydispersity index (PDI), and 15-minute fenofibrate release. A batch containing 0.471 ml of Capmul MCM oil, and 1.608 ml of Cremophor RH 40: Transcutol-P (3:1) was selected as the best formulation of SNEDDS. Prepare the checkpoint group to check the evolution balance. A so-called triple-phase diagram of a system consisting of a surfactant co-surfactant and a gas phase has been developed. The area surrounded by solid lines indicates the self-emulsifying region. In this area, the ternary mix should gradually form a good oil-in-water emulsion. This is possible because surfactants are strong on the surface of the emulsion droplets, reducing the interfacial free energy and causing thermodynamic self dissipation, providing a mechanical barrier to coalescence. Co-surfactants increase interfacial mobility by penetrating the surfactant film to create spaces between surfactant molecules. The optimized process was subjected to in vitro dissolution for evaluation of drug release compared to the commercial product. The stability study of the refined product was carried out at room temperature and 40°C and 75% relative humidity. The optimum concentration was found to be stable, with more than 90% of the solution dissolved in 15 minutes. The ideal goal can be achieved as soon as possible by establishing a standardized procedure while reducing the number of tests for fenofibrate formulation development. SNEDDS can be used as SNEDDS in different management and personal care and beauty products in the pharmaceutical industry, their quality and usage.

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