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Solubility Enhancement of Gemfibrozil Using Omega 3 Oil for a Potential Antihyperlipidemic Activity

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ABSTRACT

Objective: This study aims to enhance the solubility and bioavailability of Gemfibrozil, a lipid-regulating drug used for treating hyperlipidemia, by formulating it into a self-nanoemulsifying drug delivery system (SNEDDS) using omega-3 oil. **Methods:** Gemfibrozil's solubility was assessed in various oils, surfactants, and co-surfactants. Omega-3 oil, Cremophor RH40, and PEG 400 were selected as the oil, surfactant, and co-surfactant, respectively, based on their solubility profiles. Pseudo-ternary phase diagrams were developed to identify the best nanoemulsion compositions. The formulations were prepared through high-speed homogenization and encapsulated in gelatin capsules. The nanoemulsion was characterized for droplet size, zeta potential, viscosity, and stability. In vitro drug release and thermodynamic stability studies were also conducted. **Results:** The optimized nanoemulsion showed a significant improvement in Gemfibrozil's solubility, with omega-3 oil exhibiting the highest solubility at 79.42 mg/mL. The formulation achieved a droplet size of 90.7 nm and a zeta potential of -39.46 mV, indicating stability. In vitro drug release studies demonstrated that the nanoemulsion capsule released 88.51% of the drug within 45 minutes, compared to 34.28% from a plain drug suspension. Stability tests confirmed the robustness of the formulation under varying conditions. **Conclusion:** The omega-3 oil-based SNEDDS formulation significantly enhances the solubility, bioavailability, and therapeutic potential of Gemfibrozil. This approach provides a promising alternative for improving the management of hyperlipidemia.

Keywords: Hyperlipidemia**,** Self-nanoemulsifying drug delivery system (SNEDDS), Gemfibrozil, Omega oil, Bioavailability, Solubility enhancement.

INTRODUCTION

Hyperlipidemia is a condition characterized by abnormally elevated levels of lipids in the blood. These lipids include cholesterol and triglycerides, essential for normal body functions but can cause health problems in higher concentrations. Hyperlipidemia is often associated with other risk factors such as hypertension, diabetes, obesity, and metabolic syndrome. This multifactorial risk profile increases the burden of cardiovascular diseases [1-3].

Within the domain of therapeutic interventions, Gemfibrozil is a lipid-regulating medication used to lower triglyceride levels by decreasing low-density lipoprotein (LDL) cholesterol, raising high-density lipoprotein (HDL) cholesterol, and enhancing fatty acid oxidation. Gemfibrozil also increases the synthesis of apolipoproteins A-I and A-II, resulting in higher HDL cholesterol levels. By activating peroxisome proliferator-activated receptors (PPARs), Gemfibrozil facilitates the catabolism of lipoprotein lipase, leading to the reduction of triglyceride-rich particles. This multi-faceted mechanism of action makes Gemfibrozil an effective treatment option for patients with hyperlipidemia and other related cardiovascular conditions [4,5].

Gemfibrozil (Gem) belongs to BCS Class II drug which poses challenges in achieving optimal solubility in water-based formulations, which limits its effective absorption and bioavailability on oral administration. Gemfibrozil has short t half and also undergoes significant first-pass metabolism in the liver thereby reducing the amount of active drug that reaches systemic circulation. Gemfibrozil has a relatively short half-life, requiring multiple doses throughout the day to maintain therapeutic levels [6,7].

Omega-3 was utilized as an oil in preparation for Gemfibrozil-loaded self-nanoemulsifying drug delivery systems which also synergizes antihyperlipidemic activity. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been well-documented for their role in reducing hyperlipidemic conditions through their anti-inflammatory

properties, which contribute to the reduction of arterial plaque formation and prevention of atherosclerosis. By enhancing cell membrane fluidity, omega-3s support the function of membrane-bound receptors and enzymes, aiding in lipid metabolism. Their combined effects on lipid metabolism, inflammation regulation, and cellular function make omega-3s pivotal in managing hyperlipidemic conditions [8-10].

Different formulation strategies were introduced to overcome this barrier. Among them, Self-nano emulsifying drug delivery systems (SNEDDS) have attracted significant attention as lipid-based formulations designed to enhance the delivery of drugs characterized by low aqueous solubility. These systems typically comprise a mixture of lipids, surfactants, co-surfactants, and co-solvents, which upon contact with digestive fluids spontaneously form an emulsion. This emulsification facilitates the transport of the encapsulated drugs across the intestinal epithelium [11,12].

Gemfibrozil SNEEDS incorporated into gelatin capsules for oral administration. This approach leverages the advantages like ease of administration and improved patient compliance due to its non-invasive nature. By incorporating the formulation into gelatin capsules, the drug can be effectively administered, minimizing potential side effects and optimizing therapeutic outcomes.

Hence this study aimed to formulate Gemfibrozil self-nanoemulsifying drug delivery systems using omega-3 oil to enhance an effective efficacy of Gemfibrozil. By leveraging the unique properties of SNEDDS, this approach seeks to improve the bioavailability and therapeutic efficacy of Gemfibrozil, thereby offering a promising alternative for lipid-regulating therapy.

MATERIALS AND METHOD

Materials: Gemfibrozil was purchased by Carbanio (Hyderabad, India). Omega-3 oil was purchased from BBC Medicals (Solapur, India), Peppermint essential oil and Soybean oil was purchased from Naturalis (Malur, Karnataka, India), Cremophor RH40, Polyvinyl alcohol (PVA) and Tween 80 were provided by Loba Chemie Pvt. Ltd (Mumbai, India). Ethanol, Methanol, Polyethylene glycol 400 (PEG 400), Polyethylene glycol 600 and Polyethylene glycol 200 were procured by S.D. Fine Chem Ltd (Mumbai, India).

Methodology

Solubility of Gemfibrozil

The solubility of Gemfibrozil in oils (omega oil, peppermint essential oil, soybean oil), surfactant (tween 80, cremophor RH40, and polyvinyl alcohol), and co-surfactant (PEG600, PEG400, PEG200) was estimated by dissolving excess amount of Gemfibrozil in 2 ml of each oil, surfactant, and co-surfactant in stoppered vials. The vials were then subjected to preliminary mixing and placed on a magnetic stirrer for 24 hours at room temperature to attain equilibrium, further mixtures were centrifuged at 10,000 rpm for 10 minutes. The supernatant was separated and filtered through 0.45µm PTFE (Polytetrafluoroethylene) syringe filters. The filtered solution was then diluted with methanol, and the absorbance was measured at a wavelength of 274nm. This analysis helped determine the solubility of Gemfibrozil in different oils, surfactants, and co-surfactants, aiding in the selection of suitable components for further formulation development [13].

Selection of components for nanoemulsion

Oil was selected based on the maximum solubilization amount of Gemfibrozil in different oils. Surfactant and cosurfactant were selected for nanoemulsion formulation on percent transmittance criteria. The emulsification potency of the surfactant was determined by adding 200 mg surfactant in 200 mg of selected oil. The mixture was homogenized (IKA T-25Ultra Turrax) by gentle heating (40 °C) for 1 minute. From this mixture, 40 mg was taken and diluted up to 40 ml with water to get nanoemulsion. Then emulsion was kept for 2 h and analyzed with the help of UV-VIS spectroscopy (Shimadzu-1900i, Japan) at 274nm. The selection process for cosurfactants was identical to that of surfactants for the nanoemulsion formulation [14].

Phase diagrams studies:

To confirm the presence of a nanoemulsion region, pseudo-ternary phase diagrams were constructed. Omega oil was selected as the oil phase, cremophor RH40 as the surfactant, and PEG 400 as the co-surfactant based on the highest solubility of Gemfibrozil. The phase diagrams were generated using the aqueous titration method without the drug, with incremental addition of water. The surfactants and co-surfactants were mixed in different ratios (4:1, 3:1, 2:1, and 1:1). Each S_{mix} (surfactant/co-surfactant mixture) was then combined with the oil in various ratios (oil: S_{mix}) ranging from 1:9 to 9:1. These mixtures of oil and S_{mix} were vortex mixed to form a homogeneous mixture. Distilled water was then titrated into the mixtures until turbidity was observed, indicating the formation of phases. Visual observations were made and reported for each phase diagram. These pseudo-ternary phase

diagrams helped determine the appropriate compositions for the nanoemulsion region and determination of best ratio based on the maximum coverage area of the nanoemulsion, facilitating the formulation of stable and effective nanoemulsions [15,16].

Formulation of nanoemulsion:

Three different centroids (Table 1) within the appropriate regions of the phase diagram were selected based on the desired formulation characteristics, such as transparency and stability. The oil, S_{mix}, and water concentrations at these centroids were determined and used as a guide to prepare the formulations. By selecting different centroids, it is possible to explore and evaluate the effect of varying compositions on the properties of the formulations, allowing for optimization and customization based on specific requirements. Nanoemulsions were prepared by weighing a precise amount of Gemfibrozil and dissolved in a measured volume of omega 3 oil along with a predetermined amount of PEG 400 (Mixture A), ensuring continuous stirring with a magnetic stirrer to promote uniform mixing. Cremophor RH40 and water were then mixed together to create "Mixture B," which was stirred thoroughly for proper blending. Mixture B was gradually added dropwise into Mixture A, containing the dissolved drug, oil, and co-surfactant, while maintaining continuous stirring to achieve uniform dispersion and prevent the formation of large droplets. The resultant mixture was subjected to high-speed homogenization at 15,000 rpm for approximately 15 minutes, a critical step for reducing droplet size, enhancing emulsion stability, and obtaining a clear nanoemulsion. Following homogenization, the emulsion was visually inspected for clarity and uniformity, with additional evaluations such as droplet size analysis and stability studies conducted to assess the quality and performance of the nanoemulsion formulation [17,18].

Characterization of Gemfibrozil-loaded nanoemulsions

Determination of pH and viscosity:

The pH of the Gemfibrozil nanoemulsions was measured using a digital pH meter, the electrode was fully submerged in the sample and the pH was measured. The 4, 7, and 9 pH buffer solution was used for calibration of the pH meter. The pH was noted in a triplicate manner and mean values were calculated [14]. The viscosity of each formulation was assessed using a Brookfield digital viscometer, spindle 2 with 100 rpm at 25 ± 2 ºC. The viscosity determined in triplicate [19].

Determination of droplet size, polydispersity index and zeta potential:

Droplet size and polydispersity index (PDI) measurements were determined using malvern zetasizer (ZSU3100). For analysis, the samples were diluted with Mill-Q water type I (1 ml in 10 ml). The measurements were taken at a 90° angle with a side scatter and temperature of 25 ± 2°C. These metrics indicate the vesicle size, homogeneity, and monodispersed distribution. Zeta potential of Gemfibrozil SNEEDS was analyzed using malvern zetasizer (ZSU3100) for stability of the vesicles. Zeta potential was evaluated using a capillary cuvette [20].

Surface morphology of nanoemulsion:

Transmission electron microscopy (Tecnai G2 Spirit Biotwin) was employed to examine the morphology of the prepared SEDDS vesicles. 0.5 µl SEDDS sample was diluted with 4 mL distilled water and 0.2 µl of the above-diluted sample was coated on a Cu-corban grid (200 mesh). Then, it was negatively stained with a 2% PTA (Phosphotungustic Acid) solution and dried at room temperature. These samples were observed at 100 kV.

Percent transmittance:

To assess the clarity of a formulation, the percent transmittance is measured. Percentage transmittance was measured using a UV spectrophotometer (UV-1900i, Shimadzu, Japan). 0.1 ml of the nanoemulsion was diluted with 10 ml of distilled water. The resulting solution was then analyzed using a UV spectrophotometer to determine the percent transmittance at a wavelength of 274 nm using double distilled water as blank [21].

Thermodynamic Stability Study:

Thermodynamic stability tests provide valuable insights into the performance of the nanoemulsion formulations under different conditions. These tests assess the formulation's resistance to phase separation, creaming, or cracking, while the heating-cooling and freeze-thaw cycle tests determine their stability in response to temperature fluctuations [22,23].

A) Centrifugation Test

All nanoemulsion formulations were subjected to a centrifugation test at 3000 rpm for 20 minutes to evaluate the occurrence of phase separation, creaming, or cracking. Formulations that successfully passed the centrifugation test were selected for further investigation through additional thermodynamic stability studies.

B) Heating-Cooling Cycle Test

Formulations that passed the centrifugation test were then subjected to heating-cooling cycles. They were stored at 40°C for 48 hours, followed by cooling at 4°C for an additional 48 hours. This test was conducted in triplicate to assess the impact of temperature fluctuations on the stability of the formulations.

C) Freeze-Thaw Cycle Test

To further analyze the thermodynamic stability of the nanoemulsions, formulations that passed the heating-cooling cycle test were selected for the freeze-thaw cycle test. These formulations were frozen overnight at -20°C and then thawed at 25°C. This cycle was repeated to evaluate the formulation's ability to withstand temperature variations and maintain stability.

***In vitro* drug release comparative study**

Drug release from the liquid-filled gelatin capsules was evaluated by carrying out dissolution studies in phosphate buffer (pH 6.8) using a USP type II (paddle type) dissolution tester with 50 RPM. The dissolution medium was preheated to 37 ± 0.5°C to mimic physiological conditions. Samples of the dissolution medium were withdrawn at predetermined time intervals (5, 10, 15, 20, 30, 45 minutes) The absorbance is measured in UV Spectrophotometry at the drug at 274nm. A comparative dissolution study of formulated capsules with optimized Gemfibrozil-loaded nanoemulsions and Gemfibrozil suspension was studied.

Stability studies

Stability investigation for optimized SNEDDS was conducted for 3 months at room temperature, 25±2°C with relative humidity 60±5%, in accordance with ICH Q recommendations. Parameters were characterized for particle size, PDI and zeta potential [24,25].

RESULTS AND DISCUSSION

Solubility studies:

To formulate a Gemfibrozil-loaded nanoemulsion for oral administration, it should contain good solubility constituents in the system because the soluble drug can provide higher bioavailability. The solubility of Gemfibrozil in omega oil, peppermint oil and soybean oil were estimated and result is shown in Figure 1. The solubility of Gemfibrozil in surfactants and co-surfactants were estimated and shown in Figure 2 and Figure 3 respectively. Omega 3 oil was identified as the optimal oil phase due to its remarkable solubility of 79.42 mg/ml. For the surfactant role, cremophor RH40 was selected based on its solubility of 82.72 mg/ml, while PEG 400 with a solubility of 86.37 mg/ml was chosen as the appropriate cosurfactant.

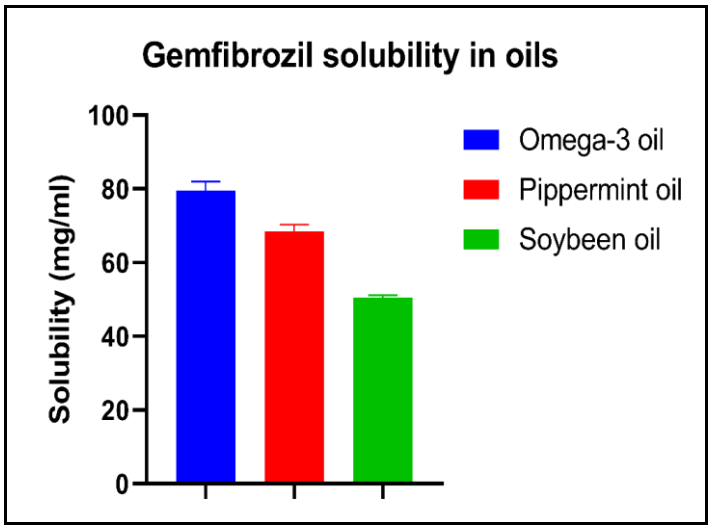

Figure 1: Solubility profile of Gemfibrozil in different oils

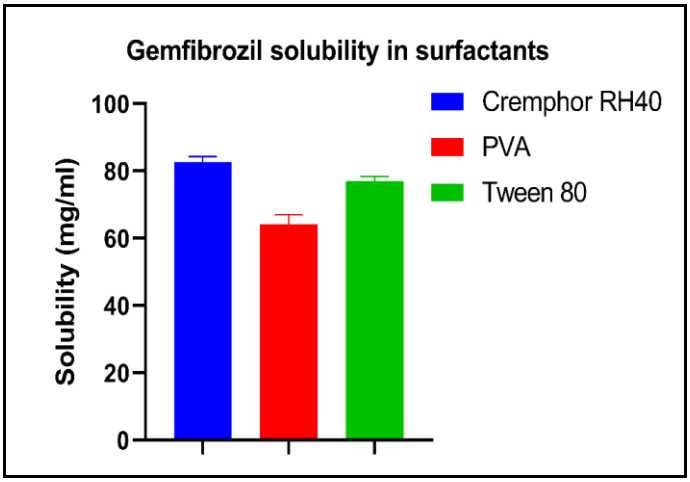

Figure 2: Solubility profile of Gemfibrozil in different surfactants

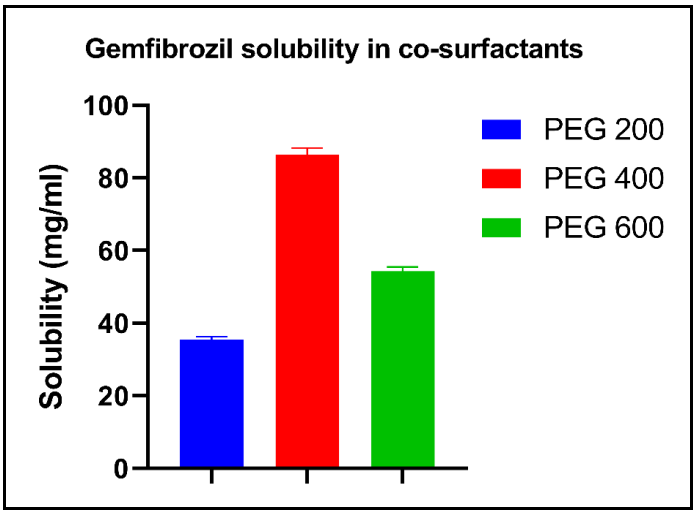

Figure 3: Solubility profile of Gemfibrozil in different co-surfactants

Journal of Current Pharma Research (JCPR)

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Development of pseudo ternary phase diagram

Pseudo-ternary phase diagrams were constructed by titrating the blend of oil and S_{mix} without Gemfibrozil by an incremental amount of water. S_{mix} (cremophor RH40 and PEG 400) were prepared with different ratios of surfactant and co-surfactant (4:1, 3:1, 2:1, 1:1). Each S_{mix} was mixed with oil (Omega 3 oil) in different weight ratios (oil: S_{mix}) 1:9, 1:7, 1:6, 1:4, 3:7, and 8:2. Each mixture were subjected to vortex mixing and then titrated with aqueous medium until turbidity is formed. The change in composition upon incremental addition of water was noted and the values were used to determine the boundaries of the nanoemulsion region. The mixtures that formed transparent oil/water systems were marked and plotted on the triangle graph using the software, the maximum nanoemulsion area was achieved for the 1:1 ratio and thus its centroid points were chosen for the nanoemulsion formulation (Table 1). A visual representation of the results can be seen in Figure 4.

Table 1: Components of formulation of nanoemulsions

Components	F1	F2	F3	F4
Cremophor RH40 (mL)	7	6	3.9	2
PEG 400 (mL)	7	6	3.9	2
Omega 3 oil (mL)	1.98	5.98	10	13.96
Water (mL)	4	2.02	2.02	2.04
Total (mL)	20	20	20	20

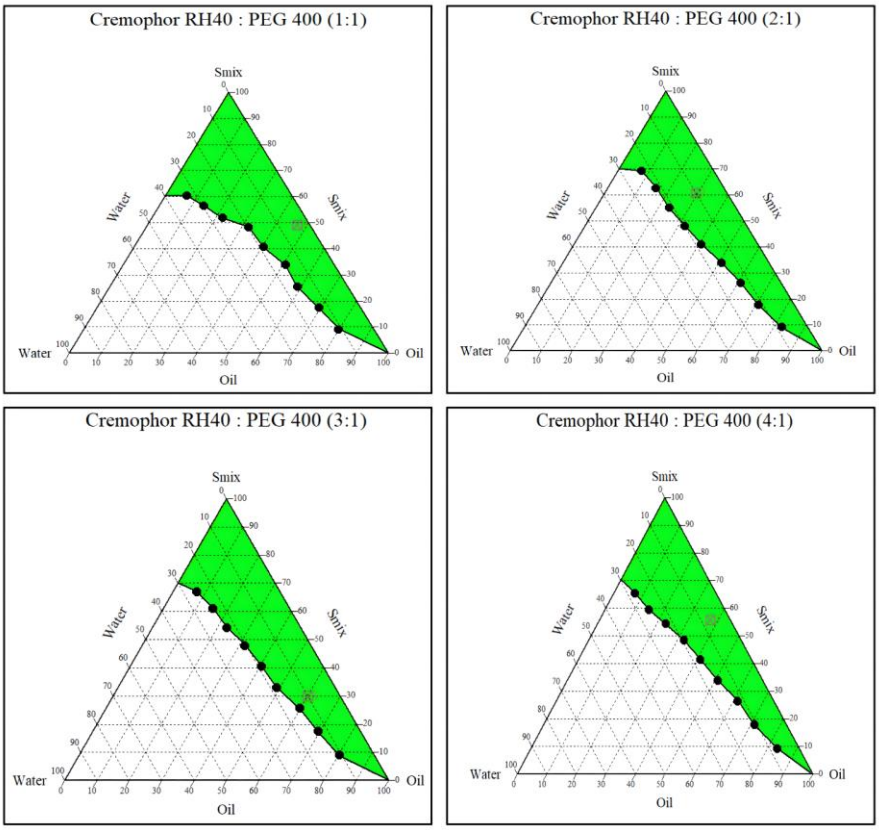

Figure 4: Pseudo-ternary phase diagram with different rations of surfactant and co-surfactants

Evaluation of nanoemulsion:

pH determination

The pH levels of the formulations, as documented in Table 2 were found to range from 6.0 to 7.4, which falls within the acceptable range. This is crucial for ensuring the compatibility of oral formulation with intestinal pH to avoid drug degradation.

Viscosity determination

The viscosity of all formulations was measured using a Brookfield digital viscometer at a temperature of 37˚C. The viscosity values obtained ranged from 170 ± 1.24 cPs to 204.1 ± 0.97 cPs. The viscosity of nanoemulsion formulations is influenced by the composition and concentration of oils, surfactants, and co-surfactants. All the formulations exhibited the optimum viscosity. The detailed results regarding viscosity measurements for each formulation are presented in Table 2.

Determination of Droplet size and PDI

Droplet size and polydispersity index (PDI) are crucial parameters in nanoemulsion formulations. The droplet size plays a significant role in enhancing bioavailability. A smaller droplet size leads to a larger surface area, thereby increasing the potential for improved bioavailability. Nanoemulsion droplet sizes typically ranged from 50 to 130 nm and PDI was found to be less than 0.5 indicating monodispersed droplet distribution. The findings are presented in Table 2.

Zeta potential

The Malvern zeta sizer (ZSU3100) was utilized to ascertain the zeta potential of the nanoemulsion. Zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in a dispersion. High zeta potential values (either positive or negative) typically indicate good physical stability and prevent aggregation. Nanoemulsion zeta potential typically ranges from -25.16mV to -39.46mV. The findings are presented in Table 2.

Surface morphological analysis

High-resolution transmission electron microscopy (HR-TEM) was used to examine and validate the surface morphology and structure of the Gemfibrozil nanoemulsion. The HR-TEM images revealed that the nanoemulsion exhibited droplet sizes ranging from 85nm to 125 nm. This imaging technique provided detailed insights into the individual particles, allowing for a precise assessment of their size distribution. The observed droplet size range of 85 nm-125 nm indicates the successful formation of a uniform and stable nanoemulsion. The results obtained are displayed in Figure 5.

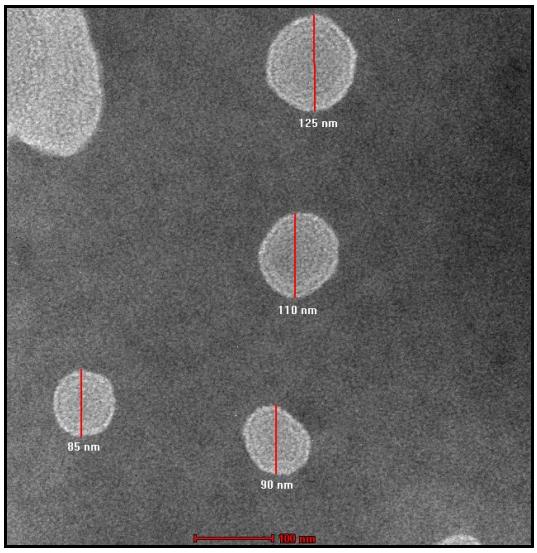

Figure 5: Transmission electron microscopic images of nanoemulsion at 100nm

Transmittance (%)

Percent transmittance serves as an indicator of the clarity of a formulation by comparing it to the clarity of the water. All four formulations displayed percent transmittance values within the acceptable range. Higher percent transmittance values indicate greater clarity, while lower values suggest reduced clarity or increased opacity of the formulation. The results of these measurements are detailed in Table 2.

Drug Content

The drug content analysis is instrumental in quantifying the concentration of the active pharmaceutical ingredient (API) within each formulation. This analysis is pivotal for maintaining consistency and ensuring the accuracy of dosages, which is critical for therapeutic efficacy. The outcomes of the drug content analysis provide a foundation for evaluating the formulation's potency and aid in establishing appropriate dosage regimens to achieve optimal therapeutic results. Drug content analysis was conducted for all four formulations in this study, and the results are comprehensively summarized in Table 2.

Table 2: Evaluation results of nanoemulsion

Formulation	F 1	F 2	F 3	F 4
pH	7.2	6.0	6.8	7.4
Viscosity (cPs)	197.1	170	199	204.1
Droplet size (nm)	90.7	50.6	121.5	130.04
Poly dispersity index	0.414	0.462	0.288	0.321
Zeta potential (mV)	-26.2	-32.18	-39.46	-25.16
Transmittance (%)	88.21	92.16	98.01	92.59
Drug content (%)	93.62	96.18	98.46	95.21

Thermodynamic Stability Study

The thermodynamic stability study is essential for the identification and elimination of unstable nanoemulsion formulations. The results of this study confirm the efficacy of the employed method, as stable nanoemulsions exhibited no phase separation, creaming, cracking, or drug precipitation under elevated conditions. This investigation is critical in the development of nanoemulsions that maintain structural integrity and prevent undesirable physicochemical changes.

Optimized nanoemulsion selection

Out of 4 nanoemulsions, F3 which contains 10ml of omega oil, 3.9ml of cremophor RH 40, 3.9ml of PEG 400 and 2.02ml of water showed superior characteristics such as pH, viscosity, drug content, droplet size, transmittance and thermal stability. The F3 formulation was further incorporated in the capsule and characterized for *in vitro* release study.

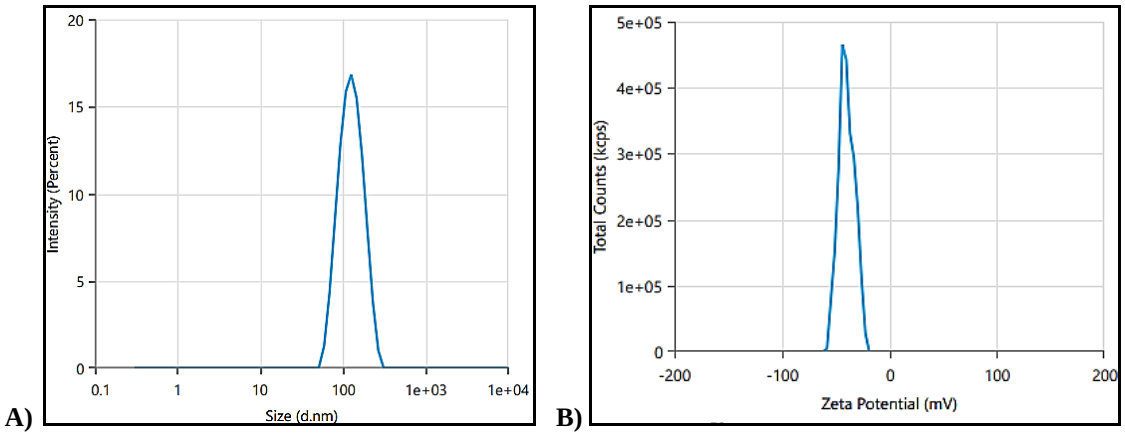

Figure 6: Gemfibrozil loaded optimized nanoemulsion characterization A) Droplet size B) Zeta potential

***In vitro* drug release**

A significant enhancement in drug release was observed with the Gemfibrozil nanoemulsion capsule, reaching approximately 88.51% within 45 minutes, compared to the 34.28% release from the plain Gemfibrozil suspension capsule. The nanoemulsion formulation enhances the solubility and permeability of Gemfibrozil, contributing to its superior bioavailability and the nanoscale size and increased surface area of the nanoemulsion droplets facilitates a more rapid dissolution and absorption of the drug. Additionally, the absence of aggregation and the homogenous distribution of the drug within the nanoemulsion matrix further ensure consistent and efficient drug release. Figure 7 illustrates the drug release profiles of the respective formulations.

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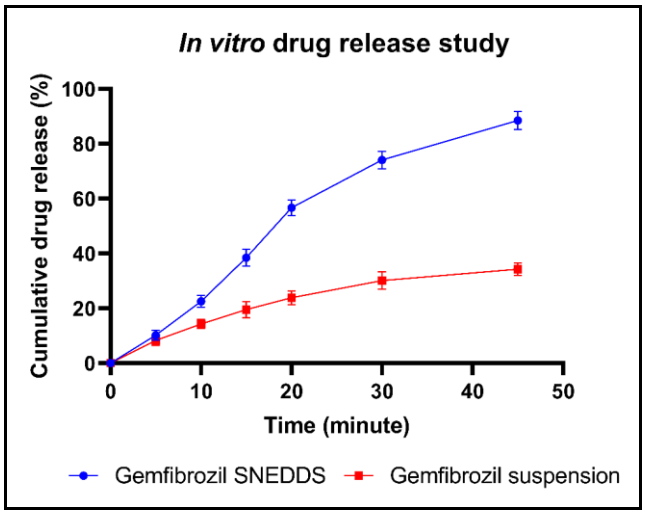

Figure 7: *In vitro* drug release comparative study in phosphate buffer pH 6.8

Drug release kinetic study

The release kinetics were evaluated using the DD solver software. The cumulative drug release of the Gemfibrozil nanoemulsion capsule was found to be 88.51% for 45 minutes. R^2 value of 0.9620 was reported to be the highest for the first order kinetics model, suggesting immediate drug release. The Crowell model provided the highest regression coefficient (R^2) of 0.9810. This stated the release mechanism follows both diffusion and relaxation of polymer chain. Figure 8 illustrate release kinetic graphs.

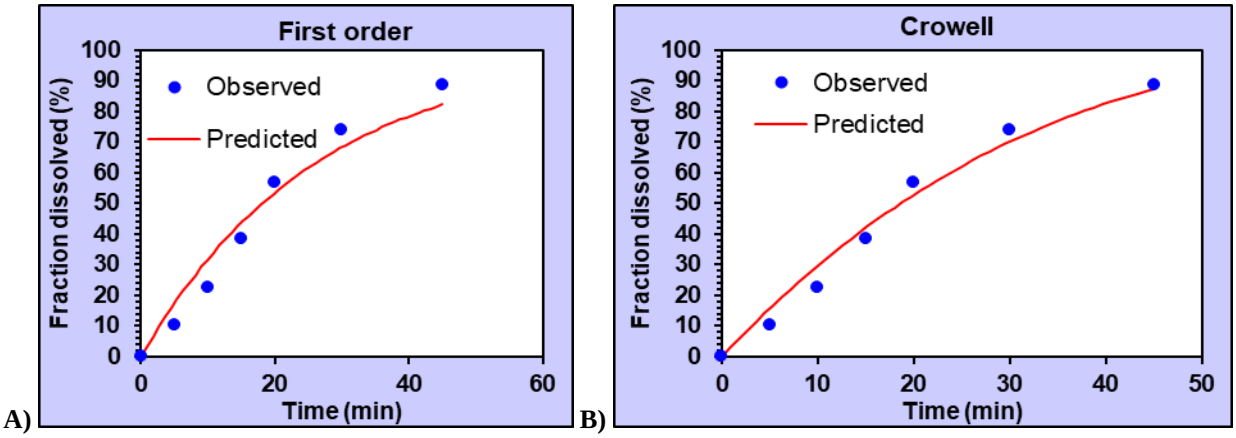

Figure 8: Kinetics models for in vitro release pattern A) First order B) Crowell model

Stability study

Short term stability studies were conducted according to ICH GCP guidelines to establish the stability of Gemfibrozil nanoemulsion. These studies were carried out in room temperature (30°C ± 2°C / 65% RH ± 5% RH). The study results were tabulated in Table 3.

Table 3: Stability studies of optimized Gemfibrozil nanosuspension at room temperature.

EVALUATION PARAMETERS	BEFORE	ROOM TEMPERATURE (30°C ± 2°C /65 % RH)		
	Day 0	30 days	60 days	90 days
Droplet size (nm)	121.5 ± 1.8	120.5 ± 0.21	118.1 ± 1.8	115.2 ± 3.25
Polydispersity Index	0.288 ± 0.07	0.301 ± 0.04	0.329 ± 0.07	0.346 ± 0.08
Zeta potential (mV)	-39.46 ± 0.08	-28.98 ± 0.4	-24.87 ± 0.7	-20.18 ± 0.81

Conclusion:

This study successfully demonstrated the formulation and optimization of a self-nanoemulsifying drug delivery system (SNEDDS) for Gemfibrozil using omega-3 oil, aimed at enhancing its solubility and bioavailability for the treatment of hyperlipidemia. The optimized formulation (F3) exhibited desirable physicochemical properties, including small droplet size, low polydispersity index, and high zeta potential, indicating stability and uniformity. The in vitro drug release studies revealed a significant improvement in the dissolution rate of Gemfibrozil from the SNEDDS formulation, achieving 88.51% drug release within 45 minutes, compared to 34.28% from the plain drug suspension.

The findings highlight the potential of SNEDDS in overcoming the solubility challenges associated with gemfibrozil, thereby enhancing therapeutic efficacy. The formulation strategy employed not only improves the bioavailability but also provides a promising approach for lipid-lowering therapies with improved patient compliance due to reduced dosing frequency.

Future research should focus on conducting in vivo studies to confirm the enhanced pharmacokinetic profile of the SNEDDS formulation. Additionally, clinical studies will be necessary to evaluate the safety and efficacy of the optimized formulation in hyperlipidemic patients, thereby advancing its potential as a viable alternative in lipid-lowering therapy.

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DECLARATIONS:

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Consent to publication: All authors consent to the publication of this research material.

Availability of data and material: Authors declare to produce the data and material on demand/request.

Competing interests: Authors do not have any conflict of interest.

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Authors' contributions: All the authors equally contributed to experimental works and manuscript preparation. All authors have read and approved the manuscript.

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