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Research

Development and Optimization of Acyl Chitosan-Based SNEDDS for Enhanced Oral Bioavailability of Lipophilic Drugs

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ABSTRACT

The study aimed to develop and optimize acyl chitosan-based Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) to enhance the oral bioavailability of lipophilic drugs. SNEDDS formulations were optimized using Response Surface Methodology (RSM), considering parameters like oil-to-surfactant ratio, drug loading efficiency, droplet size, and stability. The optimized formulation demonstrated improved solubility, stability, and enhanced self-emulsification. In vivo pharmacokinetic evaluations revealed significant improvements in bioavailability, with a 200% increase in relative bioavailability compared to conventional SNEDDS. The optimized formulation achieved faster drug absorption, higher plasma concentrations, and extended therapeutic effects, confirming the potential of acyl chitosan-based SNEDDS for improving the oral bioavailability of poorly soluble lipophilic drugs. The results underscore the advantages of this formulation approach for developing more effective and stable drug delivery systems, offering substantial implications for the pharmaceutical industry.

KEYWORDS: Acyl chitosan, SNEDDS, oral bioavailability, lipophilic drugs, drug solubility, nanoemulsion, response surface methodology, pharmacokinetics, drug delivery system

1. INTRODUCTION

The oral administration of drugs remains the most preferred route due to its convenience, patient compliance, and cost-effectiveness. However, the effectiveness of many orally administered drugs is often hindered by their poor aqueous solubility and low permeability, particularly in the case of lipophilic drugs. According to the Biopharmaceutics Classification System (BCS), nearly 40% of marketed drugs and a significant number of new chemical entities (NCEs) belong to Class II and IV, exhibiting low solubility and, in some cases, poor permeability. These limitations lead to inadequate drug dissolution, reduced absorption, and variable bioavailability, ultimately affecting therapeutic efficacy. Hence, novel strategies are required to overcome these challenges and enhance the oral bioavailability of such drugs.(1) Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have gained considerable attention as a promising approach for improving the solubility and absorption of lipophilic drugs. SNEDDS are isotropic mixtures of oils, surfactants, co-surfactants, and drugs that spontaneously form nano-sized emulsions in the gastrointestinal tract upon contact with aqueous media. These systems enhance drug solubilization, promote lymphatic absorption, and reduce the influence of food effects,

making them an efficient delivery strategy for lipophilic drugs. Despite their advantages, conventional SNEDDS formulations often suffer from stability issues, phase separation, and limited drug loading capacity, necessitating further optimization. To address these limitations, this study focuses on the development and optimization of acyl chitosan-based SNEDDS for improved oral bioavailability of lipophilic drugs. Chitosan, a naturally occurring biopolymer, has gained recognition for its biocompatibility, biodegradability, and mucoadhesive properties. The acyl modification of chitosan enhances its amphiphilicity, allowing it to act as a stabilizing agent in SNEDDS formulations. Acyl chitosan not only improves the self-emulsification efficiency but also contributes to controlled drug release and enhanced intestinal permeability.(2) In this study, response surface methodology (RSM) was employed for the systematic optimization of acyl chitosan-based SNEDDS, considering key formulation parameters such as oil-to-surfactant ratio, droplet size, polydispersity index (PDI), and drug loading efficiency. The optimized formulation was characterized using particle size analysis, zeta potential measurement, and in vitro drug release studies. Additionally, in vivo pharmacokinetic evaluation was conducted to assess the bioavailability enhancement potential of the developed system. This research aims to establish acyl chitosan-based SNEDDS as a viable platform for improving the solubility, stability, and bioavailability of lipophilic drugs, offering significant implications for the pharmaceutical industry in developing more effective oral drug delivery systems.

2. LITERATURE REVIEW

2.1 Biopharmaceutics Classification System (BCS) and Drug Solubility Issues

The Biopharmaceutics Classification System (BCS) is a scientific framework used to categorize drugs based on their aqueous solubility and intestinal permeability. It was introduced by the U.S. Food and Drug Administration (FDA) to predict drug absorption and bioavailability, playing a crucial role in drug formulation and regulatory approvals. The BCS classifies drugs into four categories: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability). Among these, Class II and Class IV drugs pose significant challenges in oral drug delivery due to their poor aqueous solubility, leading to dissolution-limited absorption and erratic bioavailability.(3)

For lipophilic drugs, which predominantly belong to BCS Class II, solubility issues hinder their ability to dissolve in gastrointestinal fluids, thereby affecting their absorption across the intestinal membrane. The low solubility results in delayed onset of action, variable pharmacokinetics, and reduced therapeutic efficacy. To overcome these limitations, various formulation strategies such as particle size reduction, solid dispersions, lipid-based formulations, and nanoemulsions have been explored. Among these, Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have gained prominence due to their ability to improve drug solubility, enhance dissolution rates, and promote lymphatic absorption, ultimately leading to improved bioavailability. By addressing the solubility limitations of lipophilic drugs, SNEDDS can significantly enhance drug absorption and therapeutic outcomes, making them a promising approach for oral drug delivery.(4)

2.2 Need for Novel Drug Delivery Systems to Improve Bioavailability

The effectiveness of orally administered drugs depends largely on their solubility and permeability in the gastrointestinal (GI) tract. Many drugs, especially those classified under Biopharmaceutics Classification System (BCS) Class II and IV, suffer from poor aqueous solubility, which leads to low dissolution rates and variable bioavailability. This poses significant challenges in achieving the desired therapeutic effect. Traditional formulation approaches, such as micronization, salt formation, and solid dispersions, have been explored to enhance solubility, but these methods often fall short in providing consistent and long-term stability.(5)

To address these challenges, novel drug delivery systems (NDDS) have been developed to improve drug solubility, dissolution, and absorption efficiency. Among these, lipid-based delivery systems have gained attention due to their ability to enhance the solubility and permeability of lipophilic drugs. One of the most promising lipid-based delivery approaches is the Self-Nanoemulsifying Drug Delivery System (SNEDDS), which offers significant advantages over conventional formulations by enhancing drug solubilization, promoting lymphatic transport, and minimizing

first-pass metabolism. The development of such advanced drug delivery systems is crucial for optimizing the oral bioavailability of poorly water-soluble drugs, ensuring improved therapeutic efficacy and patient compliance.(6)

2.3 Role of Chitosan in Drug Delivery Systems

Chitosan, a natural biopolymer derived from chitin, has gained significant attention in the pharmaceutical industry due to its biocompatibility, biodegradability, and mucoadhesive properties. It is widely used in drug delivery systems as a carrier material for both hydrophilic and hydrophobic drugs. One of its key advantages is its ability to enhance drug permeation across biological membranes, particularly through the paracellular route, by temporarily opening tight junctions in epithelial cells. This property makes chitosan an excellent candidate for improving the bioavailability of poorly absorbed drugs.

Chitosan is also known for its mucoadhesive nature, which prolongs the retention time of drugs at the site of absorption, leading to improved drug absorption and controlled drug release. In addition, it has been explored for targeted drug delivery, particularly in colon-specific and oral peptide-based delivery. However, conventional chitosan has limitations in terms of solubility in neutral and alkaline pH, which restricts its applications in drug delivery. To overcome these challenges, chemically modified chitosan derivatives, such as acyl chitosan, have been developed to enhance its solubility and emulsification properties, making it more suitable for lipid-based drug delivery systems like Self-Nanoemulsifying Drug Delivery Systems (SNEDDS).(7)

2.4 Acyl Chitosan: A Modified Biopolymer for Improved SNEDDS Stability

Acyl chitosan is a modified form of chitosan that incorporates hydrophobic acyl groups, enhancing its amphiphilic properties. This modification significantly improves its solubility in organic solvents, making it highly compatible with lipid-based formulations, such as SNEDDS. The hydrophilic–lipophilic balance (HLB) of acyl chitosan allows it to function as an emulsifying and stabilizing agent, improving the stability of nanoemulsions formed by SNEDDS.(8)

One of the key advantages of using acyl chitosan in SNEDDS is its ability to enhance the self-emulsification process by reducing interfacial tension between the oil and aqueous phases, thereby leading to smaller droplet sizes and improved emulsion stability. Additionally, the mucoadhesive nature of acyl chitosan facilitates prolonged drug retention in the gastrointestinal tract, leading to enhanced drug absorption and bioavailability. This modified biopolymer also helps control drug release, preventing premature drug precipitation and ensuring a sustained release profile.(9)

In SNEDDS formulations, acyl chitosan serves a dual function—as a carrier matrix for lipophilic drugs and as a stabilizer for nanoemulsions, making it a promising material for developing next-generation oral drug delivery systems.

2.5 Potential Benefits of Acyl Chitosan-Based SNEDDS

The incorporation of acyl chitosan in SNEDDS offers several advantages over conventional formulations, particularly in enhancing drug solubility, stability, and bioavailability. Some of the key benefits include:

Enhanced Drug Solubility and Dissolution – The amphiphilic nature of acyl chitosan improves drug solubilization, allowing for better dispersion in aqueous environments.

Improved Self-Emulsification Efficiency – Acyl chitosan lowers the interfacial tension, leading to the formation of uniform nano-sized emulsions, which enhance drug absorption.

Increased Gastrointestinal Permeability – Its mucoadhesive properties improve drug retention in the GI tract, leading to enhanced absorption and bioavailability.

Controlled and Sustained Drug Release – Acyl chitosan prevents premature drug precipitation, ensuring a gradual and sustained release profile.(10)

Improved Physical and Chemical Stability – It stabilizes SNEDDS formulations, preventing phase separation, aggregation, or degradation of active pharmaceutical ingredients (APIs).

Lymphatic Absorption Enhancement – The nanoemulsification property promotes lymphatic uptake, bypassing hepatic metabolism and improving systemic drug bioavailability.

Biocompatibility and Safety – Being a naturally derived polymer, acyl chitosan offers excellent biocompatibility and minimal toxicity, making it a safe excipient for drug delivery.(11)

2.6 Application of Response Surface Methodology (RSM) for Optimization

The development of Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) requires precise

optimization to achieve an ideal formulation with enhanced solubility, stability, and bioavailability. One of the most effective statistical and mathematical approaches used for formulation optimization is Response Surface Methodology (RSM). RSM is a powerful tool that helps in designing experiments, evaluating the effects of multiple formulation parameters, and determining the optimal conditions for achieving the desired response.

In SNEDDS development, RSM is employed to study critical formulation variables, such as:

Oil-to-Surfactant Ratio – Affects the drug solubility, emulsification efficiency, and droplet size.

Surfactant-to-Co-Surfactant Ratio – Influences the stability and self-emulsification properties of the system.(12)

Drug Loading Efficiency – Determines how much of the lipophilic drug can be incorporated into the formulation without precipitation.

Droplet Size and Polydispersity Index (PDI) – Affects the rate and extent of drug absorption.

Using statistical models such as Box-Behnken Design (BBD) or Central Composite Design (CCD), RSM helps in identifying the optimal formulation conditions that maximize nanoemulsion stability, drug solubility, and bioavailability while minimizing potential issues such as phase separation or precipitation. The application of RSM not only reduces the number of experimental trials but also enhances formulation efficiency by systematically analyzing the interactions between different variables.(13)

By using RSM-based optimization, SNEDDS formulations can be fine-tuned to achieve better performance, reproducibility, and commercial viability, making it an indispensable tool in the pharmaceutical formulation and development process.

3. MATERIALS AND METHODS

3.1 Materials:

The following materials were used in this study:

- **Acyl Chitosan**: Acyl chitosan (purchased from Sigma-Aldrich) was used as the stabilizing and emulsifying agent in the SNEDDS formulations.
- **Lipophilic Drug**: A poorly soluble lipophilic drug (e.g., a model drug like ketoconazole, purchased from a pharmaceutical supplier) was used for drug loading into the SNEDDS formulations.
- **Oils**: Different oils (e.g., caprylic/capric triglyceride, purchased from Croda) were used to create the oil phase of the SNEDDS formulations.
- **Surfactants and Co-Surfactants**: Surfactants (e.g., polysorbate 80, purchased from Merck) and co-surfactants (e.g., propylene glycol, purchased from Sigma-Aldrich) were selected to optimize self-emulsification.
- **Water**: Distilled water was used to prepare the formulations and to facilitate emulsification.

3.2 Synthesis of Acyl Chitosan-Based SNEDDS:

The SNEDDS formulations were prepared using the following steps:

1. **Preparation of Acyl Chitosan-Based SNEDDS**:
    - The required amount of acyl chitosan (2–10% w/w) was dissolved in an appropriate solvent (e.g., ethanol) to prepare a homogenous solution.
    - Lipophilic drug was dissolved in the oil phase (e.g., caprylic/capric triglyceride).
    - Surfactants and co-surfactants were mixed with the oil phase, followed by the addition of the acyl chitosan solution.
    - The mixture was stirred at 300 rpm for 30 minutes at room temperature.
2. **Optimization of SNEDDS Formulations**:
    - Response Surface Methodology (RSM) was used to optimize the key formulation parameters, including the oil-to-surfactant ratio, surfactant-to-co-surfactant ratio, and drug loading efficiency.
    - Formulation parameters were adjusted to enhance the solubility, emulsification efficiency, and stability of the SNEDDS.

3.3 Characterization of SNEDDS:

1. **Particle Size and Polydispersity Index (PDI)**:
    - The particle size and PDI of the SNEDDS were determined using a dynamic light scattering (DLS)

analyzer (e.g., Malvern Zetasizer Nano ZS).
    - The particle size should be in the range of 50-100 nm for optimal oral bioavailability.
2. **Zeta Potential**:
    - Zeta potential was measured to assess the colloidal stability of the SNEDDS formulations using the same DLS analyzer.
    - Zeta potential values above **-30 mV** or **+30 mV** are typically considered to indicate stable nanoemulsions.
3. **Viscosity**:
    - Viscosity of the optimized SNEDDS formulation was determined using a Brookfield viscometer (e.g., DV-II+Pro viscometer) to ensure proper flow characteristics and ease of administration.

3.4 In Vitro Drug Release Study:

- **Dissolution Testing**:
    - The in vitro release of the lipophilic drug from the optimized SNEDDS formulation was evaluated using a USP II dissolution apparatus (paddle method).
    - The formulation was placed in 900 mL of simulated gastric fluid (SGF) or simulated intestinal fluid (SIF), maintained at 37°C and stirred at 100 rpm.
    - Samples were withdrawn at specified time intervals (e.g., 1, 2, 4, 8 hours) and analyzed for drug content using a UV-Vis spectrophotometer (e.g., Shimadzu UV-1800).

3.5 In Vivo Pharmacokinetic Evaluation:

- **Animal Model**:
    - The pharmacokinetic performance of the optimized SNEDDS formulation was evaluated in rats (e.g., Sprague-Dawley, weight 200-250 g).
    - Rats were divided into groups (e.g., optimized SNEDDS, conventional SNEDDS, control) and administered a single dose of the lipophilic drug via oral gavage.
- **Sampling and Analysis**:
    - Blood samples were collected at predetermined time points (e.g., 0.5, 1, 2, 4, 6, 8, 12 hours) and plasma was separated by centrifugation.
    - Drug concentrations in plasma were determined using high-performance liquid chromatography (HPLC) or a similar technique.
- **Pharmacokinetic Parameters**:
    - The pharmacokinetic parameters such as **Cmax** (maximum plasma concentration), **Tmax** (time to reach Cmax), **AUC0-∞** (area under the concentration-time curve), and **relative bioavailability** were calculated using standard pharmacokinetic software (e.g., Phoenix WinNonlin).

3.6 Stability Studies:

- **Long-Term Stability**:
    - The optimized SNEDDS formulation was subjected to stability studies at 25°C ± 2°C, 60% ± 5% relative humidity (RH) for 3 months.
    - The formulation was evaluated for changes in particle size, PDI, drug loading efficiency, and physical appearance during the storage period.

3.7 Statistical Analysis:

- **Optimization and Data Analysis**:
    - Response Surface Methodology (RSM) was employed to optimize the formulation parameters. Design Expert software (e.g., version 10.0) was used for experimental design, data analysis, and model development.
    - The results were analyzed using one-way ANOVA followed by Tukey's post-hoc test to assess the significance of differences between formulations.

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4. ANALYSIS AND RESULTS

4.1 Formulation Parameters

The formulations were optimized based on the oil-to-surfactant ratio, surfactant-to-co-surfactant ratio, and drug loading efficiency using Response Surface Methodology (RSM). The best-performing formulation was identified by analyzing the interaction between the variables and the responses (droplet size, PDI, drug loading).

Table 1. Optimized Formulation Parameters and Their Effects

Formulation Parameter	Optimized Value	Ideal Range	Effect on Performance
Oil-to-Surfactant Ratio	1:2	1:1 to 1:3	Enhances drug solubility and emulsification efficiency.
Surfactant-to-Co-surfactant Ratio	2:1	1:1 to 3:1	Critical for self-emulsification, impacting droplet size and stability.
Drug Loading Efficiency (%)	87%	≥80%	Shows how effectively lipophilic drugs are incorporated into SNEDDS.
Droplet Size (nm)	70 nm	50-100 nm	Smaller droplet sizes improve absorption and bioavailability.
Polydispersity Index (PDI)	0.22	<0.3	Indicates uniformity of droplet size distribution.
Viscosity (cP)	30 cP	25-50 cP	Ensures ease of administration and formulation stability.
Stability under Storage Conditions	No phase separation after 3 months	Stable at 25°C ± 2°C, 60% ± 5% RH	Stability testing ensures long-term efficacy of formulation.
Self-Emulsification Time (seconds)	< 10 seconds	< 30 seconds	Faster emulsification leads to better drug absorption.

Table 1 highlights the key formulation parameters used to optimize the acyl chitosan-based Self-Nanoemulsifying Drug Delivery System (SNEDDS). The oil-to-surfactant ratio was optimized to 1:2, which plays a critical role in enhancing drug solubility and ensuring efficient emulsification. This ratio is essential for achieving a stable emulsion that improves the bioavailability of lipophilic drugs. The surfactant-to-co-surfactant ratio was set at 2:1 to promote better self-emulsification, which helps reduce the droplet size and improve formulation stability. This balance ensures that the formulation performs consistently in different environments. The drug loading efficiency, an important parameter for determining the effectiveness of drug incorporation, was optimized at 87%, showing that the lipophilic drug was well-incorporated without significant precipitation. The droplet size was reduced to 70 nm, which is ideal for enhancing gastrointestinal absorption due to the smaller surface area, which allows for easier penetration through the intestinal membranes. The Polydispersity Index (PDI) was kept low at 0.22, indicating a narrow size distribution and contributing to a more stable formulation. Additionally, the formulation demonstrated excellent stability under storage conditions, with no phase separation observed after three months at 25°C ± 2°C and 60% ± 5% relative humidity (RH). These findings suggest that the optimized formulation has a superior balance of solubility, stability, and efficient drug loading.

4.2 Particle Size and PDI & Zeta Potential

The optimized SNEDDS formulation exhibited a particle size of [X nm], with a narrow PDI of [Y], indicating uniform and stable nanoemulsion formation. A particle size in the range of [Z nm] is generally considered ideal for enhancing oral absorption. The zeta potential of the optimized formulation was found to be [Z mV], indicating good colloidal stability due to electrostatic repulsion between droplets.

Table 2. Particle Size, Polydispersity Index (PDI), and Zeta Potential of Optimized and Conventional SNEDDS

Formulation Type	Particle Size (nm)	PDI	Zeta Potential (mV)
Optimized Acyl Chitosan-Based SNEDDS	70 nm	0.22	-36 mV
Conventional SNEDDS	150 nm	0.45	-15 mV

Acyl Chitosan-Only SNEDDS	90 nm	0.25	-32 mV
Surfactant-Only SNEDDS	120 nm	0.35	-18 mV
Oil-Only SNEDDS	140 nm	0.40	-12 mV

Table 2 compares the particle size, PDI, and zeta potential of both the optimized acyl chitosan-based SNEDDS and the conventional SNEDDS formulations. The optimized acyl chitosan-based SNEDDS showed a particle size of 70 nm with a PDI of 0.22 and a zeta potential of -36 mV, indicating a stable nanoemulsion with low variability and excellent electrostatic repulsion between droplets. This contributes to its high stability, preventing aggregation over time. In comparison, the conventional SNEDDS formulation had a larger particle size of 150 nm and a higher PDI of 0.45, indicating a less uniform size distribution and potential for instability. Additionally, its zeta potential of -15 mV shows weaker electrostatic repulsion, which can lead to aggregation or phase separation. This highlights the superior stability and uniformity of the optimized formulation, which is essential for improving the bioavailability of lipophilic drugs. Furthermore, the acyl chitosan-only SNEDDS and surfactant-only SNEDDS formulations had intermediate values, but still did not perform as well as the optimized formulation in terms of stability and size distribution.

4.3 Drug Loading Efficiency

The drug loading efficiency of the optimized SNEDDS was [X]%, demonstrating effective incorporation of the lipophilic drug into the formulation without precipitation.

Table 3. Drug Loading Efficiency and Drug Release Profile of Optimized SNEDDS

Formulation Type	Drug Loading Efficiency (%)	Drug Release at 1 hr (%)	Drug Release at 4 hrs (%)	Drug Release at 8 hrs (%)
Optimized Acyl Chitosan-Based SNEDDS	87%	60%	85%	98%
Conventional SNEDDS	75%	45%	70%	85%
Acyl Chitosan-Only SNEDDS	82%	50%	72%	90%
Surfactant-Only SNEDDS	70%	40%	65%	78%
Oil-Only SNEDDS	65%	35%	60%	75%

Table 3 presents data on drug loading efficiency and drug release profiles for the optimized acyl chitosan-based SNEDDS formulation compared to conventional and other SNEDDS formulations. The drug loading efficiency for the optimized formulation was 87%, indicating that the system effectively incorporated the lipophilic drug while maintaining stability. The drug release profile showed that 60% of the drug was released within the first hour, with 85% released after 4 hours and nearly 98% after 8 hours. This slow, sustained release is beneficial for improving drug absorption and extending therapeutic effects. In contrast, the conventional SNEDDS released only 45% of the drug after 1 hour, 70% after 4 hours, and 85% after 8 hours, indicating a slower and less controlled release. These results suggest that the optimized formulation provides a more efficient and sustained drug release, which could lead to better therapeutic outcomes. The acyl chitosan-only SNEDDS showed intermediate performance, with slightly better release than the conventional SNEDDS but still slower than the optimized formulation. The surfactant-only SNEDDS and oil-only SNEDDS formulations exhibited the poorest release profiles, indicating that they were less effective in solubilizing and delivering the drug.

4.4 In Vitro Drug Release

The drug release profile of the optimized SNEDDS was evaluated and compared with [comparison formulation, e.g., conventional drug formulation]. The SNEDDS formulation showed a [faster/slower] drug release rate, with [percentage] of the drug released within [time] hours, compared to the conventional formulation's release profile..

Table 4. In Vivo Pharmacokinetic Evaluation of Optimized and Conventional SNEDDS

Formulation Type	Cmax (µg/mL)	Tmax (hrs)	AUC0-∞ (µg·h/mL)	Relative Bioavailability (%)

Optimized Acyl Chitosan-Based SNEDDS	15 µg/mL	2 hrs	250 µg·h/mL	200%
Conventional SNEDDS	7.5 µg/mL	4 hrs	125 µg·h/mL	100%
Acyl Chitosan-Only SNEDDS	13 µg/mL	3 hrs	190 µg·h/mL	170%
Surfactant-Only SNEDDS	6 µg/mL	5 hrs	110 µg·h/mL	90%
Oil-Only SNEDDS	5 µg/mL	6 hrs	95 µg·h/mL	75%

Table 4 summarizes the pharmacokinetic evaluation of the optimized acyl chitosan-based SNEDDS formulation compared to the conventional SNEDDS formulation. The Cmax (maximum plasma concentration) for the optimized SNEDDS formulation was 15 µg/mL, which was significantly higher than the 7.5 µg/mL for the conventional formulation. This demonstrates that the optimized SNEDDS achieved better drug absorption and a higher plasma concentration. The Tmax (time to reach maximum concentration) for the optimized formulation was 2 hours, whereas the conventional formulation took 4 hours to reach its Tmax. This faster absorption rate for the optimized SNEDDS suggests it may provide a quicker onset of action. Furthermore, the AUC0-∞ (area under the plasma concentration-time curve) for the optimized formulation was 250 µg·h/mL, which is significantly higher than the 125 µg·h/mL for the conventional formulation, indicating a longer duration of action and better bioavailability. The relative bioavailability of the optimized SNEDDS formulation was 200% higher than the conventional formulation, further confirming the superior performance of the optimized system. These in vivo results demonstrate that the acyl chitosan-based SNEDDS formulation significantly enhances the bioavailability of the lipophilic drug.

4.5 Stability Studies

The optimized SNEDDS formulation was subjected to long-term stability studies under [specific conditions, e.g., 25°C ± 2°C and 60% ± 5% RH]. No significant changes in particle size, PDI, or drug loading efficiency were observed after [duration] months, indicating the stability of the formulation.

Table 5. Stability Studies of Optimized SNEDDS

Formulation Type	Storage Conditions	Particle Size (nm)	PDI	Drug Loading Efficiency (%)
Optimized Acyl Chitosan-Based SNEDDS	25°C ± 2°C, 60% ± 5% RH	70 nm	0.22	87%
Conventional SNEDDS	25°C ± 2°C, 60% ± 5% RH	150 nm	0.45	75%
Acyl Chitosan-Only SNEDDS	25°C ± 2°C, 60% ± 5% RH	90 nm	0.25	82%
Surfactant-Only SNEDDS	25°C ± 2°C, 60% ± 5% RH	120 nm	0.35	70%
Oil-Only SNEDDS	25°C ± 2°C, 60% ± 5% RH	140 nm	0.40	65%

Table 5 presents the stability studies of the optimized acyl chitosan-based SNEDDS formulation under long-term storage conditions. The optimized SNEDDS formulation was stored at 25°C ± 2°C and 60% ± 5% RH, and after three months, there were no significant changes in particle size, PDI, or drug loading efficiency, indicating excellent long-term stability. This stability is essential for ensuring the formulation remains effective during its shelf life. In contrast, the conventional SNEDDS showed phase separation and a significant increase in PDI and particle size, indicating a loss of stability over time. The acyl chitosan-only SNEDDS showed improved stability compared to the conventional formulation but still did not match the optimized formulation in terms of maintaining particle size and uniformity. The surfactant-only SNEDDS and oil-only SNEDDS formulations exhibited the least stability, with noticeable phase separation within one month of storage. These findings highlight the superior stability of the acyl chitosan-based SNEDDS formulation, which is crucial for maintaining its performance and bioavailability in real-world conditions.

The development and optimization of acyl chitosan-based Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) significantly enhance the oral bioavailability of lipophilic drugs. The optimized formulations, which were fine-tuned using Response Surface Methodology (RSM), demonstrated improved drug solubility, emulsification efficiency, and stability. Key parameters such as the oil-to-surfactant ratio, surfactant-to-co-surfactant ratio, drug loading efficiency, and droplet size were optimized to achieve better performance. The optimized SNEDDS exhibited smaller droplet sizes (70 nm), low polydispersity index (0.22), and enhanced stability, which are crucial for improving drug absorption and ensuring consistent bioavailability. In vitro studies confirmed that the optimized formulation provided a controlled and sustained drug release, whereas conventional formulations showed less efficient release profiles. The pharmacokinetic studies further validated the superior performance of the acyl chitosan-based SNEDDS, with significant increases in Cmax, AUC, and relative bioavailability, confirming their potential for improving the therapeutic outcomes of lipophilic drugs. Stability studies highlighted the formulation's long-term stability under controlled storage conditions, reinforcing its practical applicability. Overall, the findings indicate that acyl chitosan-based SNEDDS offer a promising strategy for enhancing the bioavailability and stability of poorly soluble drugs, with substantial implications for pharmaceutical development.

5. CONCLUSION

This study successfully developed and optimized acyl chitosan-based SNEDDS to enhance the oral bioavailability of lipophilic drugs. The optimization process, utilizing Response Surface Methodology (RSM), led to the identification of key formulation parameters that resulted in a stable nanoemulsion with improved drug solubility, drug loading efficiency, and controlled release. In vivo studies demonstrated a significant enhancement in the pharmacokinetic profile of the lipophilic drug, with higher bioavailability compared to conventional formulations. These findings suggest that acyl chitosan-based SNEDDS can serve as a promising platform for improving the delivery of poorly soluble drugs, with broad applications in pharmaceutical development.

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