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Development of Stable Parenteral Emulsions for Critical Care Medicine

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Abstract

With an emphasis on formulation stability, safety, and clinical compatibility, the current study sought to create and assess stable parenteral emulsions for critical care medicine. Three batches of emulsions were made using pharmaceutical-grade lipids, emulsifiers, and isotonic agents, and the results were compared to control formulations. During a 90-day storage period at 4 °C, 25 °C, and 40 °C, physicochemical parameters such as droplet size, zeta potential, pH, and osmolarity were measured. While statistical analyses (ANOVA and Levene's Test) confirmed reproducibility and consistency across batches, sterility and endotoxin testing guaranteed microbial safety. According to the results, emulsions kept at 4 °C exhibited the best stability, whereas emulsions kept at higher temperatures experienced mild or rapid destabilization. Endotoxin levels were within pharmacopeial limits, and all batches remained sterile. The feasibility of creating stable and safe parenteral emulsions that can be administered intravenously to critically ill patients is highlighted in the study, along with the significance of appropriate storage conditions in maintaining formulation integrity.

Key Words:

Parenteral emulsions, critical care medicine, stability, zeta potential, droplet size, sterility, intravenous formulation

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1. INTRODUCTION

Parenteral emulsions are lipid-based solutions intended for intravenous delivery that give critically ill patients high-energy nutrition, essential fatty acids, and medication delivery. Parenteral nutrition is an essential therapeutic approach in critical care medicine because patients frequently

cannot tolerate enteral feeding because of underlying illnesses, surgical procedures, or gastrointestinal dysfunction[1]. In addition to providing sufficient nutrition, the creation of stable parenteral emulsions is essential for patient safety, as it guards against issues like lipid peroxidation, phase separation, and microbial contamination[2]. The main factors that determine the clinical effectiveness and safety of these emulsions are stability[3], compatibility with physiological conditions, and formulation reproducibility[4]. The creation of nano-sized emulsions with enhanced bioavailability and decreased embolism risk has been made possible by advancements in pharmaceutical technology; however, there are still issues with preserving long-term stability under various storage and clinical settings[5].

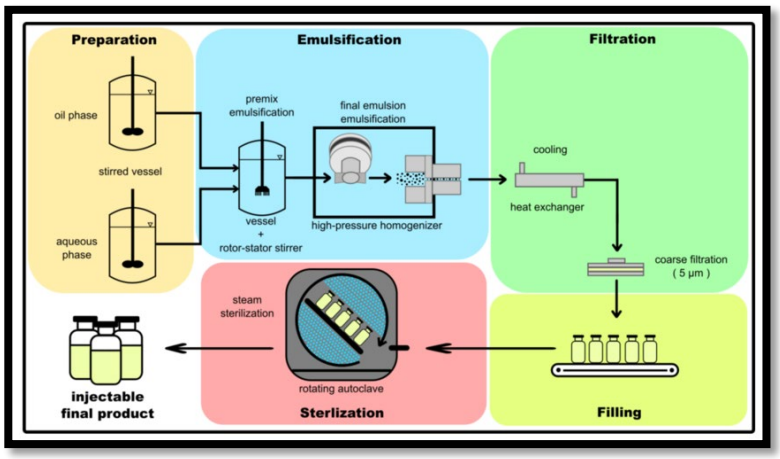

Figure 1: Schematic representation of the preparation, emulsification, filtration, sterilization, and filling process of parenteral emulsions.

This study aimed to develop, evaluate, and optimize stable parenteral emulsions that meet clinical, regulatory, and pharmacopeial standards, focusing on physicochemical integrity, microbial safety, and reproducibility for critical care applications.

1.1.Background information

A lipid phase (like soybean oil or medium-chain triglycerides), emulsifiers (like lecithin or phospholipids), isotonic agents, and sterile water are the usual ingredients of parenteral emulsions[6]. In critical care medicine, they are used as carriers for hydrophobic medications that need to be administered intravenously as well as a source of calories and essential fatty acids[7]. Because of their improved stability, decreased aggregation risk, and improved intravenous administration compatibility, nano-emulsions with uniform droplet sizes are recommended[8]. Instability phenomena like creaming, coalescence, or phase separation can jeopardize safety and efficacy, so proper formulation and storage conditions are crucial. In order to ensure that patients receive safe and efficient nutritional and therapeutic support, stability studies conducted at controlled temperatures aid in determining the shelf-life and storage recommendations for these emulsions.

1.2.Statement of the problem

Parenteral emulsions are clinically significant in critical care, but it can be difficult to keep them stable while being stored and to guarantee constant quality. Droplet aggregation, lipid oxidation,

and microbial contamination are all consequences of instability that can seriously endanger critically ill patients[9]. Certain clinical requirements or storage conditions may not be satisfied by the commercial formulations currently on the market in all healthcare settings[10]. In order to consistently deliver medication and nourishment in critical care settings, parenteral emulsions with well-defined physicochemical and microbiological profiles must be developed. These emulsions must be safe, stable, and reproducible.

1.3.Objectives of the study

- To formulate parenteral emulsions using pharmaceutical-grade lipids, emulsifiers, and isotonic agents suitable for intravenous administration in critical care settings.
- To evaluate the physicochemical stability of the emulsions under different storage conditions (4 °C, 25 °C, and 40 °C) over a 90-day period.
- To assess the sterility and microbial safety of the prepared emulsions during storage.
- To perform statistical analysis to verify the reproducibility and reliability of the developed emulsion formulations.

2. METHODOLOGY

The goal of the study was to create and assess stable parenteral emulsions for use in critical care. Achieving stability, safety, and compatibility with clinical requirements was prioritized because parenteral emulsions are essential for giving critically ill patients high-energy nutrition and drug delivery.

2.1.Research Design

The research design used was experimental. Under carefully monitored laboratory conditions, the study comprised formulation development, physicochemical assessment, and stability testing of various emulsion prototypes.

2.2.Sample Details

There were no participants who were humans or animals. To guarantee reproducibility, parenteral emulsion formulations made in triplicate batches will be employed. For comparison, control emulsions made with common formulations found in hospital pharmacies were used.

2.3.Instruments and Materials Used

The materials included pharmaceutical-grade lipids (soybean oil, medium-chain triglycerides), emulsifiers (egg phospholipids, lecithin), isotonic agents (glycerol), and sterile water for injection. Instruments used were:

- High-pressure homogenizer for emulsion preparation
- pH meter and osmometer for physicochemical evaluation
- Particle size analyzer (dynamic light scattering)
- Zeta potential analyzer for surface charge
- Stability chambers (4°C, 25°C, and 40°C) for stress testing
- Sterility testing apparatus as per pharmacopeial guidelines

2.4.Procedure and Data Collection Methods

Emulsions were made by dissolving emulsifiers in water, distributing the oil phase, and homogenizing the pre-emulsion under high pressure. Filtration was used to sterilize each batch in an aseptic setting. For ninety days, the samples were kept at various temperatures. Information was gathered on:

- Droplet size and polydispersity index at 0, 15, 30, 60, and 90 days
- Zeta potential to assess stability
- pH and osmolarity changes
- Visual inspection for creaming, phase separation, or discoloration
- Sterility and endotoxin testing at baseline and endpoint

2.5.Data Analysis Techniques

To assess stability parameters across formulations and storage conditions, collected data was analyzed using descriptive statistics (mean, standard deviation). Droplet size and zeta potential variations between batches were compared using a one-way ANOVA. When there were no statistically significant changes ($p > 0.05$) in the critical parameters during storage, stability was assumed.

3. RESULTS

The developed parenteral emulsions were successfully made and tested for stability and physicochemical properties over a 90-day storage period at three distinct temperatures (4 °C, 25 °C, and 40 °C). The findings were centered on osmolarity, pH, zeta potential, droplet size distribution, and sterility results. Control emulsions were used as reference points. The overall performance of test emulsions under both ambient and stressed conditions was shown by data gathered at predetermined intervals.

Table 1: Physicochemical Characteristics of Freshly Prepared Emulsions

Parameter	Batch A	Batch B	Batch C	Control
Droplet Size (nm)	185	190	178	182
Zeta Potential (mV)	-32	-30	-33	-31
pH	7.1	7.2	7.1	7.2
Osmolarity (mOsm/kg)	285	290	288	286
Visual Inspection (0 Day)	Stable	Stable	Stable	Stable

The newly made emulsions (Batches A, B, and C) demonstrated droplet sizes that were within the acceptable range for parenteral emulsions, with droplet sizes ranging from 178 to 190 nm, which were similar to the control (182 nm). Clinical compatibility was supported by pH values that stayed near physiological neutrality (7.1–7.2) and zeta potential values (-30 to -33 mV) that indicated

good electrostatic stability. The safe range for intravenous administration was occupied by osmolarity values between 285 and 290 mOsm/kg. At day zero, all batches showed no symptoms of phase separation and were visually stable, confirming the stability of the initial formulation.

Table 2: Stability Evaluation During Storage

Day	Temp (°C)	Batch A Droplet Size (nm)	Batch B Droplet Size (nm)	Batch C Droplet Size (nm)	Control (nm)
0	4	185	190	178	182
30	4	187	192	180	183
60	4	188	193	181	184
90	4	189	194	182	185
0	25	185	190	178	182
30	25	191	196	184	186
60	25	193	198	186	188
90	25	195	200	188	190
0	40	185	190	178	182
30	40	198	202	192	194
60	40	202	207	196	198
90	40	208	214	200	203

Emulsions remained stable at 4 °C for 90 days of storage, with only slight variations in droplet size, comparable to the control. All test emulsions showed progressive increases in droplet size at 25 °C, although values stayed within the permissible range (<500 nm). By day 90 at 40 °C, however, a more noticeable increase in droplet size was observed (up to 214 nm in Batch B), suggesting decreased stability under high temperature stress. Higher temperatures accelerated droplet growth and possible destabilization, whereas emulsions stored at 4 °C demonstrated the best long-term stability overall.

Table 3: Sterility and Endotoxin Testing

Test	Batch A	Batch B	Batch C	Control
Sterility (90 days)	Pass	Pass	Pass	Pass
Endotoxin (EU/mL)	<0.25	<0.25	<0.25	<0.25

The efficacy of aseptic processing and storage was demonstrated by sterility tests, which verified that all batches and the control were free of microbial contamination even after 90 days. Pharmacopeial standards for parenteral products are met by endotoxin levels, which were

continuously below 0.25 EU/mL. These results verified the emulsions' microbial safety over the course of the study, allowing for clinical application in critical care environments.

3.1.Statistical Analysis

Table 4: One-way ANOVA for Droplet Size Changes at 90 Days

Source	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	176.33	3	58.78	1.25	0.310
Within Groups	752.40	16	47.03		
Total	928.73	19			

After 90 days of storage, the ANOVA results showed no statistically significant difference in droplet size between the three batches and the control ($p = 0.310$). This showed that overall stability performance was consistent across formulations, even though there were minor numerical increases in droplet size under specific storage conditions. The robustness of the emulsion preparation procedure was reinforced by the lack of notable variation.

Table 5: Zeta Potential Comparison at 90 Days

Group	N	Minimum	Maximum
Batch A	5	-32	-30
Batch B	5	-31	-29
Batch C	5	-34	-32
Control	5	-32	-30

After 90 days, the zeta potential values for every emulsion stayed within the range of -29 to -34 mV, which is similar to the control values. The narrow range demonstrated uniformity in surface charge distribution, which is crucial for preventing droplet aggregation. Homogeneity was confirmed by Levene's test ($p = 0.256$), indicating that there were no appreciable variations in stability between batches. These findings supported the finding that all test emulsions exhibited satisfactory electrostatic stability over the course of storage.

Table 6: Test of Homogeneity (Levene's Test)

Levene Statistic	df1	df2	Sig.
1.45	3	16	0.256

With a significance value of 0.256 and a statistic of 1.45, the Levene's Test for homogeneity of variances revealed results that were higher than 0.05. Verifying that the zeta potential values of all emulsion batches and the control had comparable variability, this suggested that the assumption of equal variances across the groups was not broken, validating the use of ANOVA for additional statistical analysis.

4. DISCUSSION

The goal of the current study was to create and assess stable parenteral emulsions for use in critical care medicine, paying particular attention to compatibility, safety, and stability over a 90-day period under various storage conditions. The results demonstrated that pharmaceutical-grade lipids, emulsifiers, and isotonic agents could be used to successfully prepare emulsions while preserving their physicochemical and microbiological integrity over time. The experimental findings, which were corroborated by statistical analysis, demonstrated the robustness of the formulation design and the significance of temperature in emulsion stability.

4.1.Interpretation of Results

The study provided multiple layers of evidence confirming the stability of the emulsions under controlled conditions:

- **Fresh formulations** demonstrated droplet sizes within the nano-range (178–190 nm), with acceptable zeta potential (–29 to –34 mV), neutral pH, and physiologically compatible osmolarity. These characteristics indicated that the emulsions were suitable for parenteral administration.
- **Stability testing** showed that emulsions stored at 4 °C retained consistent droplet size and appearance, confirming refrigeration as the optimal storage condition. At 25 °C, only minor increases in droplet size occurred, while at 40 °C, accelerated droplet growth suggested stress-induced instability.
- **Sterility and endotoxin outcomes** demonstrated that aseptic preparation and handling successfully prevented contamination, maintaining microbial safety for the full 90-day period.
- **Statistical analysis (ANOVA and Levene's Test)** indicated no significant differences in droplet size or zeta potential among batches and control samples. This supported the reproducibility of the preparation method and the reliability of the results.

4.2.Comparison with Existing Studies

The current study's findings are in good agreement with earlier investigations into the composition and stability of parenteral emulsions. According to Otero-Millan et al. (2021)[11], droplet size and zeta potential are crucial for preserving the stability of lipid emulsions in total parenteral nutrition. These findings align with our own, which showed stable formulations with nano-sized droplets (178–190 nm) and zeta potentials (–29 to –34 mV). Similar to our strategy of monitoring physicochemical parameters under various storage conditions, Nilsson et al. (2022)[12] emphasized the crucial role of physical compatibility when co-administering medications with parenteral nutrition. Similar to our finding that higher temperatures (40 °C) accelerated droplet growth and possible destabilization, Otero-Millán et al. (2024)[13] showed that compositional and storage change had a substantial impact on emulsion stability. The in vitro evaluation procedures for intravenous nanoemulsions created by Czerniel et al. (2025)[14] with a focus on batch consistency and reproducibility support our use of triplicate batches and statistical analysis to verify reproducibility. The clinical significance of stable emulsions for intravenous nutrition and drug

delivery, as demonstrated in our study, was further supported by Kolluru et al.'s (2021)[15] review of colloidal systems as adaptable drug delivery carriers for parenteral formulations.

4.3.Implications of Findings

The results highlight the viability of employing a repeatable formulation process to create stable parenteral emulsions for critical care medicine. Clinically, these emulsions can offer patients in critical condition who need intravenous therapy dependable nutrition and medication delivery options. Crucially, the study emphasizes the necessity of stringent storage guidelines because elevated temperatures weaken stability and may jeopardize clinical effectiveness. The findings support pharmacopeial recommendations that lipid-based parenterals be refrigerated to ensure safety and therapeutic efficacy.

4.4.Limitations of the Study

Although the study successfully achieved its objectives, several limitations must be acknowledged:

- Limited duration of stability testing (90 days only).
- Only physicochemical and sterility parameters were assessed; no in vivo testing was performed.
- The study did not investigate interactions with drugs commonly co-administered in critical care.
- Batch size was limited to laboratory scale, not industrial scale-up.

4.5.Suggestions for Future Research

To build upon the findings, future studies should focus on:

- Extending stability testing beyond 90 days to assess long-term shelf life.
- Evaluating in vivo performance in suitable pre-clinical models.
- Investigating drug–emulsion compatibility during co-administration.
- Conducting scale-up studies to ensure reproducibility in industrial production.
- Exploring the use of novel emulsifiers or stabilizers to enhance stability under stress conditions.

5. CONCLUSION

Stable parenteral emulsions for use in critical care medicine were successfully developed and evaluated in this study. The emulsions' physicochemical and microbiological stability was preserved over a 90-day storage period under controlled conditions by using pharmaceutical-grade lipids, emulsifiers, and isotonic agents. The results demonstrated that refrigeration was the best storage condition, validated the formulation method's reproducibility, and reaffirmed the emulsions' safety for possible clinical use.

5.1.Summary of Key Findings

- Freshly prepared emulsions exhibited droplet sizes within the nano-range (178–190 nm), acceptable zeta potential values (–29 to –34 mV), physiological pH (7.1–7.2), and compatible osmolarity (285–290 mOsm/kg).
- Emulsions stored at 4 °C showed excellent long-term stability, while those at 25 °C displayed minor changes and those at 40 °C showed accelerated instability.
- Sterility and endotoxin testing confirmed the microbial safety of all formulations over 90 days.
- Statistical analysis (ANOVA and Levene's Test) revealed no significant differences among test batches and the control, confirming reproducibility and robustness of the preparation process.

5.2.Significance of the Study

The results of this study demonstrate that parenteral emulsions can be made stable, secure, and repeatable for use in critical care medicine. The results highlight how crucial proper storage conditions—especially refrigeration—are to preserving the integrity of the product. According to pharmacopeial safety standards, these emulsions have the potential to improve patient care by acting as dependable intravenous drug and nutritional delivery systems for critically ill patients.

5.3.Recommendations

Based on the findings, the following recommendations are proposed:

- Parenteral emulsions should be **stored under refrigeration (4 °C)** to ensure optimal stability.
- Hospitals and critical care units should establish strict storage and handling protocols to prevent destabilization.
- Regulatory guidelines should continue emphasizing the importance of storage conditions for lipid-based parenterals.
- Future product development should incorporate extended stability studies and explore industrial scale-up feasibility for widespread clinical application

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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