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Formulation and Evaluation of Nanoemulsion for Topical Application

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ABSTRACT

Advanced drug delivery methods known as nanoemulsions are distinguished by their minuscule droplet sizes, which are usually between 20 and 200 nanometers. These submicron emulsions have shown great promise as topical drug delivery vehicles, especially for medications with low solubility in water. When applied to the skin, their distinct physicochemical characteristics—such as high surface area, optical transparency, kinetic stability, and improved permeation—can greatly increase the solubility, bioavailability, and therapeutic efficacy of lipophilic medications.

The different formulation and assessment characteristics of nanoemulsions meant for topical administration are the main topics of this review paper. In order to determine the stability, droplet size, and drug loading efficiency of the nanoemulsion, it examines the strategic selection of formulation ingredients such as oils, surfactants, and co-surfactants. The preparation processes are covered in detail, with a focus on high-energy and low-energy emulsification methods and their significance in reaching the appropriate droplet size and stability profile.

To assess the caliber and functionality of the created formulations, characterization methods including droplet size analysis, zeta potential measurement, pH determination, viscosity testing, and thermodynamic stability investigations are examined. In order to validate the effectiveness and safety of topical nanoemulsions, the study also highlights in vitro and in vivo evaluation metrics such drug release profiles, skin permeation tests, and skin irritation assessments.

The ultimate goal of this analysis is to present a thorough understanding of topical delivery systems based on nanoemulsions, bolstering their potential for use in cosmetic and dermatological treatments.

Keywords: *Nanoemulsion, Topical application, Formulation, Characterisation, Refractive index and Transparency.*

1. INTRODUCTION

Compared to oral or parenteral routes, topical medication delivery offers a number of advantages and is a successful way to deliver therapeutic substances directly to the site of action. One of the main benefits is the ability to treat patients locally, which drastically lowers the likelihood of negative side effects and systemic drug exposure(1). For localized infections, pain control, wound healing, and dermatological problems, this route of administration is especially helpful. Topical formulations can provide sustained drug release at the target region, enhance patient compliance, and circumvent first-pass metabolism.

Notwithstanding these benefits, the stratum corneum, the epidermis' topmost layer, acts as a strong barrier to drug penetration(2). As a defense mechanism against environmental aggressors, this layer is made up of densely packed, keratinized

cells encased in lipid bilayers that block the entry of external substances, including medicinal drugs. As a result, when administered through traditional topical formulations like creams or ointments, many medications, especially hydrophobic or high-molecular-weight chemicals, show low transdermal penetration[2].

One innovative and intriguing way to get around this problem is with nanoemulsions. These are colloidal dispersions with droplet sizes typically between 20 and 200 nanometers, made up of two immiscible liquids (usually water and oil) stabilized by surfactants and co-surfactants[1,2]. The tiny droplet size improves the drug's thermodynamic activity at the interface and expands the surface area available for drug absorption, which results in better skin penetration.

Apart from enhanced penetration, nanoemulsions demonstrate exceptional thermodynamic stability, which means that they are less likely than traditional emulsions to experience phase separation, creaming, or sedimentation. Longer shelf life and reliable drug delivery are guaranteed by this stability[3]. Additionally, they are cosmetically acceptable due to their non-greasy texture and translucent or transparent appearance, which is important for dermatological and cosmetic applications. Nanoemulsions' biocompatibility and minimal skin irritation are further enhanced by the incorporation of non-ionic surfactants.

An important development in topical medication administration is the use of nanoemulsion systems, which provide answers to the fundamental drawbacks of conventional topical formulations. Nanoemulsions have enormous potential for the efficient treatment of a variety of skin-related conditions because they increase solubility, improve penetration, and provide controlled drug release[4].

Methodology

This review study was prepared utilizing a systematic and structured methodology to ensure comprehensive coverage and accuracy with relation to the formulation and evaluation of nanoemulsions for topical applications. A wide range of peer-reviewed research articles, review papers, pharmacopeial textbooks, and technical documents published between 2015 and 2025 were studied in order to collect, contrast, and synthesize relevant data.

Using scientific databases such as PubMed, ScienceDirect, SpringerLink, Scopus, and Google Scholar, a focused literature search was carried out. The search yield was maximized by using keywords like "nanoemulsion," "topical drug delivery," "formulation of nanoemulsions," "evaluation of nanoemulsions," "transdermal delivery," and "dermatological nanoformulations" both alone and in different Boolean combinations. Relevance to the subject, scientific legitimacy, methodological clarity, and the availability of comprehensive formulation or assessment data were additional inclusion criteria for the selection of articles.

Following that, the chosen studies were divided into groups according to their main areas of interest: formulation elements (oil, surfactants, co-surfactants, and aqueous phase); preparation techniques (high-energy and low-energy emulsification); characterization methods (droplet size, zeta potential, viscosity, etc.); and evaluation protocols (drug release, stability, and skin penetration). Research on topical nanoemulsions for medications with improved skin penetration or limited water solubility was given special attention.

Key formulation methodologies, benefits, and limitations were highlighted by extracting, summarizing, and comparing critical data from these investigations. In order to identify best practices and provide generalizable findings for creating stable, efficient nanoemulsion systems appropriate for cutaneous application, the approaches described in the literature were examined.

To improve the transparency and caliber of reporting, this review complies with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations where appropriate. Without replicating copyrighted content, the analysis was supported by the interpretation and citation of graphic abstracts, tables, and figures from the original research.

2. ADVANTAGES OF NANOEMULSIONS IN TOPICAL DELIVERY

- **Enhanced Drug Solubility**: Enhancing the solubility of poorly water-soluble (lipophilic) medications is one of the most important benefits of nanoemulsions. The restricted water solubility of many topical active pharmaceutical ingredients (APIs) limits their absorption and therapeutic effectiveness[1,3]. These lipophilic medications can stay in solution even at high concentrations because the oil phase in a nanoemulsion system acts as a solubilizing reservoir for them. The drug's thermodynamic activity is improved by this more solubilization, which makes it easier for it to pass through the formulation and into the skin. Nanoemulsions can therefore greatly increase the drug's local bioavailability, guaranteeing more efficient treatment at the intended location[2].
- **Improved Skin Penetration**: These emulsions' nanoscale droplet size, which usually ranges from 20 to 200 nanometers, is essential for improving skin penetration. The formulation's capacity to pass through the stratum corneum, the main barrier to transdermal drug administration, is enhanced by its small size, which also permits closer contact with the skin's surface[5]. Additionally, the tiny droplets' vast surface area produces a greater concentration gradient across the skin, which promotes diffusion. In addition to increasing permeability, surfactants

and co-surfactants in the formulation may also alter the stratum corneum's lipid structure. Because of this, nanoemulsions are especially useful for systemic distribution through transdermal routes or for distributing active substances into deeper skin layers[1].

- **Controlled Drug Release**: The potential of nanoemulsion devices to deliver regulated or sustained release of the integrated medication is another important benefit. Formulators can create systems that release the medicine at a specific rate by adjusting the oil phase's composition as well as the kind and concentration of surfactants[1,4]. By lowering the frequency of applications and improving patient adherence, this prolonged release profile helps sustain therapeutic medication levels over an extended period of time. This regulated distribution can enhance therapeutic results while reducing negative effects linked to peak plasma concentrations for chronic skin disorders like psoriasis or eczema that need long-term therapy[6].
- **Non-irritant and Cosmetically Acceptable**: To guarantee consistent use, topical formulations need to be both efficient and easy to apply. Nanoemulsions also perform exceptionally well in this area. They distribute quickly across the skin without leaving an oily or sticky residue, are usually non-greasy, and have a pleasant sensory experience[2-4]. Because of these qualities, they are aesthetically pleasing, which is especially crucial for cosmetic and dermatological products. Furthermore, the use of non-ionic, biocompatible surfactants reduces the possibility of allergic responses and irritation, which makes nanoemulsions appropriate for delicate skin. In cosmetic applications, where aesthetic appeal is crucial, their clear or somewhat translucent appearance is also favored.

3. FORMULATION COMPONENTS

- **Oil Phase**: When creating a nanoemulsion, the oil phase is essential, particularly when it comes to dissolving medications that are lipophilic or poorly soluble in water. The formulation's overall stability, droplet size, and drug-loading capability are all directly impacted by the oil selection[7]. Oils affect skin penetration in addition to serving as solvents for lipophilic medications. Isopropyl myristate, oleic acid, caprylic/capric triglycerides, and medium-chain triglycerides (MCTs) are among the frequently utilized oils. These oils have been shown to improve medication penetration through the stratum corneum and have outstanding solubilizing properties. Oleic acid, for example, is known to improve medication penetration by breaking down the skin's lipid bilayer. In order to guarantee optimal drug loading and formulation efficiency, solubility screening investigations are typically the basis for choosing an appropriate oil[3].
- **Aqueous Phase:**Distilled water, buffer solutions, and occasionally humectants like glycerin make up the aqueous phase. In oil-in-water (O/W) nanoemulsions, which are frequently used for topical treatments because of their non-greasy texture and skin-friendliness, this phase forms the continuous medium. The stability of the medicine, the solubility of excipients, and the final formulation's skin compatibility can all be impacted by the pH and content of the aqueous phase[1]. To maintain an ideal and stable pH environment for medications that are sensitive to pH, buffer solutions like phosphate or acetate buffers may be utilized. To improve formulation performance, the aqueous phase may also act as a carrier for hydrophilic preservatives or additives.
- **Surfactants and Co-surfactants**: By lowering the interfacial tension between the water and oil phases and promoting the creation of tiny, homogeneous droplets, surfactants and co-surfactants play a critical role in stabilizing nanoemulsions[2]. Because of their superior skin compatibility and minimal toxicity, non-ionic surfactants like Tween 80 (polysorbate 80), Span 20, and PEG-based surfactants are recommended. These surfactants aid in creating a flexible interfacial layer around oil droplets, which inhibits coalescence and improves the emulsion's kinetic stability[1]. Co-surfactants, such as ethanol, propylene glycol, or polyethylene glycol (PEG), are added to surfactants to increase their stability and lower their necessary concentration. Co-surfactants improve the solubilization of the oil and surfactant phases and make the interfacial film more fluid. Phase diagram studies are used to determine the nanoemulsion area and guarantee long-term stability by optimizing the correct ratio between surfactant and co-surfactant, also known as the Smix ratio[2].

4. PREPARATION METHODS

4.1 High-Energy Emulsification

- When reducing droplet size to the nanoscale range is needed, high-energy emulsification techniques are frequently employed to create nanoemulsions. These methods convert coarse emulsions into fine droplets by using external mechanical energy[8]. The creation of nano-sized droplets is facilitated by the large shear pressures produced by these techniques, which overcome the interfacial tension between water and oil.
- The most popular high-energy method is high-pressure homogenization. This technique uses extremely high pressures (up to 2000 bar) to force a pre-emulsion—a coarse mixture of water, oil, surfactant, and co-surfactant—through a small opening. As a result, the droplet size is reduced to the nanoscale scale by strong turbulence,

cavitation, and shear forces[9]. It can take several rounds to get a stable and homogeneous nanoemulsion.

- Another efficient high-energy technique is ultrasonication, which produces acoustic cavitation—the development, expansion, and collapse of small bubbles—by using high-frequency sound waves[1]. When these bubbles burst, shock waves and extremely high local temperatures and pressures are created, which causes the droplets to break apart into nanometer-sized pieces.
- High-energy techniques yield extremely stable formulations and provide exact control over droplet size[2,6]. However, because of localized heating during processing, they may not be appropriate for heat-sensitive medications, sometimes call for costly equipment, and use a lot of energy.

4.2 Low-Energy Emulsification

- Low-energy techniques provide a more energy-efficient option by utilizing the system's inherent physicochemical characteristics, such as phase behavior and variations in interfacial tension, to create nanoemulsions. Since these methods do not require outside mechanical energy, they can be used with sensitive or thermolabile active medicinal substances[10].
- The Phase Inversion Temperature (PIT) method is a popular low-energy technology. With this method, temperature fluctuations cause the emulsion to undergo a phase inversion (from oil-in-water to water-in-oil or vice versa)[3]. A temporary microemulsion-like condition arises at the PIT, balancing the surfactant's affinity for water and oil and enabling the formation of minuscule droplets. The system is "frozen" into a stable nanoemulsion upon rapid cooling.
- The Emulsion Inversion Point (EIP) approach is an additional technique that induces a phase inversion by changing the composition, usually the water-to-oil ratio[11]. The system goes through a bicontinuous phase during the transition, which makes it easier for nanoparticles to develop on their own.
- Low-energy techniques are beneficial because they are easy to use, economical, and appropriate for medications that are sensitive[1,9]. To attain and preserve nanoemulsion stability, they necessitate meticulous formulation parameter optimization and rely heavily on the choice of certain surfactant systems.

5. CHARACTERIZATION OF NANOEMULSIONS

- **Droplet Size and Distribution**: One of the most important factors in assessing nanoemulsions is the size and distribution of the droplets. Dynamic Light Scattering (DLS), also referred to as photon correlation spectroscopy, is frequently used for this assessment. The droplet sizes of nanoemulsions designed for topical administration are usually between 20 and 200 nanometers[12]. A high surface area is ensured by keeping the droplet size below 200 nm, which improves medication absorption and skin penetration. Furthermore, a homogeneous formulation is indicated by a narrow droplet size distribution, which is frequently represented by the polydispersity index (PDI)[1,9]. A low PDI (usually less than 0.3) indicates strong homogeneity and long-term physical stability of the nanoemulsion, reducing the possibility of phase separation and droplet coalescence.
- **Zeta Potential**: One important determinant of the electrostatic stability of nanoemulsion droplets is their zeta potential, which is a measurement of their surface charge. It establishes how strongly nearby, similarly charged particles in dispersion repel one another[13]. A zeta potential of more than ±30 mV is usually regarded as optimal for a stable nanoemulsion since it indicates that there are enough repulsive forces to keep the droplets from aggregating. Long-term physical stability is ensured by a high zeta potential, which is essential for application and storage[1-3]. Even with lower zeta potential levels, steric stabilization by non-ionic surfactants can help maintain stability in some formulations.
- **Viscosity**: The spreadability, adhesion, and residence time of a topical nanoemulsion on the skin are all significantly influenced by its viscosity. Rheometers and viscometers are used to measure it. An ideal viscosity in a formulation guarantees user acceptability, appropriate medication release, and simplicity of application[1,10]. While a too high viscosity might impair spreadability and lessen user comfort, a low viscosity may cause the formulation to run off the skin's surface. The right viscosity must strike a compromise between these factors and preserve the emulsion's physical stability.
- **pH**: To reduce the possibility of irritation or allergic reactions, the pH of the nanoemulsion should be near to the skin's natural pH, which is approximately 5.5[14]. Dryness, irritation, or sensitivity may result from a formulation that disturbs the skin's acid layer by having a pH that is noticeably higher or lower than the healthy range. Therefore, to guarantee that the formulation is safe for dermatology and well-tolerated over time, pH modification with buffers or mild acids/bases is frequently required[7].
- **Refractive Index and Transparency**: The physical stability and homogeneity of a nanoemulsion can be inferred from its transparency and refractive index (RI). High transparency or translucency and a refractive index near that

of skin or water are characteristics of a stable nanoemulsion, which suggests tiny droplet dispersion and steady phase behavior[1,8]. Refractive index variations over time may indicate instability, such as phase separation or droplet coalescence. Furthermore, for aesthetic reasons, cosmetic and dermatological products are frequently favored to have a clear or somewhat opalescent appearance[15].

6. EVALUATION PARAMETERS

6.1 Thermodynamic Stability Studies

To make sure that the nanoemulsion formulation maintains its physical stability under a range of stressors and environmental circumstances, thermodynamic stability studies are crucial[4]. Although nanoemulsions are kinetically stable, they may become unstable over time as a result of phase separation, Ostwald ripening, or coalescence, in contrast to macroemulsions. The formulation undergoes expedited stress testing, such as the following, to evaluate long-term stability quickly:

- **Centrifugation (typically at 3000 rpm for 30 minutes):** Helps detect phase separation, creaming, or sedimentation.
- **Heating–cooling cycles:** The nanoemulsion is cycled between high and low temperatures (e.g., 4°C to 45°C) for several cycles to test its resistance to thermal stress.
- **Freeze–thaw cycles:** Involves alternating between freezing (-20°C) and room temperature to evaluate the emulsion's integrity under extreme conditions[9].

Following these tests, nanoemulsions that maintain their homogeneity and do not separate, precipitate, or change color are deemed thermodynamically stable and appropriate for additional development.

6.2 In Vitro Drug Release Studies

To assess the pace and magnitude of drug release from the nanoemulsion, in vitro release tests are conducted. Franz diffusion cells are commonly used for these studies, in which the nanoemulsion is positioned in the donor compartment and isolated from the receptor compartment by a biological or synthetic membrane (such as animal skin or dialysis membrane)[1,12]. The receptor media, which is often phosphate buffer, is kept at physiological temperature (32–37°C). Samples are taken out at predetermined intervals and examined, typically by HPLC or UV-visible spectrophotometry.

The speed and effectiveness of the drug's release from the formulation, which is essential for attaining the intended therapeutic impact, is better understood thanks to this study.

6.3 Skin Permeation Studies

The purpose of these investigations is to assess the drug's skin penetration capacity, which is especially important for topical and transdermal applications. Franz diffusion cells are used to mount excised human or animal skin (such as rat or pig skin), and the stratum corneum side is coated with the nanoemulsion. The amount of medication that gradually seeps into or through the skin is then measured[7,13].

In order to optimize the formulation for improved dermal administration, these investigations offer crucial insights into the drug's penetration capacity, rate of absorption, and distribution across various skin layers.

6.4 Skin Irritation Tests

Skin irritation tests are carried out either in vivo (usually in rabbits or rodents) or in vitro (using rebuilt human epidermis models) to guarantee the safety and biocompatibility of the nanoemulsion. A tiny quantity of nanoemulsion is given to a shaved skin region in the in vivo approach, and the area is monitored for indications of erythema (redness), edema (swelling), or allergic reactions over the course of 24 to 72 hours[15].

This is a crucial step before clinical use since a formulation is deemed dermatologically safe and appropriate for human application if it exhibits no discernible discomfort.

7. APPLICATIONS IN DERMATOLOGY

The potential of nanoemulsions to improve medication solubility, stability, and skin penetration has drawn a lot of interest in them as efficient topical drug delivery methods for a range of therapeutic treatments[1,7]. Their ability to deliver antifungal medications, such as econazole nitrate, which have better penetration and can more effectively treat superficial fungal infections, has been extensively investigated. In a similar vein, anti-inflammatory drugs like ibuprofen and diclofenac that are prepared in nanoemulsions exhibit improved localized drug accumulation, offering long-lasting relief from inflammatory skin disorders like psoriasis and eczema while reducing systemic side effects[6]. When added to nanoemulsions, antibiotics such as clindamycin and mupirocin exhibit better diffusion and retention in infected tissues, enhancing the effectiveness of treatment for bacterial skin infections. Furthermore, because nanoemulsions provide non-greasy, readily spreadable, and visually pleasing formulations, they are perfect for long-term dermatological disorders including rosacea and acne, where

patient compliance and consistent therapy are essential[11]. Overall, because of their special qualities, nanoemulsions can deliver medications to the skin in a focused, regulated, and effective manner, which makes them a viable treatment option for a variety of dermatological conditions.

8. DISCUSSION

A possible method for improving the solubility, stability, and bioavailability of medications that are not particularly soluble in water, such econazole nitrate, is the creation of nanoemulsions for topical drug delivery. Using a spontaneous emulsification process, nanoemulsions were effectively created in this investigation, and suitable excipients were chosen based on their physicochemical compatibility with the medication. Phase diagram investigations showed that the optimal oil, surfactant, and co-surfactant combinations promoted the creation of stable and transparent emulsions (Shaikh et al., 2019)[1].

The produced nanoemulsions showed good thermodynamic and physical stability. They demonstrated strong structural integrity and appropriateness for topical application by withstanding typical stress conditions such temperature changes and mechanical forces without exhibiting any indications of phase separation or degradation. Additionally, FTIR spectroscopy compatibility experiments confirmed the formulation's chemical stability by revealing no discernible interactions between the medication and excipients (Bakshi et al., 2018)[2].

In order to ensure skin compatibility and reduce the possibility of irritation, the pH of the nanoemulsion compositions was kept within a dermatologically acceptable range. The compositions' viscosity allowed for sufficient skin spreadability and retention, which made topical application easy. The consistency and dependability of the preparation process were demonstrated by the consistent medication content among formulations (Salim et al., 2021)[5].

Studies on drug release in vitro showed that the nanoemulsions had a sustained release profile, indicating that the formulations might administer the medication for a long time. The small droplet size, which increases surface area, and the emulsifying ingredients, which facilitate drug penetration through the epidermal barrier, are responsible for the better release behavior. In terms of drug release efficiency, some compositions performed better than others among the evaluated formulations, highlighting the significance of maximizing the oil-to-surfactant ratio (Azhar et al., 2020)[6].

9. CONCLUSION

The unique physicochemical properties of nanoemulsions have made them a very alluring platform for the topical administration of medications. The ability of active pharmacological ingredients to make poorly water-soluble drugs more soluble, which can occasionally be a significant challenge in topical formulations, significantly increases the bioavailability of these ingredients. Because nanoemulsions reduce droplet size to the nanoscale, they improve drug penetration through the stratum corneum, the skin's primary barrier. This produces an enormous surface area that enhances medication dispersion and allows for closer contact with the skin's surface. This improved penetration allows for lower drug dosages, which reduces the danger of systemic side effects while also increasing the therapeutic efficacy of topical medicines.

Stability is a key component that qualifies nanoemulsions for topical therapies. Since they can endure phase separation, creaming, and coalescence, nanoemulsions are more thermodynamically stable than conventional emulsions. Stability of the product ensures stable drug administration and a longer shelf life during the course of use. However, to attain such stability, careful selection of formulation elements, such as oils, surfactants, and co-surfactants, as well as optimization of preparation technique, are required. The ability of each component to solubilize the drug, be skin-compatible, and maintain the integrity of the nanoemulsion must all be carefully considered.

Lastly, an extensive and thorough investigation is required to confirm the safety and effectiveness of the nanoemulsion compositions. This includes determining the stability under various stress conditions and describing the pH, zeta potential, droplet size, and viscosity. Additionally, skin penetration studies and in vitro drug release provide valuable insights into the efficacy of the formulation, while skin irritation testing ensures biocompatibility. Together, these techniques enhance treatment outcomes and patient compliance by producing the best possible nanoemulsions that deliver medicinal chemicals in a safe and efficient manner. With careful planning and extensive testing, nanoemulsions can thereby revolutionize topical drug delivery in the pharmaceutical and cosmetic sectors.

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