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POMEGRANATE SEED OIL NANOEMULSION AS AN ADVANCED CARRIER FOR ENHANCING SKIN PERMEATION OF POORLY WATER-SOLUBLE THERAPEUTIC AGENTS

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ABSTRACT

Poor aqueous solubility is a major formulation challenge that can limit the bioavailability and therapeutic effectiveness of many pharmaceutical agents. Transdermal delivery provides an alternative route capable of avoiding gastrointestinal degradation and hepatic first-pass metabolism, but drug transport is restricted by the highly organized barrier properties of the stratum corneum. Nanoemulsions have attracted considerable interest as advanced delivery systems because their nanoscale droplets provide high interfacial area and can improve solubilization and skin interaction. Pomegranate seed oil is a promising natural lipid component containing characteristic unsaturated fatty acids and has demonstrated potential in topical applications. This research examines pomegranate seed oil nanoemulsion as a carrier for enhancing skin permeation of poorly water-soluble therapeutic agents. The proposed formulation strategy involves drug-solubility screening, selection of surfactant and cosurfactant, nanoemulsion preparation, physicochemical characterization, in-vitro release, ex-vivo permeation, skin retention, stability, and safety evaluation. The approach emphasizes optimization of formulation composition and permeation performance while maintaining acceptable physicochemical stability and skin compatibility.

Keywords: Pomegranate Seed Oil, Nanoemulsion, Skin Permeation, Poorly Water-Soluble Drugs, Transdermal Delivery, Nanocarrier, Drug Solubilization, Skin Barrier

I. INTRODUCTION

The development of poorly water-soluble drugs has increased the need for advanced pharmaceutical delivery systems capable of improving drug dissolution, dispersion, absorption, and bioavailability. Low aqueous solubility can result in incomplete dissolution and variable absorption when conventional dosage forms are used. Transdermal delivery provides an alternative route because drug molecules can potentially enter systemic circulation through the skin without passing through the gastrointestinal tract. It may also avoid hepatic first-pass metabolism for compounds capable of crossing the skin. However, the stratum corneum presents a formidable barrier and restricts the passage of many molecules, particularly those that do not possess suitable physicochemical properties for passive diffusion.

Nanoemulsions have emerged as flexible systems for addressing some of these limitations. They consist of finely dispersed oil and aqueous phases stabilized by appropriate surface-active components. Their small droplet size and large interfacial area can support incorporation of lipophilic drugs and facilitate interaction with the skin. Nanoemulsions have been investigated for both dermal and transdermal administration of hydrophobic therapeutic agents, with reported advantages including improved solubilization, enhanced release, and increased skin permeation. Their performance, however, depends strongly on oil type, surfactant composition, droplet characteristics, surface properties, and the physicochemical characteristics of the incorporated drug.

Pomegranate seed oil offers an alternative to conventional synthetic or commonly used pharmaceutical oils. It is obtained from the seeds of *Punica granatum* and contains substantial amounts of unsaturated fatty acids, including punicic acid. Research into pomegranate seed oil has historically focused on nutritional and biological properties, but its potential as a topical formulation ingredient is increasingly being investigated. A recent study reported that pomegranate seed oil demonstrated acceptable cellular compatibility under the tested conditions and showed anti-inflammatory and wound-closure-related effects in human keratinocyte and dermal fibroblast models. These findings provide a basis for investigating its role in pharmaceutical skin-delivery systems.

The use of pomegranate seed oil in nanoemulsion technology is especially relevant because research has already examined pomegranate seed oil nanoemulsions for delivery of pomegranate peel polyphenols. The reported findings indicated improved skin retention of certain compounds and delivery into viable epidermal and dermal layers compared with free extract. This evidence suggests that pomegranate seed oil can function not merely as an inert lipid phase but potentially as a component of a delivery system with additional topical relevance. The present research therefore investigates the formulation principles, characterization requirements, permeation mechanisms, and pharmaceutical significance of pomegranate seed oil nanoemulsions for poorly water-soluble therapeutic agents.

II. RATIONALE AND FORMULATION STRATEGY FOR POMEGRANATE SEED OIL NANOEMULSION

The first stage of formulation development involves determining the suitability of pomegranate seed oil for solubilizing the selected poorly water-soluble drug. Excess drug should not be incorporated simply to increase loading because supersaturation can result in precipitation and physical instability. Solubility screening can be conducted using an excess-drug method followed by appropriate analytical quantification. Compatibility between the drug and pomegranate seed oil should also be assessed through thermal and spectroscopic techniques where appropriate. The selected formulation should provide sufficient drug incorporation while retaining physical stability during processing and storage.

The surfactant system is equally important because it determines the interfacial characteristics of the nanoemulsion. Nonionic surfactants may be considered because of their widespread pharmaceutical use and generally favorable compatibility profiles, although the specific choice should depend on the drug, oil, intended route, and regulatory acceptability. A cosurfactant may be incorporated to facilitate interfacial film formation and reduce the energy required for emulsification. Since excessive surfactant levels can potentially affect skin barrier integrity and cause irritation, optimization should consider permeation enhancement together with safety. Reviews emphasize that the choice and concentration of emulsifiers are important determinants of nanoemulsion performance.

An oil-in-water nanoemulsion may be particularly suitable when the intended product requires good skin spreadability and a relatively non-greasy external phase. The oil phase would contain the poorly soluble therapeutic agent, while the aqueous phase would provide

the continuous vehicle. The formulation can be prepared using high-energy methods such as ultrasonication or homogenization, or through suitable low-energy approaches. Selection of manufacturing technique should consider droplet size, reproducibility, energy consumption, scale-up feasibility, and thermal sensitivity of the drug and oil. High-energy methods can produce small droplets but may require specialized equipment and process optimization.

Optimization can be conducted using a systematic experimental design. Independent variables could include pomegranate seed oil concentration, surfactant-to-cosurfactant ratio, total surfactant concentration, aqueous-phase proportion, and processing time. Dependent variables may include droplet size, polydispersity, zeta potential, viscosity, drug content, release, and skin permeation. A response-surface methodology can be used to identify a composition that provides acceptable performance across multiple responses. Such an approach reduces reliance on trial-and-error formulation and provides a quantitative basis for selecting an optimized formulation.

The optimized nanoemulsion should possess suitable physical characteristics for topical administration. It should be homogeneous, free from visible phase separation, and sufficiently stable under relevant storage conditions. The formulation should demonstrate appropriate pH and viscosity and should maintain drug content during storage. Droplet size should remain reasonably consistent, and significant aggregation or coalescence should not occur. The relationship between physicochemical properties and permeation should be investigated because a formulation with favorable appearance may not necessarily provide superior transdermal performance.

The final formulation strategy should also consider the possibility of converting the liquid nanoemulsion into a nanoemulgel or other semisolid system if improved residence time is required. Nanoemulsions are fluid systems, and their low viscosity can limit residence time on the skin. Recent literature has highlighted nanoemulgels as a means of improving spreadability, adhesion, residence time, and acceptability while retaining nanoemulsion-related delivery advantages. Such modifications may therefore be relevant if the primary objective is sustained skin contact rather than rapid systemic absorption.

III. MECHANISMS OF SKIN PERMEATION ENHANCEMENT AND EVALUATION

The effectiveness of a transdermal nanoemulsion depends on overcoming or modifying the barrier properties of the stratum corneum. Passive drug transport generally requires an appropriate balance between aqueous and lipid solubility. Many poorly soluble drugs may have inadequate partitioning characteristics or insufficient thermodynamic activity at the skin surface. Nanoemulsions can modify the formulation environment surrounding the drug and may improve its effective delivery to the skin. Their nanosized droplets also create extensive interfacial contact between the formulation and skin surface.

The surfactant and cosurfactant components can contribute to permeation enhancement by interacting with the lipid structure of the stratum corneum. Such interactions may increase fluidity or modify the organization of skin lipids, facilitating drug diffusion. However, this mechanism must be carefully controlled because excessive disruption can produce irritation or compromise barrier function. The objective is therefore not simply to maximize penetration but to achieve therapeutically meaningful delivery while maintaining acceptable skin integrity. The literature on nanoemulsion-based transdermal systems emphasizes the importance of optimizing composition and evaluating both delivery and safety.

Pomegranate seed oil may contribute to the formulation through its lipid composition. The presence of unsaturated fatty acids may influence the interaction between the formulation and skin lipids. Punicic acid is particularly characteristic of pomegranate seed oil and may provide distinctive physicochemical properties. However, the contribution of individual fatty acids to transdermal permeation should be investigated experimentally rather than inferred solely from oil composition. Recent evidence demonstrating biological activity of pomegranate seed oil in skin-related cell models supports continued investigation but does not by itself establish enhanced drug permeation.

Franz diffusion-cell experiments provide an appropriate experimental platform for assessing ex-vivo skin permeation. Important parameters include cumulative drug permeated per unit area, steady-state flux, permeability coefficient, lag time, and drug retained within the skin. Comparison between the optimized pomegranate seed oil nanoemulsion, a conventional formulation, and an appropriate control can determine whether the nanoemulsion provides a

meaningful enhancement. Skin deposition is also important because the desired therapeutic outcome may involve localized dermal delivery rather than systemic absorption.

Drug distribution across different skin layers can provide additional mechanistic information. The formulation can be evaluated for drug content in the stratum corneum, viable epidermis, and dermis. Microscopic techniques, including fluorescence-based confocal microscopy when a suitable marker is available, may help visualize formulation-associated distribution. Previous research using pomegranate seed oil nanoemulsions demonstrated enhanced delivery of selected pomegranate polyphenols into deeper skin layers and supported the permeation findings using confocal microscopy. This provides a useful methodological precedent for future investigations.

Safety assessment should accompany permeation studies. Cytotoxicity testing in relevant skin-cell models, irritation studies, and histological examination can help establish whether improved permeation is associated with undesirable barrier disruption. This is particularly important because penetration-enhancing surfactants can influence skin structure. Reviews have emphasized that skin irritation and toxicity should receive greater attention in the development of nanoemulsion systems for dermal and transdermal delivery. Thus, an effective formulation should be defined by the combined achievement of delivery efficiency, physicochemical stability, and biological safety.

IV. CHARACTERIZATION, STABILITY, AND THERAPEUTIC POTENTIAL

Comprehensive characterization is essential for establishing the quality and reproducibility of a pomegranate seed oil nanoemulsion. Droplet size and polydispersity should be measured using dynamic light scattering, while zeta potential can provide information about surface charge. The pH should be determined to establish compatibility with skin application, and viscosity should be measured to assess spreadability and residence characteristics. Drug content and assay should be determined using a validated analytical procedure. These parameters provide a basic quality profile for the formulation.

Morphological analysis can supplement particle-size measurements by providing visual information about droplet distribution and shape. Transmission electron microscopy, scanning electron microscopy, or other suitable microscopy methods may be considered depending on formulation characteristics and available instrumentation. However, microscopy should complement rather than replace quantitative particle-size analysis. A

complete characterization programme should integrate multiple techniques to provide a reliable description of the formulation.

Stability evaluation should be conducted under different storage conditions. Changes in droplet size, polydispersity, zeta potential, pH, viscosity, drug content, and visual appearance should be monitored. Centrifugation and temperature-cycling studies may provide preliminary information regarding physical robustness, while long-term stability studies provide more meaningful evidence for product development. Pomegranate seed oil itself may be susceptible to oxidative changes because of its unsaturated fatty-acid composition, making protection from oxidation and appropriate packaging particularly important. Research on pomegranate seed oil formulation has identified stability as an important consideration in preserving its physicochemical and functional properties.

Drug-release studies should be conducted before skin-permeation experiments to understand the release behaviour of the formulation. Depending on the intended application, controlled or sustained release may be desirable. Mathematical modelling can provide information regarding the apparent release mechanism. Nevertheless, release testing should be interpreted alongside skin permeation because membrane diffusion and biological barriers can produce substantially different behaviours. A formulation demonstrating controlled release may still provide inadequate skin delivery if the active drug has poor partitioning into the stratum corneum.

The therapeutic potential of the system is particularly relevant for drugs with poor aqueous solubility and inadequate conventional transdermal performance. Nanoemulsions can provide a lipid environment capable of incorporating hydrophobic compounds and improving their distribution at the skin surface. Reviews have reported their utility for hydrophobic and hydrophilic drugs and emphasized their potential to improve delivery characteristics. The incorporation of pomegranate seed oil may further provide a natural lipid component with potential skin-related biological properties.

Despite these advantages, translation into pharmaceutical application requires consideration of limitations. Surfactant toxicity, formulation instability, oxidative degradation, manufacturing reproducibility, energy consumption, packaging, scale-up, and regulatory requirements can influence the feasibility of nanoemulsion products. Recent reviews have specifically identified surfactant optimization, production energy requirements, stability, and

regulatory issues as continuing challenges in transdermal nanoemulsion development. These limitations should therefore be incorporated into formulation design from the beginning rather than addressed only after laboratory optimization.

Future development should progress from formulation screening to detailed ex-vivo permeation, skin-safety studies, pharmacokinetic assessment, and therapeutic efficacy evaluation. If systemic delivery is intended, plasma drug concentration and pharmacokinetic parameters should be examined in suitable animal models before clinical translation. If localized dermal treatment is intended, tissue drug concentration and pharmacodynamic response may be more appropriate endpoints. The final product should demonstrate reproducible manufacturing, adequate stability, acceptable safety, and meaningful therapeutic benefit.

V. CONCLUSION

Pomegranate seed oil nanoemulsion represents a promising advanced carrier for improving the skin delivery of poorly water-soluble therapeutic agents. The major challenge in transdermal delivery is the barrier function of the stratum corneum, which restricts the passage of many pharmaceutical molecules. Nanoemulsions can potentially address this limitation by increasing drug solubilization, providing a large interfacial area, improving skin contact, and facilitating drug partitioning into skin layers.

The incorporation of pomegranate seed oil provides an additional dimension to the formulation strategy. Its unsaturated fatty-acid-rich composition and emerging evidence of topical biological activity make it an interesting natural lipid for advanced pharmaceutical delivery. Experimental evidence involving pomegranate seed oil nanoemulsions has demonstrated enhanced skin retention and delivery of selected pomegranate-derived compounds, supporting further exploration of this platform.

A successful formulation requires systematic optimization and comprehensive characterization. Drug solubility, oil concentration, surfactant and cosurfactant composition, droplet size, polydispersity, zeta potential, pH, viscosity, drug content, release behaviour, skin deposition, permeation, stability, and safety should be evaluated. Particular attention should be given to oxidative stability of the oil phase, surfactant-related irritation, and maintenance of formulation characteristics during storage. These factors are essential for transforming a laboratory nanoemulsion into a reproducible pharmaceutical system.

In conclusion, pomegranate seed oil-based nanoemulsions offer a scientifically relevant platform for overcoming some limitations associated with poorly water-soluble drugs and conventional transdermal formulations. Nevertheless, their pharmaceutical potential must be established through formulation-specific experimental studies rather than assumed from nanoemulsion technology alone. Future investigations should focus on optimization, mechanistic permeation studies, long-term stability, skin safety, pharmacokinetic evaluation, and therapeutic validation. Such systematic development could support the emergence of natural-oil-based nanoemulsion systems as advanced carriers for transdermal drug delivery.

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