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Transdermal Drug Delivery of Nanoemulgel to Treat Skin Diseases

Sweety Verma

Research Scholar - Department of Pharmacy, Rameshwaram Institute of Technology and Management Sitapur Road, Lucknow, U.P., India
Corresponding Author Email: *vermasweety8052[at]gmail.com*

Abstract: ***The emergence of nanoemulgels represents a thoughtful leap in the field of topical drug delivery, especially when addressing the long-standing challenges posed by conventional ointments, creams, and gels. Unlike traditional methods that often struggle with poor penetration and inconsistent drug release, nanoemulgels offer a promising alternative by blending nanoemulsion technology with a gel-based matrix. This unique combination enhances skin permeability, facilitates controlled drug release, and allows for more targeted therapeutic action, particularly for dermatological treatments. It is evident that the incorporation of natural oils like oleic acid and emu oil not only improves drug absorption but also brings additional therapeutic benefits such as anti-inflammatory and antioxidant properties. That said, the formulation process is far from simple; the careful selection of surfactants, cosurfactants, and gelling agents is critical to balancing stability, efficacy, and skin compatibility. One cannot overlook the fact that nanoemulgels also present certain hurdles-variability in skin physiology, potential instability of nano-sized particles, and the complexity of maintaining a consistent formulation are just a few examples. This suggests that while the technology holds great promise, it requires meticulous design and rigorous testing to unlock its full clinical potential. Taking this further, the application of nanoemulgels in treating conditions like acne, alopecia, and other skin disorders could redefine how we approach transdermal drug delivery in the future. By refining formulation techniques and embracing the bio-friendly characteristics of nanoemulgels, the pharmaceutical and cosmetic industries may find themselves on the brink of a transformative shift in patient care.***

Keywords: nanoemulgel, transdermal delivery, skin permeability, targeted therapy, controlled drug release

1. Introduction

Oral, sublingual, rectal, parental, and other traditional methods have been used to treat illnesses throughout the past few decades. Topical medication administration uses the skin, vagina, rectal, and ocular channels to administer drugs locally anywhere in the body. The primary benefit of topical administration is its ability to circumvent first-pass metabolism. Other benefits of topical preparations include avoiding the hazards and hassles of intravenous therapy as well as the various circumstances of absorption, such as pH fluctuations, the presence of enzymes, and the time it takes for the stomach to empty. They are using a variety of dermatological and cosmetic preparations on their healthy or sick skin. Although dermatological solutions come in a variety of formulations and consistency ranges from liquid to powder, semisolid preparations are the most widely used. Transparent gels have become more widely used in pharmaceutical and cosmetic preparations within the main category of semisolid preparations. Large volumes of aqueous or hydroalcoholic liquid are trapped in a network of colloidal solid particles to make gels, a relatively novel class of dosage form. In general, gel formulations release drugs more quickly than traditional ointments and creams. The challenge of delivering hydrophobic medications is a significant drawback of gels, despite their many benefits. Emulsions are elegant to a certain extent and can be removed with ease at any time. They are also quite good at penetrating the skin. Thixotropic, greaseless, easily spreadable, readily removable, emollient, non-staining, water-soluble, having a longer shelf life, being bio-friendly, clear, and having a nice look are just a few of the advantageous qualities of Emulgels for dermatological usage.[1]

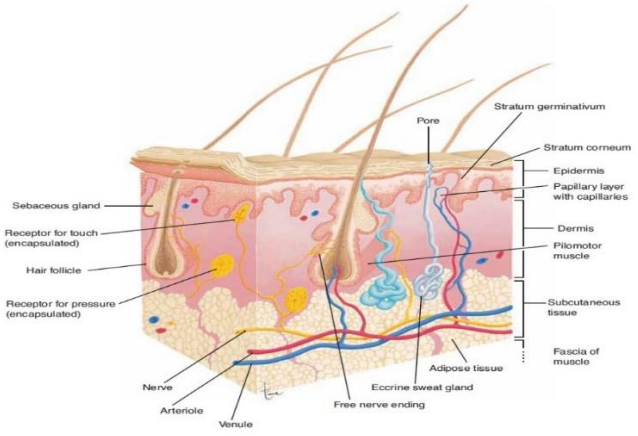
Topical medication delivery method classification: -

1) Solid: Ointments, plasters, powders,
2) Semi-solid: Pastes, Gels, Creams, and Poultices
3) Liquid: Paints, tinctures, emulsions, suspensions, lotions, liniments, and solutions
4) Other: Topical aerosol, rubbing alcohols, tapes and gauzes, transdermal medicine delivery devices, and liquid cleanser.[2]

Layers of Skin: -

1) Epidermis: outermost layer that acts as a barrier
2) Dermis: The middle layer that includes hair follicles, nerve endings, and blood vessels
3) Hypodermis: The innermost layer that connects the skin to the structure's underneath.[3]

Skin structure:



- Stratum corneum: The stratum corneum, the outermost layer of the epidermis, serves as a barrier.

[1] Redkar, Patil, and Rukari, "EMULGEL: A MODERN TOOL FOR TOPICAL DRUG DELIVERY."
[2] Redkar, Patil, and Rukari.
[3] Chellapa et al., "Nanoemulsion and Nanoemulgel as a Topical Formulation."

- Keratinocytes: The primary cell type in the epidermis, keratinocytes, create keratin.
- Melanocytes: Melanocytes are the cells that produce melanin, which gives skin its colour.

Functions of the Skin:
- Barrier function: The barrier function shields against outside influences.
- Regulation: Controls water loss and body temperature
- Sensation: Enables the perception of warmth, pressure, and touch.[4]

Mechanism of action: -
- **Penetration:** The stratum corneum layer, the outermost layer of the epidermis, is penetrated by nanoemulgel particles. The nanoemulgel particles can readily penetrate the skin's natural barriers because of their small size.
- **Diffusion:** The medication is liberated from the nanoemulgel particles after they have entered the skin and permeates the layers of the skin. Temperature and skin humidity are two variables that might affect this process, which is fuelled by concentration gradients.
- **Absorption:** The medication enters the circulation or enters the specific skin tissues. Factors including skin metabolism, molecular weight, and lipophilicity can all affect the absorption process.

Important Elements Affecting the Mechanism of Action
- **Particle size:** By expanding the surface area available for diffusion, smaller particles improve penetration and absorption.
- **Lipophilicity:** Because the stratum corneum layer of the skin is lipophilic, lipophilic medications are more readily absorbed through the skin.
- **Skin hydration:** Hydrating the skin increases its permeability, which improves penetration and absorption. **Skin metabolism:** Drugs can be metabolized by skin enzymes, which lowers their effectiveness.

NANOEMULGEL:

The insertion of a nanoemulsion system intergraded into a hydrogel matrix results in nanoemulgel, sometimes referred to as the development of nanoemulsion based on hydrogel, which improves skin penetration. Many scientists are interested in this nanoemulgel mixture because it can be used to create a variety of medications that cure different types of skin conditions. The topical delivery system's nanoemulgel formulation functions as a drug reservoir, influencing the release of medications from the inner phase to the outer phase and ultimately onto the skin. The crosslink density and network polymer chain composition determine these release mechanisms. In addition, a drug's inclination to diffuse out of the vehicle and pass through barriers affects its capacity to penetrate the skin and effectively release the therapeutic agent.

The oily droplets will be released from the gel network when the skin is still attached to the nanoemulgel. The drug molecules will therefore be delivered directly via the oil droplets into the stratum corneum of the epidermis, bypassing the hydrophilic phase of nanoemulsions.[5]

Formulation Components Consideration: An oil phase and an aqueous phase make up either an o/w or w/o nanoemulsion. A thin layer of surfactant, occasionally enhanced by the presence of cosurfactant, enervates the microscopic dispersed phase. The connected section provides an overview of oil selection techniques that make use of several of the incorporated oil's intrinsic features.

Oil Selection: The lipid component, or oil, is one of the key elements of the nanoemulgel. To choose the right oil phase based on the created nanoemulsions stability, permeability, and viscosity, multiple studies are needed.

Due to its well-known percutaneous absorption enhancer property and formulation stabilization property, oleic acid-a biocompatible and biodegradable omega-9 fatty acid that can be found in a variety of vegetable and animal products-is frequently used as an oil phase in nanoemulgel formulation. Furthermore, oleic acid's antioxidants, which are known to support the integrity of cell membranes, aid in the replacement of damaged cells and tissues. The creation of topical nanoemulgel containing piroxicam has made use of this oleic acid as a permeation enhancer for numerous medications because of its beneficial qualities.

Natural oils have been shown to have extra medicinal benefits, and researchers worldwide are becoming more interested in using these benefits for therapeutic purposes. Because of its anti-inflammatory, analgesic, aesthetic, antipruritic, and antioxidant qualities, emu oil-another oil derived from emu birds-also attracted attention from the pharmaceutical industry. Jeengar et al. made use of emu oil's significant medicinal properties.[6]

Surfactant and Cosurfactant Selections

Surfactant: Surfactants are essential parts of nanoemulsion systems, which stabilize thermodynamically unstable mixtures of two immiscible liquids by altering the dispersion entropy and lowering the interfacial tension between them. The fundamental needs for the surfactants used in the creation of nanoemulsions are safety, stability, and a high drug loading capacity in addition to good emulsification qualities. When creating a nanoemulsion, an appropriate surfactant should be quickly adsorbed onto the interface between the two immiscible phases. This will drastically lower the interfacial tension and stop the nanodroplets from coalescing. The choice of surfactants is determined by several parameters. The first and most crucial aspect is the surfactant's related toxicity. Choosing the right surfactant is crucial since too much of it might irritate the skin and digestive system when used topically and orally, respectively. As a result, using the least quantity of surfactant possible in the formulation was recommended. The surfactant's HLB value is an additional

[4] Azhar and Mishra, "REVIEW OF NANOEMULGEL FOR TREATMENT OF FUNGAL INFECTIONS."
[5] Chellapa et al., "Nanoemulsion and Nanoemulgel as a Topical Formulation."
[6] Azhar and Mishra, "REVIEW OF NANOEMULGEL FOR TREATMENT OF FUNGAL INFECTIONS."

selection criterion. The available surfactants are categorized as w/o emulsifying agents (HLB 3-8) and o/w emulsifying agents (HLB 8-16) according to their HLB values. Consequently, the HLB value of the chosen surfactant must be greater than 10 to create an o/w nanoemulsion. Tweens and spans with an HLB value greater than 8 are therefore utilized in o/w emulsion. Additionally, when compared to pure Tween or Span systems, the combination of Span 20 and Tween 20 contributes to the emulsions' increased stability.[7]

Cosurfactant: In the nanoemulsion system, cosurfactant aids surfactant in emulsifying oil in the aqueous phase. Cosurfactant breaks the interfacial film in such a system by combining with surfactant and penetrating the surfactant layer. This provides the necessary fluidity, reduces interfacial tension, and aids in the emulsification process. Because the partitioning of therapeutic agents or lipophilic medicines in the aqueous and oil phases is influenced by the interaction between surfactant and cosurfactant, choosing the right cosurfactant is crucial. 33 In nanoemulgel and nanoemulsion systems, cosurfactants such as Transcutol® HP, 1,2-propylene glycol, PEG-400, carbitol, absolute ethyl alcohol, propanol, and butanol are commonly utilized. Propylene glycol, 1-butanol, ethanol, and isopropyl alcohol are being chosen as cosurfactants. Carbitol and PEG 400 were also chosen since they are reasonably palatable and exhibit enhanced penetration when added to formulations. 71 When creating nanoemulsions, the criterion for choosing surfactants and cosurfactants is based on their transmittance percentage. Using oleic acid as the oil phase, Arora et al.54 evaluated Transcutol P, propylene glycol, and ethanol as cosurfactants and Tween 80, Labrasol, and Labrafac as surfactants. [8]

Preparation of Nanoemulsion and Change in Its Physical State by Addition of Gelling Agent: The process of creating nanoemulgels involves two steps: the first is the creation of the nanoemulsion, and the second is the introduction of the nanoemulsion into the gelling agent Nanoemulsions can be created by applying external energy to a heterogeneous mixture or by combining the compositions and lowering the interfacial tension between the oil and water interfaces. Thus, high energy and low energy emulsification techniques can be used to create a thermodynamically stable nanoemulsion.

High energy emulsification method: By optimizing the necessary time, temperature, and component properties to minimize the size of the dispersed to the nonorange, high shear force generated by ultrasonicators, high pressure homogenizers, microfluidizers, and other devices is used to rupture the oil phase and form nanosized droplets in the aqueous phase. Consequently, this process of creating nanoemulsions necessitates the use of external energy, which renders the created formulations thermodynamically unstable because of the free energy they contain. Additionally, by modifying the components, this approach can achieve a dispersed phase size as small as 1 nm, however it cannot be used with thermolabile components.

Low energy emulsification method: Method of Low Energy Emulsification Because high energy is incorporated during the manufacturing process, low energy methods for creating nanoemulsions, such as the spontaneous method and phase inversion method, are found to be more beneficial than high energy emulsification techniques in terms of the final formulation's thermodynamic stability. Carbomer 940,54 chitosan,117 Carbopol 934,39,42,118 Carbopol 940,32,40,119 Carbopol 980,120 Poloxamer 407,42 methyl cellulose,121 Carbopol 971,58, and so forth are some of the frequently utilized gelling agents that are used in the creation of nanoemulsion gel.[9]

The advantages of nanoemulgels

- **Increased bioavailability:** Better penetration and diffusion result in increased medication absorption and effectiveness.
  Targeted delivery: By delivering the medication to particular skin tissues, adverse effects are decreased and therapeutic results are enhanced.
- **Controlled release:** By enabling controlled release of the medication, nanoemulgels can lessen the frequency of dosage.

Obstacles and Restrictions:

- **Skin variability:** The effectiveness of nanoemulgels may be impacted by individual differences in skin thickness, moisture, and metabolism.
- **Stability:** The particles in nanoemulgels may aggregate or degrade because of their instability. [10]

2. Discussion

Because of its potential to increase skin permeability, offer controlled release, and target certain skin tissues, nanoemulgels have drawn a lot of attention recently for use in transdermal medication delivery. Nanoemulgels work by penetrating the stratum corneum layer of the skin, releasing the medication, and allowing it to enter the bloodstream or specific skin tissues. Skin moisture, skin metabolism, lipophilicity, and particle size are some of the variables that affect this intricate process.

The capacity of nanoemulgels to increase skin permeability, which enables more effective delivery of medicinal substances, is one of their main advantages. This is especially crucial when treating skin conditions because the deeper layers of the skin are frequently the target location of action. Nanoemulgels can improve treatment results by increasing the amount of medicine that reaches the target site by improving skin permeability.

Additionally, by targeting particular skin regions, nanoemulgels might lessen the negative consequences of systemic distribution. For instance, nanoemulgels can be made to specifically target the pilosebaceous unit, which makes them effective in treating alopecia and acne.

[7] Azhar and Mishra.
[8] Azhar and Mishra.
[9] Kumar et al., "Techniques for Formulation of Nanoemulsion Drug Delivery System."
[10] Kumar et al.

3. Conclusion

Transdermal medication delivery using nanoemulgels shows promise in the treatment of skin conditions. They provide focused delivery of medicinal substances, regulated release, and enhanced skin permeability. Although their creation and application present certain difficulties, these difficulties can be addressed with careful formulation design and optimization. To fully realize the potential of nanoemulgels and implement them in therapeutic settings, more research is required. All things considered, nanoemulgels are a promising method for transdermal medication delivery; however, more study is required to fully explore their potential. We can realize the full potential of nanoemulgels and enhance the management of skin conditions by tackling the difficulties related to their creation and application.

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