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TOPICAL NANO-EMULGEL FOR SKIN DISORDERS: A COMPREHENSIVE REVIEW

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ABSTRACT

Nanoemulgel is a powerful delivery method for lipophilic medicines. The word nanoemulgel refers to an emulsion that has gelled due to the presence of a gelling agent. The attention on nanoemulgels has also increased due to their ability to achieve targeted distribution, ease of application, lack of gastrointestinal degradation or first pass metabolism, and safety. They come in o/w or w/o forms, with one immiscible liquid spread as droplets inside another. Hydrogel-based nanoemulsion systems, also known as nanoemulgels, are homogeneously distributed systems in which the hydrogel matrix enhances nanoemulsion skin penetration (10-200 nm droplets). With greater drug loading due to higher solubilizing effectiveness, better bioavailability due to superior permeability, and the capacity to modulate drug release, it is a potent alternative delivery strategy for treating a range of disorders. It has been demonstrated that nanoemulgel formulations are considerably more effective in treating inflammation caused by rheumatoid arthritis, psoriasis, fungal infections, acne, and pimples. A nanoemulgel's outstanding features, such as thermodynamic stability, permeability enhancement, and prolonged release, make it an ideal dosage form. This review focuses on the varieties, advantages, and downsides of nanoemulgels, as well as their constituents, preparation methods, and numerous characterisation investigations.

KEYWORDS: Inflammation, Nanoemulgel, Topical application, solubility.

INTRODUCTION

Skin is one of the most distinctive and biggest organs in the human body, accounting for around 10% of total body mass and covering an average person's surface area of 1.7 m.[1,2]

Skin diseases are typically accompanied by chronic inflammation issues with a complex pathophysiology and a significant genetic component. Some of them have an immune-mediated systemic illness condition with skin cutaneous component involvement, such as psoriasis, rheumatoid arthritis, eczema, fungal infections, and so on, which affects approximately 11.43 percent of the general population globally, making it a critical global challenge for approximately 100 million people.[3,4]

Inflammation is a defensive reaction to external stimuli or internal cellular damage that triggers the release of immune response mediators at the site of injury. Normal inflammatory defense responses can target and degrade outsiders like bacteria, foreign objects, or cancer cells. Inflammatory illnesses can reduce patients' quality of life and have a significant economic impact.[5,6] According to research, patients are now receiving ineffective medications and are unsatisfied with the utility of available prescription formulations, as demonstrated by a higher prevalence of endurance. Because skin inflammatory illnesses require long-term treatment, it must be safe, useful, and successful, with high aesthetic approval. Currently, 90% of medications in the discovery pipeline and more than 40% of pharmaceuticals on the market have lipophilic properties. The lipophilic nature of the medications causes difficulties such as low solubility, variable absorption, and pharmacokinetic heterogeneity between and within subjects. As a result, several ways have been explored to address these fundamental shortcomings.[7,8]

There have been several approaches proposed to address the concerns of low solubility and bioavailability. For example, many delivery systems have been developed, pharmacologically active molecules have been chemically or physically altered, citrus pectin has been encapsulated in a micro/nano delivery system, and research has been conducted on salt formation, solid dispersion, size reduction, crystal engineering and complexation, among others. Among these, lipid-based formulations have received a lot of interest for their capacity to increase the solubility of lipophilic medicines. This includes creating formulations using carrier systems such liposomes, niosomes, solid-lipid nanoparticles, macroemulsions, and nanoemulgels.[9,10]

One of the most popular innovative dosage forms for topical distribution is the nanoemulgel drug delivery system, which is a formulation-based intervention targeted at increasing lipophilic medicine systemic transport in the skin.[11,12] It is a hybrid of two systems, a nanoemulsion-containing medication and a gel base, so it benefits from the combination of

both. Because of the presence of finely dispersed droplets in the nanoemulsion phase, lipophilic medicines are easily integrated, and the skin permeability of the medications increases.[13]

Nanoemulgel as a topical drug delivery system

Nanoemulgel is created by combining nanoemulsion (NE) and a gel basis. The nanoemulsion is thickened with a gelling agent that aids transcutaneous delivery, resulting in a nanoemulgel.[14] Nanoemulgel is an integral part of the topical medication delivery system. Nanoemulsion is a thermodynamically stable, optically isotropic, transparent colloidal system with droplet sizes < 100nm. Topical nanoemulsion gel outperforms traditional lipophilic drug formulations in terms of pharmacokinetic profile, therapeutic efficacy, and absorption capacity.[15,16]

It is a new topical medication delivery method that is greaseless, easily spreadable, non-staining, safer, biocompatible, transparent or milky in appearance, and more effective than conventional topical drug delivery systems such as creams and ointments.[17] Drawbacks associated to traditional topical formulations, such as powders that display hygroscopicity, creams that show instabilities, such as phase inversion or breaking, in their formulations, components in ointments that develop rancid, lotions that are sticky in nature, etc., contribute to patient noncompliance. There are no such disadvantages associated with NEG formulations. Most notably, a medication given by nanoemulgel results in a bigger concentration gradient towards the skin due to its high solubilizing ability, resulting in improved skin penetration.[18,19]

Nanoemulgels are frequently used, notably as topical administration methods, to improve skin penetration, decrease instability, and increase half-life. These kinetically stable and optically transparent nano-vehicles offer a viable alternative for increasing the solubility, skin penetration, and bioactivity of different compounds. Furthermore, varied combinations of components (oils, surfactant, co-surfactant, and water) might improve drug encapsulation while preventing surface buildup and discoloration. NEGs may regulate drug release for a longer length of time, which is advantageous for drugs having a short half-life. They provide a higher concentration gradient and increase skin permeability due to their improved skin adhesion and medication solubility.[20]

According to the literature, nanoemulgels can be utilized for local and systemic diseases/disorders such as alopecia, periodontitis, and Parkinson's if supplied via ophthalmic, dental, vaginal, and nose-to-brain pathways.

Components used in nanoemulgel preparation

Oils and lipids: The lipid phase utilized for nanoemulsion creation is critical, and the number of oils and lipid components employed is typically determined by the kind of emulsion and the solubility of the active ingredient in the formulation. In most circumstances, the oil with the best capacity to dissolve the medication candidate is selected. Because the oil phase must dissolve and keep the medication in its dissolved condition. for ex., Isopropyl myristate, Olive oil Arachis oil, Caproyl 90.

Aqueous Phase: Distilled water is commonly utilized as an aqueous phase for the preparation of Nanomulsion and Hydrogel.[21]

Surfactant: The surfactant's amphiphilic structure produces a sufficiently stable film that may deform around the droplets with the perfect curvature, allowing the dispersion of two immiscible phases and decreasing interfacial tension. Surfactants are substances that can alter the stratum corneum (SC) diffusion coefficient and increase penetration into the skin by reversibly sticking to keratin filaments, destroying corneocytes, and so on.

Cosurfactants: Cosurfactants are used to help surfactants when creating nanoemulsion systems with low surfactant concentrations. The cosurfactant and surfactant can work together to help in the emulsification process by disturbing the interfacial layer and increasing oil solubility. The co-surfactant and concentration to be employed must be carefully selected since they may affect the surfactant's capacity to emulsify the system.[22,23]

Emulsifiers: they are used to enhance emulsification throughout the manufacturing process as well as to manage stability during the shelf life of commercial preparations. Examples include polyethylene glycol 40 stearate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, stearic acid, and sodium stearate.

Gelling Agent: These agents are used to enhance the consistency of any dosage form and can also be used as a thickener. Carbopol 934, Carbopol 940, HPMCK4M, and HPMC are typical gelling polymers used in emulgel formulation.[24]

Carbomers are acrylic acid polymers with a high molecular weight that have been crosslinked with allyl sucrose or pentaerythritol ethers. Different grades of carbomer are available based on the degree of cross-linking and manufacturing requirements, including carbopol 934 (lowest cross-linking density), carbopol 981 (intermediate cross-linking density), and carbopol 940 (maximum cross-linking density).[25]

Other Components: Other additives, such as preservatives and antioxidants, may be utilized in nanoemulsion. Water-based systems should normally include a preservative chemical to inhibit microbial development. Essential oils (EOs) are naturally occurring antimicrobials hence preservatives are often unnecessary in EO-based systems. Antioxidants keep oxidation from degrading the formulation's ingredients.[26]

Preparation of Nanoemulgel

The manufacture of the nanoemulgel involves two steps. The drug, surfactant, and cosurfactant are dissolved according to their solubility in either the oil or aqueous phase. The oil and aqueous phases are rapidly heated before being mixed by gradually introducing one into the other while continuously stirring until they reach room temperature.[27]

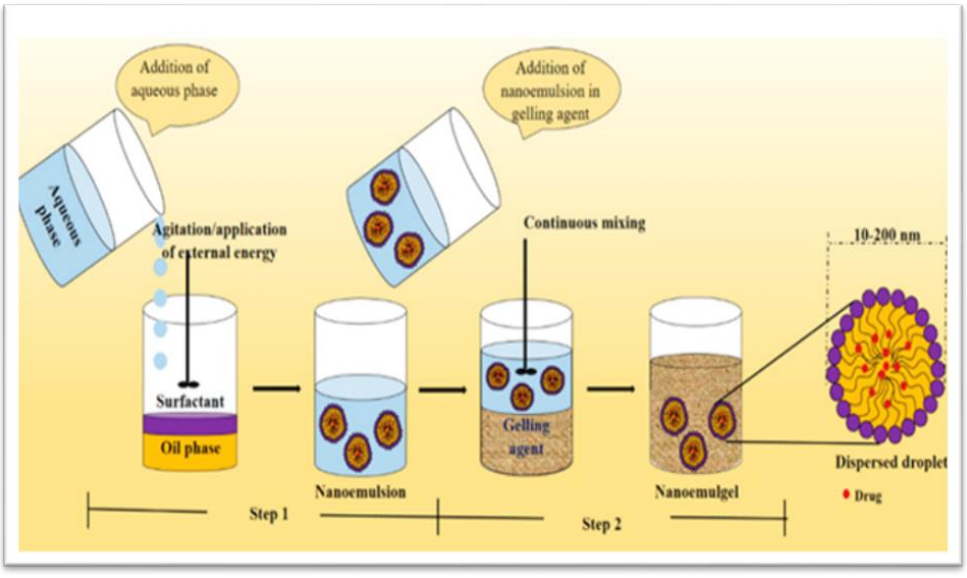

Fig. 1: Preparation of Nanoemugel.

Nanoemulsions can be produced using either high-energy or low-energy emulsification processes. External energy is used in high-energy emulsification procedures to rupture the oil phase, resulting in nanosized droplets in the aqueous phase. It employs ultrasonic emulsification and high-pressure homogenization. Low-energy emulsification methods

include solvent displacement, phase inversion composition, and phase inversion temperature. The generated nanoemulsion requires little energy.[28,29]

Characterization of nanoemulgel

1. **Visual inspection:** The produced nanoemulgels may be examined visually to determine their color, appearance, and uniformity.
2. **pH measurements**: The pH of nanoemulgel changes depending on its intended use, such as on the skin or another form of mucous membrane. According to reports, the pH of human skin ranges between 4.5 and 6. The pH simply indicates the acidity or basicity of a composition. In the case of topical formulations, an excessively high or low pH might induce irritation or allergy on the skin's surface. It also influences the drug's stability and release from the formulation. Digital pH meters can be used for measuring pH.[30,31]
3. **Spreadability:** As Mutimer indicates, it may be measured using the Slip and Drag basis. Two grams of Nanoemulgel are placed on a lower ground slide secured with a wooden block, and another glass slide of comparable size is created and secured with a hook that contains a 500 mg weight. After five minutes, the pan connecting to the second slide received more weight. The time required to span a 5 cm distance on the upper slide was measured, and spreadability was calculated using the following equation:
   Spreadability (S) = M*L / T, Where,
   M =weight linked to the top slide, L = glass slide length, T = distance travelled by the top slide in a single slide**.**
4. **Swelling index**: 1 gram of produced topical nanoemulgel is applied on porous aluminium foil, which is then put on 10 milliliters of 0.1 N NaOH solution. Samples are withdrawn from time to time, and weight is recorded until there is no more change in weight.
   Swelling Index (SW) percentage = [[Wt-Wo] / Wo]*100.
   Where, (SW)% = percentage of swelling, Wo = original weight of the nanoemulgel.[32,33]
5. **Droplet Size:** Measurement and Polydispersity Index (PDI) Droplet size is commonly measured using the dynamic light scattering (DLS) method. The polydispersity index (PDI) measurement indicates droplet size uniformity within the prepared nanoemulgel.
6. **Drug content:** Drug content is an essential characteristic that defines the overall quantity of drug included in the prepared formulations; higher drug content is connected with less drug loss throughout the manufacturing process.[34]
7. **Globule size and zeta potential:** Zeta trac was used to assess the globular size and zeta potential of emulsions. Zeta tracing estimates the Zeta Potential by measuring the reaction

of charged particles to an electric field. A variety of instruments may be used to assess zeta potential, including the Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600, the ZC-2000, and others.

8. **Adhesive Property:** The bio-adhesive strength is used to assess how much force is required to remove the drug delivery system from a biological surface. This characteristic is required for a topical dosage form if longer contact is needed. Because of its similarities to human skin, this test is generally performed on rat or pig skin. Although there are various ways for assessing adhesive strength, none of them are FDA approved.[35,36]
9. **Extrudability:** Extrudability was examined by the aluminum collapsible tubes. The formulation was thoroughly loaded into the aluminum collapsible tubes. The tube was subjected to a pressure of approximately 500g, and the amount of extruded material was measured. The formulation ribbon should be discharged from the aluminum collapsible tubes at a rate of around 0.2 meters per second. If the amount exceeds 0.2 meter per second, the formulation is said to be outstanding.

   Extrudability = Applied weight to extrude gel from tube (g) divided by area (cm2).[37]
10. **In vitro Drug Release:** An in vitro drug release study was conducted to investigate the release of drugs via the skin, which essentially mimicked skin activity. The Franz diffusion cell apparatus was employed in this study. The 1g drug was placed on the dialysis membrane and finally penetrated when it comes into touch with the phosphate buffered saline (7.4 pH at 37±1°C). The experiment was run for 8 hours to determine the percentage of medication release. Every hour, 1 ml of sample was collected and evaluated using ultraviolet visible spectrophotometer.[38]

CONCLUSION

The transdermal drug delivery method is an excellent alternative to many conventional drug delivery techniques, but it has certain disadvantages. Nanoemulgel is a nanoemulsion-based system with a gelling ingredient that gives the system a three-dimensional structure. Nanoemulgel provides the benefit of a nano-size range, which allows for easier deep entrance. Furthermore, it may be employed to administer lipophilic drugs to the internal structure while maintaining an appropriate watery outside structure. This research reveals that NEGs have considerable potential as a unique drug delivery strategy for increasing the percutaneous permeability and bioavailability of anti-inflammatory drugs. NEGs have showed significant advantages for such drugs as compared to alternate formulations,

particularly in the case of topical administration. Nanoemulgels are ideally suited for topical medication administration due to their dual properties, which include the combination of a nanoscale emulsion and a gel foundation in a single formulation. Despite a few barriers in terms of long-term stability, mass manufacture, and commercialization, NEGs have enormous promise for topical anti-inflammatory therapeutic applications.

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