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A REVIEW ON NANOEMULGELS: IN PHARMACEUTICALS AND COSMETICS

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ABSTRACT

Skin, the largest organ in the human body, plays vital roles in protection, sensory functions, temperature regulation, and more. Topical drug delivery, particularly through nanoemulgel formulations, offers targeted drug delivery with advantages such as reduced systemic toxicity, enhanced patient compliance, and improved drug absorption. Nanoemulgel combines nano emulsion with hydrogel systems to enhance skin penetration, incorporating lipophilic drugs while improving drug viscosity. Nano emulsions Preparation methods include high-energy and low-energy emulsification. Nanoemulgel preparation involves incorporating the Nano emulsion into a gel base to improve drug loading, release control, and skin permeation. Characterization studies for nanoemulgel formulations include zeta potential, rheology, droplet size and polydispersity index (PDI), spreadability testing, in-vitro release testing (IVRT), and bio-adhesive properties, ensuring stability, effective drug release and skin adhesion.

KEYWORDS: Skin, Topical drug delivery, Nanoemulgel, Nano emulsion.

INTRODUCTION

Skin is the largest organ part of the human body as it covers the entire body with a surface area of 2 m,[2] average thickness of 1.2 mm, average volume of 3.5 dm[3] and it takes about 16% of the body weight.[1,7,8] Skin is composed of three layers Epidermis, Dermis, and Hypodermis. The outermost layer epidermis acts as a skin barrier.[2,9,10] The specific functions of the skin include protection from harmful things which may come from external physical,

mechanical and chemical forces. In one aspect skin acts as a chemical barrier by limiting the entry of foreign substances preventing water and depletion of endogenous fluids. One amazing fact about skin is its self healing property where skin is able to maintain and repair itself except for appendages such as hair, nails, eccrine sweat glands, sebaceous glands and apocrine glands. Other skin functions exerted in conjunction with other organs are production of vitamin D, immune function, sensory function as well as regulation of body temperature.[1,7,8]

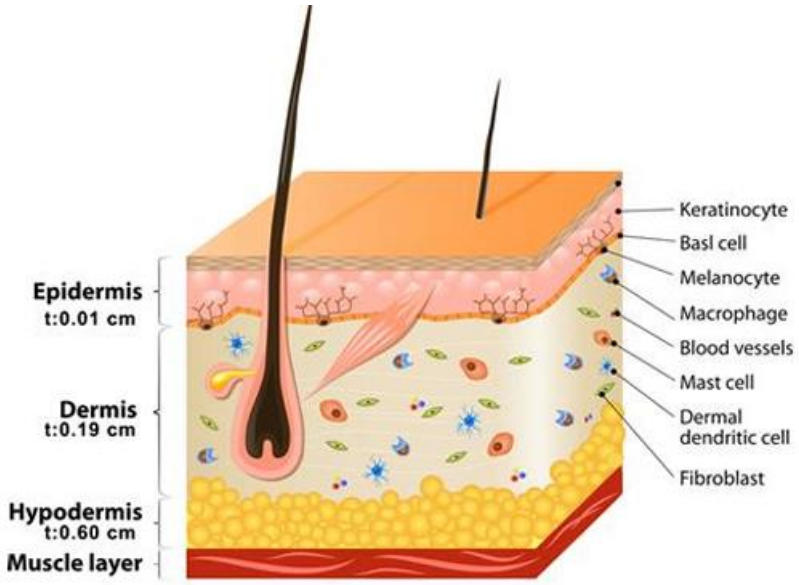


Fig. 1: Structure of skin.

Topical delivery offers many benefits such as targeted drug delivery, decreased risk of systemic toxicity, enhanced patient adherence, improved treatment effectiveness and increased drug absorption.[3] The benefits of the topical route of administration comprise of avoiding the hepatic first-pass effect, decreased side effects due to the local site of action, enhancement in percutaneous absorption and topical usage may even increase bioavailability with a sustained deposition. Further, the reduced drug loss due to metabolism or decomposition and the ability to specifically target the drug at the desired site are also some of the advantages. Minimization of drug breakdown coupled with constant delivery of drug for a prolonged period results in prominent movement of the drug across the barrier of stratum corneum leading to improved bioavailability.[4]

Emulsion as a dispersed system consists of small droplets which is well distributed in to immiscible vehicle. The types of emulsions which classified in according to their droplets

size are Macroemulsion (droplet of 1 to 100 µm of diameter) also known as the conventional emulsion/colloid.[5]

Nanoemulsions consist of nano-sized droplets of one liquid dispersed in another liquid forming heterogeneous isotropic systems. The droplet sizes typically fall within the range of 20 to 500 nm. These systems are thermodynamically unstable but kinetically stable.[3] Nanoemulsion is a promising alternative to increase drug delivery system penetration and targeting poorly soluble drugs by increasing its absorption through the skin better retention time of drug in the target area and eventually result in less side effects.[5]

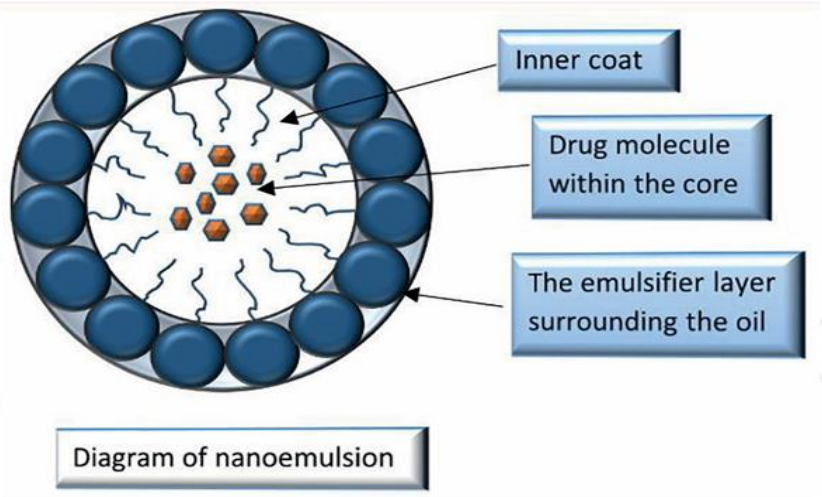


Fig. 2: Diagram of nanoemulsion.

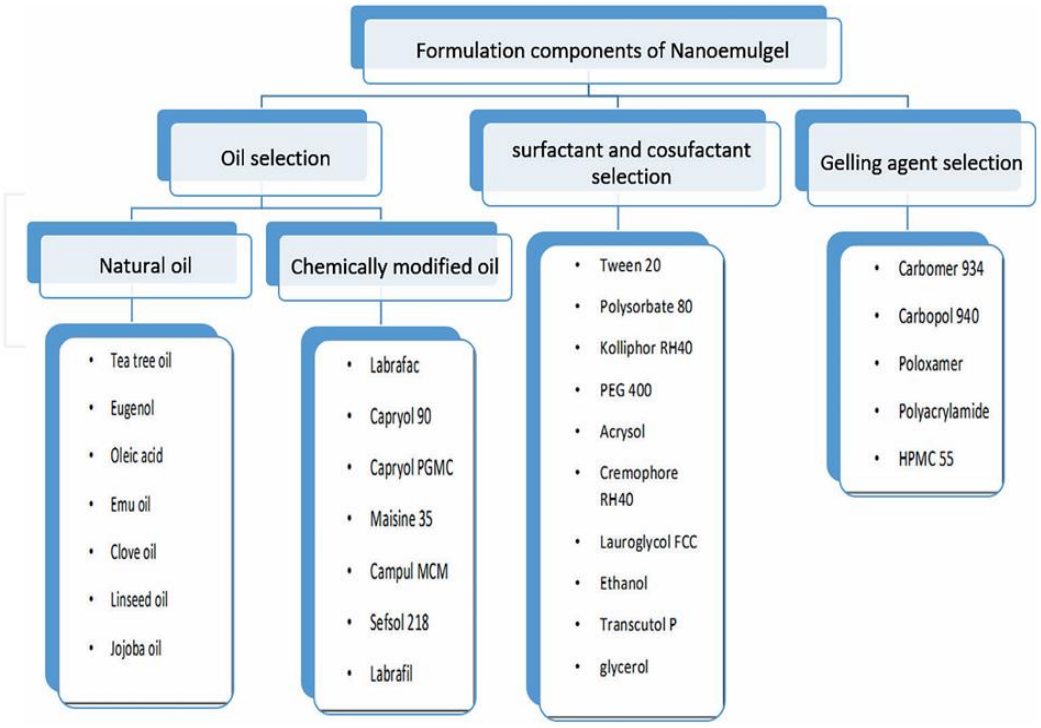
Nanoemulgel which known as the formation of nano emulsion based on hydrogel is the addition of nano emulsion system intergraded into hydrogel matrix which influences a better skin penetration.[5] Nanoemulgel is the fusion of two systems i.e nanoemulsion system and hydrogel system. Both the systems have some limitations such as nanoemulsion that suffers low spreadability and poor retention whereas hydrogels are incapable of incorporating lipophilic molecule. Nanoemulgel has different types of polymeric materials, surfactants and fatty substances of natural, synthetic and semisynthetic nature with a droplet size range from 5 to 500 nm. Nanoemulgel has the capability to overcome the limitation of both the systems. The lipophilic drug is dissolved in the oil phase of nanoemulsion which is then added to hydrogel base to form nanoemulgel which enables the incorporation of lipophilic drug into a hydrogel simultaneously improving the viscosity of nanoemulsion.[6]

Potent components for nanoemulgel formulation

Nanoemulgel is a fusion of two separate systems, viz. the nanoemulsion and a gel system. Nanoemulsion acting as a vehicle for drug delivery can be either water-in-oil or oil-in-water type. In both cases, it consists of an oil phase, aqueous phase, surfactant and sometime co-surfactant. Overview of commonly used major components of nanoemulgel formulation has been apprehended in this section.[6]

Oils

Oil is an important component of the nanoemulgel formulation that should be selected appropriately based on the solubility, stability, permeability and viscosity of the formulation. Vegetable oils/edible oils are not frequently used in nanoemulgel formulation had shown poor emulsification properties and drug solubility. Thus, chemically modified oils such as mono or diglyceride or medium-chain triglycerides are commonly used as an oil phase in the nanoemulgel formulation for lipophilic drug delivery.[6]



Preparation of nanoemulgel formulation

Two steps are involved in the manufacturing of nanoemulgel. The first step is nanoemulsion formulation which is then incorporated into a gelling agent in the second step to form nanoemulgel.

Methods used for the preparation of nanoemulsion are

1. High-Energy Emulsification Methods
2. Low-Energy Emulsification Methods.

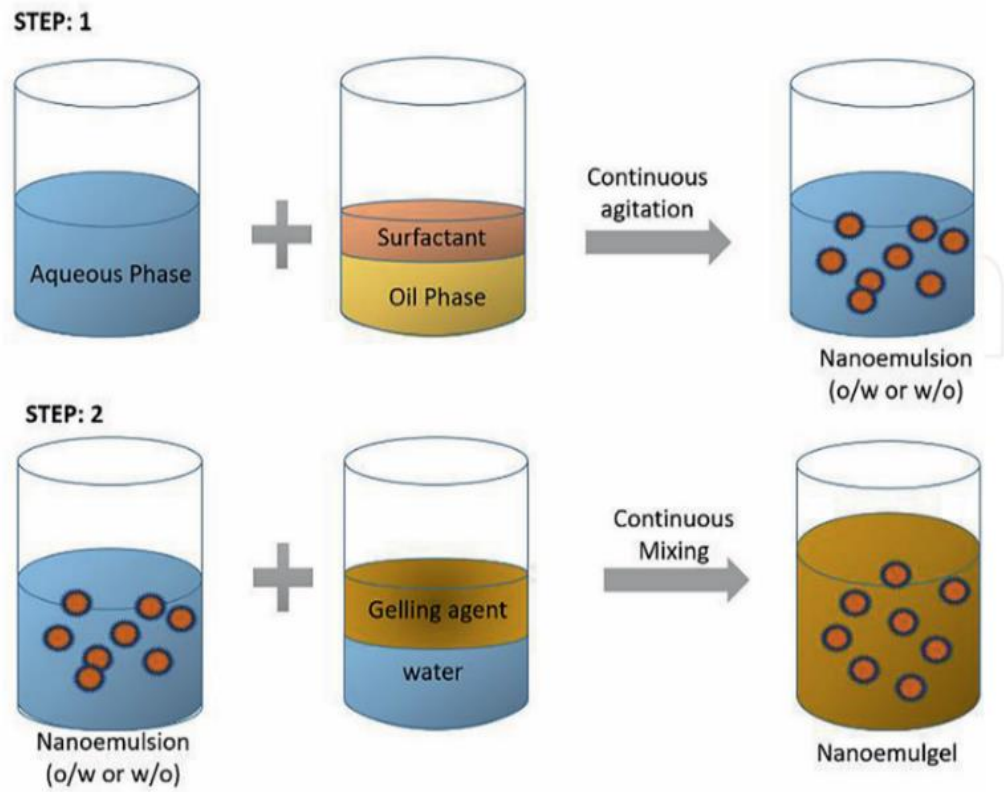


Fig. 3: Preparation of nanoemulgel.

In high-energy emulsification methods external energy is applied which rupture the oil phase to form nanosized droplets in the aqueous phase. It includes ultrasonic emulsification and high-pressure homogenization.

Solvent displacement method, phase inversion composition method and phase inversion temperature method are low-energy emulsification in which low energy is required for prepared nanoemulsion.[6]

Procedure for nanoemulsion preparation

The selected surfactant is dissolved in either the aqueous phase or the oil phase. Based on the solubility the drug is then added and solubilized in the oil phase or aqueous phase followed by heating. Then one phase is gradually added into another with continuous stirring till the temperature of the mixture reaches to room temperature.[6]

Procedure for nanoemulgel preparation

The appropriate gelling agent is dissolved in distilled water with continuous stirring to prepare gel base. The pH of prepared gel is adjusted then the nanoemulsion system is incorporated slowly into the prepared gel at a particular ratio with continuous stirring to get nanoemulgel preparation.[6]

Advantages of nanoemulgel

1. Better loading capacity
2. Better skin permeability of drug
3. Better stability
4. Better safety profile
5. Incorporation of lipophilic drug
6. Controlled release
7. Better patient compliance
8. Better pharmacodynamics activity
9. Better pharmacokinetic profile

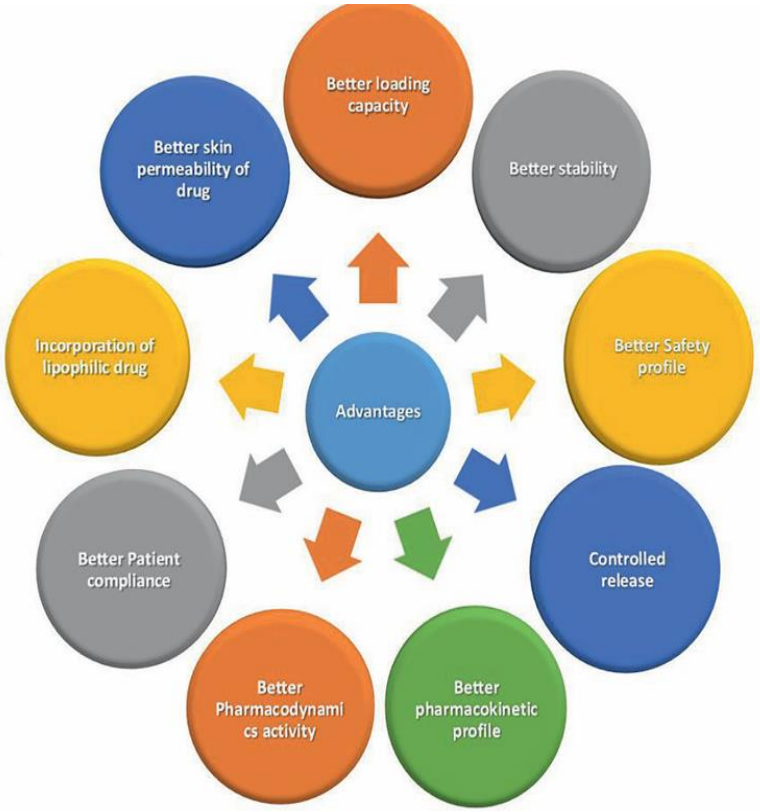


Fig. 4: Advantages of nanoemulgel.

Characterization studies of nanoemulgel

1. Zeta potential

The measurement of zeta potential, which can be done using different instruments like the ZC-2000 (Zeecom-2000, Microtec Co. Ltd., Chiba, Japan), Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments, Westborough, MA, USA) and other similar devices is crucial in understanding this role.[3]

2. Rheological characterizations

Rheology is the study of the deformation and flowof materials. The rheological charac terization of materials reveals the influence of excipient concentrations like oils, surfactants, and gelling agents on the formulation's viscoelastic flow behavior. If a formulation's vis cosity and flow characteristics vary this may influence its stability, drug release and other *In-Vivo* parameters.[4]

3. Droplet Size Measurement and Polydispersity Index (PDI)

The size of globule in nanoemulgel is referred as its hydrodynamic diameter, which is a diameter of equivalent hard sphere that diffuses at the same rate as the active moiety. The PDI determines the distribution of droplet size and is defined as the standard deviation of droplet size divided by mean droplet size. The droplet size and the polydispersity index are closely connected to the stability and drug release, as well as the ex-vivo and in-vivo performance of the dosage form. In addition, it is important to measure consistency between different batches. The globule size and PDI of the formulation can be measured using a zeta sizer or master sizer. The globule size of the emulsion can be determined using the principle of dynamic light scattering, in which the transitional diffusion coefficient is measured by monitoring the interaction between the laser beam and dispersion as well as the Polydispersity index.[4]

4. Spreadability testing

The spreadability of the nanoemulgel is heavily influenced by its viscosity**.** The experimental setup comprises of two glass slides of equal length. One of the slides is fixed to a wooden block, while the other slide is attached to a pulley at one end to measure spreadability. The spreadability of the emulgel is determined by its 'Slip' and 'Drag' characteristics. To measure spreadability the nanoemulgel dosage form is placed on the stationary glass slide and then compressed between the stationary and mobile glass slides. The formulation is firmly squeezed to ensure uniform spreading and to eliminate any air bubbles. Known weights are

gradually added to the pulley until the upper slide slips off from the lower slide. The time taken for the slipping off is recorded, and this information is used to calculate the spreadability using the provided equation. The equation S = M * l/T represents the relationship between spreadability (S), weight (M), length (L) and time (T) in detaching slides.[3]

5. *In-Vitro* Release Test *(IVRT)*

The efficacy and safety of the API are associated with drug release from the dosage form. The IVRT serves as a tool for assessing the quality of the drug product. According to FDA the IVRT studies for semi-solid dosage forms are conducted using either the vertical diffusion cell or an immersion cell. The vertical diffusion cell consists of receptor and donor chambers, separated by a receptor membrane. The donor chamber holds the sample of dosage form, while the receptor chamber holds the receptor media. The receptor media can be a buffer or hydro-alcoholic solution selected based on the solubility, sink condition and stability of the API. The skin-like receptor membrane is selected based on the effective pore size, high permeability and expected inertness towards the API. If necessary the receptor membrane should be saturated with release media. The temperature of the media should be maintained around 32 C 1 C for topical administering products for products intended for mucosal membrane the temperature should be 37 C 1 C. A Teflon-coated magnetic stirrer is used for stirring the receptor media. While the immersion cell model has a cell body, which acts as a reservoir. The cell body is covered with a membrane and closed using a leakproof seal (retaining ring cap) that ensures no leakage of the dosage form. The retaining ring cap possesses an opening on the top, and it should be adjusted in such a way that the membrane is in contact with the dosage form on the bottom and release media on the top. The whole setup is used along with the USP-2 apparatus, wherein the immersion cell is placed in flat bottomed dissolution vessel with a usual volume of 150–200 mL. A mini spin-paddle is used for stirring or agitating the media.[4]

6. Bio-Adhesive property

Bio-adhesive strength is used to determine the force required to detach the drug carrier system from a biological surface. This property is important for a topical dosage form if prolonged contact is required. This test is usually performed using rat or pig skin, the latter is preferred because of its resemblance to human skin. There are various techniques to measure this property but none of them is approved by FDA. The texture analyzer is one such

technique, where the upper mobile probe and stationary lower base plate will be covered with skin. The dosage form is placed on the skin of the base plate. The upper probe is lowered to contact the lower base plate and the contact is maintained for at least a minute. The upper probe is lifted slowly until the separation of skin sheets. The force required to separate the two skin sheets will be measured by the instrument and represented as the area under the force-distance curve.[4]

CONCLUSION

Nanoemulgels are a promising and versatile platform for the development of advanced drug delivery systems, offering improved performance, reduced side effects, and targeted delivery. However, challenges such as scaling up production, ensuring regulatory approval, and long-term stability need to be addressed for their widespread adoption in clinical settings.

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