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REVIEW ARTICLE

Nanoemulgel as Topical Drug Delivery System: Review

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ABSTRACT
A nanoemulgel new drug delivery method it's aims to improve the therapeutics effectiveness properties of medications which are lipophilic in nature. The ability to poor dissolve, uneven absorption, and limited oral bioavailability are few of the drawbacks of lipophilic formulations. Lipophilic drugs can be easily incorporated and the skin permeability of the incorporated drugs can be enhanced in several folds due to the finely distributed oil droplets in gel phase. It that various component use for formulation of nanoemulgel are mentioned; like oil phase, surfactant, co-surfactant, aqueous solvent, gelling agent. The novel method developed by introducing nanoemulsion to gel increases stability and allows for fast and controlled release medication administration. Because of its targeted drug delivery, simplicity of use, lack of first-pass metabolism, and protection outline that's why attention has been shifted to nanoemulgel. These assessment concentrations on the protection characteristics and formulation elements of nanoemulgel for topical drug administration.
Keywords: *Bioavailability, Nanoemulgel, Permeation, Surfactant*

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INTRODUCTION

The current developments in drug manufacturing have focused on lipophilic drug molecules. 90% of medicines are in the discovery process while more than 40% of drugs available in the market. [1] The medicines lipophilic characteristic causes issues with kinetics such as a lack of solubility, variable absorption. To active moieties make more soluble, many methods have been used. As shown in Figure 1, these methods include reducing the size of particles, the process of complexation, amorphization, and drug delivery systems modifying of API. [2].

Oral medication delivery is not always practical due to the pharmaceuticals low bioavailability caused by less absorption, first-pass metabolism, enzymatic chemical degradation so applying a variety of technologies to increase solubility. [3]

Drug distribution via the oral route is made more difficult by due to low drug concentrations at the location of the action. For instance, the oral ingestion of to treat arthritis is linked to a number of adverse reactions, including carcinogenicity, hepatotoxicity, and hematologic. By applying the medication via the topical method, these adverse effects can be avoided. [4-5]

When an API is administered topically, the skin, which serves as the body's primary line of defense, views the APIs as exterior components and prevents them from entering the body. The first and hardest layer to penetrate for drugs to reach the skin it is the stratum corneum, which is the outermost region of the epidermis. [6] Multiple processes have been investigated to improve drug penetration. One such process entails disruption of the structure of the outermost layer of the skin, which can be done by methods such as micro needling, ultrasound, iontophoresis, sonophoresis, chemical penetration enhancers, and the electroporation. [7]

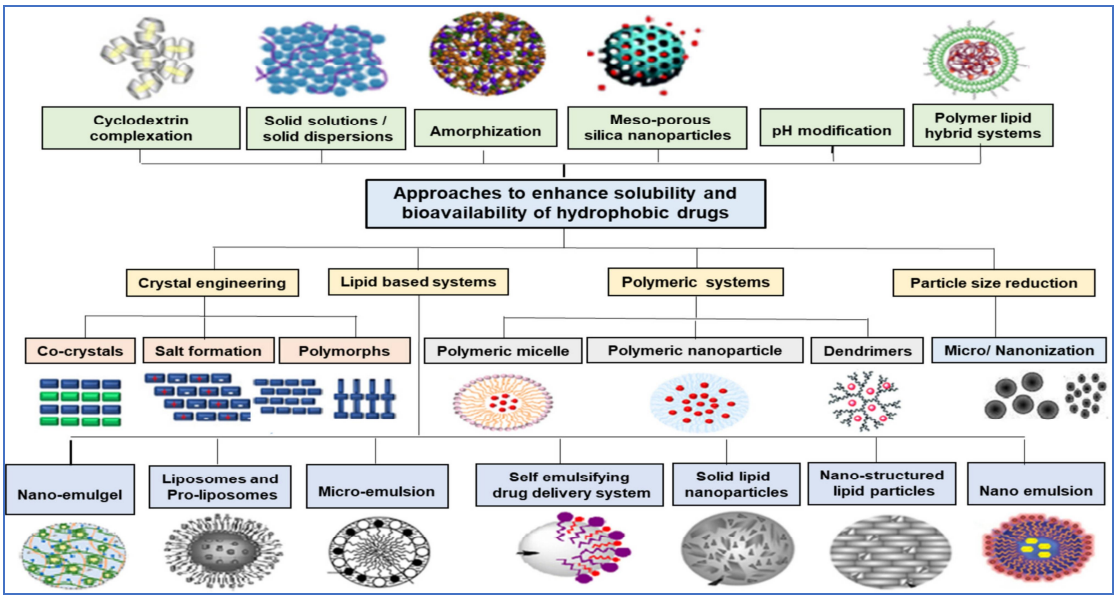

Figure 1: Strategies to improve solubility and bioavailability of lipophilic drugs

The use of nanocarriers, on the other hand, was found to be a successful tactic for getting through the avoiding worsening skin damage and ensuring effective medication absorption. Emulsions (nano/micro), micelles, dendrimers, liposomes, SLNP are just a few examples of new carriers for topical delivery. [8–9] Emulsion due to their excellent medication-loading abilities, soluble abilities, simplicity in production, and regulated releasing structures, nano-emulsions stand out as a possible drug delivery technology. In comparison to liposomes, the tiny emulsion allowed a greater number of lipophilic compounds to pass topical barriers due to their lipophilic core. [10] Also, liposome stability remains a problem because they break down during administration. similarly, the use of solid-lipid nanoparticles for cutaneous medication administration is hampered by its pharmaceutical loading ability and uncontrollable release. Micelles also have ineffective durability as well as encapsulation. Dendrimers' topical use is also constrained by their toxic effects and less control releasing behavior. [11]

A bilayer mixture of water and oil is described as a nanoemulsion. At the point of separation between the dispersion and continuous phases, a surfactant uses as called an emulsifier helps in reducing surface tension and stabilize the phases. Nanoemulsion is compared to others like emulsions, micelles, and suspensions they have a longer shelf life due to their great thermodynamic stability. Nano-emulsions, despite having numerous advantages, but have limitations by their low viscosity, which results in reduced retention duration and spreading capacity. To overcome this problem by adding a suitable gelling agent, the nano-emulsion can be changed into a nano-emulgel. [12] The nanoemulgel shows colloidal behavior.

Along with improving the drug's skin absorption, it's also essential to maintain the medication's therapeutic concentrations for a suitable duration. The gel component enhances viscosity and spreadability, which leads to increased retention durations. It also lowers surface and interfacial tension, which increases thermal stability. [13]

This paper attempts to some illumination on the choice of chemicals for a nanoemulgels formulation, as well as the benefits, pharmaceutical kinetics pharmaceutical dynamics, as well as safety of the product. The purpose of this article is to provide a summary of the potential and justification for the nano-emulgel drug delivery technology.

Some requirement for as a topical drug delivery

It required the following criteria

1.Half-life of drug ≤10 h

2. Molecular mass should be ≤500 Daltons

3.Non-polar in nature

4.Log P value should be 0.8–5 pKa

5. Non-irritating on skin. [14]

Formulation of nanoemulgel as topical drug delivery:

The hydrogel and tiny emulsion methods are combined to create the nanoemulgel. Both technologies have some drawbacks, including the low spreadability and poor retention of tiny emulsions, and a failure of hydrogels to include molecules with high lipophilicity [15]. droplet's size range nanoproducts should

be 5 to 100 nanometers. Nanoemulgel contains various components, surfactants, Co- surfactant, and Fatty substances as well as [16]. Both of the limitations can be solved via nanoemulgel. The lipophilic medicament will dissolve in the oil phase, which is then combined with the gel base to create nanoemulgel. This makes it possible the lipophilic drug to be embedded in a hydrogel, also increasing the nanoemulsion's viscosity. The active ingredient is kept in nanoemulgel during transdermal drug administration. Before reaching the skin's surface, the medication first passes from the inside to the outside phase. The oily particles came out from the gel's matrix of the nanoemulgel when it was applied to the skin. These droplets traveled deep into the stratum corneum, where they transported the drug moiety [17].

Table 1. Comparison between nanoemulgel and conventional emulgel

Parameter	Nanoemulgel	Conventional emulgel
Particle size	Less than 100 nm	More than 500 nm
Bioavailability	More bioavailability	Less bioavailability
Thermodynamic stability	Stable	Not stable
Permeation	High permeation	Less permeation
Formulation	Require low and high energy	Require high energy

Advantages:

- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- More selective to a specific site.
- Improve patient compliance.
- Suitability for self-medication.
- Providing utilisation of drug with short biological half-life and narrow therapeutic window.
- The ability to easily discontinue medicine when necessary
- Convenient and easy to apply.
- Incorporation of hydrophobic drugs
- Better loading capacity
- Better stability
- Production feasibility and low preparation cost
- Controlled release
- No intensive sonication

Disadvantages:

- Skin irritation on contact dermatitis.
- The possibility of allergenic reactions.
- The poor permeability of some drug through the skin.
- Drugs with large particle sizes are difficult to absorb via the skin.
- The occurrence of the bubble during formation of Emulgel.

COMPONENT FOR NANOEMULGEL PREPARATION

A nanoemulsion and a gel system are combined to form a nanoemulgel. You can use either a w/o or an o/w type of nanoemulsion as a delivery system for drugs. It includes an oil phase, an aqueous phase, a surfactant, co- surfactant. This section provides a review of the main elements of nanoemulgel composition that are most frequently employed (Figure 2).

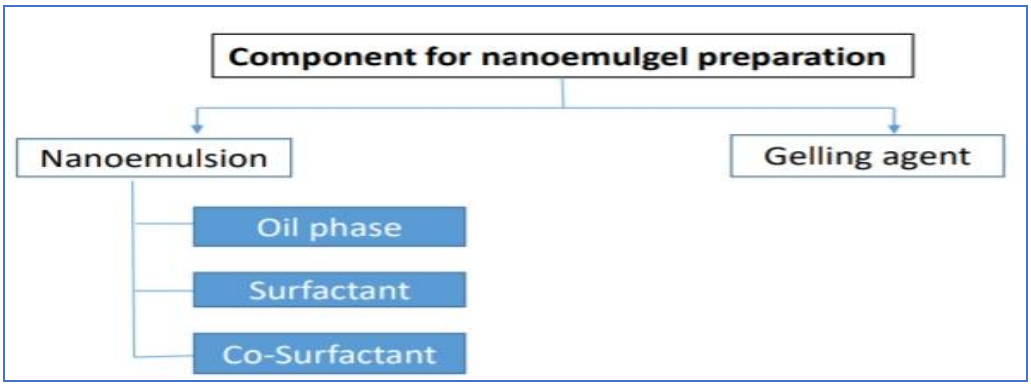

Figure 2: Component for nanoemulgel preparation

1. Oil Phase

Oil is an essential component in the nanoemulgel composition and must be carefully chosen depending on the formulation's solubility, stability, permeability, and viscosity. Although they have demonstrated poor emulsifying capabilities and solubility of drugs, vegetable, edible oils are not use. Therefore, chemically altered oils are frequently employed as an oil phase in the nanoemulgel formulation, such as mono- or diglycerides or medium-chain triglycerides. eg. Coconut oil, almond oil, castor oil, Monotriglyceride, olive oil, eucalyptus oil etc. [18]

2. Surfactant

Surfactants are a crucial component of nano-emulsions because they help to stabilize the two immiscible phases. This is accomplished by reducing the friction between the two phases. The Surfactants have to exhibit rapid adsorption at the liquid-liquid interface. Interfacial tension is reduced, and the coalescence of each of the nanoparticles is inhibited, as a result. Based on factors like safety, stability, high drug loading capacity, and effective emulsification capabilities, the right surfactant should be chosen for a nanoemulgel. [19] When choosing the right surfactant, the HLB value of the surfactants is a crucial factor. There are two types of surfactants: w/o type (HLB 3-8) and o/w type (HLB 8-16). Low HLB value surfactants, or those with a value of less than 8, are used in w/o emulsions. For o/w emulsion, Spans and Tweens are alternately employed since their HLB values are more than 8. An emulsion system is more stable when Span and Tween are combined. Therefore, selecting the right combination of surface-active agents is crucial to creating the perfect nanoemulsion. [20] The surfactants can be divided into four main groups according to charge: cationic, non-ionic, anionic, and Zwitterionic shown in figure 3.

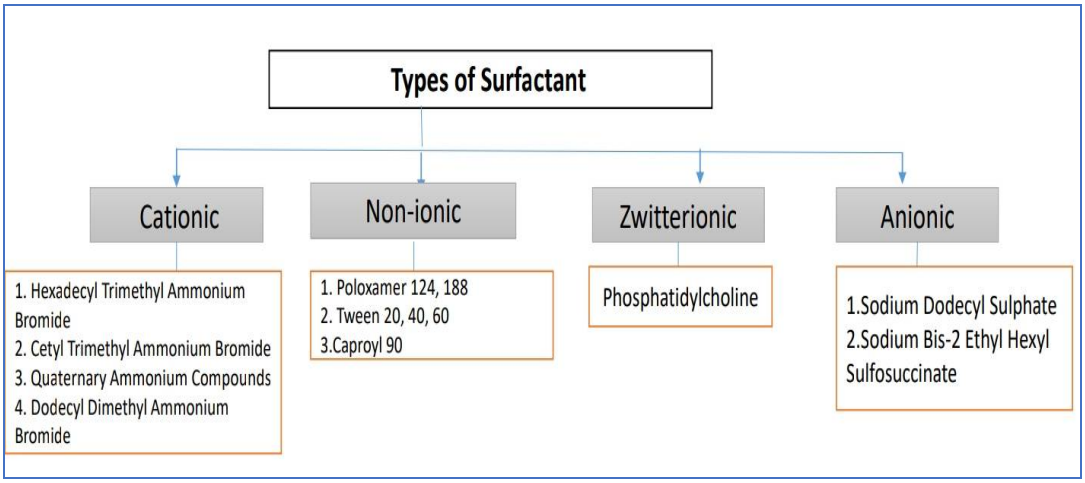

Figure 3: Types of surfactants

3.Co-Surfactant

Co-surfactants aid in the emulsion of oil in the aqueous phase by supporting surfactants. For reducing interfacial tension and enhancing emulsification, co-surfactants are necessary [114]. Due to co-surfactants, the interfacial layer gains flexibility and achieves temporary negative interfacial tension. The drug release from the nano-emulgel is determined by the association between the surfactant and co-surfactant as well as the partitioning of the drug into immiscible phases. So choosing a co-surfactant is just as crucial. The most recommended co-surfactants are those based on alcohol because they may partition between the oil and water phases, boosting their miscibility. [21]

Additionally, a stable emulsion cannot be created by combining a surfactant and a co-surfactant with similar HLB values. This is in contrast to non-ionic surfactants with differing HLB values. Lower HLB value surfactants, on the other hand, solubilize in the non-aqueous phase, allowing for a stronger connection with the surfactant and co-surfactant mixture. Therefore, selecting different formulation components and explaining their logic is a very challenging and stimulating activity. Eg. Transcutol P, Carbitol, Ethanol, Propylene Glycol, PEG 400 etc. [22].

4. Aqueous solvent

In emulsion, aqueous solvents serve as the water phase. Water and ethanol are two common solvents that are used globally.

5. Gelling Agents

For nanoemulgel, the gelling agents carbopol 934, carbopol 940, and hydroxy propyl methyl cellulose (HPMC) are frequently used They made the formulation thicker and might have interacted to the surfactants to change its viscosity. It is added to the nanoemulsion preparation to alter the nanoemulsion formulation's physical state from liquid to gel, resolving the issue of the nanoemulsion's poor skin retention, low spreadability, and low viscosity. [23]

6. Miscellaneous agent

Preservatives have been added to the preparation to safeguard the finished product from microbial contamination. Preservatives like methyl paraben, benzoic acid, propyl paraben, and benzalkonium chloride are most frequently used to avoid the oxidative breakdown of formulation ingredients, antioxidants such butylate hydroxyl toluene, butylate hydroxyl anisole, and ascorbic palmitate are utilized. Humectants like glycerin and propylene glycol are used to minimize moisture loss. As a result, the nanoemulsion and nanoemulgel preparation's stability improved. [24]

FORMULATION OF NANOEMULGEL

The manufacture of nanoemulgel takes two processes. Nanoemulsion formulation is the initial stage, and nanoemulgel is created by combining it with a gelling agent in the following step. The creation of nanoemulgel is depicted schematically in Figure.

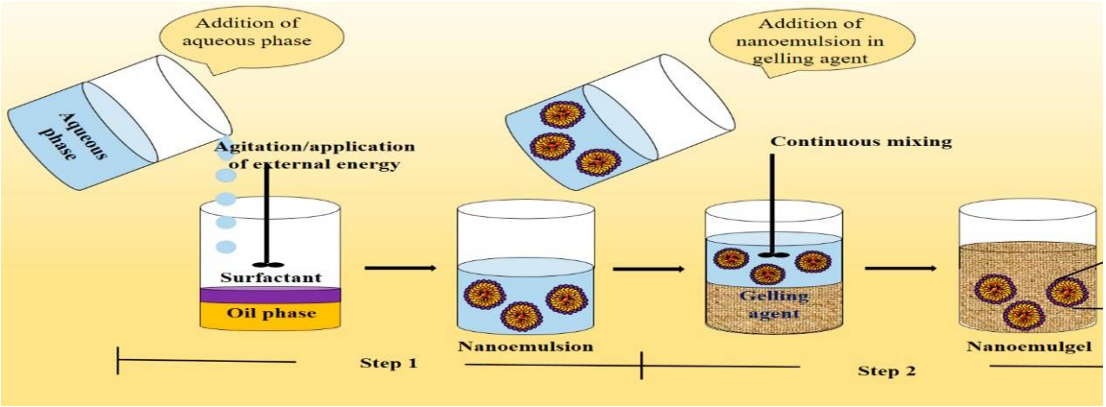

Figure 4: Formulation of Nanoemulgel

Low-energy emulsification techniques as well as high-energy emulsification techniques can be employed to create nanoemulsions. External energy is used in high-energy emulsification techniques to rupture the oil phase and create nanoscale droplets in the aqueous phase. High-pressure homogenization and ultrasonic emulsification are both included. Low-energy emulsification techniques include the solvent displacement method, the phase inversion composition method, and the phase inversion temperature method.

In the aqueous phase or the oil phase, the chosen surfactant dissolves. The medicine is then introduced, solubilized in the oil phase or aqueous phase, and heated based on its solubility. After that, one phase is progressively put into another while being continuously stirred until the combination reaches room temperature.

Incorporation of nanoemulsion into gel nanoemulgel

Gel base is made by dissolving the appropriate gelling ingredient in distilled water while stirring constantly. To create nanoemulgel, the pH of the prepared gel is first adjusted, and then a certain ratio of the nanoemulsion system is gently added while the gel is continuously stirred. [25-26]

Table 3. Examples of marketed emulgels for topical application.

Marketed Product	Active Pharmaceutical Ingredient	Manufacturing Company
Miconaz-H Emulgel	Miconazole nitrate & Hydrocartisone	Medical Union Pharmaceuticals
Isofen Emulgel	Ibuprofen	Beit Jala Pharmaceutical Co.
Derma Feet	Urea	Herbitas
Benzolait Emulgel	Benzoyl peroxide & Biguanide	Roydermal
Voltaren Emulgel	Diclofenac diethylamine	GlaxoSmithKline
Nucoxia Emulgel	Etoricoxib	Zydus Cadila Healthcare LTD

CONCLUSION

The choice of ingredients and their suitable proportions are key factors in determining a nanoemulgel's characteristics. As a result, the former is a superior option for delivering lipophilic moieties primarily because it has greater penetration, which enhances the pharmacological action. Due to its non-greasy and enhanced topical spreading capabilities, patient compliance is also increased. Despite its benefits, the pharmaceutical industry is only just beginning to explore the potential of nanoemulgel. Thus, because it is safe, effective, and convenient for topical medication delivery. Despite several drawbacks, nanoemulgel is a technology for the future that could replace conventional formulations.

Competing Interests

The authors declare that they have no competing interests

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Ethics approval and consent to participate

Not applicable.

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