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NANOEMULGEL: A NOVEL APPROACH FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Nanoemulgel is a new and promising drug delivery system employed in the pharmaceutical industry, with droplet diameters ranging from 10 to 100 nm, it is a stable dispersion consisting of an oil, surfactant, and clear aqueous phase that can be stable either thermodynamically or kinetically. the usage of nanoemulgel as a new transdermal drug delivery technique has grown because of its advantages over its existing oral and topical drug delivery methods, including its ability to prevent poor drug bioavailability and phramacokinetic variability. the Novel technique developed by adding nano-emulsion with gel improves stability and permits fast, controlled drug release. the nanoemulgel drug delivery system is a formulation-related technology designed to enhance drug absorption and lipophilic drug therapeutic profile. a significant growth in nanoemulgel has been noted in recent years owing to the high toleration of the formulation to the patients, the application of nanoemulgel has grown recently as a result of the preparation's enhanced patient acceptance since it is non greasy, easy application, convenient spreadability and has a favourable safety and therapeutic profile. nanoemulgel, despite facing challenges, has a strong potential to become the primary topical administration method for lipophilic drugs in the future.

Keywords: Nanoemulsion, Nanoemulgel, topical drug delivery, lipophilic, *In vitro* profile

INTRODUCTION

It is believed that the human skin is a useful and accessible part of the body for topical treatments. An adult's skin surface area is 1.8 m², with 200-300 sweat ducts and 40-70 hair follicles. Its pH ranges from 4 to 5.6, influenced by sweat gland exudate and stratum corneum. Drugs must overcome obstacle like skin separation to to deliver the drug at the desired area, a nanoemulgel will be the most effective medication for this purpose [1]. The purpose of this action was to achieve the desired therapeutic effect. the transdermal drug delivery system (TDDS), which has significantly contributed to healthcare by replacing oral drug administration methods and enabling patient drug administration through a more convenient and efficient method [2]. Topical drug delivery methods provide various benefits, such as the ability to deliver medication more effectively and selectively to a particular area while avoiding the metabolic breakdown linked to systemic

administration [3]. The drug needs to get through these barriers in order to reach systemic circulation and the desired concentration at the site of action. for this kind of need, a nanoemulsion gel with globule-shaped colloidal carriers would be the perfect formulation [4].

DRUG DELIVERY THROUGH A TOPICAL ROUTE

The characteristics of the Ideal formulations include patient compliance, self-administration, non-invasiveness, fewer side effects, and better pharmacological action. topical route administration offers benefits such as avoiding hepatic first-pass effects and it also reduces drug loss due to metabolism and allows drug targeting at the desired site improving bioavailability [5]. The development of a concentration gradient is one of the key processes in percutaneous absorption, which supplies the force required for drug adsorption through the skin [6].

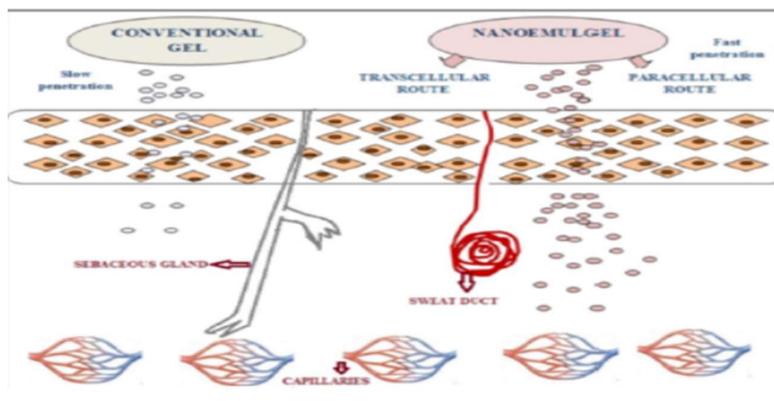


Figure 1: A graphical depiction of the nanoemulgel's path of action shows its penetration via both the paracellular and transcellular routes [1]

Table 1: Comparison between conventional emulgel and nano-emulgel [5]

Parameter	Conventional Emulgel	Nano-emulgel
Thermodynamic stability	Not stable due to the natural tendency of coalescence that causes creaming or sedimentation	Stable-because of their smaller particle size, Brownian motion provides enough stability against gravity, avoiding sedimentation or creaming
Particle size	Greater than >500nm	Less than 100nm
Bioavailability	Comparatively less bioavailable than Nano-emulgel	Enhanced bioavailability, attributed to small size and large surface area
Permeation	Comparatively lower permeation	High permeation owing to its lower particle size
Preparation	Require high energy techniques	It can be prepared either by using high or low energy techniques
Systemic absorption	Very minimal	Higher compared to conventional emulgel due to the small particle size and large surface area
Ability to cross BBB	Cannot cross BBB	Can cross BBB because of its small particle size

NANOEMULGEL AS TOPICAL DRUG DELIVERY SYSTEM

The combination of the hydrogel and nanoemulsion systems is known as nanoemulgel [6]. With droplet sizes ranging from 5 to 500 nm, nanoemulgel contains a variety of polymeric components, surfactants, and fatty compounds of natural and synthetic origin [7]. Nanoemulgel is used in transdermal medication delivery as a drug reservoir, the medication enters the skin's outer phase and moves to the skin's surface, releasing oily droplets from the nanoemulgel's gel matrix, which penetrate the stratum corneum to deliver the drug moiety directly [8].

NANOEMULSION:

Nanoemulsion is a promising method for drug delivery, optimizing effectiveness and reducing toxicity. It consists of combining nano ranges of two immiscible liquids (water and oil) to form a homogeneous solution, with appropriate surfactants or cosurfactants. The stable, thermodynamic system ranges from 10-100 nm. Nanoemulsion enhances drug delivery by targeting poorly soluble drugs, increasing absorption through the skin, improving drug processing time, and reducing side effects [10].

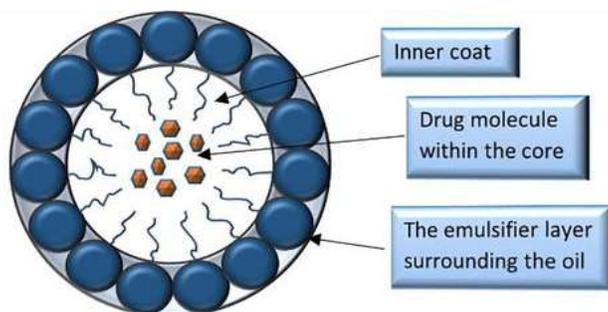


Figure 2: Structure of Nanoemulsion [9]

NANOEMULGEL

Nanoemulgel is a gel base formation that contains nanoemulsion. It is created by incorporating a nanoemulsion system into a gel matrix, which improves skin penetration [11]. The drug reservoirs in this mixture of nanoemulgel affect the drug's release from the inner phase to the outer phase and beyond. oil droplets are released from nanoemulgel when skin is still intact. These droplets enter the skin's dermal capillaries and transport the medication to the desired location. the drug is more likely to penetrate the skin when applied in nanoemulsion-gel form because of its strong adhesion properties and high drug solubilization in the oil phase, which results in a greater concentration gradient [12].

Important content of Nanoemulgel:

A gel based nanoemulsion preparation for topical application comprises of specialized components apart from lipids and surfactants such as gelling agents, permeation enhancers, preservatives and antioxidants.

Aqueous phase

In this impendence of gelling agent, this element is responsible for transforming the emulsion into an emulgel. for the composition of nanoemulgel generally ultra-purified water or the distilled water is used [1].

Oily phase

The selection of oil components must ensure that the oily phase is real and shielded from impurities like peroxides, free radicals, and other fatty acids, the selection of lipids for nanoemulgels is based on their hydrocarbon chains, considering emulsification and consistency principles. common oils used in nanoemulsions include mineral oil, arachis oil, olive oil and eucalyptus oil, as drug vehicles.

Surfactants and Co-surfactants

The surfactant's amphiphilic nature allows for the dispersion of two immiscible phases, reducing interfacial tension and forming a stable film around droplets with optimal curvature.

[13]. surfactants enhance skin penetration by reversibly attaching to keratin filaments, and improving the stratum corneum diffusion coefficient [14]. depending on the concentration of the surfactant combination, different medications have varying effects on skin penetration [15].

Co-surfactants are typically employed to reduce the concentration of surfactant and improve the final product's thermodynamic stability. example- Transcutol HP, PEGs, glycerine etc. [1].

Penetration enhancers

One of the greatest approaches to improve transportation efficiency through the skin and related layers has been to use penetration enhancers, these penetration enhancers in topical nanoemulgel typically

function by interacting with the constituents of skin, resulting in a transient and cumulative elevation of skin permeability.

Gelling agent

One of the key components of nanoemulgel that provides the formulation its ideal structure is the gelling agent. These are cross-linking agents logically. among the gelling agents that are employed are Carbopol, HPMC, and tragacanth.

Preservatives

Preservatives are chemicals that are added to a product to prolong its shelf life by protecting the item from microbiological interference. phenoxyethanol, benzalkonium chloride, methyl paraben, propyl paraben, and other preservatives are often employed.

Antioxidants

Antioxidants are chemical substances that are used in compositions to prevent

oxidation of the different elements. Ex. Butylated hydroxyl toluene, Ascorbyl palmitate etc. [1].

PSEUDOTERNARY PHASE DIAGRAM

Surfactant and cosurfactant (Nmix) were mixed in different ratios (2:1, 3:1 and 5:1). each ratio chosen in increasing amount of surfactant respect to co surfactant for a study on the phase diagrams. here aqueous phase (Distilled water) used as dilution media. Oil and Nmix was mixed at different ratios from 9:1 to 1:9 in different vials for each Nmix. the study aims to determine the boundaries of phases formed in diagrams using titration methods with water as aqueous media. Slow titration of oil and Nmix is performed, and visual observations are made to assess the transparency of the nanoemulsion. the axis represents the aqueous phase, oil phase, and Nmix phase [6].

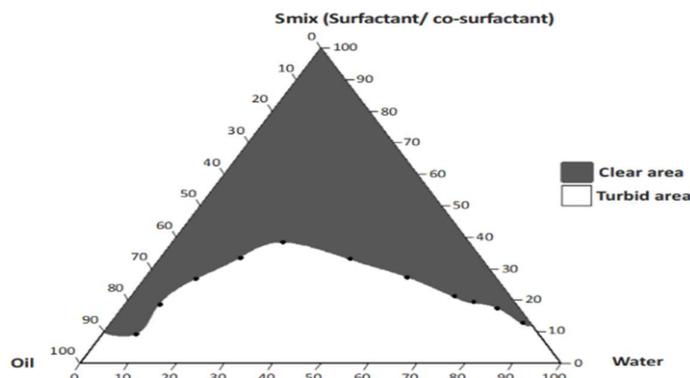


Figure 3: Diagrammatic representation of the formation of a pseudoternary phase diagram using the aqueous titration method; the turbidity is represented by the unshaded region and the clear, transparent area of the nanoemulsion is represented by the shaded area [3]

ADVANTAGES OF NANOEMULGELS

The nanoemulgel has a various of advantages over other topical formulations

as well as conventional preparation, which are as follows-

- Avoid first pass metabolism.
- Easily accepted by the patient

- Appropriate for self-administration of medicines
- Provide local delivery of drugs.
- Simple medication discontinuation [2].
- Easily adapted to the environment of the skin.
- Proven efficacy for a controlled and sustained medication delivery system.
- Nanoemulgels don't cause irritation or toxicity.
- Improved medication loading as compared to other formulations.
- Enhance medication deposition and skin permeability [6].
- Offer a formulation with a higher spreadability than creams [12].
- **Limitations**
 - It is an expensive process because a homogenizer is required to maintain nanoscale particle size.
 - In order to maintain a nanoscale particle, the method is expensive due to the requirement for a homogenizer [16].
 - **Enhanced drug permeability through skin**
 - The permeability of the drug through the skin has been significantly improved by nanoemulgel compared to other formulations because, in nanoemulgel preparation, the drug can permeate the skin layer through both paracellular and transcellular routes, whereas in nanoemulsion, only transcellular permeation route is observed [9].

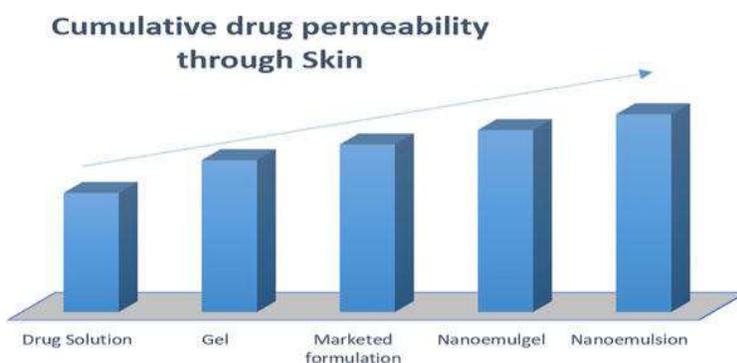


Figure 4: Comparison of cumulative medication permeability through the skin from various formulations [9]

METHODS OF PREPARATION

The oil phase or the aqueous phase both dissolve the selected surfactant. the drug is then introduced and dissolved in the aqueous or oil phase, depending on its solubility, then heated after that. After that, the mixture is continuously stirred while one

phase is progressively added till it reaches room temperature [9].

Step 1: Preparation of nanoemulsion

A spontaneously formed nanoemulsion can be produced by adding high energy to the heterogeneous mixture or by mixing the compositions and reducing the interfacial

tension between the oil/water interfaces. In order to create a thermodynamically stable nanoemulsion, both high-energy and low-energy emulsification techniques may be applied.

Step 2: Preparation of nanoemulgel

The polymer is dissolved in purified water and continuously stirred with a mechanical stirrer to create the gel basis. The gelling agent and the nanoemulsion are prepared, and then the two are continually mixed until a nanoemulgel forms. Using various polymeric gelling agents, water in oil (w/o) or oil in water (o/w) the process involves transforming nanoemulsion into thick, semisolid nanoemulgels by dissolved gelling ingredient in distilled water while stirring continuously, and adjusting the pH of the prepared nanoemulgel and then the nanoemulsion system is gradually added to the gel at a certain ratio while being stirred continuously [9].

Preparation of Gelling Agent

The goal of using a gelling agent in the formation of a nanoemulgel is to change its physical shape from liquid to semi-solid, which offers several benefits for patient compliance. In order to make different types of gel bases for gelling, the polymer can be added to purified water and continually agitated with an appropriate mechanical device until the required texture is formed. Afterwards, the pH should be adjusted [16].

Incorporation of Gelling Agent

A nanoemulgel is produced by mixing the nanoemulsion and gelling agent once they have been manufactured. Here, several polymeric gelling agents are used to transform a liquefied version of water in oil (w/o) or oil in water (o/w) nanoemulsion into a thick and semisolid nanoemulgel. This gel form can be transformed back into a solution form by rubbing or using another mechanical force. Polymers like methyl cellulose, carbopol 940, and chitosan are used as gelling agents to create nanoemulgel [17].

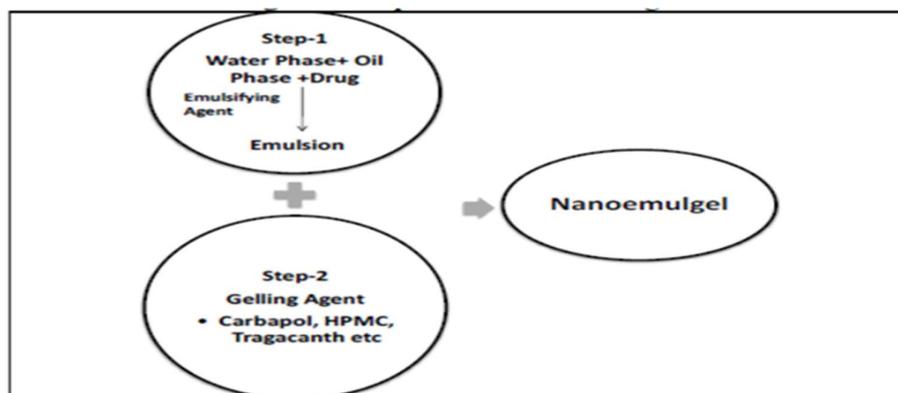


Figure 5: preparation of nanoemulgel [18]

EVALUATION OF NANOEMULGEL

1. Visual inspection-To determine the colour, appearance, and homogeneity of the produced nanoemulgel, visual inspection may be performed [19].

2. pH measurement -The pH of a Nanoemulgel varies according to its intended application, such as on the skin or other mucous membranes. For example, the pH of human skin ranges from 4.5 to 6.

3. Determination of Viscosity-The gel's viscosity is essential for effective skin application. comprehending gel's rheological behaviour is essential. the fluid's resistance to flowing is known as its viscosity; a higher viscosity is associated with a higher flow resistance.

4. Spreadability measurement-The medical efficacy of the suggested formulation will be determined by how well the topical medicine spreads. the ease with which a gel covers the affected area and the skin's application site is referred to as spreadability. spreadability of a nanoemulgel is evaluated based on its "Slip" and "Drag" properties [20].

5. Droplet Size Measurement and Polydispersity Index (PDI)-The dynamic light scattering (DLS) method is commonly used to calculate droplet size. the generated nanoemulsion's homogeneity of droplet size can be determined through the measurement of the polydispersity index (PDI).

6. Zeta Potential-The combination of nanoemulsion and a gelling agent in nanoemulgel allows for the formulation to take on an electrical charge due to the presence of several surface-active components [21].

7 Drug content-Drug content is a crucial factor that determines how much drug is overall present in prepared formulas; a higher drug content is associated with minimal drug loss during the production process [22].

8 Accelerated stability study- The International Council for Harmonization's (ICH) guidelines should be followed for an accelerated stability study, which involves storing formulations in an oven at 37 ± 2 , 45 ± 2 , and 60 ± 2 degrees Celsius for 3 months, and checking nanoemulgel every two weeks using the proper analytical method to check the drug content [19].

9. In vitro release study-Drug release studies are conducted in vitro using franz diffusion cell, which has an effective diffusion area of 3.14 cm² and a cell capacity of 15.5 ml, the diffusion cell dissolves a drug using a nanoemulsion, adds phosphate-buffered saline to the receptor compartment, and uses a magnetic stirrer to collect samples, UV-Vis is used to determine drug concentration, and the total amount of drug released [12].

APPLICATIONS OF NANOEMULSION

Nanoemulsion for oral route-

When poorly water-soluble drugs are administered orally, their solubility, absorption, and bioavailability are increased by the o/w nanoemulsion, which increases the drug's rate of dissolution and low bioavailability.

Nanoemulsion for ocular delivery-

To enhance the absorption of lipophilic medicines, such as erythromycin and pilocarpine, o/w nanoemulsion is utilized.

Nanoemulsion for nasal delivery- When considering the nasal route in comparison to the perioral and parenteral routes, there are numerous advantages. For example, the nasal mucosa's prolonged contact with the nanoemulsion droplet enhances drug absorption, bypassing the liver's initial processing.

Nanoemulsion for transdermal delivery- the drug can penetrate the skin via sweat ducts, hair follicles, or the stratum corneum, regulating absorption, bioavailability and enhancing drug targeting. the capacity of nano-sized emulsion to enter skin pores and achieve systemic administration makes it a viable technology.

Nanoemulsion in cosmetic-

Nanoemulsion is considered to be an excellent carrier for delivering cosmetics in a controlled manner and helps disperse active ingredients throughout the skin layer, therefore it is utilized in cosmetics [23].

CURRENT AND FUTURE PROSPECTS OF NANOEMULGEL

Hydrophobic drugs are difficult to develop formulations due to their poorly soluble and bioavailable nature, topical formulations such as creams, ointments, and lotions have good emollient qualities but sluggish drug release. topical aqueous-based formulations like gels enhance medication release by combining oily bases and hydrophobic APIs to create an emulgel, which is then nanonized to create a nanoemulgel with improved characteristics.

Nanoemulgels are a great dose form because they provide sustained release, improved permeability, and thermodynamic stability, because nano-emulgel has advantages over conventional formulations, there has been a massive surge in production of nano-emulgel can be foreseen [18]. topical nanoemulsion gel is superior to conventional lipophilic drug formulations due to improved pharmacokinetics, longer half-life, and increased therapeutic efficacy. Its spreading properties and less stickiness contribute to higher patient approval.

In spite of several obstacles, nanoemulgel is likely to be the mainstay for the topical administration of lipophilic medications in the future [24].

CONCLUSION

Topical nanoemulgels have proven to be a more beneficial option for a dependable and useful medication delivery system

nanoemulsion-gels offer improved drug administration due to improved spreadability, stronger drug loading, and better drug release regulation. In comparison to other formulations, its gel-like and non-greasy qualities aid patients with improved compliance and oil deficit by offering superior medication release from the substrate. formulation becomes a dual control system release upon the incorporation of the nanoemulsion into the gel matrix. the most efficient and useful medication delivery option has been found to be topical nanoemulgel.

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