JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

AN OVERVIEW OF NANOEMULGEL

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Abstract:

A Nanoemul gel is a topical gel that contains a nanoemulsion dispersed within a gel matrix. The nanoemulsion is typically prepared using high-shear mixing techniques and contains droplets of an oil phase dispersed in an aqueous phase, stabilised by surfactants or stabilisers. The resulting Nanoemul gel has several advantages over traditional emulsion-based gels, including improved stability, enhanced drug penetration, and increased bioavailability. Nanoemulsions have been studied for their potential applications in dermatology and drug delivery, yielding promising results in reducing acne lesions, improving skin appearance, and enhancing drug delivery while reducing inflammation. Further research is needed to optimise the formulation and assess the safety and effectiveness of Nanoemulsions for different applications. Nanoemulgel consist of two different systems in which a drug-containing nanoemulsion is incorporated into a gel base. The fusion of these two systems makes this formulation advantageous in several ways. Lipophilic drugs can be easily incorporated, and the skin permeability of the incorporated drugs can be enhanced several-fold due to the finely distributed oil droplets in the gel phase. Simultaneously, it can be targeted more specifically to the site of action and can avoid first-pass metabolism and relieve the user from gastric/systemic incompatibilities. The nanoemulgel drug delivery system is a formulation-related intervention to improve drug absorption and therapeutic profile of lipophilic drugs. An increasing trend in nanoemulgel use in recent years has been noticed because of the better acceptability of the preparation to the patients due to their non-greasy, convenient spreadability, easy applicability and good therapeutic and safety profile. Despite having a few limitations, nanoemulgel formulation can be considered as a potential and promising candidate for the topical delivery of lipophilic drugs in the future.

Keywords: Nanoemulgel; Topical Formulation; Drug Delivery through skin

INTRODUCTION:

There are many advantages of topical drug delivery systems, like the possibility to administer drugs more selectively and efficiently to a specific location, with the elimination of metabolic breakdown associated with systemic administration. Furthermore, topical delivery improves bioavailability by minimising the first-pass metabolism by the liver and allows for constant delivery throughout time. Due to a recent trend in current chemical synthesis techniques, the discovery of low water-soluble drug molecules has increased significantly. Lipophilic medications account for roughly 40% of newly identified medications, meaning they have low water solubility, and their bioavailability is a major concern. Different strategies are being developed to solve the challenges of lipophilic drugs' low bioavailability and poor aqueous solubility. Various types of delivery systems are being developed, and there is now a growing interest in emulsions(micro/nano), self-emulsifying systems, niosomes, and liposomes etc. Among these, emulsion-based formulations might be designed to overcome the poor systemic bioavailability.

SCOPE OF NANOEMULGEL:

A type of structural fluid known as a nanoemulsion gel combines the characteristics of nanoemulsions and gels. Nanoemulsions are clear or translucent, thermodynamically stable dispersions of oil and water, with typical droplet sizes ranging from 20 to 200 nm. Due to their large surface area and potential to improve drug solubility, bioavailability, and targeted distribution, they are frequently used as drug delivery systems.

Gels, on the other hand, are semisolid systems made up of a three-dimensional network of crosslinked polymer chains, and they can offer advantageous qualities like increased adhesion, extended residence time, and improved skin penetration.

Nanoemulsion gels can offer a special set of benefits in drug delivery by combining these two systems, including increased stability, controlled release, and improved skin permeability. Nanoemulsions are a type of emulsion that has droplets in the nanometer range. They are considered to have better stability and bioavailability than traditional emulsions due to their small droplet size. Nanoemulsions are commonly used in various industries, including the food, cosmetic, and pharmaceutical industries.

Nanoemulgels are topical gels that contain nanoemulsions. They are commonly used in dermatology for the treatment of skin conditions such as eczema, psoriasis, and acne. They can also be used to deliver medications for pain relief, anti-inflammatory agents, and anti-infective agents. Nanogels are nanoparticle-based - based hydrogels that have been studied for their potential in drug delivery, tissue engineering and other biomedical applications. They are commonly used due to their biocompatibility, biodegradability and high drug loading capacity.

ADVANTAGES:

1. The ability to resist First-pass metabolism.

2. The effectiveness of a managed and long-term drug delivery system has been proven.

3. Skin-friendly.

4. Appropriate for self-medication.

5. Patient accepts it quickly.

6. Nanoemulsion provides a large surface area and free energy, which makes an efficient delivery system.

7. Emulsion defect like Creaming, phase separation, flocculation, and coalescence is not found in nanoemulsions.

8. Nanoemulsion prepared in a variety of formulations, foams, creams, sprays and many other cosmetic formulations.

9.It is safe on transdermal application due to its non-toxic nature.

10. By using a biocompatible surfactant in nanoemulsion formulation, it can be administered orally.

11.It shows better penetration of the drug because the nano-sized particles can easily enter through the rough skin surface.

12. By the process of precipitation and interfacial polycondensation of nanoemulsion, nanocapsule and nanospheres are prepared.

DISADVANTAGES:

1. Bubbles formed during emulgel formulation.

2. For utilisation in pharmaceutical applications, the surfactant used ought to be non-poisonous.

3. Possibility of allergenic reactions.

4. Skin irritation on contact dermatitis.

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG:

a. Physiological factors

i. Lipid content of the skin acts as a barrier for drug absorption, and lowering this barrier property leads to increased penetration.

ii. Thickness of different skin layers -The Greater the thickness lower the penetration rate, like palm and sole show a higher diffusion rate compared to other surfaces.

iii. Hair follicle density.

iv. Skin pH.

v. Hydration of skin.

vi. Sweat gland density.

vii. Inflammation of the skin, the disrupted stratum corneum has higher permeability.

viii. Blood flow.

ix. Skin temperature

b. Physicochemical factors

i. Partition coefficient - a higher log p value gives rise to absorption.

ii. Effect of vehicles - hydro alcoholic gel provides the most efficient absorption through the skin.

iii. Degree of ionisation.

iv. Molecular Weight. (less than 400 Dalton).

FORMULATIVE COMPONENTS OF NANOEMULGEL

1. Oil phase

When choosing oil or other lipid components, care must be taken to ensure that the oily phase is real and shielded from impurities like peroxides, free radicals, and other fatty acids like sterols and polymers.

One of the primary factors in the choice of lipids for the creation of nanoemulsions is the bulk of hydrocarbon chains; the rationale for this is the uniformity and essence of emulsification. Mineral oil as a drug vehicle, cottonseed oil, maize oil, Arachis oil, olive oil, coconut oil, eucalyptus oil, rose oil, clove oil, etc., are among the oils that are frequently employed in nanoemulsions.

2. Aqueous phase

This component is in charge of turning the emulsion into an emulgel, in this instance, of the gelling agent. Generally, distilled or ultra-purified water is used to create the nanoemulgel's composition.

3. Surfactant

Surfactants are utilised in the production of nanoemulgel to give the final formulation stability and emulsification. Non-ionic surfactants are employed in the creation of nanoemulgel due to their low toxicity. Among the nonionic surfactants that are frequently utilised are the esters of sorbitan and polyoxyethylene fatty acids.

4. Co-surfactant

Co-surfactants are typically employed to increase the final product's thermodynamic stability while reducing the concentration of surfactant. Ethyl alcohol, PGs, Transcutol HP, and PEGs are a few examples of co-surfactants.

5. Penetration enhancers:

One of the finest methods to improve transportation efficiency through the skin and related layers has been to use penetration enhancers. One of the main components of the traditional drug delivery system is a penetration enhancer, which is typically utilised in topical nanoemulgel. Usually, these penetration enhancers function by interacting with the constituents of skin, resulting in a transient and cumulative rise in skin permeability.

6. Gelling agent

One of the key components of nanoemulgel, the gelling agent, gives the formulation a flawless structure. These make sense as cross-linking agents. Tragacanth, HPMC, Carbopol, etc., are a few of the gelling agents that are employed.

7. Preservatives:

Preservatives are chemical substances used to protect a substance from microbiological degradation and extend a product's shelf life. Preservatives, including methylparaben, propylparaben, Benzalkonium chloride, and phenoxyethanol, are frequently utilised.

8. Antioxidant:

Antioxidants are chemical compounds used in compositions to prevent various components from oxidising. For example, Ascorbyl palmitate, Butylated hydroxytoluene, etc.

9. pH modifiers:

The pH value also indicated the stability of the nanoemulsion. The mean value of pH should lie in the range of 5.4 - 5.9 (pH of skin). The most commonly used pH modifier is Triethanolamine.

METHODS OF PREPARATION OF NANOEMULGEL

I.SCREENING OF COMPONENTS

Based on the findings of the preformulation tests, the formulation's final composition should be carefully chosen. The oily phase is chosen in this step according to how well it dissolves the drug moiety. Based on the characteristic parameters utilised to create the nano-sized emulsion, their compatibility with the oil, and the kind of emulsion (o/w or w/o), the ratios for the surfactant and cosurfactant are chosen. Plotting a pseudoternary phase diagram is one method used to critically examine whether the concentration of these components can produce a nanoemulsion. The ratio of these three elements, which serves as the nanoemulsification region's stable nanoemulsion development point, is shown by this phase diagram.

II.PREPARATION OF NANOEMULSION

The medication, cosurfactant, and surfactant are dissolved according to how soluble they are in the selected aqueous or oil phase. The aqueous and oil phases are heated independently, and after they reach room temperature, they are mixed by progressively introducing one into the other while stirring continuously.

Both low- and high-energy techniques can be used to formulate the nanoemulsion. Self-nanoemulsification, phase inversion (including phase inversion temperature (PIT) and phase inversion composition (PIC)), emulsification, and solvent diffusion are examples of low-energy techniques. In contrast, ultrasonication, microfluidization, and high-pressure homogenization are examples

of high-energy techniques. It is recommended to employ low-energy techniques instead of high-energy ones due to their greater effectiveness and lack of need for sophisticated equipment.

By using high-energy techniques, the particle size can be adjusted and controlled using different formulation compositions. With high-energy methods, the emulsion's stability, rheology, and colour can also be managed.

The high-energy method reduces the size of both phases by creating an extremely disruptive force with mechanical instruments. Thus, this method might cause the formulation's constituent parts to overheat, which would cause the emulsion to become thermodynamically unstable and render it inappropriate for medications that are thermolabile.

Using the system's inherent chemical energy to increase energy efficiency is a characteristic of low-energy emulsification techniques. Because this method uses less energy, heat-labile components are not degraded. In order to create essential oil-based nanoemulsions and prevent the volatile compounds in essential oils from evaporating, the low-energy or spontaneous technique is widely employed.

1. High-energy method

Since nanoemulsion droplet sizes usually range from 5 to 500 nm, achieving this size requires a lot of mechanical energy. High-energy input for fabrication can be accomplished using a variety of techniques, including high-pressure homogenisers, ultrasound generators, microfluidisers, and high-speed homogenisers. The use of low Emulsifier concentrations is the most important benefit of a high-energy mediated nanoemulsion formulation. The formation of an emulsion by mechanical stirring, with droplet size in the micron range, is the first step in using high-energy techniques. To turn the emulsion into a nanoemulsion, the second step is breaking huge droplets into small droplets with high-energy equipment.

Ultrasonication

The rough emulsion is converted into desirable nano-sized emulsion droplets using a sonicator probe. High-intensity sound waves having a frequency of even more than 20 kHz are generated by the sonicator probe. which can shatter the rough emulsion into nano-sized droplets (5-500nm).

High-pressure homogenization technique

Numerous forces, such as hydraulic shear, severe turbulence, and cavitation, are frequently utilised for the development of nanoemulsions. The surfactants and co-surfactants are passed through a small orifice of a piston homogeniser under high pressure (500-5000 psi) to generate nanoemulsions. The problem of coalescence that would occur can be solved by incorporating excess surfactants into the mixture.

Microfluidization

This approach uses a microfluidiser device, which utilises a high-pressure positive displacement pump (500-20,000 psi) to force the product through an interaction chamber with stainless steel microchannels on the contact area, resulting in the creation of very small sub-micron particles. The mixture is circulated through the microfluidiser till it reaches the desired particle size. The final product is filtered to separate the smaller droplets from the bigger ones and produce a homogeneous nanoemulsion.

High-speed homogenization (rotor-stator homogeniser)

High-speed homogenisers are commonly used in industry for emulsification, dispersion, and comminution. They are simple to mount in existing vessels and tanks, and they are inexpensive to buy. Rotor-stator processes are often the emulsification method of preference in many manufacturing industries. Many studies prove that it is possible to produce nanoscale droplets through the use of rotor-stator processes. However, this necessitates the precise selection of method and formulation parameters.

2. Low-energy method

The production of nanoemulsions using a low-energy emulsification process uses less energy than high-energy methods. They produce nanoemulsions by utilizing the system's inherent chemical energy and just requiring mild stirring. Low-energy approaches include phase inversion methods and spontaneous emulsification.

Spontaneous emulsification

One of the most practical methods of nanoemulsion preparation is spontaneous emulsification. It has two liquid components, one of which is aqueous and the other is organic. Solvents, surfactants, and co-surfactants that are water miscible are shifted from the organic phase to the aqueous phase. The process starts with an organic phase, such as oil and surfactant, being introduced into an aqueous phase, which is made up of water and co-surfactant. Massive turbulence at the phase interface is caused by the rapid migration of water-miscible components into the aqueousphase, which increases the oil–water interfacial area. As a result, small oil droplets form spontaneously.

Phase Inversion Composition (PIC)

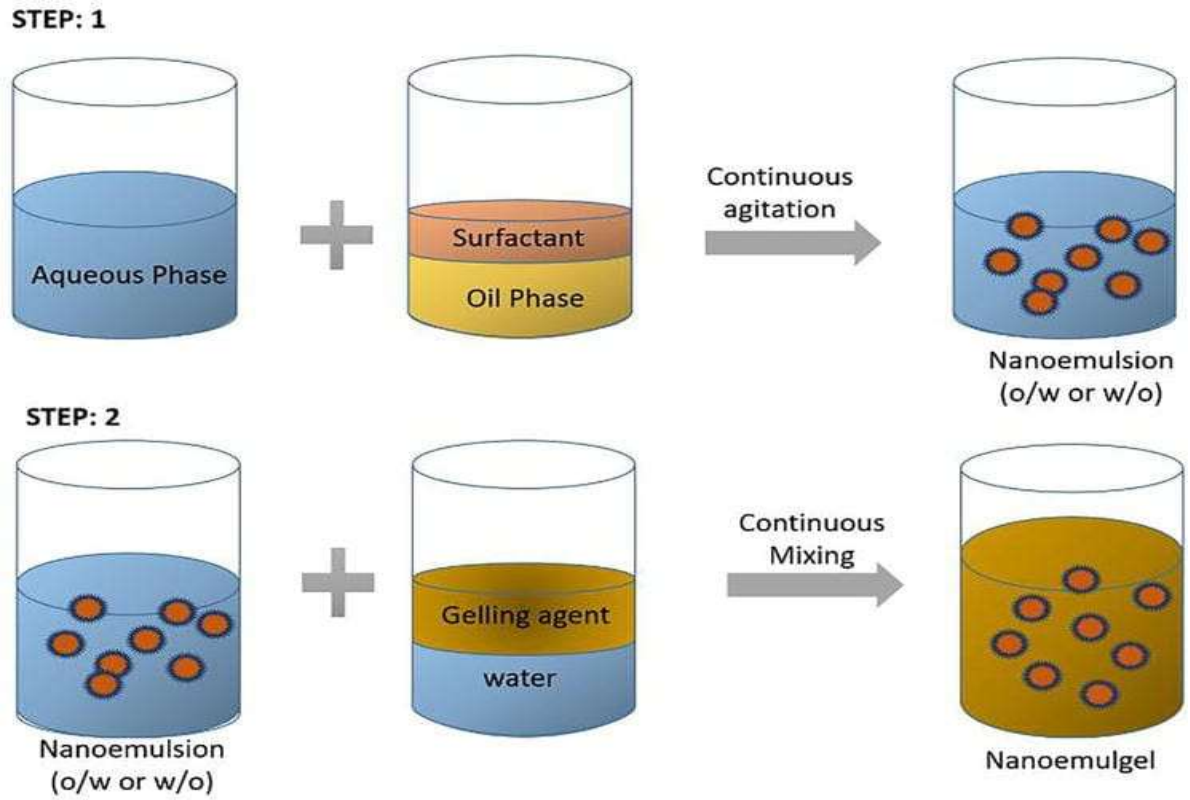
A more advanced type of spontaneous emulsification is phase inversion composition (PIC). Unlike the high-energy method, this method produces nanoemulsions at room temperature and does not necessitate the use of energy-intensive equipment. A laboratory-grade magnetic stirrer is used to mix oil and surfactant while water is added drop by drop. Then, as the volume of water is elevated, a w/o nanoemulsion is produced initially, followed by an o/w nanoemulsion at the inversion point, all without using much energy.

Phase inversion temperature technique (PIT)

In the PIT technique, a change in the temperature reverses spontaneous surfactant curvature. Nonionic surfactants, such as polyethoxylated surfactants, dehydrate in polyoxyethelene (POE) groups, making them more lipophilic and changing the curvature of surfactants. As a result, phase inversion occurs, and a nanoemulsion is produced.

III. PREPARATION OF NANOEMULGEL

The preparation of gelling media involves dissolving gelling agents into an aqueous medium until complete swelling is achieved. For this, the selected polymer is dispersed in pure water while being continuously stirred by mechanical means at specified conditions for a specific time and a constant rate to achieve complete swelling. Lastly, the gel base is adjusted for pH, which can be delivered effectively to the topical system.



Schematic representation for the preparation of nano-emulgel

EVALUATION TECHNIQUES

Physical appearance:

The prepared Emulgel is checked visually for its colour, homogeneity, consistency and phase separation.

pH Evaluation:

pH evaluation is the important criterion, especially for the topical formulation. The pH of emulgel should be between 5.8 - 6 to mimic the skin condition. If the pH of the prepared emulgel is acidic or basic, it may irritate the patient. The pH of the prepared emulgel was measured using a digital pH meter by dipping the glass electrode into the emulgel. The measurement of the pH of each formulation was done in triplicate, and average values were calculated.

Spreadability:

Spreadability of emulgel is measured in terms of the diameter of the emulgel circle produced when emulgel is placed between two glass plates of definite weight. A weighed quantity (350 mg) of emulgel is taken on one glass plate and another glass plate is dropped from a distance of 5 cm. The diameter of the circle of the spread emulgel is measured.

It is calculated by using the formula:

S-M.L/T

Where,

S= spredability.

M= weight tied to upper slide.

L= length of glass slide.

T= time taken to separate the slides completely.

Droplet size, polydispersity, and Zeta potential of Nanoemulsions

Dynamic light scattering (DLS), otherwise called photon correlation spectroscopy (PCS) is used to analyse the fluctuations in the intensity of scattering by droplets/particles due to Brownian motion. Nanoemulsions droplet size, zeta potential and polydispersity can be assessed by PCS using a particle size analyser.

Swelling index

1 gm of prepared topical nanoemulgel is taken on porous aluminium foil, which is then placed on 10 ml of 0.1 N NaOH solution. The sample is removed from time to time, and the weight is noted till no further change in weight:

Swelling Index (SW) % = [[Wt-Wo] / Wo]*100

Where, (SW) % = Percentage swelling,

Wo = Original weight of nanoemulgel

Wt = Weight of swollen nanoemulgel at time t.

Viscosity measurements and rheological behaviour

A Brookfield L was connected to a thermostatic water bath adjusted to 25°C. Viscosity was measured on each base by using spindle 40. A defined amount (1 g) of each gel base was placed inside the plate and carefully closed. The measurement was started by operating the viscometer at 0.6 rpm, the speed was gradually increased, and the measurement was recorded when the torque reached 10% was obtained by plotting the shear rate as a function of the shear stress.

In vitro diffusion studies

The Franz diffusion cell is used to perform a diffusion study of the prepared nanoemulgel. A cellophane membrane is used for study, and 0.5g of sample is applied on the membrane and diffusion is carried out for 8 hr at 37±1°C using phosphate buffer (pH 7.4). At a time interval of 1 hr, a 1 ml sample is collected and replaced with a new buffer solution. Collected samples are analyzed by using a suitable analytical method.

Release kinetics

To study the release kinetics, data obtained from ex vivo permeation studies were fitted in various kinetic models:

Zero order as a cumulative percentage of drug released versus time,

First order as log cumulative percentage of drug remaining versus time.

Higuchi's model is cumulative per cent drug released versus the square root of time.

To determine the mechanism of drug release, the data were fitted into the Korsmeyer and Peppas equation as log cumulative percentage of drug released versus log time and the exponent n was calculated from the slope of the straight line.

For the slab matrix, if the exponent is 0.5, then the diffusion mechanism is Fickian; if $0.5 < n < 1.0$, the mechanism is non-Fickian.

Current and Future Prospects of Nanoemulgel

Delivering hydrophobic drugs to the biological systems has been a major challenge in formulation development owing to their low solubility, leading to poor bioavailability. Some of the topical formulations include creams, ointments, and lotions. They possess good emollient characteristics; however, they have slow drug release kinetics due to the presence of hydrophobic oleaginous bases such as petrolatum, beeswax, and vegetable oils, which inhibit the incorporation of water or aqueous phase. On the contrary, topical

aqueous-based Formulations like gels enhance the drug release from the medication since it provides an aqueous environment for the medicament. Therefore, hydrophobic APIs are blended with oily bases to form an emulgel, which further undergoes nanonization to form a nanoemulgel with enhanced properties. The superior properties of a nanoemulgel, like thermodynamic stability, permeation enhancement, and sustained release, make it an excellent dosage form. There are several marketed emulgels and patents being filed for the same,

demonstrating its tremendous progress in this field. By making advancements in the ongoing research, nanoemulgel, as a delivery system, would outshine, in formulating the drugs that are being eliminated from the development pipeline owing to their poor bioavailability, therapeutic non-efficacy, etc. Despite these advantages, the manufacturing of nano-emulsions limits their commercialisation. However, with the progressing technology, commercially feasible and profitable manufacturing techniques could be possible in the

future. With the advantages of nano-emulgel over other formulations, a tremendousincrease in the production of nano-emulgel can be foreseen.

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