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NANOEMULGEL: AN EMERGING PLATFORM FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The majority of newly developed drugs are lipophilic, which results in pharmacokinetic variations, low oral bioavailability, and uneven absorption. In order to prevent such disruptions, it has been demonstrated this innovative transdermal delivery method is superior to traditional oral route. Nanoemulgel, a newly developed transdermal delivery technology has demonstrated the good results for lipophilic medicines when compared to existing formulations. Nanoemulgel is a fusion of two different delivery systems, involves the physical state of drug containing nanoemulsion which is changed by adding it to the gel matrix. These nanoemulgels are essentially gelled oil-in-water nanoemulsions that have been mixed with a gelling agent to enhances stability and permits controlled and immediate release of medication. Additionally, nanoemulgel is receiving increased attention due to its ability to achieve a safe, targeted distribution, and non-gastrointestinal degradation or first-pass metabolism. In Nanoemulgel it is also possible to promote the drug's solubility in the vehicle and are a good option for analgesics and antifungal medications. In essence, high and low-energy methods are used to combine a hydrogel matrix with a nanoemulsion system to create nano-emulgel. Nanoemulgel provide compelling evidence for these nanocarriers stability in terms of their effectiveness and safety. The nanoemulgel with their non-greasy, gel-like properties and relatively high drug release rates, they can be effectively used for transdermal application.

KEYWORDS: Nanoemulgel, Lipophilic drugs, Transdermal drug delivery, Gelling agent.

INTRODUCTION

Currently, 74% of drugs are taken orally and aren't useful as most people think. Transdermal drug delivery systems were developed in order to further these characters. Transdermal drug delivery system (TDDS) became a significant component of innovative drug delivery systems with the development of modern pharmaceutical dosage forms. Due to their unique benefits, transdermal dosage forms while still a more expensive option than traditional formulations are gaining traction. Some potential benefits of transdermal drug delivery include increased bioavailability, regulated absorption, more uniform plasma levels, painless and minimal side effects, ease of application, and flexibility in stopping drug administration by simply removing the patch from the skin. Transdermal drug delivery systems (TDDS) are defined as discrete, self-contained dosage forms that, when applied to intact skin, allow the drugs to be delivered to the systemic circulation at a controlled rate through the skin. One possible route for both local and systemic drug delivery is the transdermal route of administration. In addition to enabling continuous delivery of medications with brief biological half-lives, transdermal delivery also prevents pulsed entry into systemic circulation, which frequently results in undesired side effects. As a result, numerous novel drug delivery methods, including transdermal and transmucosal delivery systems and controlled release systems, were developed.[1]

The two immiscible liquid phases in a dispersed system, namely water, oil, and emulsifier, are called nanoemulsion. A layer of surfactant and co-surfactant molecules forms an interfacial film that stabilises the multiphase colloidal dispersion of oil and water in a nano emulsion.[2] With a mean droplet size of less than 500 nm, nanoemulsions (NEs) are a transparent colloidal dispersion made up of a mixture of immiscible liquid phases that are kinetically stable and stabilised by using the right ratio of surfactant. Unlike traditional emulsions, which are milky or white, nanoemulsions are clear and translucent due to their small droplet size, which also allows for a higher drug loading capacity. Although they should not be confused with microemulsion (ME), the terms nanoemulsion and submicron emulsion are frequently used synonymously. Despite having the same droplet size, nanoemulsions differ in their structural properties and long-term thermodynamic stability. Using water-in-oil (w/o) and oil-in-water (o/w) preparations, nanoemulsion has proven to be an inventive transdermal delivery method capable of delivering both hydrophilic and hydrophobic drugs.[3]

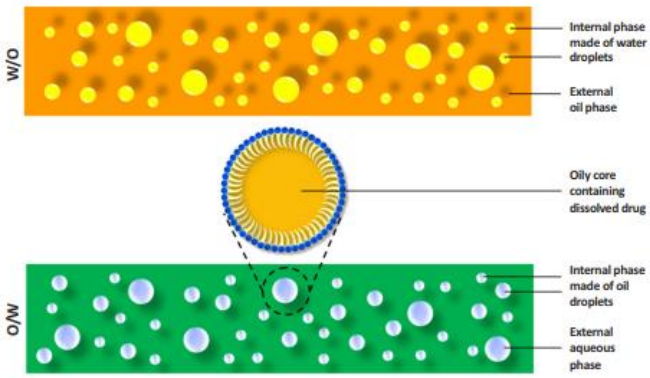

Figure 1: The various components of a stable nanoemulsions.

Nanoemulgel is the fusion of two systems: nanoemulsion system and hydrogel system. Both systems have certain drawbacks, such as the low spreadability and retention of the nanoemulsion and the inability of hydrogels to incorporate lipophilic molecules. There are various kinds of polymeric materials in nanoemulgel surfactants, and fatty materials with droplet sizes ranging from 5 to 500 nm that are naturally occurring, synthetic, or semi-synthetic. Nanoemulgel possesses the ability to surpass the constraints of both systems. In order to create nanoemulgel, the lipophilic drug is dissolved in the oil phase of the nanoemulsion and added to the hydrogel base. This allows the lipophilic drug to be incorporated into a hydrogel while also increasing the viscosity of the nanoemulsion. In transdermal medication delivery, nanoemulgel serves as a drug reservoir. The medication first enters the outer phase, then moves into the skin's surface from the inner phase. When the gel matrix of the nanoemulgel was applied to the skin, oily droplets were released and penetrated. Through the stratum corneum, they penetrate deeply into the skin, directly delivering the drug component.[4]

Drug reservoirs in the nanoemulgel formulation for the topical delivery system affect the release of medications from the inner phase to the outer phase and ultimately onto the skin. The crosslink density and the network polymer chain composition determine these release mechanisms. In addition, drug affinity for diffusing out of the vehicle and passing through barriers affects a drug's capacity to penetrate the skin and effectively release the therapeutic agent.[5]

In addition, medication administered via nanoemulgel has a higher solubilizing capacity and superior adhesion on the skin's surface, resulting in a larger concentration gradient towards the skin and improved skin penetration. Additionally, improved properties such as

thixotropic, non-greasy, easily removed, emollient, not staining, soluble in water, longer shelf life, bio-friendly, translucent, and pleasing appearance are displayed by the gel-based formulation of nanoemulgel. The formulation's lack of stickiness makes it easier to spread and promotes patient acceptance during administration.[6]

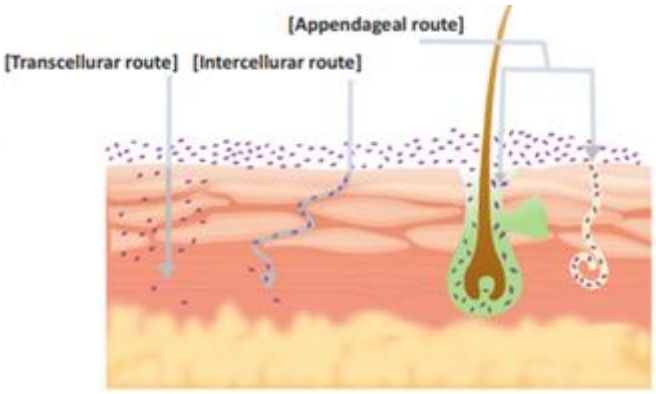

Figure 2: Penetration Through Stratum Corneum.

Advantages of Nanoemulgel[7]

1) These formulations enhance patient compliance and support the delivery of lipophilic and poorly water-soluble medications.
2) Provide higher spreadability of the formulation than creams.
3) Nanoemulgels are non-irritating and non-toxic.
4) Improved drug loading in comparison to alternative formulations.
5) Promote drug deposition and skin permeability.

Materials for nanoemulgel formulation

The combination of two distinct systems a gel system and a nanoemulsion is known as nanoemulgel. Oil-in-water or water-in-oil nanoemulsions can be used as drug delivery vehicles. It is composed of an oil phase, an aqueous phase, a surfactant, and occasionally a cosurfactant in both situations.

This section provides an overview of the primary ingredients of nanoemulgel formulation that are frequently used.

Oils

The selection and amount of oil chosen is determined by how the nano-emulgel will be used. The amount of the selected lipid component or oil phase, determines the prepared nanoemulsions permeability, stability, and viscosity. The oil phase is composed of lipids

derived from natural or synthetic sources, primarily in the case of pharmaceutical and cosmetic applications, unless the oil phase is an active ingredient. An oil's hydrophobicity is a critical factor in the formation of a stable emulsion; low hydrophobicity has been demonstrated to enhance emulsification while also impacting the solubility of lipophilic moieties. Selecting an oil is therefore a necessary first step in developing nano-emulgel as a novel drug delivery system.[8]

Mineral oils are widely used in externally applied emulsions, either alone or in combination with soft or hard paraffins, for their occlusive and sensory properties.[9]

Aqueous phase

Nanoemulgels are frequently made with distilled water or ultra-purified water in order to maximise the aqueous phase. Emulgels are formed when an emulsion contains a gelling agent and undergoes a phase change.[10]

Surfactants

Surfactants are surface-active molecules with a molecular structure that combines a lipophilic and hydrophilic domain. Surfactants' amphiphilic properties enable the dispersion of two immiscible phases, lowering the interfacial tension and creating a sufficiently flexible film that can flex to the droplets' ideal curvature. They are quickly absorbed at the oil–water interface during the emulsification process, which stops the droplets from aggregating.

Additionally, surfactants can be categorised as.

(i) non-ionic,
(ii) zwitterionic,
(iii) cationic,
(iv) anionic

according to their electrical charge. In fact, ionic surfactants are additionally stabilised by electrostatic interactions, whereas non-ionic surfactants are stabilised by dipole and hydrogen bond interactions with the hydration layer of water as well as by repulsive forces resulting from steric hindrance. Non-ionic surfactants, on the other hand, are preferred over ionic ones due to their safer toxicological profile and widespread acceptance, even for oral ingestion.

The most widely utilised ones are polyoxyethylene sorbitan fatty acid esters (polysorbates), glycerol fatty acid esters (polyglycerols), sucrose esters, and polyoxyethylene ether surfactants.[11]

Co-Surfactant

A cosurfactant may also be necessary for the formation of nanoemulsions. Medium chain length alcohols have been employed as cosurfactants for a variety of purposes, including assisting in the formation of nanoemulsion. To a lesser extent, amines and acids have also been utilised. By enhancing the fluidity of the interface and decreasing the interfacial tension even more, the cosurfactant raises the system's entropy. By dividing between the surfactant chains' tails, cosurfactants can also modify the curvature of the interfacial film and increase the amount of oil that can pass through.

When a cosurfactant-containing nanoemulsion is diluted, the cosurfactant may separate from the interface and enter the continuous phase, which would destabilise the interface and cause the nanoemulsion structure to break down. Cosurfactants are necessary for nanoemulsions that might dilute because they stay at the interface and keep the interfacial tension low.[12]

Gelling agents

Gelling agents are polymers that provide the structural network needed to prepare gels. For example, natural sources include cellulose derivatives (HPMC) and semisynthetic and synthetic sources like Carbapol, Polloxamer, Guar gum, Xanthan gum, and Agar.[13]

Other Components

Preservatives and antioxidants are examples of other additives that could be added to a nanoemulsion. Preservative agents are usually included in water-based systems to stop the growth of microorganisms. Essential oil-based systems (EOs) typically don't require preservatives since EOs are naturally occurring antimicrobials. Antioxidants stop oxidation from causing the constituents of the formulation to deteriorate.[14]

Method of preparation of nanoemulgel

Nanoemulgel development involves multiple steps, in which a formed nanoemulsion is combined with a suitable gel base.

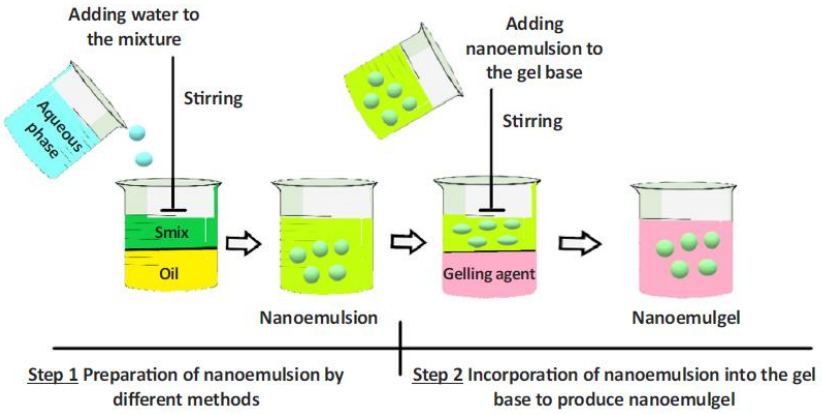

Figure 3: Schematic representation of nanoemulgels preparation.

Step 1: Preparation of nanoemulsion

Nanoemulsions can be spontaneously formed by mixing components that reduces interfacial tension between oil and water phase. However, applying external energy to a heterogeneous mixture is often required to produce nanoemulsions. As such, thermodynamically stable nanoemulsions are typically prepared using either high-energy methods or low-energy emulsification techniques.[15]

High-energy method

Nanoemulsion droplet sizes are typically between 5 to 500 nm achieving this size requires a lot of mechanical energy. High-energy techniques used in nanoemulsion formulation include high-pressure homogenizers, ultrasound generators, microfluidizers, and high-speed homogenizers. A key benefit of high-energy approaches for creating nanoemulsions is the ability to use low emulsifier concentrations.

The process involves first making a coarse emulsion with micron sized droplets via mechanical stirring. Then in the second step, the large emulsion droplets are broken down into nano-sized droplets using high-energy devices resulting in the nanoemulsion.[16]

Ultrasonication

The coarse emulsion is converted into the desired nano-sized emulsion droplets using a sonicator probe. The sonicator probe generates high-intensity sound waves with frequencies exceeding 20 kHz capable of breaking down the coarse emulsion into nano-sized droplets ranging from 5-500 nm. Various probes of different dimensions are available to reduce droplet size to the desired range. Factors such as sonication intensity, duration, and probe

type impact the resulting droplet size. By controlling these parameters, the coarse emulsion can be sonicated into a nanoemulsion with droplets at the intended nanoscale.[17]

High-pressure homogenization technique

Nanoemulsions are formed using forces like hydraulic shear, intense turbulence, and cavitation. In high pressure homogenization, surfactants and co-surfactants are passed at high pressures (500-5000 psi) through a narrow orifice in a piston homogenizer to generate nanoemulsions. Adding excess surfactants prevents droplet coalescence. This effective and economical technology produces nanoemulsions with very small droplet sizes (as low as 1 nm) in both small and large-scale operations. Droplet size depends on parameters like number of homogenization cycles and the viscosities of dispersed and continuous phases. Drawbacks are high energy consumption and heat build-up during processing which can deteriorate components. This method works best for emulsions with <20% oil as higher oil content reduces efficiency.[18]

Microfluidization

This technique employs a microfluidizer device containing a high-pressure positive displacement pump (500-20,000 psi). The pump forces the product through an interaction chamber lined with microchannels on the contact surface. As the product flows through these stainless steel microchannels, extremely fine sub-micron particles are generated. The coarse emulsion is passed repeatedly through the microfluidizer to progressively decrease the droplet size to the desired nanoscale. Finally, the resulting nanoemulsion is filtered to remove any residual large droplets, yielding a homogeneous nanoemulsion with uniform tiny droplets.[19]

High-speed homogenization (rotor-stator homogenizer)

High-speed homogenizers are widely used in industrial equipment for emulsification, dispersion, and comminution. They are simple to install in existing vessels and tanks at low costs. Rotor-stator homogenization is a frequently used emulsification approach in many manufacturing industries. Reports have shown that rotor-stator processes can generate nanoscale droplets, although this requires careful selection of process parameters and formulation conditions. The simplicity and affordability of high-speed rotor-stator homogenizers make them suitable for nanoemulsion production when optimized appropriately.[20]

Low-energy method

Low-energy emulsification processes require less energy than high-energy for producing nanoemulsions. They use the natural chemical energy of the system to create nanoemulsions with only a little stirring. Low-energy approaches include phase inversion methods and spontaneous emulsification.[21]

Spontaneous emulsification

One of the most practical methods of nanoemulsion preparation is spontaneous emulsification. It consists of two liquid components: an organic component and an aqueous component. Water soluble solvents, co-surfactants, and surfactants are transferred from the organic phase into the aqueous phase. The procedure begins with the introduction of an organic phase such as oil and surfactant into an aqueous phase, which is composed of co-surfactant and water. The fast migration of water-miscible components into the aqueous phase, which raises the oil–water interfacial area causes massive turbulence at the phase interface. As a result, small oil droplets form spontaneously.[22]

Phase Inversion composition (PIC)

Phase inversion composition is a more sophisticated kind of spontaneous emulsification (PIC). This method does not require the use of energy-intensive equipment and can produce nanoemulsions at room temperature, in contrast to the high-energy method. Water is added drop by drop while oil and surfactant are mixed using a magnetic stirrer of laboratory quality. Then, without consuming much energy, a w/o nanoemulsion is created initially as the water volume is increased, followed by an o/w nanoemulsion at the inversion point.[22]

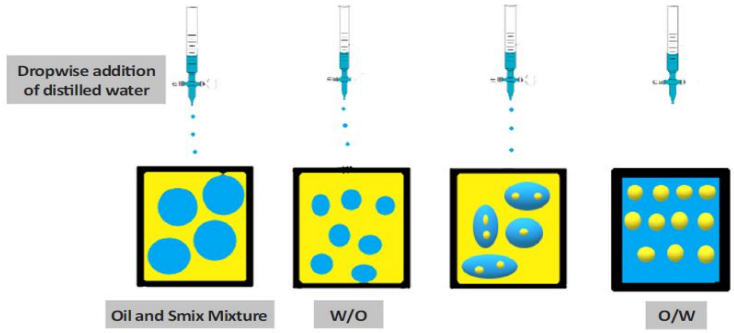

Figure 4: Formation of Nanoemulsion by Phase Inversion Composition.

Phase inversion temperature technique (PIT)

In the PIT technique, spontaneous surfactant curvature is reversed by temperature change. The dehydration of polyoxyethelene (POE) groups in non-ionic surfactants, like

polyethoxylated surfactants, increase their lipophilicity and modifies the surfactants curvature. Phase inversion consequently take place and a nanoemulsion is created.[21]

Step 2: Preparation of nanoemulgel

By dissolving the polymer in purified water and continuously stirring it with a mechanical stirrer, the gel base is produced. Following the preparation of the nanoemulsion and the gelling agent, the two are continuously stirred until a nanoemulgel is formed. Various polymeric gelling agents help to transform water in oil (w/o) or oil in water (o/w) nanoemulsion into thick and semisolid nanoemulgels.[23]

Characterization of nanoemulgel

Visual inspection

The prepared nanoemulgel were visually inspected for their color, appearance and homogeneity.[24]

pH measurement

The pH of nanoemulgel varies according to its intended use, whether for skin or for other mucous membrane, for example the pH of human skin is known to be between 4.5 and 6.[25]

Spreadability measurement

The therapeutic efficacy of the developed formulation will be determined by the spreadability of the topical preparation. Spreadability is the term used to describe how easily a gel covers the affected area and the skin at the application site. Spreadability of nanoemulgels is determined by their 'Slip' and 'Drag' properties.[26]

Droplet Size Measurement and Polydispersity Index (PDI)

A common method for determining droplet size is dynamic light scattering (DLS). The polydispersity index (PDI) measurement provides information on the droplet size homogeneity within the prepared nanoemulsion.[27]

Zeta Potential

Since nanoemulgel is essentially made up of gelling agent and nanoscale emulsion droplets, the presence of different kinds of surface-active agents in the formulation can cause it to exhibit an electrical charge.[27]

Drug content determination

Drug concentration in emulsified gel was measured by HPLC. By accurately weighing 5 gm and dissolving it in 50 ml of emulsified gel in purified water, the amount of drug present in the gel was determined using sonication with phosphate buffer at pH 7.4. Sonication for 15 minutes and heating for 5 minutes. The test was conducted into the triplicate, and the average percentage of drug content was calculated.[26]

The % drug content of nanoemulgel preparation was determined by using following formula %drug content = Sample absorbance /standard absorbance.

Accelerated stability study

The formulations are kept in an oven for three months at three different temperatures: 37±2°C, 45±2°C, and 60±2°C, as per the ICH guidelines. Every two weeks, drug content is analysed using an appropriate analytical technique. Measuring stability is based on changes in gel pH or drug degradation.[7]

Future prospective

Nanoemulgel has emerged as a highly promising option for topical medication delivery, supported by multiple reviewed studies. Its prominence as a leading drug delivery method arises from the necessity to enhance the pharmacokinetics and pharmacodynamics of drugs with limited bioavailability and patient usability. Nanoemulgel formulations demonstrate the ability to effectively administer a broad spectrum of lipophilic drugs from diverse therapeutic categories, leading to improved therapeutic outcomes. These formulations are actively used in healthcare for managing both acute and chronic conditions such as fungal infections, inflammation, cardiovascular issues, psoriasis, and alopecia. Furthermore, the utilization of nanoemulgel presents significant potential for financial gain and could breathe new life into drug categories previously abandoned due to challenges like low bioavailability and clinical ineffectiveness. As a result, the future prospects of nanoemulgel as a drug delivery system appear promising, especially for addressing drug categories struggling with efficient delivery.[10]

CONCLUSION

The transdermal drug delivery system serves as a promising alternative to various conventional drug delivery method, it is accompanied by several limitations. A nanoemulgel, which is structured on nanoemulsion and incorporates a gelling agent for its three-

dimensional framework, emerges as a favourable solution. Nanoemulgel has the advantage of nano-sized particles, facilitating deep penetration, and offers the capability to administer lipophilic drugs within its internal structure, while maintaining an acceptable aqueous exterior structure. Furthermore, its user-friendly application and non-greasy attributes contribute to an aesthetically pleasing appearance. In conclusion, nanoemulgel stands out as an effective and practical drug delivery system that ensures prolonged contact when applied to tissues.

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