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REVIEW ARTICLE

NANOEMULGEL AS A RECENT DRUG DELIVERY SYSTEM

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Summary

Every year many drug molecules discovered to be effective in treatment of many diseases, however not all of these drugs succeed in reaching the market. One of the main reasons for such failure is the lipophilicity or low water solubility of these chemicals which results in poor bioavailability. Nanoemulsion has the ability to deliver these drugs in an efficient way. Nanoemulsion, which is usually o/w emulsion can incorporate this lipophilic drug into nanolipoidal droplets. However, the difficulty in applying liquid dosage form can be overcome by using nanoemulgel system. Nanoemulgel considered as a suitable way to deliver lipophilic drugs through topical route. This review tries to highlight the importance of nanoemulgel as a drug delivery system. The components of the systems have been explored and the methods of preparations including high energy methods and low energy methods have been discussed. Different methods were used in characterization of such delivery system; all of these methods and techniques were reviewed briefly. Finally, the recent researches about different applications of emulgel in local delivery or systemic delivery has been discussed. To conclude, the nanoemulgel applications in drug delivery is very promising and many products will find their way to the markets soon.

Key words: Nanoemulgel; nanoemulsions; drug delivery system; transdermal drug delivery system

1. 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 minimizing the first-pass metabolism by the liver and allows for constant delivery throughout time (1).

Due to a recent trend in current chemical synthesis techniques, the discovery of low water-soluble drug molecules has increased significantly. Lipophilic medicaments 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

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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 (2).

1.1 Nanoemulsion

Nanoemulsions (NEs) are a transparent colloidal dispersion comprised of a combination of immiscible liquids phases which are kinetically stable and stabilized by the use of the appropriate ratio of surfactant, with the mean droplet size less than 500 nm. Figure 1 illustrates the various components of a stable nanoemulsion (3). The small droplets size of nanoemulsion makes them clear, translucent that differ from the milky or white conventional emulsion and allowed higher capacity of drug loading (4). The terms nanoemulsion and submicron emulsion are often used interchangeably, although they should not be confused with microemulsion (ME). Nanoemulsions differ in structural characteristics and long-term thermodynamic stability, although they have the same droplet size (5). Nanoemulsion has been demonstrated to be an innovative transdermal delivery strategy that can carry both hydrophilic and hydrophobic drugs utilizing water-in-oil (w/o) and oil-in-water (o/w) preparations (6).

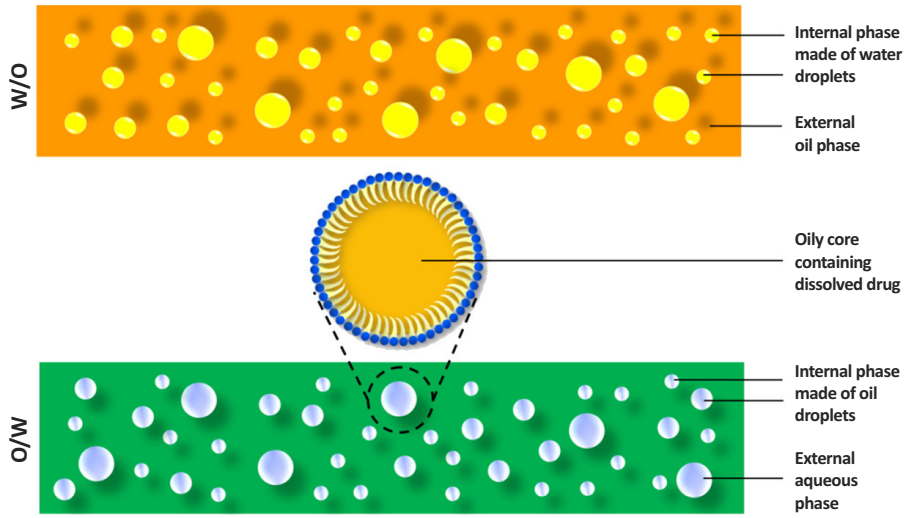

Figure 1. The various components of a stable nanoemulsions (3)

Several mechanisms for improved delivery from nanoemulsions have been proposed. One of these proposition is the components of nanoemulsion such as surfactant that contain fatty acids or penetration enhancers that can affect the integrity of stratum corneum and disrupts lipid bilayer and increase their fluidity, therefore the diffusional resistance to the drugs will be reduced. Nanoemulsion may also enhance skin absorption by the movement of drug between their lipophilic and hydrophilic domains into the stratum corneum, which leads to a constant supply of drugs in the external phase. In certain circumstances, drugs can permeate through skin appendages such as hair follicle, sebaceous gland and possibly sweat glands. The presence of sebum in hair follicles and sweet ducts may facilitate transfollicular delivery of the nanoemulsion (7). Figure 2 shows the different pathways of penetration through stratum corneum (SC) (8).

1.2 Nanoemulgel as a topical drug delivery system

Despite its many benefits, nanoemulsion has issues with spreadability and skin retention due to its low viscosity (9). These drawbacks limit the therapeutic use of nanoemulsion platforms for topical applications (10). The integration of a gelling system has been proposed as a solution to this issue (11). Gels are made by combining a polymer with a large amount of aqueous or hydroalcoholic bases. Since there are more aqueous ingredients in this network, it makes a faster drug dissolution and releases as compared to creams or ointments (12). One of the drawbacks of hydrogel is its inability to integrate hydrophobic molecules in their structure (13). By mixing nanoemulsion

and gel frame, nanoemulgel formulation solves the disadvantages of both nanoemulsion and hydrogel. Hydrophobic compounds can be incorporated first into the oil phase of a nanoemulsion and then adding them to the gel base. (14). Topical nanoemulgels can improve patient compliance by being non-greasy, non-irritant, and have improved drug release characteristics. (12). Because of the homogeneous behavior and consistency of the hydrogel matrix, nanoemulgels are gaining popularity in recent years (13).

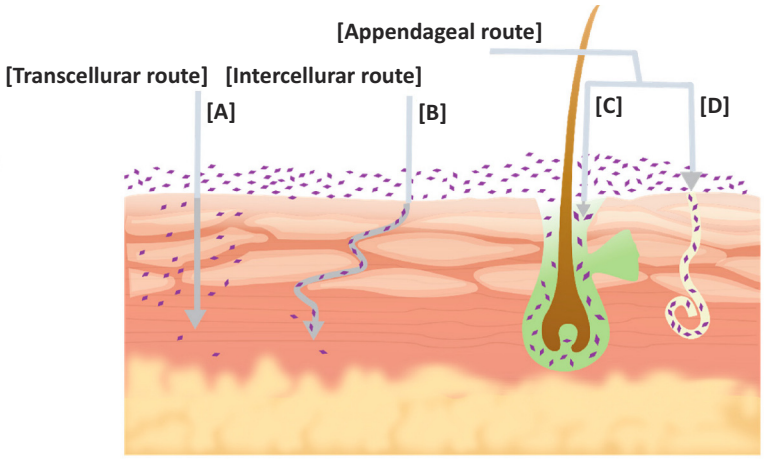

Figure 2. Skin penetration paths through stratum corneum (SC) (8).

1.2.1 Components of topical nanoemulgel

Formulation of topical nanoemulgel requires a variety of materials such as oil/lipids, surfactant, co-surfactant and water that should be compatible with the skin. Nanoemulgel formulation requires the inclusion of some special components such as polymers that used as gelling agents, preservatives and antioxidants.

1.2.1.1 Aqueous phase

In the formulation of nanoemulgel, distilled water is usually used as an aqueous phase (15).

1.2.1.2 Oils and lipids

The choice of lipid phase for nanoemulsion preparation is a very important and usually the amount of oils and lipid component used is based on the type of emulsion and the solubility of the active ingredient in the formulation (3). In most cases, the oil with the greatest ability to dissolve drug candidate is chosen. Since the oil phase must dissolve and retain the drug in a dissolved state (16). The oils and lipids which are approved to be used in the formulation of nanoemulsion are categorized as long-chain triglycerides (LCTs), medium-chain triglycerides (MCTs) and short-chain triglycerides (SCTs). Fractions of oils and lipids that derived from plant origins such as soybean oil, sesame oil are widely used as an oil phase (3).

1.2.1.3 Surfactant

The surfactant's amphiphilic structure allows for the dispersion of two immiscible phases, reducing interfacial tension and resulting in a sufficiently stable film capable of deforming around the droplets with the optimum curvature (17).

Surfactants are molecules that can improve permeation across the skin, by reversibly attaching to keratin filaments, causing corneocyte destruction and thereby changing the stratum corneum (SC) diffusion coefficient (18, 19). The penetration of various drugs through the skin is affected differently depending on the surfactant mixture concentration (20). The permeation of hydrophilic drugs was greatly improved when the concentration of surfactant increased (21).

Non-ionic surfactants, are commonly preferred because, in comparison to ionic surfactants, they are more safe and are widely tolerated also for systemic absorption (22). The polysorbates Tween 80® and Tween 20®, are the two most commonly used surfactants for the lipid based formulation (23).

1.2.1.4 Co-surfactant

A co-surfactant cannot stabilize an emulsion by itself. Instead, it aids in the development of microemulsions (MEs) and nanoemulsion (NEs) by synergistically supporting surfactant activity. A co-surfactant, in particular, will decrease interfacial tension even further (24). Furthermore, it allows for greater oil penetration between the surfactant tails, favoring the optimum curvature of the interfacial film (25).

Variations in surfactant and co-surfactant packing at the oil/water interface affect phase properties, and the surfactant/co-surfactant ratio is a key factor in defining phase properties. As a result, fixed ratios cannot be established because they can vary depending on the surfactant, co-surfactant, and oil phase used. In this case, a formulation study is commonly used to determine the best qualitative-quantitative composition. The pseudo-ternary phase diagram is the most widely used screening method (23). This technique was used to determine the accurate concentration range for development of nanoemulsion utilizing water titration method. Different diagrams can be constructed by varying the Smix weight ratio (26). Figure 3 shows the pseudoternanry phase diagram.

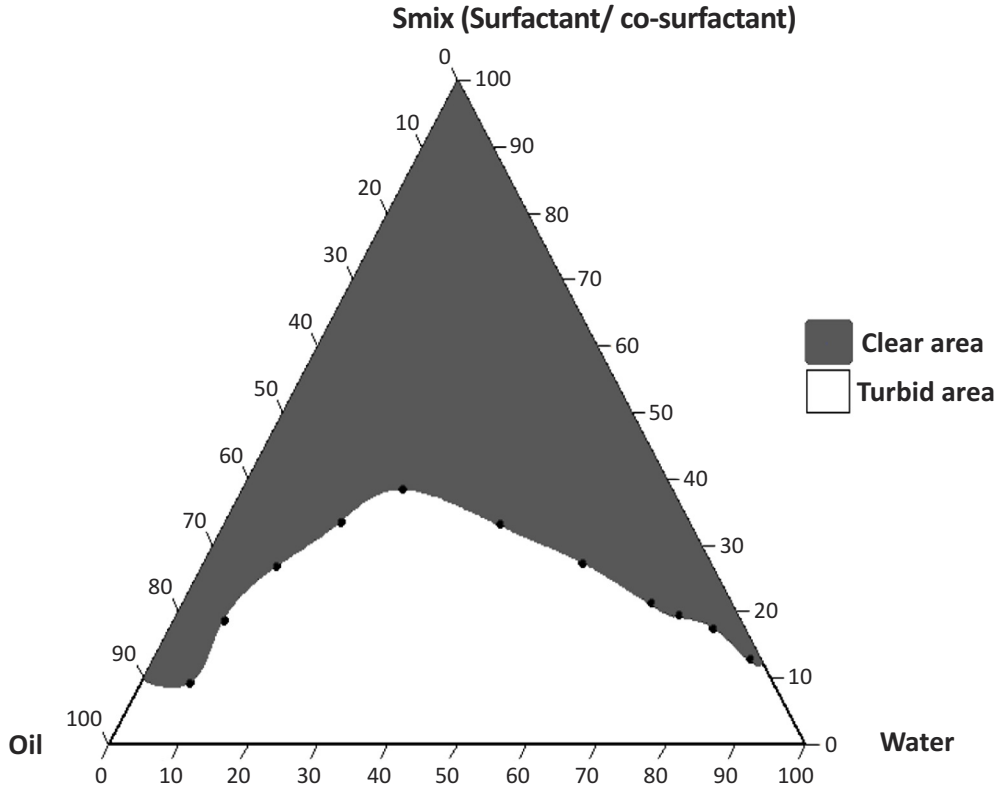

Figure 3. Schematic representation of pseudoternary phase diagram construction by aqueous titration method, the shaded area represents the clear transparent area of nanoemulsion and the unshaded area represent the turbidity.

1.2.1.5 Gelling agents

One of the most important components of nanoemulgel is the gelling agent, which gives the formulation texture. When a gelling agent is added to the formulations, the result is a gelled structure. There are two kinds of gelling agents: natural and synthetic (27).

The effect of a gelling agent on the rate of drug release from emulgel has been investigated. It has been discovered that the concentration of gelling agent and the amount of drug released have an opposite relationship. The prepared emulgel exhibited Non-Newtonian shear thinning behavior, with little to no thixotropy and variable viscosity that changed depending on the concentration and type of gelling agent. Stability tests under a wide range of conditions (centrifugation, temperature cycle test, or one-year storage) revealed that formulations with a low level of carbopol or a mixture of two gelling agents have greater stability than other formulations (28).

Gel forming agents can be classified as follows (29)

A. Natural polymers like collagen, gelatin, alginic acid and tragacanth.
B. Semisynthetic polymers such as carboxymethyl cellulose, methylcellulose and hydroxypropyl methylcellulose.
C. Synthetic polymers like carbomer and poloxamer
D. Inorganic materials like Aluminum hydroxide and bentonite
E. Surfactants: cetosteryl alcohol.

1.2.1.5.1 Carbomers

Carbomers are high-molecular-weight acrylic acid polymers that are crosslinked with allyl sucrose or allyl ethers of pentaerythritol. Depending on the degree of cross-linking and production needs, different grades of carbomer are available, such as carbopol 934 (lowest cross-linking density), carbopol 981 (intermediate cross-linking density) and carbopol 940 (highest cross-linking density) (30). Carbopols, in general, have a high water sorption capacity, when exposed to a pH range of 4.0 to 6.0 they swell in water to 1000 times their original volume and 10 times their original diameter, forming a gel (31). It is thus possible to jellify Carbopol particles in water by using organic amines as a neutralizing agent.

1.2.1.6 Other components

Other additives could be used in nanoemulsion like preservatives and antioxidants. To prevent the growth of microorganisms, water-based systems should typically have a preservative agent. Preservatives are generally unnecessary in essential oil-based systems (EOs) because EOs are naturally occurring antimicrobials (32). Antioxidants prevent oxidation from degrading the formulation's components (2).

1.2.2 Method of preparation of nanoemulgel

Nanoemulgel development is a multistep process in which a formed nanoemulsion is combined with a suitable gel base as shown in Figure 4.

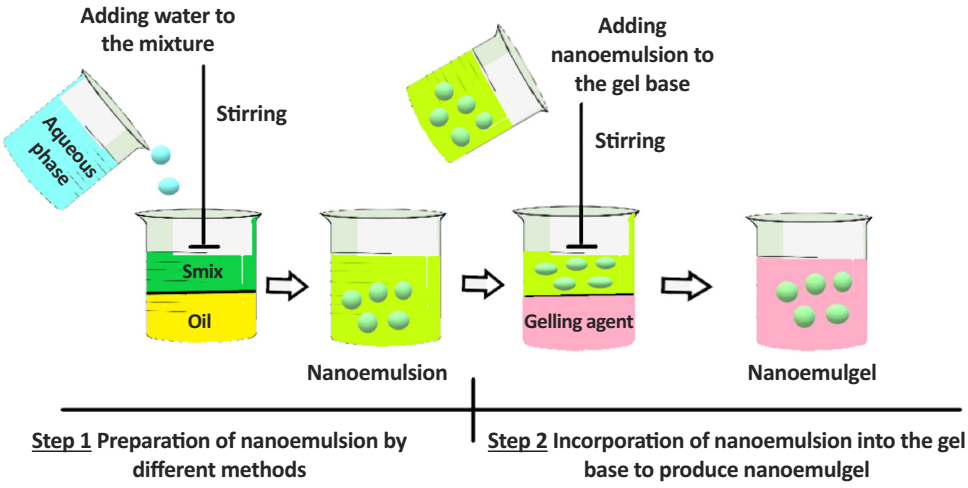

Figure 4. Schematic representation of nanoemulgels preparation

1.2.2.1 Step 1: Preparation of nanoemulsion

Nanoemulsions may be made spontaneously by blending the compositions and lowering the interfacial tension between the oil/water interfaces, or by introducing high energy into the heterogeneous mixture. Thus, high-energy and low-energy emulsification processes may be used to develop a thermodynamically stable nanoemulsion (33).

1.2.2.1.1 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 homogenizers, ultrasound generators, microfluidizers, and high-speed homogenizer (34, 35). The use of low emulsifier concentrations is the most important benefit of a high-energy mediated nanoemulsion formulation (36).

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's (23).

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 has the ability to shatter the rough emulsion into nano-sized droplets (5-500nm). Different types of probes with varying dimensions are available for reduction in size up to recommended values. The sonication input intensity, time, and the probe type affect the droplet scale (37).

High-pressure homogenization technique

Numerous forces such as hydraulic shear, severe turbulence, and cavitation, are frequently utilized for the development of nanoemulsions. The surfactants and co-surfactants that are passed through a small orifice of a piston homogenizer 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. High-pressure homogenization is a highly effective method and a cost-effective technology that can be used on both a small and a large scale to produce nanoemulsions of extremely low particle size (up to 1 nm). The droplet size varies according to homogenization cycles and dispersed and continuous phase viscosities. The main drawbacks include consumption of a lot of energy and raising the temperature during the processing, which may lead to component deterioration. This approach works well for a nanoemulsion that has a 20% oil content since a high volume of oil in the formulation decreases the method's productivity (38).

Microfluidization

This approach uses a microfluidizer device, which utilizes 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 microfluidizer 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 (39).

High-speed homogenization (rotor-stator homogenizer)

High-speed homogenizers 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 using rotor-stator processes. However, this necessitates the precise selection of method and formulation parameters (40).

1.2.2.1.2 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 (41).

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 aqueous phase, which increases the oil–water interfacial area. As a result, small oil droplets form spontaneously (42).

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 (42). PIC method for preparation of nanoemulsion was shown in figure 5.

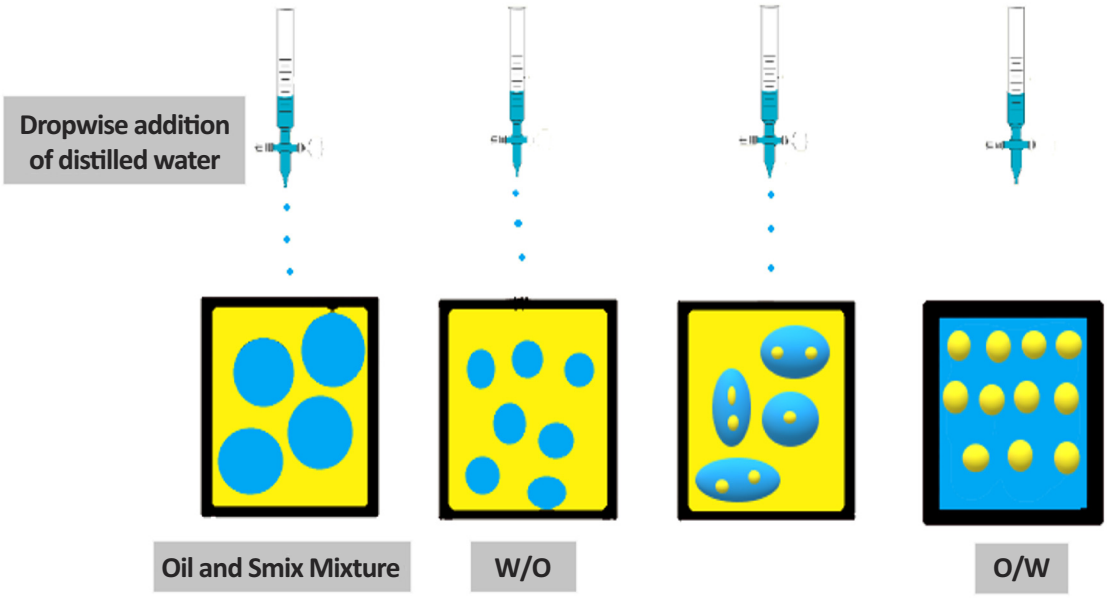

Figure 5. Formation of nanoemulsion by phase inversion composition

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 (41).

1.2.2.2 Step 2: preparation of nanoemulgel

The gel base is produced by dissolving the polymer in purified water and continually stirring it with a mechanical stirrer (4). Following the preparation of the nanoemulsion and the gelling agent, the two are continuously stirred until a nanoemulgel is formed. Water in oil (w/o) or oil in water (o/w) nanoemulsion is turned into thick and semisolid nanoemulgels with the aid of different polymeric gelling agents (2).

1.2.3 Characterization of nanoemulgel

1.2.3.1 Visual inspection

The prepared nanoemulgel could be checked visually to detect the color, appearance and homogeneity of the nanoemulgels (43).

1.2.3.2 pH measurement

The pH of nanoemulgel depends on the applications whether for skin or for other mucous membrane, for example The pH of human skin is known to be between 4.5 and 6 (44).

1.2.3.3 Determination of Viscosity

The gel's viscosity is crucial for effective application to the skin. It is important for gel to know the rheological behavior. Viscosity can be defined as the resistance of fluid to flow and higher viscosity means higher resistance to flow. Fluids generally are classified into Newtonian and non-Newtonian systems. In Newtonian flow, the fluid with higher viscosity, requires greater force per unit area (shear stress) to generate a certain shear rate. In Newtonian flow, the viscosity is constant with different shear rate. In contrast to the Newtonian fluid, non-Newtonian flow does not comply with newton low and the viscosity is changed with the differences in shear rate (45).

1.2.3.4 Spreadability measurement

The therapeutic efficacy of the developed formulation will be determined by the spreadability of the topical preparation. The ease with which a gel spreads over the application site on the skin and the affected area is referred to as spreadability. The 'Slip' and 'Drag' properties of nanoemulgels are used to determine their spreadability (46).

1.2.3.5 Droplet Size Measurement and Polydispersity Index (PDI)

Droplet size is typically determined using the dynamic light scattering (DLS) approach. The polydispersity index (PDI) measurement provides information on the droplet size homogeneity within the prepared nanoemulsion (47).

1.2.3.6 Zeta Potential

Because nanoemulgel is made up of nanoemulsion and a gelling agent, the formulation can acquire an electrical charge as a result of the presence of different surface-active ingredients (47).

1.2.3.7 Drug content

Drug content is a very important parameter which determines the total amount of drug that is present in the prepared formulae and higher drug content is associated with little loss of drug during production steps (44).

1.2.3.8 Accelerated stability study

Accelerated stability study should be conducted in accordance with International Council for Harmonization (ICH) regulations. The formulations should be kept 3 months in the oven at 37±2°C, 45±2°C, and 60±2°C. The samples

should be tested every two weeks using an appropriate analytical procedure to determine the drug content. The change in pH of the gel or drug deterioration is used to measure the stability (48).

1.2.4 Different applications of nanoemulgel formulations

W. Soliman et al, 2021 (43) aimed to formulate curcumin as nanoemulgel to improve its efficacy, because curcumin has a low water solubility and bioavailability. The produced nanoemulsion was made with the help of a high-speed homogenizer and ultrasonication methods were applied. The results reveal that nanoemulgel has better skin penetration than curcumin-based gels and emulgels, as well as the best enhancement ratio and steady state transdermal flux values. Curcumin loaded nanoemulgel showed the least percentage of swelling *in-vivo* anti-inflammatory studies.

E. Yeo et al, 2021 (49) developed and evaluated a tocotrienol-rich naringenin nanoemulgel for the treatment of diabetic patients who suffer from chronic wounds. In this study, within a 24-hour time frame, *in-vitro* release of naringenin demonstrated a prolonged release profile from the formulated nanoemulgel (NG1). The release from nanoemulsion, on the other hand, was significantly greater , possibly owing to the lack of polymer covering on the dispersed oil droplets.

Finasteride nanoemulgel was prepared by *D. Upadhyay et al, 2020* (44) for treatment of male patterned baldness and they tried to improve drug permeability through the skin and enhance patient compliance by prolonging the contact time with the skin. The drug release from nanoemulgel was significantly higher than drug release from solution. In the case of nanoemulgel, macroscopic inspection revealed enhanced hair growth. When compared to the testosterone-treated group, the hair diameter and length of the skin of the rat were shown to be considerably enhanced in the nanoemulgel treated group.

A. Morsy et al, 2019 (50) have developed atorvastatin loaded nanoemulgel for wound healing. Various formulations (atorvastatin loaded gel, emulgel, and nanoemulgel) were prepared. The *in-vitro* drugrelease profile of atorvastatin from all prepared formulations was 65% from gel, 55% from nanoemulgel and 44% from emulgel after 6 hours. When atorvastatin was developed as a nanoemulgel, its skin penetration capacity was considerably increased. The atorvastatin-loaded nanoemulgel showed the greatest percentage of wound contraction in the *in-vivo* wound healing tests. After 21 days of atorvastatin loaded nanoemulgel therapy, histopathological analysis revealed a significant improvement in the skin's histological structure.

Retinyl palmitate nanoemulgel was studied for enhanced topical delivery by *M. Algahtani et al, 2020* (51). In comparison to the aqueous dispersion, the result shows that nanoemulsion systems released 89–94% of retinyl palmitate in 24 hours. The retinyl palmitate loaded nanoemulgel delivery system greatly increased permeability following topical administration.

In comparison to other delivery systems, nanoemulgel delivery of anti-inflammatory and pain killer drugs is supposed to have improved pharmacodynamic action. *Md. Shadab et al, 2020* (52) develop diclofenac sodium loaded nanoemulgel and they tried to assess the anti-inflammatory effect of the produced nanoemulgel through conducting the carrageenan-induced paw edema test. When compared to marketed and traditional diclofenac gels, the created nanoemulgel had a considerably greater impact on reducing pain and inflammatory symptoms.

The nanoemulgel delivery system for antipsoriatic drugs offers a lot of potential. Clobetasol propionate is a highly effective topical corticosteroid for the treatment of psoriasis. Dadwal and his team attempted to make a clobetasol propionate topical nanoemulgel employing squarticles as a lipidic nanosystem in order to improve the therapeutic effect and penetration of clobetasol propionate into the sebaceous glands. The developed nanoemulgel retained more clobetasol propionate than the commercial product in terms of cumulative percentage retention (53).

M. M. Elmataeeshy et al, 2018 (54) recently developed a nanoemulgel containing terbinafine Hcl and demonstrated that the terbinafine nanoemulgel is more expensive than conventional emulsions. In comparison to the commercial emulgel, terbinafine skin penetration from all of the developed nanoemulgel formulas was considerably enhanced. The *in-vivo* antifungal activity of the nanoemulgel formula was superior to that of the commercial emulgel for the treatment of Candida infection.

In terms of drug delivery, oil-based nanoemulgel is also a promising alternative to traditional eye drops for the treatment of a variety of ocular diseases. *M. M. Mehanna et al, 2020* (55) prepared an *in-situ* ocular limonene-based nanoemulgel to improve the effectiveness of levofloxacin against *Methicillin-resistant Staphylococcus Aureus* (MRSA) strains that are associated with ocular infection. The results showed that levofloxacin-loaded limonene-based nanoemulsions enhanced MRSA biofilm eradication effectiveness, with the loaded nanoemulgel minimum inhibitory concentration of 3.12 mg/ml being substantially lower than the antibiotic alone (6.25 mg/ml).

Tooth staining is a dental condition that has to be addressed. Tooth bleaching or whitening products are primarily based on hydrogen peroxide. One of the hydrogen peroxide precursors, carbamide peroxide (CP), is a powerful oxidizer. *S. Okonogi et al, 2021* (56) developed a novel controlled release carbamide peroxide nanoemulgel (CP-NG) to reduce the release rate of carbamide peroxide (CP) utilizing a controlled release formulation of o/w nanoemulsion and a solid dispersion method, using modified rice as a gelling agent.

Conclusion

Transdermal drug delivery system is a good alternative to many conventional drug delivery systems, however it suffers from many limitations. Nanoemulgel is a nanoemulsion-based system incorporated a gelling agent that provides the system its three dimensional structure. Nanoemulgel has the advantages of nano-size range that allow facilitated deep entry. In addition, it can be used for applying lipophilic drug in the interior structure with the acceptable aqueous exterior structure. Moreover, nanoemulgel has the advantages of easy application and non-greasy characteristics that impart aesthetic appearance. It can be concluded that nanoemulgel is considered as effective and practical drug delivery system that impart prolong contact when applied to the tissue.

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Adherence to Ethical Standards

Not applicable (review article)

Conflict of Interest

The authors have no conflicts of interest regarding the publication of this article.

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