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Nanoemulgel: A Novel Approach for Topical Delivery System: Updated Review

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Abstract

The incorporation of a nanoemulsions system integrated into the hydrogel matrix affects better skin penetration. Nanoemulgels are known as the formulation of nanoemulsion based on hydrogel. Nanoemulgel improves the stability of a nanoemulsion formulation by lowering surface and interfacial tension, which increases the aqueous phase viscosity. Because the system has a higher viscosity than the nanoemulsion system, nanoemulgel is also known as hydrogel-thickened nanoemulsions. Hydrophobic medication delivery using nanoemulgel is extremely effective. With greater drug loading due to improved solubilizing efficiency, improved bioavailability due to superior permeability, and the ability to control drug release, it is an efficient alternative delivery technique for the treatment of many disorders. Nanogels protect biomolecules like enzymes and genetic material from destruction, while their macromolecular features let tiny molecules circulate longer and serve as a handy platform for combining therapeutic compounds. Nanoemulgel use has increased in recent years as a result of the preparation's improved acceptability among patients due to its non-greasy, convenient Spread ability, easy application, and good therapeutic and safety profile. Nanoemulgel has a strong potential of being the primary topical delivery route for lipophilic medications in the future, despite several challenges.

Keywords: Nanoemulgel; Spreadability; Nanoemulsions

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Introduction

Emulsions have been used in drug delivery systems from the beginning of time. Because of their inability to swell in other solid dosage forms, our forefathers were always forced to utilize emulsion to deliver medications to the elderly and children. By that time, various revolutions in the emulsion had been made to improve the preparation in terms of safety, efficacy, patient compliance, and side effects. The emulsion preparation is now utilized topically by transforming it into gel formulations, in addition to being used orally [1-10]. The novel emulsion-gel combination idea has been developed to make the Due to its wide acceptability as a topical preparation for both medication and cosmetic purposes around the world; nanoemulgel has recently drawn the attention of various scientists to develop nanoemulgel preparations. Nanoemulgel preparation induces its effect for a longer period as the entire system acts like a drug reservoir and allows the drug to release in a very controlled manner. The releasing mechanism is influenced by the crosslink density and the type of the network polymer chains [11]. The tendency of a drug to diffuse out of the vehicle and pass through the barrier influences its ability to enter the skin and release therapeutic molecules (**Figure 1**).

From the inner phase to the outer phase topical administration systems act as drug reservoirs, affecting drug release from the inner phase to the outside phase and, eventually, onto the skin. The releasing mechanism is influenced by the crosslink density and the type of the network polymer chains [12]. The tendency of a drug to diffuse out of the vehicle and pass through the barrier influences its ability to enter the skin and release therapeutic molecules. The therapeutic effect of the drug is produced by liberating the drug in droplet form from the gel network and then reaching the stratum corneum and penetrating it and reaching into the systemic circulation [13].

The method of preparation of nanoemulgel is as simple as emulsion like water in oil and oil in water emulsion with a gel basis. Nanoemulgels are appealing possibilities for drug delivery

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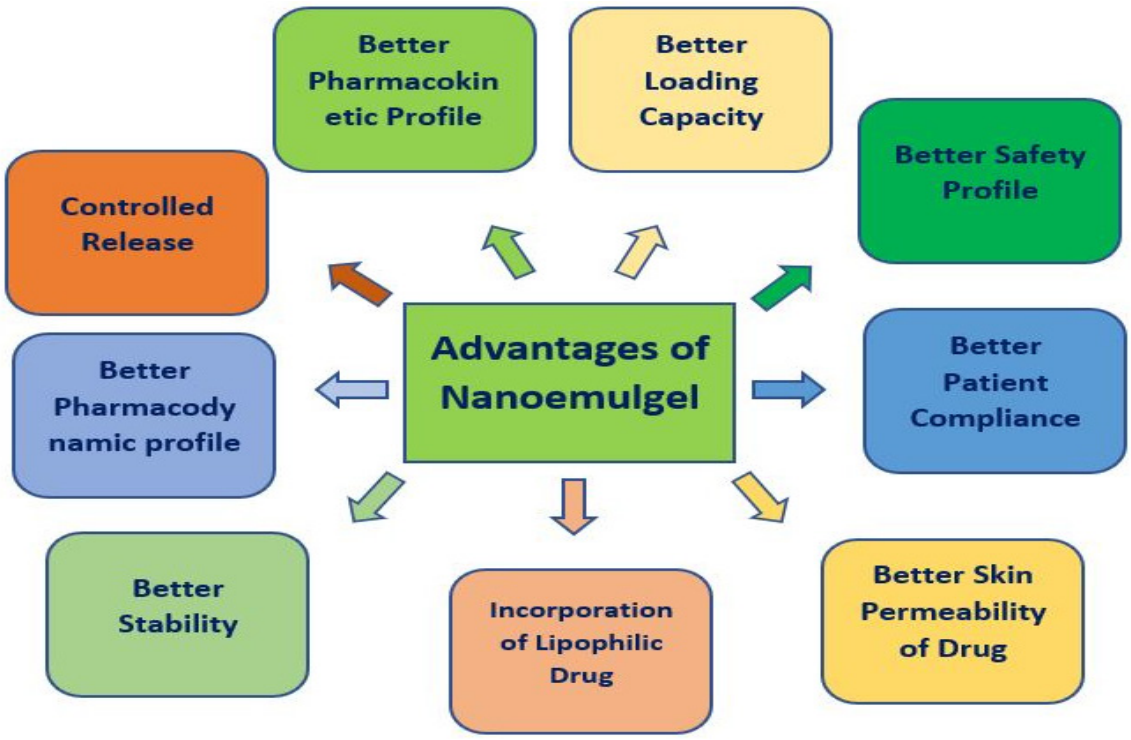

Figure 1 Advantages of Nanoemulgel.

because they have a dual nature, namely a nanoscale emulsion and a gel base, both combined in a single formulation. The oil droplets will then reach the stratum corneum of the epidermis, skipping the hydrophilic phase of nanoemulsions and transporting the medicine molecules directly to the stratum corneum [14].

The nanoemulgel has several benefits over other topical formulations that have been studied, including It is preferable to avoid first-pass metabolism. Acceptance is uncomplicated for the patient and perfectly safe to self-medicate. Medication can easily be discontinued. It is well tolerated by the skin's environment and proven, well-controlled, and long-lasting medication administration technique [15].

Many scientists gave their reviews about the nanoemulgel by using different methods and drugs:

Raemdonck Koen et al., (2009) have reported that as multifunctional polymer-based drug delivery methods, nanosized hydrogels (nanogels) have gotten a lot of interest. Both drug encapsulation and drug release reveal their flexibility. Nanogels may be made to allow for the encapsulation of a wide range of bioactive substances. Nanogels may be tailored to sense and respond to environmental changes by optimizing their chemical composition, size, and shape to enable spatial and stimuli-controlled drug release in vivo. The goal of this paper is to highlight recent breakthroughs in the interaction between biology and nanomedicine, with a focus on nanogels as drug-delivery vehicles [16].

Choudhury Hira., et al (2017) reported that Nanoemulgel, as a new transdermal delivery method, has been shown to provide unexpected benefits for lipophilic medicines when compared to previous formulations. Because of the lipophilic character of newer medications created in this age, they have low oral bioavailability, unpredictable absorption, and pharmacokinetic variability. As a result, this unique transdermal delivery technique is superior to traditional oral and topical medication delivery systems in preventing such disruptions. These nanoemulgels are essentially oil-in-water nanoemulsions that have been gelled with the addition of a gelling agent. This formulation's gel phase is nongreasy, which improves user compliance and stabilizes the formulation by lowering surface and interfacial tension. At the same time, it can be directed more precisely to the site of action, avoiding first-pass metabolism and relieving the user of gastric/systemic incompatibilities. This brief review focuses on nanoemulgel as a superior topical drug delivery technology, covering component screening, formulation procedure, and current pharmacokinetic and pharmacodynamics advances in research investigations conducted by experts throughout the world. As a result, after this study, nanoemulgel may be a more effective and efficient drug delivery technique for the topical system [17-20] (**Figure 2**).

Kumar Anand et al., (2019) reported that many recently licensed medications nanoemulgel formulations are being effectively employed in various fields of health care, redefining the importance of topical administration above other methods. However, toxicological analyses of the ingredients employed in such formulations must be considered, in addition to other changes in the existing state of the delivery system (44).

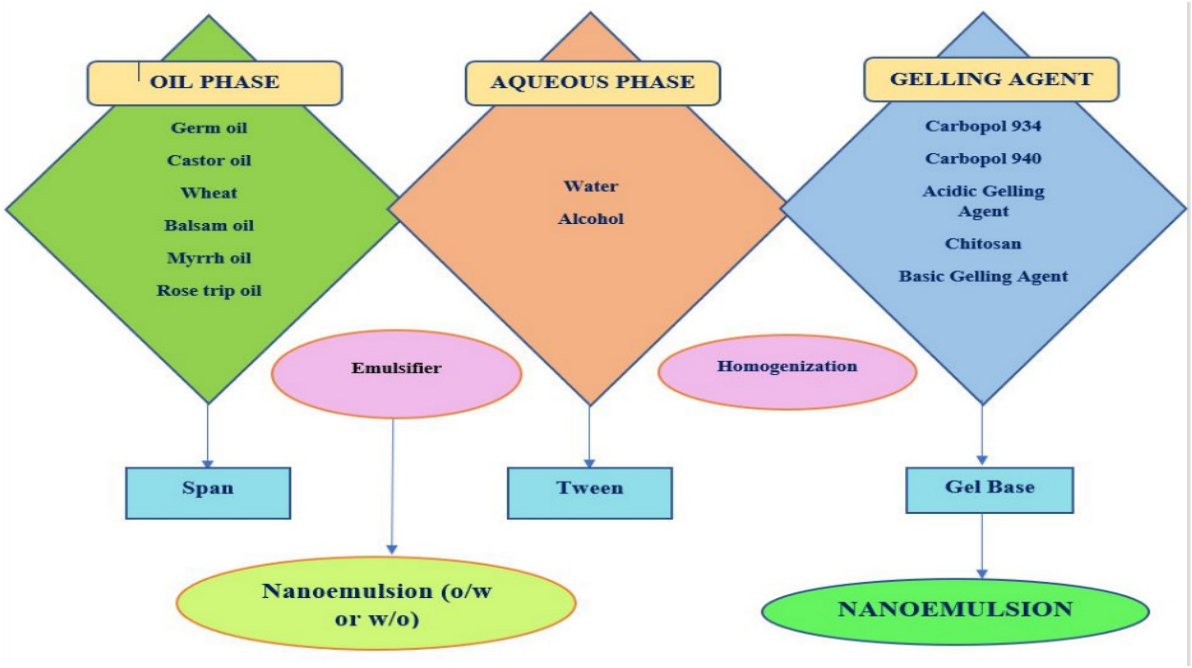

Figure 2 Schematic representation of formulation of typical nanoemulgel.

Morsy A. Mohamed et al., (2019) reported that Tissue repair and wound healing are intricate processes including inflammation, granulation, and tissue remodelling. It was discovered that several statins, particularly atorvastatin (ATR), could promote wound healing. The goal of this study was to develop and test a topical application of ATR-based nanoemulgel for wound healing. The physical appearance, rheological behavior, in vitro drug release, and ex vivo drug permeation of the produced formulations (ATR gel, ATR emulgel, and ATR nanoemulgel) were all assessed. In wound-induced rats, the in vivo wound healing impact was assessed. The physical characteristics of the produced ATR gel formulations were satisfactory and similar. Drug release characteristics from gel, emulgel, and nanoemulgel were all different [18, 19].

Harshitha V et al., (2020) reported that Nanoemulsions are a non-equilibrium, optically transparent, thermodynamically stable, metastable dispersion of nano-sized particles with established surface tension produced by certain shears, made up of appropriate oil and a specific mixture of surfactants and co-surfactants, and capable of dissolving large amounts of hydrophobic drugs. Homogenizers, low-energy emulsification, and phase temperature inversion approaches can all be used to achieve the nanoemulsion mechanism. Nanoemulgel is often referred to as hydrogel-thickened nanoemulsion (HTN) since it has a higher viscosity than nanoemulsion. Nanoemulgel improves the stability of nanoemulsion formulations by lowering surface and interfacial tension, resulting in higher aqueous phase viscosity [20].

Aithal GC et al., (2020) have reported that Nanoemulgels are good candidates for drug delivery because they have a dual nature, namely, a nanoscale emulsion and a gel foundation, both integrated into a single formulation. The active moiety is protected by the nanoemulsion component of the nanoemulgel, which prevents enzymatic degradation and certain processes like hydrolysis. The gel base gives the emulsion thermodynamic stability by raising the aqueous phase's viscosity and lowering interfacial and surface tension. Nanoemulgels have rheological properties that make them ideal for topical and other kinds of delivery, such as dental delivery since they improve patient acceptability. Because the globule size is present in the nano form, using penetration enhancers can improve the formulation's efficiency by increasing permeability and diffusibility. According to reports, several commercially available topical dosage forms have a poor spreading coefficient when compared to nanoemulgels, focusing on the use of nanoemulgels in dermatology, despite opening the way for numerous other disciplines has not been fully utilized. With an overview of a few illustrations supporting the case, this detailed analysis illustrates the merits of nanoemulgel as a viable carrier for medication delivery [21-25].

Mohammed S. Algahtani et al., (2020) reported in their review that a retinyl palmitate-containing nano-emulgel system was successfully produced for topical distribution using a low-energy emulsification approach. This study found that nanoencapsulation of nutraceutical, cosmeceutical, and pharmaceutical goods results in improved UV and storage stability as well as increased skin permeability following topical administration, despite poor biopharmaceutical performance and chemical/photo-instability. This increase in outcomes can be explained by the nanoemulsion system's improved solubilization ability, as well as the nano dimension of the encapsulating delivery vehicle, which favors a more permeable distribution of retinyl palmitate into the skin via several epidermal mechanisms/routes. Controlling HLB of the oil phase and vertexing duration in the preparation of a nanoemulsion with a droplet dimension of 50 nm using

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low-energy emulsification techniques are critical aspects for topical delivery of hydrophobic nutraceuticals, cosmetics, and pharmaceuticals into the skin, according to the findings of this study [26,27].

Sreeharsha Nagaraja et al., (2021) transcutaneous medication penetration through the keratinized stratum corneum is a significant barrier and problem for topical administration. Furthermore, the existing available skin cancer therapy has severe negative effects. As a result, skin-permeable and suitable formulations are essential. Using the therapeutic qualities of herbal components allows for the development of non-toxic, non-irritating, and suitable formulations. Self-nano-emulsifying drug delivery systems containing chrysin have been successfully created and tested for use in cancer therapies, particularly skin cancer. The physicochemical analysis revealed that the formulations' mean droplet size was nanoscale, with limited size distribution and adequate thermodynamic stability [28]. The nanoemulgels mechanical qualities, as evaluated by the force-time relationship and mechanical texture features, were ideal for their quick and simple application to the skin surface. In vivo experiments showed that the nano-emulsified formulation dramatically increased chrysin transcutaneous penetration and skin deposition, indicating that it might be used as a topical treatment. After being converted into nanoemulgel form, chrysin demonstrated an improved therapeutic response in cytotoxicity assays. The findings indicate that the developed self-emulsifying drug delivery system is safe and biocompatible and that it will significantly lower total dosage and chrysin consumption. By taking into consideration the increased physicochemical qualities, the findings of this study might lead to a slew of new uses for the chrysin self-emulsifying drug delivery system, such as oral, nasal, and rectal distribution, giving herbal nutraceuticals a new lease of life. The formulation is a flexible platform technology that may be tweaked to include a range of hydrophobic, drug-loaded lipid nanocomplexes that enable localized therapeutic agent delivery at the afflicted spot. The present platform technology for skin illnesses has unique benefits such as versatility, longer skin preservation, and the avoidance of systemic penetration [29, 30].

Advanced Technologies used in Nanoemulgel:

Topical Application of a Nanoemulgel from a Self-Nanoemulsifying Concentrate: The gel was made by dispersing the self-nano emulsifying preconcentrate in water containing the gelling ingredient. Pluronic® F127 was dissolved in cold water (20% w/w). By adding a -nano emulsifying preconcentrate (10 percent v/w) containing chrysin 100 mg/mL to a transparent Pluronic® F127 solution at 10 °C, a 1 percent w/w chrysin concentration was produced. The mixture was sonicated for 5 minutes in an ultrasonic water bath to remove the trapped air. For comparison, a gel with a chrysin dispersion (1 percent w/w) was created by entirely dispersing the same amount of chrysin in Pluronic® F127 gel.

Droplet size, polydispersity index, electron microscopy, and viscosity were all used to characterize the chrysin nanoemulgel for topical application. The gel sample was diluted with water (1:100) and the droplet size was determined using the same approach as the nano-emulsifying drug delivery system. As previously noted, the nanoemulgel was photographed in cryo-mode for SEM. To investigate the impacts on size and size distribution, the droplet size of the nanoemulgel was examined over three months. Chrysin analysis using RP-HPLC, for accuracy, precision, specificity, and solution stability, the RP-HPLC technique for determining chrysin content was verified. The technique was determined to be specific, as evidenced by the lack of any interfering peaks during the analyte's retention period [31-35].

Nanosized Nasal Emulgel of Resveratrol: The goal of this study is to create a nasal nano-emulgel for resveratrol using Carbopol 934 and poloxamer 407 as gelling agents. Further characterization of the chosen system yielded the best nano-emulsion(57). With slight changes, the cold approach was used to make nasal mucoadhesive nasal nanoemulgel. To avoid air bubbles, Carbopol 934 was gently added to the developed optimal nano-emulsion and blended at a constant slow stirring rate, and then the mixture was chilled overnight to allow complete swelling. Following that, poloxamer 407 was added and mixed slowly to get a clean dispersion. Finally, triethanolamine was added to neutralize the dispersion, and the gel was kept at 4°C until the investigation was completed. FTIR was used to characterize the produced mucoadhesive nasal nano-emulgel. The IR spectra of a mucoadhesive nasal nano-emulgel physical combination, The RES and each component's spectra were then compared to the RES spectra [36-40].

Thymoquinone Loaded Topical Nanoemulgel for Wound Healing: In the further study of Thymoquinone loaded topical nanoemulgel for wound healing, it has been observed that the oil phase and Smix phase (combination of surfactant and co-surfactant) for the synthesis of thymoquinone loaded nanoemulsions are determined using the results of the solubility study and emulsification efficiency inquiry (TQM-NE). TQM-NE was created using a high-energy ultrasonication process. The coarse emulsion was made by mixing 5 percent w/w (50 mg/g) of TQM in the oil phase and Smix through the vortex mixture, then adding the aqueous phase while continuously vertexing for 1 minute. The ultrasonically agitated coarse emulsion phase was further ultrasonically agitated in a water bath for a separate time interval (3, 5, and 10 minutes) at a 40 percent ultrasonication amplitude. To find the best TQM-NE formulation, researchers created and tested eighteen formulations with various compositions. Thermodynamic stability, droplet size distribution, polydispersity index (PDI), zeta potential, viscosity, and drug concentration of TQM-NE formulations were all tested in triplicate. In the Drug Content analysis, the content of TQM in the improved TQM-NE formulations was measured by diluting 100 L of TQM-NE 1000 times with methanol and measuring the TQM content using a UV-visible spectrophotometer at max at 254 nm [41-45].

Methylcellulose-Based Nanoemulgel Loaded with Nigella Sativa Oil for Oral Health Management: As a gelling agent, high-viscosity methylcellulose E461 was utilized in this work. It dissolves in cold liquids to generate a transparent, viscous solution or gel that is naturally non-toxic and non-allergenic. The dental formulation was created in three steps, with minor adjustments, utilizing procedures from the literature. The dental nanoemulgel formulation was optimized using the response

surface methodology (RSM) of Box–Behnken statistical design with a quadratic model with 17 runs. With the use of columns, cubes (standard error of design), and 3D graphs, the impacts of formulation elements and variables, such as water (A), oil (B), and gelling agent (C), were seen on the two responses of the formulation, pH (R1) and viscosity (R2). The statistical analysis of answers was done using ANOVA [46].

Because of the favorable and practical properties for topical distribution of NSO, the produced NSO nanoemulgel demonstrated high promise for the treatment of periodontal disorders. The addition of NSO to a nanoemulgel formulation will enhance patient compliance by making it easier to apply while also improving effectiveness. The nanoemulgels cost-effectiveness and improved mucoadhesiveness are two additional benefits that make them an appealing alternative to traditional topical formulations. The nanosized NSO droplets are predicted to assist sustain tighter mucosal contact, allowing for more surface area for NSO penetration and higher medication concentration in the target region [47].

The impact of different emulsifiers and gelling agents on the globule size, stability, drug release, viscosity, and pH of the formulation can also be investigated. NSO can also be mixed with other natural or synthetic antimicrobial agents, and the resulting nanoemulgel formulations can be utilized for preclinical and clinical testing. More preclinical and clinical research is needed to determine the efficacy of this formulation in the treatment of periodontal diseases [48].

Novel Formulation of Fusidic Acid Incorporated into a Myrrh-oil-based Nanoemulgel for the Enhancement of Skin Bacterial Infection Treatment: The BBD technique was used to create and optimize several nanoemulsions made with myrrh essential oil. FA-NEG was created using the optimized nanoemulsion and a hydrogel basis. The FA-NEG that was created has physical qualities that were suitable for topical application. Following application to the skin, it demonstrated improved permeability and no irritation. When compared to commercial Fusidic acid, FA-NEG and the blank nanoemulgel had a lot more antibacterial activity. The study found that myrrh essential oil and Fusidic acid have a strong antibacterial effect and that their actions are synergistic. Fusidic acid and myrrh essential oil nanoemulgel systems might be potential nanocarriers for imparting antibacterial effects via topical application. Our long-term aim is to investigate the effect of the formulation's action on animal wounds infected with various bacteria and compare healing rates to those given by commercial Fusidic acid solutions [49-50].

Techno-bio functionality of Mangostin extract-loaded virgin coconut oil nanoemulgel: Ultrasonication effectively generated nanoemulsions loaded with Mangostin extracts made from mangosteen peel extracts recovered by VCO, combined VCO-PG, and PG in the dispersed phase containing mixed surfactants (Tween20/Span20) with an HLB value of 15.1 On the nanoscale, the resulting nanoemulsions were globular and evenly dispersed, with an average droplet size of less than 100 nm. The particles' zeta potentials exerted the greatest negative charge, indicating a steady dispersion. All nanoemulsions generated with a surfactant with an HLB value of 15.1 remained stable after numerous freeze-thaw cycles. Furthermore, as compared to their bulk extracts, the nanoemulsions' smaller droplet sizes showed higher antioxidant and antibacterial properties [51, 52-60].

Scope of Nanoemulgel for Topical Delivery

In the topical delivery system, Nanoemulgel plays an important role. The various scopes of nanoemulgel for the topical delivery system are as follows:

Because of its greater absorption capabilities, enhanced pharmacokinetic profile, and therefore higher therapeutic effectiveness, topical nanoemulsion gel can be regarded as a preferable alternative to traditional lipophilic drug formulations. One of the main reasons for the nanoemulgel formulation's increased patient acceptance when compared to other topical administration alternatives is its lower stickiness and superior spreading qualities [61, 62-70].

Topical Nanoemulgels are a more effective and convenient method of medication administration. Patient compliance is higher thanks to the gel and non-greasy qualities, and the lack of an oily foundation allows for greater medication release when compared to other formulations. With the incorporation of Nanoemulsion into the gel matrix, problems like creaming and phase separation that are linked with traditional emulsions are overcome, as is increased spared ability. In some topical conditions, a nanoemulsion-loaded gel is more beneficial [71, 72-80]. Nanoemulsion-Gel-based formulations might be a better and more dependable way to deliver hydrophobic medications in the future. Many drugs used to treat skin infections are hydrophobic in nature, and these treatments can be delivered successfully as Nanoemulgels, in which the drug is integrated into the Nano emulsion’s oil phase and subsequently merged with the gel basis. Despite a few roadblocks, nanoemulgel has a good chance of becoming the focal point for the topical delivery of lipophilic medicines in the future [81, 82].

Nanoemulgel has been discovered to be an excellent vehicle for the delivery of hydrophobic drugs. It's a potent alternative delivery method in the treatment of numerous illnesses, with high drug loading due to increased solubilizing effectiveness, enhanced bioavailability due to better permeability, and the capacity to modulate drug release. The use of nanoemulgel preparation in the treatment of acne, pimples, psoriasis, fungal infection, osteoarthritis, and rheumatoid arthritis inflammation has been demonstrated to be much more effective [83]. It can be used for ophthalmic, vaginal, dental, and nose-to-brain medication administration for the treatment of a variety of local and systemic diseases such as alopecia, periodontitis, and Parkinson's disease, in addition to transdermal use. In the cosmetics business, nanoemulgel has been used as a UV absorber nanoemulgel to protect skin from sunburn. The nanoemulgel technology has remarkable potential to treat a wide range of local and systemic illnesses. Some preparations are currently on the market, while others require more clinical testing before being released [84, 85-105].

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Conclusion

Topical Nanoemulgels have shown to be a more advantageous choice for a reliable and practical drug delivery mechanism. In comparison to previous formulations, the gel-like and non-greasy qualities increase patient compliance and the absence of oil as a basis improves drug release. With enhanced Spread ability, problems with typical emulsions such as creaming and phase separation are eliminated based on formulations of nanoemulsion-gel may offer a better and more dependable approach for the administration of hydrophobic medications. Many of the drugs used to treat skin infections are hydrophobic in nature. These drugs can be effectively delivered as Nanoemulgels by first being integrated into the oil phase of the nanoemulsion and then being combined with the gel basis. Despite a few obstacles, nanoemulgel has a good chance of being the main topical delivery system for lipophilic medicines in the future. It offers a variety of delivery options for topical medications used to treat a wide range of ailments, including the ability to adjust drug release as well as high drug loading owing to improved solubilizing efficiency. In addition to the transdermal application, it may be utilized for the ocular, vaginal, dental, and nose-to-brain delivery of medicine for the treatment of several local and systemic disorders such as alopecia, periodontitis, and Parkinson's disease.

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