Chapter

Nanoemulgel: For Promising Topical and Systemic Delivery

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Abstract

Nanoemulgel delivery system is a fusion of two different delivery systems, wherein the physical state of drug containing nanoemulsion is changed by adding it to the gel matrix, thus enabling more lipophilic drugs to be used in treatment therapies. It solves the major issues such as limiting use of lipophilic drugs, poor oral bioavailability, and unpredictable pharmacokinetic and absorption variations. Simultaneously, its nongreasy nature and easily spreading ability support the patient compliance. Nanoemulgel can be widely used in the treatment of acne, pimple, psoriasis, fungal infection, and inflammation cause by osteoarthritis and rheumatoid arthritis. The delivery of drug via ocular, vaginal, dental, and nose to brain routes for the treatment of diverse local and systemic ailments for instance alopecia, periodontitis, and Parkinson's are possible. In the cosmetic industries, UV absorber nanoemulgel protected skin from sunburn.

Keywords: nanoemulgel, lipophilic, bioavailability, permeability

1. Introduction

Extensive research in the chemical synthetic approaches has led to a huge increment in the poorly water-soluble drug's development [1]. In the present scenario, statistical reports suggest that there are approximately 70% of poor water-soluble new chemical entities (NCEs) [2]. These newly developed drugs possess lipophilic characteristic and are challenging to deliver through the oral route. They have poor oral bioavailability, show variation in intra- as well as intersubject pharmacokinetics, have poor dose proportionality, and have erratic absorption [3]. Researchers have made many strategies to overcome the limitation of poor solubility and bioavailability. Different delivery system formulation development and chemical and/or physical modification of drug moiety can be used to solve the poor solubility issue of drugs. Though there are many drug delivery system approaches, lipid-based drug delivery system has gained much interest in lipophilic drug delivery. It includes macroemulsion, nanoemulsion, niosomes, self-emulsifying formulation, liposomes, solid-lipid nanoparticle, etc. Among all these formulation approaches, emulsion-based preparation can be considered an industrially feasible approach

to overcome the limitation of poor bioavailability [4]. Nanoemulsion is capable of improving the topical drug absorption thereby increasing the bioavailability and permeability of lipophilic drug; thus, it can be a good alternative option for drug delivery [5]. Nanoemulsion is further incorporated into gel matrix to prepare nanoemulgel which has even better permeation and stability. So far, there is no review article reported on the promising future of nanoemulgel applications as a delivery system in the treatment of various diseases. This article is a complete package of nanoemulgel comprising information of potent selected formulation component, formulation procedure, advantages over other delivery system, and widespread possible application of nanoemulgel in the treatment therapy. In this article, we have mentioned only reported applications, and there are many to still go in the upcoming future.

Though oral route offers better patient compliance, it has various limitations like gastric irritation, unavoidable side effects, systemic toxicity, and hepatic first-pass metabolism [6]. To avoid all these issues, a nonirritating, non-painful, and a noninvasive topical drug delivery system can be a suitable alternative. It has several advantages over oral route such as targeted site-specific delivery of drug with least systemic toxicity, no gastric irritation, first-pass metabolism bypass, and improved bioavailability of a drug [7, 8]. Apart from many advantages, traditional topical formulations, namely lotions, creams, and ointments suffer from sticky nature, stability issue, low spreadability, etc. which affect the patient's compliance. Whereas, modern transdermal preparations like transparent gel, nanogel, and (micro/nano) emulgel not only have shown improved patient compliance but also improves the formulation efficacy, stability, and safety. Several studies have reported that topical drug delivery system improves the bioavailability of the drug [9, 10]. Bioavailability of lacidipine given through transdermal route was found to be increased by 3.5-fold than the oral route. It may be due to the avoidance of the first-pass metabolism of the drug [9]. In another study conducted by Bhaskar and team, it was found that the topical nanoemulsion of flurbiprofen exhibits 4.4 times more bioavailability than oral delivery [10]. Thus, the bioavailability of a lipophilic drug can be enhanced by the topical drug delivery system. Topical delivery not only reduces the drug metabolism but also improves the permeation across the skin by maintaining longer steady-state delivery of the drug [9].

2. Emulsion-based nano-carrier in topical application

Delivery of a lipophilic drug is a big obstacle for the conventional transdermal delivery system due to low therapeutic potential and poor skin permeability capability. Researches propose that nanoscale-sized transdermal preparation can increase the drug permeability by disrupting the skin bilayer of lipid [11] and extending the drug retention time at the site of action [12, 13]. Nanoemulsion can be a promising carrier delivery of hydrophobic drug, since it has greater thermodynamic stability and higher capability of drug solubilization over emulsion and other dispersion systems. It also has longer shelf life and requires a small amount of external energy for manufacturing [14]. Nanoemulsion is a dispersed system which consists of nanoscale-sized (20–200 nm diameter) droplets solvent composed of an oil phase and water phase and stabilized by the suitable surfactant. Drug is entrapped in the core which is surrounded by emulsifier layer as shown in **Figure 1**. Generally, permeation enhancers are not required when nanoemulsion is used as a carrier for delivery of the lipophilic

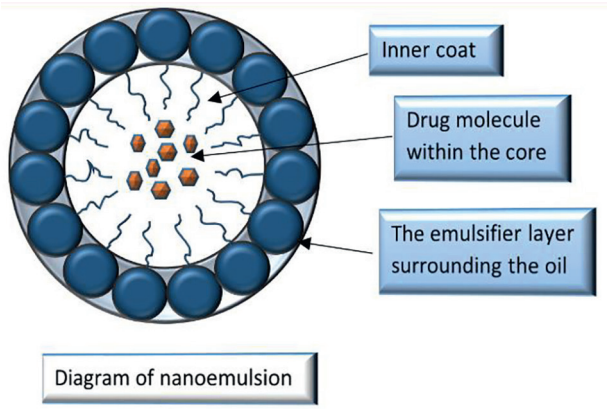

Figure 1.
Structure of nanoemulsion.

drug [15]. It has less tendency of phase separation than other ordinary emulsions which makes it more stable [16]. Different studies have reported better permeation of drug into the skin through nanoemulsion delivery system than conventional ointment [17], cream [18], gel [19], and emulsion [20]. Depending on the type of nanoemulsion, viz. oil-in-water or water-in-oil, it can solubilize both hydrophobic and hydrophilic drug in its structure [21].

In spite of lots of advantages, nanoemulsion suffers from low spreadability, low viscosity, and poor skin retention issue [22]. Due to these, the clinical application of topical nanoemulsion is restrained [23]. Researchers converted nanoemulsion into nanoemulgel by incorporating it into the gel matrix and solved this problem.

2.1 Nanoemulgel as topical drug delivery system

Nanoemulgel is the fusion of two systems: nanoemulsion system and hydrogel system. Both the systems have some limitations, such as nanoemulsion that suffers low spreadability and poor retention, whereas hydrogels are incapable of incorporating lipophilic molecule [24, 25]. Nanoemulgel has different types of polymeric materials, surfactants, and fatty substances of natural, synthetic, and semisynthetic nature with a droplet size range from 5 to 500 nm [26]. Nanoemulgel has the capability to overcome the limitation of both the systems. The lipophilic drug is dissolved in the oil phase of nanoemulsion which is then added to hydrogel base to form nanoemulgel [27] which enables the incorporation of lipophilic drug into a hydrogel, simultaneously improving the viscosity of nanoemulsion. In transdermal drug delivery, nanoemulgel acts as a reservoir of the drug. The drug is first to release from the inner phase to the outer phase and from there into the skin surface. When applied on skin, oily droplets were released from the gel matrix of nanoemulgel, which then penetrate deep into the skin via stratum corneum, and there they directly deliver the drug moiety [23]. The mechanism of drug release depends on the crosslink density as well as the composition of a network of polymer chains [28].

2.2 Potent components for nanoemulgel formulation

Nanoemulgel is a fusion of two separate systems, viz. the nanoemulsion and a gel system. Nanoemulsion acting as a vehicle for drug delivery can be either water-in-oil

or oil-in-water type. In both cases, it consists of an oil phase, aqueous phase, surfactant, and sometime cosurfactant. Overview of commonly used major components of nanoemulgel formulation has been apprehended in this section (**Figure 2**).

2.2.1 Oils

Oil is an important component of the nanoemulgel formulation that should be selected appropriately based on the solubility, stability, permeability, and viscosity of the formulation. Vegetable oils/edible oils are not frequently used in nanoemulgel formulation, since they had shown poor emulsification properties and drug solubility [29–31]. Thus, chemically modified oils such as mono or diglyceride or medium-chain triglycerides are commonly used as an oil phase in the nanoemulgel formulation for lipophilic drug delivery [15]. A medium-chain triglyceride, Labrafac, has been used by Syamala and his group to prepare butenafine nanoemulgel [32]. Capryol 90 is another example used as an oil phase in the preparation of nanoemulsion, which has shown better stability of the nanoemulsion formulation of leflunomide and paclitaxel [3, 33].

On the other hand, scientists are focusing on utilizing the supplementary benefit of natural oil in therapeutic effect. Antimicrobial activity of tea tree oil was combined with an antifungal agent itraconazole for a synergistic effect of nanoemulgel preparation against vaginal candidiasis [34]. Another nanoemulgel of curcumin has been reported by Jeengar and team with emu oil. Emu oil obtained from emu bird has analgesic, antipruritic, anesthetic, antioxidants, and anti-inflammatory properties, and it has shown the improvement in permeability of drug in the treatment of joint synovial [35]. Various oils used by different researchers in nanoemulgel preparation are listed in **Table 1**.

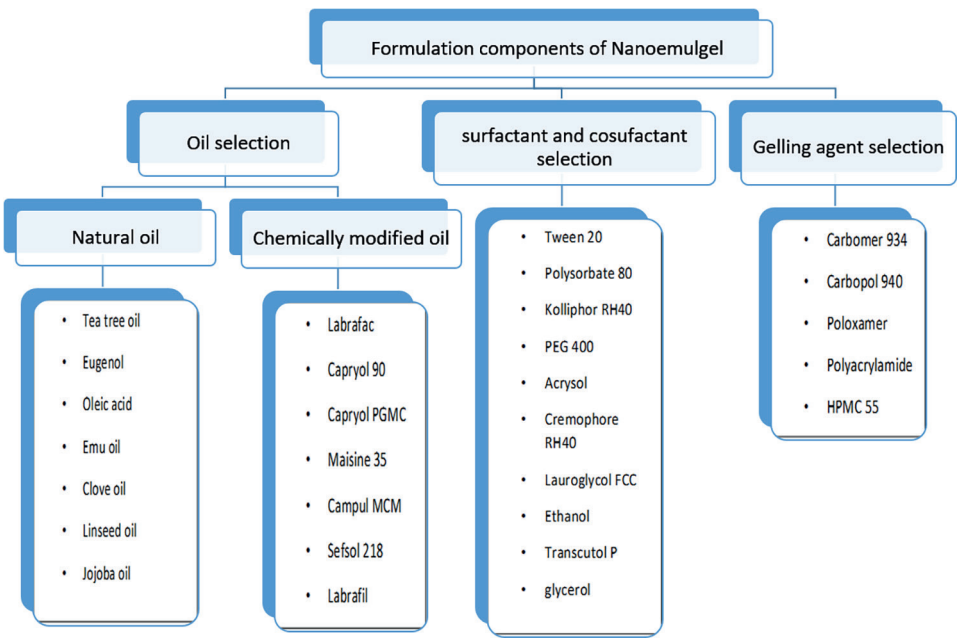

Figure 2.
Potent formulation component of nanoemulgel.

Active Drug	**Oil**	**Surfactant**	**Cosurfactant**	**Gelling agents**	**Reference**
Thymol	Caprylic acid, isopropyl myristate, and tea tree oil	Tween 20	PEG 400	Carbopol 940	[36]
Curcumin	Emu oil	Cremophor RH40	Labrafil M2125CS	Carbopol	[35]
Flurbiprofen	Linseed oil, isopropyl myristate and triacetin	Tween 80	Ethanol + PEG 400 + propylene glycol	Carbopol 940	[37]
Ketoconazole	Labrafac™ LipophileWL1349	Tween 80	PEG 400	Carbopol	[38]
Cyclosporine	Oleic acid	Tween 80	Transcutol P	Guar gum	[24]
Ferulic acid	Isosteryl isostearate	Labrasol	Plurol isostearique	Carbopol 940	[39]
Ropinirole	Capryol 90	Tween 20	Carbitol	Carbopol 934	[15]
Butenafine	Labrafac	Cremophore RH40	Ethanol	Carbopol	[32]
Ketoprofen	Oleic acid	Tween 80	Transcutol P	Carbopol 940	[40]
Piroxicam	Oleic acid	Tween 80	Ethanol	Carbopol 934	[41]
Amphotericin B	Sefsol-218	Tween 80	Transcutol-P	Carbopol	[42]
Aceclofenac and capsaicin	Olive oil and miglyol	Polysorbate 80	Transcutol	Propylene glycol	[43]
Terbinafine hydrochloride	Liquid paraffin	Polysorbate 80	Glycerin	Carbopol 940	[44]
Glibenclamide	Labrafac and triacetin	Tween 80	Diethylene glycol monorthyl ether	Carbopol 934	[45]
Carvedilol	Oleic acid and IPM	Tween 20	Carbitol	Carbopol 934	[46]
Telmisartan	Labrafil	Acrysol	Carbitol	Carbopol	[47]

Table 1.
Various components used in different nanoemulgel formulations.

2.2.2 Surfactant and cosurfactant

Surfactant reduces the interfacial tension between the mixtures of two immiscible liquids and changes the dispersion entropy, thus stabilizing thermodynamically unstable emulsion system. Selection of appropriate surfactant for nanoemulgel is based on the safety, stability, high drug loading capacity as well as good emulsification properties [31]. Also, the surfactant should be selected based on the solubility with oil like Tween 20 that was used on the basis of solubility of Capryol 90 and oleic acid [15, 40].

Cosurfactant may combine with surfactant and help in the emulsification process by disrupting the interfacial film. It may also help in solubilization of oil [15].

Depending on the physicochemical properties, most frequently used cosurfactants in nanoemulsion and nanoemulgel preparation are propylene glycol, PEG 400, ethanol, transcutol P, carbitol, etc. [35, 40]. Studies suggest that with the increase in the concentration of cosurfactant, the area of nanoemulsion in phase diagram decreases [48, 49].

2.2.3 Aqueous solvents

Aqueous solvents act as the aqueous phase in emulsion preparation. Worldwide widely used aqueous solvents are ethanol and water.

2.2.4 Gelling agents

Carbapol 934, Carbapol 940, and hydroxy propyl methyl cellulose (HPMC) are widely used gelling agent for nanoemulgel. They increased the thickness of the formulation and may interact with the surfactant to modify the viscosity of the formulation [41]. It is added to the nanoemulsion preparation to change the physical state of nanoemulsion formulation from liquid to gel, thus solving the problem of low spreadability, low viscosity, and poor skin retention issue of nanoemulsion.

2.2.5 Miscellaneous components

To protect the formulation from microbial attack and increase the shelf life of formulation, preservatives are added in the preparation. Most commonly used preservatives are methylparaben, benzoic acid, propylparaben, benzalkonium chloride, etc. Antioxidants like butylate hydroxyl toluene, butylate hydroxyl anisole, and ascorbyl palmitate are used to prevent oxidative degradation of formulation components and to prevent loss of moisture, glycerin and propylene glycol are used as humectants [50]. Hence, the stability of the nanoemulsion and nanoemulgel preparation increased.

2.3 Preparation of nanoemulgel formulation

Two steps are involved in the manufacturing of nanoemulgel. The first step is nanoemulsion formulation which is then incorporated into a gelling agent in the second step to form nanoemulgel. **Figure 3** schematically represents the procedure of preparation of nanoemulgel.

Methods used for the preparation of nanoemulsion can be high-energy emulsification methods or low-energy emulsification methods [49, 51]. In high-energy emulsification methods, external energy is applied which rupture the oil phase to form nanosized droplets in the aqueous phase. It includes ultrasonic emulsification and high-pressure homogenization. Solvent displacement method, phase inversion composition method, and phase inversion temperature method are low-energy emulsification in which low energy is required for prepared nanoemulsion [21].

2.3.1 Procedure for nanoemulsion preparation

The selected surfactant is dissolved in either the aqueous phase or the oil phase. Based on the solubility, the drug is then added and solubilized in the oil phase or

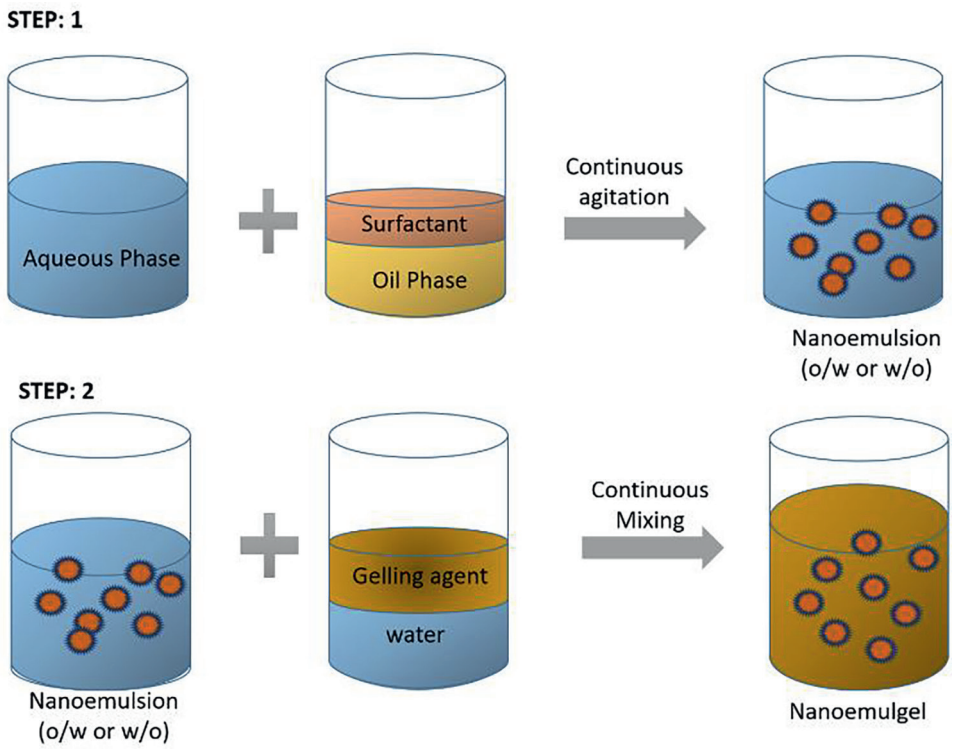

Figure 3.
Procedure of nanoemulgel preparation.

aqueous phase followed by heating. Then one phase is gradually added into another with continuous stirring till the temperature of the mixture reaches to room temperature.

2.3.2 Procedure for nanoemulgel preparation

The appropriate gelling agent is dissolved in distilled water with continuous stirring to prepare gel base. The pH of prepared gel is adjusted, then the nanoemulsion system is incorporated slowly into the prepared gel at a particular ratio with continuous stirring to get nanoemulgel preparation.

2.4 Advantages of nanoemulgel

Nanoemulgel preparations have various advantages over other topical as well as conventional preparation. Some of the advantages are listed as follows (**Figure 4**).

2.4.1 Incorporation of lipophilic drug

The lipophilic drug moieties base show improper drug release mechanism in the gel due to its insolubility in aqueous base. Fusion of the hydrogel system with emulsion system enables the incorporation of lipophilic drug into the aqueous base, thus improving the release mechanism of the drug. Lipophilic drug is dissolved in the oil phase of emulsion which is then incorporated into hydrogel system [52].

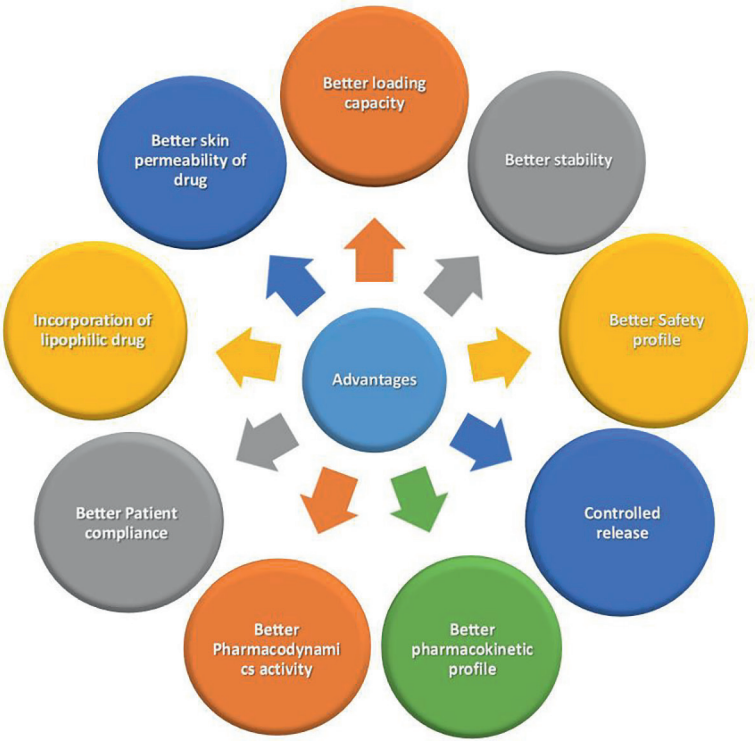

Figure 4.
Advantages of nanoemulgel preparation.

2.4.2 Better loading capacity

Better loading capacity has been observed by nanoemulgel as compared to than other novel drug delivery systems. Due to its nanoscale size, it has a larger surface area and better entrapment efficiency which enable it to load more amount of drugs in its network-like system [52].

2.4.3 Better stability

Nanoemulgel system is more stable than other transdermal drug delivery system, because it decreases the interfacial as well as the surface tension of the formulation, which make it superior from a conventional transdermal delivery system [53].

2.4.4 Controlled release

Nanoemulgel acts as a drug reservoir and has shown prolong residence time leading to sustain release of the drug. Thus, it is beneficial for the drugs having shorter half-life [52].

2.4.5 Better pharmacokinetic profile

Nanoemulgel formulation gives higher T_{max} and peak plasma concentration of lipophilic drugs than the conventional gel as well as oral formulation. Thereby,

nanoemulgel preparation improves the bioavailability of lipophilic drug many folds than the other lipophilic drug formulations [53].

2.4.6 Better pharmacodynamics activity

Improved permeability of nanoemulgel preparation through the skin enables more drugs to penetrate into the site of action. This enhances the pharmacodynamic activity of the drug increasing its therapeutic efficacy.

2.4.7 Better patient compliance

Major issue with the transdermal preparation is the sticky nature and low spreading coefficient which require rubbing mechanism. Nanoemulgel being nonsticky and easily spreadable preparation results in better patient compliance than other transdermal preparations [28].

2.4.8 Enhanced drug permeability through skin

Nanoemulgel has shown significant enhancement in the permeability of the drug through skin than other formulation since from nanoemulgel preparation, the drug can permeate the skin layer through both paracellular and transcellular route, whereas, in nanoemulsion, only transcellular permeation route is seen [53]. Comparison of cumulative drug permeability through the skin from different formulation is represented in **Figure 5** [24].

2.4.9 Better safety profile

Nanoemulgel bypasses the first-pass metabolism, thus solving one of the major problems of drug, that is, the oral side effect. It does not cause skin irritation or any toxicity on the application [53].

3. Health claim

A significant number of the nanoemulgel formulation of drugs has been carried out and reported by various researchers to show its application as a more potent and effective drug delivery system. Some of the studies have shown outstanding result over the conventional oral drug delivery system, suggesting a promising future of nanoemulgel application.

3.1 Acne and pimple

Thymol nanoemulgel formulation for acne vulgaris, a common chronic skin disease, was prepared by Ahmad and team. The preparation showed better efficacy [36].

3.2 Psoriasis

It is the skin condition in which skin cells build up and form itchy, dry patches, and scales. A nanoemulgel formulation of leflunomide by Pund and team showed considerably higher anti-psoriatic and anti-melanoma activity in human keratinocyte

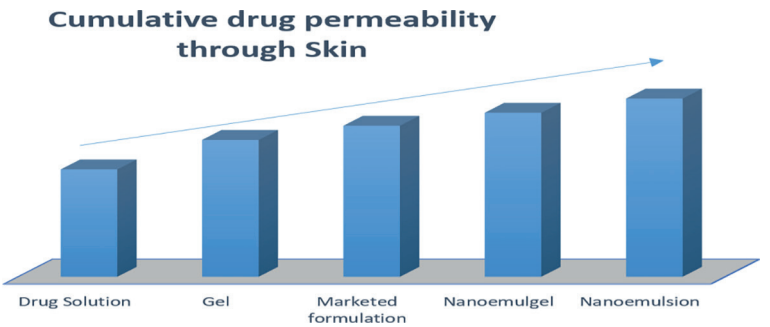

Figure 5.
Comparative representation of cumulative cyclosporine permeated through the skin of albino rat from different formulations. Regenerated from [24].

cell line due to improved permeability of drug. Amount of drug deposited in the skin after 12 hours by nanoemulgel was found to be sixfold more than ordinary gel [33]. In another study by Somagoni and team, nanoemulgel showed 3.22- and 2.01-fold more reduction of ear swelling than drug solution and marketed product, respectively, in psoriatic-like model [43].

3.3 Fungal infection

High skin permeability of nanoemulgel has made it a better alternative for the faster treatment of fungal infection. Syamala has reported that it took only 12 days to Butenafine nanoemulgel to cure fungus-infected rat skin, whereas cream took 16 days [32]. Nanoemulgel has also shown a notable increase in antifungal activity of the drug. Higher area of inhibition zone was observed with Ketoconazole nanoemulgel than drug solution when incubated for 48 hours [38]. Nanoemulgel of Amphotericin B can overcome formulation limitation of Amphotericin B making it a better alternative to painful intravenous administration. It could be used as a stable, effective, and safe carrier for sustained and enhanced localized delivery of Amphotericin B against fungal infection [42].

3.4 Inflammation and pain due to osteoarthritis and rheumatic arthritis

Nanoemulgel is a better alternative for poor water-soluble anti-inflammatory drugs, and it also bypasses the related oral side effects of drugs like gastrointestinal irritation, renal, and cardiovascular problems, etc. Many researchers have reported remarkably higher activity of anti-inflammatory drugs in nanoemulgel formulation than other drug carrier system [35, 40, 54–57]. Nanoemulgel of ketoprofen, an extensively utilized non steroidal anti inflammatory drugs (NSAIDs) for rheumatoid arthritis and osteoarthritis treatment, was developed by Arora and team. Along with enhancing the skin permeability and solubility of ketoprofen, it also bypasses the problems related to chronic oral delivery of ketoprofen. Comparison of the optimized formulation with the marketed product and drug solution showed 1.5- and 2-fold higher permeability, respectively [40].

Another common drug used in osteoarthritis and rheumatoid arthritis is piroxicam. It is also used in the treatment of the musculoskeletal and joint disorder. It also possesses the problem of poor solubility along with undesirable side effect on stomach and kidney. Dhawan and team reported that piroxicam nanoemulgel can be used as a feasible alternative [41].

Apart from these, attempt has also made to establish the stability, efficacy, and safety of certain drugs with anti-inflammatory activity which has poor solubility and permeability profile and/or oral side effect like curcumin [35], Swietenia macrophylla [27], Lornoxicam [54], Nimesulide [55], mangosteen [56], and diclofenac diethylamine [57]. **Figure 6** represents the comparison of anti-inflammatory effect of flurbiprofen nanoemulgel by Radhika and Guruprasad with marketed preparation [37].

3.5 Periodontal disease

Dental nanoemulgel preparation is intended for periodontal delivery of drug to treat chronic bacterial infection of the gum and bone supporting teeth. Periodontal disease causes inflammation of gum forming pockets which may lead to gum tissue and bone damage. Srivastava and team formulated syringeable ketoprofen nanoemulgel for intra-pocket delivery and found satisfied pharmaceutical characterization offering sustained release of ketoprofen into the pocket. Significant reduction was observed in alveolar bone loss, gingival index, and tooth motility by ketoprofen nanoemulgel due to decreased cytokine levels [58]. Whereas, the study of Nayak and team suggested that controlled released delivery of Quercetin nanoemulgel can be used successfully in periodontitis [59].

3.6 Corneal fungus infection

Ocular nanoemulgel can be better alternative drug delivery system to the conventional eye drops to cure corneal fungal infection. Permeation of fluconazole from nanoemulgel preparation was found four times that of commercial fluconazole eye drop due to high permeation, sustained release of drug, and prolongation in the precorneal residence time. Prolong release was achieved by in situ gelation of Gellan gum due to its crosslinking with tear fluid. Fluconazole nanoemulgel formulation showed no sign of any ocular irritation and tissue damage [60]. Whereas, Tayel used a rabbit model to successfully control the release rate of terbinafine-HCL nanoemulgel, which can be an effective alternative to conventional eye drop for ocular fungal infection, into the rabbit aqueous humor [61].

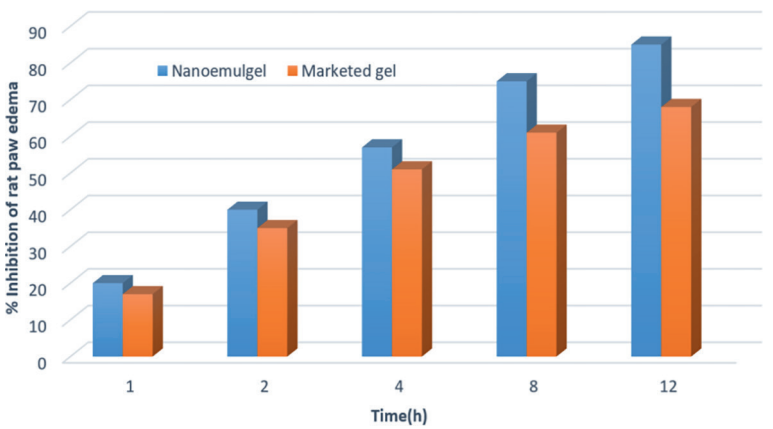

Figure 6.
Graphical representation of improvement in anti-inflammatory effect of nanoemulgel of flurbiprofen. Regenerated from [56].

3.7 Vaginal candidiasis

A thermo-sensitive nanoemulgel of itraconazole with tea tree oil was prepared for patients suffering from periodic vaginal candidiasis. Antimicrobial activity of itraconazole and tea tree oil combined to give synergistic effect covering cure for wide range microbial infection [34].

3.8 Alopecia

Minoxidil is the commonly used drug for the treatment of hair loss also known as alopecia. Nanoemulgel is capable of increasing solubility and permeability of drug through the skin; hence, nanoemulgel preparation of minoxidil will be more effective and safer than conventional preparation present in the market for the treatment of alopecia areata [62].

3.9 Insomnia

Nasal nanoemulgel of zaleplon was formulated by Hosny and Banjar for the treatment of insomnia. The main objective was to solve the problem with marketed zaleplon tablet. Zaleplon tablet suffers from poor bioavailability due to extensive first-pass metabolism and delayed onset of action due to poor aqueous solubility. Nasal zaleplon nanoemulgel showed eight times more bioavailability than the marketed zaleplon tablet [63].

3.10 Parkinson's disease

Selegiline HCL-loaded nanoemulgel possess better sustains release effect of the drug and higher bioavailability than the conventional gel and a marketed tablet. Bioavailability was reported to be 5.53 and 6.56 times that of normal gel and tablet [64].

Product brand name	Active pharmaceutical ingredient(s)	Manufacturers	Application
Benzolait AZ emulgel	Benzoylperoxide	Roydermal	Pimple and blacks on skin
Coolnac Gel emulgel 1%	Diclofenac diethyl ammonium	Chumchon	Inflammation and pain due to trauma
Diclobar emulgel	Diclofenac diethyl amine	Barakat Pharma	Inflammation due to trauma and rheumatic diseases
Levorage emulgel	Liquorice, hibiscus, and natural extract	THD Ltd	Anal fissures
Meloxic emulgel	Meloxicum	Laboratories Provet	Musculoskeletal pain management and inflammation
Miconaz-H-emulgel	Miconazole nitrate, hydrocortisone	Medical Union Pharmaceutics	Skin infection by candida
Reumadep emulgel	Ashwagandha, myrrh, arnica, rosemary, mint, and cloves	Erbozeta	Inflammation and pain due to trauma
Voltaren emulgel	Diclofenac diethyl ammonium	Novartis Pharma	Osteoarthritis joint pain
Voveron emulgel	Diclofenac diethyl amine	Novartis Pharma	Osteoarthritis joint pain

Table 2.
Available marketed emulgel preparations.

Microemulgel loaded with rotigotine has also shown significantly higher bioavailability than marketed patch of rotigotine in the treatment of Parkinson's disease [65].

3.11 Cosmetics

Use of nanotechnology in cosmetics is very common. Fullerenes, solid-lipid nanoparticle, liposomes, nanosomes, etc., are already nourishing in cosmetic industries. Ferulic acid nanoemulgel was developed by Harwansh and team to protect the skin damage from harmful UV radiation. Ferulic acid strongly absorbs the UV radiation. Its incorporation into nanoemulgel system made it effective for more than 4 hours on the UV-exposed skin [39].

Currently available marketed emulgel products for the treatment of acne and pimple, inflammation, and pain caused by osteoarthritis and rheumatoid arthritis and skin infection have been listed in **Table 2**.

4. Mechanism involved to enhance permeability and bioavailability from nanoemulgel preparations

The skin permeability as well as bioavailability of nanoemulgel may be enhanced by various mechanisms. Some of the studied mechanisms with types of nanoemulgel are listed in **Table 3**.

Types of nanoemulgel	Mechanism of permeability/bioavailability	References
Conjugate of curcumin	Induced apoptosis in cancer cells, suppressing the expression of NF-κB, TNF-α, and COX-2 cellular targets	[66]
Clove essential oil	Dispersion of the nanoemulsion in the polymeric matrices of the prepared nanoemulgel	[67]
Snakehead fish (pphiocephalus striatus)	Ex vivo transdermal permeation value	[68]
Methotrexate	Change in temperature experienced by the nanogel	[69]
Terbinafine	Ex vivo drug permeation and in vivo antifungal activity	[70]
Paclitaxel	Nanogel exerts high cytotoxicity to cancer cells and reverses multidrug resistance effectively	[71]
Diphenhydramine	First-order kinetics and Fickian diffusion	[72]
Raloxifene hydrochloride	Ex vivo permeation, histopathology, SEM, DSC, and CLSM studies	[73]
Desonide	DES, Franz diffusion cell system, CLSM	[74]
Ketoconazole	Ex vivo permeation	[75]
Telmisartan	Ex vivo permeation, first-order reaction, and Higuchi model with non-Fickian diffusion	[76]
Ibuprofen	Drug diffusion, however, drug partition, and matrix erosion	[77]
Piroxicam	Franz diffusion cell	[78]

NF: nuclear factor, TNF: tumor necrosis factor, SEM: scanning electron microscopy, DSC: differential scan calorimetry, DES: dielectric spectroscopy, CLSM: confocal laser scanning microscopy.

Table 3.
Mechanism involved in enhancing permeability and bioavailability of some nanoemulgel preparations.

5. Conclusion

Nanoemulgel has been found to be extraordinarily good vehicle system for hydrophobic drug delivery. High drug loading due to better solubilizing efficacy, improved bioavailability due to better permeability, and capability to control the release of drug make it a potent alternative delivery system in the treatment of various diseases. Application of nanoemulgel preparation in the treatment of acne, pimple, psoriasis, fungal infection, and inflammation due to osteoarthritis as well as rheumatoid arthritis has shown significantly higher efficacy. Besides transdermal application, it can also be applied for ocular, vaginal, dental, and nose to brain delivery of drug for the treatment of diverse local and systemic ailments such as alopecia, periodontitis, and Parkinson's disease. Nanoemulgel has also shown its application in the cosmetic industries as a UV absorber nanoemulgel to protect skin from sunburn. Precisely, the nanoemulgel system has a marvelous ability to be applied in various local and systemic ailments. Some preparations are already present in the market, whereas others need a further clinical study to launch the product in the market.

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