REVIEW ARTICLE

Nanoemulgels: A new approach for the treatment of skin-related disorders

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ABSTRACT

Skin-related disorders like psoriasis, dermatitis, acne, and wounds affect a major sector of the global population. Conventional treatment modalities exhibit limitations encompassing systemic adverse effects, suboptimal skin permeability, and variable drug release kinetics. Nanoemulsion-based hydrogels, also known as nanoemulgels, have emerged as a promising approach for topical and transdermal drug delivery, particularly in treating skin disorders. These have the advantages of nanoemulsions and hydrogels, offering enhanced therapeutic efficacy. Further, nanoemulgels can facilitate controlled and sustained drug delivery, reducing the frequency of application and improving patient compliance. These nanoemulgels hold significant prospects in topical and transdermal applications, particularly in delivering therapeutic cargo in diseases such as mycoses, atopic dermatitis, and psoriasis. This review will outline the functions of nanoemulgels, the building blocks of nanoemulgels, their formulation techniques, evaluation parameters, and their pharmacological applications. Further, an overview of the current state of research in the field of nanoemulgels, future directions, and challenges associated with nanoemulgels was also provided.

Keywords: Nanoemulgels, Skin disorders, Topical, Transdermal.

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INTRODUCTION

Skin-related disorders like psoriasis, dermatitis, acne, and wounds affect a major sector of the global population. These disorders can cause psychological stress, discomfort, and a reduced life quality. Conventional treatment modalities, such as oral medications and topical formulations, frequently exhibit limitations encompassing systemic adverse effects, suboptimal skin permeability, and variable drug release kinetics. As a result, there is an emerging demand for more efficacious and targeted therapeutic approaches. Nanoemulsion-based hydrogels, also known as nanoemulgels, have emerged as a promising approach for topical and transdermal drug delivery, particularly in treating skin disorders.[1] These innovative formulations combine the advantages of nanoemulsions and hydrogels, offering enhanced therapeutic efficacy and improved patient compliance. Nanoemulsions are colloidal dispersions of oil in water or water in oil and stabilized by surfactants and droplet sizes generally ranging from 20nm to 200 nm. These nanoemulsions, when encapsulated within a hydrogel matrix, provide a combined advantage of both a hydrogel and nanoemulsion system. Nanoemulsion improves drug dissolution and permeation into the skin, hydrogel forms a good base for topical application, and the rate of diffusion through the skin is prolonged.[2] The advantages of using nanoemulsion for hydrogels on topical and transdermal utilization of drugs are primarily the penetration enhancement with small droplet sizes, which have a large droplet surface, favoring the stratum corneum drug absorption. Secondly, these systems can dissolve both hydrophilic and lipophilic drugs, which enhances the scope for the number of active pharmaceutical ingredients that can be included in the system.[3] Further, nanoemulgels can facilitate controlled as well as sustained drug delivery, reducing the frequency of application and improving patient compliance. These nanoemulgels hold significant prospects in topical and transdermal applications, particularly in delivering therapeutic cargo in diseases such as mycoses, atopic dermatitis, and psoriasis.[4] This review will outline the functions of nanoemulgels, the building blocks of nanoemulgels, their formulation techniques, evaluation parameters, and their pharmacological applications. Further, an overview of the current state of research in the field of nanoemulgels, future directions, and challenges associated with nanoemulgels was also provided.

Function of Nanoemulgels in Topical Drug Delivery Systems

Nanoemulgels combine the unique properties of both nanoemulsions and hydrogels, making them to be functionally more advantageous. The globule size of nanoemulsions makes them have improved skin permeability and bioavailability,

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whereas the viscosity hydrogel component plays a major role in the maintenance of the formulation in the application site. The gel matrix of the hydrogels acts as a reservoir, maintaining the required concentrations at the site of delivery and releasing the drug gradually over a period. This reduces the frequency of application. Moreover, the water content of the hydrogels improves the water content of the skin and forms occlusive barriers, reducing transepidermal water loss (TEWL) and improving skin hydration. This leads to the softening of the stratum corneum layer and enhanced drug permeability. Further, the hydrogel component makes them nongreasy, more biocompatible, and easier to apply, thus improving patient adherence to the treatment regimen. Therefore, by integrating the benefits of nanoemulsions and hydrogels, nanoemulgels make an effective approach as a topical/transdermal drug delivery system, addressing the limitations associated with traditional formulations and improving therapeutic outcomes.[4]

Building Blocks of Nanoemulgels

Nanoemulgels consist of various ingredients, which include vehicles, surfactants, co-surfactants, gelling agents, emulsifying agents, permeation enhancers, humectants, and preservatives.[5,6]

Vehicles

The vehicles in nanoemulgels are typically divided into the oil phase and aqueous phase, each playing a crucial role in the formulation.

Oil phase

The oil phase in nanoemulgels helps dissolve lipophilic drugs and forms the dispersed phase of the nanoemulsion. It also contributes to the texture and occlusive properties of the final product. The selection of an oil for nanoemulsion formulation is based on key factors such as permeability, solubility, and viscosity. In some cases, particularly with natural oils, the medicinal activity of the oil also influences the choice. Studies have shown that vegetable oils generally possess weak emulsifying properties due to the presence of long-chain fatty acids. This limitation is less pronounced in oils with lower hydrophobicity. Therefore, careful selection of the oil phase is a critical step in the formulation of nanoemulgels.[7,8]

Tea tree oil, known for its broad-spectrum antimicrobial activity, has been used by Mondello *et al.* and Mirza *et al.* in itraconazole nanoemulgels, demonstrating synergistic effects against vaginal candidiasis. However, its component 1,8-cineole can cause skin irritation, although formulations with up to 25% concentration are generally safe. Capmul MCM, a medium-chain triglyceride with high solubilizing potential and aqueous solubility, was employed by Pathak *et al.* for ocular nanoemulgels due to its non-irritant properties. Oleic acid, another popular oil phase, enhances skin permeability and stability, as seen in formulations with ketoprofen and diclofenac diethylamine. Eugenol, with its anti-inflammatory and antibacterial properties, was used by Srivastava *et al.* in ketoconazole nanoemulgels, showing efficacy against *E. coli* and *Staphylococcus aureus*. Swietenia macrophylla oil,

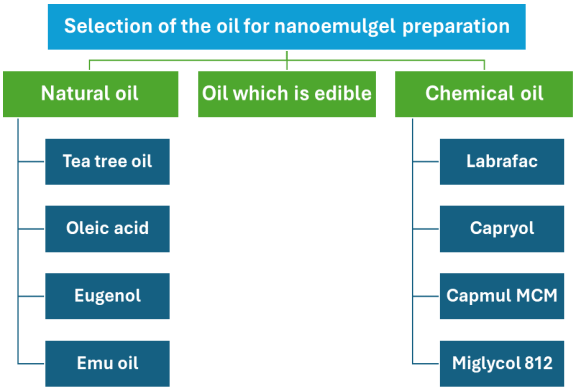

Figure 1: Different types of oil used in the preparation of nanoemulgel

serving both as the oil phase and active ingredient, enhanced its anti-inflammatory properties in nanoemulgel form. Emu oil, utilized by Jeengar *et al.* for curcumin nanoemulgels, offers anti-pruritic, analgesic, and antioxidant benefits, along with enhanced skin permeation. Vegetable oils are less commonly used due to poor solubility and emulsifying properties, whereas chemically modified oils like diglycerides and triglycerides, including Labrafac and Capryol 90, are preferred for delivering lipophilic drugs. Miglyol 812, despite its high molecular weight, provides improved bioavailability and sustained release in ocular nanoemulgels when combined with terbinafine hydrochloride.[9-17]

Aqueous phase

The aqueous phase in nanoemulgel formulations is just as critical as the oil phase, playing a vital role in the solubilization of hydrophilic drugs, the stability of the formulation, and the overall efficacy of the delivery system. Various components are used in the aqueous phase, each contributing to the formulation's properties. The primary component is usually purified water, which serves as a solvent for hydrophilic drugs and other aqueous phase ingredients, maintaining overall hydration and stability. Buffers, such as phosphate-buffered saline (PBS), are often used to maintain the pH of the nanoemulgel, which is essential for drug stability and skin comfort. For example, Pathak *et al.* used PBS to maintain pH stability in their fluconazole nanoemulgel for ocular application, ensuring safety and efficacy.[4,5,18]

Table 1: Different oils used in the formulation of nanoemulgel

S. No	*Drug*	*Oil*	*References*
1	Itraconazole	Tea tree oil	[9]
2	Fluconazole	Capmul MCM	[10]
3	Ketoprofen	Oleic acid	[11]
4	Ketoconazole	Eugenol	[12]
5	Curcumin	Emu oil	[13,14]
6	Ketoprofen	Labrafac	[15]
7	Leflunomide	Capryol 90	[16]
8	Terbinafine hydrochloride	Miglyol 812	[17]

Surfactant

Surfactants play a crucial role in stabilizing nanoemulgels by decreasing interfacial tension and altering dispersion entropy between immiscible liquid mixtures. For nanoemulsion formulations, the primary considerations for surfactants are stability, safety, good emulsification properties, and drug loading capacity. An ideal surfactant should quickly adsorb at the interface of the immiscible phases, reducing interfacial tension and preventing the coalescence of nanodroplets. The selection of surfactants is influenced by several factors, with toxicity being a significant concern, as high surfactant concentrations can cause skin and gastrointestinal irritation. Hence, minimal amounts of surfactant are preferred. The hydrophilic-lipophilic balance (HLB) value is another critical criterion; surfactants for oil-in-water (O/W) nanoemulsions typically have HLB values above 10, while those for water-in-oil (W/O) emulsions have values below 8. Combining surfactants like Tween 20 and Span 20, based on their HLB values, can enhance emulsion stability. Non-ionic surfactants are often chosen due to their compatibility with biological systems and lack of ionic strength changes, whereas ionic surfactants are less favored due to their toxicity. Solubility is another key factor; for instance, Abdelaziz *et al.* used propylene glycol and Tween 20 to enhance indomethacin solubility. Natural surfactants, or biosurfactants, such as those derived from microorganisms, are increasingly used due to their lower toxicity. Examples include rhamnolipids, which McClements and Bai found effective in replacing synthetic surfactants, and cellobioside and alkyl-O-glucoside, used in stable O/W emulsions of heavy Mexican crude oil. These biosurfactants often feature shorter fatty acid tails and polar heads, contributing to their effectiveness in reducing interfacial tension and enhancing formulation stability.[4,5,18]

Cosurfactant

Cosurfactants play a crucial role in nanoemulsions by enhancing the emulsification process initiated by surfactants. The combination of cosurfactant and surfactant disrupts the interfacial film by penetrating the surfactant layer, thereby reducing interfacial tension and aiding in emulsification. Cosurfactants improve oil solubility by altering the curvature of the oil-water interface. Selecting the right cosurfactant involves considering its interaction with the surfactant and its transmittance properties. However, high concentrations of cosurfactants can cause skin irritation, so their amounts need to be carefully controlled. Combining surfactants and cosurfactants can create a broad nanoemulsification region, enhancing the formulation's stability and efficacy. For example, Bali *et al.* prepared two formulations using capryol 90 as the oil phase, labrasol as the surfactant, and Transcutol P as the cosurfactant. They found that while high concentrations of high HLB surfactants facilitated nanoemulsion formation, combining them with cosurfactants reduced nanoemulsion formation. In another formulation, reducing the concentrations of surfactant and cosurfactant led to using a larger amount of surfactant but only a small amount of oil being emulsified. This highlights the importance of balancing surfactant and cosurfactant concentrations for optimal nanoemulsion formulation.[4,5,18]

Table 2: Surfactants and cosurfactants used in the formulation of nanoemulgels

S. No.	*Surfactant*	*Cosurfactant*
1	Labrasol	Plurol isostearique
2	Cremophor RH 40	Labrafil M2125CS
3	Tween 80	Transcutol P
4	Tween 20	Carbitol
5	Polysorbate 80	Ethanol
6	Acrysol	PEG 400

Gelling agents

Nanoemulgels are required to show thixotropic behaviors for ease of application at the site of application, improved skin hydration by retention of moisture, and forming an occlusive barrier over the skin. Gelling agents play an important role in showing this behavior. Further, the concentration, stability, and performance of these gelling agents play a significant role in controlling the release rate of the drug from the nanoemulgel formulations. For instance, the drug release rates of emulgel with HPLC as gelling agents show higher release profiles than those with Carbopol as a gelling agent.[19,20] These gelling agents used in nanoemulgel formulations come from various sources, which include natural, synthetic, and semisynthetic. However, natural gelling agents are more susceptible to microbial contamination and degradation, hence, synthetic and semisynthetic agents are often preferred. Commonly preferred gelling agents in nanoemulgel preparations include hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (CMC), Carbopol 934, Poloxamer 407, Pluronic® F127, Carbopol 940, Pemulen. These agents are selected based on their ability to impart the desired rheological properties and stability to the nanoemulgel formulation.[4,5,18]

Penetration enhancers

Penetration enhancers are mainly used in the transdermal drug delivery system. Permeation or penetration of the drug into the skin depends on the concentration and type of penetration enhancer. Properties of the penetration enhancer which is used should be less toxic, non-irritant, and increased permeability. The use of these agents helps in increasing the absorption of the drug by disturbing the barrier of the skin, changing the drug partition into the skin.[8]

Preservatives

Preservatives play an important role in preventing the formulation from microbial contamination hence increasing the shelf life of the formulation. Preservatives that are mostly used are benzalkonium chloride and methylparaben. Potassium nitrate, calcium sorbate etc.[5]

Table 3: Gelling agents and their role in the preparation of nanoemulgel[16]

S. No.	*Gelling agent*	*API*	*Concentration required (% w/w)*	*Pharmaceutical action*
1	HPMC 2910	Chlorphenesin	2.5%	Resistant to microbial action, stable
2	Carbopol 934	Chlorphenesin	1%	Control release of the drug
3	Sodium CMC	Benzydamine	3–4%	Withstand the autoclaving process hence suitable for sterile gels
4	Carbopol 940	Mefenamic acid	1%	Due to its high viscosity, drug is released in a controlled manner
5	Pluronic® F127	Piroxicam	1–3%	Clear gel is formed and is easily soluble in cold water.
6	Pemulen	Flurbiprofen	0.1–0.4%	Oil phase is released rapidly

Table 4: An overall view of the different excipients used and their role in treating different diseases.[21]

S. No.	*Disease*	*API*	*Composition*			
			Gelling agent	*Oil*	*Surfactant*	*Co-surfactant*
1	Anti-hyperglycaemic	Glibenclamide	Carbopol 984	1:1 ratio of triacetin and labrafac	Tween 80	Di ethylene glycol Mono ethyl ether
2	Anti-fungal	Itraconazole	Carbopol	Eugenol	Labrasol	Lecithin, Transcutol IP
3	Antifungal	Fluconazole	Carbopol 934	Capmul MCM	Tween 80	Transcutol P
4	Anti-inflammatory	Curcumin	Carbopol	Emu oil	Cremophor RH 40	Labrafil M2125CS
5	Anti-hypertensive	Carvedilol	Carbopol 935	IPM: oleic acid	Tween 20	Carbitol
6	Wound healing	Atorvastatin calcium	Sodium CMC	Liquid paraffin	Tween 80	Propylene glycol
7	Antifungal	Ebselen	Soluplus (10%w/v) and HPMC K4M	Captex	Kolliphor ELP	Dimethyl acetamide
8	Anticancer	Chrysin	Pluronic F127	Capryol 90	Tween 80	Transcutol HP
9	Anti-inflammatory	Meloxicam	Carbopol 940	Almond: peppermint oil (1:2)	Tween 80	Ethanol
10	Antifungal	Terbinafine HCl	Carbopol 940	Peceol oil	Tween 80	Propanol
11	Anti-inflammatory	Diclofenac sodium	Carbopol 980	Isopropyl myristate	Tween 20	Labrafil M2135CS
12	Wound healing	Curcumin	Carbopol 940	Labrafac PG	Tween 80	PEG 400
13	Anti-inflammatory and Anti-microbial	Quercetin	Poloxamer	Cinnamon oil	Tween 80	Carbitol
14	Immunosuppressive agent	Cyclosporine	Guar gum	Oleic acid	Tween 80	Transcutol P

Humectants

Humactants help in preventing the escape of moisture from the formulation. Commonly used humectants are sorbitol, salicylic acid, propylene glycol, glycolic acid, glycerine, etc.[5]

Hence table 5 gives information about the role of different excipients in treating different diseases.

Formulation Techniques for Nanoemulgels

Nanoemulgels are prepared by a variety of techniques including high energy techniques and low energy techniques.[4,5,22]

High-energy methods

High-energy methods are techniques used to form nano-sized droplets in nanoemulsions, requiring significant shear force produced by specialized equipment such as microfluidizers, ultrasonicators, and high-pressure homogenizers. These methods aim to break down the oil phase into nano-sized droplets dispersed in the aqueous phase, capable of producing droplets in the dispersed phase with sizes of 1 μm or less. However, they are not suitable for thermolabile substances, and the high external energy input can make the formulation thermodynamically unstable due to the presence of free energy.

High-pressure homogenization

High-pressure homogenization involves using a microfluidizer or a piston homogenizer to reduce globule size to the nano

range. This technique applies pressures between 500 and 20,000 psi, combined with shear and hydraulic forces, to transform a macro-sized emulsion into a finer emulsion. The process continues until the desired droplet size is achieved. The polydispersity index of the droplets is also assessed to gauge uniformity. The efficiency of emulsification depends on the number of homogenization cycles. This method typically requires low surfactant concentrations, reducing the risk of contamination. In piston-type homogenizers, the operation is based on the principles of colloidal milling.[23]

Ultrasonication

In this method sound waves are used in particle size reduction of the emulsion. By using the probe sonicator, the coarse emulsion is broken down into emulsion containing nano sized droplets. The intensity of the sound waves used is greater than 20 KHz. Different probes are available based on different dimensions. Droplet size also depends on power applied and time taken for sonification.[4,5]

Low-energy methods

Low-energy methods for preparing nanoemulsions offer several advantages over high-energy methods, primarily due to their use of phase inversion and spontaneous emulsification techniques. These methods do not lead to thermodynamic instability in the formulation, which can occur with high-energy methods. Low-energy approaches typically employ Phase inversion temperature(PIT), phase inversion composition (PIC) or spontaneous emulsification (SE) techniques.

Phase inversion temperature (PIT) method

The Phase Inversion Temperature (PIT) method is based on altering the geometry of the surfactant interface while keeping the composition constant and varying the temperature. This process results in the transformation of the emulsion type, from oil-in-water (o/w) to water-in-oil (w/o), and vice versa. As temperature increases, the emulsion's temperature rises, leading to the solubilization of the oil phase and a subsequent phase inversion. This method is effective but has limitations for thermosensitive formulations.[24]

Phase inversion composition (PIC) method

In the Phase Inversion Composition (PIC) method, the formulation temperature remains constant while the composition is varied. This method involves adjusting the surfactant ratio and other components to induce phase inversion. While effective, PIC often requires the use of a large amount of surfactant.[25]

Spontaneous emulsification

Spontaneous emulsification is a widely used technique in both industrial and laboratory settings. It involves the preparation of an aqueous phase with hydrophilic surfactants (e.g., Span, Tween) and an oil phase containing solvents like acetone, methanol, or Capryol 90, in which the drug is soluble. Nanoemulsions are formed spontaneously as the organic phase is gradually added to the aqueous phase, followed by evaporation of the organic solvent. The process is facilitated by a magnetic stirrer, which creates convection currents that help distribute oil droplets throughout the bulk solvent.[26]

Incorporation of Nanoemulsion into Hydrogel base

Preparation of the gelling agent

In the preparation of nanoemulgel, gelling agents play a major role in the transformation of the emulsion from liquid state to semisolid state, which helps in providing better patient compliance. The gel is prepared by the addition of the polymer to distilled water by continuous stirring with the help of a glass rod using a mechanical stirrer. Later, the pH of the gel is adjusted. An alternative method for the preparation of gel is also present, which includes the addition of the polymer into the purified water in cold conditions. In this method, all the ingredients are added into the distilled water at a temperature of 30ºC. Later the gel polymer was added, and the water was cooled up to a temperature of 4ºC.[21,27]

Incorporation of the gel polymer

Nanoemulgel is prepared by mixing the nanoemulsion with the gelling agent. By using various gelling agents, the emulsion o/w or w/o gets converted into semisolid consistency, resulting in the formation of a nanoemulgel. After applying an external force, the gel can be transformed into a solution. This phenomenon of conversion of sol to gel and gel to sol is known as thixotropy. The transformation from sol to gel and gel to sol without change in volume is due to the application of shear stress. Commonly used polymers include carbopol 934, carbopol 943, carbopol 940, poloxamer 407, etc.[4]

Mechanism of action of nanoemulgel

Nanoemulgels exert their therapeutic effects through a combination of mechanisms that enhance drug delivery and penetration through the skin. The nano-sized droplets of the oil phase in the nanoemulsion provide a large surface area for drug solubilization and interaction with the skin. When applied topically, the nanoemulgel's unique structure allows for increased drug partitioning into the stratum corneum. The gel network helps retain the formulation on the skin surface, creating an occlusive effect that improves hydration and further enhances penetration. Further, the surfactants and co-surfactants act as permeation enhancers and facilitate improved drug penetration via the stratum corneum layer. This is further improved by the small globule size of the nanoemulsions, which penetrate through the hair follicles and

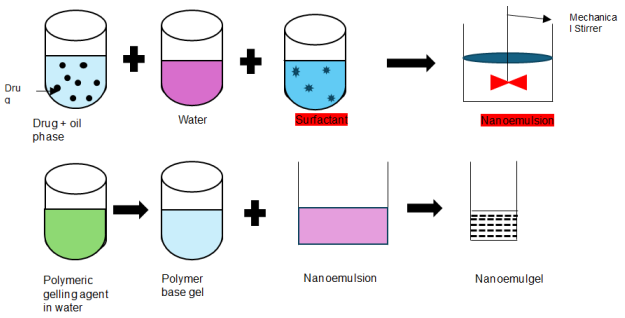

Figure 2: Procedure for the preparation of nanoemulgel

sweat glands, thereby improving the overall drug delivery. The emulgels property of sustained drug release helps in maintaining the concentration gradient of the drug and thereby promotes continuous drug penetration. When combined, these processes provide the encapsulated medication with better bioavailability and efficacy than traditional topical preparations.[3,4]

Evaluation of nanoemulgels

Nanoemulgels are semisolid formulations made of nanoemulsions and hydrogel and are suitable for topical applications. A wide range of analytical methods are required for evaluating these drug delivery systems. These evaluation methods include methods that are suitable for evaluating both nanoemulsions and hydrogels, and these include.[4,22]

Physicochemical characterization

Physical appearance

Ideally, nanoemulgels should be either clear or slightly opalescent. The clarity of the nanoemulgels indicates the well-dispersed, uniform-sized globules. Further clarity also indicates the presence of a uniform phase. Any visible turbidity can be due to aggregation, instability, or degradation in the nanoemulgel formulation.

Particle size and zeta potential

Particle size and zeta potential are important parameters in the evaluation of emulgels, as they play an important role in skin penetration. Particle size majorly influences the appearance, stability, and drug delivery efficiency of nanoemulgels. The smaller the droplets, the better the nanoemulgel. Techniques like scanning electron microscopy (SEM), and dynamic light scattering (DLS) are used to measure particle size. Whereas zeta potential is responsible for maintaining electrostatic stability and preventing aggregation of globules, thereby preventing aggregation and maintaining formulation stability. Zeta potential is measured by measuring the charge density over the globules using Zetasizer.

Viscosity and spreadability

Viscosity and spreadability are two other essential factors in nanoemulgels that affect their performance. Viscosity determines the thickness and flow properties of the emulgels and affects the drug release properties. Further, they should have enough consistency to the skin or mucosal surfaces at ease. Viscosity is measured by viscometers. Spreadability, on the other hand, determines how well the product covers the application area. Good spreadability is an indication of uniform dispersion with uniform globular size. Spreadability is measured by tests such as the 'slip drag test', which measures the extent to which the nanoemulgel spreads under the given force.

pH and conductivity

Nanoemulgels should be stable and compatible with the skin microenvironment. Nanoemulgels should have a pH, which is sightly acidic as that of skin. Nanoemulgels with a pH either basic or more acidic can lead to skin irritation and ineffectiveness. pH is generally measured with pH by dilution of nanoemulgel with pure water. Conductivity is measured with a conductivity meter and is the indication of the ionic content of the nanoemulgel formulation. High conductivity may indicate a high concentration of electrolytes, potentially affecting the emulsion's stability and release properties.

Drug content and uniformity

The efficacy and performance of the emulgels depend on the drug content and uniformity.

drug content is determined by any suitable analytical techniques such as uv spectrophotometry, high-performance liquid chromatography (HPLC) etc. Uniformity assessment involves the verification of drug concentration and its consistency throughout the formulation, which ensures predictable and uniform doses, thereby maintaining therapeutic efficiency and reliability.

Bioadhesive strength

Nanoemulgels are also intended to be applied to mucosal membranes and should have suitable bioadhesive strength for ensuring prolonged contact and for ensuring effective drug release. Bioadhesive strength is determined by techniques that can determine the force required to detach the gel from tissues (peel test). The higher the bioadhesive strength, the longer the time, the nanoemulgels stay in the site of application.

Drug Release Studies

In vitro drug release studies and release kinetics

Nanoemulgels should be able to release drugs at a predetermined rate for effective pharmacological action. *In-vitro* drug release studies assess the rate of drug release from the nanoemulgels over a period of time under controlled conditions. Franz diffusion cells are typically used for determining the drug release rates from gels. In a common setup, the gel is placed on the semi-permeable membrane separating the upper and lower compartments, where the lower compartment contains buffer and acts as a receptor, whereas the upper compartment serves as a drug reservoir. At predetermined intervals, samples were withdrawn from the receptor medium and were analyzed using techniques such as HPLC or UV-vis spectroscopy to measure the concentration of the drug released.

Further, the drug release data is treated with various mathematical models to understand the rate and mechanism of drug release.

Ex-vivo skin permeation studies

Ex-vivo skin permeation studies are performed similar to *in vitro* drug release studies. However, in the Franz diffusion cell assembly, the semi-permeable membrane is replaced with defoliated human skin or excised animal skin. The amount of drug permeating the skin and reaching the receptor compartment is measured by periodic sampling and analyzing by suitable analytical techniques. Parameters like drug permeation rate, cumulative drug release, flux, and lag time can be determined. Further, the amount of skin retention of the drug can also be determined at the end of the study.

Animal Studies

Skin irritancy studies

Nanoemulgels are applied to the surface of the skin or mucosal surfaces, and they are in contact with the applied surface for a prolonged time. Due to this prolonged contact, these formulations can cause some irritation or discomfort at the applied site. Skin irritancy studies evaluate the potential of these formulations to cause irritation or adverse reactions. These studies are generally performed on human volunteers or animal models, where the nanoemulgel formulation is applied to a small area of the skin of the subject and is monitored for any signs of itching, irritation, redness, or swelling. Ensuring minimal skin irritancy is very essential for enhanced patient comfort and safety, especially when intended for frequent or long-term usage.

In-vivo performance studies

In-vivo, performance studies assess the efficacy and safety of a nanoemulgel in animal models. These studies involve applying the formulation to the desired site and evaluating therapeutic effects, such as efficacy, and potential side effects over time. *In-vivo* studies provide key insights into the practical effectiveness and safety of the nanoemulgel in real-world scenarios.

Stability testing

Evaluating the long-term stability and viability of nanoemulgel formulations involves assessing various physical, chemical, and functional properties over time under diverse storage conditions. This encompasses examining changes in visual appearance, viscosity, pH, and drug content, as well as monitoring any phase separation or degradation of the formulation. Stability studies are conducted by exposing the nanoemulgel to different temperature, humidity, and light conditions to mimic real-world storage environments. These tests serve to determine the product's shelf life, identify potential stability issues, and ensure the formulation remains effective, safe, and usable throughout its intended lifespan.

Pharmacological Applications of Nanoemulgels

Treatment of skin and hair disorders (e.g. psoriasis, atopic dermatitis)

- (Mulia *et al.* 2018) prepared mangosteen nanoemulgel extract for topical formulation in virgin coconut oil. The oil phase used was virgin coconut oil, span 80 and tween 80 were used as surfactants and the gelling agent was xanthan gum. Due to better skin permeation, it was concluded that VCO-mangosteen nanoemulgel can be used as formulation.[28]
- (Ermawati *et al.* 2019) formulated nanoemulgel of gold particles and vitamin E. by using self nano emulsifying drug delivery system technique to disperse the gold particles and decrease the size. The oil phase used was olive oil tween 80 and propylene glycol were used as surfactant and co surfactant. The results showed that regeneration of the skin occurred.[29]
- (Nagaraja S *et al.* 2021) prepared nanoemulgel using chrysin for the treatment of skin melanoma. The formulation was prepared by using a nano complex system consisting of chrysin which is hydrophobic in nature is dissolved in a lipid mixture. Further this mixture was emulsified in gel called Pluronic® F-127. They used caproyl® 90 as a surfactant and tween ®80.[30]
- (Mulleria *et al.* 2021) prepared Apremilast nanoemulgel for the treatment of psoriasis they formulated nanoemulsions loaded with Apremilast, which was further incorporated with a gel using carbopol 940. Results showed that *in vitro* release of the drug by using Franz diffusion cell apparatus followed zero-order release kinetics.[31]
- Nanoemulgel containing calcipotriol is used in the treatment of psoriasis (Naga Sravan Kumar Varma *et al.* 2014) with high bioavailability, reduced dose and toxicity levels compared to topically applied agents. Psoriasis can be defined as a chronic disorder where abnormal patches on the skin form because of epidermal hyperproliferation and angiogenesis.[32]
- (Phaugat *et al.* 2022) developed a topical nanoemulgel formulation by combining two drugs which are curcumin (CUR) and tretinoin (TRT) for the treatment of skin-related ailments such as aging, acne vulgaris and psoriasis result showed that the TRT-CUR-nanoemulgel showed better drug release.[33]
- (Mohammadi-Samani *et al.* 2021) prepared oxybutynin nanoemulgel used ion then treatment of hyperhidrosis. The OXB-NEMGEL which is nanoemulgel containing oxybutynin was prepared using a Design Expert software®. 17 formulations of OXB-NE were prepared. For the preparation of OXB-NEM GEL about three polymers were used. This model used quadratic equations and found out that there is a relation between the response variables like zeta potential particle size and independent variable like ratio of the oil and surfactant oil and water and surfactants. Further studies showed that Nanoemulgel prepared by using carboxymethyl cellulose (CMC-NEMGEL) showed better release of then drug of oxybutynin and therefore OXB-NEMGEL is very effective for the treatment of hyperhidrosis.[34]
- Loss of hair, which is known as alopecia (Usmania *et al.* 2017). Minoxidil is used in the treatment of this condition, but it is less effective in terms of pharmacokinetics profile in many delivery systems; hence, nanoemulgel is a suitable means for the delivery of minoxidil in the treatment of alopecia.[35]
- Immunosuppressive agent cyclosporine (Begur *et al.* 2015) composed of oleic acid, tween 80, transcutol P and Guar gum proved improved permeation as compared to nanoemulsion and marketed formulation.[36]

Delivery of antimicrobial agents

- Syamala U. (2013) developed and optimized alkyl amine antifungal nanoemulgel using 23 Factorial Design for treatment of tinea pedus using DOE which stand for

Table 5: *In-vivo* studies done on nanoemulgels

S. No.	*Drug used*	*Disease*	*Species/Animal*	*Objective*	*Method used*	*Results*	*Reference*
1	Tamoxifen citrate	Breast cancer	Skin excised from albino rats	Deposition of the drug on the skin and skin permeability	Franz diffusion cell apparatus	Permeation of the tamoxifen citrate (TAM) was three times higher than the drug present on the skin	[49]
2	Eprinomectin	Treatment of endoparasites and ectoparasites	ICR mice	Skin permeability and retention studies	Bioadhesion	The nanoemulgel of BPR had good bioadhesive property	[50]
3	Curcumin and emu oil	Skin melanoma	Male Sprague dawley (SD) rats	Evaluation of anti-inflammatory efficacy in carrageenan induced paw edema and FDA induced arthritic rat model.	Franz diffusion cell	Study from *ex vivo* skin permeation showed that the nano emulsion loaded with curcumin had better permeability when compared to dispersion of curcumin in	[40]
4	Lysostatin	Skin infection	Murine skin model	Introduction of a non-conventional anti-microbial agent in order to add antimicrobial arsenal required to fight the MDR infections which are caused by S-aureus	Phase inversion composition (PIC)	Lysostatin (LST) improved the rate of recovery of the infected mice.	[51]
5	Dasatinib	Rheumatoid arthritis	Sprague Dawley (SD) rats	*Ex vivo* skin permeation	Franz diffusion cell apparatus	Results showed that the optimized emulgel (CF018) showed decrease in swelling of paw when compared to the control group containing adjuvants induced arthritis (AIA)	[18]
6	Diphenhy-dramine	Allergic rhinitis	New Zealand white male rabbits	To study the effect of histamine based on haematologic values in blood of healthy and treated, allergic and treated, allergic and untreated, white rabbits	Haematology and nasal membrane permeation study	On comparing DPH conventional nasal spray And DPH nanoemulgel, there was excellent drug delivery in the management of allergic rhinitis in animal model.	[52]
7	Diclofenac sodium	Analgesic and anti-inflammatory effect.	Albino Wistar rats	Evaluation of anti-inflammatory effect of the formulation	Carrageenan-induced paw edema test	The formulated nanoemulgel of diclofenac showed reduced anti-inflammatory effect when compared to conventional diclofenac gel and marketed formulation	[53]
8	Atorvastatin	Wound healing	Wistar rats	*Ex vivo* drug permeation	Simple dialysis method	ATR nanoemulgel showed highest percentage of wound healing property.	[54]
9	Brucine	Arthritis and traumatic pain	Male balb mice	*Ex vivo* skin permeation	Franz diffusion cell apparatus	Brucine loaded nanoemulgel showed more anti-norciceptive1 and anti-inflammatory activity when compared to brucine loaded emulgel and brucine loaded gel	[55]

design of experiments which is a statical tool for finding optimum combination based on relationship between factors affecting a process and process output which is preparation method which advanced and produce a drug with better permeation. Thus, it was concluded that nanoemulgel formulation of alkyl amine (Syamala 2013) showed efficient treatment of fungal infection when compared to marketed cream (MC).[37]

- Antifungal agent itraconazole (Sunitha *et al*. 2014) consist of eugenol, labrasol, carbopol, lecithin and transcutol nanoemulgel showed enhanced permeation, diffusional control as result of PK/PD effects.[38]

- Antifungal fluconazole consists of capmul carbopol transcutol and tween 80 showed 3.71 folds higher permeation in comparison to commercial eye drop with increased antifungal activity (Pathak *et al.* 2013), antifungal, antimalarial, antiviral, antioxidant and antibacterial.[10]
- (Eid *et al.* 2021) developed a coriander oil nanoemulgel and also evaluated its anticancer properties and this nanoemulgel was formulated by a method called self-nanoemulsifying technique by using span80 and tween 80. The hydrogen agent used was carbopol 940 which was incorporated into the nanoemulsion to form the nanoemulgel the result proved that nanoemulgel of coriander oil was prepared by using a self-nanoemulsifying technique which demonstrated bioactive property.[39]

Transdermal delivery of analgesic, anti-inflammatory and antioxidant drugs

- Anti-inflammatory curcumin (Jeengar *et al.* 2016) made with aid of Emu oil, Cremaphor RH40, carbopol and Labrafil M2125CS.[40]
- Characteristic redness, odour and swelling produced by natural physical reaction of the body is often associated with inflammation and in the treatment of inflammation nanoemulgel (Dasgupta *et al*. 2014) exhibit better pharmacodynamic profile of action compared to other drug delivery systems example: nanoemulgel formulation of NSAID lornoxicam.[41]
- Antimicrobial and anti-inflammatory quercetin (Aithal *et al.* 2018) composed of cinnamon oil, tween 80, poloxamer and carbitol showed 192.4% release in about 6 hours where quercetin loaded gel shows <3% release in the same time.[42]
- Anti-inflammatory meloxicam (Kadhim Drais and A. Hussein 2017) with higher in vitro release rate and enhanced bioavailability outcome is composed of carbopol 940, tween 80 and ethanol.[43]
- Antioxidant ferulic acid (Harwansh *et al.* 2015) exhibited enhanced permeation of nanoemulgel (96.95%) compared to gel (61%) made of carbopol, plurol isostearique, Isostearyl isostearate and labrasol.[44]

Other applications (e.g. anti-aging, skin lightening)

- Antihyperglycemic Glibenclamide (Wais *et al.* 2013) made with aid of carbopol 934, tween 80, Labrafac triacetin and diethylene glycol monoethyl ether exhibited 3.92-fold increase in relative bioavailability in comparison to oral drug suspension.[45]
- (Sukumaran and Abhimanyu et el 2022) formulated nanoemulgel loaded with methocarbamol where cocoon oil is used as oil phase along with surfactant and co-surfactants hence is further concluded that due to the presence large amount of oil phrase in the nanoemulsion sustained and delayed release oil the drug was found therefore it was concluded that NE-Gel showed better treatment as a muscle relaxant.[46]
- Telmisartan (Aparna *et al.* 2015) is delivered to systemic circulation in treatment of cardiovascular diseases using nanoemulgel drug delivery system which shows better pharmacokinetic profile compared to conventional systems of delivery, it is prepared by using Labrafil M 2125 CS as oil component, carbopol for conversion of nanoemulsion into nanoemulgel of telmisartan and either carbitol or acrysol are used as surfactants.[47]
- Antihypertensive carvedilol (Pratap *et al.*2012) with plasma conc increased 6.41fold compared to the marketed formulation and enhanced bioavailability made with aid of tween 20, carbitol, carbopol 934 and oleic acid.[48]

Conclusion and Future Perspectives

Nanoemulgels have shown significant promise in enhancing the delivery of lipophilic drugs, particularly those classified as class II and class IV, by improving drug permeation and absorption across the skin, thereby enhancing therapeutic efficacy and pharmacokinetic profiles. The unique advantages of nanoemulgels, such as good spreadability, less oily nature, and ease of application, have significantly improved patient compliance. By incorporating nanoemulsions into a gel-based matrix, nanoemulgels have successfully addressed challenges like decreased bioavailability, poor aqueous solubility, fluctuations in pharmacokinetic profiles, poor spreadability, and low viscosity. This formulation has proven effective for various routes of administration, including dental, ocular, vaginal, topical, and transdermal. In topical applications, nanoemulgels are used to treat conditions such as rheumatoid arthritis, alopecia, fungal infections, wound healing, and allergic rhinitis. For transdermal delivery, they show potential in treating Alzheimer's, endoparasites, ectoparasites, post-menopausal osteoporosis, and rheumatism. Despite these advantages, challenges remain in achieving consistent, targeted transdermal delivery for specific skin disorders.

However, more clinical trials are needed to fully establish the efficacy and safety profiles of nanoemulgels. The growing interest from pharmaceutical companies, coupled with the potential for expanded applications in the transdermal delivery of systemic medications, suggests that nanoemulgels have a strong future in dermatological treatments. As research continues and formulation techniques are refined, nanoemulgels are likely to play an increasingly important role in addressing various skin disorders, potentially revolutionizing topical drug delivery in the coming years. The past decade of research indicates that nanoemulgels are a widely accepted formulation, with 70% of developments aimed at local delivery, underscoring their potential for commercialization and clinical translation.

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AUTHORS' CONTRIBUTION

Both authors have been involved equally in all stages of the development of the manuscript.

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