International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 16, Issue 9, 2024

Review Article

REVIEW OF NANOEMULGEL FOR TREATMENT OF FUNGAL INFECTIONS

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Received: 21 May 2024, Revised and Accepted: 18 Jun 2024

ABSTRACT

The skin is the largest of the body's organs and it has a big role to play in maintaining homeostasis and defending against microbial invaders. Fungal infections are responsible for a large proportion of the global burden of skin diseases; affecting millions, especially in developing countries. The application of antifungal drugs as topical agents is one of the best techniques to treat major fungal infections that affect the skin, which involves several advantages such as localized delivery, and lower systemic toxicity among others. These findings also suggest that nano-emulgel could be used as an alternative system for delivering drugs through topical administration. However, issues such as the inability to load bulky drug molecules and safety concerns about surfactants and gelling agents limit their potential use as drug carriers by this pathway. It is necessary to carefully study these issues further so that we can exploit fully what this nano-emulgel may offer in terms of dermatological medications.

Keywords: Nanoemulgel, Fungal infections, Nanotechnology, Nanoemulsion, Anti-fungal treatment

DOI: https://dx.doi.org/10.22159/ijpps.2024v16i9.51528 Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

The skin serves as the body's largest organ, playing a crucial role in maintaining fluid balance, regulating body temperature, protecting against microorganisms, preventing infections, and preserving essential nutrients, water, electrolytes, and other substances. Additionally, the skin acts as a barrier between the body and the external environment, coming into contact with various bacteria like staphylococci, streptococci, candidiasis, and non-pathogenic mycobacteria. Any damage to the skin can make it susceptible to infections from external sources, allowing microorganisms to gather around wounds and lead to potential infections. Despite being a protective shield, the skin is constantly exposed to numerous factors that can potentially harm it [1, 2].

The global burden of skin disease is significantly impacted by fungal infections. It is estimated that approximately 40 million individuals in developing and underdeveloped countries are affected by these infections. Initially, fungi tend to attack the surface of the skin and subsequently penetrate deeper layers through desquamation. Among the various types of fungi, Candida species are known to cause superficial cutaneous infections [1-5]. Cutaneous mycoses, also known as dermatophytes, refer to fungal infections that affect the deeper layer of the skin. Various types of dermatomycoses, such as Tinea corporis, Tinea pedis, and Tinea cruris, are frequently caused by fungi [6-8]. Subcutaneous mycosis refers to the condition where fungal infection extends into the deeper layers of the skin tissue [9].

The most effective method to combat major skin dermatophytes is through the topical application of anti-fungal drugs. This approach allows for direct access to the affected area and increases the likelihood of the drug staying in place. Additionally, topical delivery minimizes the risk of systemic toxicity and prevents pre-systemic metabolism. Commonly used drugs such as ketoconazole, Iitraconazole, and Clotrimazole are applied to the skin through spreading or rubbing [10-12].

Topical delivery offers benefits such as targeted drug delivery, decreased risk of systemic toxicity, enhanced patient adherence, improved treatment effectiveness, and increased drug absorption [13]. However, the application of anti-fungal medications through topical means may result in undesirable skin responses such as allergic reactions and itchiness [14-16]. Additionally, traditional formulation requires high doses and frequent administration, leading to a higher chance of experiencing both local and systemic toxicity. Therefore, a new drug delivery system is being developed in order to minimize local side effects and enhance the effectiveness of treatment.

Various skin problems have been extensively studied in recent years, leading to the investigation of different nanocarriers including nanoemulsions, nanostructured lipid carriers, solid lipid nanoparticles, polymeric nanoparticles, liposomes, ethosomes, transferosomes, niosomes, aquasomes, and menthosomes as potential solutions [17].

Search methodology

This review encompasses information collected from peer-reviewed journal articles sourced from databases like lens.org, PubMed, Google Scholar, and Science Direct, covering the period between 2000 and 2024. Keywords such as Nanoemulsion, Nanoemulgel, Topical formulation and Antifungal treatment were employed during the search process. The review offers a comprehensive understanding of Nanoemulgel topical formulation for the treatment of fungal infections.

Nanoemulsions

Nanoemulsions consist of nano-sized droplets of one liquid dispersed in another liquid, forming heterogeneous isotropic systems. The droplet sizes typically fall within the range of 20 to 500 nm. These systems are thermodynamically unstable but kinetically stable, requiring energy for their creation and surfactants and/or co-surfactants to maintain colloidal stability [18, 19]. Nanoemulsions, with their increased surface area-to-volume ratio, function as a drug reservoir, leading to enhanced drug bioavailability compared to traditional emulsions. They offer various benefits including improved drug release, extended effectiveness, reduced side effects, and protection of drugs from enzymatic or oxidative degradation [20]. Nanoemulsions have the ability to be transformed into a wide range of dosage forms, including liquids, creams, sprays, gels, aerosols, and foams. These versatile formulations can be applied through various routes such as oral, intravenous, intranasal, pulmonary, ocular, and topical administration, catering to different application areas. Nanoemulsion exhibits none of the undesirable effects such as creaming, sedimentation, flocculation, or coalescence that are commonly observed in macroemulsions. Additionally, nanoemulsion shows promise as an effective carrier in topical treatments due to its ability to enhance the dispersion of active ingredients within the skin layer [21].

Nanoemulgels

A gel matrix infused with nanoemulsions forms a nanoemulgel, which can enhance the skin's capacity to absorb substances. Nanoemulgel offers advantages over ointments and creams, such as being non-greasy, non-irritating, and providing better drug-release properties. These characteristics make nanoemulgel superior to traditional topical formulations. Additionally, the uniform dosage form and the consistent hydrogel matrix further contribute to the increasing interest in nanoemulgel.

Due to their dual character, which includes both nanoemulsion and gel base, nanoemulgels are considered suitable options for drug delivery systems. The nanoemulsion within the nanoemulgel structure offers protection to the active substance, while the gel base enhances thermodynamic stability by increasing the viscosity of the aqueous phase. In the field of dermatology, nanoemulgels have gained attention due to their higher spreading coefficient compared to some commercially available topical dosage forms. Nanoemulgel offers additional benefits, such as its enhanced adherence to the skin surface and the resulting higher concentration gradients towards the skin, ensuring improved penetration [22, 23].

Nano-emulsions, while advantageous in many aspects, suffer from a lack of spreadability due to their low viscosity, leading to inadequate retention of the formulation on the skin [24]. The clinical applications of nano-emulsions are hindered by this restriction [25]. The problem has been solved by adding a gelling agent to the nano-emulsion, resulting in the creation of a nano-emulgel [26]. Gels are prepared in a colloidal particulate system by utilizing large amounts of aqueous or hydroalcoholic bases [27] Nano-emulgel is created by blending the nano-emulsion with a hydrogel matrix, resulting in a decrease in the thermodynamic instability of the emulsion. The enhanced thermodynamic stability is a result of the decreased mobility of the non-aqueous phase, brought about by the heightened viscosity of the surrounding medium. This prolonged retention time and improved thermodynamic stability allow for a gradual release of the drug, transforming nano-emulgel into a controlled release dosage form suitable for topical application, particularly advantageous for drugs with a brief half-life [28, 29].

The integration of nano-emulsion into a gelling system eliminates the drawbacks of each system individually. The combined nano-emulgel possesses the characteristics of a gel along with the refined features of a nano-emulsion. The advantages of nano-emulgel over traditional emulgel are revealed in table 1, attributed to its particle size and thermodynamic stability. Nano-emulgels offer a range of benefits including enhanced skin permeation, increased loading of active ingredients, reduced irritation, and improved spreadability. This is evident when compared to other nano-carriers such as solid lipid nanoparticles and liposomes. The nano-emulsion is rendered suitable for topical application by enhancing the viscosity of the gel. To achieve this, various gelling agents compatible with the skin, such as xanthan gum, carbomer 980, Pluronic's, carrageenan, and carbomer 934, are utilized for topical use [30]. Nano-emulsions enable effective localization and dispersion of drugs by facilitating optimal percutaneous absorption through the skin. This not only enhances local efficacy but also enables systemic delivery via the skin. Moreover, this innovative system exhibits the potential to transport drugs to the central nervous system (CNS) by effectively crossing the blood-brain barrier when administered nasally [31, 32]. The non-irritating and non-greasy characteristics of nano-emulgel promote improved patient adherence. Furthermore, the pharmacokinetic features such as increased bioavailability and reduced side effects provide additional benefits for these formulations [33]. The emphasis on nano-emulgels has been heightened by the hydrogel matrix, its consistency, and homogeneity. Additionally, several research studies have indicated that nanoemulgel exhibits enhanced stability as a result of reduced Oswalt ripening, which is caused by the decreased mobility of oil globules within the gel matrix [34].

Table 1: Comparison between conventional emulgel and nano-emulgel

S. No.	Parameter	Conventional emulgel	Nano-emulgel
1.	Thermodynamic stability	Unstable due to the inherent tendency of particles to come together, resulting in sedimentation or creaming [37]	Due to their reduced particle size, nanoparticles exhibit stability through Brownian motion, effectively counteracting the force of gravity and preventing sedimentation or creaming [28]
2.	Particle size	Greater than>500 nm [36]	Less than 100 nm [38]
3.	Bioavailability	Nano-emulgel exhibits higher bioavailability compared to this alternative [39]	Improved bioavailability is linked to the reduced size and increased surface area [40]
4.	Permeation	Relatively reduced permeability [41]	Due to its smaller particle size, it exhibits a high permeation rate [28, 41]
5.	Preparation	High levels of energy are needed for these techniques [42]	It can be prepared using either high or low energy methods [35]
6.	Systemic absorption	Extremely limited.	Superior to traditional emulgel because of its reduced particle size and increased surface area [28]
7.	Ability to cross BBB	The blood-brain barrier cannot be crossed [43]	Due to its diminutive particle size, it is capable of traversing the blood-brain barrier [44]

In addition to these, nano-emulgel does not have any other issues related to formulation stability. It does not face the problem of destabilization that is commonly encountered with conventional emulgels, nor does it have the issue of moisture entrapment that is often seen with powders. Furthermore, it does not suffer from cake formation as experienced with suspensions, the coalescence of oil globules, or the formation of agglomerates that can occur with suspensions. Additionally, nano-emulgel does not have the problems of poor adherence and excessive spreadability that are typically associated with nano-emulsions [27].

Components of nano emulgel formulation

Nano-emulgels consist of two distinct systems: the gelling agent and the nano-emulsion, specifically an emulsion containing nano droplets that are either o/w or w/o in nature. Each type of emulsion contains both an aqueous and an oily phase. The gel foundation is composed of polymers that have the ability to expand upon liquid absorption. The different ingredients in the antifungal nano-emulgel formulation can be found in table 2 [27, 45].

Table 2: Commonly used excipients in Antifungal nano-emulgel formulations

Itraconazole	Eugenol	Labrasol	TranscutolP, Lecithin	Carbolpol [46]
Fluconazole	Capmul MCM	Tween 80	Transcutol P	Carbopol 934 [47]

The overview of the selection criteria of the essential components in a nano-emulgel have been discussed below.

Oil phase

The oil selection and quantity are determined by the specific use and purpose of the nano-emulgel. The permeability, stability, and viscosity of the Nano-emulsion are influenced by the type and amount of lipid component chosen for the oil phase. In pharmaceutical and cosmetic applications, the oil phase typically consists of naturally or synthetically derived lipids, unless the oil itself serves as an active ingredient. The consistency of the lipids can range from liquid to high molecular solids. The hydrophobic nature of the oil is essential for creating a stable emulsion, as poor hydrophobicity can lead to increased emulsification and impact the solubility of lipophilic substances [48]. Selecting an oil is a crucial requirement for the advancement of nano-emulgel as an innovative method for drug delivery [49].

The medicinal importance of natural oils contributes to a rise in the researcher's curiosity to utilize their additive properties, which aid in the pharmacological effects of the active component. One such oil, oleic acid, is commonly employed in nano-emulgel formulations and is derived from both vegetable and animal sources. It possesses biodegradable and biocompatible qualities as an omega-nine fatty acid, and it also enhances solubilization properties while improving the absorption through the skin [101, 50]. Oleic acid's antioxidants play a crucial role in maintaining cellular membrane integrity, repairing cell damage, and ensuring formulation stabilization [30, 51]. Arora and colleagues have verified that augmenting the oleic acid content in the formulation enhances the permeation rate. In their investigation, substituting 3% oleic acid with 6% in the nano-emulgel preparation significantly enhanced the permeability of ketoprofen [30].

Surfactant system

Surfactants play a crucial role in nano-emulsion formulations, as they help stabilize the mixture of two immiscible phases. This is accomplished by reducing the interfacial tension between the two phases and modifying the dispersion entropy. The surfactant must rapidly adsorb at the liquid interface to achieve this. As a result, the interfacial tension decreases, preventing the coalescence of individual nano-sized droplets [52].

The selection of the appropriate surfactant relies heavily on the HLB value. Surfactants can be categorized into two types: w/o (HLB of 3-8) and o/w (HLB of 8-16). In w/o emulsions, surfactants with a low HLB value (less than 8) are preferred. On the other hand, o/w emulsions require surfactants with a higher HLB value (more than 8), such as Spans and Tweens. When combined, Spans and Tweens enhance the stability of the emulsion system compared to using either one alone. Therefore, formulating an ideal nano-emulsion necessitates the use of a proper mixture of surface-active agents. Surfactants can also be classified into four main categories based on their charge: cationic, non-ionic, anionic, and zwitterionic. Examples of cationic surfactants include hexadecyl trimethyl ammonium bromide, cetyl trimethyl ammonium bromide, quaternary ammonium compounds, and dodecyl dimethyl ammonium bromide [53, 54]. Poloxamer 124, Poloxamer 188, Tween 20, and Caproyl 90 are examples of non-ionic surfactants [55, 56]. Sodium dodecyl sulphate and sodium bis-2-ethylhexylsulfosuccinate are examples of anionic surfactants [57]. Phospholipids, including phosphatidylcholine, are components of zwitterionic surfactants [58]. It is important to take into account the toxicity when choosing a surfactant, as it can cause irritation to the gastrointestinal tract or skin depending on how it is administered. Ionic surfactants are generally not recommended due to their toxicity and lack of biocompatibility. Non-ionic surfactants, on the other hand, are a suitable option because they are safe, biocompatible, and unaffected by changes in pH or ionic strength [59].

Surfactants obtained from bacteria, fungi, and animals are being explored as a viable alternative due to their safety, ability to degrade naturally, and compatibility with living organisms. Bio-surfactants exhibit a comparable mechanism of reducing surface tension at the interface, thanks to their amphiphilic properties. This is primarily attributed to the existence of non-polar short fatty acids as the tail and polar functionalities as the head [60]. They are more bio-compatible and safer than synthetic surfactants.

Co-surfactant system

During the emulsification process of oil in the water phase, co-surfactants play a crucial role in supporting surfactants. Their presence is necessary to reduce the interfacial tension and enhance the emulsification process [61]. The interfacial film gains flexibility and achieves temporary negative interfacial tension by incorporating co-surfactants. The drug release from the nano-emulgel is determined by the interaction between the surfactant and co-surfactant, as well as the distribution of the drug in immiscible phases. Therefore, the choice of co-surfactant is just as crucial as the surfactant. Some commonly employed co-surfactants include PEG-400, transcutol® HP, absolute ethyl alcohol, and carbitol [62]. Alcohol-based co-surfactants are highly favored due to their capability to distribute between the oil and water phases, thus enhancing their miscibility. It is crucial to carefully select the concentration of co-surfactant used, as it can impact the emulsification process by the surfactant. Moreover, a combination of surfactant and co-surfactant with similar HLB values does not yield a stable emulsion compared to non-ionic surfactants with varying HLB values. This could be attributed to the higher HLB value surfactants being solubilized in the aqueous phase, while lower HLB value surfactants are solubilized in the non-aqueous phase, allowing for a stronger interaction with the mixture of surfactant and co-surfactant [63]. Therefore, the choice of various formulation components and the rationale behind them is a very demanding and stimulating exercise.

Gelling agents

Upon introduction to the suitable medium, gelling agents create a colloidal mixture that results in the formation of a loosely bound three-dimensional structural network. This network exhibits a significant level of cross-linking, either through physical or chemical means, thereby imparting a consistent texture to the nano-emulgel [64-66]. These agents are utilized in topical applications to stabilize the formulation and achieve optimal drug delivery through the skin. They play a crucial role in determining various aspects of the formulation such as consistency, rheological properties, bio-adhesive properties, pharmacokinetics, spreadability, and extrudability. Gelling agents are categorized into natural, synthetic, and semi-synthetic based on their origin. Table 3 provides information on the concentration and pharmaceutical adaptability of different gelling agents used in the preparation of nano-emulgel. Natural gelling agents include bio-polysaccharides or their derivatives and proteins. Examples of bio-polysaccharides are pectin, carrageenan, alginic acid, locust bean gum, and gelatine, while derivatives of bio-polysaccharides include xanthan gum, starch, dextran, and acacia gum. Although natural gelling agents offer excellent biocompatibility and biodegradability, their main limitation is microbial degradation [66, 67]. Semisynthetic gelling agents, similar to natural gelling agents, provide favorable biocompatibility and biodegradability [68]. The agents typically derived from cellulose, such as hydroxypropyl cellulose, ethyl cellulose, and sodium alginate, are known as semisynthetic agents. These semisynthetic agents exhibit greater stability compared to natural gelling agents, and they are more sensitive to variations in pH, temperature, and other chemical, biological, and environmental factors [69]. Chemical synthesis is employed to create synthetic gelling agents, with certain examples such as carbomers and poloxamers being FDA-approved [70, 71]. Carbomers consist of polymerized acrylic acids, whereas poloxamers are composed of triblock non-ionic copolymers with two hydrophilic polyoxyethylene units linked to a central hydrophobic polypropylene chain [71, 72]. The synthetic agents approved by the FDA are safe and provide various rheological properties depending on the polymer's molecular weight, making them suitable for a diverse array of applications.

Preparation of nano-emulgel

Nano-emulgel is a formulation of structured liquids that is created through the combination of energy, surfactant, or both. It is formed spontaneously by mixing the various components together. This process involves introducing energy into the biphasic system or reducing the interfacial tension between the interfaces of the two immiscible phases [82].

Different methods for preparing nano-emulgel have been documented, depending on the sequence in which the oil and aqueous phases are mixed [83]. The oil phase is introduced into the aqueous gel phase while stirring, then homogenized to create an emulsion. The sol state of the gelling agent within the emulsion is transformed into a gel through different methods such as incorporating a complexing agent or adjusting the pH to the desired level [84] Jeengar *et al.* (2016) prepared the emulsion and gel separately, followed by mixing them together in a 1:1 w/w ratio [85].

There are two types of nano-emulgel formulation preparation, which can be classified based on the implementation of high-energy and low-energy emulsification techniques. The high-energy method involves the utilization of mechanical devices to generate a powerful disruptive force, resulting in size reduction of both phases. However, this method may cause the components in the formulation to heat up, leading to thermodynamic instability. As a result, it is not suitable for thermo-labile drugs. High-pressure homogenizers, microfluidizers, and ultrasonicators are examples of high-energy methods used to achieve a nanosized emulsion. This particular method is employed to prepare nano-formulations with sizes of approximately 1 nm.

Phase inversion, self-emulsification, temperature, and phase transition are low energy techniques used to achieve thermodynamic stability in nano-emulsions. These methods are particularly effective for thermolabile compounds. The spontaneous method involves carefully mixing oil, surfactant, and water in the optimal ratio. The success of the emulsification process relies on the characteristics of the surfactant and co-surfactant, as well as the order in which they are added. Temperature-based adjustments in HLB (hydrophilic-lipophilic balance) are commonly employed for non-ionic surfactants such as Tween 20, Tween 60, Tween 80, and Labrasol [86]. This technique is primarily employed for phase transition in the process of phase inversion. Employing cooling alongside continuous stirring will result in the transformation of the emulsion prepared at the inversion temperature. Lowering the phase inversion temperature enables the incorporation of thermolabile components through this method [87]. The next phase involves adding a gelling agent to transform the liquid form into a gel within the nano-emulsion. The thixotropic properties of the gelling agent enable the conversion from gel to solution when subjected to shear stress during the preparation process while maintaining a constant volume. Consequently, this results in the thickening of the o/w nano-emulsion due to the formation of a gelled structure.

Table 3: Various gelling agents and their pharmaceutical adaptability for use in topical emulgel

S. No.	Gelling agent	Concentration range (%*w*/*w*)	Pharmaceutical adaptability	Reference
1.	HPMC	2–6%	• Produces gels with a neutral pH. • Can offer excellent stability. • Inhibits the growth of microorganisms.	[73, 74]
2.	Carbomer (Carbopol) Grades–ETD 2020, 171, 910, 934, 934P, 940, 1342 NF, 1971P	0.1–1.5%	• Ability to form a gel with a high viscosity • Gel formation occurs at extremely low concentrations. • Offers regulated pH-responsive gel formation.	[73, 75]
3.	NaCMC	3–6%	• It is capable of enduring autoclaving, thus making it suitable for use in sterile gels. • Remains stable within the pH range of 2 to 10.	[76, 77]
4.	Poloxamer Grades–124, 182, 188, 407	20–30%	• Exhibits improved solubility in cold water. • The gel formed by thermoreversible gelation exhibits a solid state at room temperature and transforms into a liquid state when refrigerated.	[78, 79]
5.	Combination of HPMC and Carbopol	1.2%	• The combination of components can enhance the stability of an emulsion when compared to their individual counterparts.	[80, 81]

Permeability of nano-emulgel

When preparing emulsion-based gels, it is crucial to analyze the key process parameters that greatly impact the size and stability of the formulation. To achieve this, it is essential to choose the appropriate preparation method during the initial stages. Emulsions can be created using various techniques, including mechanical (or rotor-stator), high-pressure, microfluidization, and ultrasonic methods. The mechanical system involves a colloid mill with a complex geometry, and the resulting emulsion droplets produced by this system are several microns in size, making it the least favorable approach for manufacturing nanoemulsions [88]. It is extremely difficult to attain the ideal droplet size. Nevertheless, employing high-pressure homogenization and sonication techniques can result in droplets smaller than a micron, thereby enhancing the longevity of emulsions by reducing the rate of creaming. Consequently, homogenization and sonication are regarded as effective approaches for creating nanoemulsions [89, 90]. Furthermore, simply increasing the speed or duration of homogenization is insufficient to reduce the size of the globules. It is essential to use the optimal concentration of an emulsifier in order to maintain control over the re-coalescence of the emulsion. For example, Sabna Kotta *et al.* successfully created a nanoemulsion using both phase inversion and homogenization methods. They utilized gelucire 44/14 as a surfactant and transcutol-HP as a co-surfactant in their formulation. By employing these techniques, they were able to produce nano-sized emulsion globules. However, when homogenization was performed alone, they observed larger globule sizes even with increased pressure and cycles at lower emulsifier concentrations. This indicates that homogenization alone cannot decrease the size of the globules. Only when the optimal concentration of an emulsifier is combined with increased homogenization pressure and cycles, can the size of the globules be reduced. This is because homogenization alone can break down the globule size to the nano level, but with a lower concentration of surfactant, the newly formed globule surface may not be adequately covered, leading to re-coalescence. By using the optimal concentration of an emulsifier and increasing homogenization pressure and cycles, a smaller globule size with a good polydispersity index can be achieved. Consequently, the author concluded that the desired particle size, along with a lower polydispersity index, was obtained throughout the preparation process by combining the surfactant, homogenization pressure, and cycle duration [89].

Mohammed S. and his colleagues utilized ultrasonication as a method to create a thymoquinone-loaded topical nanoemulgel for wound healing. The ingredients used in this formulation were black seed oil as the oil vehicle, Kolliphor El as the surfactant, and Transcutol HP as the co-surfactant. The nanoemulgel was prepared by subjecting it to ultrasonication for different time intervals (3, 5, and 10 min) at a 40% amplitude. It was observed that when the surfactant concentration decreased during 10 min of ultrasonication, the size of the globules increased. Conversely, increasing the surfactant concentration during 10 min of sonication resulted in smaller globules. The authors concluded that the effectiveness of sonication is dependent on the appropriate concentration of surfactant [91]. Monitoring the control parameters

of the process and considering the composition of the excipients are essential measures in the optimization of the formulation.

The skin possesses an innate characteristic of serving as a safeguard against external substances. Consequently, the permeation of substances through the skin poses a significant challenge for topical delivery systems. The outermost layer of the skin is known as the stratum corneum, which is succeeded by the stratum granulosum and stratum lucidum. Comprised of keratinized cells, waxy lipids, fatty acids, and cholesterol, the stratum corneum aids in moisture retention and forms a hydrophobic barrier on the skin [92]. Following the stratum corneum, the epidermis is located, which is then followed by the dermis and subcutaneous layer. Once the subcutaneous layer is crossed, the active moiety will finally enter the systemic circulation. The main obstacle for the drug moiety, after being released from the gel matrix, is to cross the stratum corneum. At this point, the nano-sized droplet, due to its small diameter, can traverse through two different pathways as illustrated in fig. 4. One pathway involves cell-to-cell transfer, which is driven by concentration gradients and is referred to as transcellular transport or intracellular transport. The other pathway involves passing through intercellular spaces, known as paracellular transport [93]. While the third pathway known as transappendageal transport exists, its impact on drug penetration is restricted due to the fact that hair follicles and glandular ducts account for a small fraction of the overall skin surface area [94].

Ex-vivo permeation experiments typically involve assessing the impact of nano-emulgel formulations on isolated tissue in a simulated biological environment. These studies provide a comparative evaluation of penetration between various topical dosage forms and offer insights into the drug's flux rate through the skin. Jeengar *et al.* developed a nano-emulsion utilizing emu oil as the oil phase. The optimized nanoemulsion was combined with Carbopol gel to create a nano emulgel, which was then utilized for the topical administration of curcumin as an anti-inflammatory agent in rheumatoid arthritis. Results from ex-vivo permeation studies indicated that skin permeation was more pronounced with the nano-emulgel due to higher formulation retention compared to the nano-emulsion [95, 96]. Elmateeshy and his team created a nano-emulgel by incorporating terbinafine HCl (TB) nano-emulsion, which was formed using peceol as the oil phase and a surfactant mixture of TWEEN 80 and propanolol. They also used Carbopol as a gelling agent. In ex-vivo studies, it was observed that the peceol oil-based nano-emulgel had enhanced permeation compared to the available marketed products [97]. Similarly, Mulia *et al.* developed a nano-emulgel for mangosteen extract, which consisted of an o/w nano-emulsion with virgin coconut oil as the oil phase and a surfactant mixture of Tween 80 and SPAN 80. The gel base was made using xanthan gum, and phenoxyethanol was added as a preservative. *In vitro* permeation studies showed increased penetration compared to the nano-emulsion [98-100]. Furthermore, Bhattacharya and colleagues developed a celecoxib nano-emulgel using carbopol-940 hydrogel base, along with Tween 80 and Acconon MC8-2EP as surfactants. The results from both *in vitro* drug release and ex-vivo studies were favorable. By the twelfth hour of diffusion, the enhanced formulation exhibited a 95.5% cumulative drug release, surpassing the 56.90% release seen with the commercially available product. Nano-emulgel demonstrated a superior penetration coefficient when compared to the standard formulation [101]. Similarly, Chin *et al.* formulated a telmisartan nano-emulgel for intranasal administration utilizing various molecular weight chitosan polymers. Enhanced permeation characteristics were observed in ex-vivo penetration studies. The researchers highlighted that the enhanced permeation was linked to the molecular weight of the polymer, with medium molecular weight chitosan exhibiting superior permeation properties [102].

Begur *et al.* developed a nano-emulgel containing tacrolimus for transdermal delivery, utilizing almond gum as the gel base and oleic acid as the lipophilic component. The addition of Cremophor as a surfactant enhanced penetration, as evidenced by significant improvements in skin permeation observed during tests on rat abdominal skin [103]. In a similar manner, Syamala *et al.* developed a nano-emulgel formulation of butenafine, an antifungal agent that is commercially available as a cream. Their research yielded significant findings, as ex-vivo penetration studies demonstrated a notable enhancement in permeation compared to the creams currently available in the market. Similarly, a 53% increase in ketoconazole permeation was noted when administering the drug in nano-emulgel formulation as opposed to the standard cream available in the market. Utilizing such dosage forms could enhance the patient's quality of life [104]. These studies demonstrate the efficacy of nano-emulgel in enhancing the penetration of the active ingredient when compared to nano-emulsion and traditional topical formulations. The penetration of the nano-emulgel is influenced by several factors such as gelling agents, surfactants, and permeation enhancers. Gelling agents enhance penetration by improving the formulation's adherence to the skin. On the other hand, surfactants, either alone or in combination with a co-surfactant, enhance penetration by disrupting the lipid bilayer. All of these components contribute to the improved penetration of the active ingredient.

Characterization studies of nano-emulgel

The quality and consistency of the pharmaceutical product must be assessed through various tests to ensure uniformity between different batches. These tests are crucial in determining the behavior and stability of the product. According to USP standards, there are several universal tests applicable to any dosage form such as description, identification, assay, and impurities. In the case of a topical dosage form, specific tests mandated by USP include uniformity of dosage units, water content, microbial limits, antimicrobial and antioxidant content, pH, particle size, sterility, and the polymorphic nature of the API. In addition to these tests, nanoemulgel, which comprises nanosized globules, must undergo evaluation for zeta potential, droplet size, and polydispersity index (PDI). Furthermore, physiochemical tests like *in vitro* release, spreadability, bio-adhesive properties, skin-irritation, ex-vivo permeability, and *in vivo* bioavailability should be conducted to comprehensively understand the behavior of nanoemulgel.

Zeta potential

The stern layer is a layer of ions that typically coats the particles in a solution. In addition to the stern layer, there is a diffuse layer of loosely bound ions. Together, these layers form an electrical double layer. At the boundary between the ions in the diffuse layer that move with the particle and the ions that stay with the bulk dispersant, there is an electrostatic potential known as the zeta potential. This potential is measured at the "slipping plane" boundary [105]. Zeta potential analysis offers an indirect assessment of the overall charge and serves as a means to evaluate consistency between different batches. Increased zeta potential leads to stronger repulsion, enhancing the stability of the product. For instance, the elevated zeta potential of emulsion droplets prevents them from merging. Additionally, a surface charge modifier can be applied to regulate the surface charge. If a negatively charged surface modifier is utilized, the zeta potential value turns negative, and vice versa [106, 107]. Surface active components, such as anionic or cationic surfactants, have a significant impact on the stability of emulsions. The measurement of zeta potential, which can be done using different instruments like the ZC-2000 (Zeecom-2000, Microtec Co. Ltd., Chiba, Japan), Malvern Nanosizer/Zetasizer® nano-ZS ZEN 3600 (Malvern Instruments, Westborough, MA, USA), and other similar devices, is crucial in understanding this role.

Rheological characterizations

The field of rheology focuses on the study of how materials deform and flow. By characterizing the rheological properties of materials, we can understand how different concentrations of excipients, such as oils, surfactants, and gelling agents, affect the viscoelastic flow behavior of a formulation. Variations in viscosity and flow characteristics can have an impact on the stability, drug release, and other *in vivo* parameters of the formulation. For example, a formulation with shear thinning tendencies can create a thin layer on the skin surface, enhancing permeability, while a thicker formulation may decrease permeation. Therefore, understanding the rheological behavior is crucial in the development of nanoemulgel formulations, and various types of viscometers can be employed to determine this behavior [35]. The FDA advises assessing comprehensive flow curves

whenever feasible, represented as heat stress versus shear rate and viscosity versus shear rate at various shear rates until reaching low or high plateaus. In the case of a formulation demonstrating plastic flow, it is essential to assess yield stress values.

Spreadability testing

The even distribution of the topical medication is guaranteed by its spreadability, which in turn impacts the effectiveness of the treatment. The spreadability of the nanoemulgel is heavily influenced by its viscosity. Until now, there has been no universally accepted procedure for quantifying the spreadability of a pharmaceutical formulation. Several tests, such as the parallel-plate method and human subject assessment, are frequently employed to provide a reasonable estimation of spreadability. The parallel-plate method, also known as the slip and drag method, is particularly popular due to its straightforwardness and cost-effectiveness [108]. The experimental setup comprises of two glass slides of equal length. One of the slides is fixed to a wooden block, while the other slide is attached to a pulley at one end to measure spreadability. The spreadability of the emulgel is determined by its 'Slip' and 'Drag' characteristics. To measure spreadability, the nanoemulgel dosage form is placed on the stationary glass slide and then compressed between the stationary and mobile glass slides. The formulation is firmly squeezed to ensure uniform spreading and to eliminate any air bubbles. Known weights are gradually added to the pulley until the upper slide slips off from the lower slide. The time taken for the slipping off is recorded, and this information is used to calculate the spreadability using the provided equation [109]. The equation S = M * l/T represents the relationship between spreadability (S), weight (M), length (L), and time (T) in detaching slides.

Safety concerns

Toxicity and skin irritation are significant considerations during the development of a formulation related to the skin [110]. Enzyme activity impairment, disruption of regular physiological processes, and occasionally carcinogenic impacts (such as those induced by Sodium dodecyl benzene sulfonate) are typical toxicity concerns associated with surfactants [111]. Smith and his team conducted an examination on the impact of two surface active agents, namely sodium dodecyl sulfate and dodecyl trimethyl ammonium bromide, on the process of penetration and skin perturbation. Their findings indicated that the primary cause of disruption in the skin layer is the presence of high concentrations of micelle agglomerate and monomers [112].

The assessment of irritation resulting from the application of topical nano-emulgel can be conducted by administering it on the shaved skin of a rat. Subsequently, careful observation of any redness or other indications of inflammation on the skin is performed. These observations are then categorized and evaluated based on the quantity of eurythmic spots, as outlined in table 4, to determine their clinical significance [112]. Typically, a grade scale that goes up to 2 is considered to be a secure range. Azeem and colleagues formulated a ropinirole nano-emulgel by utilizing caproyl 90, tween 20, and carbital. The assessment of skin irritation revealed a grade 2 erythema index, indicating that it is safe [113]. Gannu and colleagues conducted skin irritation experiments on a nano-emulgel formulated with the non-ionic surfactant Tween 80 and the co-surfactant labrasol. Their findings revealed the absence of any indications of skin irritation, as these surfactants are widely recognized as safe [25, 36]. Major adverse effects are typically seen with cationic surfactants, leading to their exclusion from formulations intended for topical application. Nonionic surfactants, on the other hand, are generally favored due to their minimal disruption of the skin barrier [104, 111].

Table 4: Skin irritation grading scale and their clinical implications

Clinical portrayal	Grade
No erythema	0
Slight erythema that is barely perceptible	1
Moderate erythema that is visible	2
Erythema and papules	3
Severe Edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application sight	7

Difficulties or challenges

The administration of bulky drug molecules with a molecular weight greater than 400 Dalton is impeded in this formulation, as they encounter challenges in being reduced in size and tend to seep out of the gel structure. There are only a few safe surfactants and co-surfactants that can be used in the preparation of emulgel. Careful consideration must be given to the choice of surfactant, as it may result in harmful effects. Excessive use of surfactants in emulgel formulations can cause skin issues such as contact dermatitis, erythema, and disruption of the skin barrier [114]. The gelling agent is highly sensitive to changes in pH and temperature, which may result in the disruption of the gel structure and the release of chemicals [115].

Capricious behavior in nano-emulsion arises from Ostwald ripening, a phenomenon linked to the small size of oil droplets. It is advisable to prepare nano-emulsion shortly before use. Key tasks crucial for the stability of nano-emulgel include optimizing the stirrer speed in the homogenizer to achieve a firm and crack-free gel, blending the right amounts of surface-active agents, and choosing a dependable packaging material [116]. Specialized equipment is necessary to reduce the size to the nanoscale, and this task must be carried out by skilled workers. The high cost of maintaining energy-intensive homogenizers and the overall production expenses pose significant challenges when scaling up the production of nano-emulgel formulations. Despite these drawbacks, nano-emulgel offers the advantage of improved adhesion and enhanced entrapment of the drug within the gel matrix [53, 27]. Furthermore, emulgel effectively addresses the common limitations observed in traditional topical dosage forms like emulsion, ointment, and lotions. These drawbacks include creaming, phase disruption, and the degradation of ointments caused by oxidation. However, by utilizing emulgel, these issues are successfully mitigated [44, 117].

Nanoemulgel: present and future outlook

The formulation development of hydrophobic drugs has faced significant challenges due to their low solubility, resulting in poor bioavailability. Creams, ointments, and lotions are some of the topical formulations used, which possess good emollient characteristics. However, these formulations have slow drug release kinetics because of the presence of hydrophobic oleaginous bases like petrolatum, beeswax, and vegetable oils, which hinder the incorporation of water or aqueous phase. On the other hand, gels, which are aqueous-based formulations, enhance the release of drugs from the medication by providing an aqueous environment. Therefore, hydrophobic APIs are combined with oily bases to create an emulgel, which is then nanonized to form a nanoemulgel with improved properties. The superior properties of a nanoemulgel, such as thermodynamic stability, permeation enhancement, and sustained release, make it an excellent dosage form. By advancing research in nanoemulgel delivery systems, it is possible to formulate drugs that are currently being eliminated from the development pipeline due to poor bioavailability and therapeutic non-efficacy. Despite these advantages, the commercialization of nanoemulsion manufacturing is currently limited. However, with advancing technology, commercially viable and profitable manufacturing techniques may become possible in the future. With the advantages of nanoemulgel over other formulations, a substantial increase in its production can be anticipated.

CONCLUSION

In conclusion, the topical delivery of antifungal drugs, supported by the use of nanoemulgels, is a viable approach. This type of drug delivery system has multiple advantages, including targeted delivery, increased stability, enhanced permeation, and reduced side effects. Nanoemulsion encapsulated in the gelling system takes benefits from both: stable drug release and increased localization. Nanoemulgels can be considered a relevant avenue in the delivery of dermatological solutions. They have the capacity to solve the existing problems with the current antifungal drug delivery systems and offer a substantial promise for multiple other applications. However, additional research and investment in the field are needed to cover their beneficial properties fully.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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