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Review Article

A Review On Biomedical Applications Of Antifungal Microemulsions

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ABSTRACT

Fungal infections are a global concern. Essential preparations are used to obtain local effects at the application site by penetrating the drug into the lower layers of the skin or irritation. About 40% of new chemicals have poor water solubility, which is a major challenge for modern drug delivery systems, leading to poor absorption, poor bioavailability and dose inconsistency. Microemulsions consist of a water phase, an oil phase, a surfactant, and a cosurfactant. By transferring the hydrophilic part to the water phase and the hydrophobic part to the oil phase, surfactant molecules form a layer on top of the oil droplet, resulting in an increase in surface tension at the oil-water interface. At very low temperatures, microemulsions are formed spontaneously at the optimal temperature and ratio of components, but in practice, low energy such as heat and mixing are used to promote formation. Examples of antifungal agents: miconazole, ketoconazole, and itraconazole, which are lipophilic, improve self-assembly, thermodynamic stability, clear appearance, drug loading, biomembrane penetration, and formulation as microemulsions increased Bioavailability compared to conventional dosage forms.

INTRODUCTION

Fungal infections are a major concern worldwide. It is estimated that more than 40 million people in developed and developing countries suffer from fungal infections [1]. The incidence and prevalence of invasive fungal infections have increased since the 1980s, especially in immunocompromised patients and hospitalized patients with underlying conditions [2]. Candida yeast is a microorganism associated with the normal microbiota of healthy people, mainly in the oral mucosa, digestive tract, and urinary tract of women [3]. However, these fungi are responsible for a variety of clinical conditions, ranging from skin and mucosal infections to systemic infections, especially in immunocompromised patients [4]. Their importance comes from the high frequency of colonization and infection of the human host,

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and they are the fourth most common pathogen associated with nasal infections [5,6]. Fungal skin infections usually affect the skin because keratin, the protein that makes up the skin, hair and nails, is destroyed. Symptoms of fungal skin infection include a variety of skin rashes, including redness, swelling, itching, and dry skin [7]. Essential preparations are used to obtain local effects at the application site by penetrating the drug into the lower layers of the skin or irritation. The main advantage of topical delivery systems is the ability to deliver drugs selectively to a specific location (local action). This allows the use of drugs with a short biological half-life and a narrow therapeutic interval to extend the duration of action [8]. About 40% of new chemicals have poor water solubility, which is a major challenge for modern drug delivery systems, leading to poor absorption, poor bioavailability and dose inconsistency. However, oral administration is inappropriate if the drug is significantly degraded in the digestive tract or extensively metabolized by first-pass effects in the liver. This weakness led to the search for alternative drugs in the form of microemulsion-based hydrogels for local delivery [9].

MICROEMULSION DRUG DELIVERY SYSTEM:

Microemulsions consist of water phase, oil phase, surfactant, and cosurfactant [10]. By changing the hydrophilic part to the water phase and the hydrophobic part to the oil phase, surfactant molecules form a layer on top of the oil droplets, which leads to a very high drag value at the oil-water interface. [11] The particle size of microemulsions is about 10-100 nm, the microemulsion drug delivery system is transparent and thermodynamically stable [12,13]. Microemulsions containing essential oils enhance the medicinal and biopharmaceutical properties of the bioactive compounds in the oil. It improves physical and chemical stability, controlled release, solubility, bioavailability and improves skin penetration and retention of bioactive compounds in essential oils [14]. Panapisal et al reported that a microemulsion containing labrazol as a surfactant increased the solubilization of silymarin and protected it from oxidation. Skin permeability and microemulsion of citrulline phenylethanoid glycosides increased significantly compared to aqueous solution. The authors report that microemulsions act as penetration enhancers by affecting the structure of the stratum corneum and reducing the diffusion barrier. Longer skin retention in microemulsions associated with faster release compared to phenylethanoid glycosides in aqueous solution and high solubility of phenylethanoid glycosides microemulsions [15,16].

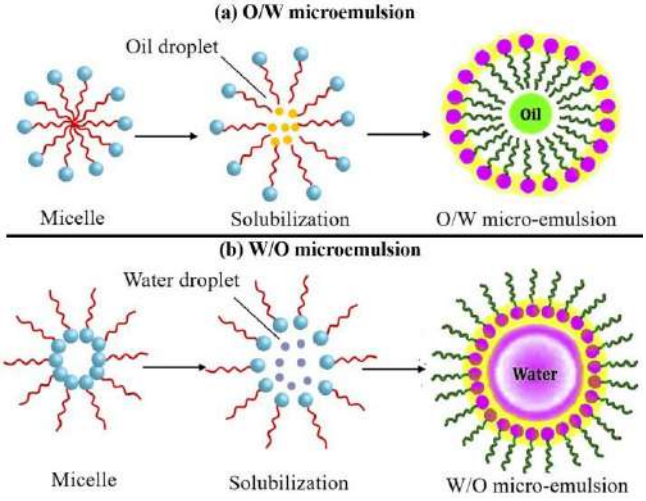

Figure 1: Microemulsion skeletal structure (O/W and W/O microemulsion)

There are basically three types of microemulsion. Microemulsion classification is based on the amount of oil and water used. 1) Oil in water (o / w) Winsor I, 2) Water in oil (w / o) Winsor II and 3) Two continuous microemulsions or Winsor III [16].

Advantages of microemulsions:

Microemulsions are superior to conventional creams, gels, and topical treatments. The main disadvantage of current formulations, such as base gels and solutions for the treatment of fungal infections, is the low solubility of lipophilic drugs. The main advantage of microemulsions over gels is that they are used to dissolve drugs and increase the local availability of drugs. The advantage of microemulsions over creams is the improvement of hydration of the stratum corneum and the penetration of drugs into the bloodstream and skin [17]. Although microemulsions offer many advantages for topical delivery, they are difficult to stabilize due to their low permeability [18]. This problem can be overcome by preparing microemulsion-based hydrogels using polymers such as hydroxypropyl methylcellulose (HPMC), carbopol and xanthan gum (Table 1) [19].

Table 1: List of various excipients used in microemulsion formulation

Oil / Lipids	Cottonseed oil, Soybean oil, Palm oil, Castor oil, Hydrogenated specialty oil (hydrolyzed corn oil) etc. Labrafac GG, Isopropyl myristate, Brij, Stepan GDL, Labrasol etc.
Surfactants	Potassium laurate, Sodium lauryl sulphate, Quaternary ammonium halide, Sulfobetaines, Sorbitan esters (Spans), Polysorbates (Tweens), Labrasol, Targat TQ.
Co-Surfactants	Hexanol, Pentanol, Octanol, Ethanol, PEG 400, PEG 300, ALkoline MCM, Transcutol P.
Co-solvents	Ethanol, PEG, Carbitol, Transcutol P, PG, Glycerin, Butanol, Menzyl alcohol, Glycerol.

Anatomy of human skin:

The skin is the largest organ in the body and is a complex organ containing many different cells. The structure of the skin is shown in Figure 2. The skin accounts for 12-16% of the adult body weight and consists of three main layers: epidermis, dermis, and subcutaneous tissue [20]. The basal layer acts as a bridge between the skin and underlying tissue, providing insulation and protection from impact. Skin is made up of connective tissue, collagen fibers, and elastic tissue that give skin elasticity. The skin contains blood vessels, lymphatic vessels, nerve endings, sweat glands, sebaceous glands, and hair follicles [21]. The outer layer of the skin, the epidermis, is a barrier against external factors and varies in thickness (0.06 - 0.80 mm). It consists of four main layers: stratum corneum, stratum granulosum, stratum corneum, and stratum basal. The outermost layer, the stratum corneum, consists of 20-30 flat corneal layers surrounded by a lipid bilayer [22]. This prevents the entry of unwanted substances and prevents water loss from the body [23]. Below the stratum corneum there is a layer of granulosomes with keratohyalin and stratum corneum connective cells. The circulation layer, called stratum corneum, contains keratinocytes bounded by desmosomes and Langerhans cells, which are responsible for the immune response. The basal layer, or germinal layer, surrounds the dermis and contains melanocytes and Merkel cells, which are responsible for melanin production and light touch [24].

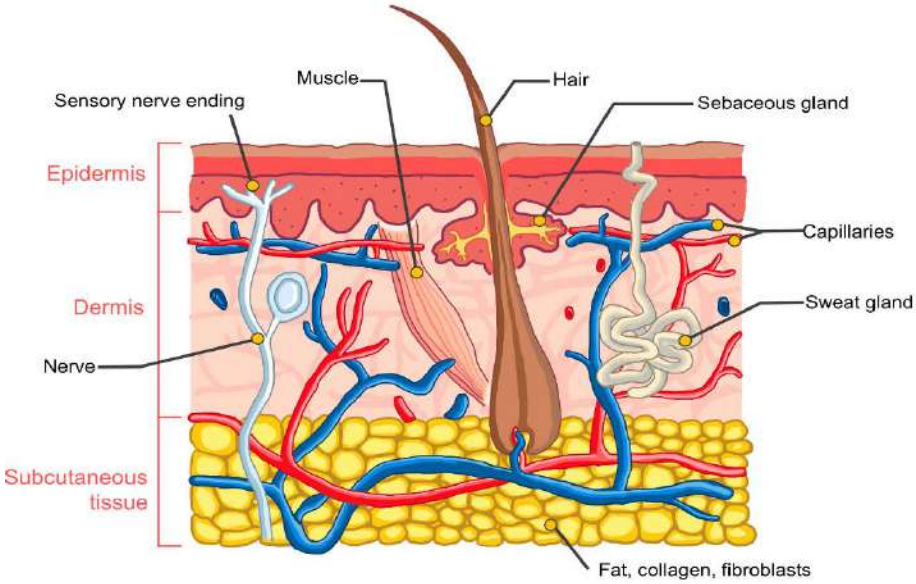

Figure 2: Anatomy of human skin [24]

Mechanism of drug penetration and enhancement of penetration:

The skin is the outer covering of the body and primarily acts as a protective layer that protects the person from harmful external stimuli such as light, temperature, and radiation, and limits the entry of pathogens and other foreign substances. This protective nature of the skin makes it very difficult to deliver drugs topically or transdermally. Therefore, various new strategies have been adopted to improve drug delivery and improve skin absorption, including delivery systems, penetration enhancers, novel drug delivery systems, transdermal adhesives, etc. All of these strategies increase drug penetration by temporarily disrupting the skin stratum corneum [25]. Microemulsions reduce the drag force on the surface of the skin and dissolve the drug. Penetration enhancers used in formulations are sometimes surfactants or lipids that can dissolve or disrupt the lipid bilayer structure of the stratum corneum. Thus, the layer minimizes the barrier function of the cornea and opens pores or channels for drug transport across the skin [26, 27]. Penetration enhancers change the lipid bilayer and the arrangement of keratinocytes in the stratum corneum, allowing the drug to penetrate at a specific rate. The interaction between stratum corneum (skin barrier) and transmission enhancers is best explained by the lipid-protein partitioning theory. According to this theory, drug penetration is mainly due to 1) drug interaction with cellular lipid bilayer, 2) interaction with keratinocytes, and 3) an additional solvent or intervening enhancer. Skin stratum corneum; this can reverse the skin barrier and facilitate transdermal drug delivery [28]. After the contraction is reduced, drug release can occur through three important pathways. 1) Intracellular: Pathways between cells are favorable for hydrophilic substances. 2) Intracellular: drug transport between cells is ideal for lipophilic substances. 3) follicular / transadnexal: drug delivery through hair follicles or other skin appendages [26, 29].

Formulation Parameters: Composition and Preparation Methods:

Although microemulsions (MEs) can form spontaneously in the optimal concentration of components and temperature, in practice low energy such as heat and mixing favor their formation. MEs are classified as either oil-in-water (w/o) or water-in-water (o/w), which represents the dispersed phase in the continuous phase. There are also more complex systems such as o/w/o and

w/o/w. Continuous microemulsions can also exist, where the water and oil phases are interconnected and stabilized by the surfactant region similar to the interfacial region [30]. Lindemann et al showed that continuous paths can exist between round, planar, tubular, and other interconnected structures in the ME system. The continuous structure is characterized by dynamic and high amphiphilic properties, surface modification, lower drag and better access properties compared to w/o or spherical MEs. [31,32]. Navi et al. compared to the penetration of hydrophilic drug caffeine into the skin of cut pigs when administered continuously, containing the same components as O/W, W/O, and microemulsions. Percutaneous penetration of caffeine in the order w/o < 2 continuous < o/w ME, and o / w ME resulted in penetration of 50% of the applied dose over 24 h [33]. In contrast, Bhatia et al found that the microstructure of the ME used for the lipophilic drug adapalene changed from O/W to O/W, with an increase of about 3-fold in both cases with increasing microemulsions water content. Medicine in the continuous phase of microemulsions provides the highest drug delivery and the continuous system acts as an intermediate system [32].

Preparation Methods:

Microemulsion formation is usually a two-step process, where a macroemulsion is prepared and then converted to microemulsions. It requires external energy applied through high energy (HEE) or low energy (LEE) methods. HEE techniques, such as high-pressure homogenizers, microfluidization, and sonicators, produce high disruptive forces that disrupt the oil and water phases and lead to the formation of nanometer droplets. LEE methods include thermal, kinetic, and phase transformations. Nanoemulsion droplet size control is related to preparation method and formulation composition.

Melting can be used as a method to produce microemulsion final products. Microemulsions can be prepared as o/w microemulsions, bicontinuous microemulsions, or by mixing MEs with water [34,35]. When o/w microemulsion is mixed with water, a certain fraction of the surfactant will dissolve in the water phase. Surfactant molecules remaining at the oil/water interface cannot maintain the low surface tension required for thermodynamic stability, and ME droplets also form nanoemulsion droplets [36].

When microemulsion is aggregated, microemulsion is formed through a homogeneous core that is spontaneously formed in the emulsion process [37]. Despite the existence of this mechanism, nanoemulsion can be formed by surfactant or cosurfactant migration across the oil-water interface due to the "Ozo effect" in continuous microemulsion or microemulsion-free solutions [38]. When mixed with ME, oil can act as a nucleator, leading to homogeneous nucleation and thus producing large and numerous droplets [39]. Nanoemulsions formed by dissolving microemulsion o/w or continuous ME are more stable and also contain small droplets [40].

Table 1: List of various excipients used in micro-emulsion formulation

Oil / Lipids	Cottonseed oil, Soybean oil, Palm oil, Castor oil, Hydrogenated specialty oil (hydrolyzed corn oil) etc. Labrafac GG, Isopropyl myristate, Brij, Stepan GDL, Labrasol etc.
Surfactants	Potassium laurate, Sodium lauryl sulphate, Quaternary ammonium halide, Sulfobetaines, Sorbitan esters (Spans), Polysorbates (Tweens), Labrasol, Targat TQ.
Co-Surfactants	Hexanol, Pentanol, Octanol, Ethanol, PEG 400, PEG 300, ALkoline MCM, Transcutol P.
Co-solvents	Ethanol, PEG, Carbitol, Transcutol P, PG, Glycerin, Butanol, Menzyl alcohol, Glycerol.

Compositions:

The selection of emulsion components and the ratio of these components is important to create a stable fluid system with the right particle size. Various components and compounds were analyzed (Table 1). Phase components include fatty acids (eg oleic acid), fatty acid esters and alcohols (eg isopropyl myristate, isopropyl palmitate, ethyl oleate), medium chain triglycerides, tristanes, and terpenes (eg limonene etc.) Availability of enhancers these can be used alone or in combination to form the oil phase. The aqueous phase may contain sodium chloride, buffer salts, preservatives, and intermediate additives. Dissolving agents (eg, Carbopol®, Aerosil®, gelatin) are incorporated to reduce flow and create the desired final product consistency [38,40]. A variety of materials are used as surfactants and cosurfactants (see Table 1 for example). Attention should be given to ingredients that reduce surface tension and produce a stable liquid with the right particle size, as well as reduce skin irritation. Therefore, nonionic surfactants are preferred. Commonly used surfactants include Tween® (polysorbate), Cremophor® (macrogol glycerol hydroxystarch, castor oil PEG-40, and polyoxyl 40 hydrogenated castor oil), and transscotol P (diethylene glycol monoethyl ether) 3-3 etc. Organogels contain lecithin-based ME and nonpolar organic solvents, forming a gel-like reverse micellar system with high viscosity, dispersibility, thermodynamic stability, and clarity and biocompatibility. [42]. Cosurfactants are usually short and medium chain alcohols and polyglyceryl derivatives such as ethanol, isopropanol, isopropyl myristate, and propylene glycol (PG). Nonionic surfactants have also been used to prepare less reactive cosurfactants [41,43]. Table 1 shows examples of different ME compounds and their skin distribution. Lopez provides an excellent review focusing on the formulation and physical properties of microemulsion [44].

Physical Characteristics of Pseudo Ternary Phase Diagrams:

Microemulsions are characterized by a set of physical properties that are important determinants of their composition, drug release, and stability. Pseudo-three-phase diagrams are often constructed to show the different phase boundaries as a function of water, oil, and surfactant/cosurfactant composition [45]. A mixture of oil, surfactant, and cosurfactant in a specific weight ratio is mixed with an aqueous solution at ambient temperature (25°C) with moderate temperature. After equilibrium, the composition of the three components producing a transparent liquid is plotted on a phase diagram determined by visual inspection or polarized light microscopy. An example of a quasi-binary phase diagram for an oil-water mixture showing different phase regions and different ratios of surfactants and cosurfactants (Twin 80 and Bridge 52) is shown in Figure 3 [46].

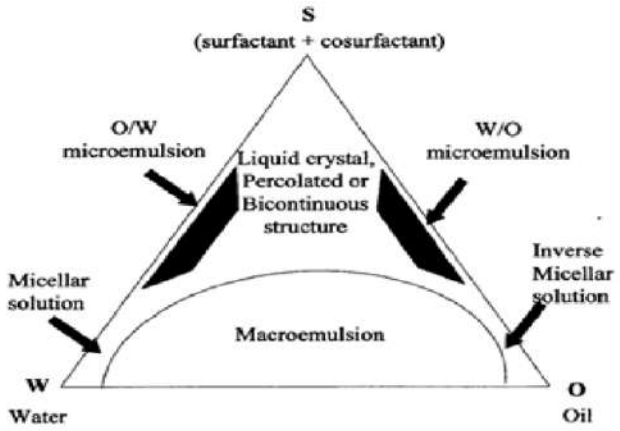

Figure 3: Pseudo Ternary Phase Diagrams for microemulsion.

BIOMEDICAL APPLICATIONS OF MICROEMULSION:

Microemulsions are promising systems for sustained or controlled drug release for transdermal, oral, topical, transdermal, ocular and parenteral administration. Increased drug absorption, altered drug kinetics, and reduced

toxicity are some of the benefits of the delivery process [47,48].

Table 2: Applications of microemulsion based formulations.

Category	Active ingredients	Application
Antibiotics	Metronidazole	Reduce the bacterial infection and improve healing.
Antifungal	Fluconazole, Voriconazole, Ketoconazole, Miconazole, clotrimazole	Reduce fungal infections around the skin.
Antiviral	Penciclovir	Treatment of herpes labialis infection.
Anti-inflammatory	Ibuprofen, Ketoprofen	In the early stages of inflammation symptoms.
Antioxidant	Quercetin	It is used in skin care and cosmetic products.

Antifungal applications:

Superficial mycoses often respond to topical treatment. In the treatment of eczema, topical antifungal medications such as ketoconazole are used to reduce fungal infections caused by Pityrosporum (Malassezia furfur) spores. Examples of antifungal agents: miconazole, ketoconazole, and itraconazole, which are lipophilic, improve self-assembly, thermodynamic stability, clear appearance, drug loading, and penetration into biological membranes and are formulated as microemulsions. Increase bioavailability compared to conventional dosage forms [48]. Microemulsions of water-soluble antifungal drugs miconazole, ketoconazole, and itraconazole are designed and prepared with mineral oil or olive oil as the oil phase. Labrafil M 1944 CS and Purulor Olake (1: 1). Labrafil M 1944 CS and Purulor Olake (1: 2). or Labrafil M 1944 CS, Capmul MCM C-8, Plurol Oleique and dehydrated ethyl alcohol (3:3:1:1) [49]. A water-soluble antifungal microemulsion with an in vitro release rate comparable to the gel formulation has been successfully developed. The results of the study of miconazole nitrate formulated as a positively charged microemulsion demonstrate drug targeting without increasing systemic absorption. Lauranin benzyl ester, a natural amino acid ester, is an ionic charge carrier [50]. A microemulsion-based gel for vaginal delivery of clotrimazole and fluconazole was developed and compared in vitro with commercially available clotrimazole gel (Candid-V gel). This microemulsion-based gel showed significantly higher antifungal activity and bioadhesion in vitro compared to Candid-V gel. Fluconazole microemulsion-based gel does not cause skin irritation [51,52].

Table 3: Microemulsion based topical and transdermal formulations [53]

Name of drug	Oil	Surfactant	Co-surfactant
Amphotericin B	Lemon oil	Tween 20	Propylene glycol
Voriconazole	Cinnamon oil	Cremophor RH 40	Transcutol P
Fluconazole	Olive oil	Tween 80	Labrafac lipofile
Ketoconazole	Olive oil	Tween 80	PEG 400
Itraconazole	Castor oil	Tween 80	PEG 400

CONCLUSION:

A fungal skin infection is an infection of the skin caused by a fungus. Fungal skin infections usually affect the skin because keratin, the protein that makes up skin, hair and nails, is destroyed. Microemulsions are optically isotropic and thermodynamically stable solutions of oil, water, and amphiphiles. Microemulsions differ from

conventional liquids by their clarity, low viscosity, and most importantly, their thermodynamic stability. Microemulsion-mediated drug delivery is an area of ongoing research aimed at achieving controlled release by increasing bioavailability and targeting drugs to different sites in the body. Despite advances in antifungal therapy, infection prevalence and antifungal resistance remain high, making disease control with antifungal agents difficult.

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