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Enhancing topical antifungal efficacy through microemulsion drug delivery systems

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Abstract
To reduce systemic adverse effects, topical medication is often required for fungal infections (mycoses) affecting the skin, nails, and mucous membranes. However, many antifungal drugs such as itraconazole, clotrimazole, and bifonazole have poor water solubility, limited skin penetration, and reduced therapeutic efficacy in conventional topical formulations. An attractive approach is to use microemulsions due to their high drug loading capacity, thermodynamic stability and their potential ability in improving penetration across the stratum corneum by lipid perturbation. Due to the unique properties of these transparent, nano-sized (5-200 nm) carriers that allow for solubilization of hydrophilic and lipophilic drugs with controlled and sustained release; this promise turned into reality. The preparation method mainly consists of the construction of a pseudo-ternary phase diagram Tosa = allowing for an oil and surfactant screening for their solubilization process, factorial optimization, and characterization in terms of droplet size (Dv), zetapotential (mV m) and viscosity as well as TEM imaging stability. Microemulsion-based hydrogels further improve patient acceptability and retention time by overcoming the inherently low viscosity of microemulsions alone. These systems have applications in parenteral, oral, nasal, and especially topical drug delivery. Despite their advantages, certain challenges remain, including surfactant-induced irritation, stability issues, and limited penetration into hair follicles and nails. Future research is expected to focus on combination therapies, mucoadhesive and film-forming technologies, nano-enabled systems, new antifungal agents, targeted delivery strategies, and improved safety profiles. Overall, microemulsions represent a versatile and effective approach for enhancing the solubility, stability, and topical penetration of antifungal medications.

Keywords: Clotrimazole, Bifonazole, Microemulsion, topical antifungals, drug solubility, skin penetration, pseudo-ternary phase diagram, hydrogels

Introduction
Fungal infections, also called mycoses, occurs when hazardous fungi like dermatophytes, Molds, or yeasts infiltrate and thrive on your skin, nails, mucous membranes, or even deeper inside your body. These can be modest and surface-level think athlete's foot or jock itch can turn serious and life-threatening in persons with compromised immune systems, spreading systemically. Fungi love keratin, the protein in your skin, hair, and nails, which is why they commonly target those regions, showing up as red, scaly, itchy, or dry rashes. For anything like jock itch or athlete's foot, try applying aloe vera gel everyday for a month to calm it naturally but if it doesn't clear up, consult a doctor for proper treatment [1].

Topical therapies combat the infection locally by penetrating deeper skin layers or mucous membranes where they are applied. The main bonus is placing the medicine exactly where it's required for a focused effect, which is perfect for drugs with a tight safety window or ones that don't hang around long in the body this keeps their action lasting longer while cutting down on side effects elsewhere [2].

A key challenge in current medication administration is that roughly 40% of new pharmaceuticals barely dissolve in water, leading to limited absorption, low bioavailability, and variable dosing. Pills sometimes fall short too, since the liver's first-pass action or harsh intestinal conditions break them down swiftly. Because they avoid these problems while improving solubility and skin delivery, researchers enthusiastically turned to substitutes such microemulsion-based hydrogels for topical application [3].

Skin acts as a natural barrier to topical medicine administration, making it challenging. Considering this, microemulsions are created that have a high medication loading capacity, minimal skin irritation, and the potential to lower the stratum corneum's diffusion barrier by dissolving the lipids there and improving drug penetration [4].

Microemulsions are transparent, stable mixtures of oil and water stuff that ordinarily doesn't mix held together by surfactants that coat the boundary between them. Their extremely small droplets (only 5-200 nm across) and nearly low surface tension are what make them unique and ideal for dissolving difficult medications that detest water. Microemulsions excel at dissolving and helping your body absorb medications that don't mix well with water, whether you rub them on your skin or take them another way. That's exactly why they're such a huge issue in medication delivery research nowadays [6]. Microemulsions can manage both water-loving hydrophilic and oil-loving lipophilic medications thanks to their tiny zones or microdomains with varied levels of polarity all in one smooth, homogeneous mix. On top of that, they add bonuses like rock-solid thermodynamic stability, a clear look, easier prep, and speedier diffusion with greater absorption than old-school solvents without surfactants [5].

Microemulsions are far superior to traditional creams, gels, and liquids when it comes to applying medications to the skin. Regular topicals flunk at dissolving oily (lipophilic) antifungal medications, whereas microemulsions ratchet up solubility and get more active material right to the infection location. In contrast to creams, they also moisturize the stratum corneum, the skin's tough outer layer, which facilitates improved drug absorption [7].

Although microemulsions have several benefits for topical distribution, their low viscosity makes it challenging to stabilize the system [8]. Polymers like HPMC or Carbopol can be used to create microemulsion-based hydrogels that have a pleasant, spreadable texture. Bifonazole, a potent broad-spectrum azole antifungal, attacks all sorts of skin infections like tinea, athlete's foot (tinea pedis), and ringworm by striking yeasts, Molds, dermatophytes, and other nasty fungi. For athlete's foot, apply it topically once a day (approximately 100 mg) for 2-3 weeks but conventional gels only absorb a tiny portion (0.6% of what you put on), so not much gets through [9]. Therefore, a microemulsion formulation was created to improve the topical skin permeability and solubility of bifonazole. Furthermore, bifonazole has a short half-life of one to two hours. Therefore, a hydrogel based on microemulsion was developed to prolong the duration of action and maintain the release of bifonazole [9]. Clotrimazole vaginal tablets work equally as effectively as normal nystatin tablets for clearing up vaginal candidiasis, with identical cure rates. That yet, there's no good data comparing them to nystatin creams or fizzy vaginal pills, which some doctors prefer. Even better, clotrimazole steps in well for those who didn't respond to other antifungals like amphotericin B or nystatin but it doesn't shine much against trichomonas vaginitis [10].

Research indicates that topical clotrimazole efficiently treats skin infections caused by Candida or dermatophytes. According to clinical testing, its cream works better against skin candidiasis than nystatin and is comparable to Whitfield's ointment or tolnaftate for dermatophytosis. Although unusual local irritation has led some patients to discontinue treatment, most people take it well [11].

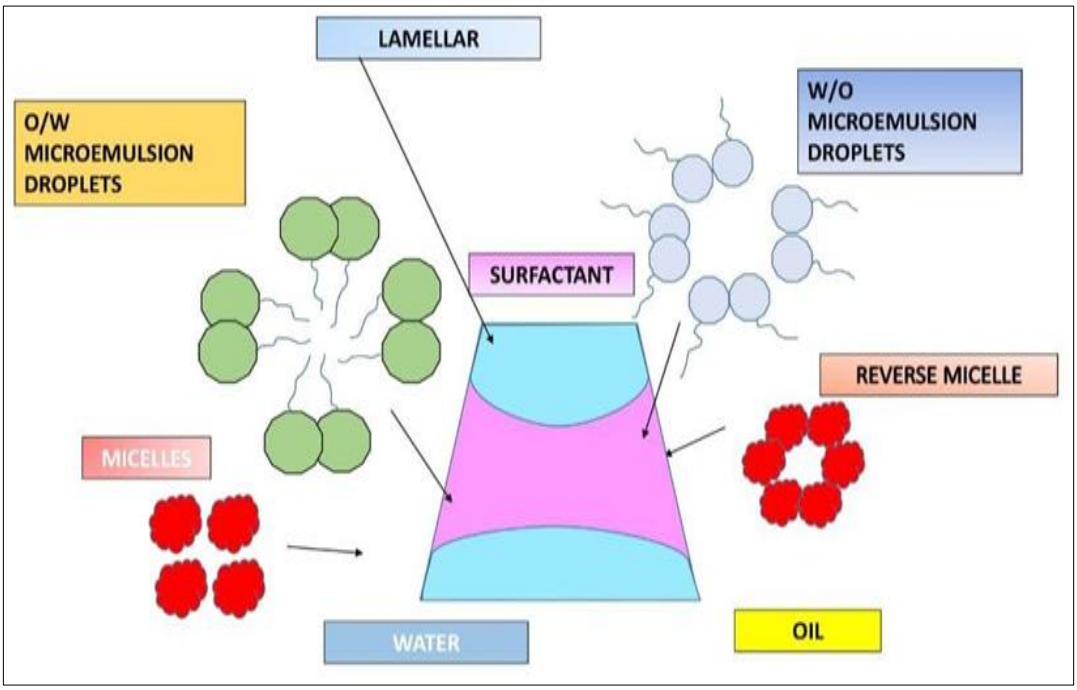

Fig 1: Phase diagram of microemulsion system

Azole antifungals, including clotrimazole, all target ergosterol a critical building ingredient of fungal cell membranes by preventing its formation. They tamper with a CYP450 enzyme that handles 14α-lanosterol demethylation, a vital stage in ergosterol synthesis, which leaves the membrane leaky and weak, inhibiting fungal development. Due to ergosterol's involvement in promoting fungal development, this causes ergosterol shortages, accumulation of defective 14-methyl sterols, enzyme shutdowns for cell wall construction, and leaking of fungal contents, all of which occur based on dose and time.

Composition

Table 1: Selection of oils, Surfactants and Co-surfactants used as solvents.

Oils	Solvent
	Oleic acid
	Cotton seed oil
	Olive oil
Surfactant	Solvent
	Tween*20
	Tween*80
	Span*20
Co-Surfactant	Solvent
	Propylene glycol
	Ethanol
	Methanol
	n-Butanol

The Reason for Topical Use of Microemulsions

Microemulsions get employed a lot in skin treatments since they improve drug penetration, dissolve drugs better, and release them in a controlled method just where needed. Their unique mix of oil, water, surfactants, and co-surfactants makes them perfect for antifungal and other skin meds.

Purpose

- **Improved penetration of the skin:** Drug penetration through the stratum corneum, the skin's primary barrier, is enhanced by microemulsions. Lipid layers are loosened by surfactants and co-surfactants. Deeper penetration is possible with small droplet sizes (< 100 nm). As a result, the medication is better localized at the site of infection.
- **To enhanced water-soluble drug solubility:** Numerous antifungals, such as itraconazole, bifonazole, and clotrimazole, are poorly soluble and lipophilic. Both are soluble in microemulsions: Hydrophilic lipophilic medications effectively, increasing their bioavailability.
- **To enhanced drug loading capability:** Compared to gels or creams, microemulsions can contain more medication since they contain both water and oil phases.
- **Stability of Thermodynamics:** Microemulsions are thermodynamically stable, in contrast to emulsions, which means Absence of creaming, absence of phase separation, extended shelf life they are therefore simple to produce and store.
- **Equitable distribution of drugs:** Microemulsions provide transparent, uniform systems that guarantee reliable medication administration repeatable treatment outcomes.

Materials

- **Preparation of microemulsion:** Once you've plotted out the microemulsion zone on the phase diagram, pick the proper ratios of oil, water, surfactant, and co-surfactant. To make your stable microemulsion ready to use, simply weigh them out, mix, and stir until you have a clear, uniform liquid.
- **Construction pseudo-ternary phase diagram:** To create pseudo-ternary phase diagrams at a constant temperature, researchers employ the water titration approach. To identify the stable microemulsion zone, they combine oil with varying weight ratios (w/w) of surfactant and co-surfactant, then gradually drip in water while stirring until the mixture remains clear. This creates three pictures.

Table 2: Ratios of the systems containing oil, mixed surfactants and water

Label	Water	Oil	Smix
P1	60	30	10
P2	55	35	10
P3	50	40	10
P4	45	45	10
P5	40	50	10
P6	35	55	10
P7	30	60	10

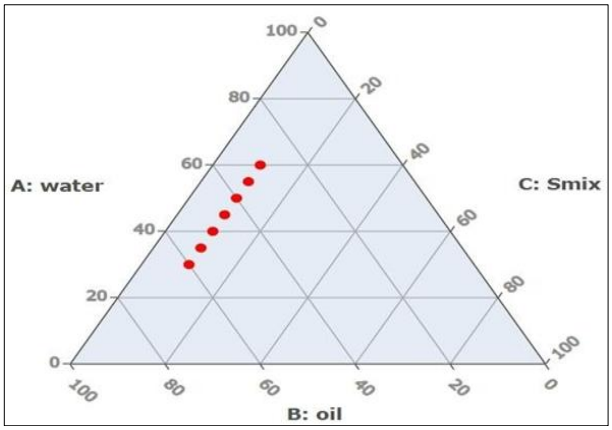

Fig 2: Phase diagram of the system containing oils, mixed surfactants and water

At room temperature, they swirl the mixes magnetically while adding water drop by drop. Keep going until the mix goes murky (turbid) that's the tipping point; note the exact water amount where it stays completely clear and translucent for each one [12].

Microemulsion optimization using a 32-factorial design

After early test runs narrowed down good ranges 2.5-10% w/w oil and 50-60% w/w surfactant/co-surfactant mix a 3^2 factorial design fine-tuned the optimum composition. The performance of the actual microemulsions (globule size, zeta potential, drug release, permeability) was compared to the predictions made by the mathematical model. For additional testing, Batch F5 emerged victorious, achieving all those important KPIs.

Solubility analysis

They tested various oils and additives that dissolve antifungals well, picking Karanja oil as a top choice for microemulsions after reviewing studies right alongside oleic acid and olive oil for its strong drug-dissolving power. Karanja oil works great as the oil phase because it boosts drug solubility and stability, plus its natural bioactive traits play nice with surfactants. Solubility tests also screened surfactants like Tween-20 and Tween-80 to nail down the best combo. Co-surfactants such as PEG-200, PEG-400, propylene glycol, and isopropyl alcohol were also evaluated for their effectiveness. A specific amount of the drug was added to 3 mL of the selected oil, surfactant, and co-surfactant mixture in 10 mL Stoppard vials. Initial mixing was carried out using a magnetic stirrer for a few minutes, followed by storage of the vials in a mechanical bath shaker at 37±0.5 °C for 72 hours.

After shaking the vials at 37 °C for 72 hours to thoroughly equilibrate, they spin the samples in a Remi centrifuge at 3,000 rpm for 15 minutes. Next, they capture the clear supernatant (upper liquid layer), filter it through a membrane, and measure it with a spectrophotometer at 262 nm after diluting adequately with methanol to check solubility. For dependable results, the entire procedure is repeated three times [13].

Microemulsions' organoleptic characteristics

As soon as the microemulsions were prepared, their colour, clarity, and phase separation were assessed. All the micro emulsions were transparent and had a light-yellow tint.

***In vitro* skin permeation studies**

Over 12 hours, they assessed drug release from the microemulsion and a reference sample across a hydrophobic nylon membrane. The microemulsion released up almost 80% of the medication, exceeding the reference's 63.48% proving a quicker release rate. Its greater flux value also revealed speedier drug transport through the membrane compared to the norm [14].

Pseudo-ternary phase diagram construction

Scientists alter the soap-like surfactant and helper (co-surfactant) combination to get the optimal ratio (Km) by checking the stable zone on a phase diagram. The four primary ingredients oil, surfactant, co-surfactant, and water are mapped using a straightforward triangle chart. The oil is added drop by drop at room temperature to balanced batches of the remaining ingredients. Across nine experiments (ratios 1:9 to 9:1), they drip in water first for clarity, lock water and total surfactants at 2g each, vortex-shake during adds, and halt oil when it merely clouds up [14].

Ternary phase diagram construction

First, they narrow down the ideal weight ratio (Km) for surfactant and co-surfactant.With Km locked in, they blend oil and mixed surfactants in ratios from 9:1 to 1:9, then slowly drip purified water (totalling 1.0 g) into each while stirring magnetically to let it settle evenly.

They watch until it just starts getting hazy, marking the edge of the clear, stable zone [15].

ME tests, both qualitative and quantitative test for dilution

They dilute 1 ml of the microemulsion with 100 ml of water to verify that it formed appropriately and see if it remains clear without layering or becoming hazy. This straight-forward test indicates the type such as water-in-oil or oil-in-water by demonstrating how well it blends with the additional liquid.

Centrifugation

Using a centrifugation test, we examine and assess the micro-emulsion's physical stability. By utilizing a centrifuge manufactured by Remi Laboratories in Mumbai, India, at 5000 rpm for ten minutes, the system was assessed for creaming or ocular check for phase separation.

pH of microemulsion

pH of micro-emulsion We are using as a pH meter for micro-emulsion (Siltronic's).

Transmittance percentage (%T)

We use a UV-VIS spectrophotometer set at 650 nm to measure the % transmittance of 2ML ME(s) in comparison to distilled water.

To evaluate how much itraconazole is truly in the microemulsion, they grab a sample with 5 mg of the medicine, drop it into a 50 ml flask of methanol, and shake it hard for 30 minutes to dissolve everything entirely. To properly measure the amount of medication, they top it up to precisely 50 ml with more methanol, filter off 2 ml, dilute that into another 50 ml of methanol, and then use a Shimadzu UV equipment to beam light through it at 262 nm.

Dispersion stability studies

The microemulsion formulation was tested for stability by centrifuging it for 30 minutes at 3500 rpm. It also underwent heating and cooling cycles using a freeze-thaw method, where the formulation was exposed to six cycles of temperatures ranging from 4°C (refrigerator temperature) to 45°C, with each temperature maintained for at least 48 hours in a hot air oven. Formulations that remained stable and showed no phase separation during these tests were selected for further study [16].

Transmission electron microscopy

We are investigating the micro-emulsion's shape. Transmission electron microscopy (CM200, Philips, FEI Company) is required to examine the micro-emulsion's morphology. We're a take. One drop of samples that had been diluted was being negatively dyed with 2% phosphotungstic acid (PTA), placed on film-coated copper grids, dried, then examined under an electron microscope [17].

Index of refraction

A refractometer was used to determine the refractive index of various formulations. Measurements were made in given as mean ± S.D. 11 in triplicate.

Viscosity of microemulsion

Rheological analysis showed that all formulations exhibited non-Newtonian behavior. Specifically, they displayed pseudoplastic flow, where viscosity decreases as shear rates increase. This shear-thinning property was consistently observed across the microemulsion formulations, with viscosity dropping progressively at higher shear rates.

Advantages

- Microemulsions are thermodynamically stable systems that enable self-medication.
- Both lipophilic and hydrophilic medications can dissolve microemulsions.
- The dispersed phase, lipophilic or hydrophilic (oil in water, o/w, or water in oil, w/o microemulsions) can operate as a possible reservoir of hydrophilic or lipophilic medicines.
- The viscosity of microemulsions is lower than that of primary and multiple emulsions.

Disadvantages

- Need a lot of S/Cs to stabilize droplets.
- For usage in pharmaceutical applications, the surfactant must be nontoxic.
- Environmental factors like pH and temperature have an impact on microemulsion stability.

Limitation

- The following factors restrict the use of microemulsion in pharmaceutical applications:
- For toxicological reasons, the concentration of surfactants and cosurfactants utilized must be kept low for various reasons.
- Phase separation restrictions also affect microemulsion.
- The formulation must meet strict toxicity requirements for intravenous use, and only a small number of trials have been published too far.

Microemulsions are divided into the following categories based on the type of dispersed particles:

Microemulsion of water and oil

A dispersion of water or an aqueous solution in a water-immiscible liquid is known as a W/O type microemulsion. The In this instance, the oil is the "continuous" (outer) phase and the water is the "discontinuous" (inner) phase (Fig 3).

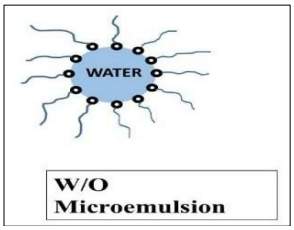

Fig 3: Water in oil type of microemulsion

A microemulsion of oil and water

An oil-in-water type is when a liquid that doesn't mix with water is spread out in water. In this case, the aqueous phase is the "continuous" (outer) phase, and the oil is the "discontinuous" (inner) phase (Figure 4).

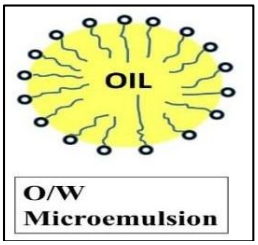

Fig 4: Oil in water type of microemulsion

Microemulsion that is BI continuous

A bicontinuous microemulsion consists of a continuous, interconnected bilayer structure that resembles a sponge with many tiny passageways. This structure extends uniformly over large distances and separates space into two distinct solvent regions water and oil that both exist as continuous phases. When the concentrations of water and oil are similar, the system forms this bicontinuous structure. The surfactant layer between them has an average curvature close to zero, allowing the water and oil to flow freely and coexist throughout the mixture.

Methods of preparation of microemulsion

Phase Titration Method

Microemulsions produce simply with the spontaneous emulsification (or phase titration) method no fancy machines needed. As you gradually combine oil, water, and surfactants, you monitor phase diagrams to observe what forms, such as gels, small micelles, or multilayer structures. The ultimate kind, water-in-oil (w/o) or oil-in-water (o/w), is determined by the ratios of the ingredients: More water indicates o/w, and more oil indicates w/o [18].

Phase Inversion Method

The microemulsion method's phase inversion can result in both physical and particle size changes. Changing the system's temperature can eventually impact drug release in vitro and in vivo for non-ionic surfactants; in these procedures, an o/w microemulsion at low temperature transforms into a w/o microemulsion. Another term for this technique is the transitional phase inversion method. The system crosses the zero-point spontaneous shape during cooling, preserving surface tension and promoting the dispersion of oil droplet [30].

You can change the droplet radius by adjusting the amount of water in phase inversion. Heating also increases the water fraction, which prevents surfactants from maintaining the stability of a water-in-oil (w/o) system [19].

Droplet size measurements

They spray 1 ml of the microemulsion sample into a special cuvette using a syringe, let it settle for 2 minutes, then run it through a Malvern Nano ZSE analyser at 25 °C three times per sample for an accurate average droplet size.This method delivers spot-on, repeated readings of the microscopic particles, verifying the formula's purity.

Characterizations of cryogenic-transmission electron microscopy

The dispersion and microemulsion droplet morphology were examined using a Cryo-TEM (Gracious, Thermo Scientific, USA). Microemulsion's behaviour. Three millilitres of the liquid sample were dropped onto the copper mesh using a pipette, and the filter paper was pressed to create a thin layer of the liquid sample. The samples were moved to a Cryo-TEM for examination after being snap-frozen in liquid nitrogen.

Measurements of zeta potential

The samples' zeta potential was determined using a zeta potential analyzer (Nano ZSE, Malvern, UK). The samples were first dissolved in water, and either 0.1 mol/L HCl or NaOH solution was added to modify the samples' pH. The heavier particles were allowed to separate when the samples

were allowed to settle for 12 hours. After that, a pH meter was used to measure the pH of the clear supernatant. To keep the pH at the right level, little amounts of base or acid were added as needed. In order to evaluate the zeta potential, 1 mL of this prepared suspension was finally added to the sample cell. This meticulous preparation guarantees precise surface charge measurement, which aids in evaluating the microemulsion system's stability. The zeta potential was measured using a zeta potentiometer (Nano ZSE, Malvern, UK). The samples were initially dispersed in water, and their pH was adjusted by adding 0.1 mol/L HCl or NaOH as needed. The clear supernatant was carefully collected after the samples were allowed to settle for 12 hours. The pH of this supernatant was tested, and little amounts of acid or base were added to ensure the pH stayed at the appropriate value. Finally, 1 mL of the prepared suspension was put into the sample cell for the measurement. Understanding the stability of the microemulsion system depends on a precise measurement of the surface charge on the particles, which is made possible by this meticulous preparation [20].

Measurements using Fourier transform infrared spectroscopy (FT-IR)

FT-IR (Nicolet iS20, Thermo Scientific, USA) was used to analyze the functional groups on the surfaces of the coal samples. Before the measurement, 100 mg of KBr and 1 mg of coal samples were mixed, crushed into fine particles in a dry environment, and then compressed using a press tablet into a light-transmissive sheet. The scanning range and spectral resolution were set at 4000-400 cm1 and 4 cm, respectively [21].

Evaluation of Microemulsion

- Visual Inspection.
- Thermodynamic stability.
- Measurement of pH.
- Viscosity measurements.
- Zeta potential determination.
- Particle size determination.
- Drug content estimation.

Visual Examination

Every time water was added to the oil and surfactant, a visual check was conducted and combination of co-surfactants. By visual inspection, the samples were classified as microemulsion, emulsion, or gel formation.

Thermo-dynamic stability tests were used to address the issue of metastable formulation carried out:

- **Centrifugation:** To guarantee physical stability, the formulation was centrifuged for 30 minutes at 3500 rpm.
- **Stress examination:** The purpose of this test was to determine the optimal microemulsion formulation under severe circumstances. Stress was applied for six cycles at 4 °C and 45 °C for 48 hours each, then for roughly three cycles at 25 °C and 21 °C for 48 hours each. Phase separation, coalescence, and cracking were examined in the samples.
- **pH measurement:** The pH of the optimized formulation was measured by directly immersing the electrode into the sample using a calibrated pH meter (Digital Potentiometer Model EQ-601, Equip Tronics). This direct immersion method ensures accurate pH readings after proper calibration with standard buffers.
- **Measurements of viscosity:** The Brookfield Viscometer (DV-E Brookfield Viscometer Model-LVDVE) was used to measure the optimized formulation's viscosity without dilution.
- **Determination of zeta potential:** Zeta sizer was used to measure the samples' zeta potential. Samples were placed in clear, disposable Zeta cells, and the results were recorded. Cuvettes were cleaned with methanol and rinsed with the sample to be examined before every experiment.
- **Determination of particle size:** The mean particle size and size distribution of the drug-loaded microemulsion were measured at 28 °C using the Horiba SZ-100 nanoparticle analyser. This instrument works by detecting changes in scattered light intensity caused by the movement of particles. Each sample was measured three times to ensure accuracy, and the average of these readings was taken as the final value. This method provides precise particle size measurements critical for characterizing microemulsion formulations.
- **Estimating drug content:** In a volumetric flask, a microemulsion containing 100 mg of medication was dissolved in 100 ml of 0.1N HCl. Following solvent filtration, 1 ml was collected in a 50 ml volumetric solution, diluted with 0.1N HCl to the proper level, and measured at 295 nm using a spectrometric ally. The drug's standard calibration curve was used to determine the drug's concentration in milligrams per millilitre. For every batch of formulations, drug content analyses were conducted in triplicate.

Application

These are a few uses for microemulsions in medicine delivery. Microemulsions have been used as a drug delivery method for the past 20 years; they offer advantages such easy penetration, clarity of vision, and thermodynamic stability.

Parenteral Delivery

Developing parenteral dosage forms for hydrophilic and lipophilic drugs has proven difficult. The creation of w/o microemulsions is beneficial when parenteral administration of sparingly soluble drugs does not require the use of suspensions. It takes a lot of focus to administer drugs. Compared to liposomes or other carriers, microemulsions are more physically stable in plasma, and their inner oil phase lessens medication leakage. Certain medications with low water solubility have been developed as oil-in-water microemulsions for parenteral administration. A. Von Corsewant and Thoren developed a new strategy by replacing C3-C4 alcohols with co-surfactants that are safer for injection, such as polyethylene glycol (PEG 400), polyethylene glycol (PEG 600) 12-hydroxy stearate, and ethanol. These co-surfactants aid to preserve a balanced middle phase and the flexibility of the surfactant film by producing almost little spontaneous curvature in the microemulsion. The durability and efficacy of the microemulsion as a medication delivery mechanism are enhanced by this balanced structure. [22]

Oral Administration

It has proven difficult to create efficient oral administration systems since pharmaceutical efficiency can range limited by poor solubility in gastric fluid or instability. Because they significantly increase the solubilization of poorly water-soluble substances and assist in resolving dissolution-related bioavailability problems, microemulsions are especially useful for BCS class II and class IV medications. Hydrophilic medications with different solubilities in macromolecules can be accommodated by these systems' polar, non-polar, and interfacial domains. Additionally, they enhance membrane permeability and guard against agonist oxidation and enzymatic degradation. Commercially available oral microemulsions include Norvir® (ritonavir), Fortovase® (saquinavir), and Sandimmune Neoral® (cyclosporine A). Making poorly water-soluble medications more soluble in gastrointestinal fluids can increase their oral bioavailability, which could be useful for creating microemulsions [16].

Topical Administration

Benefits of topical medication delivery include avoiding the drug's first-pass metabolism in the liver and related poisoning symptoms. These include the medication's targetability and direct administration to the affected skin and ocular areas. the quantity of research on medication penetration into the skin. Both hydrophilic (5-fluroracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate) and lipophilic (oestradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide) medications are included in these drug penetration tests to improve their penetration. When making microemulsions, a high surfactant concentration is required. Particularly when they are supposed to be used for a longer amount of time, skin-irritating aspects need to be considered [23].

Nasal Administration

Microemulsions have lately received attention as a technique to improve drug absorption through the nasal mucosa. By using mucoadhesive polymers, the formulation adheres to the mucosal surface for a longer period, increasing the amount of time the medication can be absorbed. For example, leanly *et al*. studied the nasal delivery of diazepam for emergency treatment of status epilepticus. They discovered that at a dose of 2 mg per kg, diazepam was absorbed quite fast by the nasal route, reaching its peak concentration in the blood within just 2 to 3 minutes. This quick absorption and extended contact time make nasal microemulsions appealing for delivering drugs swiftly and effectively [24].

Future Prospects

Topical antifungal medicines are still evolving because of the limitations of existing formulations, which include poor skin penetration, irritation, resistance development, and limited spectrum. The following key areas are anticipated to be the focus of future research:

- **Cutting-Edge Medication Administration Systems:** Emerging formulation innovations aim to improve drug penetration into the deeper layers of the skin and nails: Antifungal medications that are poorly soluble in water can have their solubility and penetration enhanced by microemulsions and nanoemulsions. Drug stability, skin retention, and controlled release are enhanced by solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Flexible vesicles with low discomfort that can penetrate deeply into the skin are supplied by liposomes and transferosomes. Tailored delivery and reduced systemic exposure are offered by micelles and polymeric nanoparticles [25].
- **Novel Antifungal drugs:** Research is being done on novel chemical compounds and repurposed drugs with higher potency and decreased resistance: azoles of the next generation with improved resistance profiles and broad-spectrum action. Echinocandin analogues with improved topical administration. Squalene epoxidase inhibitors that are more efficient against dermatophytes. Repurposed materials with antifungal properties, including antimicrobial peptides, immunomodulators, and essential oil components [26].
- **Formulations for Combination Therapy:** When antifungal drugs are coupled with other functional agents, they can: Overcome fungal resistance Boost the permeability of medicines Provide symptom alleviation faster Extend the use of antifungals Formulations containing azole together with corticosteroids, keratolytic medications, or penetration enhancers are expected to be of interest [27].
- **Better Film-Forming and Mucoadhesive Systems:** Topical products of the future will presumably use: Bioadhesive gels Spray-on films Patches constructed of polymers By lengthening the period of pharmaceutical residency on the skin or nail surface, these devices boost therapeutic efficacy and compliance [28].
- **Methods of Targeted Delivery:** Improvements in tailored or stimuli-responsive administration could lead to better treatment results: pH-responsive polymers for the release of particular infections. Fungal enzymes activate enzyme-responsive systems Selective binding of ligand-targeted nanoparticles to fungal cells. These techniques could increase potency and lessen off-target effects [29].
- **Less Skin Irritation and Enhanced Security:** Current topical microemulsions with high surfactant concentrations may irritate the skin. Future systems will seek for: Reduced quantities of surfactants, Biocompatible or natural surfactants, Excipients that minimize inflammation greater patient tolerance, particularly with long-term treatment [30].

Challenges

- **Inadequate Skin Infiltration:** Many antifungal drugs, such as azoles, have a high molecular weight and are lipophilic, which makes it difficult for them to penetrate through the stratum corneum, the major skin barrier. Results in a delayed start of action and low therapeutic levels at the infection site.
- **Short Skin Retention Period:** Gels may dry fast, cutting down on residence time and enabling drug removal from perspiration, friction, or washing. This reduces efficacy and interferes with drug absorption.
- **Many antifungal drugs have low solubility:** Many antifungal drugs, including clotrimazole, bifonazole, and itraconazole, are poorly soluble in water. Incorporating hydrophilic gel bases without precipitation is problematic.

- **Stability issues:** Light, heat, oxidation, pH sensitivity, and interactions with gel polymers can all cause antifungals to break down. Long-term chemical stability is difficult to maintain.
- **Ineffective Drug Release:** Gels' polymeric network structure may limit the diffusion of drugs. Requires careful gelling agent selection (Carbopol, HPMC, Poloxamer) to guarantee a suitable release profile.
- **Sensitivity and Irritation:** Skin irritation, redness, or burning may result from gel bases or penetration enhancers (alcohols, glycols). Restricts patient adherence and acceptability.
- **Nail and hair-bearing area treatment difficulties:** Gels function less effectively in: Nail infections induced by the hard keratin barrier are known as onychomycosis. Gel's failure to enter deep hair follicles, which can lead to scalp infections.

Conclusion

For topical antifungal therapy, microemulsions offer a very promising and adaptable drug delivery method. They enhance medication solubility, thermodynamic stability, and skin penetration by breaking the stratum corneum lipid barrier, permitting better localization of the antifungal agents at the site of infection. Microemulsion-based hydrogels extend the retention duration on skin, overcoming the poor viscosity of plain microemulsions, hence boosting patient compliance and therapeutic efficacy.

Surfactant-induced discomfort, stability issues, and restricted penetration into hair follicles and nails are some of the obstacles associated with their administration, despite their many benefits, including high drug loading capacity and dual solubilization ability for hydrophilic and lipophilic medicines. Future research is likely to focus on developing combination therapy, mucoadhesive and film-forming systems, nano-enabled technologies, and the development of novel antifungal drugs with better safety profiles.

Overall, microemulsions stand as a viable approach to improve topical antifungal treatment by enhancing drug penetration, controlled drug release, and stability, potentially overcoming limitations of current topical formulations.

References

1. James WD, Elston DM, Treat JR, Rosenbach MA, Neuhaus I. Andrews' diseases of the skin: clinical dermatology. 13th Ed. Philadelphia: Elsevier; 2020.
2. Hay RJ, Ashbee HR, Borman AM. Superficial mycoses and dermatophytosis. In: Gorbach SL, editor. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 10th Ed. Philadelphia: Elsevier; 2022.
3. Bolognia JL, Schaffer JV, Cerroni L. Dermatology. 4th Ed. Philadelphia: Elsevier; 2018.
4. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev. 2000;45(1):89-121.
5. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst. 1999;16(5):461-521.
6. Sharma B, Sharma A. Future prospects of nanoemulsions in drug delivery. Int J Pharm Pharm Sci. 2011;3(4):40-46.
7. Tenjarla S. Microemulsions: An overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst. 1999;16(5):461-521.
8. Kreilgaard M. Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev. 2002;54(Suppl 1):S77-S98.
9. Gupta AK, Cooper EA. Update in antifungal therapy of dermatomycoses. Mycopathologia. 2008;166(5-6):353-367.
10. Gilman AG, *et al*. Antifungal agents and clinical effectiveness of clotrimazole and nystatin. In: Goodman & Gilman's the pharmacological basis of therapeutics. 13th Ed. New York: McGraw-Hill; 2017.
11. Sweet RL, Gibbs RS. Infectious diseases of the female genital tract. 5th Ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
12. Nabi SUS, Shakeel F, Talegaonkar S, Ali J, Baboota S, Ahuja A, *et al*. Formulation development and optimization using nanoemulsion technique: A new paradigm. J Pharm Pharm Sci. 2007;10(3):326-331.
13. Shaikh S, *et al*. Screening of oils, surfactants, and co-surfactants for antifungal microemulsion formulation. Int J Adv Res.
14. Ahuja A, Dhawan S. Microemulsions: a potential drug delivery system. Int. J Pharm.
15. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev. 2000;45(1):89-121.
16. Hayat MA. Principles and techniques of electron microscopy: biological applications. 4th Ed. Boca Raton (FL): CRC Press; 2000.
17. Hayat MA. Principles and techniques of electron microscopy: biological applications. 4th Ed. Boca Raton (FL): CRC Press; 2000.
18. Tenjarla S. Microemulsions: An overview and pharmaceutical applications. Crit Rev Ther Drug Carrier Syst. 1999;16(5):461-521.
19. Shinoda K, Saito H. The stability of O/W type emulsions as a function of temperature and the HLB of emulsifiers: theoretical consideration. J Colloid Interface Sci. 1968;26(1):70-74.
20. Malvern Instruments. Zetasizer Nano Series user manual. Malvern (UK): Malvern Instruments Ltd.; 2014.
21. Coates J. Interpretation of infrared spectra: a practical approach. In: Meyers RA, editor. Encyclopaedia of analytical chemistry. Chichester: Wiley; 2000.
22. Corsewant VC, Thoren P. Microemulsions for parenteral delivery of sparingly soluble drugs. J Pharm Sci. 1997;86(4):361-366.
23. Sintov AC, Botner S. Transdermal drug delivery using microemulsion and aqueous systems: influence of skin condition on permeability. Int J Pharm. 2006;311(1-2):55-62.
24. Liang J, Liu Q, Williams RO. Nasal delivery of diazepam using a microemulsion formulation: development and in vivo evaluation. Int. J Pharm. 2002;233(1-2):61-70.
25. Dutra JA, *et al*. Development of lipid nanoparticles containing antifungal agents. Colloids Surf B Biointerfaces. 2014;123:452-461.
26. Fang JY, Hong CT. Potential of liposomes and niosomes as topical delivery systems. Int. J Pharm. 1999;194:201-207.

27. Patel P, *et al*. Polymeric micelles for drug delivery. Drug Dev Ind Pharm. 2011;37:865-873.
28. Kligman AM, *et al*. Azole-corticosteroid combinations for dermatoses. Arch Dermatol. 1976;112:347-353.
29. Ghannoum MA, Rice LB. Antifungal combination therapy. Clin Microbiol Rev. 1999;12:530.
30. Gupta P, *et al*. pH-responsive polymeric systems. Acta Biomater. 2014;10:451-466.