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REVIEW ON NANOEMULGEL USED IN THE TREATMENT OF FUNGAL INFECTION

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1. ABSTRACT

Fungal infections affect many people around the world and are a major health concern. One reason they are difficult to treat is that several Fungi have developed resistance to commonly used antifungal medicines. because of this, many drugs do not work as well as they used to. Another problem is that most antifungal drugs cannot easily pass through the outer layer of the skin, so only a small amount reaches the infected area, many of these medicines also do not dissolve well in water, which reduces their effectiveness when applied on the skin. Nanoemulgel technology, which mixes very small nanoemulsion droplets with a gel base, has become a promising method to improve the delivery of antifungal drugs. The tiny size of the droplets helps increase drug solubility, allows more drug to be carried, and improves movement of the drug into deeper skin layers. The gel part makes the product easier to apply, helps it spread smoothly, and allows it to stay longer on the skin. This increases comfort for the patient and helps the drug work better at the infection site. nanoemulgels can greatly improve the action of lipophilic antifungal drugs such as clotrimazole, ketoconazole, luliconazole and fluconazole. These formulations can deliver the drug more effectively, improve treatment results, and reduce the need for frequent application.

KEYWORDS: Nanoemulgel, Fungal Infections, Topical Drug Delivery, Antifungal Agents, Nanoemulsion, Lipophilic drugs.

2. INTRODUCTION

Fungal infections, ranging from superficial skin mycoses to life-threatening systemic diseases, have increased significantly over the last two decades, this rise is primarily due to widespread immunosuppression, increased use of broad-spectrum antibiotics, organ transplantation, and lifestyle-related factors. The management of fungal infections remains challenging because of the limited number of antifungal agents, increasing resistance, and poor delivery efficiency of many conventional formulations.[1]

Topical antifungal formulations such as creams, lotions, and ointments are the first line of treatment for skin infections like dermatophytosis, candidiasis, and pityriasis versicolor. However, these dosage forms often fail to deliver adequate concentrations of the active drug to the deeper skin layers, leading to recurrence and incomplete eradication of the infection.[2]

To overcome these limitations, novel delivery systems such as liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulgels have been developed. Nanoemulgels are hybrid systems where nanoemulsions are incorporated into a gel matrix, combining the high drug-loading and penetration capability of nanoemulsions with the convenience and spreadability of gels. This system improves drug retention at the site of application and enhances the permeation of lipophilic antifungal drugs through the stratu corneum. Nanoemulgels are particularly beneficial for transdermal and topical applications, where controlled drug release and patient acceptability are crucial.

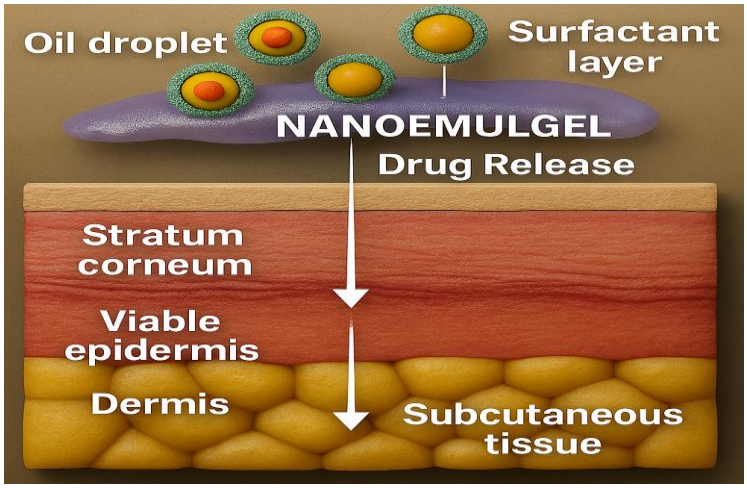

Fig. 1: Mechanistic Representation of Nanoemulgel Delivery on Skin.

3. OVERVIEW OF FUNGAL INFECTION

Fungal infections (mycoses) are infections caused by pathogenic Fungi that invade tissues of humans and animals. Although many fungi are harmless saprophytes, several species can act as opportunistic pathogens, particularly in immunocompromised hosts. In recent decades, the global burden of fungal diseases has increased, largely due to medical advances that prolong the lives of patients with chronic diseases but simultaneously increase immune suppression, thereby increasing susceptibility to fungal pathogens.

3.1 Verious Types of Fungal Infections

Fig. 2: Types of Fungal Infection.

3.2 Causes of Fungal Infections

1. Weak immune system (HIV, cancer therapy, steroids, diabetes).
2. Warm, moist environment (sweating, humid climate, wet clothes).
3. Poor hygiene and sharing personal items.
4. Skin injuries or breaks that allow fungal entry.
5. Overuse of antibiotics leading to imbalance of normal flora.
6. Contact with infected persons, animals, or contaminated surfaces.

3.3 Current Treatment Challenges

Fungal infections are broadly classified into superficial, subcutaneous, and systemic mycoses, depending on the depth of tissue involvement. Superficial infections like tinea corporis and tinea pedis primarily affect the skin, hair, and nails. Subcutaneous infections involve deeper layers of the dermis and subcutaneous tissue, often resulting from traumatic implantation of fungi. Systemic infections such as aspergillosis and cryptococcosis can be life-threatening, particularly in immunocompromised patients.[5]

Common fungal pathogens include Candida albicans, Aspergillus niger, Trichophyton rubrum, Microsporum gypseum, and Epidermophyton floccosum. The global prevalence of superficial mycoses is estimated to affect more than one billion individuals annually, making them among the Despite the availability of several antifungal agents—such as azoles, allylamines, and polyenes— their clinical utility is restricted by poor aqueous solubility, limited permeability across the stratum corneum, and the need for frequent applications.[7] Long-term systemic use can lead to hepatic toxicity, gastrointestinal disturbances, and potential drug interactions. Therefore, a formulation that can deliver antifungal drugs effectively to the target site while minimizing systemic exposure is of great clinical interes.

3.4 Significance of Nanoemulgel in Antifungal Therapy

Traditional antifungal formulations often suffer from drawbacks like low bioavailability, systemic toxicity, and rapid drug degradation. The development of nanoemulgels provides an opportunity to address these challenges effectively,[3] owing to their nanometric droplet size (usually <200 nm), nanoemulgels increase surface area and facilitate better interaction with the biological membrane, improving drug diffusion.

Furthermore, the gelling matrix enhances viscosity, ensuring better contact time with the infected site and reducing the frequency of application. This combination of nanoscale dispersion and gelbased stability has made nanoemulgel one of the most extensively studied drug delivery systems for topical antifungal agents in recent years.[4]

4. BACKGROUND AND DEVELOPMENT OF NANOEMULGEL

1. Conceptual Birth of Nanoemulgels

Emulsified gels were proposed for transdermal drug delivery, The term “Nanoemulgel” gained academic recognition in the early 2000s as advances in nanotechnology enabled the production of stable emulsions with droplet sizes below 200 nm.[10]

Since then, the field has grown rapidly, particularly in dermatological, cosmetic, and antifungal formulations. Between 2010 and 2024, more than 200 papers have reported nanoemulgel-based topical systems, with antifungal drugs such as clotrimazole, fluconazole, terbinafine, and ketoconazole being among the most studied.[11]

The continuous development of safer surfactants, biocompatible oils, and novel gelling polymers has further improved the stability and therapeutic performance of nanoemulgels, making them one of the most promising nanocarriers in modern pharmaceutics.

2. Evolution of Topical Drug Delivery Systems

Topical drug delivery has long been used for local treatment of skin disorders because of its noninvasive nature and ability to bypass first-pass metabolism. Early dosage forms—ointments, creams, and lotions—were simple dispersions of drugs in semisolid bases. However, these preparations often showed limited drug diffusion, greasy texture, and low patient compliance.[8]

To overcome these issues, researchers began exploring microemulsions and nanoemulsions, which provided higher solubilizing capacity for lipophilic drugs and improved permeation through the skin. Despite these advantages, their low viscosity made topical application inconvenient. The logical evolution was the incorporation of nanoemulsions into a gel matrix to create a nanoemulgel—a hybrid system combining the merits of both approaches.[9]

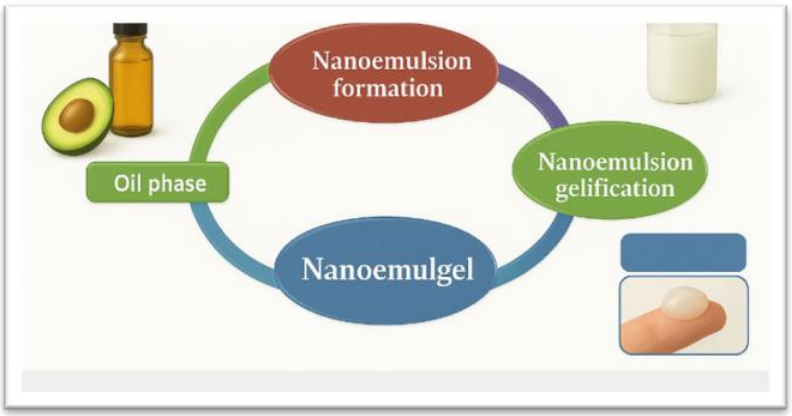

Fig. 3: Devlopment of Nanoemulgel.

4.1 BASIC CONCEPTS OF NANOEMULGEL

a) Nanoemulgel

Nanoemulgel is a biphasic system composed of nano-sized oil droplets dispersed within an aqueus medium and immobilized in a three-dimensional gel matrix. It combines the advantages of a nanoemulsion—such as high solubilization capacity and enhanced penetration—with those of a gel—such as ease of application, stability, and patient acceptability.[12]

b) Nanoemulsion

A nanoemulsion is a colloidal dispersion consisting of two immiscible liquids, typically oil and water, in which one liquid is dispersed in the other in the form of nanometer-sized droplets, usually ranging from 20 to 200 nanometers in diameter. Nanoemulsions are stabilized by surfactants and co-surfactants, which prevent droplet aggregation.

Nanoemulsions appear transparent or translucent due to their small droplet size and exhibit high kinetic stability, enhanced penetration, and improved bioavailability of drugs, making them widely useful in pharmaceutical, cosmetic, and food industries.

c) Advantages

1. **Enhanced solubility:** Ability to solubilize poorly water-soluble antifungal drugs.
2. **Improved permeation:** Nanometric droplets increase surface area and reduce diffusional barriers across the stratum corneum.
3. **Controlled release:** The gel matrix modulates drug diffusion and prolongs contact time.
4. **Non-greasy texture:** Provides pleasant sensory feel and better patient compliance.
5. **Site-specific delivery:** Reduces systemic absorption and side effects.
6. **Formulation flexibility:** Can accommodate both hydrophilic and lipophilic drugs.

d) Limitations

1. Although nanoemulgels offer numerous benefits, challenges remain:

Physical instability such as creaming, coalescence.

2. phase separation under temperature stress.
3. Scale-up difficulties due to high-energy homogenization requirements.
4. Limited shelf life caused by potential degradation of surfactants or gelling agents' Regulatory uncertainty, since nano-based topical products require additional safety evaluation.[13]

e) Drugs Used in the Preparetion of Nanoemulgel

Drug Name	Class	Mechanism of Action	Therapeutic Use
Clotrimazole	Imidazole Antifungal	Inhibits ergosterol synthesis by blocking 14-α-demethylase, leading to disruption of fungal cell membrane.	Used for tinea pedis, tinea corporis, candidiasis, ringworm.
Ketoconazole	Azole Antifungal	Inhibits lanosterol 14-α-demethylase, preventing formation of ergosterol, causing cell membrane instability and death.	Used to treat seborrheic dermatitis, pityriasis versicolor, athlete's foot.

Luliconazole	Imidazole Antifungal	Inhibits lanosterol demethylase, suppressing ergosterol synthesis and disrupting fungal membrane integrity.	Used for tinea cruris, tinea pedis, tinea corporis, dermatophytosis.
Fluconazole	Triazole Antifungal	Blocks CYP450-dependent 14-α-demethylase, preventing conversion of lanosterol to ergosterol, leading to fungal cell death.	Used for cutaneous candidiasis, pityriasis versicolor, dermatophyte infections

5. COMPOSITION OF NANOEMULGEL

5.1 API of Nanoemulgel

The Active Pharmaceutical Ingredient (API) in a nanoemulgel is the therapeutic drug incorporated mainly into the oil phase of the nanoemulsion, which is then dispersed into a gel base. The API is usually lipophilic, allowing better solubility within nano-sized oil droplets that enhance skin penetration, local retention, and controlled drug release. This improves drug absorption through the stratum corneum and increases therapeutic effectiveness while reducing systemic side effects. (e.g. Ketoconazole, clotrimazole, fluconazole, luliconazole).

5.2 Oil Phase

The oil phase acts as the primary solvent for lipophilic antifungal drugs and contributes to skin penetration. Commonly used oils include isopropyl myristate, oleic acid, caprylic/capric triglycerides, and eucalyptus oil.[14] Oils should be pharmaceutically acceptable, non-irritant, and compatible with both the drug and surfactant system.

5.3 Surfactants and Co-surfactants

Surfactants reduce interfacial tension and facilitate the formation of stable nano-sized droplets. Non-ionic surfactants such as Tween 80, Span 20, and Labrasol are preferred for topical use due to their low toxicity. Co-surfactants (e.g., ethanol, propylene glycol, Transcutol P) help in achieving thermodynamic stability and finer droplet size by further reducing interfacial energy.[15]

5.4 Aqueous Phase

The aqueous phase generally consists of purified water containing hydrophilic stabilizers or humectants like glycerin or polyethylene glycol 400. This phase helps in maintaining osmotic balance and contributes to the overall rheological properties of the final gel.

5.5 Gelling Agents

After nanoemulsion preparation, the system is incorporated into a gel base to obtain the required consistency. Commonly used gelling agents include Carbopol 934/940, Hydroxypropyl Methylcellulose (HPMC), Xanthan gum, and Sodium Alginate.[16]

These polymers provide viscosity, stability, and controlled drug release. The concentration of gelling agent (usually 0.5– 2% w/w) directly affects the spreadability and bioadhesive properties of the nanoemulg.

5.6 Preservatives and Additives

To prevent microbial contamination and maintain product stability, preservatives like methyl paraben and propyl paraben are used. pH adjusters (e.g., triethanolamine) are added to achive skin compatible pH (5.0–6.5).

6. METHOD OF PREPARETION

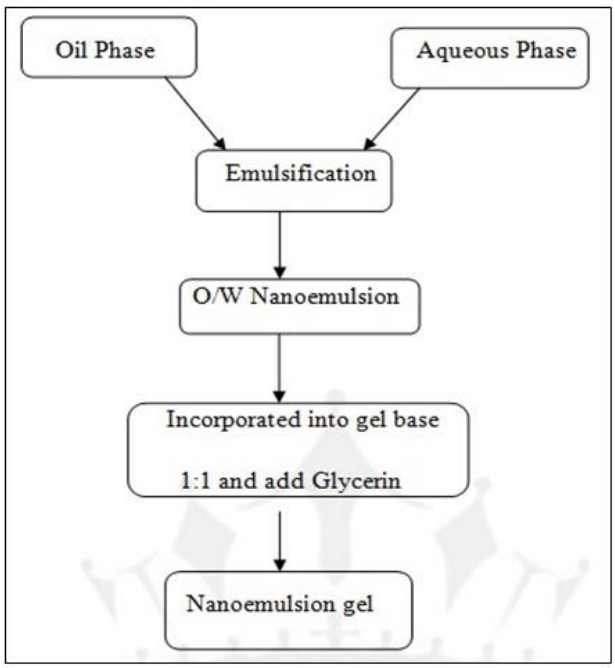

Fig. 4: Method of Preparation of Nanoemulgel.

6.1 Preparation of Nanoemulsion

1. Pre-formulation & Component Selection

a) Oil phase: Choose a suitable oil depending on the solubility of the active.

Example: Curcumin study used Labrafac PG; turmeric–neem study used olive oil.[1]

b) Surfactant + Co-surfactant (Smix): Select appropriate surfactant and co-surfactant.

Example: Tween 80 (surfactant) + PEG 400 or PEG 600 (co-surfactant).[1]

c) Gelling agent / Gel base: Use Carbopol 934 or Carbopol 940 to form the gel matrix.[2]

d) Optional: Perform solubility screening and/or pseudo-ternary phase diagram (oil: Smix: water) to find optimal ratios for stable nano-emulsion.[3]

2. Preparation of Nano-Emulsion

e) Dissolve your active (if lipophilic) in the oil phase, mix with surfactant + co-surfactant under stirring

f) Prepare aqueous phase (water or buffer) separately.[17]

g) Use an appropriate emulsification technique. High-energy methods (ultrasonication, high-pressure homogenization) or low-energy methods (self-emulsification / spontaneous emulsification / phase inversion) are valid depending on formulation.[19]

h) Example: In the curcumin nano-emulgel study, ultrasonication with optimized Smix yielded nano-emulsion with droplet size ~56 nm and low PDI.[17]

i) After emulsification, characterize the nano-emulsion: measure droplet size, polydispersity index (PDI), and zeta potential to ensure stability before gel conversion.[19]

3. Preparation of Gel Base (Hydrogel)

a) Disperse the gelling agent (Carbopol 934/940) in distilled water and stir until fully hydrated

b) Adjust pH using a neutralizing / pH-adjusting agent (e.g., triethanolamine) to obtain proper gel consistency and skin-compatible pH (typically 5–6 for topical use).[18]

4. Incorporation of Nano-Emulsion into Gel → Formation of Nano-Emulgel

a) Combine the nano-emulsion and gel base (or vice versa) under stirring. Typically, Nano emulsion: gel base is 1:1 (wt/wt)

b) Stir at moderate speed (e.g., 120 rpm at room temperature) until the mixture is homogeneous and no separation occurs.[17]

c) Adjust final pH (if needed) to ensure skin/mucosal compatibility.[18]

6.2 Marrketed Formulations of Nanoemulgel

Active agent	Common brand examples	Typical marketed formulation	Emulgel / Nanoemulgel (commercial)
Clotrimazole	Canesten, Lotrimin	Cream, solution, powder	No – standard creams/solutions dominate.
Miconazole	Daktarin, Monistat-Derm	Cream, gel, spray	Gel/cream available; nanoemulgel label rarely use
Terbinafine	Lamisil	Cream, gel, spray	Marketed cream/gel; nanoemulgel prototypes

			reported in literature but not widely commercialized
Ketoconazole	Nizoral topical	Cream, shampoo	Cream/shampoo marketed; emulgel label uncommon
Luliconazole	Luzu	Cream	Marketed cream; nanoemulgel research prototypes exist
Posaconazole	— (systemic clinically)	Oral/IV; topical experimental	Topical nanoemulgel studies exist in research; no widely marketed topical product

Fig. 5: Marketed Formulation of Luliconazole Cream.

7. FACTORS AFFECTING NANOEMULGEL PERFORMANCE

1. **Droplet Size and Polydispersity Index (PDI):** Smaller droplets (< 200 nm) with low PDI (< 0.3) provide better uniformity and stability.
2. **Zeta Potential:** Indicates surface charge; values ±30 mV usually ensures electrostatic stabilization.
3. **Viscosity:** Controls the residence time at the application site; optimal range lies between 5 000–20 000 cP.
4. **pH:** Should be compatible with skin to avoid irritation.
5. **Drug Loading:** Determines therapeutic strength and release characteristics.
6. **Temperature and Storage:** Higher temperatures may accelerate coalescence or drug degradation.
7. Careful control of these factors is necessary to achieve a nanoemulgel with consistent performance and patient acceptability

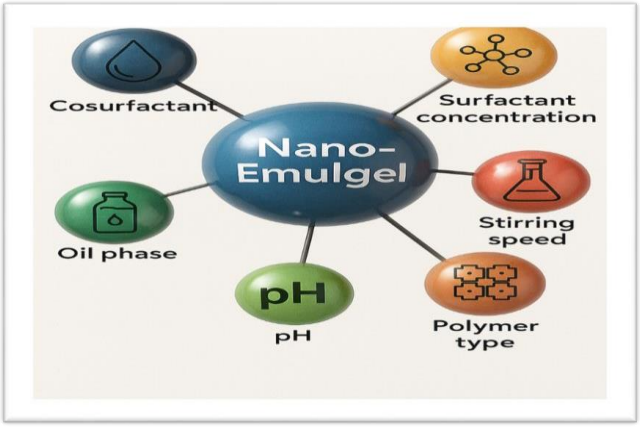

Fig. 6: Mechanistic Representesion of Factors Affecting Nanoemulgel.

8. MECHANISM OF NANOEMULGEL IN DRUG DELIVERY

A) Skin as a Barrier

The human skin serves as the first line of defense against environmental insults and microbial invasion. Its outermost layer, the stratum corneum, is composed of keratinized cells embedded in a lipid matrix, forming a highly efficient barrier to the penetration of most molecules.[21] For effective topical antifungal therapy, the formulation must deliver the drug through this barrier to reach the viable epidermis and dermis where the fungal infection often resides. Traditional creams and ointments struggle to achieve adequate penetration because of the limited solubility of many antifungal drugs and their poor diffusibility through the dense lipid layer. Nanoemulgels, by contrast, utilize nanosized oil droplets that can fuse with skin lipids and facilitate the transport of the drug molecule into deeper layers.

B) Mechanism of Permeation Enhancement

1. The enhanced permeation achieved by nanoemulgels can be attributed to several mechanisms working simultaneously:
2. Increased Surface Area: The nanometric droplets provide a large interfacial surface, leading to greater drug partitioning between the formulation and the stratum corneum.
3. Lipid Disruption: The surfactants and co-surfactants present in nanoemulgels can fluidize the lipid bilayers of the stratum corneum, thereby decreasing its barrier resistance.
4. Thermodynamic Activity: The high internal energy of nanoemulsions creates a driving force for drug diffusion.
5. Hydration Effect: The gel matrix maintains occlusion and hydration of the skin surface, which enhances drug solubility and penetration.

6. Controlled Release: The polymeric network of the gel controls the rate of diffusion, leading to sustained release and prolonged therapeutic action.[22]

C) Role of Individual Components in Drug Delivery

1. Each component of a nanoemulgel plays a specific role in promoting penetration:
2. Oil phase acts as a penetration enhancer by interacting with skin lipids.
3. Surfactant and co-surfactant reduce interfacial tension, allowing drug molecules to partition more easily.
4. Gelling agents increase contact time and ensure uniform distribution of the drug at the site of infection.
5. The synergistic combination of these elements ensures higher local drug concentration while reducing systemic exposure—a desirable feature in antifungal.

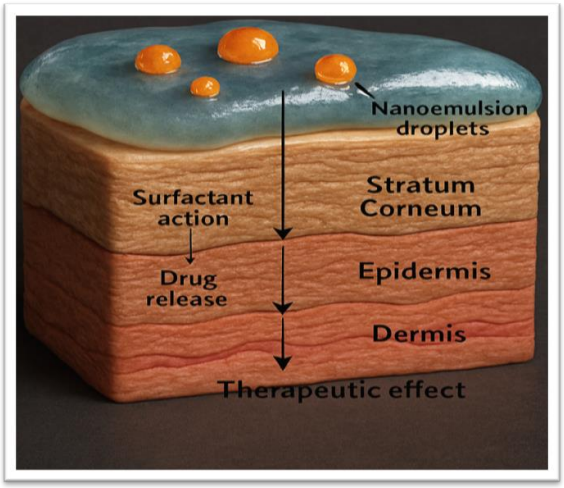

Fig. 7: Mechanism of action of nanoemulgel.

D) Mechanism of Ketoconazole

Ketoconazole, when formulated as a nanoemulgel, is a nano-sized topical antifungal system that enhances the drug's solubility, skin penetration, and therapeutic effectiveness by delivering ketoconazole deep into infected skin layers to inhibit ergosterol synthesis and kill fungal cells.

a) Drug Class

Imidazole antifungal.

b) Main Function

Treats fungal infections by blocking ergosterol synthesis, an essential component of fungal cell membranes.

c) Mechanism of Action of Ketoconazole

1. **Enhanced Penetration:** Nano-sized droplets (20–200 nm) carry ketoconazole deep into epidermis and hair follicles.
2. **Localized Delivery:** Gel matrix retains drug at the site, increasing local concentration.
3. **Enzyme Inhibition:** Ketoconazole binds to fungal 14-α-demethylase (CYP450).
4. **Ergosterol Blockade:** Prevents lanosterol → ergosterol conversion, essential for fungal membranes.
5. **Membrane Disruption:** Accumulation of toxic sterols causes leaky, unstable membranes.
6. **Growth Suppression:** Impaired replication, hyphal elongation, and metabolism.
7. **Fungal Cell Death:** Severe membrane and metabolic disruption lead to fungicidal effect/

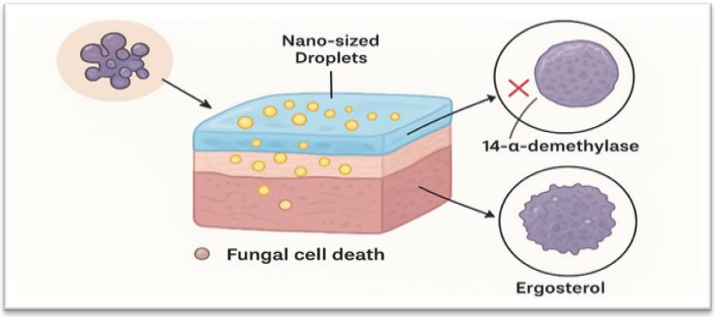

Fig. 8: Mechanism of Ketoconazole.

9. CHARACTERIZATION OF NANOEMULGEL

The physicochemical characterization of nanoemulgel is critical to ensure consistency, stability, and therapeutic efficacy. Several analytical techniques are employed to evaluate key parameters such as droplet size, zeta potential, viscosity, and drug release profile.

a) Droplet Size and Distribution

The mean droplet size and polydispersity index (PDI) of the nanoemulsion are measured using Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS). A smaller droplet size (typically <200 nm) indicates better stability and improved drug absorption. A low PDI (<0.3) reflects a uniform size distribution, which minimizes the risk of coalescence and phase separation.[23]

b) Potential

The zeta potential represents the surface charge of nano-droplets and is measured using a Zettaliter. High absolute zeta potential values (±30 mV or more) suggest strong electrostatic repulsion among droplets, contributing to colloidal stability. A stable nanoemulsion is less likely to aggregate or undergo creaming during storage.[24]

c) Viscosity and Rheological Studies

Rheological behavior plays a vital role in determining the spreadability and residence time of a nanoemulgel on the skin. Measurements are carried out using a Brookfield viscometer or coneplate rheometer at different shear rates. Nanoemulgels usually exhibit pseudoplastic flow, meaning their viscosity decreases with increasing shear rate—this ensures easy application under stress but high viscosity at rest for retention.[25]

d) pH Measurement

The pH of nanoemulgels is measured using a digital pH meter at room temperature. Ideal formulations should have a pH between 5.0 and 6.5, close to the skin's natural pH, to prevent irritation and maintain skin integrity.[26]

e) Drug Content and Uniformity

Drug content is determined by dissolving a known amount of the nanoemulgel in an appropriate solvent (e.g., methanol or ethanol), followed by analysis using UV–Visible spectrophotometry or HPLC. Uniform distribution of the drug ensures consistent therapeutic performance across the formulation.

10. EVALUATION PARAMETERS OF NANOEMULGEL

a) Physical Appearance and Homogeneity

The visual appearance of nanoemulgel is inspected for color, odor, and phase separation. The formulation should appear smooth, homogenous, and free from grittiness or lumps. Microscopic examination under an optical or polarized microscope can confirm the uniform distribution of droplets within the gel matrix.[27]

b) Spreadability Test

Spreadability is evaluated using the parallel-plate method, where a known amount of gel is placed between two glass slides and compressed under a certain load. The time taken for the

upper slide to move a fixed distance indicates the spreadability. Higher spreadability values correspond to easier application and better patient compliance.

c) Extrudability

Extrudability measures the ease with which the gel can be expelled from a collapsible tube. It is assessed by applying pressure on the tube and recording the quantity of gel extruded within a specific time. Optimal extrudability ensures convenient usage and accurate dosing.[28]

d) In-vitro Drug Release Studies

Drug release studies are performed using Franz diffusion cells fitted with a semi-permeable membrane such as cellophane or dialysis membrane. The donor compartment contains the nanoemulgel, while the receptor compartment is filled with phosphate buffer (pH 7.4). Samples are withdrawn at predetermined intervals and analysed spectrophotometrically. The release data are fitted into mathematical models to understand the kinetics of drug release.[29]

e) Ex-vivo Skin Permeation Studies

Ex-vivo permeation studies utilize animal or human cadaver skin mounted on Franz diffusion cells. The amount of drug permeated across the skin is quantified over time, providing insight into the formulation's penetration efficiency. Such studies are crucial for evaluating the potential of nanoemulgels as topical antifungal carriers.[30]

f) In-vivo Evaluation

suitable animal models (e.g., rat, guinea pig). Parameters like skin retention, therapeutic response, and irritation potential are examined. Histopathological analysis of treated skin sections can confirm the absence of tissue damage or inflammation. Ethical approval is mandatory for all in-vivo experiments.[31]

10.1 STABILITY STUDIES

a) Accelerated Stability Testing

Accelerated studies are performed according to ICH guidelines (Q1A-R2). Samples are stored at 40 °C ± 2 °C / 75% RH ± 5% RH for 3 months. At regular intervals (0, 30, 60, and 90 days), formulations are evaluated for phase separation, viscosity, pH, and drug content.[32]

b) Centrifugation and Freeze–Thaw Cycles

Centrifugation (at 5000 rpm for 30 min) and multiple freeze–thaw cycles (−20 °C to +40 °C) help assess the formulation's resistance to stress conditions. Stable nanoemulgels should show no phase separation or precipitation after these tests.

c) Long-term Stability

For long-term evaluation, samples are stored at 25 °C ± 2 °C / 60% RH ± 5% RH for up to 12 months. Periodic assessment ensures that the product retains its viscosity, consistency, and therapeutic potential under normal storage conditions.

11. ROLE OF NANOEMULGEL IN CONTROLLED AND TARGETED DELIVERY

1. Nanoemulgels not only improve local delivery but can also act as controlled-release systems capable of maintaining therapeutic concentrations over extended durations.
2. Controlled release: The gel matrix acts as a diffusion barrier, ensuring gradual release of the antifungal drug.
3. Targeted delivery: Nanoemulsion droplets can preferentially localize within infected tissues due to their affinity for lipid-rich environments.
4. Reduced systemic toxicity: By minimizing drug entry into systemic circulation, nanoemulgels lower the risk of hepatic and renal side effects commonly seen with oral antifungal therapy.[33]
5. This targeted and controlled mechanism is especially beneficial in chronic fungal infections where long-term treatment is necessary.

11.1 APPLICATIONS OF NANOEMULGEL IN FUNGAL INFECTIONS

Fungal skin diseases such as dermatophytosis, onychomycosis, and cutaneous candidiasis are the most common infections addressed using nanoemulgel formulations. These conditions often require prolonged topical therapy; thus, improved drug penetration and retention are essential. Nanoemulgels have proven particularly effective because of their ability to deliver both hydrophilic and lipophilic antifungal agents across the skin barrier while maintaining patient comfort and cosmetic appeal.[34]

a) Topical Nanoemulgel for Superficial Mycoses

Superficial infections, especially those caused by Trichophyton and Microsporum species, are the primary targets of topical nanoemulgel systems. Formulations containing clotrimazole,

ketoconazole, or terbinafine in nanoemulgel bases have shown improved therapeutic response compared with commercial creams.

Clotrimazole Nanoemulgel: A study by Sakeena et al. reported a two-fold increase in skin permeation and enhanced antifungal activity against Candida albicans when clotrimazole was incorporated into a carbopol-based nanoemulgel.[35]

Ketoconazole Nanoemulgel: Formulated with eucalyptus oil as the oil phase, it achieved rapid onset of action with sustained release over 24 h and minimal irritation.[36]

Terbinafine Nanoemulgel: Demonstrated higher zone of inhibition against T. rubrum compared with standard terbinafine cream, confirming superior efficacy.[37]

b) Transdermal Applications

While primarily used for local infections, nanoemulgels also have potential for transdermal systemic delivery of antifungal drugs. Drugs like itraconazole and fluconazole, which suffer from poor oral bioavailability due to first-pass metabolism, can be incorporated into nanoemulgel systems to achieve controlled systemic levels. Ex-vivo permeation studies using rat skin have demonstrated up to a three-fold increase in flux compared with hydroalcoholic gels.[38]

c) Ophthalmic and Vaginal Applications

Certain ocular and vaginal fungal infections can also be targeted using nanoemulgel formulations. For instance, fluconazole nanoemulgel prepared using carbopol 934 showed sustained drug release and higher corneal permeation for fungal keratitis [39]. Similarly, miconazole nanoemulgel designed for vaginal candidiasis exhibited prolonged retention and better patient tolerance than suppositories.

11.2 FUTURE PROSPECTS IN THERAPEUTIC APPLICATIONS

The ongoing integration of nanotechnology, polymer science, and biopharmaceutics is expected to further enhance the capabilities of nanoemulgel systems. Future directions include:

1. **Smart Nanoemulgels:** Responsive to stimuli such as pH, temperature, or enzymatic activity for site-specific release.
2. **Multifunctional Systems:** Incorporation of antioxidants, anti-inflammatory agents, or herbal extracts to provide synergistic therapeutic effects.

3. **Clinical Translation:** Expanded human trials to validate efficacy and safety across larger populations.
4. **Regulatory Frameworks:** Development of harmonized global guidelines for evaluation and approval of nanoemulgel products.[40]

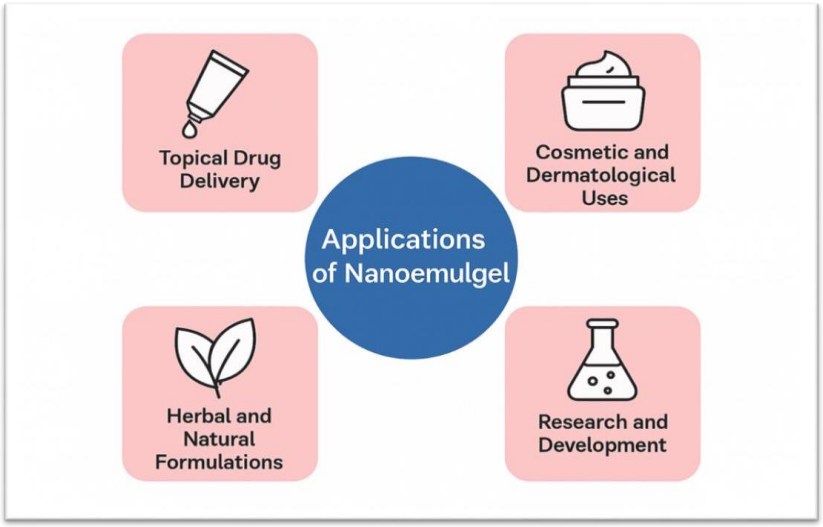

Fig. 9: Applications of Nanoemulgel.

11.3 CHALLENGES AND LIMITATIONS OF NANOEMULGEL SYSTEMS

a) Stability Concerns

Although nanoemulgels exhibit improved stability over simple nanoemulsions, they are still susceptible to physical and chemical degradation during storage. Factors such as droplet coalescence, phase separation, or polymer degradation under varying temperature and humidity can affect the product's performance.[41] The choice of compatible excipients and appropriate storage conditions is therefore critical for maintaining stability over the intended shelf life.

b) Scale-Up and Manufacturing Challenges

At the laboratory scale, nanoemulgels are typically prepared using small-scale high-shear mixers or ultrasonic homogenizers. However, scaling up these methods to an industrial level presents difficulties such as energy consumption, equipment cost, and batch-to-batch variability.[42] Consistent droplet size and homogeneity must be maintained during large-scale production, requiring specialized equipment like high-pressure homogenizers or microfluidizers.

c) Limited Clinical Data

Despite promising pre-clinical results, there is still a lack of robust clinical trial data supporting the safety and efficacy of nanoemulgels for antifungal therapy. Most available studies are small scale or short-term, making it difficult to draw definitive conclusions about long-term outcomes or side effects.[43] Regulatory authorities demand extensive toxicological evaluation before nanoemulgel-based formulations can be marketed.

d) Cost and Regulatory Barriers

The inclusion of nanosized components, specialized surfactants, and advanced manufacturing techniques increases production costs. Moreover, regulatory frameworks for nano-based pharmaceuticals are still evolving, with uncertainties regarding classification, safety testing, and labeling. These hurdles may delay commercialization despite the strong therapeutic potential of nanoemulgels.[44]

e) Patient Awareness and Acceptance

Although nanoemulgels are generally safe and well-tolerated, public perception and awareness of "nano-based" products can influence market success. Education and transparency regarding safety, mechanism, and benefits are vital to gain patient trust.

12. FUTURE PERSPECTIVES

a) Integration with Emerging Technologies

The integration of nanotechnology with biomaterials engineering and artificial intelligence (AI) promises to revolutionize the design of topical drug delivery systems. Predictive modeling using AI could optimize formulation parameters, reducing experimental workload and improving reproducibility.[45]

b) Hybrid and Multifunctional Systems

Future nanoemulgels are likely to incorporate multiple functional components such as antibacterial agents, anti-inflammatory compounds, or herbal extracts to provide synergistic effects. Hybrid systems combining nanostructured lipid carriers or polymeric nanoparticles with gels could yield enhanced stability and targeted delivery.

c) Personalized Medicine

With advances in skin diagnostics and 3D printing, personalized nanoemulgels tailored to an individual's infection type, skin characteristics, and drug sensitivity may become feasible. Such customized therapy would minimize side effects while ensuring optimal efficacy.[46]

d) Regulatory and Industrial Outlook

Global pharmaceutical agencies are working toward standardized guidelines for nanopharmaceuticals. Collaborative efforts between academia, industry, and regulators will accelerate clinical translation. Economically, nanoemulgel manufacturing could benefit from the development of continuous production systems, reducing cost and variability.[47]

e) Sustainable and Green Formulations

Another future direction lies in developing eco-friendly nanoemulgels using biodegradable polymers and naturally derived surfactants. Reducing solvent usage and adopting green chemistry principles will make production more sustainable and socially acceptable.[48]

13. CONCLUSION

Nanoemulgels have emerged as one of the most promising nanocarrier systems for the topical and transdermal delivery of antifungal agents. Their unique combination of nano-sized droplets within a gel matrix provides superior drug solubility, enhanced permeation, controlled release, and excellent patient compliance. Extensive research over the last decade demonstrates their effectiveness in delivering antifungal drugs such as clotrimazole, ketoconazole, fluconazole, and itraconazole with improved therapeutic outcomes and reduced side effects.

However, the journey from laboratory research to clinical application remains challenging due to scalability issues, limited human trials, and evolving regulatory frameworks. Continued innovation, interdisciplinary collaboration, and adoption of sustainable manufacturing approaches will be key to realizing the full potential of nanoemulgel-based antifungal therapies.

In conclusion, nanoemulgel represents a bridge between advanced nanotechnology and practical topical therapy—a formulation that embodies both scientific sopcation and clinical relevance. With future technological advances and regulatory clarity, nanoemulgels may soon

become amainstream platform for the treatment of fungal and other dermatological infections.

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