# Nanoemulgels as a Promising Topical Approach for the Management of Onychomycosis: A Review

Aarti Nishad*[1] Mrs. Priyanka maurya[2], Mr. Ashutosh Kushwaha[2], Dr. Jai Narayan Mishra[3],

1. Research Scholar, Kailash Institute of pharmacy and Management, GIDA, Gorakhpur

2. Associatet Professor, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur

3. Director, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur

## Abstract

Topical and transungual drug delivery systems are widely employed for the treatment of localized dermatological and nail disorders; however, their clinical effectiveness is often limited by the formidable barrier properties of the stratum corneum and nail plate. The nail plate, composed of densely packed keratinized cells with low lipid content, presents a major challenge for effective drug permeation, particularly in the treatment of chronic conditions such as onychomycosis. Conventional topical dosage forms such as creams, ointments, and gels frequently fail to achieve therapeutic drug concentrations at the target site, leading to prolonged treatment duration and poor patient compliance.

Nanoemulgels have emerged as a promising advanced drug delivery system that integrates the advantages of nanoemulsions and hydrogels into a single formulation. The nanoemulsion component enhances solubilization of poorly water-soluble drugs and improves permeation through skin and nail barriers due to its nano-sized droplets, while the gel matrix provides improved viscosity, spreadability, stability, and prolonged residence time at the site of application. This review comprehensively discusses the formulation strategies involved in the development of nanoemulgels, including selection of oils, surfactants, co-surfactants, gelling agents, and methods of preparation. Additionally, critical evaluation parameters such as physicochemical characterization, in vitro drug release, ex vivo skin and nail permeation studies, and antifungal efficacy assessment are highlighted.

The application of nanoemulgels in topical and transungual drug delivery, particularly for antifungal therapy, demonstrates significant potential in overcoming the limitations of conventional formulations. Overall, nanoemulgels represent a versatile and effective platform for enhanced topical and transungual drug delivery, with promising prospects for future clinical translation.

**Keywords:**
Nanoemulgel; Topical drug delivery; Transungual drug delivery; Onychomycosis; Nanoemulsion; Antifungal therapy; Nail penetration; Pharmaceutics

## 1. INTRODUCTION

### 1.1 ONYCHOMYCOSIS: DISEASE OVERVIEW AND TREATMENT CHALLENGES

Onychomycosis is a chronic fungal infection of the nail unit affecting fingernails and toenails, primarily caused by dermatophytes (*Trichophyton rubrum*, *T. mentagrophytes*), yeasts (*Candida* spp.), and non-dermatophyte molds. It is one of the most prevalent nail disorders worldwide, accounting for a significant proportion of nail infections and representing a major public health concern due to its recurrent nature and long treatment duration [1,2].

Clinically, onychomycosis is characterized by nail discoloration, thickening, brittleness, onycholysis, and subungual hyperkeratosis, which can lead to pain, secondary bacterial infections, and reduced quality of life. The prevalence of onychomycosis increases with age and is higher in patients with diabetes, peripheral vascular disease, and immunocompromised conditions [2,3 treatment of onychomycosis remains challenging due to the unique structure of the nail plate, which is composed of tightly packed keratinized cells with low lipid content. This structure significantly restricts drug diffusion, making topical therapy largely ineffective when delivered using conventional dosage forms such as creams, lacquers, and ointments [1,4]. Although oral antifungal agents such as terbinafine and itraconazole are effective, their long-term use is associated with systemic side effects, drug–drug interactions, and hepatotoxicity, limiting patient compliance [3].

As a result, there is a growing interest in developing advanced topical and transungual drug delivery systems capable of enhancing drug permeation through the nail plate while minimizing systemic exposure. Nanoemulgel-based formulations have emerged as a promising approach for onychomycosis management by improving drug solubility, nail penetration, and local drug retention, thereby enhancing therapeutic efficacy [1,4,5].

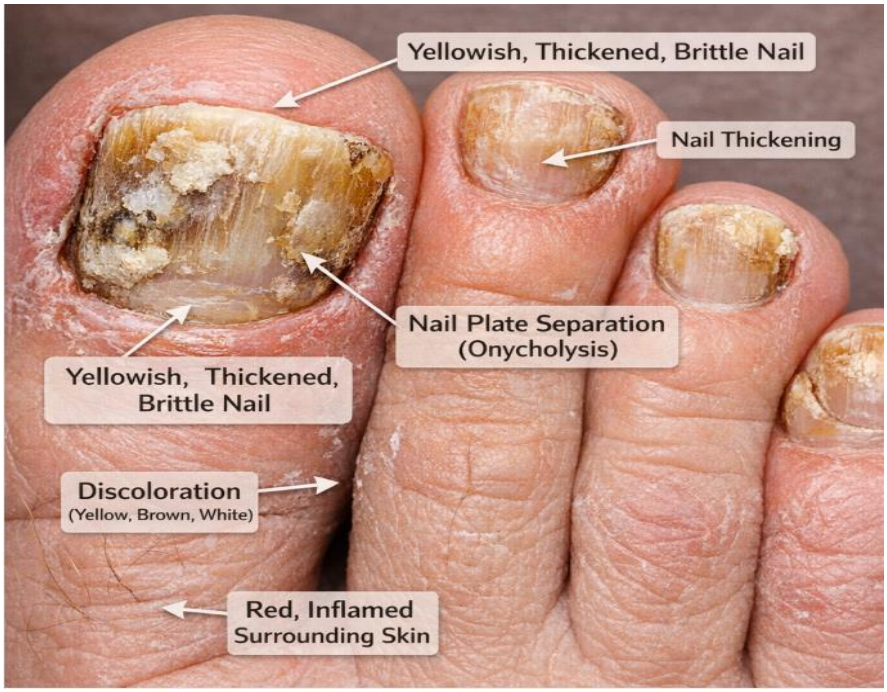


**Fig1.1 Clinical Presentation of Onychomycosis**

### 1.2 TOPICAL AND TRANSUNGUAL DRUG DELIVERY

Topical drug delivery systems are designed to deliver drugs directly to the skin or underlying tissues for localized therapeutic action. They are widely used in dermatological conditions due to advantages such as avoidance of first-pass metabolism, reduced systemic toxicity, ease of application, and improved patient compliance [1,2]. Conventional topical dosage forms include creams, ointments, lotions, and gels; however, their therapeutic efficacy is often limited by poor drug penetration through the skin and nail barriers [3].

Transungual drug delivery refers specifically to drug transport across the nail plate to treat nail disorders such as onychomycosis. The nail plate is composed of tightly packed keratinized cells with low lipid content, making it a highly resistant barrier to drug permeation compared to skin [1,4]. As a result, conventional topical antifungal formulations often fail to achieve therapeutic drug concentrations at the site of infection [2].

### 1.3 BARRIERS TO EFFECTIVE TOPICAL AND TRANSUNGUAL DRUG DELIVERY

The stratum corneum is the primary barrier to topical drug delivery, consisting of corneocytes embedded in a lipid matrix. Drug permeation depends on molecular size, lipophilicity, and formulation characteristics [3]. Similarly, the nail plate presents additional challenges due to its thickness, dense keratin network, and low hydration [1].

Low nail permeability, slow nail growth, and poor drug residence time significantly limit the effectiveness of traditional formulations used for onychomycosis treatment [4,5]. Therefore, advanced drug delivery systems capable of enhancing penetration and retention are required.

### 1.4 NEED FOR ADVANCED DRUG DELIVERY SYSTEMS

The limitations associated with conventional topical and transungual formulations have led to the development of novel drug delivery systems such as liposomes, niosomes, solid lipid nanoparticles, nanoemulsions, and nanoemulgels [6]. Among these, nanoemulgels have gained particular attention due to their ability to combine enhanced permeation with formulation stability and patient acceptability [7].

## 2. NANOEMULGELS: CONCEPT, COMPOSITION, AND ADVANTAGES

### 2.1 CONCEPT OF NANOEMULGELS

Nanoemulgels are hybrid systems formed by incorporating a nanoemulsion into a gel base. A nanoemulsion consists of oil droplets in the nanometer range stabilized by surfactants and co-surfactants, while the gel matrix provides structural integrity and ease of application [6,8].

This combination allows nanoemulgels to overcome the drawbacks of nanoemulsions such as low viscosity and poor retention at the application site [7].

### 2.2 COMPOSITION OF NANOEMULGELS

Nanoemulgels are composed of:

- Oil phase (drug solubilization and permeation enhancement)
- Surfactant and co-surfactant (stabilization of nanoemulsion)
- Aqueous phase
- Gelling agent (viscosity and bioadhesion)

The rational selection of these components plays a critical role in determining formulation performance [6,9].

### 2.3 ADVANTAGES OF NANOEMULGELS

Nanoemulgels offer several advantages over conventional topical formulations:

- Enhanced solubility of poorly water-soluble drugs [6,10].
- Improved skin and nail penetration due to nano-sized droplets [1,4].
- Sustained and controlled drug release [8].
- Improved stability and patient acceptability [7].

## 3. FORMULATION STRATEGIES FOR NANOEMULGELS

### 3.1 SELECTION OF OIL PHASE

The oil phase influences drug loading, droplet size, and permeation. Oils such as castor oil, medium-chain triglycerides, and essential oils (e.g., eucalyptus oil) are widely used due to their penetration-enhancing properties and compatibility with antifungal drugs [6,9,11].

### 3.2 SELECTION OF SURFACTANT AND CO – SURFACTANT

Non-ionic surfactants such as Tween 80 and Cremophor® ELP are preferred due to their low toxicity and high emulsification efficiency. Co-surfactants like propylene glycol and Transcutol® P enhance interfacial flexibility and nanoemulsion stability [8,10].

### 3.3 SELECTION OF GELLING AGENTS

Gelling agents such as Carbopol 934/940, HPMC, and xanthan gum are used to convert nanoemulsions into nanoemulgels. Carbopol is widely employed due to its excellent viscosity control, transparency, and bioadhesive properties [7,12].

### 3.4 METHODS OF PREPARATION

Nanoemulsions are prepared using high-energy methods such as ultrasonication or high-pressure homogenization, or low-energy techniques such as phase inversion temperature method. The optimized nanoemulsion is then incorporated into the gel base under continuous stirring [6,12].

The method of preparation plays a critical role in determining the physiochemical characteristics, stability, and drug delivery performance of nanoemulgels. The preparation of nanoemulgels generally involves two major steps:

i) Preparation of a stable nanoemulsion and

ii) Incorporation of the optimized nanoemulsion into a suitable gel base [1,2].

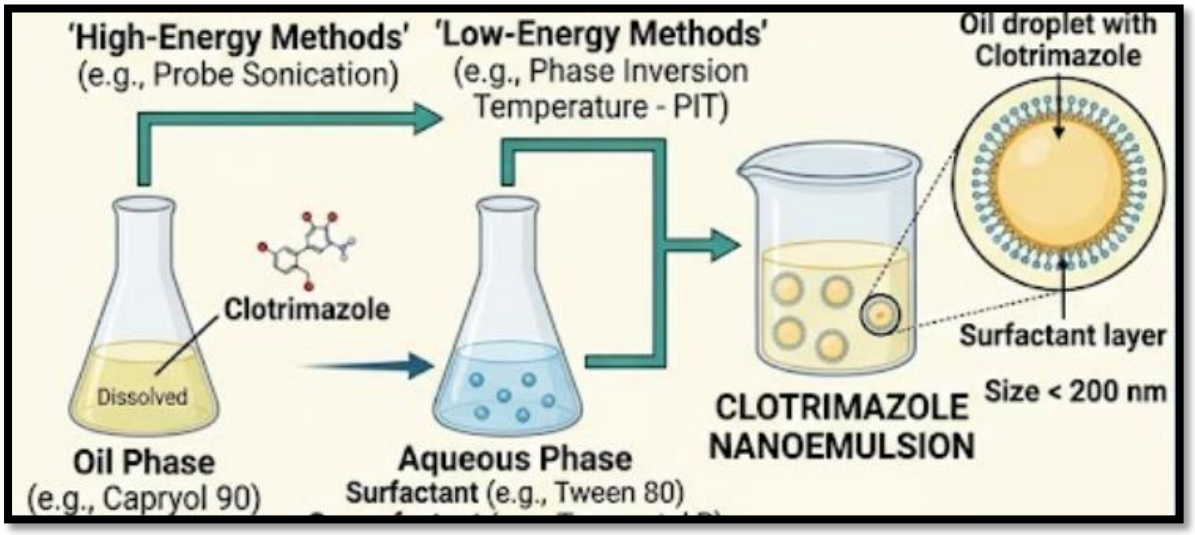


**Fig. 3.1 Schematic representation of Clotrimazole-loaded nanoemulgel formulation**

### 3.4.1 Preparation of Nanoemulsion

Nanoemulsions can be prepared using high-energy or low-energy emulsification techniques, depending on formulation requirements, scalability, and equipment availability.

High-energy methods such as ultrasonication and high-pressure homogenization are widely used to produce nano-sized droplets by applying mechanical energy to reduce droplet size. Ultrasonication employs acoustic cavitation forces to break coarse emulsions into fine nanoemulsions, resulting in uniform droplet size distribution and improved stability [3]. High-pressure homogenization forces the emulsion through narrow gaps under high pressure, producing nanoemulsions with low polydispersity index and enhanced kinetic stability [4].

Low-energy methods, including the phase inversion temperature (PIT) method and spontaneous emulsification, rely on changes in interfacial tension rather than mechanical force. In the PIT method, temperature-induced changes in surfactant affinity lead to phase inversion and formation of nano-sized droplets. These methods are energy-efficient and suitable for thermodynamically favorable systems but may be limited by surfactant selection [5].

### 3.4.2 Optimization of Nanoemulsion

Prior to gel incorporation, the nanoemulsion is optimized for droplet size, polydispersity index, zeta potential, and thermodynamic stability. Pseudo-ternary phase diagrams are often constructed to identify the nanoemulsion region and optimize oil–surfactant–co-surfactant ratios [1,6]. Only stable nanoemulsions with nanoscale droplet size and narrow size distribution are selected for nanoemulgel formulation.

### 3.4.3 Incorporation into Gel Base

The optimized nanoemulsion is incorporated into a pre-prepared gel base containing suitable gelling agents such as Carbopol 934/940, HPMC, or xanthan gum. The gel base is typically prepared by dispersing the gelling agent in purified water, followed by neutralization (in the case of Carbopol) using triethanolamine to achieve the desired viscosity and pH [2,7].

The nanoemulsion is added slowly to the gel base under continuous gentle stirring to ensure uniform distribution of nano-sized droplets without destabilization. Excessive shear is avoided during this step to prevent coalescence or phase separation [6].

### 3.4.4 Role of Processing Parameters

Processing parameters such as stirring speed, mixing time, temperature, and order of addition significantly influence the final nanoemulgel properties. Proper control of these parameters ensures homogeneity, optimal viscosity, and reproducible drug release behavior [3,7].

### 3.4.5 Scale-Up Considerations

For industrial and clinical translation, scalability of nanoemulgel preparation is an important consideration. High-pressure homogenization and low-energy emulsification techniques are considered more suitable for large-scale production due to reproducibility and regulatory acceptance. However, optimization of surfactant concentration and processing conditions is necessary to maintain formulation stability during scale-up [4,5].

## 4. EVALUATION OF NANOEMULGELS

### 4.1. PHYSIOCHEMICAL EVALUATION

Physicochemical characterization is essential to evaluate the quality, stability, and performance of nanoemulgel formulations. Key parameters include droplet size, polydispersity index (PDI), zeta potential, pH, viscosity, and spreadability [7,10].

Droplet size analysis is a critical factor as it directly influences drug permeation and stability. Nanoemulgels typically possess droplet sizes in the nanometer range (20–200 nm), which enhances surface area and facilitates better penetration through skin and nail barriers [6,8].

The polydispersity index (PDI) indicates the uniformity of droplet size distribution. A PDI value below 0.3 suggests a homogeneous and stable nanoemulsion system, which is desirable for reproducible drug delivery [6].

Zeta potential is used to assess the surface charge and stability of the formulation. Higher absolute zeta potential values (±30 mV) indicate better stability due to electrostatic repulsion between droplets, preventing aggregation [7].

The pH of nanoemulgels should be compatible with skin (typically 5–7) to avoid irritation and ensure patient safety [10].

Viscosity plays an important role in determining the retention time of the formulation at the application site. An optimum viscosity ensures ease of application while preventing runoff from the nail or skin surface [7].

Spreadability reflects the ease with which the formulation can be applied uniformly. Good spreadability enhances patient compliance and ensures adequate drug distribution over the affected area [10].

Overall, physicochemical evaluation ensures that the nanoemulgel formulation is stable, effective, and suitable for topical and transungual application [6,7].

### 4.2. IN VITRO DRUG RELEASE STUDIES

In vitro drug release studies are conducted using Franz diffusion cells. Nanoemulgels generally show prolonged drug release due to the combined effect of nanoemulsion droplets and gel matrix [8,12].

### 4.3 ANTIFUNGAL ACTIVITY EVALUATION

Antifungal efficacy is evaluated using minimum inhibitory concentration (MIC) and zone of inhibition studies. Nanoemulgels exhibit superior antifungal activity due to enhanced penetration and sustained drug release [1,2].

## 5. APPLICATION OF NANOEMULGELS IN TRANSUNGUAL DRUG DELIVERY

Nanoemulgels are promising carriers for topical and transungual drug delivery due to their ability to enhance drug penetration, improve retention, and provide controlled release [1,2].

In onychomycosis treatment, nanoemulgels improve drug permeation through the dense keratin structure of the nail, overcoming the limitations of conventional formulations. Enhanced delivery of antifungal agents such as ketoconazole, clotrimazole, and terbinafine has been reported due to nano-sized droplets and the presence of penetration enhancers [1,4,5].

In dermatological applications, nanoemulgels are effective in treating fungal infections, acne, and inflammatory skin conditions by improving drug solubilization and sustained release [2,6].

They are also suitable for delivery of lipophilic drugs, as the oil phase of nanoemulsions enhances drug solubility and bioavailability [6,8].

Additionally, nanoemulgels offer better patient compliance due to their non-greasy nature, ease of application, and reduced systemic side effects, making them ideal for long-term therapies [2,7].

Overall, nanoemulgels provide a superior alternative to conventional topical systems for effective and targeted drug delivery [1,4].

## 6. CHALLENGES AND FUTURE PERSPECTIVES

### 6.1 FORMULATION AND STABILITY CHALLENGES

One of the major challenges associated with nanoemulgel systems is maintaining long-term physical and chemical stability. Nanoemulsions are thermodynamically unstable systems and may undergo instability phenomena such as droplet coalescence, creaming, and phase separation over time [3]. Incorporation into a gel matrix improves kinetic stability; however, improper selection of surfactant concentration and gelling agents may still result in formulation instability [4].

Additionally, the presence of high surfactant concentrations, although necessary for nanoemulsion stabilization, may lead to skin irritation or toxicity upon prolonged use [5].

### 6.2 Manufacturing and Scale-Up Limitations

Laboratory-scale preparation techniques such as ultrasonication may not always be feasible for large-scale production due to equipment limitations, high energy consumption, and batch-to-batch variability [3,6]. Scale-up of nanoemulgels requires careful optimization of processing parameters such as homogenization pressure, mixing speed, and temperature to ensure reproducibility and uniform droplet size distribution [6].

### 6.3 Regulatory and Safety Concerns

Regulatory approval of nanoemulgel formulations remains challenging due to the lack of well-defined regulatory guidelines specific to nanotechnology-based topical systems. Concerns related to nanoparticle penetration into systemic circulation, long-term toxicity, and environmental impact must be thoroughly evaluated [5,7].

Comprehensive safety studies, including skin irritation, sensitization, and chronic toxicity studies, are required before clinical approval [7].

### 6.4 Limitations in Transungual Drug Delivery

Although nanoemulgels enhance nail penetration, complete drug delivery through severely thickened or diseased nails remains difficult. Nail hydration status, disease severity, and patient-to-patient variability significantly affect transungual permeation outcomes [1,8]. Therefore, individualized formulation approaches may be required.

### 6.5 FUTURE PROSPECTS

Future research should focus on:

- Development of stimuli-responsive nanoemulgels (pH-, enzyme-, or temperature-sensitive systems)
- Integration of chemical and physical penetration enhancement techniques
- Use of biocompatible and natural surfactants
- Conduct of well-designed clinical trials to establish therapeutic superiority over conventional formulations.

Advancements in nanotechnology and material science are expected to further enhance the potential of nanoemulgels as effective topical and transungual drug delivery systems.

## 7. CONCLUSION

Nanoemulgels represent a novel and versatile drug delivery platform that effectively addresses the limitations associated with conventional topical and transungual formulations. By combining the enhanced solubilization and permeation properties of nanoemulsions with the stability and patient-friendly characteristics of gels, nanoemulgels offer significant improvements in drug delivery performance.

Extensive research has demonstrated that nanoemulgels improve drug penetration through skin and nail barriers, provide sustained and controlled drug release, and enhance therapeutic efficacy, particularly in the treatment of chronic conditions such as onychomycosis. The incorporation of penetration enhancers and essential oils further strengthens their applicability in antifungal therapy.

Although challenges related to stability, scale-up, and regulatory approval remain, continued research and technological advancements are likely to overcome these limitations. With appropriate formulation optimization, comprehensive safety evaluation, and clinical validation, nanoemulgels hold strong potential to become next-generation topical and transungual drug delivery systems in pharmaceutical practice.

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