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# NANOEMULSION-BASED GEL OF TERBINAFINE FOR TOPICAL TREATMENT OF DERMATOPHYTOSIS

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**Abstract**

Superficial fungal infection of the skin is common, and terbinafine remains one of the most effective agents against the dermatophytes that cause it. Its low water solubility and the barrier function of the stratum corneum limit what a conventional cream can deliver. This review brings together published work on nanoemulsions as carriers for terbinafine and on their conversion into gels for topical use. It covers the clinical problem, the choice of oil, surfactant and co-surfactant, gelling agents, characterisation, permeation testing and tolerability. Published studies generally report small droplets, good stability and improved skin deposition over marketed creams, but most rely on in vitro or animal models. This review reports no new experimental data.

## 1. INTRODUCTION

Fungal infections confined to the skin, hair and nails affect a very large share of the world's population at any one time. Surveys of skin disease place superficial mycoses among the most frequent conditions seen in primary care, and the dermatophytes account for the bulk of them [1, 2]. In several parts of South Asia the problem has grown more stubborn in recent years, with extensive, recurrent and treatment-resistant tinea now a routine complaint in dermatology clinics [3]. Patients lose work time, share infection within households and often stop treatment as soon as the itch settles, which feeds relapse. Any improvement in how an antifungal reaches the infected stratum corneum therefore has practical value.

Terbinafine is an allylamine that blocks squalene epoxidase, an early enzyme in fungal ergosterol synthesis. The block starves the membrane of ergosterol and, just as

importantly, lets squalene accumulate to levels that are toxic to the cell, which explains why the drug is fungicidal against dermatophytes rather than merely fungistatic [4, 5]. Reviews of its pharmacology describe high lipophilicity, strong keratin affinity and long persistence in skin and nail after dosing [6]. Those same properties make it hard to formulate. The free base is poorly soluble in water, and the hydrochloride salt used in marketed creams must be dispersed in a vehicle that does not hold the drug too tightly.

A nanoemulsion is a transparent or translucent dispersion of oil in water, stabilised by surfactant, with droplets typically below 200 nm. Because the droplets are so small the system is kinetically stable, can solubilise a lipophilic drug at useful concentrations and spreads thinly over the skin [7, 8, 9]. Such liquids are runny, though, and a runny liquid is a poor fit for a lesion on the groin or trunk. Thickening the aqueous phase with a polymer gives a nanoemulsion-based gel, which keeps the small droplet size while adding the residence time and ease of handling that patients expect. This review summarises what published studies report about that approach for terbinafine and does not present new experimental data.

## 2. DERMATOPHYTOSIS AND CURRENT TOPICAL THERAPY

Dermatophytes are keratinophilic moulds of the genera *Trichophyton*, *Microsporum* and *Epidermophyton*. They colonise only dead keratin, which is why infection stays in the stratum corneum, hair shaft and nail plate rather than invading living tissue [10]. Spread is by contact with infected people, animals or soil, and warmth and humidity favour disease. The usual presentations are tinea corporis, tinea cruris and tinea pedis, each with an advancing, scaly, itchy margin and a clearer centre [11]. Diagnosis is usually clinical and confirmed by potassium hydroxide microscopy or culture when the picture is unclear.

For limited skin disease, topical treatment is the first choice, and the allylamines and azoles both have good evidence. Comparative reviews suggest that terbinafine cream applied once or twice daily for one to two weeks achieves mycological cure rates at least as high as azoles given for longer, which is one reason adherence tends to be better with it [12, 13]. Systemic therapy is held back for extensive disease, hair-bearing sites, nails and failures of local treatment. It carries interaction and hepatic concerns that most clinicians would rather avoid for an otherwise healthy patient with a few patches of tinea.

Systemic exposure after topical use is a secondary but real consideration. Pharmacokinetic reviews report that only a small fraction of an applied terbinafine dose is absorbed through intact skin, so blood levels stay far below those reached with tablets, and the liver and drug-interaction concerns attached to oral treatment are largely avoided [6]. This is a strength of local therapy and a constraint on formulators: a vehicle that pushes much more drug across the barrier would defeat part of the purpose. The sensible target is a higher and longer-lasting concentration in the keratin layer, with systemic absorption kept as low as with a good conventional cream.

Why do creams fail, then? Reviews of topical antifungal vehicles point to several reasons: the drug is held in the vehicle and released slowly, the vehicle leaves a greasy film that people dislike, application is irregular, and the amount reaching the deeper keratinised layers is modest [14, 15]. Newer formulation work, including lipid carriers, vesicles and nanoemulsions, tries to improve release without changing the molecule [16]. The expectation is not that a new vehicle will turn terbinafine into a different drug. It is that more of the dose will sit in the stratum corneum, where the organism lives, and less will be lost on clothing or remain on the surface.

A further point concerns resistance. Until recently, resistance to terbinafine was regarded as rare, but squalene epoxidase mutations have now been reported in clinical isolates from patients who failed treatment, particularly in recalcitrant Indian cases [3]. A formulation that achieves a higher local concentration may help overcome partial reduction in susceptibility, although published formulation studies seldom test this

directly. It remains a hypothesis worth keeping in view when interpreting reports of improved zone-of-inhibition values, which compare vehicles against sensitive reference strains. Susceptibility testing of clinical isolates, rather than reference strains alone, would settle the point.

## 3. NANOEMULSION DESIGN

Terminology is used loosely in this field, and the confusion affects how studies are compared. A microemulsion is thermodynamically stable and forms spontaneously, whereas a nanoemulsion is only kinetically stable and usually needs some input of energy or a carefully tuned composition [17, 18]. Both appear transparent and both may contain droplets of similar size, so authors sometimes label the same system differently. For topical work the practical distinction is surfactant load. Microemulsions often need a lot of surfactant and co-surfactant, which raises irritation concerns, while nanoemulsions can often be made with less, though they must then be protected against slow coarsening.

Formulation begins with the oil phase, because the drug has to dissolve in it. Published terbinafine work has screened medium-chain triglycerides, oleic acid, isopropyl myristate and various essential oils by measuring equilibrium solubility, then picking the oil in which the drug dissolves best and which is also acceptable on skin [9, 18]. High solubility matters more than people sometimes assume. If the oil cannot hold the drug at the target strength of one per cent, the system will crystallise on storage or the oil fraction has to rise, which makes the droplets bigger and the mixture harder to emulsify.

Surfactant and co-surfactant selection follows. Non-ionic surfactants such as polysorbate 80 are popular because they are tolerated well on skin and have a hydrophilic-lipophilic balance suited to oil-in-water systems, while short-chain alcohols, glycols or medium-chain glycerides act as co-surfactants that fluidise the interface and lower the energy needed to form small droplets [8, 19]. Pseudo-ternary phase diagrams, drawn by titrating oil and surfactant mixtures with water, map out the region in which a clear nanoemulsion forms. The diagrams are simple to produce and are the standard way of choosing a workable ratio before any drug is added [7, 18].

Preparation methods fall into high-energy and low-energy groups. High-pressure homogenisation and ultrasonication break coarse emulsions into fine droplets using mechanical force, and they are easy to scale in principle but expose the product to heat and shear [9, 20]. Spontaneous emulsification, in contrast, relies on the composition alone: oil, surfactant and co-surfactant are mixed, water is added with gentle stirring and a fine dispersion appears [7]. Many academic terbinafine studies prefer the low-energy route because it needs little equipment, although some then follow it with brief ultrasonication to narrow the size distribution.

Droplet size and polydispersity are the first quality attributes checked. Dynamic light scattering usually reports a mean diameter and a polydispersity index, and values below roughly 0.3 are generally taken to indicate a reasonably uniform population [21]. Zeta potential indicates how strongly droplets repel one another, although non-ionic systems often show only modest values and rely on steric stabilisation instead. Transmission electron microscopy is used to confirm shape. Reports on terbinafine nanoemulsions commonly describe spherical droplets in the range of about 20 to 150 nm, which is consistent with the broader literature on the type [9].

Thermodynamic stress testing separates robust systems from marginal ones. Centrifugation, repeated heating and cooling, and freeze-thaw cycles are applied to the candidate formulation, and any creaming, cracking or phase separation leads to its rejection [18, 22]. Nanoemulsions are not thermodynamically stable in the way microemulsions are, so they can slowly coarsen through Ostwald ripening, in which oil migrates from small droplets to larger ones. Choosing an oil with very low water solubility and adding a small amount of a second, even less soluble oil are two published strategies for slowing the process [9, 20].

## 4. GEL FORMATION AND CHARACTERISATION

Converting the liquid into a gel is usually done with a carbomer such as Carbopol 934 or 940, or with a cellulose derivative such as hydroxypropyl methylcellulose. Carbomers swell in water and thicken sharply when neutralised with triethanolamine, forming a clear network whose viscosity falls under shear, which is the behaviour wanted for a product that must sit on the skin yet spread easily [23]. The nanoemulsion is incorporated into the gel base with gentle mixing so that the droplets are not disturbed. Gelling agent concentration is a trade-off, because a stiffer network holds the product in place but can slow release of the drug.

Once the gel is made, a standard battery of tests is applied. The pH should sit close to that of normal skin, around 5 to 6, which avoids irritation and is achievable with carbomer gels after neutralisation. Drug content is determined by high-performance liquid chromatography or ultraviolet spectrophotometry, and uniformity is checked across the container. Viscosity is measured with a rotational viscometer, and spreadability is tested by the parallel-plate method, in which a known mass of gel is pressed between glass slides and the diameter of spread recorded [15, 23]. Extrudability from a collapsible tube is also tested, because it predicts how the product will feel to the patient.

Rheology deserves more attention than it usually gets in formulation papers. A topical gel should be viscous enough at rest to stay where it is put, yet thin out under the shear of rubbing so that a thin even layer forms. Carbomer systems show this shear-thinning behaviour and often a measurable yield stress, and the flow curve can be altered by pH, ionic strength and the presence of surfactant [23]. Reporting a single viscosity value at one spindle speed hides all of this. Flow curves across a range of shear rates, together with recovery after shearing, would say far more about how the product will behave in the tube and on the skin.

Stability studies for a product intended for storage follow the temperature and humidity conditions set out in international guidance, normally long-term storage at 25 °C and 60% relative humidity and accelerated storage at 40 °C and 75% relative humidity for six months [22]. For laboratory formulations, shorter studies are common, tracking droplet size, pH, viscosity and drug content at intervals. Reports of terbinafine nanoemulsion gels typically find little change over a few months, but the studies are short and the number of batches is small, so they show promise rather than a shelf life that a regulator would accept.

Because the gel is both a colloidal system and a polymer network, its structure is more complicated than either part alone. The carbomer network can immobilise droplets and slow their movement, which helps physical stability, yet it can also interact with ionic surfactants or charged drug molecules. Terbinafine hydrochloride is a weak base and may bind to the anionic carbomer, which in some formulations reduces release. Formulators usually avoid this by using the free base dissolved in the oil phase, or by choosing a non-ionic gelling agent when the salt form is essential [18, 23].

## 5. SKIN PERMEATION AND ANTIFUNGAL PERFORMANCE

Skin delivery is limited by the stratum corneum, a few tens of micrometres of keratin-filled cells embedded in a lipid matrix. Passive diffusion is favoured for molecules that are small, moderately lipophilic and uncharged, and the old rule of thumb that compounds above about 500 daltons cross poorly is still widely quoted [24, 25]. Terbinafine, at about 291 daltons and highly lipophilic, passes the size test but tends to be retained in the upper layers instead of crossing into the dermis. For a superficial fungal infection this retention is welcome. The aim of the formulation is deposition in the keratin, not systemic absorption.

Nanoemulsions are thought to improve delivery through several routes. The large interfacial area and small droplets provide a steep concentration gradient, the surfactants and co-surfactants can fluidise stratum corneum lipids, and the oil can partition into the skin and carry drug along with it [19, 26]. Occlusion by a thin film also increases

hydration, which loosens the keratin structure. The relative weight of each effect is hard to separate, and reviews of microemulsion and nanoemulsion delivery caution that enhanced flux can reflect mild barrier disruption as much as clever carrier design [26].

The choice of skin model influences the outcome as much as the formulation does. Human skin is the reference, but supplies are limited and ethics approval is needed, so researchers use rat, mouse, rabbit or porcine skin, or artificial membranes. Hairless rodent skin is generally more permeable than human skin, which flatters the result, while porcine ear skin is a closer match [24, 27]. Thickness, hydration, storage history and the integrity check applied before the experiment all vary between laboratories. A claim of several-fold improvement in permeation from one laboratory therefore cannot be set directly beside a similar claim from another without allowing for these differences.

In vitro permeation is normally studied in Franz-type diffusion cells with excised animal or human skin, or with synthetic membranes, and the receptor fluid is sampled over 24 hours [27]. Release data are often fitted to zero-order, first-order, Higuchi or Korsmeyer-Peppas models, with the Higuchi square-root-of-time relationship the most commonly invoked for semisolid systems [28, 29]. Studies of terbinafine nanoemulsion gels generally report greater release and higher skin retention than a marketed cream or a plain gel, and many add confocal laser scanning microscopy or tape stripping to show where the drug sits.

Antifungal activity is usually shown by agar diffusion against *Candida albicans*, *Trichophyton rubrum* or *Aspergillus* species, measuring zones of inhibition, and occasionally by broth microdilution to obtain minimum inhibitory concentrations. A larger zone for the nanoemulsion gel than for a marketed cream is the commonly reported result. The finding has to be read carefully, since diffusion through agar depends on the vehicle as much as on the drug, so a vehicle that releases faster will look better in the plate even if skin efficacy is unchanged [13, 16]. Animal infection models, most often guinea pig tinea, give stronger evidence but appear less often.

Selected findings from the published literature are collected in table 1, grouped by the aspect of the formulation they address. The grouping is shown graphically in fig. 1. Two things stand out. Most of the entries concern formulation and characterisation, since these are the parts of the work that can be completed in a laboratory without ethical approval for animals or people. Entries that address efficacy in infected animals or tolerability are fewer, and entries from controlled human studies of nanoemulsion-based terbinafine products are scarce. The imbalance shapes how far the conclusions of the field can be pushed.

**Table 1: Selected published findings on terbinafine nanoemulsions and gels, by formulation aspect**

| Aspect studied | Reported finding | Ref. |
|---|---|---|
| Oil phase selection solubility screening | Oil chosen for highest drug solubility and skin acceptability; poor solubility forces more oil and larger droplets | [9, 18] |
| Surfactant system phase diagrams | Pseudo-ternary diagrams define the clear nanoemulsion region before drug is loaded | [7, 8] |
| Preparation method low versus high energy | Spontaneous emulsification gives fine droplets with little equipment; homogenisation adds control but heat | [7, 20] |
| Droplet size light scattering | Mean diameters of tens to low hundreds of nm; low polydispersity index indicates uniform population | [9, 21] |
| Gel base carbomer network | Neutralised carbomer gives shear-thinning gel suited to spreading and retention on skin | [23] |
| Storage stability ICH conditions | Short studies show little change; long-term and multi-batch data are lacking | [18, 22] |
| Skin permeation Franz cell | Greater retention in skin than marketed cream, with mainly superficial deposition | [26, 27] |
| Release kinetics Higuchi model | Release commonly fits square-root-of-time kinetics for semisolid systems | [28, 29] |

| Aspect studied | Reported finding | Ref. |
|---|---|---|
| Mechanism of enhancement barrier effects | Lipid fluidisation and interfacial area contribute; barrier disruption may be partly responsible | [19, 26] |
| Antifungal activity agar diffusion | Larger inhibition zones than cream, though vehicle release affects the plate result | [13, 16] |
| Skin irritation rabbit or rat test | Gels generally non-irritating or mildly irritating after single application | [15, 30] |

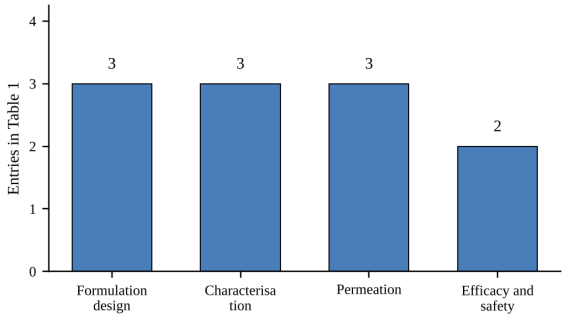



**Fig. 1: Number of entries in table 1 by aspect of the formulation studied**

Safety testing deserves a mention of its own. Surfactants at the concentrations needed for nanoemulsions can irritate, and a formulation that performs beautifully in a diffusion cell may sting when applied to inflamed skin. Published work usually reports a primary irritation index in rabbits or rats after a single application, following the acute dermal irritation test guideline, and nanoemulsion gels commonly score as non-irritating or only slightly irritating [15, 30]. Histology of treated skin is sometimes added. Repeat-exposure and sensitisation data are far less common, which leaves a gap for a product meant for weeks of use on damaged skin.

Patient-facing features are discussed less often than they deserve. Gels dry quickly, do not leave a greasy residue and are easier to apply to hairy or folded areas, all of which matter for adherence in tinea cruris and tinea corporis [14]. A once-daily regimen is easier to follow than a twice-daily one. If a nanoemulsion gel can hold drug in the keratin long enough to permit shorter or less frequent application, the benefit to the patient could be larger than any in vitro flux figure suggests, though this has not been shown in published trials of such products.

## 6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations recur across the published work. Most studies use a single formulation in one laboratory, use excised animal skin that is more permeable than human skin, and compare against a single marketed cream without a vehicle-matched control. Sample sizes are small, and statistical comparisons are often limited to one time point. Differences in surfactant type, oil, gelling agent and receptor medium make it hard to compare studies against one another, and negative results are seldom published [9, 16]. These weaknesses do not invalidate the approach, but they limit confidence in how large the benefit really is.

Scale-up is another open question. Low-energy emulsification works well in the bench-top beaker, but the composition windows are narrow and can shift with small changes in temperature, mixing rate or raw-material grade. Surfactant loadings that look acceptable in a pilot batch may be a problem for tolerability or cost at commercial scale [18, 20]. Regulatory expectations for nanomaterial-containing medicines also add characterisation requirements, including droplet size distribution control across batches and evidence that the structure survives storage in the final container [22]. Process validation across several batches is rarely described in academic reports.

Excipient safety and acceptability also bear on translation. Surfactants and co-solvents that are accepted in a few-gram tube may raise concern when used daily over weeks on inflamed or broken skin, and the sensory properties of the final gel, such as tackiness and odour from certain oils, influence whether patients keep using it [14, 30]. Cost is a further issue in the settings where dermatophytosis is most common, since a product that is much more expensive than an inexpensive generic cream will struggle to find a place regardless of its laboratory performance. Pharmacoeconomic reasoning is rarely included in formulation papers, but it will decide whether such gels reach patients.

Future work would be more convincing if it included standardised permeation protocols with human skin or validated skin models,

vehicle-matched controls, tests against clinical isolates with documented susceptibility, including terbinafine-resistant strains, and well-designed trials in patients. Comparative studies with other nanocarriers such as solid lipid nanoparticles, niosomes and ethosomes would show whether a nanoemulsion offers advantages worth its surfactant burden [15, 16]. Studies that measure drug concentration in the stratum corneum directly, rather than infer it from receptor-fluid data, would also help connect formulation properties to the thing that ultimately matters, which is clearing the infection.

## 7. CONCLUSION

Published studies support the view that terbinafine can be carried in an oil-in-water nanoemulsion and converted into a gel without losing the small droplet size that gives the system its appeal. Reported products are stable over short periods, spread well, release drug in a predictable pattern and deposit more terbinafine in skin than conventional creams do [18, 26, 27]. For a drug whose target sits in the stratum corneum, increased local retention is the right kind of improvement, and the safety data available suggest that well-chosen excipients are tolerated. Because these gels are intended for repeated use on infected skin, tolerability across several weeks matters as much as the first-day figures.

The evidence base is still thin where it counts. Efficacy is mostly inferred from agar plates and diffusion cells, human data are almost absent and resistant isolates are rarely tested [3, 16]. Clinicians should treat these gels as promising experimental formulations and not as proven replacements for existing terbinafine creams, while formulators should concentrate on standardised permeation methods, multi-batch stability and, eventually, controlled trials in patients with tinea [12, 13]. Until then, the claims are best read as encouraging laboratory evidence.

## 8. ABBREVIATIONS

DLS-Dynamic light scattering, HLB-Hydrophilic-lipophilic balance, HPLC-High-performance liquid chromatography, ICH-International Council for Harmonisation, PDI-Polydispersity index, TEM-Transmission electron microscopy, OECD-Organisation for Economic Co-operation and Development, KOH-Potassium hydroxide

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All the authors have contributed equally.

## 11. CONFLICT OF INTERESTS

Declared none

## 12. REFERENCES

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