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Topical Emulgels of Griseofulvin for Dermatophytosis: Current Trends, Characterization Techniques, and Future Prospects

Ruchi Jain¹, Piyush Jain², Dr. Tekeshwar Kumar³

¹ Sanskar City College of Pharmacy, Rajnandgaon

² Sanskar City College of Pharmacy, Rajnandgaon*

*Corresponding author: **Ruchi Jain**

e-mail: ruchijain.raipur@gmail.com



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Abstract: Dermatophytosis is among the most prevalent superficial fungal infections worldwide and has recently taken an epidemic-like course in tropical countries such as India, marked by chronic, recurrent and treatment-recalcitrant presentations and rising resistance to terbinafine and azole antifungals. Griseofulvin, the first orally effective antidermatophytic antibiotic, remains pharmacologically active against the causative dermatophyte genera (Trichophyton, Microsporum and Epidermophyton) but its clinical utility is limited by poor aqueous solubility (Biopharmaceutics Classification System [BCS] Class II behaviour), variable oral bioavailability, a prolonged treatment course and systemic adverse effects. Delivering griseofulvin directly to the site of infection through the skin could circumvent these limitations, but conventional topical vehicles such as creams and ointments provide inconsistent drug release and poor cosmetic acceptability. The emulgel — a biphasic system in which an oil-in-water or water-in-oil emulsion is dispersed within a hydrophilic or hydrophobic gelling network — has emerged as an attractive alternative because it combines the enhanced solubilisation capacity of an emulsion for lipophilic drugs with the favourable rheological, spreading and patient-acceptability profile of a gel. This review consolidates the current literature on topical antifungal emulgels, with particular emphasis on griseofulvin, and systematically describes the epidemiological rationale, the biopharmaceutical basis for topical delivery, formulation strategies (including nanoemulsion-, nanostructured-lipid-carrier- and microemulsion-based emulgels), and the physicochemical, rheological, in vitro, ex vivo and in vivo characterization techniques applied to such systems. Comparative evidence from marketed and investigational antifungal emulgels of terbinafine, luliconazole and clotrimazole is used to benchmark expected performance. Regulatory, scale-up and stability challenges are discussed, followed by future prospects including nanotechnology integration, quality-by-design optimisation and combination therapy approaches for recalcitrant dermatophytosis. The review is intended to provide a comprehensive reference framework for researchers developing griseofulvin-based topical delivery systems

Keywords: Griseofulvin; Emulgel; Dermatophytosis; Topical drug delivery; Nanoemulgel; Antifungal; Characterization

1. Introduction

Superficial fungal infections of the skin caused by keratinophilic dermatophytes — collectively termed dermatophytosis or "tinea" — represent one of the most common dermatological complaints seen in outpatient practice globally, with an estimated global prevalence reaching 20-25% in endemic tropical and

subtropical regions [1]. Over the last decade, several countries in South Asia, most notably India, have reported an unprecedented epidemic-like surge in chronic, recurrent and treatment-recalcitrant dermatophytosis, frequently attributed to indiscriminate use of over-the-counter topical steroid-antifungal-antibacterial combination creams, inadequate dosing of oral antifungals, and the emergence of resistant species such as *Trichophyton indotineae* [2,3,4,5,6].

Griseofulvin, isolated from *Penicillium griseofulvum*, was the first systemically active antidermatophytic antibiotic and remains included in current treatment guidelines, particularly for tinea capitis in children [7]. Its chemical structure (Figure 1) accounts for its physicochemical behaviour: a spiro-fused benzofuranone system bearing three methoxy substituents and a chlorine atom gives the molecule a high melting point and marked lipophilicity relative to its very low aqueous solubility, formally classifying it as a Biopharmaceutics Classification System (BCS) Class II drug (low solubility, high permeability) [8,9,10,11]. Consequently, oral griseofulvin therapy is characterised by erratic and dose-dependent bioavailability, a treatment duration extending to several weeks or months, and adverse effects including headache, gastrointestinal disturbance, photosensitivity and, rarely, hepatotoxicity [8,12]. These limitations, together with the rising resistance of dermatophytes to first-line oral agents, have renewed interest in delivering griseofulvin directly to the infected stratum corneum through a topical route, thereby achieving high local drug concentrations while minimising systemic exposure [12,13,14,15].

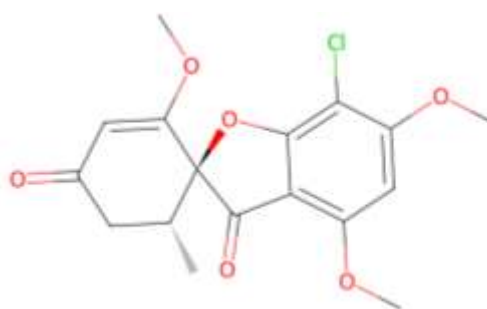


Fig 1: Two-dimensional chemical structure of griseofulvin ($C_{17}H_{17}ClO_6$; MW 352.77 g/mol), drawn with RDKit 2026.03 from the canonical SMILES corresponding to PubChem CID 441140. The three methoxy groups and the spiro-fused bicyclic core underlie its high lipophilicity and very low aqueous solubility.

Early attempts at topical griseofulvin delivery using simple sprays, hydrogels and creams demonstrated proof-of-concept antidermatophytic activity but were hampered by the poor partitioning of the crystalline drug into the vehicle and, consequently, limited skin permeation [12,13,14]. Subsequent formulation strategies — including microemulsions, nanostructured lipid carriers (NLCs) and nanohybrid emulsions — have shown that reducing the effective particle/globule size and improving drug solubilisation markedly enhances cutaneous flux and antifungal cure rates in animal models of dermatophytosis [15,16,17]. Building on these advances, the emulgel platform, which merges an emulsion (for lipophilic drug solubilisation) with a gel matrix (for favourable application characteristics and controlled release), has been increasingly explored for topical antifungal therapy of clotrimazole, terbinafine and luliconazole [18,19,20,21,22], and represents a logical and largely underexploited vehicle for griseofulvin.

This review aims to (i) summarise the epidemiological and biopharmaceutical rationale for a griseofulvin emulgel, (ii) describe emulgel composition and preparation methodologies, (iii) present a structured overview of the physicochemical, rheological, release, permeation, microbiological and stability characterization techniques applicable to such systems, (iv) critically compare emulgel-based antifungal delivery with other novel topical carriers using literature-derived quantitative data, and (v) outline current trends and future research directions, so as to provide a consolidated reference for investigators preparing manuscripts on this topic for Scopus-indexed pharmaceutical journals.

2. Literature Search Strategy

A structured literature search was conducted to identify relevant studies on griseofulvin, dermatophytosis, topical drug delivery, emulgels, nanoemulgels, microemulsions and nanostructured lipid carriers. Relevant literature was identified using PubMed, Scopus, Web of Science and Google Scholar using combinations of keywords such as “griseofulvin,” “topical delivery,” “emulgel,” “nanoemulgel,” “microemulsion,” “nanostructured lipid carrier,” “skin permeation,” and “dermatophytosis.” Published research articles, review articles and relevant regulatory or guideline documents were considered, with emphasis on

literature providing information on formulation development, physicochemical characterization, drug release, skin permeation, antifungal activity, stability and quality-by-design approaches. Older publications were also included where they provided important foundational evidence on griseofulvin pharmacology or topical delivery. Reference lists of relevant publications were additionally screened to identify pertinent studies. Where direct evidence for griseofulvin emulgels was limited, studies involving related topical antifungal emulgel and nanoemulgel systems were considered to provide comparative and supportive evidence.

3. Dermatophytosis: Epidemiology, Aetiology and the Current Treatment Challenge

Dermatophytes are filamentous keratinophilic fungi belonging predominantly to the genera *Trichophyton*, *Microsporum* and *Epidermophyton*. They secrete keratinases that allow invasion of the keratinised layers of the epidermis, hair and nail, producing the characteristic annular, pruritic plaques of tinea corporis, cruris, pedis, capitis and unguium (Figure 2) [4,23]. While historically regarded as a self-limiting and easily treatable condition, the clinical and mycological profile of dermatophytosis has changed markedly in recent years.

Multiple clinicomycological surveys from India report that a large proportion of patients now present with chronic disease (lasting beyond three months), frequent relapse after apparently successful treatment, and a shift in the predominant pathogen from *Trichophyton rubrum* toward the *Trichophyton mentagrophytes*/interdigitale complex, including the emerging terbinafine-resistant genotype *T. indotineae* [4,5,23,24]. Molecular studies have linked reduced terbinafine susceptibility to point mutations in the fungal squalene epoxidase gene, which can be rapidly screened using amplified refractory mutation system polymerase chain reaction (ARMS-PCR) assays [24,25]. A randomised pragmatic trial comparing fluconazole, griseofulvin, itraconazole and terbinafine in chronic and chronic-relapsing tinea corporis/cruris/faciei in India further confirmed that cure rates with standard oral regimens are now substantially lower than historically reported, reinforcing the need for adjunctive or alternative therapeutic strategies [6,7]. An international survey of dermatologists similarly confirmed that recalcitrant and recurrent dermatophyte infections are now a global, rather than a purely regional, clinical problem [6].

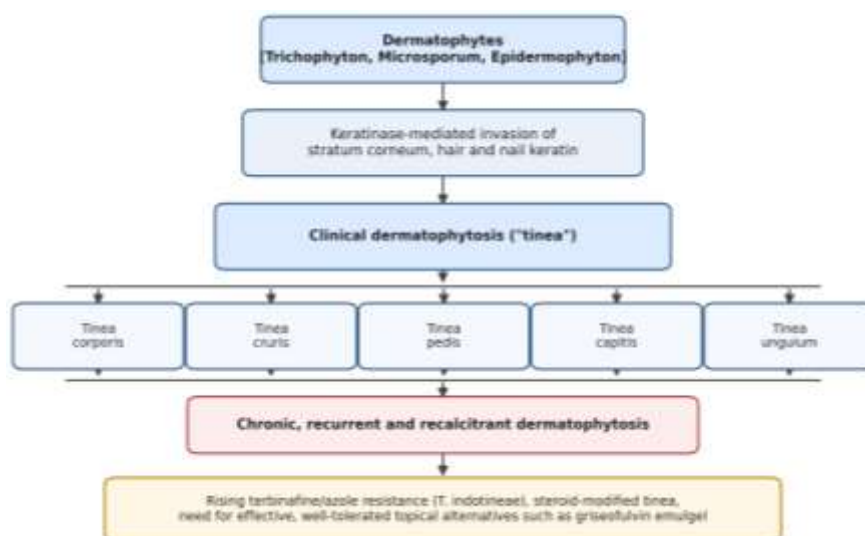


Fig 2: Aetiology, clinical spectrum and the emerging problem of chronic/recalcitrant dermatophytosis that motivates renewed interest in topical griseofulvin delivery systems.

Against this backdrop, topical antifungal therapy assumes a dual role: as monotherapy for limited, uncomplicated tinea, and as a valuable adjunct to systemic therapy in extensive or recalcitrant disease, where it can reduce the fungal load at the skin surface, shorten the effective treatment duration and lower the risk of further resistance selection associated with prolonged systemic dosing [4,6]. This clinical need underlines the pharmaceutical rationale for developing a well-characterised, effective topical griseofulvin delivery system such as an emulgel.

4. Griseofulvin: Pharmacology, Biopharmaceutical Limitations and Rationale for Topical Delivery

4.1 Mechanism of action and spectrum

Griseofulvin acts by binding to fungal microtubular proteins, disrupting the mitotic spindle and arresting fungal cell division; it also interferes with fungal cell wall synthesis. It is active against dermatophyte genera (*Trichophyton*, *Microsporum* and *Epidermophyton*) but has no clinically useful activity against yeasts, moulds or bacteria, which favours its selective use in dermatophytosis without disturbing normal cutaneous or gastrointestinal flora [12,13].

4.2 Biopharmaceutical limitations

Griseofulvin has a high melting point (218-220°C), a log P of approximately 2.17, and is practically insoluble in water, placing it firmly within BCS Class II (low solubility, high permeability) [8,10,15]. For a BCS Class II drug, the dissolution rate — rather than membrane permeability — is typically the rate-limiting step for absorption, so that small improvements in effective solubility or dissolution rate can produce disproportionately large gains in bioavailability [9,10]. When administered orally, griseofulvin also undergoes appreciable first-pass hepatic metabolism and induces hepatic microsomal enzymes, contributing to variable systemic exposure, a long treatment course (often six to eight weeks or longer for tinea corporis, and considerably longer for tinea unguis), and a recognised adverse-effect profile including headache, gastrointestinal upset, photosensitivity and, uncommonly, hepatotoxicity and blood dyscrasias [8,12].

4.3 Rationale for topical delivery

Because dermatophytosis is, by definition, confined to the keratinised layers of the skin, hair and nail, a topical delivery system capable of achieving and sustaining an adequate griseofulvin concentration within the stratum corneum offers an attractive means of maximising local antifungal exposure while minimising systemic drug load and associated adverse effects [12,13,14]. Early clinical work demonstrated that a 1% topical griseofulvin spray was significantly more effective than vehicle alone in experimentally induced dermatophyte lesions and in patients with tinea pedis, establishing proof-of-concept for cutaneous efficacy when adequate skin penetration is achieved [13,14]. Subsequent formulation research using carbomer-based hydrogels with penetration enhancers such as propylene glycol and N-methylpyrrolidone confirmed that topical application can sustain higher and more prolonged drug concentrations in the skin than are achieved after oral dosing, without inducing skin sensitisation [12]. However, the poor intrinsic solubility of griseofulvin means that simple aqueous gels or conventional creams typically provide limited thermodynamic activity and, hence, limited flux of the drug across the stratum corneum — the specific problem that emulsion- and nanocarrier-based systems, including emulgels, are designed to solve [8,15,16,17].

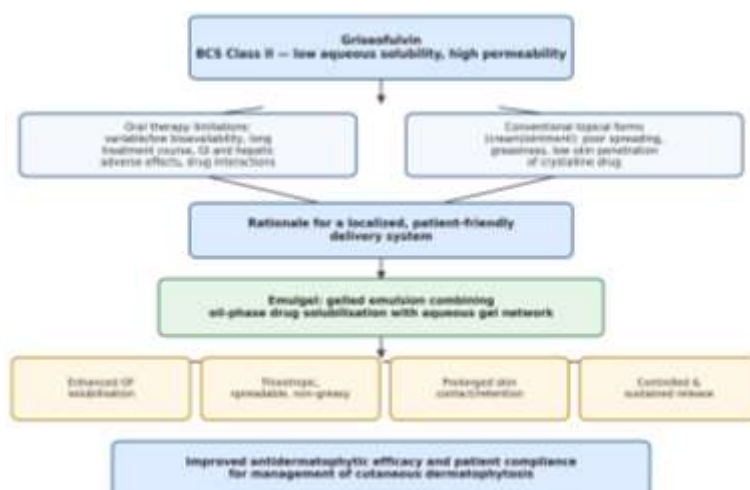


Fig 3: Biopharmaceutical rationale linking the BCS Class II character of griseofulvin, the limitations of oral and conventional topical therapy, and the properties an emulgel-based carrier is designed to deliver.

5. Emulgel as a Topical Delivery Platform

5.1 Concept, composition and rationale

An emulgel is a two-phase system in which a conventional oil-in-water (o/w) or water-in-oil (w/o) emulsion is incorporated into a hydrophilic (or, less commonly, hydrophobic) gel network. The gelling agent provides the continuous-phase rheology needed for spreadability, bioadhesion and patient

acceptability, while the internal emulsified oil phase provides a solubilisation reservoir for lipophilic actives such as griseofulvin, allowing higher effective drug loading than is achievable in a plain hydrogel [26,27,28,29]. Reported advantages of emulgels over conventional creams and ointments include thixotropic and shear-thinning rheology (easy to dispense but resistant to sagging once applied), a greaseless and non-staining after-feel, transparency, longer shelf-life, and the capacity for dual controlled release of the incorporated drug from both the internal emulsion droplets and the surrounding gel matrix [27,28,29]. Typical excipient classes used in emulgel design include gelling agents (Carbopol 934/940, xanthan gum, hydroxypropyl methylcellulose), an oil phase selected on the basis of maximal drug solubility (e.g., oleic acid, isopropyl myristate, Capryol, flaxseed oil), hydrophilic and lipophilic surfactant pairs (Tween 80/Span 80 or similar), penetration enhancers (propylene glycol, oleic acid, N-methylpyrrolidone) and a neutralising agent (triethanolamine or sodium hydroxide) to achieve a skin-compatible pH and the desired gel consistency [12,15,26,27]. A schematic representation of the resulting microstructure is shown in Figure 4.

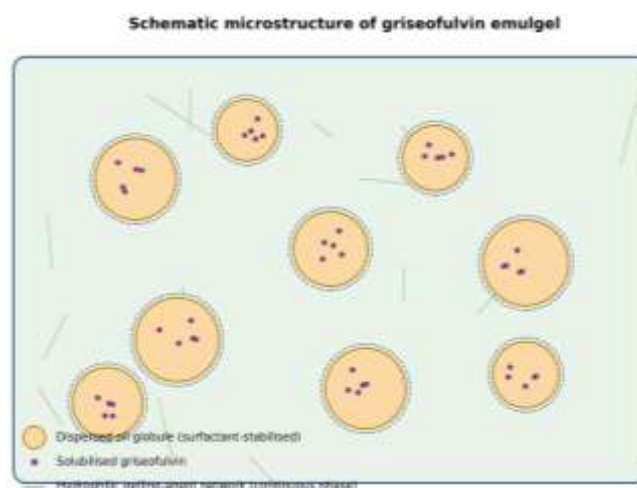


Fig 4. Conceptual microstructure of a griseofulvin emulgel: drug-loaded, surfactant-stabilised oil globules dispersed within a continuous hydrophilic gelling-agent network.

5.2 Preparation methodology

Most reported emulgels, including antifungal emulgels of clotrimazole, terbinafine and luliconazole, are prepared by a two-step process in which the aqueous gel base and the drug-loaded emulsion are formulated independently and then combined [18,19,20,21,22]. The gel phase is prepared first by soaking or dispersing the gelling agent in water, followed by neutralisation to develop the characteristic gel viscosity. In parallel, the oil phase (containing dissolved or dispersed griseofulvin and a lipophilic surfactant) and the aqueous surfactant phase are heated to a common temperature and combined under high-speed homogenisation or probe sonication to form a fine o/w emulsion, which may be further processed (e.g., by microfluidisation or high-pressure homogenisation) when a nanoemulsion or nanostructured-lipid-carrier intermediate is desired [9,16,17]. The emulsion is then incorporated into the gel base, typically in a 1:1 ratio, under continuous stirring, followed by addition of a penetration enhancer and preservative and final pH adjustment. This overall workflow, adapted specifically for a griseofulvin emulgel on the basis of the methodologies reported for related antifungal and hydrogel systems [12,15,16,26,27], is summarised in Figure 5.

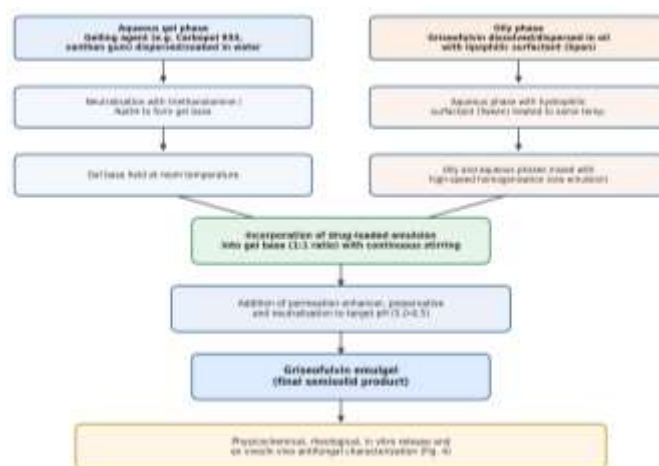


Fig 5: Representative two-step preparation flow chart for a griseofulvin emulgel, combining an independently formed gel base and drug-loaded emulsion.

5.3 Nanocarrier-integrated emulgel approaches for griseofulvin

Because the magnitude of skin flux achievable from a conventional emulsion is limited by the size of the dispersed oil globules and the thermodynamic activity of the drug within them, several groups have combined nanocarrier technology with gel-based delivery to further enhance griseofulvin performance. A griseofulvin-loaded nanostructured lipid carrier (NLC) gel, optimised by Box-Behnken design using glyceryl monostearate, oleic acid, Pluronic F68 and Tween 80, achieved a particle size of approximately 209 nm, an entrapment efficiency of about 85% and favourable HET-CAM irritancy and in vivo antifungal outcomes [16]. A microemulsion-based topical formulation using oleic acid as the oil phase and a Tween 80/ethanol surfactant mixture produced globules of around 12 nm and demonstrated three- to seven-fold higher skin permeation than an aqueous suspension, oily solution or conventional cream (Figure 6A), translating into complete clinical and mycological cure within seven days in a guinea pig model of *Microsporum canis* infection [15]. A more recent zinc-nanohybrid griseofulvin emulsion (mean particle size ~50 nm) markedly potentiated antidermatophytic and antimicrobial activity compared with free griseofulvin, a plain nanoemulsion, zinc nitrate alone or ketoconazole, illustrating the additional gains achievable by combining metal-nanoparticle and emulsion strategies [17]. Collectively, this body of work — although not yet extended to a fully characterised griseofulvin emulgel in the published literature at the time of writing — provides strong mechanistic and translational justification for applying the emulgel platform, which has already been validated for structurally similar antifungal agents such as terbinafine, luliconazole and clotrimazole [18,19,20,21], to griseofulvin.

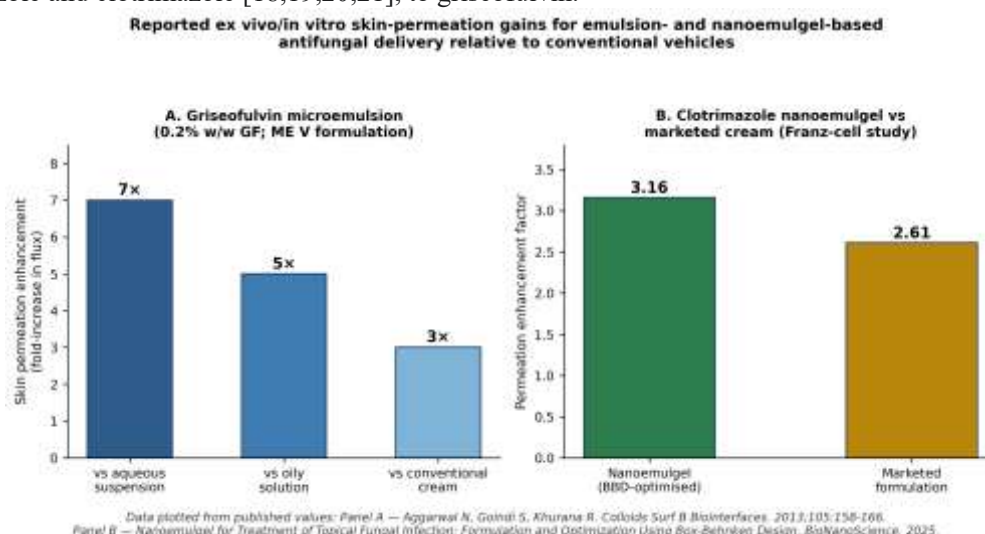


Fig 6: Literature-reported skin-permeation gains for (A) an optimised griseofulvin microemulsion relative to conventional vehicles, and (B) a Box-Behnken-optimised clotrimazole nanoemulgel relative to a

marketed cream, illustrating the magnitude of improvement achievable with emulsion/nanoemulgel-based antifungal delivery.

Table 1. Summary of reported topical delivery systems for griseofulvin

Study	Topical delivery system	Key formulation features	Major findings	Biological/functional evaluation	Ref.
Shishu and Aggarwal (2006)	Hydrogel	Griseofulvin incorporated into a hydrogel system	Demonstrated feasibility of dermal delivery of griseofulvin	Dermal application study	[12]
Aly et al. (1994)	Topical griseofulvin formulation	Topical griseofulvin preparation	Demonstrated topical antidermatophytic activity	Dermatophytosis evaluation	[13]
Zarowny et al. (1975)	Topical griseofulvin	Topical therapy compared with reference treatments	Provided early evidence for topical griseofulvin therapy	Superficial dermatophytoses	[14]
Aggarwal et al. (2013)	Microemulsion	0.2% griseofulvin; oleic acid; Tween 80/ethanol Smix	12.21 nm globule size; approximately 3–7-fold greater permeation than conventional comparators	<i>Microsporum canis</i> model; clinical and mycological cure reported	[15]
Datt et al. (2022)	Nanostructured lipid carrier gel	GMS, oleic acid, Pluronic F68 and Tween 80; Carbopol 940 gel	209 nm particle size; 85.24% entrapment; 92.12% drug release	HET-CAM, cytotoxicity and in vivo antifungal evaluation	[16]
Mosallam et al. (2024)	Zinc-nanohybrid griseofulvin formulation	Griseofulvin–zinc oxide nanohybrid	Approximately 50 nm particle size; enhanced antifungal activity compared with free griseofulvin and selected comparators	Antidermatophytic/antimicrobial evaluation	[17]

6. Characterization Techniques for Griseofulvin Emulgel

Regulatory-quality characterization of an emulgel spans five broad domains — physicochemical, rheological/mechanical, in vitro release and ex vivo permeation, microbiological/biological, and stability — summarised in Figure 7 and described individually below.

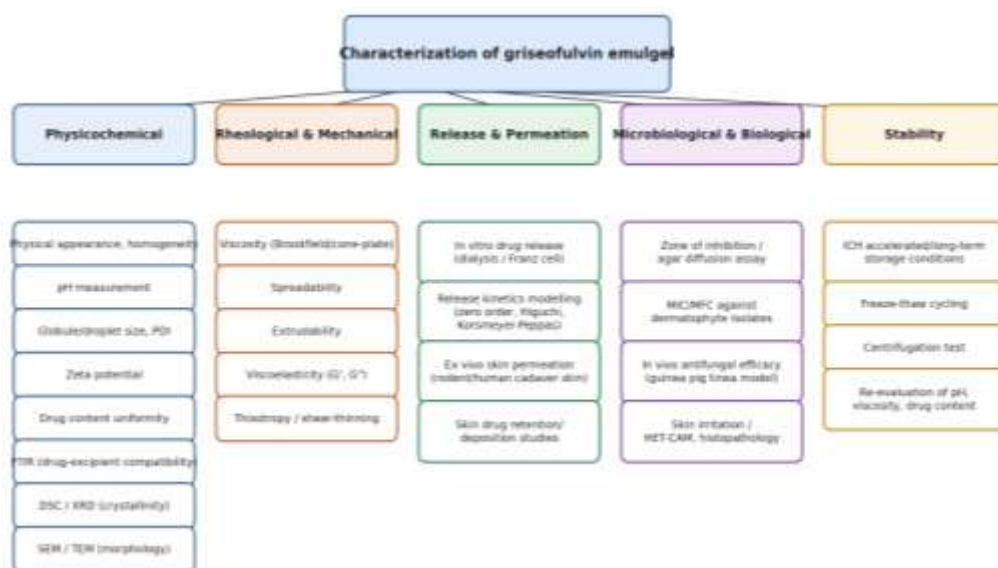


Fig 7: Consolidated characterization workflow for a griseofulvin emulgel, organised by physicochemical, rheological, release/permeation, microbiological and stability domains.

6.1 Physicochemical characterization

Visual assessment of homogeneity, colour, phase separation and grittiness is typically the first quality checkpoint, followed by pH measurement (usually targeted between 5.0 and 6.5 to match the skin surface and minimise irritation) [28,30]. Globule or droplet size and polydispersity index (PDI) are determined by dynamic light scattering, and zeta potential is used to infer physical stability of the dispersed phase; values more negative than about -30 mV, or a comparably high positive value, are generally taken to indicate an adequately stabilised system [16,17,18]. Drug content uniformity is assessed by validated ultraviolet spectrophotometric or high-performance liquid chromatographic assay of replicate samples. Fourier-transform infrared (FTIR) spectroscopy is used to confirm the absence of chemical interaction between griseofulvin and the selected excipients, while differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) are used to detect changes in drug crystallinity (e.g., a shift toward an amorphous or molecularly dispersed state within the oil globules), and scanning or transmission electron microscopy (SEM/TEM) is used to confirm globule morphology and, in nanocarrier-integrated systems, particle sphericity and surface texture [8,9,16].

6.2 Rheological and mechanical characterization

Because emulgel rheology governs both physical stability and in-use performance (spreadability, bioadhesion, sensory feel and, ultimately, drug release), viscosity is typically measured using a Brookfield or cone-and-plate viscometer across a range of shear rates to confirm the expected shear-thinning (pseudoplastic) behaviour [1,26]. Spreadability is commonly assessed by measuring the diameter of spread of a fixed mass of emulgel between glass plates under a standard load, and extrudability by the force or weight required to extrude a fixed length of product from a collapsible tube [28,30,31]. More detailed viscoelastic characterization, including the storage modulus (G') and loss modulus (G'') as a function of oscillation frequency, is used in advanced rheological studies to relate the emulgel's microstructure to its long-term physical stability and its bio-adhesive/retention behaviour on skin [26]. Thixotropy — the reversible, time-dependent decrease in viscosity under shear — is often demonstrated through hysteresis-loop analysis and is considered a desirable attribute for topical products, since it eases application while allowing the product to "set" and resist run-off once at rest [27,29].

6.3 In vitro release and ex vivo skin permeation studies

In vitro drug release is typically evaluated using a dialysis membrane or a Franz diffusion cell apparatus, with the emulgel placed in the donor compartment and a suitable receptor medium (commonly phosphate buffer, sometimes with a co-solvent to maintain sink conditions for a poorly soluble drug such as griseofulvin) sampled at intervals over 6-24 hours [28,31,32]. The resulting release profile is fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas kinetic models to infer the predominant release mechanism (commonly diffusion-controlled, matrix-type release for emulgel systems) [32]. Ex vivo

permeation is assessed using excised animal (commonly rat, mouse or guinea pig) or, less commonly, human cadaver or shed-snake skin mounted in a Franz cell, with cumulative drug permeated, flux and enhancement ratio (relative to a marketed or plain-gel comparator) reported as the principal outcome measures [18,19,20,22,33]. Skin retention or deposition studies, in which the drug remaining within the stratum corneum/epidermis after a defined application period is extracted and quantified, are particularly relevant for an agent such as griseofulvin, where local cutaneous accumulation, rather than systemic absorption, is the therapeutic goal [12,15].

6.4 Microbiological and biological evaluation

Antifungal efficacy is typically first screened in vitro by agar-diffusion (cup-plate) or broth microdilution assays against dermatophyte isolates (commonly *Trichophyton mentagrophytes*, *T. rubrum* or *Microsporum canis/gypseum*), generating a zone of inhibition and/or minimum inhibitory and fungicidal concentrations (MIC/MFC) [17,18]. In vivo antifungal efficacy is most commonly demonstrated in a guinea-pig model of experimentally induced dermatophytosis, in which clinical resolution (erythema/scaling scores) and mycological cure (negative microscopy and culture) are tracked over one to several weeks of topical treatment and compared against untreated, vehicle-treated and marketed-formulation controls [15,22]. Local tolerability is assessed through skin-irritation testing — the hen's egg test-chorioallantoic membrane (HET-CAM) assay is frequently used as a rapid, reduced-animal-use irritation screen — together with histopathological examination of treated skin to confirm the absence of structural damage or inflammatory infiltrate [16,33].

6.5 Stability studies

Stability testing follows the general principles of the International Council for Harmonisation (ICH) guidelines for semisolid topical products, with samples stored under accelerated (typically 40°C/75% relative humidity) and long-term/refrigerated conditions and periodically re-evaluated for physical appearance, phase separation, pH, viscosity, drug content and microbial quality [9,26,28,30]. Freeze-thaw cycling and centrifugation testing are additionally used as accelerated indicators of emulsion (and, by extension, emulgel) physical stability, since they can reveal incipient coalescence, creaming or phase inversion that might otherwise take months to manifest under ambient storage [16,17,18].

7. Current Trends

7.1 Nanotechnology-integrated antifungal emulgels

The clearest current trend in this field is the convergence of nanocarrier technology with the emulgel platform. Nanoemulgels — in which the internal oil phase is reduced to the nanometre range (typically below 200 nm) using high-shear homogenisation, microfluidisation or spontaneous emulsification — have been reported for several antifungal agents structurally and biopharmaceutically comparable to griseofulvin. A terbinafine nanoemulgel produced significantly greater transdermal permeability than the corresponding commercial emulgel and superior in vivo antifungal activity against a *Candida* skin infection model [19], while a later terbinafine nanoemulgel study specifically targeting dermatophytosis similarly reported an optimised, stable oil-in-water nanoemulsion base with favourable pseudo-ternary phase behaviour [20]. Luliconazole nanoemulgels have achieved sub-100 nm globule sizes with markedly enhanced ex vivo skin permeation and deposition, confirmed by confocal laser scanning microscopy, and improved in vivo efficacy with negligible systemic drug exposure [21,22]. A clotrimazole nanoemulgel optimised by Box-Behnken design achieved an enhancement factor of over three relative to the marketed formulation, as summarised in Figure 6B [18]. These findings collectively support the translational potential of a nanoemulgel approach specifically for griseofulvin, building on the solubility- and permeation-enhancing benefits already demonstrated for griseofulvin microemulsions and NLC gels [15,16,17].

Table 2. Representative antifungal nanoemulgel and related topical nanocarrier systems

Antifungal drug	Delivery system	Major reported outcome	Evaluation performed	Ref.
Terbinafine	Nanoemulgel	Enhanced transdermal permeability and antifungal performance compared with conventional formulation	In vitro and in vivo evaluation	[19]

Terbinafine	Nanoemulgel	Optimized stable oil-in-water nanoemulsion-based topical system for dermatophytosis	Formulation and characterization	[20]
Luliconazole	Nanoemulgel	Sub-100 nm globule size with enhanced skin permeation and deposition	In vitro, ex vivo and in vivo evaluation	[21]
Luliconazole	Nanostructured lipid carrier gel	Enhanced antifungal efficacy in an animal model of dermatophytosis	In vitro/ex vivo and in vivo evaluation	[22]
Clotrimazole	Nanoemulgel	Enhanced permeation compared with marketed cream	Box–Behnken optimization and permeation evaluation	[18]

7.2 Design-of-experiments (DoE)-driven optimisation

A second notable trend is the routine use of statistical design of experiments — Box-Behnken, central composite and factorial designs — to optimise emulgel composition against multiple, sometimes competing, critical quality attributes (spreadability, extrudability, viscosity, drug release) simultaneously, rather than by traditional one-factor-at-a-time methods [9,16,18,32]. This quality-by-design (QbD) approach improves formulation robustness and provides a defensible, regulator-friendly rationale for the final composition, and is increasingly expected by peer reviewers of formulation-development manuscripts.

7.3 Combination and multifunctional emulgels

Given the rise of recalcitrant and steroid-modified dermatophytosis, there is growing interest in combination emulgels — for example, pairing an antifungal with a penetration enhancer of natural origin, an anti-inflammatory agent, or a second antifungal with a complementary mechanism — as a strategy to shorten treatment duration and reduce the likelihood of resistance selection [4,6,24]. While such combination griseofulvin emulgels have not yet been extensively reported, the general feasibility of co-loading a gel/emulgel matrix with two active agents has been demonstrated for other therapeutic classes (e.g., naproxen-eugenol emulgels for analgesia) [31], providing a template that could be adapted for antifungal combination therapy.

7.4 Green and natural excipients

There is also a discernible trend toward replacing synthetic oils and surfactants with naturally derived alternatives (e.g., flaxseed oil, olive oil, clove oil) to improve the sustainability and dermatological tolerability profile of emulgel formulations, as illustrated in recent andrographolide-loaded emulgel and olive oil/clove oil-based terbinafine hydrochloride nanoemulsion studies [32,34].

8. Comparative Evaluation with Conventional and Alternative Topical Systems

Relative to conventional griseofulvin creams and simple hydrogels, emulgel-based systems are expected, on the basis of analogous antifungal agents, to offer higher effective drug loading (through emulsified-oil solubilisation of the lipophilic drug), improved and more consistent spreadability, a non-greasy after-feel that favours patient adherence over the multi-week treatment courses typical of dermatophytosis, and — where a nanoemulsion or nanostructured-lipid-carrier intermediate is used — substantially enhanced cutaneous flux compared with plain aqueous or oily vehicles, as quantified in Figure 6 [15,16,18,26,27,29]. Compared with liposomal or niosomal gels, which can offer high entrapment efficiency and controlled release but are frequently limited by relatively complex, low-yield manufacturing processes and stability concerns (vesicle aggregation, drug leakage on storage), emulgels are generally simpler and more scalable to prepare, an important practical consideration for eventual pharmaceutical manufacture [35,36]. Microemulsion-based gels can achieve very fine (sub-20 nm) globule sizes and correspondingly high flux, as demonstrated for griseofulvin itself [15], but often require a relatively high surfactant/cosurfactant concentration that can raise concerns about skin irritation on prolonged use — a consideration of direct relevance given that dermatophytosis treatment typically extends over several weeks. The emulgel platform, by combining a moderate (rather than maximal) surfactant load with the physical stability conferred by the surrounding gel network, is therefore often positioned as a practical compromise between

simple emulsions/creams and more complex nanocarrier systems, while still allowing incorporation of a nanocarrier as the internal disperse phase when maximal flux is required [18,26,27,29].

9. Challenges and Regulatory Considerations

- Physical stability: emulgels remain susceptible to creaming, coalescence and phase separation on long-term storage, particularly when the internal phase is reduced to the nano-scale, requiring careful surfactant selection and systematic stability testing under ICH-aligned conditions [16,17,26].
- Scale-up: laboratory-scale high-shear homogenisation or probe sonication used to generate nano-sized internal phases can be difficult to reproduce at pilot and commercial manufacturing scale without loss of the fine particle/globule size critical to performance [16,18].
- Standardisation of characterization: reported rheological, release and permeation methodologies vary considerably between laboratories (different membranes, receptor media, apparatus), which complicates direct comparison across published griseofulvin/antifungal emulgel studies and argues for greater methodological standardisation in future work [8,26].
- Regulatory pathway: a topical griseofulvin emulgel, particularly one incorporating a nanocarrier, would in most jurisdictions require characterization data (particle size distribution, in vitro release, and where relevant in vivo bioequivalence/efficacy) consistent with current regulatory expectations for topical nanomedicines and generic semisolid products, which continue to evolve [8,9].
- Clinical translation: despite encouraging preclinical data for griseofulvin microemulsions, NLC gels and nanohybrid emulsions [15,16,17], controlled clinical trials of a fully developed griseofulvin emulgel in patients with dermatophytosis have not yet been published, representing an important evidence gap relative to more extensively studied topical antifungals such as terbinafine and luliconazole [19,20,21,22].

10. Future Prospects

Building on the trends identified above, several directions appear particularly promising for future research on griseofulvin emulgels. First, systematic application of quality-by-design methodology, using Box-Behnken or central composite designs to co-optimize globule size, entrapment efficiency, viscosity, spreadability and in vitro release, would strengthen the scientific and regulatory robustness of new formulations, following the precedent already established for related antifungal nanoemulgels [16,18,32]. Second, incorporation of griseofulvin within nanostructured lipid carriers, microemulsions or nanoemulsions as the internal disperse phase of an emulgel — rather than as a simple oil solution — could combine the solubility- and permeation-enhancing benefits already demonstrated individually for each of these nanocarriers with the favourable application properties of the gel matrix [15,16,17,21]. Third, head-to-head ex vivo and in vivo comparative studies between a griseofulvin emulgel and the current standard topical/oral antifungal comparators (terbinafine, luliconazole, itraconazole) in models of chronic or terbinafine-resistant dermatophytosis would help define its likely place in an increasingly complex treatment landscape [4,6,7,24]. Fourth, given the rising burden of recalcitrant disease, combination emulgels pairing griseofulvin with a second antifungal of a different mechanistic class, or with an evidence-based penetration enhancer, merit systematic exploration as a means of shortening treatment duration and mitigating further resistance selection [4,6,24,31]. Finally, well-designed randomised controlled clinical trials, supported by robust in vitro-in vivo correlation data, will ultimately be required to translate the strong preclinical rationale for a griseofulvin emulgel into an evidence-based addition to the antidermatophytic therapeutic armamentarium.

11. Conclusion

Griseofulvin remains a pharmacologically valuable but biopharmaceutically challenging antidermatophytic agent, and the current epidemic-like rise in chronic, recurrent and resistant dermatophytosis has renewed the clinical case for effective topical delivery. The emulgel platform, which combines the drug-solubilising capacity of an emulsion with the favourable application and controlled-release properties of a gel, is well supported by analogous formulation and characterization work on griseofulvin microemulsions, nanostructured lipid carrier gels and nanohybrid emulsions, as well as by extensively validated antifungal emulgels of terbinafine, luliconazole and clotrimazole. A systematic characterization workflow spanning physicochemical, rheological, release/permeation, microbiological and stability domains, ideally guided by design-of-experiments optimisation, provides the evidence base needed for a scientifically rigorous and publication-ready griseofulvin emulgel. Continued research addressing scale-up, standardisation of

characterization methodology, and, ultimately, clinical evaluation will be essential to realise the full translational potential of this delivery system.

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