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A Comprehensive Review on Nanoemulgel-Based Topical Delivery of Fluconazole and *Sphaeranthus indicus* for *Tinea manuum*

Karthick M*, Manivannan R, Gnanambigai P, Mubeena S, Mukesh M, Santhosh S, Ramesh L

Excel college of pharmacy, India

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ABSTRACT

Fungal infections, particularly dermatophytosis such as Tinea manuum, represent a significant global public health concern, especially in tropical and subtropical regions. Conventional topical antifungal therapies often exhibit limitations including poor skin penetration, local irritation, recurrence, and patient non-compliance. Nanoemulgel-based drug delivery systems have emerged as promising alternatives by enhancing drug solubility, stability, penetration, and sustained release at the site of infection. This review focuses on the development of a nanoemulgel formulation incorporating Fluconazole and the herbal extract *Sphaeranthus indicus* for the effective management of tinea manuum. Fluconazole, a triazole antifungal agent, inhibits ergosterol synthesis and disrupts fungal cell membrane integrity, while *Sphaeranthus indicus* possesses documented antifungal, anti-inflammatory, and wound-healing properties. The synergistic combination within a nanoemulgel platform aims to improve therapeutic efficacy, reduce adverse effects, and enhance patient compliance. Thus, nanoemulgel systems represent a novel and effective strategy for topical management of recurrent and persistent fungal infections.

Keywords: Nanoemulgel, Tinea manuum, Fluconazole, *Sphaeranthus indicus*, Topical drug delivery, Dermatophytosis, Antifungal therapy.

INTRODUCTION

1. FUNGAL

Among the most prevalent infectious diseases that affect people are fungal infections globally. They are mostly caused by the skin, hair, nails, and mucous membranes. by numerous harmful fungi. The prevalence of superficial fungal infections in recent years, Infections have dramatically increased because of things like poor hygiene, a humid climate, immunosuppression, diabetes, overcrowding, and heavy use of broad-spectrum antibiotics. Fungal infections are regarded as a serious public health concern in tropical and subtropical nations like India Health issue.

The largest organ in the human body, the skin, serves as a barrier of defence against pathogens in the environment. But a variety of microbes, particularly fungi, can infiltrate the cutaneous mycoses, which are infections of the skin's outermost layers.

Dermatophytes are the most prevalent fungi that cause these infections, and they can infiltrate keratinized tissues, including hair, nails, and the stratum corneum. These illnesses are frequently known as tinea infections or dermatophytosis.

Tinea manuum is a relatively rare fungal infection that affects the palms, interdigital spaces, and dorsal surfaces of the hands among the different types of dermatophytosis. It is often associated with chronicity and recurrence, especially in those who engage in manual labor, work in agriculture, or are exposed to prolonged moisture.

The symptoms of the infection, which include scaling, erythema, hyperkeratosis, itching, and skin fissuring, can significantly affect a person's quality of life.

2. FUNGUS

Fungi are a type of eukaryotic organism that comprises yeasts, moulds (British English), and mushrooms. Fungi are a distinct kingdom of life from plants, mammals, protists, and bacteria. Fungal cells have chitin cell walls, while plants and some protists have cellulose

cell walls, and bacteria have bacterial cell walls. Fungi are in the Kingdom Fungi [2].

MYCOLOGY is the study of fungi

Myco- = fungi

logy = to study

Mycology is the study of fungi, including their genetic and biochemical properties, taxonomy, and use in medicine, food, and religious practices. It also examines potential risks such as poisoning and infection [3].

2.2 FUNGI:The Pathogen

Fungi are eukaryotic, widespread organisms in our environment that are generally harmless. Yeasts, filamentous fungi (moulds), dermatophytes, and dimorphic fungi are arbitrarily classified based on their cellular and structural characteristics. This section will focus on pathogenic strains, which have piqued the curiosity of medical scientists in developing novel medications. Infectious fungus primarily consists of Candida spp., Aspergillus spp., and Mucor spp. Dimorphic fungus include infectious fungus such as Blastomyces, Histoplasma, Fusarium, and Coccidioides. Respectively [4].

2.1 Cellular Structure of Fungi

Fungi are eukaryotic creatures composed of unicellular or multicellular structures.

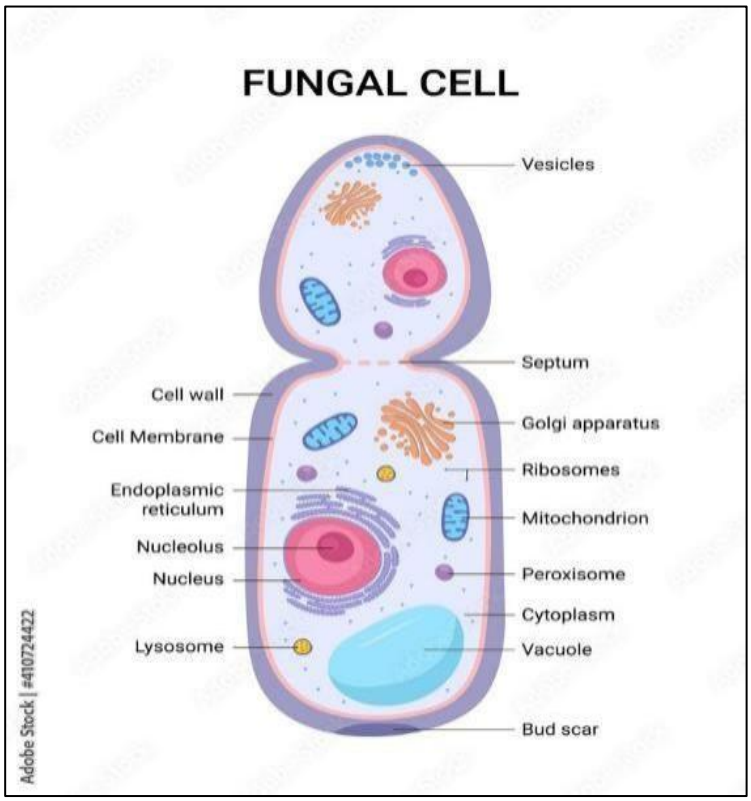

Figure 1: Cellular Structure of Fungi

3.FUNGAL INFECTION

Mycosis, also known as fungal infections, are skin conditions caused by a fungus and a kind of microbe. Millions of different species of fungi can be found in the air, soil, water, and plants and live in the human body. Additionally, they may result in skin issues like bumps or rashes [6].

Fungi normally originate from the environment that surrounds us and appears to be harmless until spores are swallowed or inhaled. Additionally, fungal infection is more likely when the immune system of the body is compromised. An infection could result from a pathogenic fungus. There are millions of different types of fungi, but only a small number appear to be dangerous to humans; those primarily found on the skin and mucous membranes have been shown to cause deadly infections [7].

3.1 Fungal Infection Epidermiology

People can suffer from a variety of diseases known as mycoses, or fungal infections worldwide. While many are harmless or self-limiting, some pose a risk of death, particularly to people whose immune systems are weakened. Over the past three decades, fungal infections have become more apparent as the number of individuals with cancer, HIV/AIDS, diabetes, as well as those undergoing organ transplants or immunosuppressive therapies. The real worldwide burden of fungal infections is still poorly understood, largely because of diagnostic difficulties.

limitations and insufficient monitoring systems. Nevertheless, current modelling initiatives and according to systematic reviews, billions of people are impacted by invasive and superficial fungal diseases each year with over 1.5 million deaths globally (Bengamin et al.,2017). This paper summarizes the available data regarding the epidemiology of fungal infections, arranged in three dimensions:

(i) incidence and prevalence

(ii) risk elements, and

(iii) The burden of global health.

4.ANTI FUNFAL AGENTS

A medication that specifically removes fungal pathogens from a host is known as an antifungal agent minimal harm to the host.

- **Antifungal polyene medications**

Amphotericin, nystatin, and pimaricin interact with cell membrane sterols (ergosterol in fungi, human cholesterol) to create passageways that allow tiny molecules to escape from the from the fungal cell's interior to its exterior.

- **Azole antifungal medication**

ketoconazole and fluconazole all inhibit cytochrome P450-dependent enzymes. (especially C14-demethylase) involved in ergosterol biosynthesis, which is necessary for the composition and operation of fungal cell membranes.

- **Morpholine and allylamine antifungal medications**

At the squalene level, allylamines (naftifine, terbinafine) prevent the synthesis of ergosterol epoxidase. The same pathway is later inhibited by the morpholine medication amorolfine.

- **Antifungal antimetabolite medicines**

Through the intracytoplasmic pathway, fluor cytosine inhibits the synthesis of both DNA and RNA transformation of 5-fluorocytosine into 5-fluorouracil. Antifungal agents have not developed as quickly as antibacterial agents. This is a predictable result of the organisms' cellular makeup. Bacteria are prokaryotic, providing a variety of structural and metabolic targets that are distinct from those of the host, a human. Since fungi are eukaryotes, most substances that are harmful to them are poisonous to the host as well. Additionally, because fungi typically grow slowly and frequently in, they are more challenging to measure than bacteria because they are multicellular forms. This challenge complicates tests intended to assess the in vitro or in vivo characteristics of a possible antifungal substance.

Despite these drawbacks, a lot of progress has been made in creating novel antifungal agents as well as in comprehending the ones that already exist. This chapter provides an overview of the more typical antifungal substances. Three drug classes are highlighted: the azoles, the polyenes, and one antimetabolite. outlines the most significant antifungal medications and their typical applications.

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Drug	Systemic Mycoses				Opportunistic Mycoses				
	Coccidioidomycosis	Histoplasmosis	Blastomycosis	Paracoccidioidomycosis	Aspergillosis	Candidiasis	Cryptococcosis	Other	Other
Polyenes									
Amphotericin B	+	+	+	+	+	+	+	+	
Nystatin	–	–	–	–	–	mct	–	–	
Pimarcin	–	–	–	–	–	–	–	–	
Imidazoles									
Clotrimazole	–	–	+	+	–	mc	+	+	
Miconazole	–	+	+	+	+	+	+	+	
Ketoconazole	+	+	+	+	+	mct	+	+	
Triazoles									
Itraconazole	+	+	+	+	+	mc	+	+	
Itraconazole	+	+	+	+	+	+	+	+	
Antimetabolite									
5-Fluorocytosine	–	–	+	+	+	+	+	+	Sporothichosis
Drug									
Itraconazole	–	+	+	+	–	mct	+	+	
Fluconazole	+	+	+	+	mct	+†	+	+	Phaeohypho-mycosis

* Inc: Mucocutaneous but not systemic candidiasis.
† Insufficient data.
‡ Used only in combination with amphotericin B.

Figure : Antifungal antimetabolite medicines

- **Antifungal polyene medications**

The alternating conjugated double bonds that give the polyene compounds their name make up a portion of their macrolide ring structure. All the polyene antibiotics are made from species of Streptomyces. These medications interact with cell membrane sterols (ergosterol in fungal cells; cholesterol in human cells) to create passageways across the membrane, resulting in the cells' turn leaky. Amphotericin B, pimaricin, and nystatin are examples of polyene antifungal agents.

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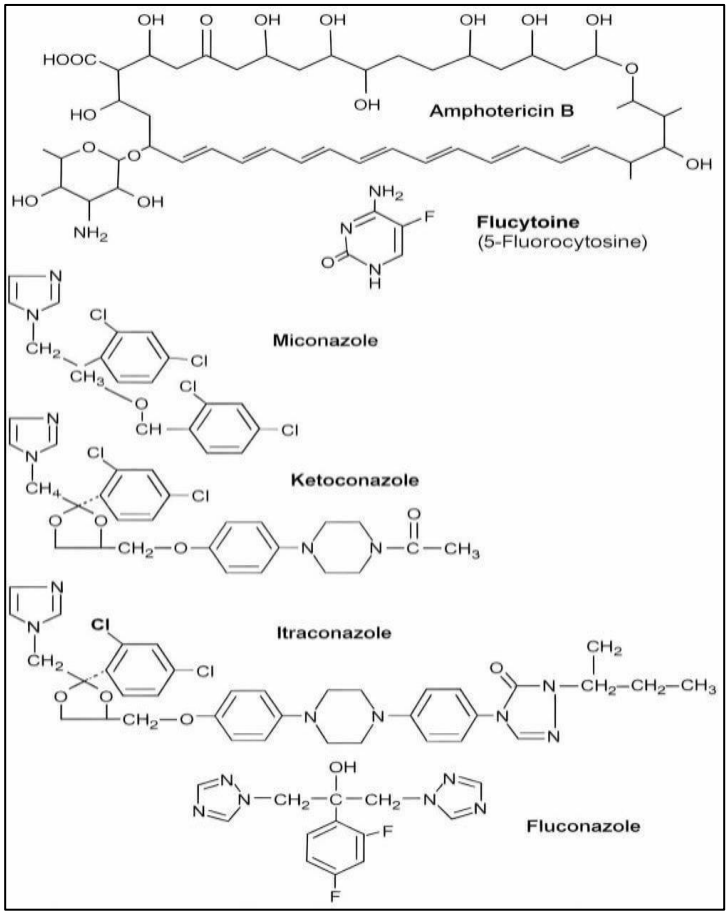

Figure 2: antifungal polyene medicines Some common antifungal agents' structures. Some common antifungal agents' structures

4.2 Classification of antifungal drugs

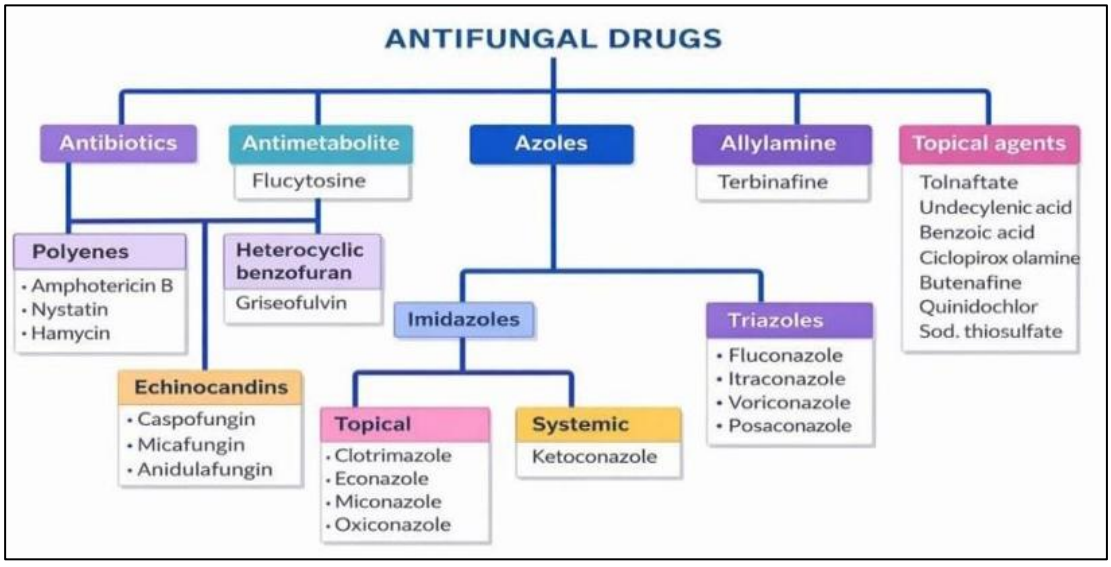

Figure 3: Classification of antifungal

5.INFECTING AGENTS

Primary pathogens and opportunistic pathogens are the two broad categories into which fungal pathogens fall. Pathogens are the former class of fungi typically has an environmental reservoir and can infect People who are immunologically naive or who have been exposed to high doses of the moulds. Opportunistic pathogens prey on immunocompromised or disabled people hosts to spread illness. They may have an environmental reservoir (e.g., Cryptococcus neoformans, Aspergillus fumigatus) or coexist with healthy organisms (like Candida species) [16].

- ***Primary pathogen***

Fungus that uses growth in vertebrate tissue to increase its dispersal or survival at any stage in its life cycle, employing a specific tissue phase if it is subcutaneous or systemic, and the ability to escape from the host.

Examples include Trichophyton concentrical with tissue phase and Histoplasma capsulatum with transmission through the skin [17].

- ***Secondary pathogen (opportunistic pathogen)***

Coincidentally, a fungus can live in vertebrate tissue because of that are used in their natural environment and can only proliferate vertebrate tissue after damage to the host's capabilities because of such as wounds, medication, or immune or metabolic disorders. For instance, Rhizopus arrhizus [18].

2.2 Pathophysiology of fungal infection

A healthy host can only be infected by a small number of human-pathogenic fungi. Most of them is relatively harmless unless they meet an immuno-compromised patient. A weakened defence system allows them to enter the body. The intact epithelial surfaces of the gastrointestinal tract will normally keep microbes out and the mucociliary barrier of the respiratory tract prevents fungal cells from aspirating and spores, while dead or damaged tissue may act as a breeding ground for an infection [19].

3. TINEA MANUUM

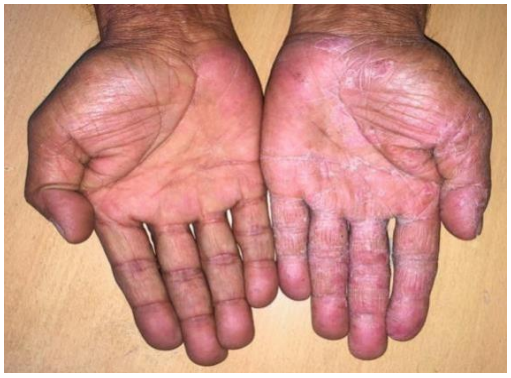

Figure 4: Tinea manuum

Tinea manuum is a superficial mycosis affecting the palms, dorsum, or interdigital folds of one or both hands. Dermatophytes are typically the culprits, however Hendersonula toruloidea and Scytalidium hyalinum have also been described as uncommon occurrences. Tinea manuum usually coexists with tinea pedis, but some cases may only affect the hands. Contact with infected people, animals, or soil is the most prevalent source of global dermatophytosis.

3.1 Etiology

Tinea manuum is typically caused by dermatophytes with Trichophyton rubrum being the most frequent worldwide. Different etiologic organisms have been described in diverse geographical regions, including

- Trichophyton mentagrophytes

- Epidermophyton floccosum
- Trichophyton verrucosum
- Trichophyton interdigitale
- Microsporum canis

Tinea manuum has been identified in patients with Trichophyton erinacei together with Microsporum gypseum, Trichophyton eriotrephon, and Arhroderma benhamiae (rarely documented). Tinea manuum infections and onychomycosis have the following risk factors and predispositions: Male, diabetes, hypertension, atherosclerosis, and immunosuppression. Risk factors include a humid atmosphere, excessive sweating and maceration, continuous use of occlusive footwear, and public swimming or sports facilities. Excoriation of the soles of the feet or picking tinea-infected toenails. Farmers and pet owners (for example, unusual pets such as guinea pigs and hedgehogs). Recurrent hand trauma, usually work-related (e.g. car mechanics, machine operators, individuals who work with chemicals).

4. SPHAERANTHUS INDICUS

Figure 5: *Sphaeranthus indicus*

Herbal medicines have been used by humans from time immemorial. Ayurveda, India's oldest traditional system, demonstrates that ancient Indians had extensive understanding of the medicinal properties of various plants. India's varied temperature and geography have resulted in a diverse flora. Science has allowed scientific research into many traditional medications. Sphaeranthus indicus Linn... is a medicinal plant commonly used in Indian traditional medicine to treat various diseases. It thrives in rice fields, dry waste areas, and cultivated regions in tropical India. It is distributed throughout from sea level to 1200 meters, India, Sri Lanka, Africa, and Australia height. Sphaeranthus hirtus Willd. is a synonym for S. indicus Linn. And Roxb. Sphaeranthus mollis [25].

Koṭṭaikkarantai is the Tamil name for Sphaeranthus indicus Linn... It is a multi- branched, fragrant herb that grows to a height of one to two feet and is found throughout the plains. India and as high as fifty feet in the hills. It is a significant medicinal plant utilized to treat anthelmintic, skin conditions, and styptic gastric disorders, glandular swelling, analgesics, antibiotics, antifungals, nerve depression, laxative and diuretic properties. It is claimed that the plant's decoction is active against scabies, bronchitis, asthma, leukoderma, and jaundice *SPHAERANTHUS INDICUS [26].*

4.1 Geographical

This species is in Africa and is commonly used in traditional medicine to treat fever and skin disorders. S. indicus is found mostly in tropical and subtropical climates, including India, Sri Lanka, Bangladesh, Bhutan, and Southeast Asia. It is also present in various parts of Africa and Australia.

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Taxonomic classification

Table 3:

Kingdom	plantae
subkingdom	viridaeplantae
phyllum	tracheophyta
subphyllum	euphyllophytina
infraphyllum	radiatopses
class	magnoliopsida
subclass	asteridae
superorder	asteranae
order	asterales
family	asteraceae
genus	sphaeranthus
species	indicus

4.2 Phytochemistry

The acetone extract of S. indicus contains 7-hydroxyeudesm-4-en-6,12-olide, 2- hydroxycostic acid, β-eudesmol, and ilicic acid, all of which are sesquiterpene lactones and acids, respectively. This plant yields three 7-hydroxyeudesmanolides and two sesquiterpenoids: cryptomeridiol and 4-epicryptomeridiol. S. indicus contains eudesmanoids, including 11α,13- dihydro3α,7α-dihydroxy-4,5-epoxy-6β,7-eudesmanolide, 11α,13-dihydro-7α-acetoxy-3β- hydroxy-6β,7-eudesm-4-enolide, and 3-keto-β-eudesmol, among others. A bicyclic sesquiterpene lactone was isolated from S. indicus aerial parts extracted with petroleum ether. This plant has also produced additional sesquiterpene lactones, according to reports. The sterol glycoside (β-d-glucoside of (24S)-24-ethylcholesta-4,22-dien-3-β-ol) was isolated and characterized. S. indicus aerial parts contain 5-hydroxy7-methoxy-6-C-glycosylflavone, a flavonoid C-glycoside. The plant produces a deep cherry-colored essential oil containing methyl chavicol, d-cadinene, α-ionone, p-methoxycinnamaldehyde, α-terpinene, citral, geraniol, geranyl acetate, β-ionone, oscimene, eugenol, sphaeranthene, sphaeranthol, estragole, Indicusene, and the alkaloid sphaeranthine.S. indicus leaves contain several carbohydrates, including arabinose, galactose, glucose, fructose, lactose, maltose, raffinose, and rhamnose. A new isoflavone glycoside, 5,4′-dimethoxy-3′-prenylbiochanin 7-O-β-dgalactoside, has been isolated from the leaves. Additionally, sphaeranthanolide, a sesquiterpene glycoside having immunostimulant properties, has been isolated from the flowers of S. Eudesmenolides, including frullanolide, 11-alpha-13-dihydro: 3, alpha-7-alpha-dihydroxy frullanolide, and two sphaeranthus peptide alkaloids, have been identified from flower extracts. The alcoholic extract of powdered capitula includes stigmasterol and β-sitosterol. A flavone glycoside, 7-hydroxy- 3',4',5,6-tetramethoxy-flavone 7-O-β-d-(1-4)-diglycosidic, was isolated from the stem of S. indicus.

10.4 Nano-emulsion

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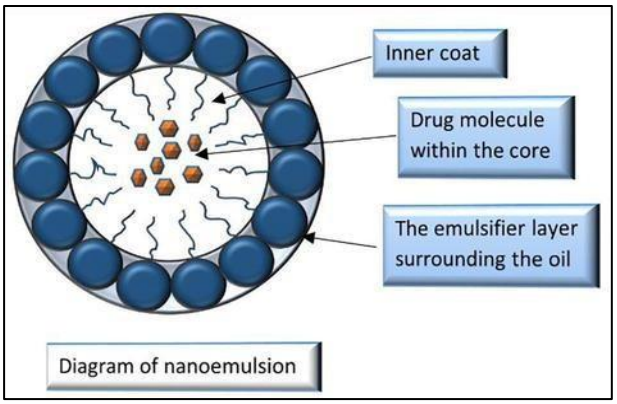

Figure 6: Nano-emulsion

Nano-emulsions are made up of nano-sized droplets of one liquid dispersed in another, creating heterogeneous isotropic systems. The droplet diameters typically range from 20 to 500 nm. These complexes are thermodynamically unstable but kinetically stable, requiring energy for formation and surfactants/cosurfactants for colloidal stability. Nano-emulsions have a higher surface area-to-

volume ratio than regular emulsions, which improves medication bioavailability. These benefits include enhanced medication release, longer effectiveness, fewer adverse effects, and protection against enzymatic or oxidative degradation. Nano-emulsions can be turned into several dosage forms, including liquids, creams, sprays, gels, aerosols, and foams. These adaptable formulations can be delivered through numerous channels such as oral, intravenous, intranasal, pulmonary, ophthalmic, and topical administration, catering to different application locations. Nano emulsion displays none of the negative effects such as creaming, sedimentation, flocculation, or coalescence that are typically observed in macroemulsions. Additionally, because nano emulsion can improve the dispersion of active substances beneath the skin layer, it shows potential as an effective carrier in topical treatments [41].

10.4 Nano-emulgel

Nano-emulgel is an effective medication delivery method for lipophilic compounds. It improves the therapeutic value of lipophilic medicines. Lipophilic medicines have poor solubility and irregular absorption, which affects medication of pharmacokinetics. Physical and chemical alterations of API, as well as formulation requirements such as particle size reduction, are utilised to increase the solubility of active moieties. To improve the utility and efficacy of topical therapy, new approaches are required. Drug delivery strategies using optically transparent Nano-emulsions with globule dimensions of 100 nm and 500 nm have piqued researchers' interest since they allow for greater skin penetration. To improve the viscosity of the nano emulsion and create a nano-emulgel, a gelling agent is added that promotes transcutaneous administration. The nanoscale's moisturising and occlusive characteristics promote medication penetration through adhesion and film formation [42].

10.4.1 Formulative components of nanoemulgel

❖ **Oil phase**

When selecting oil or other lipid components, it is critical to ensure that the oily phase is pure and free of contaminants such as peroxides, free radicals, and other fatty acids such as sterols and polymers. The bulk of hydrocarbon chains is a key consideration in selecting lipids to produce nano-emulsions; the explanation for this is the uniformity and essence of emulsification. Common oils used in nano-emulsions include mineral oil, cottonseed oil, maize oil, Arachis oil, olive oil, coconut oil, eucalyptus oil, rose oil, clove oil, and more.

❖ **Aqueous phase**

[16] This component converts the emulsion into an emulgel, which is the gelling agent. Nanoemulgels are often formulated using distilled or ultra-purified water.

❖ **Surfactant**

Nanoemulgel manufacturing uses surfactants for stability and emulsification. Nanoemulgels are made with non-ionic surfactants, which have low toxicity. Sorbitan and polyoxyethylene fatty acid esters are commonly used nonionic surfactants.

❖ **Co-surfactant**

Co-surfactants enhance product stability by decreasing surfactant concentration. Co-surfactants include ethyl alcohol, PG, Transcutol HP, and PEGs.

❖ **Penetration enhancers**

Penetration enhancers are a highly effective way to improve transportation efficiency through the skin and related tissues. Topical nanoemulgels often include a penetration enhancer, a key component of classic drug delivery systems. Penetration enhancers interact with skin constituents, increasing skin permeability temporarily and cumulatively.

❖ **Gelling agent**

The gelling agent, a fundamental component of nanoemugel, contributes to its perfect structure. These make sense for cross-linking agents. Gelling agents commonly used include Tragacanth, HPMC, and Carbopol.

❖ **Preservatives**

Preservatives are chemical chemicals used to prevent microbial decomposition and increase product shelf life. Preservatives including methylparaben, propyl paraben, benzoyl chloride, and phenoxyethanol are commonly used.

❖ **Antioxidant**

Antioxidants are chemical substances used in compositions to prevent oxidation. Examples of such compounds are ascorbyl palmitate and butylated hydroxytoluene.

❖ **pH modifiers**

Additionally, the stability of nano-emulsion was revealed by the pH value. The average pH value should fall between 5.4 and 5.9 (the pH of skin). Triethanolamine is most frequently used as a pH modifier.

10.4.5 Methods of preparation of nano-emulgel

I. Screening of components

The final composition of the formulation should be carefully selected based on the results of the preformulation tests. In this step, the oily phase is selected based on how well it dissolves the medicinal component. The ratios for the surfactant and cosurfactant are selected based on the characteristic parameters used to form the nano-sized emulsion, their compatibility with the oil, and the kind of emulsion (o/w or w/o). One technique for critically analyzing whether the concentration of these components can result in a nano-emulsion is to plot a pseudoternary phase diagram. This phase diagram illustrates the ratio of these three components, which acts as the stable nano-emulsion development point in the nano emulsification zone.

II. Preparation of nano-emulsion

The medication, cosurfactant, and surfactant are dissolved according to their solubility in the selected oil or aqueous phase. The oil and water phases are heated separately, and once at room temperature, they are mixed by gradually adding one to the other while spinning continuously.

The nano-emulsion can be made with both low- and high-energy approaches. Low-energy approaches include self-nano emulsification, phase inversion (phase inversion temperature, or PIT), phase inversion composition, or PIC), emulsification, and solvent diffusion; high-energy techniques include high-pressure homogenization, microfluidization, and ultrasonication. Low- energy techniques are preferred over high-energy ones due to their greater efficacy and lack of the need for specific equipment.

High-energy techniques allow for precise control of particle size through formulation composition. High-energy approaches improve emulsion stability, rheology, and colour.

The high-energy approach uses mechanical devices to create a disruptive force, reducing the size of both phases significantly. This approach may overheat the formulation's constituent ingredients, making the emulsion thermodynamically unstable and unsuitable for thermolabeling pharmaceuticals.

One hallmark of low-energy emulsification methods is that they use the system's intrinsic chemical energy to increase energy efficiency. Because this technique requires less energy, heat-labile components do not degrade. The low-energy or spontaneous technique is widely used to create essential oil-based nano-emulsions that prevent volatile compounds in essential oils from evaporating.

I.PREPARATION OF NANOEMULGEL

To make gelling media, gelling chemicals must be dissolved in an aqueous medium until full swelling is achieved. To accomplish full swelling, the chosen polymer is dissolved in pure water and mechanically agitated continuously for a predetermined period at a constant velocity. Finally, the pH of the gel base is adjusted to allow for effective application to the topical system.

When a gelling agent is introduced, an o/w nano-emulsion solution thickens and forms gel. This is because, when shear force is applied, the formulation converts from a gel to a solution due to the agent's thixotropic properties, which retain the formulation's volume. Any

of the procedures mentioned above can be used to create the nano-emulsion, which can then be transformed into a NEG using a gel foundation. To incorporate a nano-emulsion into a gel matrix, mix the gel and nano-emulsion in a certain ratio and stir often to guarantee homogeneity.

The process of creating nanoemulgel is shown schematically in (A) adding the oil (oil + drug) phase to the aqueous (water + gelling agent) phase and (B) adding the nano-emulsion to the aqueous (water + gelling agent) phase.

- **High-pressure homogenization method**

This method employs a high-pressure homogenizer to convert the oil phase into nanosized droplets that can be easily dispersed in a hydrophilic gel matrix. The homogenization process generates significant shear forces, which aid in droplet size reduction and the formation of a stable nanoemulgel.

- **Ultrasonication method**

This method uses ultrasonic vibrations to create Nanoemul gel. After combining the hydrophilic matrix and oil phase, high-frequency ultrasonic waves are used. Ultrasound energy breaks down the oil phase into nanosized droplets that are equally dispersed throughout the gel matrix.

- **Solvent evaporation method**

To dissolve the oil phase and hydrophilic matrix using this method, a water-miscible solvent is needed. The solvent is evaporated under low pressure, resulting in a Nanoemulgel containing oil droplets distributed throughout the matrix.

- **Microfludization method**

The oil phase and hydrophilic matrix are put through a microfluidizer to produce nanoemulgel. High shear pressures degrade the oil phase, resulting in nanoscale droplets scattered throughout the gel matrix.

- **Self-emulsifying method**

This approach uses a self-emulsifying drug delivery system (SEDDS) to generate Nanoemulgel in situ. SEDDS is a mixture of oil, surfactants, and co-solvents that emulsify when in contact with water. When SEDDS is combined with a hydrophilic gel matrix, a Nanoemulgel is produced.

- **High-energy emulsification method**

This approach employs a high-energy input to create tiny droplets of scattered oil in continuous water. This can be accomplished using several procedures such as sonication, high-pressure homogenization, and microfluidization. To create a gel, add a gelling ingredient, like a polymer or surfactant, to the emulsion.

- **Phase inversion temperature (PIT) method**

This technique utilizes a thermosensitive surfactant that transitions from water-soluble to insoluble at specific temperatures. Surfactants can trap the dispersed phase by forming a gel-like structure when heated.

- **Sol-gel transition method**

This procedure uses a soul-gel transition system, where a network of particles or polymers collect in a solvent to form a gel. To create a gel-like structure, add a thermosensitive polymer or crosslinking agent to the emulsion at certain temperatures or conditions.

- **Electrostatic complexation method**

When oppositely charged polymers or surfactants are applied, a stable emulsion is created that can be gelled or crosslinked later.

➢ **Coacervation method**

In this process, two or more polymers phase independently when an electrolyte is present or when the pH changes, creating a gel-like structure. The gel and the dispersed phase can then be combined using methods such as high-energy emulsification.

10.4.2 Characterization of nano-emulgel

➢ **Drug content determination**

To determine the amount of medication in the nanoemulgel, dilute the formulation with PBS

7.4. A UV spectrophotometer at 240 nm was used to evaluate this mixture, with PBS 7.4 serving as a blank.

➢ **pH determination**

To ensure the formulation will not irritate the skin when applied topically, a pH value was taken. A digital pH meter was used to measure the pH of the formulation at room temperature.

➢ **Spreadability**

As Multimer recommends, it can be quantified using the Slip and Drag method. To conduct the experiment, two grams of Nano-emulgel are placed on a lower ground slide secured with a wooden block. A 500 mg weight is then attached to another glass slide using a hook of similar size. After five minutes, the pan connecting to the second slide received more weight. The time required to cross a 5 cm distance on the upper slide was recorded, and spreadability was computed using the equation that follows:

$$\text{Spreadability (S)} = M*L / T$$

where L = Glass slide length and M = weight attached to top slide T = Distance traveled in a single slide by upper slide

➢ **Droplet size, polydispersity, and zeta potential of nano-emulsions**

Dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), analyses fluctuations in scattering intensity caused by Brownian motion in droplets and particles. PCS can examine nano-emulsion droplet size, zeta potential, and polydispersity with a particle size analyzer.

➢ **Swelling index**

Place gram of produced topical nanoemulgel on porous aluminum foil and cover with 10 ml of 0.1 N NaOH solution. Weigh the sample periodically until there is no further weight change. till no further change in weight:

$$\text{Swelling Index (SW)} \% = [[Wt-Wo] / Wo]*100$$ Where, (SW) % = Percentage swelling,

Wo = Original weight of nanoemulgel

Wt = Weight of swollen nanoemulgel at time t.

➢ **Viscosity measurements and rheological behavior**

A Brookfield L was linked to a thermostatic water bath set to 25 degrees Celsius. Viscosity was measured on each base with 40 spindles. A specific amount (1 g) of each gel base was added to the plate and securely closed. The viscometer started at 0.6 rpm, steadily increased, and measured until the torque reached 10%. The shear rate was plotted against the shear stress.

➢ **Skin irritation test**

0.25 gm Nanoemulgel is applied to each location (two sites per rabbit). After 24 hours of treatment, rabbit skin locations are cleansed and sanitized. Any changes in color or shape are observed and evaluated.

➢ **Invitro diffusion studies**

The Franz diffusion cell is used to conduct diffusion studies on prepared nanoemulgel. The study involves applying 0.5g of sample to a cellophane membrane and allowing it to diffuse for 8 hours at 371C in phosphate buffer (pH 7.4). Every 1 hour, a 1 ml pg sample is collected and replaced with a new buffer solution. Samples are analyzed using an appropriate analytical method.

➢ **Ex vivo drug permeation**

Franz diffusion cells were employed in ex vivo permeation studies because they are a reliable method for assessing drug transport through the skin. These studies were conducted with skin taken from Wistar rats. Using surgical blade No. 24, the hair on the dorsal side of the sacrificed animal was cut from the head to the tail. The shaved area of the animal's skin was divided with a knife to remove excess fat and connective tissue. After removal, the skin was cleansed with normal saline, examined for integrity, and then reused. The diffusion cell's receptor compartment was filled with 20 milliliters of pH 7.4 phosphate buffer. The experiment was conducted at 37 ± 0.50°C, with the assembly put on a magnetic stirrer. Magnetic beads were employed to constantly mix the solution in the receptor compartment at 100 rpm. The skin was placed on a diffusion cell assembly with an effective diffusion area of 4.91 cm2 (orifice area). One gram of the prepared formulation was applied to the donor compartment membrane. At regular intervals, a 2 mL sample aliquot was removed and replaced with an equal volume of fresh diffusion medium. The samples underwent spectrophotometric analysis. Plotting drug penetration per cm2 of membrane versus time resulted in the estimate of flux (drug permeation per cm2/h).

➢ **Comparison of permeation studies with marketed formulation**

Formulation, enhanced nanoemulgel, nano-emulsion, plain drug gel, and drug solution. The optimized nanoemulgel formulation was compared to the marketed formulation in terms of penetration and retention. The amount of medication permeated through the skin per unit area was plotted over time. The drug's steady-state penetration rate (Jss mg/cm/h) into the skin was estimated using the slope of the depicted curve. The lag time (T lag) was calculated by projecting the linear portion of the cumulative amount penetrated over time to the abscissa. The enhancement ratio (Epen) was computed by dividing the Jss of the respective formulation by that of the control formulation.

CONCLUSION

In conclusion, the developed nanoemulgel containing Fluconazole and Sphaeranthus indicus offers a promising approach for the effective management of tinea manuum. By enhancing drug solubility, skin penetration, and sustained release, the formulation overcomes limitations of conventional topical therapies. The synergistic antifungal and anti-inflammatory properties improve therapeutic efficacy, reduce recurrence, and enhance patient compliance, making nanoemulgel a novel and efficient topical drug delivery system.

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