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Harnessing Oleogels For Enhanced Topical Drug Delivery: Insights And Innovations

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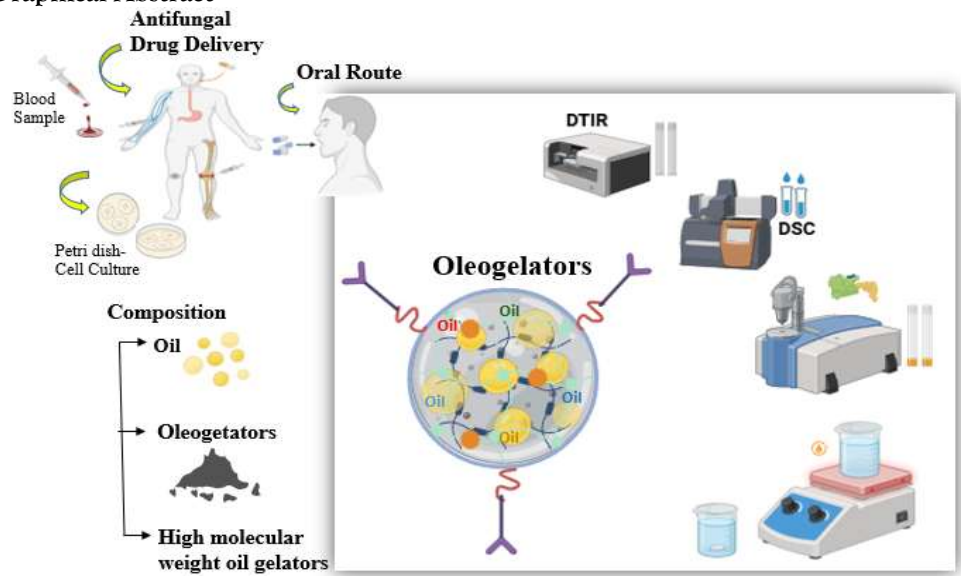
Abstract
Oleogels have garnered a lot of attention in pharmaceutical research as innovative topical carriers for antifungal medications due to their unique physicochemical properties and therapeutic potential. Oleogels, semi-solid systems designed by structuring oil with a gelling agent, offer a non-aqueous, biocompatible medium that enhances the solubility, stability, and bioavailability of lipophilic drugs. This study looks at the composition, characteristics, and applications of oleogels in the topical delivery of antifungal medications. The study highlights the significance of selecting the appropriate oils and gelling agents and how they impact the characteristics of medication release, skin penetration, and spreadability. Important formulation parameters like stability, rheological behavior, and drug-loading efficiency are investigated to optimize the efficacy of antifungal treatment.To evaluate the structural integrity and interaction between the drug and oleogel matrix, advanced characterisation methods such as scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR) are used. Because they offer prolonged drug release, improved patient compliance, and less systemic adverse effects, oleogels offer a compelling substitute for traditional formulations. Additionally, their hydrophobic nature enhances shelf-life stability by guarding against microbial contamination. Recent developments are also included in the study, such as the use of natural oils and innovative gelling agents to produce formulations that are both economical and environmentally beneficial. The results open the door for further study into the therapeutic uses and commercialization of oleogels by highlighting their adaptability as a viable platform for the topical administration of antifungal drugs. To prove their effectiveness, more clinical research is required.

Keywords: *Oleogels, semi-solid delivery system, Antifungal Agent, Topical Carrier*

Graphical Abstract-



1. INTRODUCTION

In order to treat localized illnesses or provide medications systemically, topical drug delivery devices apply pharmacological formulations directly to the skin or mucous membranes. Numerous benefits are provided by these systems, including localized treatment, less systemic adverse effects, and patient compliance because of their simplicity of use. Creams, ointments, gels, and patches are common types. Topical formulations use the surface of the skin as a delivery system, taking use of its vast surface area and circulatory system to facilitate absorption. They are frequently used to treat localized infections, discomfort, and dermatitis. Drug solubility, stability, and the vehicle's capacity to cross the epidermal barrier are all critical to the effectiveness of these systems [1].

1.1. Limitations of Conventional Topical Formulations

Conventional topical formulations are widely used, but they frequently have a number of drawbacks that compromise both their therapeutic effectiveness and user appeal. Poor drug penetration through the stratum corneum, the skin's outermost layer, is a significant problem since it acts as a strong barrier to the majority of medications, especially those with hydrophilic or high molecular weight properties. This restriction lowers the active ingredient's bioavailability, frequently requiring larger dosages that raise the possibility of adverse consequences [2].

Another major disadvantage of traditional formulations is their instability. These systems' active components have a shorter shelf life and less efficacy since they are more likely to degrade when exposed to environmental elements like heat, light, or oxygen. Furthermore, the oily or sticky nature of many conventional vehicles, including lotions and ointments, can be uncomfortable, discolor clothes, or deter patient compliance [3].

Furthermore, standard formulations frequently show unequal drug release, resulting in uneven therapeutic effects as certain regions of application get larger dosages than others. In situations when accurate, localized medication administration is necessary, this is especially challenging. These formulations' acceptability among patients with sensitive skin or pre-existing dermatological disorders is further limited by the inclusion of certain excipients that may cause local irritation or allergic responses. These difficulties highlight the need for more sophisticated delivery methods that improve medication penetration, stability, and user happiness [4].

1.2. Antifungal Topical Therapies

For the treatment of superficial fungal infections affecting the skin, nails, and mucosal surfaces, topical antifungal medications are crucial. By delivering antifungal medications straight to the infection site, these therapies minimize systemic exposure and adverse effects while providing localized relief. Topical treatments work especially well for diseases like jock itch, ringworm, athlete's foot, and candidiasis because they target the afflicted regions directly and lessen the intensity and spread of infection [5].

In topical treatments, azoles are among the most commonly utilized types of antifungal drugs. Azoles function by preventing the production of ergosterol, an essential part of the fungal cell membrane, by the enzyme lanosterol 14-α-demethylase. The fungal cells become unstable and eventually perish as a result of this disturbance. Topical azoles that are particularly effective against a variety of fungal infections, including yeasts and dermatophytes, include miconazole, clotrimazole, and ketoconazole. They can be used to treat common diseases, including ringworm, athlete's foot, and candidiasis, since they come in a variety of forms, including creams, lotions, and powders. Because of their efficacy and nonprescription availability, they are a common option for treating superficial fungal infections [6].

For the treatment of dermatophyte infections, allylamines, another family of topical antifungals, provide a powerful substitute. These substances, which include butenafine, naftifine, and terbinafine, function by blocking the enzyme squalene epoxidase, which is necessary for the formation of ergosterol. The fungal cell membrane is weakened in the absence of ergosterol, which results in cell death. Allylamines work very well to treat dermatophyte infections like ringworm and athlete's foot. They frequently provide relief more quickly than azoles and call for shorter treatment durations. Allylamines, which come in cream, gel, and spray form, are well tolerated and have a low risk of adverse effects when used to treat localized fungal infections [7].

Another choice for topical antifungal treatment, particularly for Candida infections, is polyenes, such as nystatin. The fungus is killed when polyenes attach to ergosterol in the fungal cell membrane and create holes that allow essential cellular components to escape. Nystatin is frequently included in topical treatments for Candida species infections, including cutaneous candidiasis and oral thrush. Topical versions of nystatin are useful for treating localized Candida infections, even though polyenes are usually used in systemic therapy. They come in cream, ointment, and powder form and are especially helpful for infections of the mucosa or skin folds where Candida grows. When used topically, polyenes have few adverse effects and are typically safe and well tolerated [8].

Another antifungal drug that interferes with fungal metabolism and damages the integrity of fungal cell membranes is ciclopirox. Ciclopirox works well against molds, yeasts, and dermatophytes. Since other topical antifungals may have trouble penetrating the hard nail surface, it is frequently used to treat nail infections (onychomycosis). Fungal infections of the skin, nails, and scalp can be specifically treated with ciclopirox, which is available in formulations such as lotions, shampoos, and nail lacquers. Both superficial and deeper fungal infections can be effectively treated with ciclopirox due to its broad-spectrum efficacy and comparatively low occurrence of adverse effects. All of these topical antifungal medications are essential for treating localized fungal infections because they provide focused, efficient care with no systemic effect. Patients can discover a practical and efficient way to treat fungal infections thanks to their availability in a variety of formulations, which enhances compliance and results in general [9].

2. OLEOGELS

Innovative topical medication delivery methods called oleogels efficiently integrate and administer active pharmaceutical ingredients (APIs) using a lipid-based matrix. They are mostly made up of oils that have been organized utilizing organogelators, such as lecithins, fatty acid derivatives, or low molecular weight chemicals, into a semi-solid gel consistency. Because of this structural change, oleogels have special qualities including stability, biocompatibility, and superior skin adhesion. Oleogels solve important problems with conventional topical formulations by promoting improved skin penetration through interactions with lipid-rich skin layers and enabling greater solubility for lipophilic medicines [10].*Example of Oil in Oleogel Formulation –*

Linseed Oil - Linseed oil, sometimes referred to as flaxseed oil or flax oil (when edible), is a colorless to yellowish oil that is extracted from the dried, ripened seeds of the flax plant (Linum usitatissimum). Pressing is used to obtain the oil, and solvent extraction may be done afterwards.

Due to its ability to form polymers, linseed oil is frequently mixed with other oils, resins, or solvents to be used as an impregnator, drying oil finish, or varnish in wood finishing, as a pigment binder in oil paints, as a plasticizer and hardener in putty, and in the production of linoleum. With the rise of synthetic alkyd resins, which work similarly but don't yellow, linseed oil use has decreased over the past few decades [11-12].

Figure (1) - Linseed plant

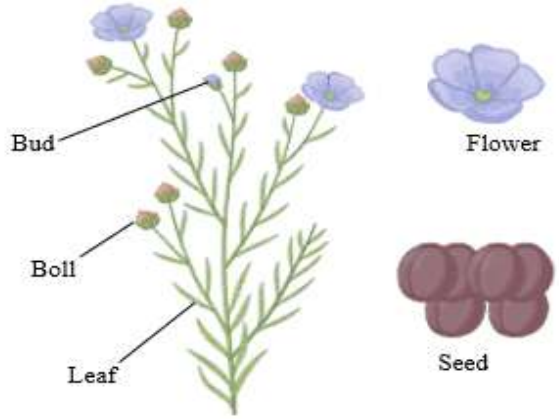
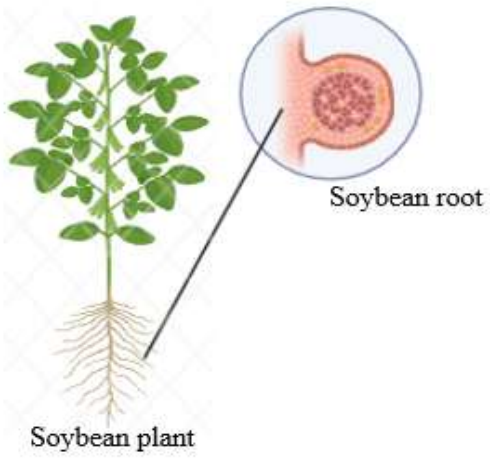


Figure 1: A twin of the Linseed plant

Soybean & Olive Oil - Around 60% of the world's oil-producing grains come from soybeans because of the oil's favorable quality and economics for a variety of industries. Soybeans are primarily composed of

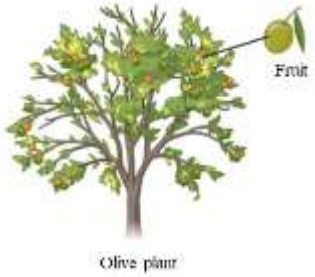
protein (up to 40%), but they also contain a significant amount of oil (18–22%) [13]. High levels of vegetable protein can be found in legumes (Leguminosae), such as soybeans (Glycine max). Particularly for Asians, soybeans are consumed virtually daily in the form of processed soybean products like tofu, tempeh, sprouts, and others [14].

Figure (2) – Soybean plant



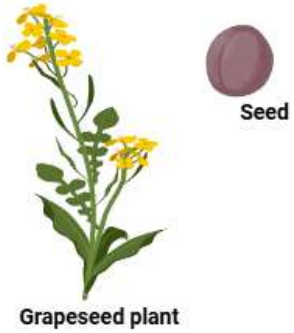
Olive Oil- The small tree species Olea europaea L., popularly known as the olive tree, is primarily found in Mediterranean nations. Because of its organoleptic properties and related positive health effects, olive oil, its primary derived product, has become more and more popular. One of the first species to be cultivated was the olive tree. According to the International Olive Council (IOC), records of the earliest trees ever cultivated in Asia Minor go back 6000 years [15].

Figure (3) - Olive plant



Grapeseed Oil & Clove Oil - Grape seed oil, sometimes known as grapeseed oil or grape oil, is a vegetable oil made from grape seeds. Grape oil is frequently used as an edible oil, while grape seeds are a by-product of winemaking [16].

Figure (4) - Grapeseed oil



Clove Oil - The clove tree's flowers, stems, and leaves (Eugenia aromatica or Eugenia caryophyllata, Fam. Myrtaceae) are distilled to produce clove oil. In dentistry, clove is widely used to treat oral ulcers, sore gums, and toothaches. Additionally, gargling with clove oil can help with bad breath and sore throats.With biological activities like antibacterial, antifungal, insecticidal, and antioxidant qualities, clove bud oil has long been used as a food flavoring and antimicrobial ingredient [17].

Thyme Essential Oil - The strong antibacterial qualities of thyme essential oil, which is derived from the Thymus vulgaris plant, are mainly due to its high thymol content. Its effectiveness against a number of pathogens, including the common foodborne fungus Aspergillus flavus, has been shown by research. According to a 2007 study by Omidbeygi et al., thyme essential oil demonstrated strong antifungal activity against A. flavus in tomato paste and liquid media [18].

Figure (5) – Thyme Essential plant

A liquid oil phase is immobilized within a network of three dimensions created by organogelators to create oleogels, which are classified as semi-solid systems. Without affecting the oil's fluidity or thermodynamic qualities, this structure turns liquid oils into a gel-like consistency. The following are the main ingredients of oleogels [19]

- **Liquid oils:** These are the main solvent and medicine carrier and can be either synthetic (like mineral oil) or natural (like castor, olive, or sunflower oil).
- **Organogelators:** Structuring agents that build a network by self-assembly or physical interactions, such as sorbitan esters, lecithins, fatty acids, or polymers, and produce a gel matrix.
- **Other excipients:** To improve performance, stability, or medication compatibility, stabilizers, emulsifiers, or co-solvents might be added [20].

Oleogels are extremely adaptable for a range of therapeutic requirements since they can hold both hydrophilic and hydrophobic medications. Depending on the therapeutic need, their composition can be modified to incorporate several types of oils, including mineral oils, vegetable oils (such sunflower or olive oil), or synthetic oils. Based on their origin and use, organogelators—which are used to solidify the oil phase—are divided into several categories, including [21]:

- **Low molecular weight organogelators (LMOGs):** These comprise substances that, at low concentrations, form gel-like structures, such as sorbitanmonostearate and N-acyl derivatives.
- **Polymeric organogelators:** These contain materials that enhance structural integrity and control drug release, such as poloxamers and polyethylene glycol (PEG).
- **Surfactant-based organogelators:**Lecithins and their derivatives are often utilized in pharmaceutical and cosmetic formulations, where they improve medication solubility and biocompatibility [22].

The smooth, non-greasy texture of oleogels greatly improves user compliance, and their regulated release profile guarantees long-lasting therapeutic benefits. Because of their versatility, oleogels may be used for a variety of purposes, including wound healing, dermatological therapies, and cosmetic formulations [23].

2.1. Relevance of Oleogels in Antifungal Therapy

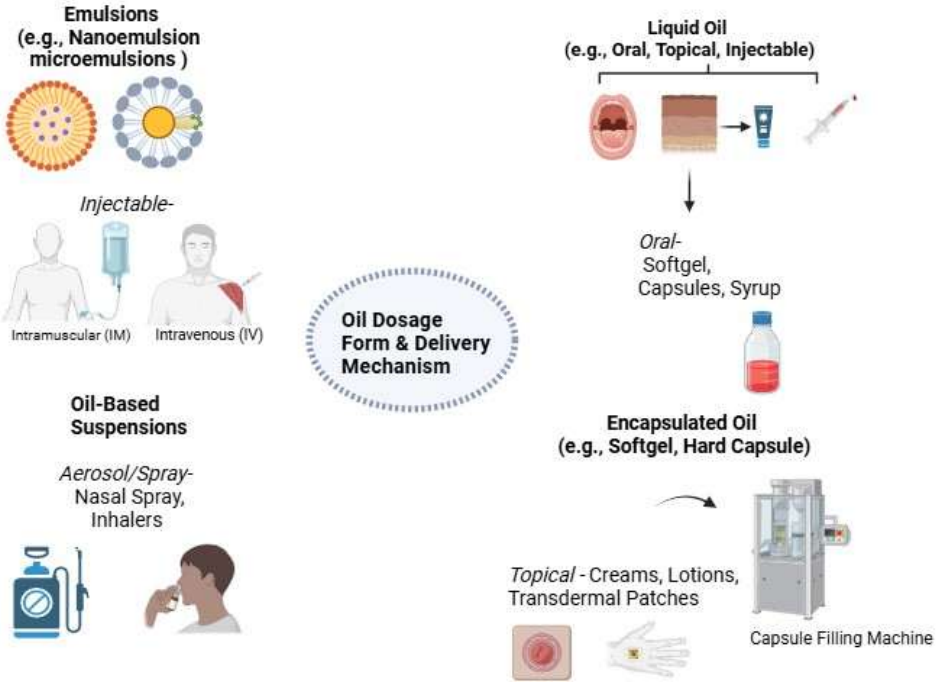
Oleogels have shown promising potential in antifungal treatment because they can overcome the limitations of conventional formulations. Fungal infections often require medications that can penetrate the thick keratinized layers of the skin and provide sustained drug release for prolonged action. Because of the remarkable skin-penetrating properties of oleogels, antifungal medications are more effectively distributed to deeper layers of the skin, improving therapeutic outcomes. Furthermore, its lipid-rich

structure serves as a barrier to prevent reinfection and enhance drug stability. Because they can be made to deliver antifungal drugs with minimal discomfort, oleogels are ideal for treating sensitive or irritated skin [24].

2.2. Mechanism of Oleogel Formation

The gelation mechanism of oleogels is the process by which organogelators create a three-dimensional network that transforms a liquid oil phase into a semi-solid gel structure. By immobilizing the liquid oil, this transition preserves the oil's fluidity and thermodynamic qualities while giving oleogels their distinctive semi-solid consistency. The kind of organogelator, concentration, temperature, and oil characteristics are some of the variables that affect the process [25].

Figure (6) - Oil Dosage Form & Delivery Mechanism-



2.2.1. Key Mechanisms Involved in Oleogel Formation:

- **Self-Assembly of Gelator Molecules:** Non-covalent interactions like hydrogen bonds, van der Waals forces, hydrophobic contacts, or π-π stacking cause organogelator molecules to cluster. As a result of this self-assembly, fibrous, crystalline, or lamellar structures are formed, giving the oil a three-dimensional network [26].
- **Physical Gelation by Cooling:** To create the majority of oleogels, the oil-organogelator combination is heated until the gelator is fully dissolved, and then it is cooled. The liquid oil phase becomes immobile when the organogelator molecules consolidate or recrystallize during cooling [27].
- **Gelation by Molecular Packing:** The gelation process can be either cross-linked in a polymeric matrix or include the alignment of gelator molecules into one-dimensional fibers, as in low molecular weight organogelators, depending on the molecular structure of the organogelator. By trapping the oil, these aggregates stop it from flowing and form a solid gel.
- **Van der Waals Forces and Hydrogen Bonding:** Weak intermolecular forces are frequently involved in gelation. For example, hydrogen bonds between the molecules stabilize the network in gelators based on fatty acids or fatty alcohols.
- **Interactions with Oil Phase:** How an oil interacts with the gelator depends on its polarity and kind. For instance, the structure and strength of the gel may be impacted by the way polar and non-polar oils interact with gelators [28].

2.2.2. Types of Structures Formed:

- Fibrillar Networks: These are present in low molecular weight organogelators, where the oil phase is trapped by fibrous structures.
- Gelators that crystallize to create ordered domains within the oil are known as crystalline networks.
- Polymeric organogelators that depend on entanglements instead of crystalline structures have been shown to exhibit amorphous networks [29].

Oleogels are adaptable carriers for topical drug administration and other applications because of their method of oleogel production, which enables customization of characteristics including drug loading, release profiles, and stability [30].

2.3. Advantages of Oleogels Over Other Topical Formulations

When it comes to stability, oleogels are far superior to traditional topical formulations. Active pharmaceutical ingredients (APIs) are well protected by their oil-based matrix, which keeps them safe from environmental deterioration brought on by light, air, and moisture. This feature is especially helpful for formulations that contain chemicals that are readily oxidized or sensitive. Furthermore, even during temperature fluctuations, oleogels retain their structural integrity due to their thermal resilience. They are a dependable option for long-term usage because of their intrinsic resistance to microbial infection, which is frequently brought about by the antibacterial qualities of the oils utilized [31].

Oleogels are superior in terms of bioavailability because they increase drug solubility and penetration, especially for lipophilic medicines. Better medication absorption and deeper penetration are made possible by oleogels' lipid-rich composition, which enhances their interaction with the stratum corneum, the skin's outermost layer. Because the oil phase effectively dissolves lipophilic medications, a greater concentration of the active component is accessible for therapeutic action. Furthermore, the three-dimensional gel network offers prolonged and regulated medication release, which lowers the frequency of administration and guarantees steady therapeutic benefits over time [32].

Another area in which oleogels perform better than conventional topical formulations is patient compliance. Their non-greasy, silky texture makes them more pleasant for consumers and solves typical issues with sticky lotions and oily ointments. Oleogels are straightforward to use since they spread evenly and readily over the skin. They are also appropriate for delicate skin because of their biocompatible and inert qualities, which lower the possibility of allergic responses or skin irritation. Oleogels' attractive appearance, which may be supplemented with pleasing scents and a sophisticated finish, adds to their consumer acceptance and makes them a popular option for both cosmetic and medicinal purposes [33].

3. FORMULATION OF OLEOGELS

Active pharmaceutical ingredients (APIs) are carried and released by oleogels, semi-solid systems utilized in topical drug administration that use a lipid-based matrix. Key elements including oils, gelling agents, and active substances like antifungal agents must be carefully chosen when creating oleogels. To attain desirable qualities including stability, improved medication penetration, and patient compliance, these elements cooperate [34].

3.1. Key Components

- **Oils, Selection of Carrier Oils**: In oleogel compositions, the oils serve as the gel's basis or carrier. Each of these oils—mineral, vegetable, or essential—offers special advantages in terms of texture, stability, and skin compatibility. Because of their stability and inability to interact with active components, mineral oils are frequently selected for use in pharmaceutical formulations. Because of their emollient qualities, compatibility with skin, and capacity to improve the solubility of lipophilic medications, vegetable oils—such as castor, olive, and sunflower oils—are frequently utilized. Essential oils can be used for their aroma or therapeutic properties, but because of their strength and tendency to irritate skin, they should be used with caution [35].
- **Gelling Agents:** Natural and Synthetic Alternatives, Gelling agents regulate the texture, spreadability, and stability of the formulation and are essential for giving the oleogel the appropriate semi-solid consistency. Gelling agents come in both natural and synthetic varieties. Because they are effective at thickening oils and forming a stable matrix, synthetic gelling agents like sorbitan monostearate are frequently utilized. Due to their biocompatibility and capacity to create stable emulsions and gels, natural

gelling agents such as lecithin—a phospholipid present in soy or sunflower—are highly recommended. When creating oleogels for sensitive skin or applications that call for natural components, lecithin is very helpful [36].

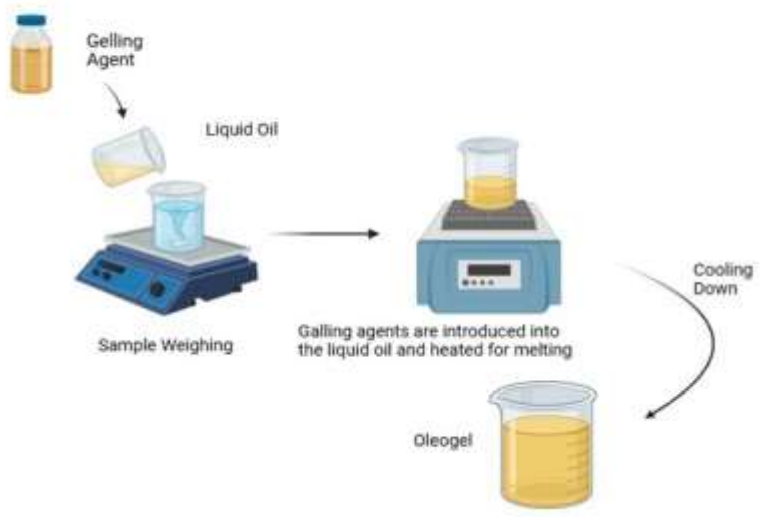
- **Antifungal Agents:** Common Substances Oleogels are frequently utilized as a topical delivery system for antifungal medications. For efficient and long-lasting release, these medications are integrated into the gel matrix. Oleogel formulations frequently contain the following antifungal agents: Clotrimazole: A broad-spectrum antifungal that affects the fungal cell membrane by preventing the formation of ergosterol. Miconazole: Another azole antifungal used to treat superficial fungal infections such as ringworm and athlete's foot, it prevents the synthesis of ergosterol. Depending on the intended therapeutic outcome, other antifungal medications such ciclopirox, terbinafine, and ketoconazole may also be added to oleogels [37].

3.2. Formulation Strategies

Ratios of Oil to Gelling Agent: For the oleogel to have the appropriate consistency and stability, the oil to gelling agent ratio is essential. A harder gel is produced by a larger proportion of gelling agent, whereas a softer, more spreadable product is produced by a lower ratio. The precise oils and gelling agents employed, together with the necessary texture and viscosity for the therapeutic application, all influence the optimal ratio [38].

Methods of Preparation: To guarantee adequate dispersion of the gelling ingredient inside the oil phase, oleogels are prepared using regulated heating, cooling, and mixing procedures. Heating: To dissolve the gelling ingredient and promote even distribution, the oil phase is normally heated to a particular temperature (often between 60 and 70°C). Cooling: To enable the gel to form, the liquid is gradually cooled to room temperature once the gelling ingredient has completely dissolved. Mixing Techniques: To avoid air pockets or uneven gel formations, homogeneous mixing is essential. For ingredients to be evenly distributed, a high-shear mixer or stirrer is frequently required [39].

Figure (7) - Direct method for Oleogel preparation



Additives to Improve Properties: To improve the performance and stability of oleogel formulations, additives are frequently added. Emollients like glycerin or stearic acid are used to enhance the moisture and spreadability of the skin. Antioxidants, such as vitamin E, can be added as stabilizers to prolong the oleogel's shelf life and stop oils from oxidizing. In formulations, especially those used in contaminated regions like the skin or mucosal membranes, preservatives like parabens or phenoxy ethanol are utilized to inhibit microbial development [40].

Oleogels may be created to provide an efficient, stable, and patient-friendly delivery method for a variety of therapeutic applications, including antifungal therapies, by carefully choosing these ingredients and adhering to exact formulation techniques [41].

4. CHARACTERIZATION OF OLEOGELS

Oleogels must be characterized to make sure they fulfill the requirements for drug administration, especially in topical treatments. The oleogel's physicochemical characteristics, drug-excipient compatibility, release kinetics, skin penetration, and stability are all evaluated in these tests. The following are essential methods for characterizing oleogels [42]:

4.1. Physicochemical Properties

- **Rheological Analysis (Viscosity, Spreadability):** Rheological study is essential for evaluating oleogels' texture and flow. Measurements of the gel's viscosity reveal how resistant it is to flow, which has a direct impact on how easily it applies and spreads on the skin. While a lower viscosity facilitates easier spreading of the composition, a greater viscosity indicates a stiffer gel. In order to guarantee patient compliance, spreadability studies evaluate how simple it is to apply the oleogel. By measuring shear stress, shear rate, and viscosity under varied circumstances (such as temperature and applied pressure), instruments such as a viscometer or rheometer are used to assess these qualities [43].
- **Drug-Excipient Compatibility Studies (FTIR, DSC)**:Medication-excipient compatibility is investigated using methods like Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) to guarantee the stability and effectiveness of the medication within the oleogel. By analyzing distinctive peaks in the infrared spectrum, FTIR assists in determining any interactions that may exist between the medicine and excipients. It can identify any chemical incompatibilities that could impact the stability or release of the medicine, such as the creation of new bonds between the drug and carrier. Understanding the melting or crystallization of the components in the oleogel can be aided by DSC's evaluation of thermal behavior and phase transitions. Instability or interactions between the active medication and other ingredients may be indicated by any notable changes in thermal characteristics throughout the formulation process [44].
- **Morphological Analysis (SEM, TEM):** Morphological characterisation makes it possible to visually inspect the oleogel's microstructure and physical characteristics. High-resolution pictures of the gel's outside and inside structure may be obtained using scanning electron microscopy, or SEM. The size and distribution of the particles in the oleogel, which might affect the drug's release and penetration, are examined using SEM. Even greater resolution is available with Transmission Electron Microscopy (TEM), which is especially helpful for examining interior structure at the nanoscale. It can offer comprehensive information about how lipid phases are arranged and how drug-loaded oleogels behave [45].

4.2. Drug Release and Permeation Studies

- **In Vitro Release Kinetics**: Studies on in vitro release mimic the way the medication is released from the oleogel when it is administered topically. These investigations, in which the oleogel is applied to a membrane and the drug's concentration in the receptor media is tracked over time, are usually carried out using Franz diffusion cells. To ascertain the rate of drug release and forecast its therapeutic efficacy, the release kinetics (such as the zero-order, first-order, and Higuchi models) are calculated. In order to ascertain if the oleogel will offer regulated or sustained drug release, these trials are essential [46].
- **Skin Penetration Studies**: Skin penetration experiments evaluate a drug's capacity to penetrate the epidermal barrier and arrive at the site of action. Franz diffusion cells and excised human or animal skin are commonly used in these investigations. Samples are taken from the receptor chamber after the oleogel is applied to the skin in order to track the drug's concentration over time. Comparing the oleogel to traditional formulations, skin penetration experiments assist ascertain whether the oleogel improves skin permeability and increases the drug's bioavailability [47].

4.3. Stability and Shelf-Life

- **Thermal Stability Testing**: Testing for thermal stability assesses the oleogel's performance at various temperatures. The structure, stability, and drug release characteristics of the gel can all be impacted by high or low temperatures. The oleogel is usually stored for lengthy periods of time at different temperatures (such as 4°C, 25°C, and 40°C) in order to conduct testing. The gel's shelf life and thermal stability are next assessed by examining its appearance, texture, and drug release profile [48].

- **Microbial Contamination and Preservation Studies:** Oleogels and other topical formulations are prone to microbial contamination, particularly if they are used topically or include water. To make sure the formulation doesn't encourage bacteria development, microbial contamination investigations are conducted. To stop such development, the oleogel may be treated with preservatives. Challenge testing, in which the formulation is exposed to bacteria and fungus and its capacity to prevent contamination is assessed, is a common technique for evaluating microbiological contamination. Minimum inhibitory concentration (MIC) testing and stability over time can be used to assess the preservative's efficacy and make sure the formulation is safe and effective for the duration of its shelf life [49].

The quality, stability, and performance of oleogels may be assessed using these thorough characterisation procedures to guarantee their appropriateness as a dependable and efficient topical drug delivery system [50].

5. CURRENT OLEOGELS FORMULATION FOR ANTI-FUNGAL PROPERTY

Table 1: Current Oleogels Formulation for Anti-Fungal Property

Formulation Name	Active Ingredient(s)	Target Fungus	Formulation Details	Usage/ Indication
Clotrimazole Oleogel	Clotrimazole	*Candida albicans*, *Trichophyton*	Oleogel-based formulation, using mineral oils as base and lecithin as a gelling agent [51]	Treatment of fungal infections like athlete's foot, ringworm, and vaginal yeast infections [52]
Miconazole Oleogel	Miconazole	*Candida*, *Dermatophytes*	Oleogel containing miconazole, enhanced with natural oils and stabilizers for prolonged release [53]	Used in topical treatment of ringworm, jock itch, and athlete's foot
TerbinafineOleogel	Terbinafine	*Dermatophytes*	Terbinafine incorporated into an oleogel base, designed for enhanced skin penetration and sustained release [54]	Treatment of athlete's foot, ringworm, and nail fungus
Ketoconazole Oleogel	Ketoconazole	*Candida*, *Malassezia*	Oleogel formulation with ketoconazole, essential oils, and gelling agents like sorbitanmonostearate	Used for dandruff, seborrheic dermatitis, and fungal skin infections [55]
EconazoleOleogel	Econazole	*Candida*, *Trichophyton*	Formulation with econazole incorporated into oleogel for antifungal activity	Treatment of superficial fungal infections like tinea corporis and candidiasis [56]

ItraconazoleOleogel	Itraconazole	*Aspergillus*, *Candida*	Itraconazole formulated into oleogel with vegetable oils for improved skin absorption	Treatment of skin fungal infections, including those caused by Aspergillus and Candida [57]
NaftifineOleogel	Naftifine	*Dermatophytes*	Oleogel with naftifine, typically enhanced with emulsifiers and stabilizers	Used for treating fungal skin infections like tinea pedis (athlete's foot) [58]
Fluconazole Oleogel	Fluconazole	*Candida*	Oleogel containing fluconazole, designed for topical application and extended release [59]	Treatment of localized Candida infections, including cutaneous and vaginal infections [60]

6. CHALLENGES FOROLEOGELS FORMULATION FOR ANTI-FUNGAL PROPERTY

The process of creating oleogels with antifungal qualities is intricate and involves several obstacles that must be overcome in order to produce a product that is stable, effective, and patient-friendly. These difficulties cover a wide range of formulation-related topics, from patient usability to component compatibility [61].

- **Selection of Oleogelator:** The stability and structural integrity of the oleogel depend on the oleogelator selection. To prevent any negative reactions that can reduce the antifungal medication's effectiveness, it must be compatible with it. The active component may occasionally become unstable or lose some of its effectiveness due to common oleogelators such as waxes, fatty acids, and polymers. To attain the intended gel strength, texture, and release characteristics without negatively impacting the stability or efficacy of the medication, the oleogelator concentration must also be adjusted [62].
- **Drug Solubility in the Oil Phase:** Incorporating antifungal medicines into the oleogel matrix can be difficult since many of them are hydrophilic or poorly soluble in oils. Because inadequately solubilized medications might precipitate over time and lose their effectiveness, it is important to ensure thorough solubilization. Formulators can improve medication dispersion by using solubilizers, co-solvents, or surfactants, although doing so may increase the danger of phase separation or instability in the oleogel system [63].
- **Stability Concerns:** One of the biggest problems with oleogel formulations is stability. Over time, rancidity and a loss of effectiveness may result from the oil phase's susceptibility to oxidative destruction. Furthermore, oleogels are susceptible to temperature changes, which may result in phase separation or gel network disintegration. To guarantee the lifespan of the antifungal product, it is essential to preserve the oleogel's structural and chemical stability under various storage circumstances [64].
- **Drug Release Optimization:** For antifungal action to be effective, medication release must be regulated and maintained. The antifungal drug must be able to be released from oleogels at a steady and therapeutically efficient rate. Achieving this balance can be challenging, though, because the gel matrix may either permit fast diffusion or unduly slow down the release, resulting in less than ideal drug concentrations at the application site. Therefore, one of the main formulation challenges is to optimize the gel matrix to provide a consistent release profile [65].

- **Compatibility with Other Ingredients:** The effectiveness and long-term stability of the formulation can be enhanced by adding extra excipients, such as stabilizers, preservatives, and penetration enhancers. These excipients, however, need to work well with the antifungal drug and the oil phase. Any incompatibilities might result in chemical or physical instability, which would lessen the product's efficacy [66].
- **Patient Acceptability:** Oleogels frequently have an oily texture that can make the skin feel greasy and unpleasant, which may make patients less compliant. To guarantee patient pleasure, it is crucial to improve the oleogel's sensory qualities, including its feel, spreadability, and absorption capabilities. One of the biggest challenges is creating a product that is both aesthetically pleasing and therapeutically effective [67].
- **Regulatory and Scalability Challenges:** Antifungal formulations frequently need to undergo extensive testing for safety, stability, and effectiveness in order to meet regulatory criteria. It might be difficult to meet these requirements and yet be cost-effective. Additionally, maintaining consistency and homogeneity between batches may become a problem when oleogel manufacturing is scaled up from laboratory to industrial levels [68].

To overcome these obstacles, a multidisciplinary strategy integrating knowledge of material chemistry, pharmaceutical sciences, and patient-centered design is needed to create oleogels that are both practical and efficient.

7. FUTURE PROSPECT:

With developments in drug delivery technology, material science, and a greater focus on patient-centered care, the future of oleogel formulations for antifungal applications seems bright. Oleogels are a promising foundation for the creation of potent and adaptable antifungal treatments due to a number of factors [69].

- **Enhanced Drug Delivery Systems:** Future studies could concentrate on creating oleogels with better drug delivery properties. In order to provide longer-lasting treatment benefits and improved patient outcomes, this involves modifying the gel matrix to permit regulated and sustained release of antifungal drugs. Drugs may become more effective against resistant fungus strains if nanotechnology advancements like the addition of nanoparticles or nanostructured oleogels improve their solubility, stability, and bioavailability [70].
- **Multifunctional Formulations:** It may be possible to use oleogels as multipurpose medication delivery systems. Further therapeutic agents, including anti-inflammatory or wound-healing chemicals, might be added to these formulations to better treat complicated fungal infections. This method works especially well for treating skin infections and onychomycosis, where fungal development is frequently accompanied by tissue damage and inflammation [72-78].
- **Use of Biocompatible and Natural Ingredients:** The move to environmentally friendly and biocompatible formulations is probably going to have an impact on how oleogels are developed in the future. Lecithin and sterols are examples of plant-based natural oleogelators that might be used to make safer, more environmentally friendly goods. Furthermore, by serving as both a carrier and an active ingredient, essential oils having antifungal qualities can be used as a foundation with double advantages [79].
- **Personalization and Smart Oleogels:** Technological developments might result in customized oleogels made to meet the requirements of certain patients. Customization according to skin type, illness severity, or even hereditary predisposition may be one of them. Furthermore, tailored medication release at the infection site may be possible using smart oleogels that react to environmental stimuli like pH or temperature changes, increasing efficacy and lowering adverse effects [80].
- **Improved Cosmetic Acceptability:** The greasy feel and oily texture of oleogels are major obstacles to their acceptability. Future formulations could make use of innovative oleogelator systems or emulsification procedures to enhance the product's sensory qualities and increase consumer appeal. Oleogels that are quick to absorb, lightweight, and leave no skin residue might greatly improve patient compliance [81].

- **Wider Applications and Delivery Routes:** Future studies might examine the use of oleogels in various delivery methods, such as transdermal or mucosal, even though they are now mainly intended for topical use. As an alternative to oral or intravenous antifungal medications, this might broaden their uses to treat systemic fungal infections. Because of their flexibility, oleogels may play a significant role in antifungal treatment [82].
- **Integration with Advanced Technologies:** Oleogels' formulation and manufacturing might be completely transformed by combining them with cutting-edge pharmaceutical technologies like 3D printing and artificial intelligence (AI). 3D printing may allow for accurate, adaptable dosage for various patient demands, while AI-driven design processes can improve medication release patterns and constituent selection [83].
- **Potential for Combination Therapies:** Co-forming oleogels with additional antifungal medications or treatments may increase their effectiveness and expand their applications. Complex infections may be fully resolved by combining antifungal therapy with immunomodulatory drugs or by using combination therapies that target several fungus species [84].
- **Global Market Expansion:** Oleogels may become more widely accepted in international markets as knowledge of fungal diseases and how to treat them increases. They are appropriate for environments with low resources, where access to cutting-edge antifungal treatments may be restricted, because to their affordability and versatility [85-110].

Oleogel compositions with antifungal qualities have a bright future ahead of them. Oleogels may become a mainstay of antifungal treatment plans with further research and development and technology improvements, which would be advantageous for patients as well as the pharmaceutical sector.

8. CONCLUSION:

One possible path toward the development of localized antifungal therapeutics is the synthesis and characterisation of oleogels as topical carriers for antifungal drugs. Oleogels provide special benefits such better stability of lipophilic antifungal drugs, controlled drug release, and increased drug solubility. They are a great platform for topical treatment because they may be made using natural or synthetic oleogelators to generate a stable gel matrix. This ensures focused delivery to the infection site while limiting systemic adverse effects. Furthermore, the use of multifunctional excipients in oleogels enables the creation of novel, patient-friendly formulations with improved therapeutic results.

But issues including medication compatibility, physical stability, and patient acceptance still need to be studied and improved. These restrictions might be addressed and the effectiveness of oleogels increased with the help of developments in nanotechnology, smart materials, and biocompatible components. Future research should concentrate on enhancing oleogels' aesthetic qualities and broadening their uses beyond topical use by investigating delivery methods including transdermal and mucosal. To sum up, oleogels are a unique and efficient drug delivery method for antifungal medications. They are positioned to become a mainstay in the treatment of fungal infections with further innovation and integration of state-of-the-art technology, offering safer, more effective, and patient-centered therapeutic choices.

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