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Review Article

Formulation Perspectives in Topical Antifungal Drug Therapy: A Review

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Abstract

Topical medication delivery is the process of directly treating a cutaneous ailment or the cutaneous manifestation of a general disease by applying a pharmaceutical dosage form to the skin with the goal of reducing the drug's pharmacological or other effects to the surface of skin. A wide range of pharmacological dosage forms, such as semisolids, liquid preparations, sprays, solid powders, gels, creams, and ointments, are used in topical drug delivery systems. A gel is a cross-linked polymer network swollen in a liquid medium. Its properties depend strongly on the interaction between solid state polymer and the liquid component. Gels don't have a flow that is steady. An interlacing three-dimensional network of dispersed phase particles is created by the interaction of the polymer and the liquid dispersion medium. Because topical gel formulations are less oily and readily removed from the skin, they provide an effective medication delivery mechanism. Compared to cream and ointments, gel composition offers greater application properties and stability. One of the most frequent issues with dermatological problems is fungal infection of the skin. The most effective option for treating cutaneous infections is topical treatment. The most popular antifungals in the treatment of both local and systemic fungal infections are azoles. The benefits of topical treatment for fungal infections include less risk of systemic adverse effects and medications that are targeted to the infection site. Important actions for boosting treatment effectiveness include formulation design and optimization. The most helpful aspects of a topical medication delivery system are the medication's physiochemical characteristics and formulation type. As a result, some recent developments in formulation have been researched for the delivery of antifungal medications via the target region of the skin. This review focuses on the research that has been done so far on antifungal gel and a thorough analysis of it.

Keywords: Topical gel, Antifungal, Drug delivery, dispersion medium, fungal infection, adverse effects

INTRODUCTION

A topical application occurs when a drug is administered topically to a specific area of the body. Topical administration, which includes a wide variety of classes such as creams, foams, gels, lotions, and ointments, most frequently refers to application to bodily surfaces like the skin or mucous membranes to treat ailments. Numerous topical drugs are administered topically, to the skin.¹ Compared to other drug delivery methods, the topical/transdermal route has several benefits, including continuous medication delivery, less side effects, and increased patient compliance.² Drugs for topical use are meant to be applied externally. They are designed to have a localizing effect on one or more skin layers.³ The wide range of pharmaceutical dosage forms used in topical drug delivery systems includes semisolids, liquid preparations, sprays, and solid powders. Gels, creams, and ointments are the most often utilized semisolid topical drug delivery preparations.⁴

GEL

According to the U.S.P., a gel is a semisolid system made up of a dispersion made up of either large organic molecules or small inorganic particles that are enclosed and contacted by fluids. Gels are a significantly dilute cross-linked system with no flow in the steady-state.¹⁸²² They are made up of a two-component semi-solid liquid-rich system. Their one distinguishing feature is the existence of a continuous

structure that provides solid-like characteristics.⁵ Gels have become a preferred medium for drug delivery formulations due to their biocompatibility, network structure, and molecular stability of the integrated bioactive ingredient.⁶

STRUCTURE OF GELS

A gel is made up of a natural or synthetic polymer that forms a three-dimensional matrix in a dispersion medium or hydrophilic liquid. After application, the liquid evaporates, trapping the medicine in a thin film of the gel-forming matrix that physically covers the skin. The existence of a network produced by the interlocking of gelling agent particles causes a gel to be stiff. The structure of the network and the properties of the gel are determined by the nature of the particles and the kind of form that is responsible for the links.⁶

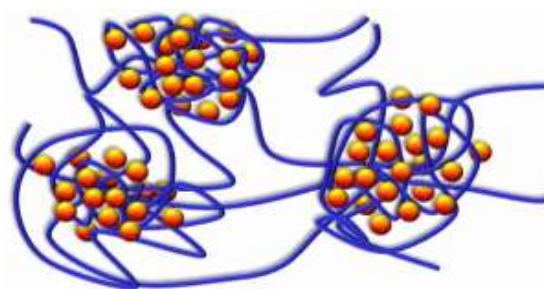


Figure 1: Structure of gels

Topical formulations have three main functions ⁷

- 1) Because of their emollient qualities, they help in skin hydration.
- 2) To protect the skin from the elements or to repair an undamaged or injured region of skin.
- 3) To apply medicine to the skin.

ADVANTAGES OF TOPICAL DRUG ADMINISTRATION⁶

- 1) Avoids issues with gastrointestinal (GI) medication absorption caused by GI pH, enzymatic activity, and drug interactions with food, drink, and other orally delivered medicines.
- 2) When other methods of administration (e.g., oral administration, intravenous injection) are ineffective, such as with vomiting, swallowing issues, resistant children, or diarrhea, this route is chosen.
- 3) Patient acceptance is improved since this medication delivery technique is non-invasive, avoiding the discomfort of parenteral therapy.
- 4) Avoids the first-pass effect, which may result in enzyme inactivation by digestive and liver enzymes.

- 5) Dose reduction as compared to oral dosing forms.
- 6) The ability to dissolve a large range of drugs with varying chemical characteristics, allowing for combination treatment with a single transdermal gel.
- 7) Improves compliance by providing longer treatment with a single application.
- 8) Drug therapy can be stopped quickly by removing the application from the skin's surface.
- 9) Less oily and easier to remove from the skin.

DISADVANTAGES OF TOPICAL DRUG ADMINISTRATION¹

- 1) This route is not suitable for medications that irritate or sensitize the skin.
- 2) Topical preparations are more costly than traditional dosing forms.
- 3) The route is constrained by the surface area of the delivery system and the dose that must be administered in the chronic stage of illness.

CLASSIFICATION OF GELS⁷

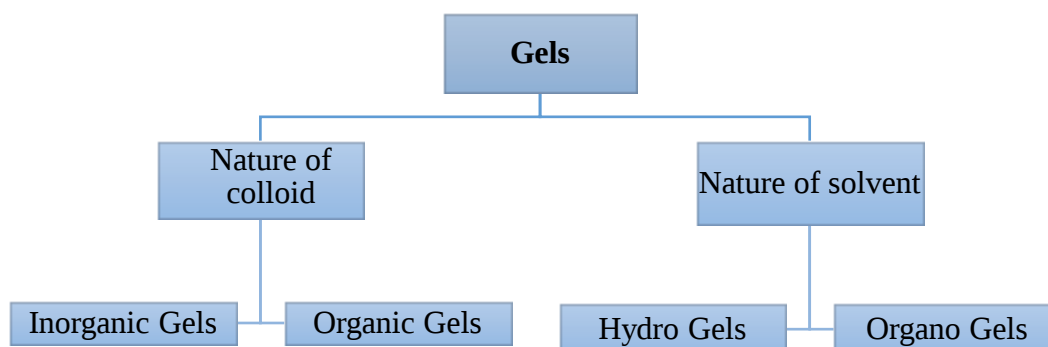


Figure 2: General Classification of Gels

There are two classification categories for topically administered gels. The first approach categorizes gels into two kinds of gel systems. These are known as inorganic and organic gel systems, respectively. Most inorganic hydrogels, such as aluminium hydroxide gel and bentonite magma, are two-phase systems. Bentonite has also been utilised as an ointment basis in quantities ranging from 10% to 25%. Most organic gels are single-phase systems that may contain gelling agents such as carbomer and tragacanth as well as organic liquids such as Plastibase. The second classification method separates gels into hydrogels and organogels, with several subcategories in between organic hydrogels, natural and synthetic gums, and inorganic hydrogels are examples of soluble in water components.⁷

CHARACTERISTICS OF GELS^{8,9}

Gels should possess the following properties

- 1) Gelling agents for pharmaceutical or cosmetic usage should ideally be inert, safe, and not react with other formulation components.

- 2) During storage, the gelling ingredient in the preparation should provide an acceptable solid-like character that is easily broken when subjected to shear forces caused by shaking the bottle, squeezing the tube, or during topical application.
- 3) It should have appropriate antimicrobial action against microbial attack.
- 4) The topical gel should be non-sticky.

a) Swelling

When a gelling agent comes into contact with a liquid that solvates it, the agent absorbs a significant amount of the liquid and its volume rises. Swelling is the term for this process. This happens as the solvent enters the matrix. Gel solvent interactions take the role of gel-gel interactions. The amount of swelling is determined by the number of connections formed between individual gelling agent molecules and the strength of these bonds.

b) Syneresis

Many gels suddenly compress and release some fluid medium when left standing. This is known to as syneresis. As the concentration of gelling agent falls, the degree of syneresis increases. The presence of syneresis suggests that the initial gel was thermodynamically unstable. The contraction process has been linked to the release of elastic tension created during gel setting. As these tensions are eased, the available interstitial space for the solvent is reduced, driving the liquid out.

c) Ageing

Slow spontaneous aggregation is common in colloidal systems. This is known as the ageing process. Ageing causes a denser network of the gelling ingredient to grow gradually in gels. Ageing causes a denser network of the gelling ingredient to grow gradually in gels.

According to this process is identical to the first gelling process and continues after the initial gelation since the fluid medium is lost from the freshly created gel.

d) Structure

The presence of a network generated by the interlinking of particles gelling agent causes the rigidity of a gel. The nature of the particles and the type of force responsible for the connections, which determines the network topology and gel characteristics. Individual hydrophilic colloid particles might be spherical or isometric collections of small molecules or single macromolecules.

e) Rheology

Solutions containing gelling agents and flocculated solid dispersion are pseudo plastic, showing Non -Newtonian flow behavior defined by a decrease in viscosity with increasing shear rate. The fragile structure of inorganic particles scattered in water is disturbed by n gels, and ageing results in the eventual creation of a denser gelling agent network.

FUNGAL INFECTION

Mycoses are prevalent fungal infections, and a number of environmental and physiological circumstances can lead to the development of fungal illnesses. Inhalation of fungal spores or localized colonization on the skin can cause long-term infections; hence, mycoses frequently begin in the lungs or on the skin. Fungal infections of the skin were the fourth most frequent illness in 2010, affecting 984 million individuals. Individuals taking medications or with compromised immune systems are more likely to get fungal infections.¹ Fungi are eukaryotic organisms that can be unicellular or multicellular and can be found all over the planet. Fungi, like mushrooms, may be seen with the naked eye, as could yeast and moulds, which can be found in a variety of forms. The illness caused by fungus kills about 1.5 million people and impacts billions more. Although it is still a neglected area for public health authorities, some deaths from fungus are still avoidable. Moderate fungal infection has been linked to health concerns such as cancer, organ transplantation, asthma, and corticosteroid use. Not all fungi are dangerous to humans, most do not cause any problems, and just a few are capable of causing disease under specific situations. Fungi cause infection by producing spores that can be collected directly, transmitted, or inhaled. Infectious disorders caused by fungus mostly affect the lungs, skin, and nails, but they can also penetrate the skin and harm organs, resulting in systemic infection. Fungal infections, often known as mycosis, are distinguished from most bacterial diseases. As a fungal infection that is chronic and kills the host on a regular basis, most intense mycoses necessitate a course of treatments that

lasts a long period. Among both viral and bacterial diseases, fungal infections are seldom communicable, which leads to less interest in health monitoring, with the result that there is little information for fungal disease prevention and occurrence.¹⁰

ANTIFUNGAL DRUGS AVAILABLE IN GEL

Sr. No.	Example
1	Fluconazole
2	Amphotericin B
3	Ketoconazole
4	Itraconazole
5	Terbinafine
6	Tioconazole
7	Clotrimazole
8	Mometasone
9	Fucidic acid

These medications are used to treat mycoses. A topical or systemic treatment may be employed, depending on the type of the illness. Fluconazole, which is the basis of many over-the-counter antifungal medicines, is an example of an antifungal. Another example is amphotericin B, which is stronger and is used to treat the most severe fungal infections that have developed resistance to previous types of therapy. It is injected intravenously. Azole drugs, such as ketoconazole, itraconazole, and terbinafine, are used to treat skin infections. Candida albicans-caused vaginal yeast infections can be treated with medicated suppositories such as tioconazole and pessaries, whilst cutaneous yeast infections are treated with medicated ointments.¹¹

ANTIFUNGAL THERAPY DRUG DELIVERY VIA SKIN

The drug that will be delivered passively through the skin must be lipophilic and have a molecular weight of 500 Da. Only a few drugs achieve these percutaneous delivery requirements. The primary purpose of delivering such medications through the skin is to obtain improved systemic absorption or for local therapy. Although the intravenous approach avoids gastrointestinal side effects, it is invasive and cumbersome as compared to barrier layer-like topical preparations that have improved patient compliance and may be self-administered. After skin administration, antifungal medicines should achieve effective therapeutic levels in viable epidermis. Transdermal medicine distribution is most difficult because to stratum corneum and the various ways utilised to improve drug permeability. Various techniques are employed. Nano particulate carriers such as solid-lipid nanoparticles, nanostructured lipid carriers, vesicular carriers such as liposomes, ethosomes, niosomes, and transferosomes, and colloidal particulate carriers such as microemulsions, micelles, and Nanoemulsions are new carriers for antifungal transdermal administration.^{14, 15, 16}

PHYSIOCHEMICAL AND PHARMACOKINETIC PROPERTIES OF ANTIFUNGAL DRUGS

The physiochemical and pharmacokinetic properties of antifungal drugs and their inherent antifungal property determine their efficacy, so they are important issue for pre-development stage. Fluconazole is more polar than other

azoles, slightly soluble in water (8 mg/ml). It is metabolically stable and low protein binding. Fluconazole is less active than ketoconazole in-vitro, its distribution throughout the body and high levels of free drug reached in blood contribute to its efficacy. Ketoconazole degrades by oxidation and hydrolysis and has poor water solubility. Fluconazole has a molecular weight of 306.3 Da and a pKa value of 3.7 (weak base), whereas ketoconazole has a molecular weight of 531.4 Da and pKa values of 6.51 and 2.94, making it a dibasic compound. Patients with impaired immune systems are also susceptible to oral infections caused by *Candida* species other than *Candida albicans*. Nystatin, an antimycotic medication from the polyene antifungal family, is used to treat oropharyngeal candidiasis. Nystatin causes leakage and permeability problems by binding to the sterols in cell membranes. It comes in ointment, powder, and cream form. It only works against *Candida*.^{17, 18}

PREPARATION AVAILABLE IN MARKET¹⁹

These categories used to according its site of infection

Example along with brand name

Sr. No.	Brand Name	Example
1)	Whitfield's Ointment	Benzoic acid
2)	Batrafen® cream, powder, solution	Ciclopiroxolamine
3)	Nilstat® cream, ointment, paste	Nystatin
4)	Canesten® Once Daily Bifonazole Cream	Bifonazole
5)	Canesten® cream, powder and candid cream, solution	Clotrimazole
6)	Ecreme® cream, powder, foaming solution	Econazole
7)	Nizoral® cream and Daktagold® cream	Ketoconazole
8)	Daktarin® cream, dusting powder, lotion, thrush cream	Miconazole
9)	Lamisil® cream, gelsprey	Terbinafine

Additional antifungal medications available internationally include naftifine, the azoles bifonazole, tioconazole, sulconazole, efinaconazole, and luliconazole, as well as the benzoxaborole tavaborole.

1) Preparation for Topical antifungal gels

These can be used to treat:

- Infections caused by dermatophytes such *tinea corporis*, *tinea cruris*, *tinea faciei*, *tinea manuum*, and *tinea pedis*
- As an alternative to oral treatment for *tinea barbae* and *tinea capitis*.
- Yeast diseases like *pityriasis versicolor* and *Candida intertrigo*.
- Infections of the nail plate and fungal skin conditions such *tinea graeca*.
- For two to four weeks, the creams are applied twice daily to the afflicted region, leaving a margin of several centimetres of healthy skin. Continue for one or two weeks following the disappearance of the final noticeable rash. Frequently, therapy must be repeated.

2) Preparation for Scalp fungal infection

In addition to being used to treat *tinea capitis* and scalp psoriasis, antifungal shampoos are mostly used to treat dandruff and seborrheic dermatitis.

Example along with brand name

Sr. No.	Brand Name	Example
1)	Daktagold shampoo, Ketopine® shampoo, Nizoral® shampoo, Sebizole® shampoo	Ketoconazole
2)	HairScience® shampoo	Miconazole
3)	Stieprox® liquid	Ciclopirox

3) Preparations for nail fold infections

To manage nail fold infections, a variety of antiseptic and antifungal medicines are available (paronychia). For several months, they should be used twice or three times every day.

Example along with brand name

Sr. No.	Brand Name	Example
1)	Canesten®	Clotrimazole topical solution
2)	Pevaryl® solution	Econazole solution
3)	Daktarin® tincture, Fungo® solution	Miconazole

4) Preparations for oral infections

It is capable of treating oral candidiasis with:

Example along with brand name

Sr. No.	Brand Name	Example
1)	Fungilin® lozenges, oral suspension	Amphotericin B
2)	Nilstat® oral drops, capsules, powder, tablets	Nystatin
3)	Daktarin® oral gel	Miconazole

5) Preparations for vaginal infections

Vulvovaginal candidiasis can be treated with:

Example along with brand name

Sr. No.	Brand Name	Example
1)	Canesten® vaginal cream and pessaries; Clocreme® pessary, vaginal cream; Clomazol® Vaginal cream; Clotrimaderm® vaginal cream	Clotrimazole
2)	Pevaryl® ovules	Econazole
3)	Nilstat® vaginal cream and pessaries	Nystatin

DRUG DELIVERY SYSTEM UNDER CURRENT DEVELOPMENT FOR IMPROVING TREATMENT OF FUNGAL DISEASES IN SKIN

1) Nanoparticulate Carriers²⁰

The newest lipid nanoparticles, known as nanostructure lipid carriers (NLC), are gaining significant interest as cutting-edge topical colloidal drug carriers. To get around the restrictions SLN had, NLC were created. Solid lipids make up SLN, whereas liquid lipids (short chains) and properly mixed solid lipids (long chains) make up NLC, preferably in a ratio of 70:30 to 99.9:0.1. Although the resultant lipid particle matrix has a lower melting point than the initial solid lipid, it is still solid at body temperature. Limited drug loading capacity, drug ejection during storage, and relatively high water content in the dispersions (70-99.9%) are all often noted drawbacks of SLN. NLC have a greater drug-loading capacity than SLN for a variety of active compounds, and they prevent or reduce the possibility of active compounds being expelled during storage. Because liquid lipid is more soluble in a variety of medications than solid lipid is, drug loading is improved. Numerous characteristics of NLC are helpful for topical application. These carriers have minimal cytotoxicity and systemic toxicity due to their physiological and biodegradable lipid composition. Due to its solid lipid matrix and compact size, which ensures intimate contact with the stratum corneum, lipid particles can improve medication flow through the skin and allow for regulated release from carriers.

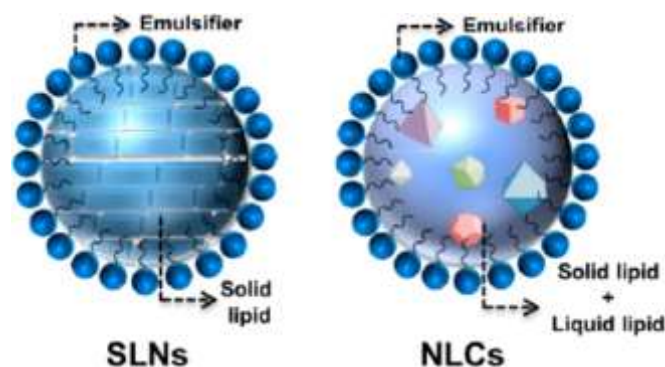


Figure 3: SLNs and NLCs.

2) Gelling Systems-polymeric Carriers

A) Nanosponges²¹

Targeting medication delivery systems has long been a goal in the effort to achieve desired results. Although the Nanosponge drug delivery method originally only had a surface use, it is now possible to inject Nanosponges orally as well as intravenously (IV).

A recent type of material known as a "nanosponge" is composed of tiny particles with a small, nanometer-wide cavity. Different kinds of materials can be used to fill these small cavities. These small particles have the potential to transport both hydrophilic and lipophilic medicinal substances which can boost the stability of molecules and drugs that are weakly water-soluble.

The nanosponges are a network or three-dimensional scaffold made of polyester that may break down organically. To create Nanosponges, these polyesters are dissolved in a solution together with a crosslinker. Here, the polyester degrades moderately in the body since it is typically biodegradable. When the nanosponges scaffold collapses, the drug molecules that were loaded are released in a damaging way.

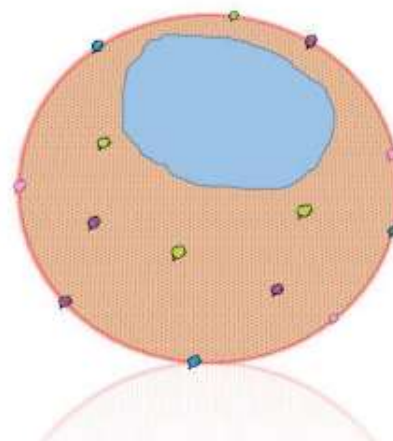


Figure 4: Structure of a Nanosponge showing a cavity for drug.

B) Amphiphilic Gels^{22, 23}

Amphiphilic macromolecule-based self-assembly methods provide distinctive and unprecedented prospects for developing novel materials for cutting-edge applications in nanotechnology. Recent investigations have shown that the thermodynamic incompatibility between the various blocks results in a spatial organisation into ordered morphologies on the nanoscale with the generation of unique structural characteristics. The execution of extremely precise cellular tasks is possible in biosystems, where assemblies of various amphiphilic macromolecular components and their coordinated actions are leading examples. The essential characteristics of conventional, head/tail(s) type, amphiphiles,

whose aggregation is fueled by soft contacts including hydrogen bonds and steric effects, as well as hydrophobic and electrostatic interaction. Steric influences, hydrophobic interaction, and electrostatic interaction. Additionally, we emphasise crucial instances where intricate processes, such as the modulation and regulation of morphology by other structure-directing interactions, might encourage expanded use in biological and pharmaceutical chemistry as well as materials research. The introduction of chirality, signal processing, and recognition processes are achieved by precisely tailoring chemical structures and the effective utilization of noncovalent forces. We conclude by providing insight into the unique structural characteristics.

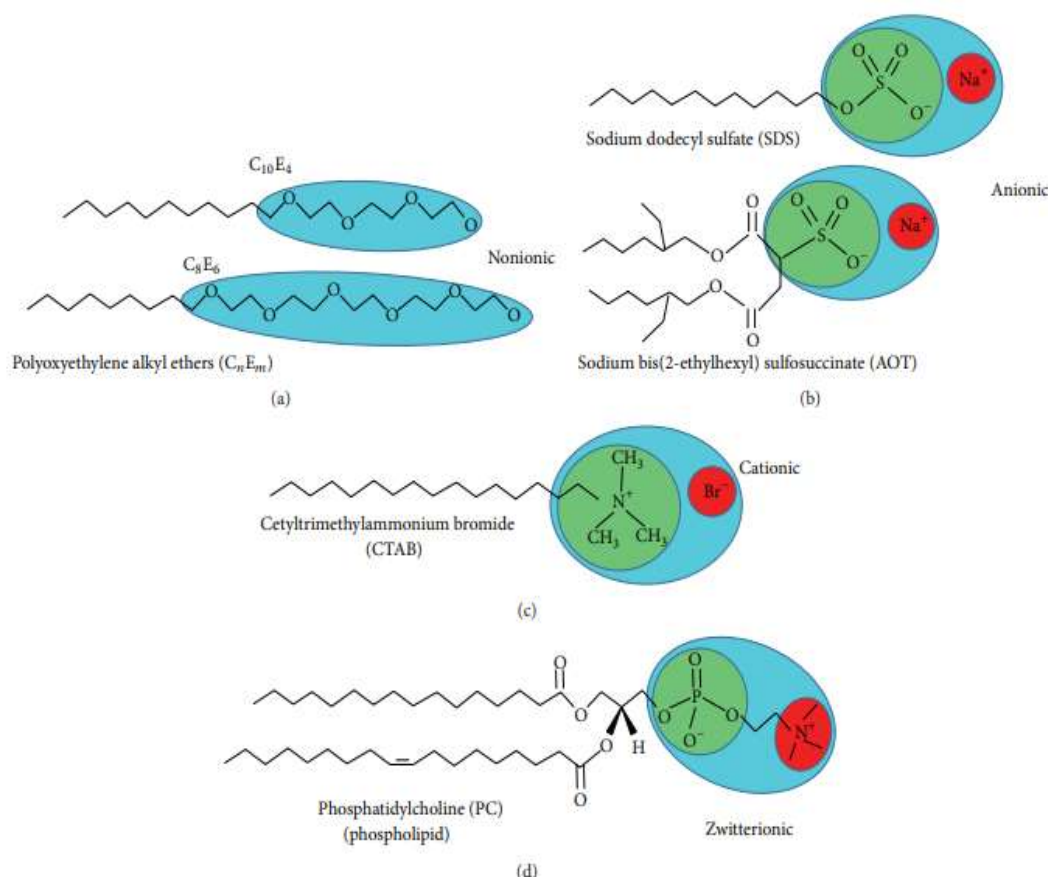


Figure 5: Example of most common Nonionic (a), Anionic (b), Cationic (c), and Zwitterionic (d) Amphiphilic molecule.

C) Emulgels^[24]

Pharmaceutical semisolid dosage forms, especially emulgels, have drawn increased interest from academic and corporate researchers during the past ten years. For both systemic and local medication delivery, the skin is a crucial organ. Despite being a convenient method for drug delivery, certain medications may not permeate the skin. Simple solutions and ointments to multiphase nanotechnology-based treatments are all accessible as topical medicinal products. Topical medication delivery methods will be heavily utilised in the upcoming years to increase patient compliance. An emulsion and gel-based preparation is called emulgel. Oil-in-water (O/W) or water-in-oil (W/O) emulsions can be utilised, and both can be combined with a gelling agent to create an emulgel. These new formulations have been created recently for topical drug administration and have demonstrated their appropriateness for transporting hydrophobic medications. Additionally, it is anticipated that emulgel will emerge as a crucial method for incorporating hydrophobic pharmaceuticals into gel formulations. Emulgel functions as a

dual-control medication release system because it combines the qualities of an emulsion and a gel. Many pharmaceutical companies have entered the commercial production of emulgels as a result of these advantages. These include the medications Diclofenac sodium (Voltaren Emulgel®), Miconaz-H (Miconazole Nitrate), Pernox® (Benzoyl Peroxide), and CLINAGEL® (Clindamycin phosphate).

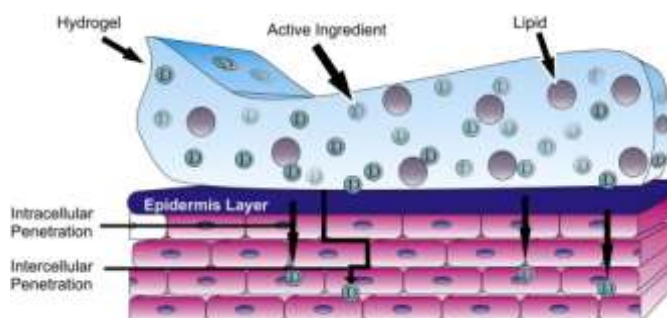


Figure 6: Structure of Emulgels

3) Colloidal Carriers

A) Microemulsion

The term "micro emulsion" refers to a colloidal dispersion with a droplet diameter typically between 10 and 100 nm that is optically isotropic and thermodynamically stable. It is made up of an oil phase, an aqueous phase, a surfactant, and a co-surfactant in the proper proportions. The bioavailability of medications that are poorly soluble has been researched extensively in relation to microemulsions. In such circumstances, they provide a practical strategy. Microemulsions exhibit significant levels of absorption and penetration due to their extremely low surface tension and tiny droplet size. These adaptable carriers are becoming more popular, and in addition to the usual oral route, they are now being used in a variety of other administration methods as well. This can be ascribed to their distinctive solubilization capabilities and thermodynamic stability, which have attracted interest for their usage as new drug delivery systems.^{25, 26}

Microemulsions are superior to traditional emulsions, suspensions, and micellar solutions as well as the colloidal systems under research, and they might be used as alternative drug carriers. They are promising drug delivery systems that provide prolonged or regulated drug release for parenteral, topical, transdermal, ophthalmic, percutaneous, and oral medication administration. They have the benefits of spontaneous synthesis, simplicity in manufacturing and scaling up, thermodynamic stability, enhanced hydrophobic drug solubilization, and bioavailability. Additionally, inverted micellar structure microemulsions may be less comedogenic than creams or solutions. A quaternary system called a microemulsion consists of an oil phase, a water system, surfactants, and a cosurfactant. Specific physicochemical characteristics, including as transparency, optical isotropy, low viscosity, and thermodynamic stability, are present in these spontaneously generated systems. The greatest size of the dispersed phase droplets in these systems cannot be greater than 150 nm, which is one-fourth of the wavelength of visible light, which accounts for the transparency that has been seen in these systems. The name "micro emulsion" is deceptive because the droplet diameter in stable microemulsions is often in the range of 10-100 nm (100-1000 °Å), indicating that these systems are truly nano-sized emulsions. Numerous investigations, largely in vitro but also some in vivo, have demonstrated that micro emulsion formulations have better transdermal and dermal distribution qualities.²⁷

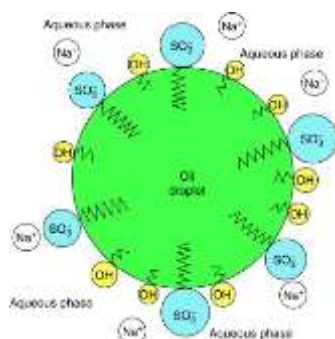


Figure 7: Microemulsion

B) Nanoemulsion²⁸

Nanoemulsions, also referred to as submicron emulsions, ultrafine emulsions, and miniemulsions, are isotropic dispersions of two immiscible liquids, such as water and oil, stabilised by an interfacial film made of a suitable surfactant and co-surfactant to form a single phase. They are submicron

sized colloidal particulate systems that are considered to be thermodynamically and kinetically stable. Such nanoemulsions have been employed with a variety of surfactants, both ionic and non-ionic, with various properties. The most popular ones among them were cationic (quaternary ammonium halide), anionic (potassium laurate, sodium lauryl sulphate), nonionic (sorbitan esters, polysorbates), and zwitterions surfactants (quaternary ammonium halide). Early nanoemulsions were of the oil-in-water (O/W) type, with droplet sizes averaging between 50 and 1000 nm. More recently, nanoemulsions have been divided into three types: O/W type (oil is dispersed in the aqueous phase), water-in-oil (W/O) type (water is disseminated in the oil phase), and bi-continuous (water and oil microdomains are interdispersed within the system). By changing the components of the emulsions, it is possible to switch between these three forms. O/W and W/O emulsions coexist in one system concurrently in multiple emulsions, another form of nanoemulsion. Both hydrophilic and lipophilic surfactants are utilised simultaneously to stabilise these two emulsions. Comparing nanoemulsions to other dosage forms, some of these benefits include:

- (1) Increased rate of absorption,
- (2) Decreased variability in absorption,
- (3) Protection from oxidation and hydrolysis in O/W nanoemulsions,
- (4) Delivery of lipophilic drugs after solubilization,
- (5) Aqueous dosage form for water-insoluble drugs,
- (6) Enhanced bioavailability for many drugs,
- (7) Ability to incorporate both lipophilic and hydrophilic drugs,
- (8) Delivery systems to enhance efficacy while reducing total dose,
- (9) As safe, non-irritating delivery methods for skin and mucosal membranes,
- (10) Drug permeation via a liquid film, whose hydrophilicity or lipophilicity as well as thickness may be carefully regulated, to control drug release.

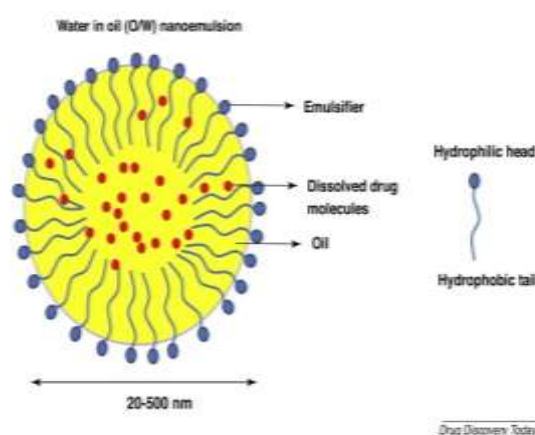


Figure 8: Nanoemulsion.

DIFFERENT TYPES OF POLYMERS USED TO PREPARE TOPICAL ANTIFUNGAL GEL:

1) Gelling agents²⁹

These substances can also be employed as thickeners to improve the consistency of any dose form.

Sr. No.	Gelling agent	Quantity [%]
1)	Carbopol-934	0.5 to 2
2)	Carbopol-940	0.5 to 2
3)	HPMC-2910	2.5
4)	HPMC	3.5
5)	Sodium CMC	1

2) Permeation enhancers²⁹

These are substances that enter the skin and interact with its components to enhance skin permeability temporarily and reversibly.

Sr. No.	Penetration Enhancer	Quantity [%]
1)	Oleic acid	1
2)	Lecithin	5
3)	Urea	10
4)	Isopropyl myristate	5
5)	Linoleic acid	5
6)	Linoleic acid	8
7)	Menthol	5
8)	Cinnamon	8

3) Emulsifier²⁹

Emulsifying compounds are used to manage stability during a shelf life that can range from days for impromptu made emulsions to months or years for commercial preparations. They are also used to enhance emulsification at the time of creation.

Sr. No.	Emulsifier
1)	Polyethylene glycol 40 stearate
2)	Sorbitan monooleate (span 80)
3)	polyoxyethylene sorbitan monooleate (tween 80)
4)	Stearic acid
5)	Sodium stearate

4) The choice of vehicle/solvent³⁰

Solvents are often made of purified water. Co-solvents, including alcohol, glycerol, PG, PEG 400, etc., can be employed to increase the therapeutic agent's solubility in the dosage form and/or to promote drug absorption through the skin.

5) Inclusion of buffers³⁰

Gels with aqueous and hydro alcoholic bases may use buffers to regulate the pH of the formulation. Buffer salt solubility is decreased in hydro alcoholic-based vehicles.

E.g., Phosphate, citrate, etc.

6) Preservatives³⁰

In order to reduce the concentration of free (antimicrobially active) preservative in the preparation, certain preservatives collaborate with the hydrophilic polymers used to make gels.

Therefore, the initial concentration of these preservatives needs to be increased to make up for this.

EVALUATION OF GELS^{30, 31, 32}

1) Homogeneity

The homogeneity of each generated gel was checked after it had been placed in the container using a visual inspection. They underwent inspections to check for aggregates and for outward signs of appearance.

2) Grittiness

All of the formulations were examined under a light microscope to determine whether any particles were present, but none were noticeable. Therefore, it is clear that the gel preparation satisfies the criteria for being free of specific materials and from grittiness as needed for any topical medication.

3) Measurement of pH

Digital pH meters were used to calculate the pH. 1g of gel should be dissolved in 100 ml of purified water and kept for two hours. Carry out the pH measurement in triplicate and determine the average readings.

4) Drug content

100 ml of the suitable solvent were combined with 1g of the gel. Clean the stock solution. Then, using the appropriate dilutions, produce serial dilutions of various concentrations and measure the absorbance. The equation, which was obtained by a linear regression analysis of the calibration curve, was used to calculate the drug content.

5) Viscosity study

A Brookfield Viscometer was used to measure the prepared gel's viscosity. Spindle number 64 was used to rotate the gels at 20 and 30 rpm. The corresponding dial reading for each speed was noted.

6) Spreadability

It shows the size of the region to which the gel spreads easily when applied to the affected area or skin. The spreading value affects the therapeutic effectiveness as well. Spreadability is measured as the amount of time, in seconds, it takes for two slides to separate from the gel that is sandwiched between them when a specific force is applied. Better spreadability is achieved with shorter gap times between two slides. The spreadability is calculated using the below formula.

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

Where,

M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

7) Extrudability study

The formulations are fill in the collapsible tubes, after it was set in the container. Extrudability is measured by the weight in gm required to extrude a 0.5 cm gel ribbon in 10 seconds.

8) Skin irritation studies

For this test, albino mice of either sex weighing 20–22gms were used. The dorsal skin was used. Three days before to the trial, the mice's hair was removed. The animals were split into two batches, and then into two groups within each batch. The gel containing drug was used on test animal. As a control, a piece of cotton wool soaked in saturated medication solution

was put on the back of albino mice. The animals were treated daily for seven days before being evaluated visually for erythema and edema.

9) Globule size and its transport in gel

The Malvern zeta sizer is used to choose globule size and course. The procedure includes dissolving a 1.0 gm test of gel in refined water and vigorously stirring to get homogenous distributing. The resultant test diffusing is to be combined into the zeta sizer photocell.

10) *In-vitro* Diffusion studies

In-vitro diffusion experiments of the produced gel were performed in a Keshary-Chien diffusion cell with a cellophane membrane. As the receptor compartment, one hundred millilitres of phosphate buffer were employed, and 500 mg of gel containing was evenly placed across the cellophane membrane. The donor compartment was kept in contact with the receptor compartment, and the temperature was kept at 37 ± 0.5 °C. At specified time intervals, the solution on the receptor side was stirred by externally driven Teflon coated magnetic bars, and 5 ml of solution from the receptor compartment was pipette out and instantly replaced with fresh 5 ml phosphate buffer. The drug concentration in the receptor fluid was measured spectrophotometrically in comparison to an appropriate blank. The experiment was conducted out three times.

CONCLUSION

Gels are becoming incredibly common since they are more stable and can give controlled release than other semisolid preparations such as creams, ointments, pastes etc. The gel formulation may give improved absorption qualities, increasing the drug's bioavailability. A thorough investigation of the gel formulation stability qualities over a prolonged length of time may enable scope for its therapeutic usage in patients. Because the polymer is water soluble, it forms a water washable gel and has more potential for application as a topical medication delivery dosage form. The primary advantage of topical drug administration is that it allows for the development of high local drug concentrations inside the tissue and its surroundings for improved drug activity. This is especially useful when medicines with short biological half-lives and a limited therapeutic window are used. Clinical data indicates that topical gel is a safe and effective therapy option for the treatment of skin disorders.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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