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A REVIEW ARTICLE ON TOPICAL GEL FOR THE TREATMENT OF SKIN FUNGAL INFECTIONS

[1]Monika.S.Jadhav, [2]Yogeeta.S.Agrawal, [3]Sonia.M.Goyal

[1]R.C.Patel Institute Of Pharmaceutical Education And Research Shirpur District Dhule 425405.

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Abstract:

Topical use of drugs has the advantages of distributing drugs directly to active site and for longer-term activities. Skin is one of the most widely available and accessible parts of the body, and is the primary route of the local distribution system. The topical drug delivery systems include a wide range of pharmaceutical dosage forms such as semi-solid, liquid preparation, sprays, solid powders, gels, creams and ointments. Fungal skin infection is one of the most common troubles faced by dermatological diseases in the world. Local therapy is the most suitable choice for treating skin infections. Formulation and optimization of formulations are key steps to increase therapeutic efficacy. Recently fungal infection of the skin of antifungal drugs is generally used as a predictable cream and gel for treatment. Formulation and optimization of formulations are key steps to increase therapeutic efficacy. The physical and chemical properties of the drug molecule and the type of preparation are the most benificial factors in the local delivery system. Therefore, some new innovations in formulations have been explored in the delivery of antifungal drugs through the target skin site. This review focuses on the research that has already been done on the fungal gels.

Corresponding author:

Monika.S.Jadhav,

R.C.Patel Institute Of Pharmaceutical Education And Research,
Shirpur District Dhule 425405.
Monikajadhav3029@gmail.com, soniagoyalfeb95@gmail.com

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INTRODUCTION:

Topical application of drugs to the skin by applying gels, ointments, creams directly to the outer surface of the body by rubbing and spreading. [1] Local preparations are formulations that are applied directly to an outer surface of the body by spraying, rubbing, spraying or infusing. The topical route of administration is used to produce regional effects for treating skin diseases or to induce systemic drug effects. In the main group of semi-solid preparations, the use of transparent gels expands in both cosmetics and pharmaceuticals. [2] Topical application is an attractive way for systemic and local treatment. The delivery of drugs to the skin is accepted as an effective remedy for local skin diseases.[3] The current application refers to the use of medications that are applied on a specific site or within the body. Most ophthalmic administration means applying to body surfaces, such as in the skin or mucosa, to treat spices by a broad range of classes, including, gels, foams, lotions, creams and ointments and so many topical drugs are epicutaneous, which means they are applied directly to the site of skin. [4] Fungal skin infections are one of the most regular dermatological diseases in the world. Local treatment is an attractive option for the treatment of skin infections infections as it has the advantage of targeting the drug target site and reducing the risk of systemic side effects. [4, 5] Fungal infection of the skin is nowadays one of the common dermatological problems. Physicians have a wide option for treatment from a solid dose to a semi-solid dosage form and a liquid dosage form. Among the local preparation, apparent transparent gels are generally accepted in both pharmaceuticals and cosmetics. [6] Incidence of surface fungal infections of the hair, nails, and skin has increased worldwide. It is probable that regarding 40 million peoples have fungal skin infections in developing and developed nations. The development of fungal infections can be rapid and severe due to co-ordination with immune function. [5] The incidence of fungal skin infections has increased rapidly, affecting about 40 million people worldwide. A wide variety of antifungal medicines is used to effectively treat numerous dermatological infections. Local treatment of skin fungal infections has established to be very useful due to a variety of factors such as targeting the site of infection, minimizing systemic side effects, increasing treatment efficacy, and increasing patient compliance. Topical antifungal agents are an important aid in the treatment of dermatophytosis. Also, specific situations such as dermatophytes during pregnancy and babies often require local therapy. Several new topical antifungal agents and newer formulations promise increased effectiveness of topical dermatophytosis therapy.[8] Topical agents that are commonly used to treat fungal skin infections are usually prepared as creams, lotions or gels. They either demonstrate fungistatic or fungicidal effects depending on the agent being delivered Because of the effects of fungicides that are less effective than their lipid compounds, it is the preferred agent. Another profit of the local formulation is that it avoids drug interactions that are more widespread in oral administration.[9] Local treatment of fungal skin infections has several superiorities, including locally targeted infection, increasing the efficacy of treatment, reducing the risk of side effects and high patient compliance. Various types of highly effective fungal compounds are used to treat skin infections. Gels often provide quick release of the drug, even though the water's medication is comparable to cream and ointments. They are highly biocompatible with a lower risk of inflammation or side effects, are easily administered and should not be removed. Dermatological use of gel have several favorable properties such as being, greaseless, easily removed, easily spreadable, thixotropic, emollient, non-staining, and miscile or water soluble and compatible with several excipients.[2]

Clinical fungal infections are typically divided into four types:

(1) superficial, together with tinea versicolor, piedra and tinea nigra; (2) skin including onychomycosis, trichophytis, tinea corporis, tinea barbae, tinea pedis and candidiasis of skin, mucous membranes and nails; (3) subcutaneously, including , sporotrichosis and chromoblastomycosis; and (4) systemic, including North American cryptococcosis and blastomycosis. Surface fungal skin infections are defined as infections in which the pathogen is confined to the stratum corneum, with little or no tissue response. Surface and skin infections are sometimes considered superficial. [11]

Classification of Antifungal drugs according to their chemical structure as: azole antifungal, polyene antifungal, allylamine antifungal, echinocandin and others.[2].

Topical application is an attractive way for systemic and local treatment. The delivery of drugs to the skin is accepted as an effective remedy for local skin diseases. It can go deeper into the skin and thus give better absorption. Topical application has many advantages over conventional dosage forms. U.S.P. Gels defined as a semi-solid system consisting of a dispersion composed of either a tiny inorganic particle or a large organic molecule surrounding and penetrating a liquid. The gels consist of a biphasic system in which the inorganic particles do not

dissolve, but only disperse in the continuous phase and the large organic particles dissolve in a continuous phase randomly wrapped in the flexible circuits.

PROPERTIES OF GELS:[3,14]

1. The gelling agent should create a sensitive solid shape during storage that easily breaks when exposed to shear forces produced by squeezing the tube, trembling the bottle or at the time of topical application.
2. The visible viscosity or strength of gel increased by increasing the effective density of the gel. However, a rise in temperature may increase or decrease the apparent viscosity, depending on the molecular interactions between the polymer and solvent.
3. Preferably, the gelling agent for cosmetic or pharmaceutical use should be safe, inert, and should not respond with other components of formulation.
4. The gelling agent incorporated in the preparation during storage must produce a rational solid character that can be effortlessly broken down when subjected to shear forces generated by trembling the bottle, pressurizing the tube or during topical application.
5. The topical gel must not be sticky.
6. The ophthalmic gel should be sterile.
7. They exhibit the mechanical properties of the solid state.

CHARACTERISTICS OF GEL:[3,12,14]

A) Swelling:

When the gelling agent is held in contact with a liquid dissolving it, then a significant amount of liquid is absorbed by the agent and the volume is increased. This process is called swelling. This incident occurs when the solvent penetrates into the matrix. The gel-gel interactions are replaced with gel solvent interactions. The extent of inflammation depends on the number of connections between the molecules, the gelling agents and the strength of these bonds.

B) Syneresis:

Many gels often spontaneously succumb to standing and emit some liquid media. This effect is called as synesthesia. The degree of synesthesia is increased by decreasing the gelling agent concentration. The onset of sinergesis indicates that the original gel is thermodynamically unstable. The mechanism of contraction is associated with the relaxation of the elastic stress that develops during gelling. When these stresses are alleviated, the available interstitial space for the solvent is reduced by displacing the liquid.

C) Ageing:

Colloidal systems usually show slow spontaneous aggregation. This process is called aging. In the gels aging leads to the steady formation of a thicker network of gelling agent.

D) Structure

The hardness of the gel results from the presence of a mesh formed by the binding of particles to the gelling agents. The character of the particle and the stress, their straightening and the decrease of the flow resistance.

E) Rheology:

Dispersion of flocculated solids and Solutions of gelling agents are pseudoplastic, i.e. exhibiting non-Newtonian flow performance is characterized by a reduce in viscosity with an enhance in shear rate. The weak structure of the inorganic particles dispersed in water is destroyed by the applied shear stress due to the breakdown of the interparticle connection, showing a greater similarity to flow. Likewise, for macromolecules, the applied shear stress aligns the molecules in the way of the organic (single-phase system)

Advantage of Gel to Other Dosage Form:[4]

1. The topical gel is easy to apply and easy to remove.
2. Topical gel to achieve stable and controlled plasma level and reduces the likelihood of over dosage.
3. Gel is a quick relief and fewer side effects are frequently used by a patient who cannot take oral medicines.
4. Gel is a quick relief and fewer side effects are often used by a patient who cannot take oral medicines.
5. Topical gel reduces the frequency of dosing of the drug.
6. Helps to provide a consistent blood level with a lower dose of drug through continuous drug delivery.
7. Avoid inconsistency with i.v. therapy

It is used to improve the permeability of the skin of the drug, for example in the case of a hydrophilic drug.

9. Avoid the metabolism of the first passage.
10. Ensure continued therapy with one application.
11. In case of vomiting and nausea, it provides an alternative route when oral therapy is not possible
12. Dose reduction compared to oral dosage form.
13. Avoid the difficulty of absorbing GI drugs caused by pH, enzyme activity and drug interaction with foods, beverages and other medicines that are administered orally.

Disadvantage of Gel to Other Dosage Form:[4]

1. Topical preparation is comparatively expensive compared to predictable dosage form.

2. Route is controlled by the surface area of delivery system and the dose that desires to be administering in the chronic state of disease.

CLASSIFICATION OF GEL:[3,12,14]

Gels are classified as colloidal phases, the character of the solvent used, rheological properties and physical nature.

1. Based on colloidal phases

They are classified into Inorganic (two phase system) type of force that is dependable for the linkages establish the structure of the complex and the characteristics of the gel.

Two phase system

The structure of the gel in this method is not constantly stable. They should be thixotropically forming semi-solids in position and become liquid under stirring.

Single-phase system

They consist of huge organic molecules presented on twined strands dissolved in a constant phase. This large organic molecule, either natural or synthetic polymers, is called a gel-forming, they tend to obstruct with each other by their random motion or interconnected by the forces of Vander Waals.

2. Based on nature of solvent

Hydro gels (water based)

Here they contain water in their subsequent liquid phase, eg. Bentonite, gelatin, cellulose extract, carbonate and potassium chloride. Hydrogel is a network of hydrophilic polymer chains that have been identified as colloidal gels, in which the water is dispersed. They are highly polar or synthetic. They also have some flexibility on the natural tissue because of their considerable amount of water.

Uses for hydrogels-

1. Sustained-release drug delivery methods
2. Rectal drug delivery and interpretation
3. As frame in tissue manufacturing
4. As environment reactivity detector
5. Contact lenses (polymacon, silicone hydrogels)
6. ECG medical electrode
7. Dressing of mending

E.g., Gelatin, carpooler, Bentonite magma cellulose derivatives and gel of poloxamer.

Organic Gels (with a non-aqueous solvent)

These have a constant phase for the non-aqueous solvent. E.g. plastibase (polyethylene of low molecular wt. dissolved in mineral oil & short Cooled) Olag (aerosol) gel and dispersion of metallic stearate in oils.

Xerogels

Solid gels with a low concentration of solvents are called as xerogels. They are obtained by solvent evaporation or freeze-drying, leaving the gel frame behind upon contact with fresh liquid, they swell and can be recovered. For example, tragacanth bands, acacia breakdown? -Cyclodextrin, dry cellulose and polystyrene.

3. Based on rheological properties

Generally, gels exhibit non-Newton flow properties. They are classified as,

(a) Plastic gels

b) Pseudoplastic gels

c) Thixotropic gels.

(a) Plastic gels

For example, Bingham bodies, flocculated aluminum hydroxide suspensions show a plastic flow, and the graph of the reogram gives the value of gelling yield over which the elastic gel alter and starts to flow.

(b) Pseudo-plastic gels

For example - Liquid dispersion of tragacanth, Na CMC, sodium alginate, Na CMC and others. Shows a pseudoplastic flow. The viscosity of these gels reduces with enhance shear rate without yielding value. The reogram is the result of a cut-off on long-chain molecules of linear polymers. As the shear stress increases, the undiluted molecules starts to support their long alliance in the way of the gel release gel release flow.

(c) Thixotropic gels

The bonds among the particles in these gels are very fragile and can be destroyed by shaking. The resulting solution will return to the gel as the particles smash together and bind again (reversible isothermal gel-gel transformation). This happens in a non-spherical colloidal system to build a frame-like structure. For example: bentonite, kaolin, and agar.

4. Based on physical nature

(a) Elastic gels

Agar, pectin, guar gum and alginate gels show elastic behavior. Fibrous molecules bind at the position of attachment with relatively fragile bonds such as dipole attraction and hydrogen bonds. If the molecule possesses free –COOH group then additional bonding takes place by salt bridge of type –COO-X-COO between two adjacent strand networks. E.g.: Alginate and Carbapol.

(b) Rigid gels
This can be formed by a macromolecule in which the frame is connected by a primary rolling link. For example: In silicagel, the silicic acid molecules are held by a Si-O-Si-O bond to obtain a polymeric structure having a pores network.

ADDITIVES USED IN GEL FORMULATION:[12]

Gelling agents:
The gelling agent is a hydrocolloid which produces a thixotrophic consistency of the gel. Gelling agents are organic in nature and are also called as hardeners or thickeners and stabilizers. Gelling agents are further soluble in frozen water than with hot water. Gelling agents such as poloxamers and methylcellulose have improved solubility in frozen water, whereas, gelatin and bentonite, sodium carboxymethylcellulose are further soluble in water in boiling water. Gelling agents need a pH adjustment chemical or neutralizer to generate the gel later than the agent has damp in the dispersing medium. This agent is used at a 0.5 to 10% concentration build upon on the agent, which most gelling agents necessitate 24-48 hours for entire hydration and transparency and maximum viscosity. It is accesible to add the active drug earlier to the gel is created if the drug does not hamper with the gel formation. The thickness of the gelling agents in the gelling layer be inside range of around 1000 cps to about 100,000 cps.

Humectant and cosolvants in gel:
Moisturizer is a material that consume or with the help of another substance to preserve moisture, such as glycerol. Moisturizer is a hygroscopic substance. It is frequently a molecule with numerous hydrophilic groups, most regularly hydroxyl groups, but carboxyl groups and amines may also be encountered, sometimes esterified; the affinity for the formation of hydrogen bonds with water molecules is crucial. Examples: Glycerin, propylene glycol (E1520) and glyceryl triacetate (EI5I8). Other may be polyols such as sorbitol (E420), xylitol or polymer polyols such as natural extracts such as cell (E999) or polydextrose (E1 200), urea or lactic acid. Lithium chloride is an excellent moisturizer.

Stabilizers:
Bases and medicaments susceptible to heavy metals are at times protected by chelating agent, such as E.D.T.A. (Ethylene diamine tetra acetic acid)

Methods of preparation of hydro-gels[12]
1. Fusion Method
2. Cold Method
3. Dispersion Method

Even if the size of the preparation is large or small, the semi-solid dosage forms are produced by one of the two general methods. Or they are made at high temperature by mixing liquid or liquefied components and dispersing the solids (synthesis method) or the drug is included in the already semi-solid base (cold inclusion). the drug is added to the already prepared semi-solid base or when the vehicle itself is heat labile, as is the case with plastibase.

The preparation of gels may occupy a fusion process or may have need of a special procedure depending on the gelling agent occupied. The Tragacanth system should be prepared at low temperature due to the extreme heat resistance of this natural resin. On the further hand, it is accecible to disperse methylcellulose in hot than cold water. Carbopol gels in a unique procedure. The polymer material is diffuse in an acid like medium. When the dispersion is the same, gelling is induced by neutralizing the system with an inorganic base (aqueous system) or an amine such as triethanolamine. This ionizes the acidic functional groups of the polymer by drawing the polymer into a colloidal solution, thereby forming the necessary structural matrix.

Dispersion method:
Disperse the polymers in distilled water by continuous stirring. Warm the colloidal viscous dispersion to get a gel. Dissolve the drug in solvent and incorporate into gel by stirring followed by penetration enhancer. Add pH adjustifier to modify the buffering capacity of the gel, if necessary.

ANATOMY OF SKIN: [3]

Skin is the major organ of the body. Its large area in direct contact with the environment offers huge opportunities for drug delivery. The human skin is organized in two separate layers, namely the epidermis and dermis directly below it (Figure 1). The strongly vascular dermis is composed of a connective tissue matrix containing the nerves, hair follicles, pseudobulum units and sweat glands. Skin is also needed to regulate heat, feel and take vitamin D. The highly vascular dermis is ended up of a connective tissue matrix consist of the nerves, hair follicles, piloseactic units and sweat glands. The epidermis is avascular, and its outer layer, the corneous layer, consists of keratin-rich dead epidermal cells, known corneocytes, surrounded in a matrix rich in lipids.

Stratum corneum is the major blockade to drug penetration, especially for water-soluble compounds. Hence, the release of drugs throughout the stratum

corneum became an essence in the arrangement of various dermal delivery systems.

The skin also helps adjust body temperature, assemble sensory information from the atmosphere, stores water, vitamin D and fat and plays a responsibility in the immune system that protects us from diseases.

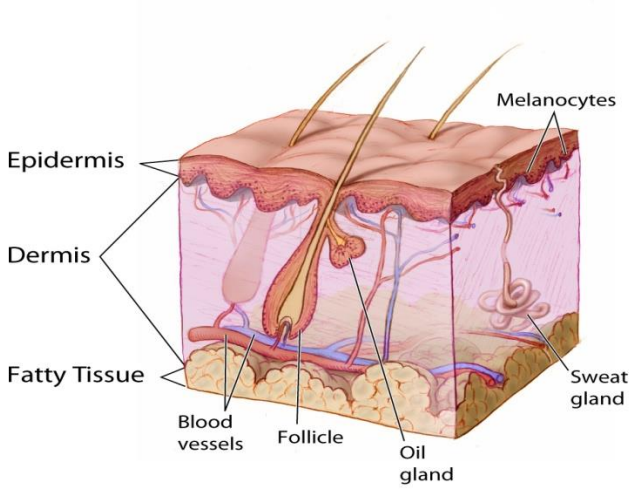

Fig 1: Human skin

Fungal skin infections:

These types of skin fungal infections are lead by fungi and most likely develop in bodies' wet areas such as legs or underarms. Some fungal infections are not contagious and these infections are usually not life-threatening. Fungal infections are often difficult to treat. Treatment often includes topical (applied to the nails or skin) or oral (ingestion) of medicines called antifungal. The type of fungicide used depends on the definite type of fungus (eg Tinea, candida) that cause the infectionDifferent types of fungal infections:

1. Athlete's foot
2. Yeast infection
3. Ringworm
4. Nail fungus
5. Oral thrush
6. Diaper rash

Tinea Pedis (Athlete's foot)	Candida (Yeast infection)	Tinea Corporis (Ringworm)	Onychomycosis (Fungal Infection of skin)
1. Cracking, peeling and scaling of foot 2.Redness/blisters, Softening ,breaking down of skin 3.Itching burning or both	1.Itching and swelling around vagina 2.Burning sensation /pain during urination 3.Redness and soreness in and around vagina 4.Unusual vaginal discharge	1.Itchy red ring shaped patch than can be scaly	1.Nail discoloration 2.Nail flaking 3.Nail Thickening

Fungal infection:[4]
A fungal infection called mycoses, which are common and diverse ecological and physiological situation, can donate to the expansion of fungal diseases. Breathing of fungal spores or limited to small area immigration on the skin may cause permanent infections; therefore mycosis often begins on the skin or in lungs. Fungal infection is the 4th mainly numerous disease in 2010, affecting 984 millions of people. Individuals treated with antibiotics or those with a damaged immune system are at larger risk of rising fungal infections. This is the case for HIV / AIDS patients, steroid patients and patients receiving chemotherapy. A patient suffering from diabetes also has a tendency to develop fungal infections. Very young and very old people are also risky groups. Although all of them are at possibility of developing fungal skin infections, the chance of these groups is higher.

Antifungal Drugs Available In Gel:[4]

S.NO.	GELS
1.	Clotrimazole
2.	Amphotericin B
3.	Fluconazole
4.	Itraconazole
5.	Mometasone
6.	Tioconazole
7.	Ketoconazole
8.	Terbinafine
9.	Fucidic acid

They are used to delight mycoses. Build upon on the nature of contamination, the drug can be used. An example of antifungal agents is: fluconazole, which is the basis of many anti-fungal treatments without prescription. Another example is amphotericin B, which is very effective and is used to diagnose fungal infections that show resistance to other treatments and are treated with blood vessels. Medicines for the treatment of skin infections include azoles: terbinafine, ketoconazole, itraconazole and others.

Antifungal Therapy Drug Delivery via Skin:[4]
The drug delivered passively throughout the skin should contain adequate a molecular weight about <500 Da and lipophilicity. Limited drugs complement these needs for percutaneous delivery. The external route of administration, having the main purpose after delivery of such drugs through the skin, is to achieve better systemic absorption or topical treatment. The intravenous route can avoid gastrointestinal side effects, but it is persistent and not comfortable compared to a barrier layer as a topical preparation that has better patient compliance and can be used on its own. After skin application, antimycotic drugs should achieve efficient therapeutic levels in the possible epidermis. Transdermal drug delivery is the most challenging due to stratum corneum and various methods are used to increase drug permeability. Different approaches are used as a nanoparticulate carrier such as nanostructured lipid carriers, solid lipid nanoparticles, , vesicular carriers such as liposomes, ethosomes, nithosomes and transferosomes, colloidal particles such as microemulsions, micelles, nanomulsions.

Different routes of administration of antifungal gel[15]
1. Topical routes of administration
2. Ophthalmic routes of administration
3. Vaginal routes of administration
4. Buccal routes of administration

Topical routes of administration:
Topical formulations are a formula that is applied directly to the outer surface of the body by rubbing, spraying, spraying or infusing. The Local route of administration is either used to produce a restricted effect for the healing of fungal skin disorders or to induce systemic drug effects. In the main group of semi-solid preparations, make use of apparent gels expand in both cosmetics and pharmaceuticals.

Uses:
Used in the treatment of a variety of dermatological skin infections such as skin infection with tinea and candidal.

Ophthalmic routes of administration:
Over the previous few decades, significant awareness has been concentrate on the growth of controlled and sustainable drug delivery systems. The exclusive arrangement of the eye limits the penetration of the

drug molecules at the site of achievement. Drug deliverance to the eye can be classified as a whole in the front and rear segments. Predictable systems such as ointments, suspensions and eye drop cannot be measured most favorable in the treatment of vision, threatening eye diseases. Widespread research has been accepted out in the design of polymer delivery systems. The enlargement of gel systems in situ has received significant attention. In situ gels are a delivery system that can be placed as drop of eye and suffer immediate gelling when in contact with the eye. *In situ*-forming hydrogels are in the liquid state when they are placed and pass a phase transition into the ophthalmic cavity to form a visco-elastic gel and this contribute a response to diversity in the environment. Gel systems are enhanced preserved in the eye than predictable eye drops and are better permitted by patients than inserts. Like ointments, it is difficult for some patients to apply gels. In this respect, gels in situ are fascinating as they are expediently dropped as a solution in the conjunctival sac where they undergo a gel evolution with their favorable habitation. The transition of sol-gel-sol arises as a effect of physical and chemical change induced by the physiological atmosphere. Ophthalmic gels in situ arranged by the pH-triggered method are described here in; the pH-triggered in-situ system of gelling is a low viscosity polymer dispersion in water that undergoes unprompted gelation and coagulation after beverage in a conjunctival cul-de-sac.

Uses:
Ophthalmic in-situ gel is usually more convenient than insoluble or solvent placing and less unclear vision than ointment. Reduced bioavailability due to increased overdose of residence reduces nasolacrimal sewerage of the drug, which causes unwanted side effects occurring due to complete absorption of the drug over the nasolated canal, has been reduced. The effect of the drug is prolonged, so frequent administration of the drug is not required. The principal benefit of this formulation is the opportunity of administering correct and reproducible amounts, unlike already jelly compositions, and, moreover, enhancing pre-retentive retention.

Vaginal routes of administration:
Vaginal delivery is an essential route for drug administration for both systemic illnesses and local. The vaginal route has a few compensation owing to its big surface area, the rich blood supply, the escaping of the primary pass effect, the relatively high permeability for many drugs and self-locking. Conventional commercial provision such as creams, foams, gels are known to be present in the vaginal cavity for a comparatively little period of time due to self-cleaning of the vaginal tract, and frequently necessitate multiple daily doses to provide the preferred beneficial effect. The vaginal route arrives to be very appropriate for bioadhesive drug delivery method to preserve drugs to treat mainly local situation or for contraceptive use. In appropriate, safety across sexually transmitted diseases is critical. Bioadhesive beneficial systems in the shape of semi-solid and solid dosage forms have been developed to extend the habitation time in the vaginal void.

Uses:
This drug is used to diagnose some types of bacterial infections in the vagina. This can assist to reduce strain, itching and other symptoms. Vandazole (metronidazole) is a vaginal gel used to diagnose bacterial vaginosis in pregnant women. Vandazole is meant for vaginal use simply and supposed not be located in the eyes, skin or mouth. While using vandazole, the use of other vaginal products and vaginal intercourse supposed to be avoided.

Buccal routes of administration:
The buccal pathways have been worn to convey drugs, such as some antifungal medicines that are metabolized in the initial pass. Fluoride rinses and gels used in few regimens for oral care are mostly used for antibacterial activity alongside gingival plaque; they are not used particularly to prevent caries. Candidate prophylaxis typically involves cleaning with nystatin or clotrimazole. If patients have entirely of dry oral cavity, the crumbs are not as efficient as they do not liquefy well in a dry environment. Washing amphotericin-B is also sometimes used instead of nystatin. Fluconazole may be worn for prophylaxis of the applicant or for the healing of assumed candidiasis.

Use:
Oral gel is used to diagnose fungal infections in the throat, mouth and gastrointestinal tract, Likewise, candida candidiasis caused by Candida yeast; in addition to avoid the extend of infection.

Gelling Systems-polymeric Carriers [4, 10]
1. Microsponge and Nanosponge:
The nanosonge and microsponge are used in this transporter system for the liberation of antifungal drugs. Microsponge for controlled discharge of local agents, it subsists of macroporous pearls with a diameter of 10-25 μm. This kind of technology is beneficial, including suitable drug grasp, enhanced stability and increased elasticity of formulation. The investigate study concludes that the nanosponge and microsponge systems are not irritating, non-allergenic,

non-mutagenic, and non-toxic. Nanosponge of econazole nitrate consists of polyvinyl alcohol: ethyl cellulose (3: 2) is prepared with Carbopol 934 NF as a hydrogel using diverse concentrations of penetration enhancers like propylene glycol and N-methyl-2-pyrrolidone. The study display that econazole nitrate is steady in the delivery of nanosponge and there is no interaction with other drugs.

2. Amphiphilic Gels:

Amphiphilic gels containing non-ionic surfactants in which one surfactant causes gelation of another. Amphiphilic gels are too used for transdermal and topical carriers for vaccines and drugs; it is supposed that the surfactant character of the gels should enhance penetration of the active agents into and or throughout the skin. The surfactants which are used in the gels are non-ionic, representative that the gels are able to be used as transdermal or topical carriers with not causing skin irritation. An amphiphilic gel with recognized surfactants such as Tween 20 and Tween 80 is prepared and a steady, safe and efficient drug delivery system (more than 90%) of fluconazole is observed.

3. Emulgels:

Gel-based emulsifiers or emulsions are also used for local drug delivery systems. The emulsifiers contain a

2. **Semisynthetic polymers:** Cellulose subordinatessuch as ethylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxyethyl cellulose, magnesium aluminum silicate (Veegum®), methylcellulose, sodium alginate etc.
3. **Synthetic polymers:** Polyvinyl alcohol, poloxamers (Pluronics®), Carbopols® (now called as carbomers).

Cellulose polymers:

A. Methylcellulose (MC) - used at 1500 cps. It composing thinner gels, but with high drug defiance. It is good with alcohol (70%), water, and propylene glycol (half). It is boosted with 1/3 fizzy heated water, after that when the left over splashing water is turned on like frozen water or ice chips.
B. Hydroxypropylcellulose - Not too bad a gelling agent if you rely on 15% or a more extraordinary determine of soluble feature to divide the dynamic solution.
C. Hydroxypropylmethylcellulose - Is a superior to the regular gel-forming organizer for time release.
D. Carboxylmethylcellulose - Used as part of centralizations from 4 to 6% of the normal gel transfer thickness. It is against alcohol. Glycerin

dual discharge control system (gel and emulsion). Also, the constancy of the emulsion enhances when integrated into the gel. These emulsifiers contain great compensation of new vesicular systems in addition to predictable systems in diverse aspects. Emulsifiers for dermatological use having characteristics such as oil-free, thixotropic, easily spreading, softening, easily removable non-oil-soluble, shelf life, water-soluble longer, transparent, bio-friendly, pleasant appearance and a variety of penetration enhancers used in emulsifiers that can improve the effect so that emulsifiers is capable to be used as good local delivery systems. Emulsifiers used to enter antifungal drugs into the skin. Clotrimazole is formulated using two types of copolymers and acrylic acid, jojoba oil is used, representative high drug release and excellent stability.

Different Types Of Polymers Used To Prepare Topical Antifungal Gel:[4]

Types of gelling agents:

1. Here is a selection of polymers acting as gelling agents **Natural polymers:** Proteins such as casein, egg protein, gelatin, collagen, polysaccharides such as acacia, guar gum, pectin , tragacanth, grain gum, starch, xanthan gum, succinoglycone, dextran, etc.
   may be additional from time to time to stay away from drying.

Carbomers:

Carbomer is not a particular name for collecting polymers called as Carbopol®. Originally, Carbopols® was used as element of the mid-1950s. As a public occurrence, they are dry powders that have higher bulk density and form acidic water streams (pH about 3.0). They are thickened at higher pHs (about 5 or 6). In the same way, they will swell up the pH up to 1,000 times the further volume. Their responses are from 0 to 80,000 centipoise (cps).

Poloxamers (Pluronics®)

These are copolymers of polyoxypropylene and polyoxyethylene. They will form boil over gels in the center, accomplishment from 15% to half. This means they are liquid at a cool (cooler) temperature; though, are gels at body temperature or room. Poloxameric copolymers are colorless, waxy granules which cover apparent liquids when dispersed in frozen water or cooled to 0-10 ° C overnight. "Pluronic® F-127 is usually unified with a isopropyl palmitate and lecithin answer for build what is called as a "PLO gel."

Polymer Name	Viscosity	Properties
Carbopol®910	3,000-7,000	• Will provide a low reliability formulation and efficient in low fixations.
Carbopol®934	30,500-39,400	•Effective in thick information, e.g., emulsions, suspensions, transdermals, sustained release formulations, and topicals.
Carbopol®934P	29,400-39,400	• Similar properties as 934, though probable for pharmaceutical plans. • "P" = extraordinarily purified product
Carbopol®940	40,000-60,000	•Efficient in thick formulations. •Very great clearness in hydro alcoholic topical gels or water •Forms apparent gels with hydro alcoholic frameworks.
Carbopol®941	4,000-11,000	•Produces low reliability gels. •Very great clearness.

Marketed Product of Antifungal Gel:[4]

BRAND NAME	INGREDIENTS COMPOSITION	MANUFACTURING
Fona plus gel	Adaplane benzoyl gel	Square pharm.pvt.
Fungi care liquid gel	Clotrimazole	Alva-Amcopharm.com
Acnif-AD	Adaplane& Clindamycin phosphate	Posmip
Candid gel	Clotrimazole	Glenmark
Gelorn oral gel	Miconazole	Square pharm.pvt.
Deriva MS Aq.gel	Adaplane	Glenmark
Fungirex gel	Miconazole nitrate	Dermarex healthcare India pvt.ltd.
Xologel	Ketoconazole	Stiefellab.Inc.
Candid-CL gel	Clotriamazole& clindamycin phosphate	Glenmark
Amfy gel	Amphotricin B	Intas
Tyza M gel	Mometosonefurote&Terbinafide hydrochloride	Abott
Candid-V-gel	Clotriamzole	Glenmark
Zocon	fluconazole	FDC limited
Dkgel	Miconazole nitrate	Hagde&hagdepharma

PREPARATION OF GELS: [3, 4, 14,]

The gels are usually on an industrialized scale, prepared at room temperature. though, few of the polymers necessitate special treatment earlier than processing. The gels can be formulated by the following methods.

1. Thermal changes
2. Flocculation
3. Chemical reaction

1) Thermal changes:
Solvated polymers (lipophilic colloids), when expose to thermal changes, cause gelatin. Many hydrogen formers are further soluble in hot than chilly water. If the temperature decreases, the amount of hydration decreases and gelatin is produced. (Cooling a concentrated boiling solution will result in a gel).
For example: - Gelatin, agar sodium oleate, guar gum, and cellulose derivatives and others. Increasing the temperature of these solutions will disturb the hydrogen bond and decrease the solubility that will cause gelling. Therefore, this method cannot be conventional for the preparation of gels as a common method.

2) Flocculation:
Gelling is achieved here by adding only enough salt to precipitate to obtain an age but inadequate to achieve complete precipitation. It is essential to ensure quick mixing to avoid the local elevated concentration of the precipitant. For example: a solution of polystyrene, ethylcellulose in benzene can be gelled by quick mixing with appropriate amounts of a non-solvent, such as petroleum ether. The adding up of salts to the hydrophobic solution results in coagulation and infrequently gelling occurs. The gels created by the flocculation method are thixotropic behavior. Hydrophilic colloids such as proteins, gelatin, and acacia are only affected by elevated concentrations of electrolytes when the effect is to "suck", the colloid and the gel do not become visible.

3) Chemical reaction:
In this method, the gel is achieved by chemical interaction between the solvent and the solute.
For example: an aluminum hydroxide gel can be prepared by reacting in an aqueous solution of sodium carbonate and aluminum salt, with an increased concentration of the reagents most important to a gel structure. Several other examples include a chemical reaction between cyanoacrylates with PVA, glycidol ether (Glycidol), toluene diisocyanates (TDI), isocyanate (MDI), methane diphenyl crosslinks of the polymer chain

EVALUATION PARAMETERS OF GELS:[3,12,14]

Clarity:
The clarity of the composition is determined by a visual check under a white and black background and is classified as follows; cloudy: +, clear: ++, very clear (glass): +++.

Measurement of pH:
The pH of diverse gel formulations was determined using a digital pH meter. In 100 ml of condense water one gram of gel is diffuse and reserved for two hours. The pH of each formulation is calculated three times and the indicate values are calculated.

Drug content:
1 g of the equipped gel is mixed with 100 ml of an appropriate solvent. Aliquots of varied concentrations are achieved by proper dilutions after filtration of the absorbance and stock solution is deliberate. The drug content is calculated using the equation access by the calibration curve of linear regression analysis.

Viscosity study:
The viscosity of the ready gel was measured using a Brookfield viscometer. The gels are rotated at 0.3, 0.6 and 1.5 revolutions per minute. At each speed the equivalent analysis of the disk was noted. The gel viscosity is obtained by multiplying the numeral digit by a given in the Brookfield viscometer catalogs.

Spreadability:
It shows the extent to which the gel easily spreads when applied to the affected part or skin. The therapeutical activity of the formulation also depends on its distribution value. The spreadability is assert as the time in seconds taken from two slip slides from the gel that is placed among the slides beneath the way of a certain load. The less time necessary to split two slides is better spread.
Calculated by the formula:
$S = M. L / T$
Where, S = Spreadability. L = Length moved on the glass slide. M = Weight tide to upper slideT = Time required to separate the slider completely apart.

Extrudability study:
After the gels were located in the container, the compositions were filled into the folding tubes. The extrudability of the composition is determined with esteem to the weight in grams essential for extruding at 0.5 cm. gel strip for 10 seconds.

Homogeneity:
Once the gels were positioned in the container, all residential gels were experienced for homogeneity via visual examination. They were tested for their presence of aggregates and appearance.

Grittiness:

All compositions were evaluated microscopically meant for the occurrence of any considerable particles that are observable under a light microscope. Hence, obviously, the gel-preparation fulfills the requirement of freedom from a exacting matter and a aspiration to bake for any local preparation.

Microbiological measure:
Ditch plate is able to be used on the portion. This is a approach used to evaluate the fungistatic or bacteriostatic development of the compound. It usually binds for semi-hard definitions. The officially Sabouraud's, agar dried plate which are formally used. Three grams of the orchestrated gel are located in a drain cut in the plaque. Typically organized public circles are placed on agar at the right end of the trench to the border of the slab. After 18 to 24 hours at 25 ° C, parasite development was observed. In one second, the obstacle of speed is measured as it is then taken.
% inhibition=L2/L1 × 100Where; L1=complete length of the streaked culture, and L2=length of inhibition.

Skin irritation study:
1. Guinea pigs (400-500 g) of together sexes were used to test skin irritation. Animals are reserved on standard nourish supply and have free access to water. The animals are set aside under standard conditions. The hair is shaved from the rear of guinea pigs and the region of 4 cm2 is marked on both sides, one side serves as a control though the other side is a test. Apply the gel (500 mg / guinea pig) twice a day for 7 days and place for each susceptibility and the reaction, if any, is classified as 0, 1, 2, 3 for lack of response, mild erythema with patches, moderate or poorly merging but irregular erythema and ruthless erythema with or without edema, respectively.

2. Patch Test
The gel is attached to properly shaved skin of rodents and its antagonistic effect such as shadow change, a change in skin morphology should be considered within 24 hours. The aggregate disposition of 8 rats can be used for the study. If it does not worry, it indicates that the test has passed. If skin disorders occur in other than 2 rats, the test should be rethought.

In vitro Diffusion studies:
Diffusion studies of the prepared gels can be performed in a Franz diffusion cell to investigate the release of gel solubility throughout a cellophane membrane. A gel sample (0.5 g) was taken in a cellophane membrane and the diffusion assays were run at 37 ± 1 using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample is withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hours and each sample is replaced by an equal volume of fresh reconstitution medium. The samples were next analyzed for the drug content using phosphate buffer as a blank sample.

Stability:
Stability studies were attended for the whole gel formulation via a freeze-thaw cycle. Here, syneresis is observed by expose the product at 4 ° C for 1 month, then at 25 ° C for 1 month and then at 40 ° C for 1 month. The gel is then exposed to room temperature and the release of liquid exudates is noted.

CONCLUSION:
The topical treatment of skin infection is mainly used because of its elevation over oral treatment to avoid systemic side effects, to target the site of infection to administer the formulation, and to increase patient consent. Local preparations are used for restricted effects at the site of their administration by penetrating the drug into the fundamental layers of the mucous membranes or skin. Formulation of a local product plays a most important role in penetrating the drug through the skin. Gels are becoming more popular today because they are steadier and can also supply controlled release than other semi-solids such as creams, pastes, ointments, and so on. The gel formulation can give better absorption characteristics and thus improve the bioavailability of the drug. Clinical data suggests that topical gel is a harmless and efficient treatment choice for treating skin diseases.

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