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REVIEW ON ANTIFUNGAL NANOGEL FOR SKIN INFECTIONS

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ABSTRACT

Antifungal nanogel used for the treatment of fungal infections such as candiasis, dermatitis, dermatophytosis and congenital candidiasis which is a skin infection. it is used for targeted site-specific drug delivery.it is used for topical route of delivery which helps in the achievement of efficacy with lower total daily dosage of drug by continuous drug input. it has properties such as their hydrophilic nature, biocompatibility and capacity of absorbing large quantities of water because of this it raised the attention of scientist. antifungal nanogel indicates that these are convenient, easy to apply and it improves patient compliance. It also improves the physiological and pharmacological response.

KEYWORDS: fungal infection, hydrophilic nature, biocompatibility, physiological and pharmacological response.

INTRODUCTION

Antifungal nanogel is commonly applied topically to the skin to cure fungal infections. The drug is mainly used for the treatment mycosis skin disease and candidiasis, congenital candidiasis intertrigo, dermatitis and dermatophytosis. (1)

Fungal infection is continuously growing skin disease throughout the world. During the initial phase fungi firstly attack the skin surface and then invade in the deeper layer. The most superficial cutaneous infection is Candida species is one of the fungi. Fungi infection expressed in deeper layer of skin is known as “cutaneous mycoses”. Cutaneous fungal infections are called as “Dermatophytes”. Fungi which is involved in various dermatomycoses include Tinea pedis, Tinea corporis, and Tinea cruris. When fungal infection further penetrates deeper skin tissue is called as “subcutaneous mycosis”. For both superficial and deep fungal infection antifungal chemotherapy is used. FIG.1 show fungal infections commonly seen in the different layers of skin.(2)

Nanotechnology is a rapidly developing field that involves the creation and use of nano-sized particles which are measured in nanometres. nanotechnology is the science, engineering, technology drug delivery, and therapies revolutionized by the art of characterizing, manipulating, and organizing matter systematically at the nanoscale scale. In which various time consuming and very expensive traditional therapies and treatment, methods are available. By the use of nanotechnology, treatments can be developed faster and for a reasonable cost in the pharmaceutical area. Using nanotechnology, drugs can be targeted to a specific location, making it more effective and reducing the risk of negative effects. The word nanogel is defined as the hydrogel nanoparticles (NPs) with tunable size range of 1-1000 nm formed by physical or chemical cross-linked networks. [3] They show better skin permeation due to their smaller size and soft material. Some nanogels have hydrophilic nature which gives good encapsulation property of hydrophobic drugs.

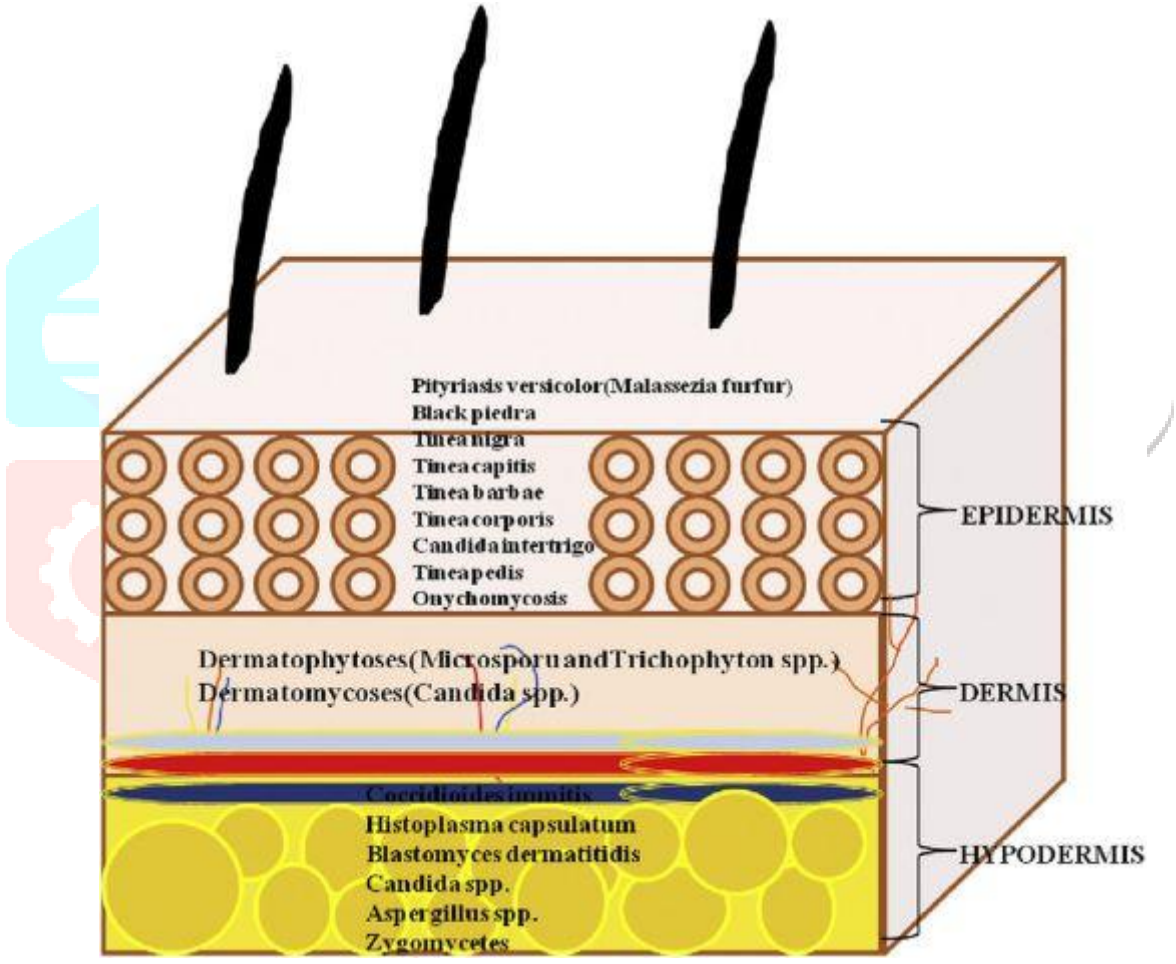

FIG.1: Layers of skin with different fungal infections.

The main areas reviewed in this article are:

1. **Pityriasis versicolor**

Pityriasis versicolor it is also called as tinea versicolor. It is caused by the overgrowth of a type of fungus i. e, yeast on the skin. It is the common, benign, superficial fungal infection which causes small, discoloured patches of skin. This infection occurs in epidermis layer of the skin. There are 14 species of Malassezia have been identified. In this skin infection the main species isolated are Malassezia furfur, Malassezia globose, Malassezia sympodialis. It has been reported worldwide, but more common in humid and warm conditions. Pityriasis versicolor most commonly seen in adolescents and young adults and it affects men and women equally and it has been no specific predominance noted. pityriais versicolor which is caused by Malassezia, a dimorphic lipophilic fungus, also called as pityrosporum. It is the component of normal skin flora. This infection is not considered as a contagious. It does not lead to either permanent scarring or pigmentary disorders. In many cases it occurs reccurence. It may be treated effectively with topical and systemic agents. Topical medications are considered as the first-line therapy for this infections. Antifungal agents which includes imidazole (miconazole, ketoconazole, isoconazole, clotrimazole are commonly used for treatment of pityriasis versicolor.[4]

2. **Black Piedra**

Black piedra it is also known as the tricomycosis nodosa. It is the superficial fungal infection of the hair shafts in which the fungal elements are attached to the hair shafts which form nodules along with hair shaft. Black Piedra affects the scalp hair, which caused by black yeast, piedraia hortae. It is mainly seen in humid tropics, Americas and southeast asia.it is treated either by cutting or shaving the affected hairs and followed by the application of anti-fungal and topical agents. For this an adjunctive treatment is ketoconazole shampoo and in some cases oral itraconazole and terbinafine have been tried.[5]

3. **Tinea nigra**

Tinea nigra is a superficial fungal infection of the stratum corneum caused by the black yeast-like mold phaeoannellomyces or hortaea werneckii (formerly called Cladosporium or exophiala werneckii).it is a dark patch of infected skin. This infection that attacks on the uppermost layer of the skin i.e, epidermis.in this infection multiple spots may be occurs, that macules get extend to the fingers, toe, chest, neck, nails and genital area. Tinea nigra diagnosed by visualisation, dermoscopy, microscopy and culture method. tinea nigra it is treated with antifungals and scraping the lesion. topical whitefield's ointment or salicylic acid ointment or oral itraconazole this medication are used for this infection. It is commonly occurs in tropical and subtropical countries of central and south America, south east asia, Europe, Australia and far east. Tinea nigra was first described by Alexandre Cerqueira from Brazil in 1891.it is most commonly seen in children and younger adults.[6]

4. **Tinea capitis**

Tinea capitis it also known as the scalp ringworm and herpes tonsurans infection. it is the superficial fungal infection which affects on the skin of the scalp, eyebrows and eyelashes.in which itchy and bald patches occurs on the scalp of the hairs. Tinea capitis is caused by the dermatophyte species Microsporum and Trichophyton which invade the hair shaft. It may be accompanied by itching, scaling, inflammation and pustules. tinea capitis mostly affects the toddlers and school age children. But it affects adults as well. The

people who has weak immune system suffers from tinea capitis. It may be persistent and very contagious. Treatment of this infection which involves the use of an oral antifungal medication. tinea capitis mostly seen in hot and humid areas like southeast Asia, Africa and central America.(7)

5. **Tinea barbae**

Tinea barbae it is also called as beard ringworm and tinea sycosis. Tinea barbae is a superficial fungal infection of the skin, hair and hair follicles caused by dermatophytes. Tinea barbae is a type of dermatophytosis which is caused by the the trichophyton mentagrophytes or trichophyton verrucosum. In which deeper infection occurs with superficial and circular patches. transmission of tinea barbae is through animal to human contact spreads frequently than rarely through the human to human contact.it mostly affects the hair and skin in the beard and mustache areas, which mainly affects only adult men. treatment of this infection varies with the people, topical medication are enough in mild cases and for serious cases oral antifungal medications are recommended.(8)

6. **Tinea corporis**

Tinea corporis is also known as the body ringworm. Tinea corporis is a superficial fungal skin infection of the body caused by dermatophytes so it is type of dermatophytosis and it also caused by Trichophyton or Microsporum. The medical term for ringworm is tinea corporis. “tinea” means fungus, and “corporis” means the body. It can affect any part of the body like neck, trunk, arms and legs. In tinea corporis pink-to-red patches occurs and rashes becomes itchy. treatment of this includes antifungal drugs or nanogels applied on this affected area or sometimes antifungal drugs should be taken by mouth.(9)

7. **Candida intertrigo**

Candida intertrigo is a superficial skin-fold fungal infection caused by the yeast, candida. Candida intertrigo is a common and treatable skin infection. It is inflammatory skin condition which caused by skin-to-skin friction because of heat and moisture condition. in which skin damages and reddish rashes occurs. The area where candida intertrigo occurs are armpit, between belly folds, between your buttocks, in your inner thigh, between your toes and fingers, in the crease(s) of your neck. topical antifungal used for this infection are azole drugs including miconazole(mitrazol), ketoconazole (Nizoral topical) or clotrimazole (lotrimin AFcream)(10)

8. **Tinea pedis**

Tinea pedis (athlete’s foot) is also known as foot ringworm. Tinea pedis it is cutaneous fungal skin infection cause by the Trichophyton rubrum, a dermatophyte and it is usually begin with the toe. It is common superficial fungal skin infection which affects the areas of skin between your toes, the top of your feet, the bottom of your feet, the edges of your feet and your heels.in which skin becomes purple white or gray, and also scaly or irrited. This infection is contagious. it is mostly seen in small regions of Southeast asia, in parts of Australia and Africa. The first report of tinea pedis was in 1908 by whitfield, who, with sabouaud, believed that infection caused by same oraganism which was very rare infection produce tinea pedis. Treatment for this infection include antifungal nanogels, creams, ointments, spray or powders. sertaconazole nitrate cream (Ertaczo) and ciclopirox gel used for treatment for tinea pedis.(11)

9. Onychomychosis

Onychomycosis it is called as nail fugus and tinea unguium. It is a fungal infection of the nails. In this infection nails becomes brittle, ragged, thickened, discoloured and crumbled nails. It is cause by the dermatophytes, non-dermatophyte molds and yeasts. Onychomycosis mostly seen in adults and in children. The most frequent dermatophyte trichophyton rubrum found in this infection. treatment of onychomycosis includes oral antifungal drugs and nail polishes, creams and nail removals.[12]

Advantages of topical drug delivery system

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of the varied
- conditions of absorption, like PH changes, presence of enzymes and gastric emptying time etc.
- Achievement of efficacy with lower total daily dosage of drug bt continuous drug input.
- Avoids fluctuation in drug levels, inter and intra-patient variations.
- Ability to easily terminate the medications when needed.
- A relatively large area of application in comparison with buccal or nasal cavity.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.
- Improving physiological and pharmacological response.
- Improved patient compliance.

Disadvantages of topical drug delivery system

- Skin irritation or contact dermatitis may occur due to the drug and/or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergenic reactions.
- Can be used only for drugs which require very small plasma concentration for action.
- Enzyme in epidermis may denatures the drugs.
- Drugs of larger particle size not easy to absorb through the skin.

Various Topical drug delivery system[13]

A. Ointments

The preparations intended for external application to the skin or mucous membrane is known as ointment. The ointments are greasy, semisolid preparations which are often anhydrous and contain medicament either dissolved or dispersed in the vehicles. It contains bases like hydrocarbon, fats and fixed oils, absorption base, emulsifying bases and water-soluble bases.

B. Creams

Creams are semisolid preparations containing one or more medicinal agents dissolved or dispersed in either a water-in-oil emulsion or an oil-in-water emulsion or in other type of water washable base.

C. Liquid preparations

These are preparations meant for external application to the skin includes simple emulsion bath, liniments, lotions, paints, varnishes and tinctures.

D. Powders

The main purpose for formulating dusting powders for application to skin by mixing together several finely divided insoluble powders. It functions like drying, protective and lubricating agent. For eg. Talk, zinc oxide, starch and kaolin.

E. Aerosols

Aerosols may function as drug delivery system for solutions, suspensions, powders, semisolids and emulsions. Solution forms of aerosols are simple products, consisting of an active ingredient dissolved in propellant or a mixture of propellant and a miscible solvent.

F. Gels

Gels are crosslinked particles made of hydrophillic polymers are transparent preparations containing cellulose ethers or carbomers in water or a water alcohol mixture. Gels liquefy on contact with the skin, dry and leave a thin film of active medication. A gels tends to be dry on application so they are useful in hairy areas they are cosmetically acceptable and has several advantages than others. The vehicle used for gels may be aqueous/ hydro alcoholic/ alcohol-based/ non-aqueous type.

G. Nanogel

Nanogels are nanometer sized hydrogel nanoparticles (<100nm) with three dimensional networks of cross-linked polymers that swells in a good solvent. Nanogel acts as a carrier to drug particle sudden outbreak in the field of nanotechnology have introduced the need for developing nanogel systems to overcome the drawbacks of conventional gel which proven their potential to deliver drugs in controlled, sustained and targetable manner.

1) Advantages

- Nanogels are highly biocompatible and biodegradable.
- It has good permeation capabilities due to extreme small size
- It provides an ease of drug delivery through various routes like oral, pulmonary, nasal, parenteral, intra ocular etc. size and chemical functionalities enables nanogels responsiveness to environmental factors and biodegradability when required.
- It has ability to reach smallest capillary vessels, due to their tiny volume and to penetrate the tissues either through the paracellular or the transcellular pathways.
- The particle size and surface properties can be manipulated to avoid rapid clearance by phagocytic cells.

2) Disadvantages of nanogels

- Expensive technique.
- Surfactant or monomer traces may remain and can impart toxicity.
- Skin sensitization and allergic reaction.

Properties of nanogels[14]

- **Swelling property in different media:** The most important property of nanogels is their rapid swelling characteristics in different conditions such as in different medias like aqueous and in different pH conditions, also temperature dependent swelling and it favour release of drug from gel network.
- **Biocompatibility and degradability:** Nanogel based drug delivery system is highly biocompatible and biodegradable due to this characteristics it is highly acceptable and promising field now a days.

- **Higher drug loading capacity:** it depends on the functional group present in the polymeric unit. These functional groups have a tremendous effect on drug carrying and drug-releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications.
- **Particle size:** Nanogels typically range in size of 20-200nm in diameter and hence are effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticuloendothelial system. Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB).
- **Solubility:** Nanogels are able to solubilise hydrophobic drugs and diagnostic agents in their core or networks of gel.
- **Electromobility:** Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating biomacromolecules.
- **Colloidal stability:** Nanogels or polymeric micellar nanogel systems have better stability over the surfactant micelles and exhibit lower critical micelle concentrations, slower rates of dissociation, and longer retention of loaded drug.
- **Non-immunologic response:** it does not produce any immunological responses.

Drug loading in nanogels:

a) Conjugation entrapment

It is most important and widely used method. Covalent conjugation of biological agents can be achieved using performed nanogels or during nanogel synthesis. For example, enzymes modified with acrylic groups were copolymerised with acrylamide either in inverse microemulsion or dilute aqueous solutions to obtain nanosized hydrogels.[15],[17]

b) Physical Entrapment

It was employed for incorporation of proteins in cholesterol-modified pullulan nanogels and siRNA in nanogels. In addition, hydrophobic molecules can incorporate into nonpolar domains formed by hydrophobic chains present in performed nanogels. For example, prostaglandin E2 was solubilized in nanogels of cholesterol-modified pullulan.[16],[17]

c) Self -Assembly

The self-assembly process, defined as the autonomous organization of components into structurally well-defined aggregates. Molecular self-assembly is characterized by diffusion followed by specific association of molecules through noncovalent interactions, including electrostatic and/or hydrophobic associations oppositely charged polysaccharides associates readily as a result of electrostatic attractions. A convenient strategy consists on linking hydrophobic grafts to e.g., a highly water-soluble polysaccharide, inducing the formation of nanoparticles via hydrophobic interactions. This kind of amphiphilic polymers can be constructed by three routes:

1. Hydrophobic chains grafted to a hydrophilic backbone
2. Hydrophilic chains grafted to a hydrophobic backbone or with
3. Alternating hydrophilic and hydrophobic segments.

Upon contact with an aqueous environment, amphiphilic polymers spontaneously form self-aggregated nanoparticles, via intra- or intermolecular associations between the hydrophobic moieties.[15],[17]

d) Direct addition method:

It is one of the conventional and simple method widely used for preparation of nanogel. In this method simply a hydrogel base is prepared by soaking gelling agent (carbomers) in water for 24 hrs. and drug nanoparticles dispersed in gel base with continuous stirring.

Classification of nanogels[17]

Nanogels can be classified on the basis of cross-linking, response to stimuli (e.g., pH, light, temperature, ionic strength, etc) and method of preparation.

Based on their behavior towards specific stimuli

1. Non-responsive nanogels
2. Stimuli-responsive nanogels

Based on type of linkage of polymeric gel structure

1. Physically cross-linked nanogels
2. Liposome Modified nanogels
3. Micellar nanogels
4. Hybrid nanogels
5. Chemically cross-linked nanogels

CONCLUSION

Nowadays, fungal infection it becomes huge problem of human health. Most of the people are suffering from fungal infections. To cure fungal infection, people are doing irrational and inappropriate use of antifungal chemotherapeutics, which occurs multidrug resistance fungal pathogens, lower therapeutic efficacy, unwanted toxicity. Treatment for fungal infections includes topical formulations which gives better skin penetration and higher efficacy. For fungal infections topical fungal therapy mostly preffered because their targeted therapy and less side effects. in which various antifungal nanogels used for fungal infections.

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