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REVIEW ARTICLE

Formulation and InVitro Evaluation of Topical Gel for the Treatment of Fungal Infections

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Abstract

Conventional dosage structures are essentially being considered for the therapy of an intense infection or constant sickness. Nonetheless, the significant downside is dose structure must be taken over and over to accomplish remedially viable reach coming about change in plasma drug levels. Subsequently, to beat the issues related with ordinary measurements, structure controlled medication conveyance framework has been presented.

The basic concept behind the development of conventional drug delivery system is to increase pharmacokinetic and pharmacodynamics of drug molecule either by using different approaches or modifying molecular structure. This article provides better understanding of how the topical gel penetrates through the skin to treat infections. Topical gel, the most promising novel drug delivery system has qualitative influence on the skin permeation and release of drug having poor rate of absorption through skin layers. Various types of topical gels as well as its benefits and faults have been discussed. Bifonazole is a subbed imidazole antifungal specialist belonging to BCS Class IV sedate having low solvency and low porousness. Bifonazole shows wide range of action against dermatophytes, molds, yeasts, dimorphic organisms and some gram-positive microorganisms. It is a profound lipophilic medication with a short half-life (1-2 h) and is insignificantly ingested following dermal application (0.6% of an applied portion).

Keywords: Permeation enhancement, Topical gel, Hydrogel, Cross-linking, Topical routes

Introduction

Topical Drug Delivery System

Topical drug delivery is described as the application of a medication containing formulation directly to the skin for treating cutaneous problems. The transdermal drug delivery system is generally used where other routes like oral, sublingual, rectal, parental of drug administration fails or do not work up to therapeutic level or in local skin infections like a fungal infection. There has been an increased interest during recent years in the use of topical vehicles that may modify drug penetration into the skin. Optimal vehicles have to exert a high capacity for incorporating both lipophilic and hydrophilic drugs as well as high skin permeability. Irritation is the major disadvantage of chronic application.[1]

Anatomy of Skin[2, 3, 4, 5]

The skin is the broadest organs of the human body covering a zone of about 2 m^2 in a normal human adult. The skin separates the hidden blood flow organize from the external condition, fills in as a hindrance against

physical, compound and microbial assaults, goes about as an indoor regulator in keeping up internal heat level, secures against destructive bright beams of the sun and assumes a job in the guideline of circulatory strain. Anatomically, the skin has numerous histologic layers, yet when all is said and done, it is portrayed as three significant tissue layers.

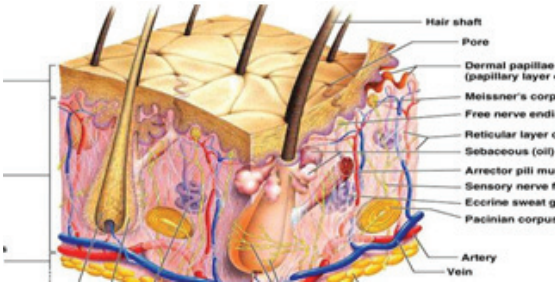

Figure 1: Structure of cross section of skin

➢ ***Epidermis***

The epidermis results from a functioning epithelial basal cell populace and is around 150 micrometers thick. It is the peripheral layer of the skin and the cycle of separation brings about relocation of cells from the basal layer towards the skin surface. The outcome of this cycle is the development of a flimsy, delineated, and very versatile layer at the skin surface.

The multilayered wrap of the epidermis differs in thickness, contingent upon cell size and number of cell layers, going from 0.8 mm on palms and soles down to 0.06 mm on the eyelids. Below this layer are the other layers of the epidermis –

- Stratum lucidum,
- Stratum granulosum,
- Stratum spinosum and
- Stratum germinativum

Together, these other layers constitute the viable epidermis. Stratum corneum and the remainder of the epidermis so called viable epidermis covers a major area of skin.

➢ ***Stratum corneum***

The layer corneum is the peripheral layer of skin and furthermore called as the horny layer. It is around 10 mm thick when dry and swells to a few times this thickness when completely hydrated. It contains 10 to 25 layers of corresponding to the skin surface lying dead, keratinized cells, called corneocytes. It is flexible but relatively impermeable. The stratum corneum is the principle barrier for penetration. It is the rate-limiting barrier that restricts the inward and outward movement of chemical substances. The interior of the cells is crisscrossed with densely packed bundles of keratin fibers. Due to this, the dry composition of the horny layer is 75-85% protein, most of which is the intracellular keratin and part being associated with a network of cell membranes. The bulk of the remainder of the substance of the stratum corneum is a complicated mixture of lipids which lies between regions, the mass of intracellular protein and the intercellular lipoidal medium. The architecture of horny layer may be modeled as a wall-like structure. In this model, the keratinized cells function as protein "bricks" embedded in lipid "mortar". The lipids are arranged in multiple bilayers and it has been suggested that there is sufficient amphiphilic material in the lipid fraction such as polar free fatty acids and cholesterol to maintain a bilayer form.

➢ ***Dermis***

The epidermis lays on a lot thicker dermis. The dermis basically comprises of about 80% of protein in a lattice of muco-polysaccharide "ground substance". It is 3 to 5 mm thick and is a rich bed of vessels, connective tissue, which contains veins, lymphatics, nerves and the epidermal members like hair follicles, sebaceous organs and sweat organs. But the bottoms of the feet, the palms of the hand, the red part of the lips and related with at least one sebaceous organs which are outgrowths of epithelial cells. The cutaneous blood supply has fundamental capacity in guideline of internal heat level which is serve by sweat organs by discharge of a weaken salt arrangement. Dermis likewise gives supplements and oxygen to the skin, while eliminating poisons and side-effects. Vessels reach to inside 0.2 mm of skin surface and give sink conditions to most iotas penetrating the skin check. The blood nimbly as needs be keeps the dermal intermingling of an especially low and the resulting center difference over the epidermis gives the central principle catalyst to transdermal immersion.

➢ ***Hypodermis***

The hypodermis or subcutaneous fat tissue supports the dermis and epidermis. It fills in as a fat accumulating zone. This layer helps with overseeing temperature, offers feeding help and repairman protection. It passes on boss veins and nerves to skin and may contain material weight organs. For transdermal medicine transport sedate requirements to enter through this load of three layers and adventure into central stream while if there ought to emerge an event of skin calm movement simply entrance through layer corneum is essential and a short time later support of drug in skin layers is needed.

Absorption of Drug Through Skin[6, 7]

➢ ***Percutaneous absorption***

Percutaneous retention is characterized by infiltration of substances into different layers of skin and penetration across the skin into fundamental course. Before a topically applied medication can act either locally or foundationally, it should saturate through the actual epidermis or disseminate through shunts, especially those offered by somewhat broadly appropriated hair follicles and eccrine glands, which percutaneous absorption of medication particles is of specific significance in transdermal medication conveyance framework on the grounds that the medication must be consumed to a sufficient degree and rate to accomplish and look after uniform, fundamental, remedial levels all through the span of utilization. As a rule, once medicate atom crosses the layer corneal hindrance, sections into more profound dermal layers, fundamental take-up happens generally rapidly and without any problem.

➢ ***Trans-epidermal absorption***

The trans-epidermal pathway is essentially responsible for dispersion over the skin. Layer corneum is considered as the primary opposition of this pathway. Saturation by this course initially includes apportioning into the layer corneum and then dispersion over this tissue. The current prevalent thinking is that most substances diffuse over the layer corneum through the intercellular lipoidal course. Nonetheless, it has all the earmarks of being another minuscule way through the layer corneum for incredibly polar mixes and particles. At the point when a pervading drug exits at the layer corneum, it enters the wet cell mass of the epidermis and since the epidermis has no immediate blood gracefully, the medication is compelled to diffuse across it to come to the vasculature quickly underneath. It is a porous field that capacities as a viscid watery system to most infiltrate. It gives the idea that solitary particles and polar non-electrolytes found at the hydrophilic extraordinary and lipophilic non-electrolytes at the hydrophobic outrageous have any genuine trouble in going through the practical field. The epidermal cell films are firmly joined and there is almost no intercellular space for particles and polar non-electrolyte atoms to diffuse through. Section through the dermal district speaks to a last obstacle to foundational passage. Penetration through the dermis is through the interlocking channels of the ground substance. Since the suitable epidermis and dermis needs major physicochemical qualification, they are commonly considered as a solitary field of dispersion, aside from when infiltrate of outrageous extremity are included, as the epidermis offers quantifiable protection from such species.

➢ ***Transfollicular absorption***

The skin's individuals offer simply discretionary streets for pervasion. Sebaceous and eccrine organs are the lone extremities which are genuinely considered as shunts bypassing the layer corneum since these are circulated over the whole body. However, eccrine organs are various, their openings are small and amounts to a miniscule part of the body's surface. In addition, they are either cleared or thereabouts plentifully dynamic that atoms can't diffuse deep down against the organ's yield. Therefore, they are not thought of as genuine course for percutaneous ingestion. Regardless, the follicular course remains a huge street for percutaneous maintenance since the opening shot of the follicular pore, where the hair shaft leaves the skin is tolerably colossal and sebum helps in spread of penetrate. Apportioning into sebum, trailed by dissemination through the sebum to the profundities of the epidermis, is the imagined system of penetration by this course. Vasculature supporting the hair follicle situated in the dermis is the possible purpose of fundamental passage.

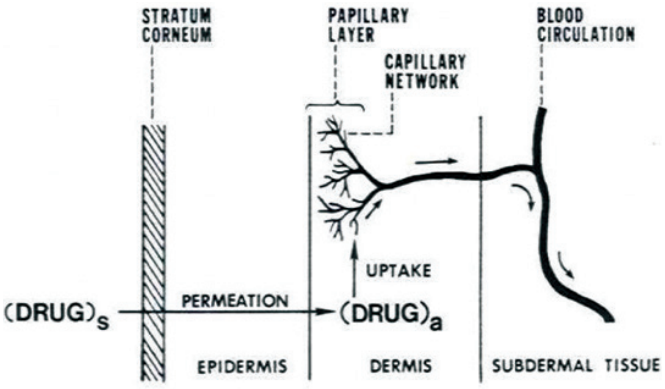

Figure 2: Skin model showing drug permeation through skin to systemic circulation

Routes of Drug Penetration Through Skin[8, 9]

➢ ***The Appendageal route***

The transappendageal routes are otherwise called the shunt courses, and incorporates saturation through the perspiration organs and over the hair follicles with their related sebaceous organs. Skin members give a nonstop channel legitimately over the SC boundary. Recent studies have re-examined the long-held assumption that the follicles occupy approximately 0.1% of the surface area of the human skin. Otberg *et al*. showed that the follicular number, opening diameter and follicular volume are important considerations in drug delivery

through these appendages and, indeed, the forehead provides 13.7 mm^2/cm^2 as follicular in fundibula, i.e. approximately 13.7% of the surface area of the forehead is available as follicles. Interestingly, the same study also showed that the historically held view of the follicles providing approximately 0.1% of the SC appears to be valid for forearm skin.

➢ ***Transcellular route***

Medications entering the skin by means of the transcellular course go through the corneocytes. Corneocytes containing exceptionally hydrated keratin gives a fluid domain from which hydrophilic medications can pass. The transcellular pathway requires not just partitioning into and dispersion through the keratin blocks but also additionally into and over the intercellular lipids.

➢ ***Intercellular route***

The intercellular route involves drug diffusion through the continuous lipid matrix. This route is a significant obstacle for two reasons: (i) recalling the "bricks and mortar" model of SC, the interdigitating idea of the corneocytes yields a convoluted pathway for intercellular medication pervasion, which is rather than the moderately immediate way of the transcellular course (ii) The intercellular domain is a region of alternating structured bilayers. Thus, a medication should successively parcel into and diffuse through rehashed fluid and lipid areas. This route is generally accepted as the most common path for small uncharged molecules penetrating the skin.[10]

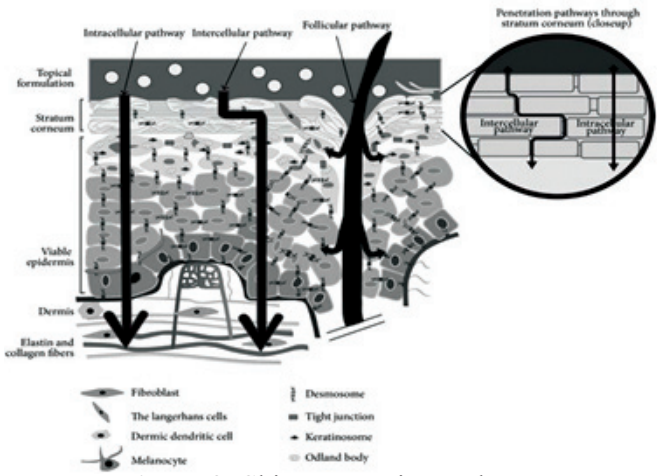

Figure 3: Skin penetration pathway

Topical Gel[11, 12]

The term 'Gel' was acquainted in the late 1800's as some semisolid material as per its physiological attributes as opposed to atomic arrangement. The U.S.P characterized gels "as a semisolid framework comprising of scattering comprised of either little inorganic molecules or enormous natural atoms encasing and interpenetrated by fluid."

Gels are a generously weakened cross-connected framework, which displays no stream when in the consistent state. They are comprised of a two-part semi-strong framework wealthy in fluid.

Properties of Topical Gel[13, 14]

Topical gels should possess the following ideal properties:

A. The topical gel should not be tacky

B. Gelling agents which are used in the formulation either in pharmaceutical or cosmetic should be: Inert, safe and should not react with other excipients during formulation

C. The topical gel should possess suitable anti-microbial activity

D. In case of ophthalmic use, the gel should be sterile

Characteristics of Gels[13, 14]

➢ **Swelling:** At the point when a gelling specialist is stayed in touch with fluid that solvates it, then at that point an obvious measure of fluid is taken up by the specialist and the volume raises. This process is known as swelling. This process occurs as the solvent gets into the matrix. Gel-gel interactions are changed by gel solvent interactions. The level of expanding relies upon the quantity of linkages between singular atoms of gelling operator and on the quality of these linkages.

➢ **Ageing:** Colloidal frameworks as a rule show moderate unconstrained collection. This wonder is alluded to as maturing. In gels, ageing results in progressive formation of a denser network of the gelling agent.

➢ **Syneresis:** Numerous gels frequently contract precipitously on standing and ooze some liquid medium. This process is known as syneresis. The extent to which syneresis occurs increases as the concentration of gelling agent decreases. The level of expanding relies upon the quantity of linkages between singular atoms of gelling operator and on the quality of these linkages.

➢ **Rheology:** Solutions of the gelling agents and dispersions of flocculated solid are pseudo plastic i.e. showing non- Newtonian flow behaviour, represented by a decrease in viscosity with increase in shear rate.

➢ **Structure:** The rigidity of a gel arises from the latency of a network formed by the inter linking of particles of the gelling agents.

Structure of Gels[15]

The gelling agent forms network by interlinking particles resulting in the rigidity of gel. Type of force which causes the linkage of particles and its nature governs the arrangement of system and gel properties. The single particles show isometric aggregates or spherical cluster of minute molecules or solo macromolecules. The arrangement of gel networks is shown in the given figure below.

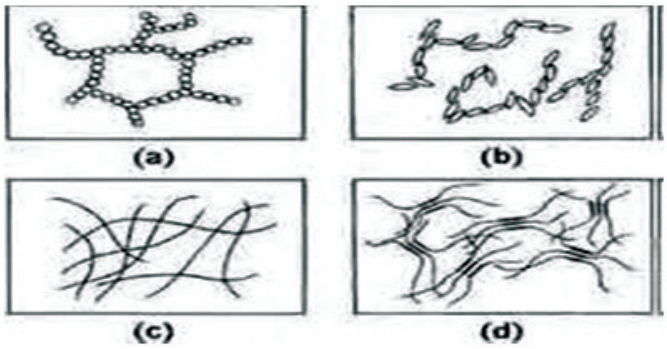

Figure 4: Gel structures (a) Flocculated particles (b) Network of stretched out particles or rods (c) Matted fibres as found in soap gels (d) Amorphous and crystalline zones in a gel

Gel-forming substances:

Polymers are used to form gel structural network. Polymers which form gel are as follows:

Natural Polymer:

A. Proteins: Collagen, Gelatin

B. Polysaccharides: Agar, Alginic acid, Guar gum, Xanthin, Pectin, Tragacanth

Semisynthetic polymers:

A. Cellulose derivative

B. Methyl cellulose

Synthetic polymers:

A. Carbomer

B. Polyethylene and its co-polymer

Surface active agents:

A. Cetostearyl alcohol

B. Brj - 96

Inorganic substance:

A. Bentonite

B. Aluminum hydroxide

Advantages of Gel Formulations[16]

- In comparison to other dosage forms, gels are easy to prepare
- Gels possess good adherence property when applied
- Gels are non-greasy and elegant in nature
- When we apply the gel, it forms a protective layer at the site of application
- Gels are non-toxic and can be removable or washable easily
- They provide good spreadability characteristics
- Both polar and non-polar drugs can be incorporated and administrated through gel
- They are biodegradable and biocompatible

Disadvantages of Gel Formulations[16]

- The gelators or additives used may induce irritation
- The effectiveness of gels is comparatively slower and sustained
- Sometimes the gelling agent which has been used may precipitate and cause salting out
- Rheology of formulated gel might be changed due to the effect of temperature, humidity and other environmental factors
- Some drugs may degrade in gel form due to the presence of polymers
- The gels may be unstable due to flocculation

Classifications of Gels[16,17]

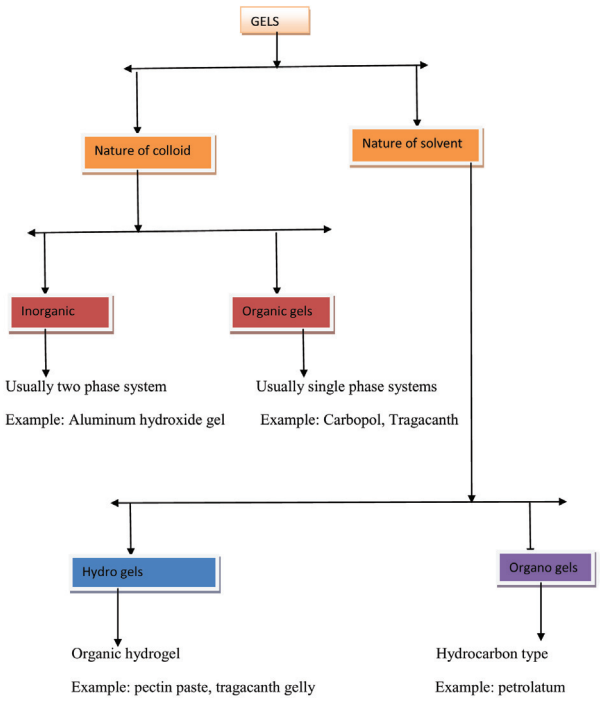

Figure 5: Schematic diagram showing general classifications of gels with examples

Mechanism of gel formulation[15]

Gels are formed via three types of cross-linking which are listed below:

a) Chemical cross-linking

b) Physical cross-linking

c) Ionic cross-linking

a) Chemical cross-linking:

Chemical cross-linkage is also found with polymer possessing bonded group in their assembly. When cross-linkage compounds are bringing together, such polymers cause an irreversible reaction among the added compound and free group. After attaining a specific concentration, viscosity increases in this type of reaction and results in gel formation. Eg: Polyacrylic acid (with multiple carboxylic acid)

b) Physical cross-linking:

By hydrogen bond formation, solution to gel transition can be obtained in cases like concentration variation, temperature variation transition, crystalline component solubilization. Physical cross-linking is shown in gel formulations such as cellulose gels, dextran gels.

c) Ionic cross-linking:

Here cross-connecting occurs by making charge on polymer (S) or different particles (Solvent) that attract one another resulting in gel. Charges on the molecules results in ionic bond formation. Eg: Polysaccharide alginate produces gel matrix in company of calcium ions resulting in gel matrix of calcium ions that encapsulates some compounds (enzymes).

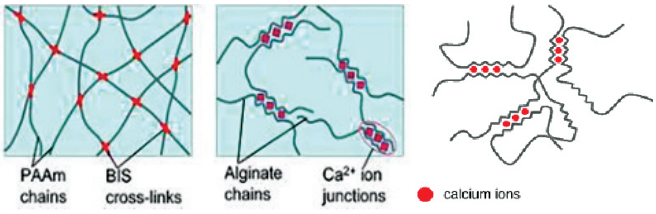

Figure 6: Various forms of cross-linking
(a) Chemical cross-linking (b) Physical cross-linking
(c) Ionic cross-linking

Antifungal

Fungal contamination is a skin sickness caused by fungus. The fungal defilement is a common place pollution which impacts two thirds of populace among the world. Various antifungal prescriptions are available for the treatment of parasitic pollution like Miconazole, Ketoconazole, etc. An antifungal medication is a drug fungicide used to treat mycoses, such as contender's foot ringworm, candidiasis. Antifungal works by mishandling contrasts among mammalian and parasitic cells to butcher the infectious living beings without unsafe effect on have.[18]

Azole antifungals work through a normal arrangement of movement. They explicitly subdue the association of infectious cell ergosterol and they change the permeability of cell film by definitive with the phospholipids in the fun-woman cell layer. The azole antifungal administrators in clinical use contains either a couple of nitrogen in the azole ring and are thus named imidazoles (e.g., keto-conazole and miconazole, clotrimazole) or triazoles (e.g., itraconazole and fluconazole), exclusively. Infectious pollutions can run in reality from shallow to risky. For example, infectious defilements affecting only the top layers of the skin are immediately treatable and have a by and large compelled impact on close to home fulfillment. Regardless, if a parasitic sickness enters crucial course, results can be deadly.[19]

Bifonazole

Bifonazole is a subbed imidazole antifungal specialist belonging to BCS Class IV sedate having low solvency and low porousness. Bifonazole shows wide range of action against dermatophytes, molds, yeasts, dimorphic organisms and some gram-positive microorganisms. It is profound lipophilic medication with a short half-life (1-2 h) and is insignificantly ingested following dermal application (0.6% of an applied portion). The significant part of applied portion stays on the skin surface or in the layers of the layer corneum. Since hyphae of parasites (mycelium) can enter profound into the epidermal layers by sliding past the corneocytes of the horny layer, improved entrance of the dynamic fixing is required in antifungal treatment of the dermis. Micro emulsions are superb up comer as potential medication conveyance framework due to them improved medication solubilization, upgraded entrance power, long time span of usability and simplicity of planning and administration.[20, 21]

Evaluation Parameters for Various Formulations of Topical Gel

A. Physical appearance: Prepared gels were observed visually for colour, clarity and presence of any other particles.

B. pH: Determined by using pH meter by dissolving 1 or 2 g of gels in water.

C. Viscosity: Determined by Brookfield Viscometer for 2 to 5 min at room temperature.

D. Spreadability: Determined by applying the gel over an even surface for any gritty nature if present in sample.

E. Ex-vivo permeation studies: Instrument: Franz diffusion cell

Aliquot: 1 ml

Interval: 30 minute

Wavelength: 276 nm

F. Skin irritation: 100 mg of gel is applied on a 2-cm area for 6 hours, on the interior surface of upper arm and covered with cotton bandage. The site is cleaned after 6 hours with acetone and readings are made according to the scale given by Draize as

1) No irritation: 0 2) Slight irritation: 1 3) Irritation: 2

(A)

(B)

(C)

Figure 7: Different antifungal gels available. A. DK gel B. Candid-v Gel C. Vaniza gel

Conclusion

From above reviewed article, it was found that gels have acquired impressive significance in the recent times because of their wide application and advantages. Their preparation is simple and straightforward but requires extensive advancement between the medication and excipients for the production of protected, compelling and stable product.

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Conflict of interest

The authors have no conflict of interest.

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