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Review Article

Topical drug delivery for treatment of fungal infection

[1]Mohd Vaseem Fateh[*], [2]Gulafshan Parveen, [2]Yusra Ahmad, [3]Nishant Kumar, [4]Navin C. Pant

[1]Deptt. of Pharmacy, SHUATS, Naini Allahabad
[2]Deptt. of Pharmacy, Uttarakhand Technical University, Dehradun 248001
[3]Burman Group of Institutions, Roorkee 247665
[4] Six sigma Institute of Science & Technology, Rudrapur Uttarakhand 263153

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ABSTRACT

Topical route of administration is the most convenient route for drug administration. In this route of administration increase the pharmacodynamic and pharmacokinetic parameters. Fluconazole is an antifungal drug which belongs to the class second drug as per BCS. Fluconazole is a triazole derivative. Fluconazole available in the market different formulation tablet, capsules, gels, creams etc. Fluconazole is the broad-spectrum antifungal agent it is inhibits the fungal infections on the superficial layer of the skin. Topical drug delivery system is classified in gels, lotions, creams, ointment, topical powder, pastes, suppositories, paints and plasters etc. Creams are formulated by the oil in water and water in oil emulsion types of cream. This review focus on the comparative study of gel and cream formulation. Creams adhered to the upper layer of the skin and help to cure fungal infections. Skin is the most preferable route for the topical dosage forms and it is upgrade the bioavailability of the drug through, the bypass metabolism.

Keywords: Cream, Dosage forms, Epidermis, Gel, Skin, Topical drug delivery

INTRODUCTION

Topical route is the most preferable route of the dosage forms and that are increase the pharmacokinetics and Pharmacodynamic parameter of the drug absorptions. Pharmacokinetic: AUC, Cmax, Tmax. Pharmacodynamic: Absorption, distribution, metabolism and excretion.

Topical drug delivery has numerous dosage forms that are like: lotion, creams, paints, gels, ointment. Topical drug delivery system across the first pass metabolism and enhance the drug release and the action of drug to it predetermined rate. Topical drug delivery is most easy to administration for the drug application. Topical drug delivery has 80-90% bioavailability of the drug. Topical drug delivery has only one of the most barriers that is

Address for Correspondence: Mohd Vaseem Fateh, Deptt. of Pharmacy, SHUATS, Naini Allahabad; E-mail: mohammad.vaseem55@yahoo.com

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stratum corneum which is the upper layer of the skin. Skin is the starting of any topical route's administration of the drug. Any topical dosage form has to penetrate the stratum corneum. Topical drug delivery system involves the layers of the skin in which the drug is absorbed and goes to the systemic circulation [1]. Creams are semisolid dosage forms. It is formulated by the oil in water and water in oil type of emulsion. Cream formulations are opaque white and creamy texture. Creams are prepared by the preparation of water phase than oil phase and mix them make an emulsion after that it is formulated the cream. Oil in water type of creamsare non-greasy and removable. Creams are thicker than gels, lotions and ointment. That's why it is adhere to the skin and shows the better bioavailability of the drug. Fluconazole is the broad-spectrum drug. It is used to treat the fungal disease. It is imidazole derivative. Fluconazole are also known as the Diflucan. It is available in market tablet, gels, and ointment and other dosage forms [2]. Fluconazole half-life is 30 hours, it slightly soluble in water. Fluconazole is the most common drug for fungal infections and most of the researchers work on this drug. Fluconazole interacts with a cytochrome P-450 enzyme necessary to convert lanosterol to ergosterol. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents. Fluconazole may also inhibit endogenous respiration, interact with membrane phospholipids, inhibit the transformation of yeast to mycelia forms, inhibit purine uptake, and impair triglyceride and /or phospholipids biosynthesis. Fluconazole cream formulation avoid the its main side effect which is gastro intestinal ulceration. Fluconazole cream should be cross the skin and its barrier most of the researchers focus on this barrier of skin for penetrate the stratum corneum [3].

ANATOMY OF SKIN:

Skin includes the most of the layers that is epidermis, stratum corneum, dermis and hypodermis. Epidermis is further divide into four layers that is stratum lucidum, stratum granulosum, stratum spinosum and stratum basales.

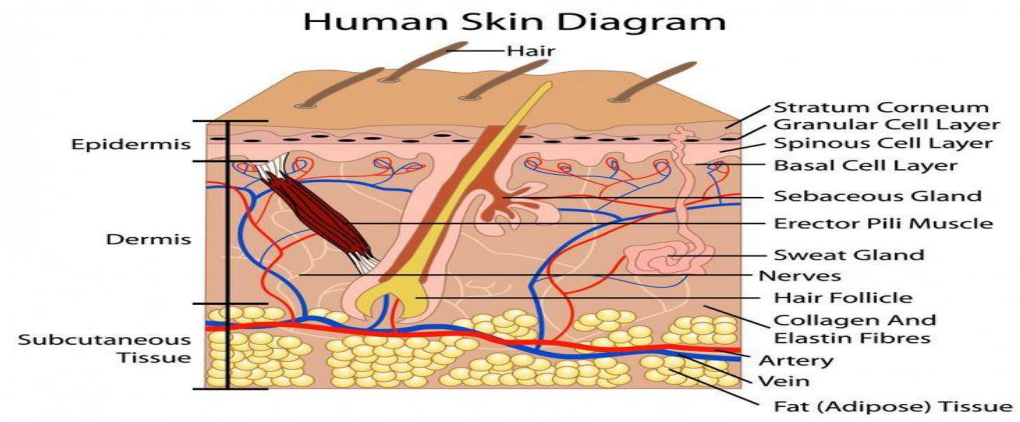

Figure 1: Anatomy of the skin

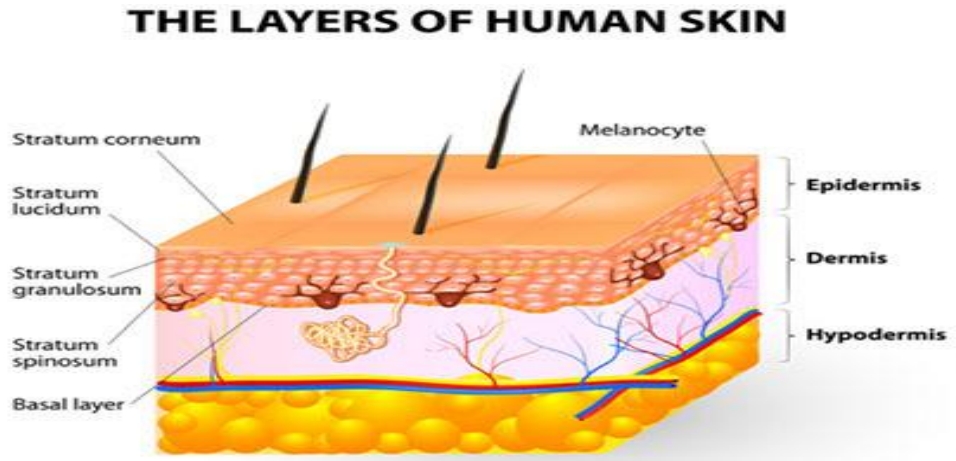

Figure 2: Layers of the epidermis layer

THE EPIDERMIS

Epidermis layer have two layers that are horny and Malpighian layer. Malpighian layer is also known as viable epidermis. Epidermis is divided into four parts.

Stratum Corneum: It is the important barrier of the skin because it is the outermost layer of the skin. The drug is firstly penetrating to the stratum corneum. It contains 75–80%proteins, 5-15% lipids, 5-10% ondansetron. Stratum corneum present the keratin. Which have a capability to recover and occur and make flexible for creating a network by the additional forces.

Viable Epidermis: It is the layer which is undertaken to the stratum corneum. It is 0.6mm thick almost in eyelids and 0.8mm thick in the palm. It is divided with a different type of layers that are stratum lucidum, stratum granulosum, stratum spinosum, stratum basales.

Dermis: It is 5mm thick layer which is formed by the connective tissue. It contains blood vessels, nerves and lymph nodes. It helps to regulate the temperature and blood circulation. And give the nutrition to the skin.

Hypodermis: It contains the fat tissue and it helps to give the all nutrition to the skin and it stores the fatty acid gives energy to the skin. It also regulates the temperature of the body.

PERCUTANEOUS ABSORPTION:
It is the absorption of the drug in which different layers cross the drug for permeate the barrier to the systemic circulation. Percutaneous absorption is done by the two route of drug absorption.

Trans epidermal route: it is the route drug after topical administration it will goes to the permeation by the skin first it goes to the stratum corneum by the diffusion process. Most of the drug under goes to the stratum corneum absorption that is called as lipoid route of drug absorption. Non- electrolyte, ionic and hydrophilic drug under goes through the viable epidermis. Hydrophobic drug can cause the problem for the transfer the drug to the viable epidermis.

Trans follicular route: it is the absorption by the follicles and glands like hair follicle, sweat glands, sebaceous gland. It is very powerful route for absorption of the drug it directly goes from the systemic circulation and it is very effective. [4,5].

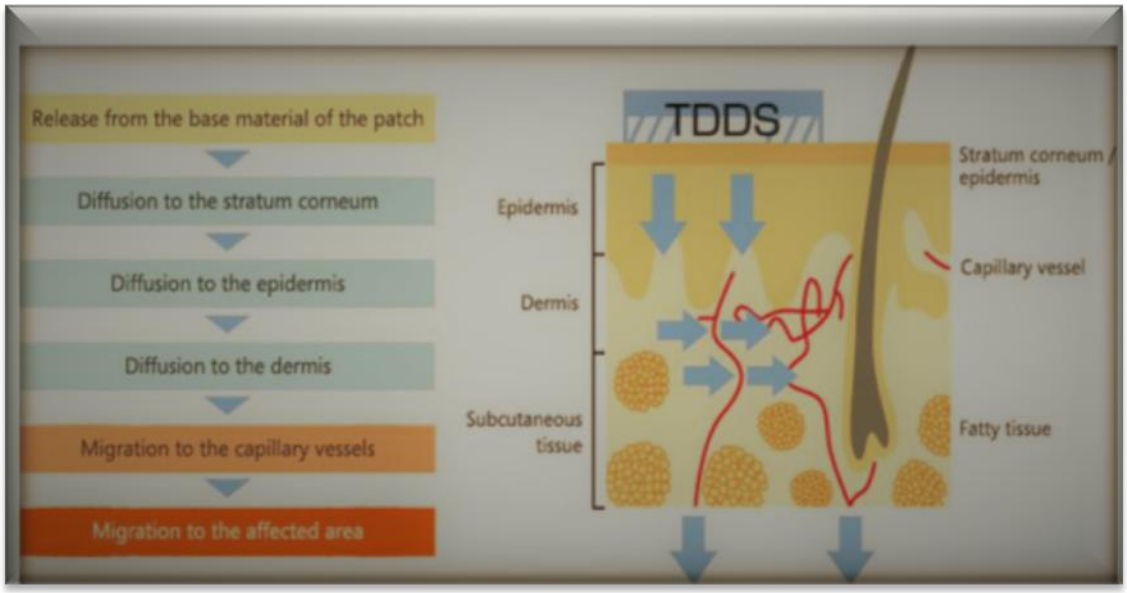

Figure 3: Topical route of drug delivery

CREAM:
Cream is a semisolid dosage form in which is viscous and non-greasy preparation. These are fully absorbed to the skin and dry out with after application sometime. Creams are prepared by the addition of the various type of ingredients like: solvent, emulsifying agent, viscosifying agent, permeability enhancers, humectant, buffering agent, and thickening agents. Cream are two types oil in water and water in oil type. These are formed by the emulsion. In this preparation both phases are melted out separately and applied the heat for melted out. Then mix both at and make an emulsion and stir. And keep side for 2 hours, and observe the creamy texture.

Constituents of cream, gel, lotion and pastes:
Vehicle: It is the aqueous system used in the formulation of any dosage form. It is the solvent used in the preparation. Like: water, methanol and other.

Emulsifying agent: It is the compound which is used for the make and emulsion and reduces the surface tension in between the two immiscible components. It is used as a surface-active agent which decrease the interfacial tension of the two components. Example: tween 80, span 60, polyethylene glycol.

Humectant: Humectant is used for the maintaining moisture and makes humid the formulation. It prevents the water loss in the formulation. Example: glycerin.

Viscosifying agent: These are the agents used for increase the viscosity of the formulation and make it viscous. These are the make consistency rheological. Example: cetostearyl alcohol.

Permeation enhancers: Permeation enhancers are used to increase the drug permeability to the skin. These agents are used for the temporary and permanently transferring the drug permeability through the skin. Example: oleic acid, propylene glycol, methanol.

Preservatives: These are the agents are used to prevent the degradation of the microbial growth in the formulation and it protect the formulation from the fungus, bacteria, molds and yeast. Examples: methyl paraben, propyl paraben.

Thickening agent: These agents are used for make the formulation thick and make the consistency thick. These are also known as gelling agent. These make a clear and transparent gel. Example: Carbopol, cellulose etc.

Moisturizing agents: it is used in the cream formulation for making the moisturize the skin. Examples: carnauba wax, bees wax [6].

Preparation of cream: Cream was prepared by the following steps:

Step 1: Preparation of drug solution- In this step drug (fluconazole) dissolve in suitable solvent propylene glycol.
Step 2: Preparation of oil phase -In this step oil soluble compounds was melted out by using the heat at 70-80^{o} C.
Step 3: Preparation of aqueous phase- in this phase all water-soluble compounds are dissolved at the same temperature 70-80^{o} C. With vigorous stirring.
Step 4: Development of cream- add slowly the oil phase in the aqueous phase with vigorous stirring at the same temperature after mixing both phases drop the temperature 40^{o} C. and stir until the creamy texture obtain.

After formulation of cream it will evaluated by some parameter: pH, viscosity, spreadibility drug content, and in vitro diffusion study.[7]

GEL:
Gel is the homogenous and clear formulation. This is also a semisolid dosage form, in this formulation containing the three-dimensional structure which create a network between the mobilize and immobilize liquids. Network can be formed by the chemical or physical interactions. This will lead to gel classified further in physical and chemical system.

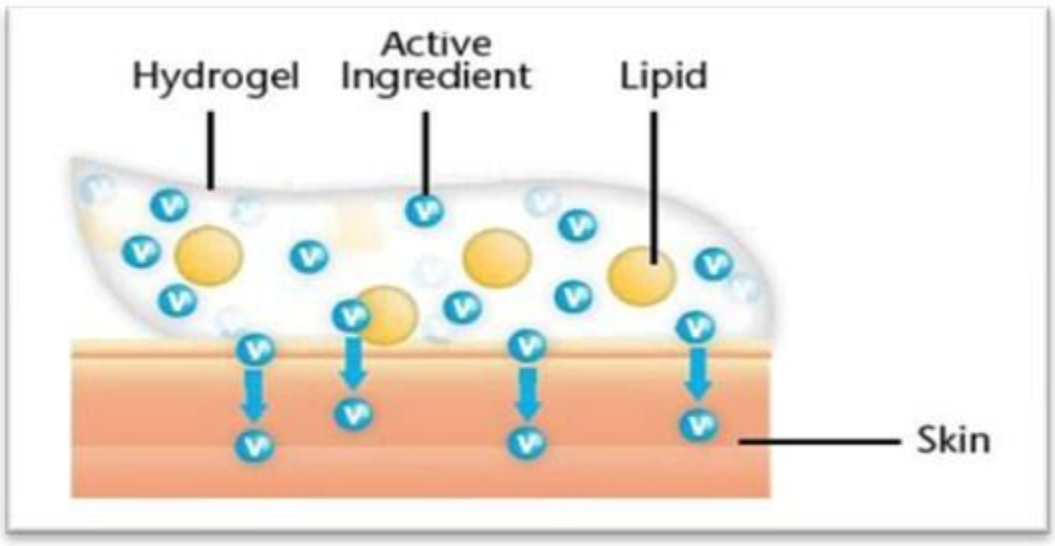

Figure 4: Gel diagram

Classification of gels:
Gels are classified on the basis nature of colloidal phase, solvent phase nature and viscosity properties.

Bases on the colloidal phase:
Inorganic phase (two phase)
Organic phase (single phase)

Single phase system: In this system include the higher organic molecules which exist on the twisted strands soluble or dissolve in the continuous phase. Higher organic molecules may be natural or synthetic polymers preferred as gel formation. These are binds with the Vander walls forces.

Two phase system: In this system the particle size is large of the dispersed phase and if it is form three-dimensional structure in the gel. So that system makes a floccule of the small particle rather than large particle of the gel. So, the gel system was not stable it must be form thixotropy semisolid when it is store and keep aside. And it was become in liquid on agitation.

Based on the nature of the solvent:
Hydro-gel: These are containing the water in the continuous phase. Examples: carbomer, gelatin, cellulose etc.
Organic gel: These are containing the non-aqueous solvent in the continuous phase. Examples: plastibase.
Xerogel: These are the solids type gel with lass amount of solvent concentration. These are formulated by the evaporation of the solvent and freeze-drying method. These are swell and recover itself. Examples: tragacanth ribbons, acacia, dry cellulose.

Bases on the viscosity property:
These have non-Newtonian property. These are classified into:

a) Plastic gels
b) Pseudo plastic gels

Plastic gels: Examples: This system is the aluminum hydroxide make a flocculated suspension in the bhingam bodies. And it excludes the plastic flow showed a plot of rheogram yield value of the gel further the elastic gel distorts and start the movement.

Pseudo plastic gel: Example: liquid dispersion of the tragacanth, sodium alginate, sodium CMC etc. excludes the pseudo plastic flow. This is inversely the increasing shear rate the viscosity will be decreases, with not yield value showed. Rheogram result is show the action of the shearing rate on the longer chain of the linear polymers. As the shearing stress increased the disarranged molecules begin to align their long axis in the direction of flow release of solvent from gel matrix.

Thixotropic gel: This gel was bonded with very weakly within particles it can be brake with shaking. Then resultant solution will become to the gel due to its particles colliding and joining together again. This is in the non-spherical particles for formation of scaffold like structure. Examples: kaolin, bentonite, agar.

Based on the physical nature:
Elastic gel: The fibrous being joint at the point of junction by the weak bonds such as hydrogen bond and dipole attraction. If the molecule has carboxylic acid group than it as bond by the additional of the salt bridge -COO-X-COO between the two groups and create the network.Examples: Carbopol and alginate.

Rigid gels: In this gel these are linked by the primary valance bond it is formed by the macromolecules. Examples: silica gel.[8].

Preparation of gel:
In this preparation the fluconazole dissolve in the suitable solvent like propylene glycol and then added it in glycerin as a moisturizing agent.

Then make a gel base for incorporation of the drug solution in the gel. Carbopol, HPMC or CMC was dissolved in the Luke warm water with vigorous stirring by mechanical or manually. Then add the fluconazole solution in it. Then the pH was adjusted by the using triethanolamine. After pH adjustment the preservatives was added by slowly and continuous stirring. After that, preparedgel was evaluated by the pH, viscosity, spreadibility, drug content and in vitro diffusion study.

Evaluation of cream and gel:
pH: pH is the main parameter for the any type of topical dosage form. pH of gel and cream tends to at 5 to 6.5.

Viscosity: Viscosity is one of the most important evaluation of the any dosage form for topical delivery. Cream and gel viscosity are evaluated by the Brookfield viscometer with the help of spindle using suitable spindle. And viscosity was measured in cps (centipoise) at the temperature 24^{o} C.

Spreadibility: Take a 0.5 gm of sample (cream or gel) on a glass slide and then pressed it well and left for the 5 min. after 5 min. see the diameter and measured it in cm. then compare each value of cream and gel.

Drug content: It is done by the take a sufficient quantity of the sample cream and gel (1gm) and dissolve it suitable 10 ml of methanol and stirred for 2hr. the solution was filtered and make a dilution. After dilution it was measured the wavelength at 260nm by using the UV spectrophotometer.
[Percentage drug content= Absorbance / slope x Dilution factor x 1/1000].

In vitro diffusion study: It was done by the Franz diffusion cell by using the cellulose membrane take a 0.5gm of drug solution and the diffusion study was carried out at the temperature 37+/-2^{o}C. in 250ml of phosphate buffer as a medium. Then the 5 ml of each sample was withdrawn and periodically time interval 1,2,3,4,5,6,7, and 8 hours. And then add the fresh solution of phosphate buffer in the cell of dissolution medium. Then the sample was examined by the UV.[9].

Importance of cream:
It is easy to formulate in comparison to other dosage formsand it is easy for washable if it is oil in water type cream. It adheres to the skin and gives it prolong site of application. If the cream is applied on the injured area of the skin then it is fast dried than other semisolid dosage forms. It is easiest path for delivering the drug from the skin. It is safe and effective delivery of drug molecules which are insoluble in the water and other solvent. It is suitable for dry and flaky skin. In oil in water type of cream causes the cooling sensation due to evaporation of the water.The temperature maintain in the formulation can prevent the thermal degradation of the formulation.

Importance of gel: Importance of the gel's formulation in the pharmaceutical field. It is the clear and transparent dosage forms which are easy to apply for the site of application. It is easily removable. It forms a protective layer to the application site. They have less long-term stability issues. It can be use one or more polymer in the formulation. Polymer is the backbone or base of the gel formulation.

Demerit of gels: These effects are slower and sustained, the pharmaceutical aids or gelating agent can causes the irritation. Water can increase the microbial growth. Evaporation of the water it can produce dryness of the gel. If the gel is in unstable state it can make floccules.

Demerits of cream: These are viscous and decrease the extrudability by the tube. Creams are not used for the internal use. [10-11].

Comparitive study of Cream & Gel formulation:

Cream	**Gels**
Cream avoid first pass metabolism	Gels are also avoided the first pass metabolism.
It adheres to the skin.	It not adheres to the skin.
It is increased the bioavailability due to the adherence	Its bioavailability is limited due to avoiding the adherence
It has less water content so it is avoiding the microbial growth.	It has higher amount of water so it can cause the microbial growth.
It prolongs contact of the skin it is increase the pharmacokinetic and dynamic parameter.	It has less contact of the skin it is decrease the pharmacokinetic and dynamic parameter.
Itincreases the patient compliance and it is less expensive	It is expensive and also increase patient compliance
It is safe and effective for the water insoluble drug or molecules.	It is safe and effective only for the water-soluble drugs.
These are easily washable.	These are also easily washable.
They are less interfering with skin functions.	They are mild interfere with skin functions.
These are non-irritating.	These can cause sometime irritation to application of the skin.
Application on the injured area can be dried quickly than gels.	Application on the injured area it can be not dried quickly.
Creams are moisturized the skin by using the moisturizer in the formulation.	Gels are not involving the moisturizer in the formulation.
It is compatible for the dried and flaky skin	It is not compatible for the dry skin.
Rheology of the cream are not altered.	Rheology of some gels altered due to the effect of

	temperature, humidity and other environmental factors.
It is not formed a floccule.	It can be making floccules and make unstable gels formulations.
It is used for both water soluble and organic solvent soluble drugs.	It is used for only water-soluble drugs.

[2,6].

CONCLUSION

On the basis of study it I was concluded that the semisolid preparation are the best for the topical application of fungal infections.Topical drug delivery has 80- 90% bioavailability of the drug. Topical drug delivery has only one of the most barrier that is stratum corneum which is the upper layer of the skin. Skin is the starting of any topical route's administration of the drug. Any topical dosage form has to penetrate the stratum corneum. Topical drug delivery system involves the layers of the skin in which the drug is absorbed and goes to the systemic circulation It is increasing the bioavailability as well as mechanism of action in comparison to the gel.

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