



A review on antifungal gels: as a topical drug Delivery system

Shreeram Bangarwa¹, Shiv Garg^{*2}, Ajay Aseri³

¹Asst. Professor, Maharishi Arvind College of Pharmacy, Ambabari, Jaipur-302023, Rajasthan, India

²Associate Professor, Maharishi Arvind College of Pharmacy, Ambabari, Jaipur-302023, Rajasthan, India

³Asst. Professor, Maharishi Arvind College of Pharmacy, Ambabari, Jaipur-302023, Rajasthan, India

ABSTRACT

Topical drug delivery systems are gaining increase in popularity and several drugs have been successfully delivered by this route for both local and systemic action. In recent years, most of Anti – Fungal drugs have been designed to deliver the drug in the form of topical gels, to avoid gastrointestinal irritation, to overcome “first pass” effect and to maximize the drug concentration at the site of action. Gels have better potential as a vehicle to administered drug topically in comparison to ointment, because they are non-sticky requires low energy during the formulation². Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. There are various skin infections caused by fungus. An antifungal medication is a pharmaceutical fungicide used to treat mycoses such as athlete’s foot ringworm, candidiasis. Antifungal works by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effect on host.

Keywords: Antifungal, Fungicide, Topical drug, Skin, GIT.

INTRODUCTION

Fungal infection of skin is now-a-days one of the common dermatological problem. The physicians have a wide choice for treatment from solid dosage to semisolid dosage form and to liquid dosage formulation. Among the topical formulation clear transparent gels have widely accepted in both cosmetics and pharmaceuticals. [1]

***Corresponding Author:**

Dr. Shiv Garg

Associate Professor, Dept. of Pharmaceutics

Maharishi Arvind College of Pharmacy,

Jaipur-302023, Rajasthan, India

E.Mail: gargshiv81@yahoo.co.in

Article Received on: 24-09-2014

Revised on: 29-09-2014

Published on: 30-09-2014

Topical preparations are formulae which are applied directly to an external body surface by spreading, rubbing, spraying or instillation. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations. Gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. They are highly biocompatible with a lower risk of inflammation or adverse reactions, easily applied and do not needs to be removed. [3]

Topical treatment of dermatological disease as well as skin care, a wide variety of vehicle ranging from solids to semisolids and liquids preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparation. [1] Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal, and skin as topical routes. Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. [4]

Fungal infections usually occur as a result of decrease in the natural human defenses due to either immunosuppressive diseases or immune suppressive agents and also in association with opportunistic heavy exposure to the fungus. When fungi infect the skin surface, they invade the stratum corneum to avoid being shed from the skin surface by desquamation, so the management of the superficial fungal infection begins with topical agent that can penetrate the stratum corneum cells. So the topical treatment is greatly valuable when there are no extensive lesions and is much favorable as it generates high local tissue levels.

It is necessary to understand the anatomy, physiology, physicochemical properties of the skin to utilize the phenomenon of percutaneous absorption successfully. The skin of an average adult human covers a surface area of approximately 2 m² and receives about one-third of the blood circulating through the body. Microscopically skin is composed of three main histological layers: Epidermis, Dermis and Hypodermis (subcutaneous layer) as shown in fig.1.

The epidermis is 0.1 – 1.5 mm thick. It is further divided into five parts: stratum germinativum, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum, the epidermis forms the pigment

melanin. The squamous cell layer is the thickest layer of the epidermis and helps to move certain substances in and out of the body. The stratum corneum (“horny layers”) is made up of 10 to 30 thin layers of the dead cells. The outermost cells are replaced by new layers of cells. The dermis lies just beneath the epidermis, is 1.5 to 4 mm thick. It contains collagen, elastin, sweat and oil glands, hair follicles, nerve endings and blood and lymph vessels. Dermis also acts as storage for water. The dermis also contains scavenger’s cells from the immune system which engulf the foreign organism and destroy it. Nerve ending also is found in the dermis which is responsible for the sense of touch. The subcutaneous tissue (hypodermis) is the deepest layer of the skin. Subcutaneous tissue acts as an insulator-conserving body heat, and as a shock absorber protecting internal organs from injury. It also stores fat. The blood vessels, nerves, lymph vessels, and hair follicles also cross through these layers. [1, 4]

ROUTE OF PENETRATION

At the skin surface, drug molecules come in contact with cellular debris, microorganisms, and other materials, which effect permeation. The applied medicinal substance has three pathways to the viable tissue-

- 1) through hair follicles,
- 2) via sweat ducts and
- 3) across continuous stratum corneum between the appendages (hair follicles, sebaceous glands, eccrine, apocrine glands and nails).

Fractional appendageal area available for transport is only about 0.1% and is important for ions and large polar molecules. The intact stratum corneum is the main barrier and therefore many enhancing techniques aim to disrupt or bypass this layer. Viable layers may metabolize a drug, or activate a prodrug.

Usually, deeper dermal regions do not significantly influence absorption. For more than two decades, researchers have attempted to find a way to use the skin as a portal of entry for drugs in order to overcome problems associated with traditional mode of drugs administration. This route of drug delivery has gained popularity because it avoids first-pass effect, gastrointestinal irritation and metabolic degradation associated with oral administration. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects. In treating skin disease, the primary purpose of applying drug to the skin is to induce local effect at the site of application. In most of the cases, only a small portion of dose finally reaches the site of action, and produce limited local activity. This has been a complicated task due to the highly effective barrier properties of the skin. The fungal infections are very common and can be topical as well as systemic. The fungal infections can be treated by topically applied medicines as well as by oral administrations. However, oral use of medicine is not much important in treating local fungal infections and also has systemic side effect.

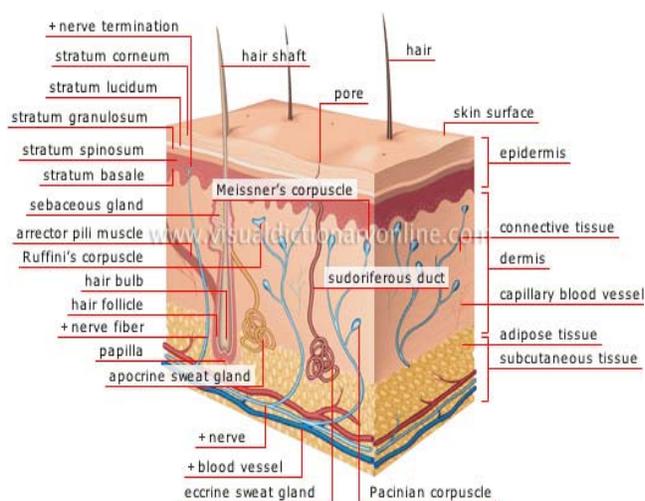


Figure 1: Structure of skin

Advantages of topical gel [4, 5]:

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks
- To avoid the first pass effect that is the initial pass of the drug substance through the systemic and partial circulation following gastrointestinal absorption, avoiding the deactivation by digestive and liver enzymes
- They are less greasy in nature and can be easily removed from the skin.
- Cost effective
- Reduction of dose as compare to the oral dosage form
- Localized effect with the minimum side effects

Disadvantages:

- 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 denature the drugs
- Larger particle size drugs not easy to absorb through the skin

Ideal properties of topical gel [5]:

- Should be inert, compatible with other additives
- Should be non-toxic
- Should be stable at storage condition

- Should be free from microbial contamination
- Should be maintain all rheological properties of gel
- Should be economical
- Should be washable with water and free from staining nature
- Should be convenient in handling and its application
- Should be passes properties such as thixotropic, greaseless and emollient

CLASSIFICATION OF ANTIFUNGAL DRUGS [6]:

1. Antibiotics:-

- A. Polyenes:- AmphotericinB, Nystatin, Hamycin, Natamycin
- B. Heterocyclic benzofuran:- Griseofulvin

2. Antimetabolite:- Flucytosine

3. Azoles:-

A. Imidazoles:- Clotrimazole, Econazole, Miconazole, Oxiconazole, Ketaconazole

B. Triazoles:- Fluconazole, Itraconazole, Voriconazole

4. Allylamine:- Terbinafine

5. Other topical agents:-

Tolnaftate, Undecylenic acid, Benzoic acid, Quiniodochlor, olamine, Butenafine, Sodium thiosulfate.

Gels are defined as “semisolid system in which a liquid phase is constrained within a polymeric matrix in which a high degree of physical and chemical cross-linking introduced”.

CLASSIFICATION OF GELS [1,7,10]:

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

1. Based on colloidal phases:

They are classified into

- Inorganic (two phase system)
- Organic (single phase system)

Two phase system:

If partial size of the dispersed phase is relatively large and form the three-dimensional structure throughout gel, such a system consists of floccules of small particles rather than larger molecules and gel structure, in this system is not always stable. They must be thixotropic-forming semisolids on standing and become liquid on agitation.

Single-phase system:

These consist of large organic molecules existing on the twisted strands dissolved in a continuous phase. This larger organic molecule either natural or synthetic polymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander walls forces.

2. Based on nature of solvent:

Hydro gels (water based):

Here they contain water as their continuous liquid phase E.g.: bentonite magma, Gelatin,

cellulose derivatives, carpooler, and poloxamer gel.

Organic Gels (with a non-aqueous solvent):

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

Xerogels:

Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and can be reconstituted. E.g. Tragacanth ribbons, acacia tear β -cyclodextrin, dry cellulose and polystyrene.

3. Based on rheological properties:

Usually gels exhibit non-Newtonian flow properties. They are classified into,

- a) Plastic gels
- b) Pseudo plastic gels
- c) Thixotropic gels.

(a) Plastic gels:

E.g. - Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

(b) Pseudo-plastic gels:

E.g.: - Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value. The rheogram results from a shearing action on

the long chain molecules of the linear polymers. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.

(c) Thixotropic gels:

The bonds between particles in these gels are very weak and can be broken down by shaking. The resultant solution will revert back to gel due to the particles colliding and linking together again. (The reversible isothermal gel-sol-gel transformation). This occurs in colloidal system with non-spherical particles to build up a scaffold like structure. E.g.: Kaolin, **bentonite and agar.**

4. Based on physical nature:

(a) Elastic gels:

Gels of agar, pectin, Guar gum and alginates exhibit an elastic behaviour. The fibrous molecules being linked at the point of junction by relatively weak bonds such as hydrogen bonds and dipole attraction. If the molecule possesses free $-\text{COOH}$ group then additional bonding takes place by salt bridge of type $-\text{COO}-\text{X}-\text{COO}$ between two adjacent strand networks. E.g.: Alginate and Carbapol.

(b) Rigid gels:

This can be formed from macromolecule in which the framework linked by primary valance bond. E.g.: In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

PREPRATION OF GELS [1, 7]:

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before

processing. Gels can be prepared by following methods.

1. Thermal changes

2. Flocculation

3. Chemical reaction

1) Thermal changes:

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. (Cooling of a concentrated hot solution will produce a gel). E.g.: - Gelatin, agar sodium oleate, guar-gummed and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

2) Flocculation:

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitant. E.g.: Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behaviour. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is

to "salt out", the colloidal and gelation doesn't occur.

3) Chemical reaction:

In this method gel is produced by chemical inter action between the solute and solvent. E.g.: aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), methane diphenyl isocyanine (MDI) that cross-links the polymeric chain

TYPES OF FUNGAL DISEASE:

- Skin infection: e.g. foot fungus (usually smelly but not life threatening, sometimes becomes serious), ring worms.
- Mucosal infections: oral or vaginal (range from annoying to painful to very difficult; uncomfortable but rarely life threatening).
- Systemic infection: fungus in the blood and tissues (immunocompromised population, usually life threatening).

EVALUATION OF GEL [5, 8, 9]:

Topical gel evaluated for following characters

- pH
- Drug contents
- Viscosity
- Spreadability
- Extrudability study
- In vitro release

- Stability
- Consistency

1. Measurement of pH

The pH of gel formulations are determined by digital pH meter. One gram of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

2. Drug content

1 g of the prepared gel is mixed with 100ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance is measured. Drug content is calculated using the equation, which is obtained by linear regression analysis of calibration curve.

3. Viscosity study

Viscosity of the prepared gel is measured by using Brookfield Viscometer. Rotations of gel are done at 0.3, 0.6 and 1.5 rotations per minute and at each speed, the corresponding dial reading is noted. The viscosity of the gel is obtained by multiplication of the dial reading with factor given in the Brooke field Viscometer catalogues.

4. Spreadability

Good spreadability is one of the criteria for a gel to meet the ideal properties. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. Spreading value effects on the therapeutic efficacy of a formulation. Spreadability is expressed in terms of time in seconds. It done by taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. Better

spread ability was shows when lesser the time taken for separation of two slides.

It is calculated by using the formula:

$$S = M. L / T$$

Where M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

5. Extrudability study

The formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

6. In vitro release

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) is taken in cellophane membrane and the diffusion studies are carried out at $37 \pm 1^\circ$ 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 h and each sample is replaced with equal volume of fresh dissolution medium. Then the samples are analyzed for the drug content by using phosphate buffer as blank.

7. Stability

The stability studies are carried out for all the gel formulation by freeze - thaw cycling. In this syneresis is observed by subjecting the product to a temperature of 4°C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted.

8. Consistency

The measurement of consistency of the prepared gels is done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The penetration by the cone is measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone is noted down after 10sec.

CONCLUSION

Nowadays gels are getting more popular because they are more stable and also can provide controlled release. Topical gel formulation by using novel approach shows enhanced drug action and active targeting with less side effects. As topical drug delivery system bypasses the G.I. system and first pass metabolism by the liver so it can be concluded that these dosage forms serves as the best in the treatment of diseases related to the GIT.

REFERENCES

1. B. Niyaz Basha, Kalyani Prakasam, Divakar Goli. "Formulation and evaluation of Gel containing Fluconazole-Antifungal Agent", *Int. J. Drug Dev. & Res.*, Oct-Dec 2011, 3(4): 109-128.
2. Phaldesai Saiesh, A.R.Shabaraya, Shripathy D. Leyana Soman, . "Formulation and evaluation of topical Gel containing Econazole nitrate", *Int. J. of Uni. Pharmacy & Biosciences*,2014:2319-8141.
3. Doaa A. Helal, Dalia Abd El-Rhman, Sally A. Abd El-Halim, Mohamed A. El-Nabarawal, " Formulation and Evaluation of Fluconazole Topical Gel ",*Int. J. Pharmacy & P'ceutical sciences*, Vol-4,Suppl 5,2012:0975-1491.
4. Prateek Chittodiya, Rajesh Singh Tomar, Umesh Ramchandani, Dr. Nimita Manocha, Dr. Shikha Agrawal, "Topical Gel-A Review", *Int.J. of Pharmaceutical & Biological Archives* 2013; 4(4): 606 – 613, ISSN 0976 – 3333.
5. S. J. Shelke, D. M. Shinkar, R.B. Saudagar, "Topical Gel: A Novel Approach For Development Of Topical Drug Delivery System", *International Journal Of Pharmacy & Technology* 2013, ISSN: 0975-766X.
6. Tripathi KD, "Essentials of Medical Pharmacology", Published by-Jaypee Brothers Medical Publishers (P) Ltd, Sixth Edition-2008, P.No.757.
7. Loveleen Preet Kaur, Tarun Kumar Guleri, "Topical Gel: A Recent Approach for Novel Drug delivery", *Asian Journal of Biomedical & Pharmaceutical Science* 2013, ISSN 2249-622X.
8. S.Roychowdhury, D.H.Singh, R.Gupta, D.Manish, "A Review on Pharmaceutical gel", *Int. J. Pharma.Res. Bio.* 2012, 1(5), pp21-36.
9. K.Saroha, S.Singh, A.Aggarwal, S.Nanda, Transdermal Gels- An alternative vehicle for drug delivery, *Int.J. Pharm. Chem. Biol. Sci.* 2013, 3(3), pp495-503.
10. Bharat Parashar, Atul Kabra, Ajay Chandel, "Formulation and Evaluation of Gel Containing Miconazole Nitrate an Antifungal Agent", *Int. J. of Pharma Research & Review*, June 2013; 2(6):18-28.