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AN OVERVIEW ON THE GEL FORMULATION

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ABSTRACT

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 readily accessible organs on human body for topical administration and is main route of topical drug delivery system. The objective of this paper is to discuss how the gel forms of drug becoming more popular due to ease of application and better percutaneous absorption.

Key words: Topical delivery, Gel, Gel forming agent.

INTRODUCTION

Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Fungal infections of skin are one of the common dermatological problems. Among the topical formulations a wide choice for the treatment from solid dosage to semisolid doses forms and to liquid dosage formulation the transparent gels have widely accepted in both cosmetics and pharmaceuticals.

A wide variety of vehicles ranging from solid to semisolids and liquid preparations are available for topical treatment of dermatological disease as well as skin care. Topical drug administration is a localised drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical route [1]. There are various medicated products that are applied to the skin that either enhances or restores fundamental functions of the skin. Such products are referred as topical or dermatological products. There are various Hydrophilic polymers such as carbopol 940, hydroxy propyl methyl cellulose (HPMC), Sodium alginate that are used in topical gel delivery system [2]. Based on molecular fraction these polymers are used concentration between 1-5 % in topical formulation

Anatomy of the human skin

The skin of an average adult body covers a surface area of approximately 2sq.m. And receives about one third of the blood circulating through the body and serves as a permeability barrier against the topical absorption of various chemical and biological agents to achieve a localized pharmacological action in the skin tissues in the various forms i.e., ointment, paste, creams, gels etc [3]. When topical gels are applied to the skin, the drug molecules are considered to diffuse to a target tissue and produce therapeutic effect prior to its systemic distribution for elimination. It is one of the most readily available organs of the body with a thickness of only a few millimetres **(**2.97 +0.28 mm**)**. The skin

- Separates the underlying blood circulation network from the outside environment.
- Serves as a barrier against physical, chemical & microbiological attacks.
- Acts as a thermostat in maintaining body temperature.
- Plays role in the regulation of blood pressure.
- Protects against the penetration of UV rays.

As skin is major factor in determining the various drug delivery aspects like permeation and absorption of drug across the dermis. The diffusion resistance of the skin is greatly dependent on its anatomy and ultra structure (fig.1). The skin is capable of metabolizing many substances and through its microvasculature, limits the transport of most substances into regions below the dermis. Although the flux of solutes through the skin should be identical for different vehicles when the solute exists as a saturated solution, the fluxes vary in accordance with the skin penetration enhancement properties of the vehicle. It is therefore desirable that the regulatory standards required for the bio-equivalence of topical products include skin studies. Deep tissue penetration can be related to solute protein binding, solute molecular size and dermal blood flow.

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Topical delivery

It is necessary to understand the anatomy, physiology and physiological properties of the skin. Microscopically skin is composed of three histological layers: epidermis, Dermis and Hypodermis (subcutaneous layer). 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 [1]. The squamous cell layer is the thickest layer of epidermis and helps to move certain substances in and out of the body. The stratum corneum is made up of 10-30 thin layers of dead cells.

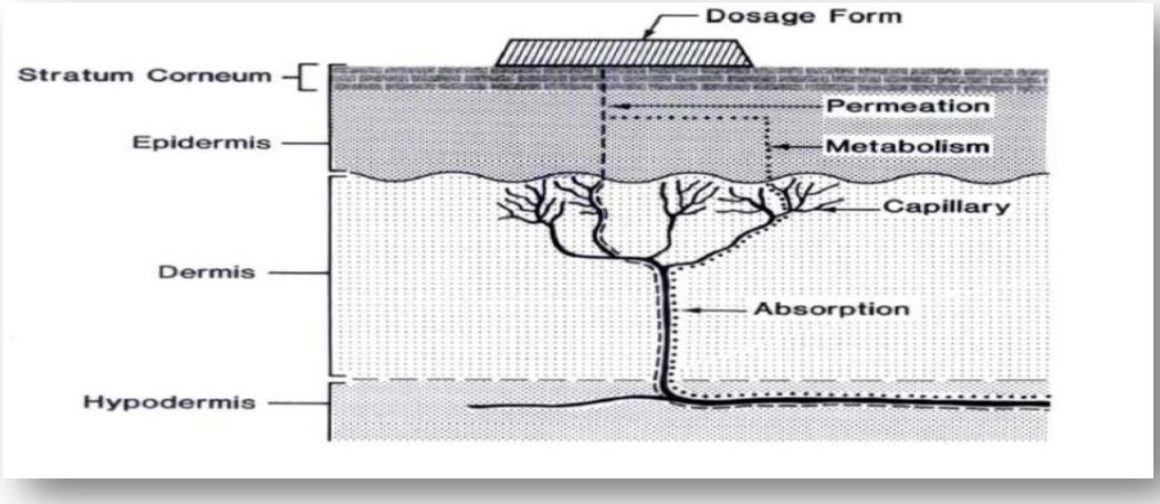

Figure 1. Skin anatomy

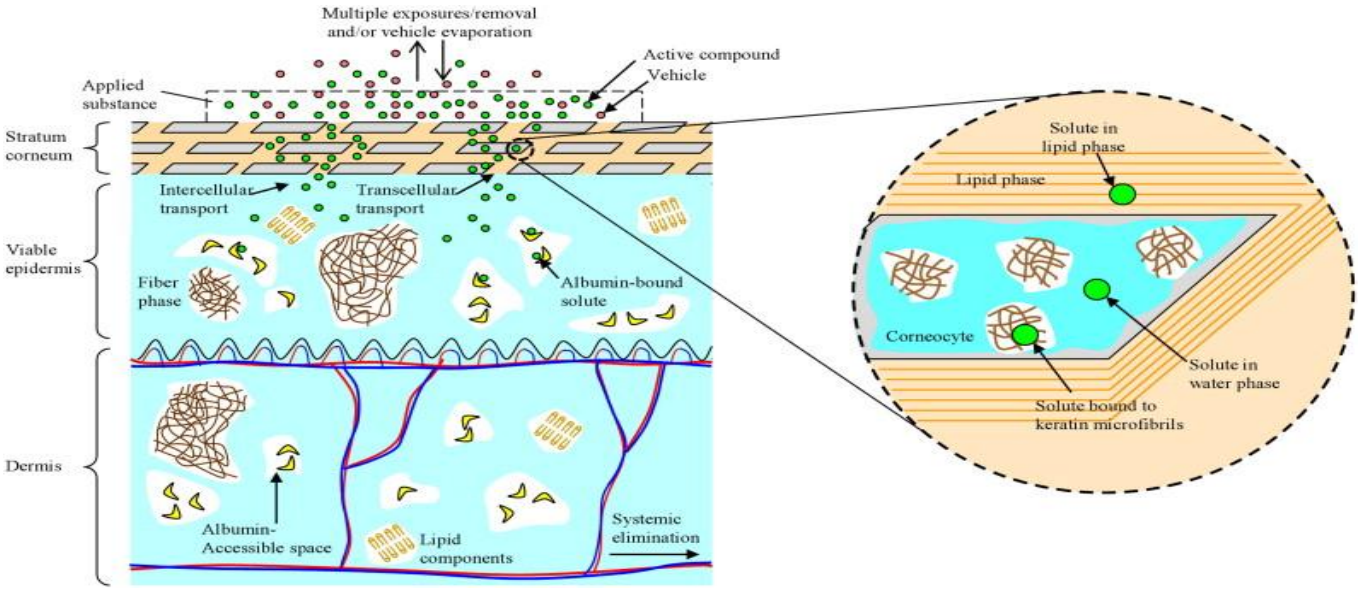

Figure 2. Mechanism of drug permeation through skin

Beneath the epidermis the layer dermis lies which is 1.5-4 mm thick. It consists of collagen elastins, sweat and oil glands, hair follicles, nerve endings, blood and lymph vessels. Dermis contain scavengers cell from the immune system which engulf the foreign organism and destroy them. Nerve endings are responsible for the sense of touch. The hypodermis also known as subcutaneous tissue is the deepest layer of skin which acts as an insulator conserving body heat and as a shock absorber protecting internal organ from injury. It also stores fat. The blood vessels, nerves, lymph vessels and hair follicles also cross linking through these layers.

Topical route of administration

Drug molecules contact at skin surface with cellular debris, microorganisms and other materials which effect permeation. The applied medicinal substances follow three pathways:

- Through hair follicles
- Across continuous stratum corneum
- Via sweat duct

This route of drug delivery has gained popularity because it avoids first pass metabolism, gastrointestinal irritation and metabolic degradation associated with oral administration. The pathway of drug movement through this layer is believed to be mainly transcellular. Although the paracellular pathways becomes important for small molecular weight compound. Being a diffusion barrier the stratum corneum also serves as a reservoir for compound such as corticosteroids, grisofulvin and many other drugs. Upon reaching the subcutaneous tissue there is evidence that some drugs e.g. Like thyroxin estradiol and corticosteroids remain in this layer for an extended period of time or for prolonged release of drugs.

Fungal infections are very common and can be topical as well as systemic. Treatment of fungal infection includes medicines like fluconazole, miconazole, ketoconazole, clotrimazole and grisofulvin [6].

Gel

The term gel was introduced in late 1800 to name sum semisolid material according to pharmacology. The USP defines gel as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing an interpenetrated by liquid. The inorganic particles form a three dimensional structure. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved into the continuous phase [7].

Classification of gels: Gels can be classified depending upon colloidal phases and nature of solvent used, physical nature and rheological properties [8].

A. Based on colloidal

- **Two phase system(Inorganic) –** If the 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 layer 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 (organic) –** These consists of large organic molecules existing on the twisted stands dissolved in a continuous phase. These organic molecules either natural or synthetic polymer are referred as gel forms.

B. Based on nature of solvent used

- **Hydro gel (water based) –** In hydro gels water acts as a continuous liquid phase. E.g. gelatin, cellulose derivatives, poloxamer gel.
- **Organic gels (with a non aqueous solvent) –** They contain a non aqueous solvent on their continuous phase. E.g. Plastibase olag gel and dispersion of metallic state in oils.
- **Xerogels –** these are solid gels with low solvent concentration. They are formed by the evaporation of solvent leaving the gel framework behind. On contact with fresh fluid they swell and can be reformed. E.g. tragacanth ribbons, dry cellulose and polystyrene.

C. Based on rheological properties they are classified into three types

- **Plastic gel –** Flocculated suspensions of aluminium hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of gels above which the elastic gel distorts and begins to flow.

- **Pseudo plastic gel –** For example liquid dispersion of tragacanth, sodium alginate etc exhibit pseudo plastic flow. There is a decrease in the viscosity of this type of the gel with the increasing rate of shear, the rheogram results from the shearing action on the long chain molecules of the linear polymer. As the shearing stress increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.

- **Thixotropic gel-** In this type of gel the bonds between the particles 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, e.g. bentonite and agar.

D. Based on physical nature

Elastic gel – Due to elastic behaviour of agar, pectin, guar gum the fibrous molecules being linked at the point of junction by relatively weak bond such as hydrogen bonds and dipole attraction. E.g. alginate and carbopol.

- **Rigid gels –** In this type of gel macromolecules in which the framework linked by primary valance bond .e.g. Silica gel [6].

Bases or gel forming polymers

Polymer is simply a compound made up of repeating units. Polymers are used to give the structural network which is essential for the preparation of gels [8].

Gel forming bases or polymers is classified as follows: -

1. Natural polymers – Natural polymers are those polymers which exist naturally and can be synthesized by living bodies, e.g. Proteins like collagen, gelatine etc and polysaccharides like agar, tragacanth, pectin and gum etc.

2. Semi synthetic polymers – These polymers are mostly derived from natural polymers by chemical modification, e.g. cellulose derivatives like carboxymethylecelulose, methylcellulose, hydroxypropyl cellulose and hydroxyethyle cellulose.

3. Synthetic polymers – The polymers which are prepared in laboratories are called synthetic polymers. These are also called man made polymers, e.g. Carbomer carbopol 940, carbopol 934, Poloxamer, Polyacrylamide, Polyvinyl alcohol and Polyethylene.

4. Inorganic substances – Aluminium hydroxide and Besitonite.

5. Surfactants – Sebrotearyle alcohol and Brij-96.

Preparation of gels

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 [6].

- 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 gelation occurs (Cooling of a concentrated hot solution will produce a gel), e.g. Gelatin, agar sodium oleate, guar gum 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.

- 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.
- 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.

Mechanism of Drug Absorption

The rate of permeation across various layers of skin tissues in the course of topical application can be expressed mathematically as

$dQ / dt = Ps (Cd – Cr)$

Where dQ / dt = rate of permeation across various layers.

Cd = concentration of drug in the donor phase.

Cr = concentration of drug in the receptor phase.

Ps = permeability coefficient of the skin tissues.

The concentration in the systemic circulation which is penetrating in the form of pharmacological active form such as:

$Ps = KcDs / hs$

Where Kc = partition coefficient of the penetrate molecules.

hs = overall thickness of the skin tissues.

Ds = apparent diffusivity for the steady state diffusion of penetrate moles.

If Cd >>> Cr than the equation is written as

$dq / dt = PsCd$

Physiological factors in percutaneous absorption

1. Skin integrity
2. Hydration
3. Temperature
4. Anatomic location
5. Age
6. Disease

Formulation factors in percutaneous absorption

1. Occlusivity
2. Drug concentration
3. pH
4. Solubility
5. Surfactant
6. Penetration enhancer

ADVANTAGES OF TOPICAL GEL

- 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 fallowing gastrointestinal absorption, avoiding the deactivation by digestive and liver enzymes.
- They are less greasy and can be easily removed from the skin.
- Cost effective
- Reduction of dose as compare to the oral dosage form.
- Localised effect with the minimum side effects.

DISSADVANTAGES OF TOPICAL DRUG DILEVERY SYSTEM

Skin irritation of contact dermatitis may occur due to the drug and/or excepients.

- 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.
- Drugs of larger particle size not easy to absorb through the skin

CONCLUSION

The gels play an important role in the topical drug delivery system. They avoid gastrointestinal drug absorption difficulties caused by gastrointestinal ph and enzymatic activity and drug interaction with food and drinks. They have localised effect with the minimum side effects. They also avoid the first pass metabolism.

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