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TOPICAL GEL AS DRUG DELIVERY AGENT: A CONCISE REVIEW

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ABSTRACT

Topical drug delivery is defined as the application of dosage form to the skin for direct treatment of skin disorder or the skin manifestation of the disease with the intent of confining the pharmacological or other effect of the drug to the surface of the skin. Topical drug delivery systems include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays and solid powders. Most widely used semisolid preparation for topical drug delivery include gels, creams and ointments. A gel is a cross-linked polymer network swollen in a liquid medium. Its properties depend strongly on the interaction between solid state polymer and the liquid component. Gels exhibit no steady-state flow. The clinical evidence indicates that topical gel is a safe and effective treatment option for use in the management of skin related disease and used for local action to reduce the side effects associated with other conventional dosage form .This review is concern with all detail information regarding advantages, disadvantages, structure of skin, methods of preparation desirable properties of gels and gellants.

KEYWORDS: Topical gel, polymer, skin, gellants.

INTRODUCTION

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 Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations.

ADVANTAGES OF TOPICAL SYSTEMS[1.2]

- Though least therapeutic interest but of practical relevance is a patient compliance. The systems are easy to apply and remove. It avoids risk and inconveniences associated with intravenous therapy.
- They eliminate the variables, which influences gastrointestinal absorption such as food intake, stomach emptying, intestinal motility and transit time.
- Produces sustained and controlled level of drug in plasma thus reduces the chance of over or under dosing.
- Reduces frequency of drug dosing.
- Topical systems are easily retractable thereby termination of drug input, if toxic effects are observed.

DISADVANTAGES OF TOPICAL SYSTEMS[2]

- Drugs with reasonable partition coefficient and possessing solubility both in oil and water are most ideal, as drug must diffuse through lipophilic stratum- corneum and hydrophilic viable epidermis to reach the systemic circulation. Only drugs, which are effectively absorbed by the percutanoeus routes or by using penetration promoters, can be considered.
- The route is not suitable for drugs that irritate or sensitize the skin.
- Topical drug delivery systems rare relatively expensive compared to conventional dosage forms.

2. Skin[3,4[

Anatomy of skin

Skin is composed of three primary layers:

- Epidermis,
- Dermis
- Hypodermis

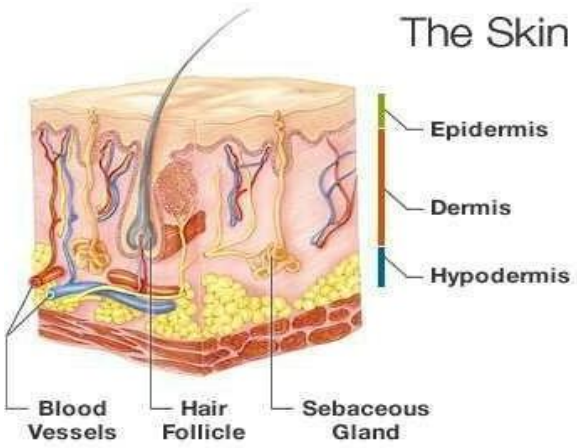

Figure 1: Structure of skin.

➢ **Epidermis**

The epidermis is the outermost layer of the skin. The average epidermal thickness is 0.1 millimeters, which is about the thickness of one sheet of paper. The epidermis acts as a protective shield for the body and totally renews itself approximately every 28 days.The epidermis contains no blood vessels, and cells in the deepest layers are nourished almost exclusively by diffused oxygen from the surrounding air and to a far lesser degree by blood capillaries extending to the outer approximately every 28 days.

Epidermis is divided into the following 5 sublayers or strata:

- **Stratum Corneum** composed of dead cells called keratinocytes, the stratum corneum is the outermost layer of skin, acting as a barrier to keep bacteria out and hold moisture in. As we age, this barrier deteriorates becoming crusty and flaky. Gentle exfoliants can help remove the outermost cells and help skin regain a youthful appearance while preserving this important layer of defense. The fifth layer, or horny layer, is called the stratum corneum. This is the top, outermost layer of the epidermis and is 25-30 layers of flattened, dead keratinocytes. This layer is the real protective layer of the skin. Keratinocytes in the stratum corneum are continuously shed by friction and replaced by the cells formed in the deeper sections of the epidermis. In between the keratinocytes in the stratum corneum are epidermal lipids (ceramides, fatty acids, and lipids) that act as a cement (or mortar) between the skin cells (bricks). This combination of keratinocytes with interspersed epidermal lipids (brick and mortar) forms a waterproof moisture barrier that minimizes transepidermal water loss (TEWL) to keep moisture in the skin. This moisture barrier protects against invading microorganisms, chemical irritants, and allergens. If the integrity of the moisture barrier is compromised, the skin will become vulnerable to dryness, itching, redness, stinging, and other skin care concerns.In the very outer layers of the stratum corneum, the moisture barrier has a slightly acidic pH (4.5 to 6.5). These slightly acidic layers of the moisture barrier are called the acid mantle. The acidity is due to a combination of secretions from the sebaceous and sweat glands. The acid mantle functions to inhibit the growth of harmful bacteria and fungi. The acidity also helps maintain the hardness of keratin proteins, keeping them tightly bound together. If the skin's surface is alkaline, keratin fibers loosen and soften, losing their protective properties. When the pH of the acid mantle is disrupted (becomes alkaline)—a side effect of common soaps—the skin becomes prone to infection, dehydration, roughness, irritation, and noticeable flaking.

- **Stratum granulosum**: It is composed of 3-5 layers of flattened keratin—a tough, fibrous protein that gives skin its protective properties. Cells in this layer are too far from the dermis to receive nutrients through diffusion, so they begin to die.

- **Stratum lucidum:** Stratum lucidum, or the clear layer. This layer is present only in the fingertips, palms, and soles of the feet. It is 3-5 layers of extremely flattened cells.

- **Stratum spinosum:** Stratum spinosum, or the prickle-cell layer. The stratum spinosum is composed of 8-10 layers of polygonal (many sided) keratinocytes. In this layer, keratinocytes are beginning to become somewhat flattened.

- **Stratum basal:** This is the deepest layer of the epidermis and sits directly on top of the dermis. It is a single layer of cube-shaped cells. New epidermal skin cells, called keratinocytes, are formed in this layer through cell division to replace those shed continuously from the upper layers of the epidermis. This regenerative process is called skin cell renewal. As we age, the rate of cell renewal decreases. Melanocytes, found in the stratum basal, are responsible for the production of skin pigment, or melanin. Melanocytes transfer the melanin to nearby keratinocytes that will eventually migrate to the surface of the skin. Melanin is photoprotective: it helps protect the skin against ultraviolet radiation (sun exposure).

➢ **Dermis:** Dermis is the layer of skin beneath the epidermis that consists of epithelial tissue and cushions the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane. It also harbors many nerve endings that provide the sense of touch and heat. It contains the hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood

vessels. The blood vessels in the dermis provide nourishment and waste removal from its own cells as well as from the stratum basal of the epidermis.

➢ **Hypodermis**

Hypodermis is not part of skin, and lies below the dermis. Its purpose is to attach the skin to underlying bone and muscle as well as supplying it with blood vessels and nerves. It consists of loose connective tissue, adipose tissue and elastin. The main cell types are fibroblasts, macrophages and adipocytes (hypodermis contains 50% of body fat). Fat serves as padding and insulation for the body.

Physiology of skin

The skin forms a relatively waterproof layer, provided mainly by its keratinised epithelium which protects the deeper and more delicate structures. Dehydrocholesterol is a lipid-based substance in the skin, and ultraviolet light from the sun converts it to vitamin D Sensory receptors consist of nerve endings in the dermis that are sensitive to touch, pressure, temperature or pain. Passive diffusion is the major process of absorption of drug molecules into the skin. The rate of drug transport across the skin layers obeys Fick's Law of diffusion. The skin is a minor excretory organ for some substances. Primarily, the chemical moieties are transported through the keratin-packed corneocytes via partitioning into and out of the cell membrane (transcellular). Secondly, the molecule is transported around the corneocytes in the lipid rich extracellular regions (intercellular).

3. Classification of gels[5,6]

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

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.

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 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.

Based on rheological properties

- **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.

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.

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.

Gel forming bases or polymers is classified as follows.

- **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.
- **Semi synthetic polymers –** These polymers are mostly derived from natural polymers by chemical modification e.g. cellulose derivatives like carboxymethylcellulose, methylcellulose, hydroxypropyl cellulose and hydroxyethyl cellulose.

- **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.
- **Inorganic substances –** Aluminium hydroxide and Besitonite.
- **Surfactants –** Sebrotearyle alcohol and Brij-96.

4. Methods of preparation of gels[7-10]

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.

- **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.

5. 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.

6. Marketed Preparations of Gel

Brand name	Composition	Company	Packing
LULICAN Gel	Luliconazole 2% w/w	GLAXO SMITHKLINE	5 gm
ITRACIN Gel	Itraconazole 1.5% w/w	INTRA LABS	5 gm
MICONA-Z Gel	Miconazole nitrate 2% w/w	IND-SWIFT	5 gm
MUCIDAL Gel	Mupirocin 2% w/w	INTAS	5 gm
MUPIN B Gel	Mupirocin 2% w/w, betamethasone dipropionate 0.05% w/w	GARY PHARMA	5 gm
ERYTHROVA Gel	Erythromycin 2.5% w/w	ZUVENTUS	5 gm
SUPIROCIN Gel	Mupirocin 3% w/w	GLENMARK	5 gm

7. Recent advancement in topical drug delivery system

Novel topical drug delivery systems

- Organogels
- Emulgels
- Microsponges
- Novel vesicular carriers
- Liposomes (liposomal gel)
- Niosomes (Proniosome gel)
- Transferosomes
- Ethosomes
- Hydrogels

Organogels[11,12]

Organogel, a viscoelastic system can be regarded as a semi-solid preparation which contains an immobilized external apolar phase. The apolar phase gets immobilized within spaces of the three-dimensional network structure formed by the physical interactions amongst the self assembled structures of compounds regarded as gelators. Generally, organogels are thermodynamically stable in nature and have been explored as matrices for delivering bioactive agents.

Emulgels[13]

Emulgels are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. It is stable and superior vehicle for

hydrophobic or poorly water soluble drugs. In short, emulgels are the combination of emulsion and gel.

Emulgel is composed of two parts.

- Emulsion
- Gel

Liposomal gel[14]

Liposomes established themselves as a promising novel drug delivery vehicle in several different basic sciences and as a feasible alternative in several applications. Liposomes are microscopic spheres with an aqueous core surrounded by one or more external shells consisting of lipids arranged in a bilayer configuration. Liposomes are acceptable and better-quality carriers having capability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. It also has affinity with keratin of horny layer of skin and can penetrate deeper into skin and hence give better absorption. Liposomes when applied on skin may act as a solublizing matrix for poorly soluble drugs, penetration enhancer and as local depot at the same time diminishing the side effects of these drugs.

Microsponges

Microsponge are uniform, spherical, porous polymeric microspheres having numerous interrelated voids of particle size range 5-300 µm. These have the capacity to entrap a wide range of active ingredients such as essential oils, emollients, fragrances, sunscreens and anti-infective, etc. are used as a topical carrier system.

Microspheres having average size of 25 µm in diameter and embedded in the vehicle, act like microscopic sponges

➢ **Vesicular carriers**[15-17]

The field of pharmaceutical science has been developing steadily over the years, and today it has become priceless in helping to keep us healthy and prevent disease.

Principal components used in different vesicular systems for topical drug delivery are.

- Liposomes
- Niosomes
- Ethosomes
- Transferosomes

- **Liposomes**

Liposomes can be defined as a colloidal, vesicular structures composed of one or more lipid bilayers surrounding a number of aqueous compartments .These are spherical vesicles with particle size ranging from 20 nm to several µm that are composed of a phospholipid bilayer membrane and are used to deliver drugs into cells.

- **Niosomes**

They consist of microscopic lamellar structures formed with a mixture of non-ionic surfactant and cholesterol having a bilayer structure formed by self-assemblage of hydrated surfactant monomers. There are mainly two types of components i.e. non- ionic surfactants and the additives.

- **Ethosomes**

Ethosomes are novel lipid carriers that are the modified forms of liposomes containing high ethanol content. They contains phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water having a size range from 10 nm to microns. Size of ethosomes depends upon the means of preparation and application of techniques like sonication. Ethosomes are mostly used for the delivery of drugs through transdermal route.

- **Transfersomes**

A novel vesicular drug carrier system called transfersomes that is composed of phospholipid, surfactant, and water to enhance transdermal delivery. Transfersomes are a form of elastic or deformable vesicle, which were first introduced in the early 1990s.

➢ **Hydrogels**[18]

Hydrogels are three-dimensional cross-linked polymer network that can respond to the fluctuations of the environmental stimuli. These biomaterials can incorporate large quantum of biological fluids and swell. When swelled, they are soft & rubbery and resemble the living tissue, exhibiting excellent biocompatibility.

Some latest novel advancemnt intopical drug delivery system.

Abitha M H, 2015	Developed Ethosomes with the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.
V.Viswanath, 2017	Clarithromycin gel was formulated with different types of gelling agents Na CMC, HPC, Guar gum and Poloxamer 407 showed favorable and acceptable physical properties concerning color, pH, homogeneity, spreadability, drug content, consistency of drug release study.
Gyati Shilakari Asthana, 2018	Niosomal formulation was successfully prepared by thin film hydration technique using different ratios of cholesterol and surfactant (Span 60) and dicetyl phosphate (DCP). It was found that niosomal formulation N2 having cholesterol : surfactant ratio (1 : 1) showed better entrapment efficiency and *in vitro* release profile.
Upendra Nagaich, 2017	Develops hydrogels and found that the cooling effect of the hydrophilic gels provided more effect on reduction of aging than the vasoconstriction of caffeine. Glycerol is a better alternative for the

	Improvement of the solubility and penetration through the skin.
Abhijeet Ojha, 2017	Developed emulgels, have ahigher aqueous component which permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid.
Flowerlet Mathew, 2018	Developed microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to130°C). Microsponges exhibit good compatibility with various vehicles and ingredients. Microsponges have high entrapment efficiency up to 50 to 60%.

8. CONCLUSION

Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. The main advantage of topical delivery system is to bypass first pass metabolism. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time are other advantage of topical preparations. Moreover, patient acceptability is better than other drug delivery systems owing to its noninvasiveness. The topical drug delivery system is generally used where the others system of drug administration fails. Gels have become a premier materials used for drug delivery formulations due to its biocompatibility, network structure, and molecular stability of the incorporated bioactive agent.

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