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# A Review on Topical Gels as Drug Delivery System

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## ABSTRACT

The clinical evidence indicates that topical gel is a safe and most 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. 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 includes 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 interaction between polymer and the liquid dispersion medium form an interlacing three dimensional network of particles of dispersed phase. The increased viscosity caused by interlacing and consequential internal friction is responsible for the semisolid state. Topical gel formulation provides a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Gel formulation provides better application property and stability in comparison to cream and ointments.

**Keywords:** Topical, drug delivery, gels, review, skin. Percutaneous penetration, drug delivery, organogels, Hydrogel.

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## INTRODUCTION

Topical drug delivery can be defined as application of drug via skin to directly treat or cure the skin disorders. These topical drug delivery systems are generally used for local skin infection like fungal infection or where other route of administration are no suitable.[1]It can penetrate deeper into skin and hence give better absorption. Topical application has no of advantages over the conventional dosage forms. In general, they are deemed more effective less toxic than conventional formulations due to the bilayered composition and structure. In the formulation of topical dosage forms, attempts has being made to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to ensure adequate Percutaneous absorption.[2] Topical preparation prevents the GI-irritation, prevent the metabolism of drug in the liver so as increase the bioavailability of the drug. Topical preparations give its action directly at the site of action. A gel is a two-component, cross linked three-dimensional network consisting of structural materials. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarilypolymers.[3]

U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. 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 in the continuous phase, randomly coiled in the flexible chains.[3]

### 1. Topical Drug Delivery System

A topical delivery system defined as the substance that carries a specific drug into contact with and through the skin. The challenge to topical drug delivery is the transport across the skin barrier.

Topical delivery includes two basic types of product:

External topical that are spread, sprayed, or otherwise dispersed on to cutaneous tissues to cover the affected area.

Internal topical that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity.

For the most part 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. Although some unintended drug absorption may occur, it is sub therapeutics quantities and generally of minor concern.

**1.1.Advantages of topical drug delivery systems**[1, 4]

Avoidance of the first pass metabolism.

Convenient and easy to apply.

Avoidance of risks and inconveniences of the intravenous therapy and of diverse conditions of absorption like pH changes, presence of enzymes, gastric emptying time.

Easily terminate the medications, when needed.

Deliver drug more selectively to a specific site.

Avoidance of the gastro-intestinal incompatibility.

Providing utilization of drugs with short biological half life, narrow therapeutic window.

Improved patient compliance.

Provide suitability for self-medication.

Achievement of effectiveness with lower total daily dose of drug by continuous drug input.

Prevents fluctuation in drug levels, inter- and intra patient variations.

A quite large area of application in comparison with buccal cavity.

Ability to deliver drugs more selectively to a specific site.[1, 4]

**1.2. Disadvantages of topical drug delivery systems**:

Skin irritation or dermatitis may occur due to the drug or excipients.

Poor permeability of some drugs through skin.

Drugs with larger particle size can't be easily absorbed through the skin.

Possibility of allergic reactions.[5]

Can be used only for those drugs which need very small plasma concentration for action

The route is not suitable for those drugs that irritate or sensitize the skin[1, 4, 5]

## 2. Anatomy of Skin

Human skin comprises of three but mutually dependent tissues:

The stratified, vascular, cellular called as "epidermis" ·

Underlying dermis of connective tissues.

Hypodermis.[6] (fig.1)[7]

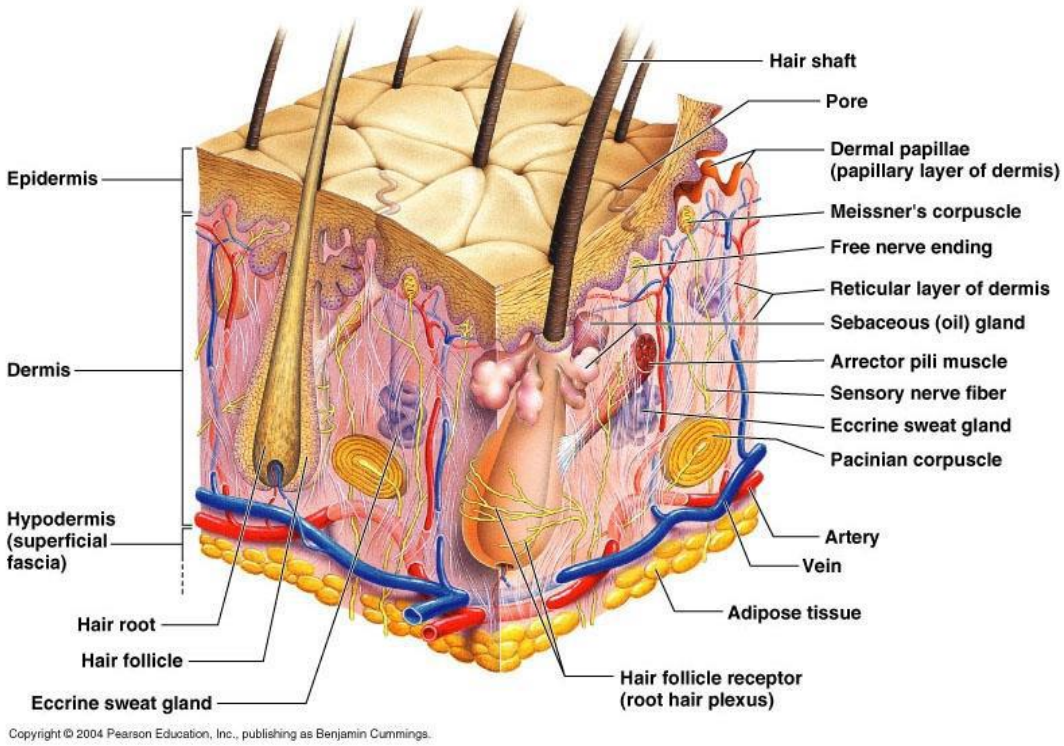


**Fig.1: Anatomy Of Skin**

### 2.1. Epidermis

The epidermis of the skin is formed by stratified epithelium, which is made up of 5 layers: [7, 8]

1. Stratum corneum.To (fig.2)[9]

2. Stratumlucidum

3. Stratum granulosum

4. Stratum spinosum and

5. Stratum germinativum

The most important feature of epidermis is that, it does not have blood vessels. The nutrition is provided by the capillaries of dermis.The epidermis is a stratified, squamous, keratinizing epithelium which is the topmost layer of skin. Above 90% are the keratinocytes, which is accountable for the barrier characteristics of the skin.[10] (see Figure 2)[1]

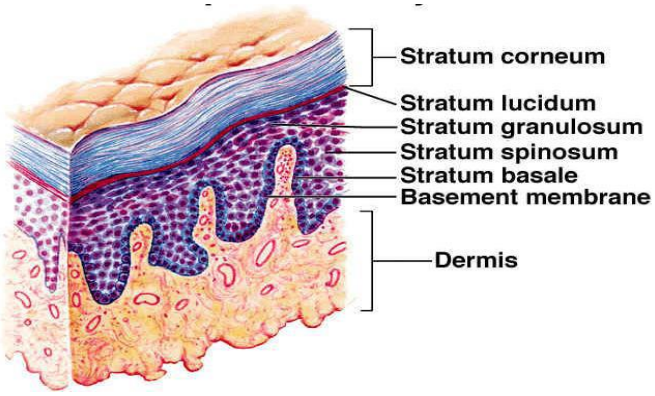


**Figure 2: Epidermal Layer**

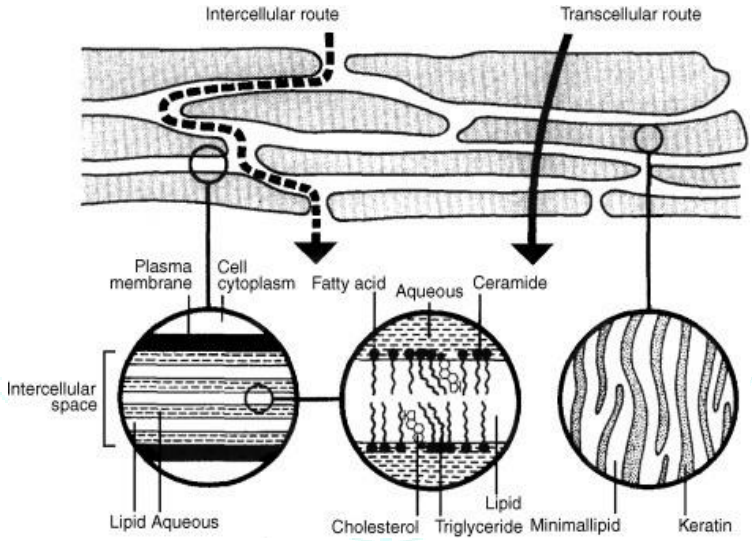


**Fig 3: Structure Of Stratum Coeneum**

**2.2. Dermis**: [11]

The dermis skin next layer is a thick layer of fibrous and elastic tissue mostly of collagen, elastin, and fibrillin give its flexibility and strength. the dermis contains nerve ending, sweat gland, oil gland, hair follicles and blood vessels[9].The dermis is a vascularized collagen-rich connective tissue containing mucopolysaccharides collectively known as the ground substance.[11]

**2.3. Hypodermis: [12]**

Hypodermis is the inner layer of skin. It is the contact layer between skin and the underlying tissues in body such as muscles and bone. Sweat glands, sebaceous glands and hair follicles enfold in epidermis but they stem from dermis. Sweat glands release a dilute salt solution into the surface of skin. The evaporation of this dilute salt solution makes skin cool and this is important for temperature regulation of both body and skin. Sweet glands are present all over the body. The amount of dilutions (sweet) that gets produced depends on environmental temperature, the amount of heat generating skeletal muscle activity and various emotional factors.Sebum is an oily liquid released into hair follicles and from there onto the skin surface. Sebum protects both hair and skin from drying out and provides waterproof layer[12]

## 3. Factors affecting topical absorption of drug[13, 14]

The factors that affect the topical absorption of drug are as follows

3.1. Physiological factors.

Skin thickness.

Lipid content.

Density of hair follicles.

Density of sweat glands.

Skin pH.

Blood flow.

Hydration of skin.

Inflammation of skin.

3.2.Physiochemical factors.

Molecular weight

Partition coefficient.

## 4. Classification of Gels[15, 16]

Gels are classified mainly by two methods based on:

**1) Nature of colloid phase**

a. Inorganic gels (Two phase system)

b. Organic gels (single phase system)

**2) Based on nature of solvent**

a. Hydrogel (Aqueous gels)

b. Xerogel[15]

c. Organicgel (Non aqueous gels)

**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

**4. Based on physical nature**

a. Elastic gel

b rigid gel[16]

## 5. Hydrogel[17]

Gels that consist of an aqueous dispersion medium that is gelled with a suitable hydrophilic gelling agent are known as hydrogels. By definition, hydrogels are polymeric networks with three-dimensional configuration capable of imbibing high amounts of water or biological fluids. Their affinity to absorb water is attributed to the presence of hydrophilic groups such as –OH, – CONH–, –CONH2–, and –SO3H in polymers forming hydrogel structures. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to different degrees, depending on the nature of the aqueous environment and polymer composition.[17]

**5.1.Type of Hydrogels**: [18]

pH – Sensitive Hydrogel

Temperature Sensitive Hydrogel

Nanohydrogels

Glucose Sensitive Hydrogel

## 6. Organogels[19]

Organogels may also be referred as oleaginous gels. They are composed of both polar and nonpolar groups but the ratio of the non-polar part is very high. They may contain 35% water as the gels tend to swell in water. Organogelators are usually low molecular weight small molecules that have the ability to thicken in organic solvents in physical organogels has grown rapidly with the discovery and synthesis of a very large number of diverse molecules, which can gel organic solvents at low concentrations.[19]

## 7. Desirable Properties Of Gels[4, 20]

Ideally, the gelling agent must be inert, safe and cannot react with other formulation constituents.

The gelling agent should produce a sensible solid-like nature at the time of storage which is easily broken when exposed to shear.

It should have suitable anti-microbial agent.

It should be no sticky.

The ophthalmic gel must be sterile.

The apparent viscosity or gel strength increases with an increase in the effective crosslink density of the gel. However, a rise in temperature may increase or decrease the apparent viscosity, depending on the molecular interactions between the polymer and solvent.

They exhibit the mechanical characteristics of the solid state.

Each component is continuous throughout the system.[4, 20]

## 8. Characteristics of Gels [21, 22]

**Swelling**: When a gelling agent is left in contact with a liquid that solvates it, then a considerable amount of liquid is absorbed by the agent and the volume increases. This process is called swelling. This phenomenon occurs as a result of solvent penetration into the matrix .

**Syneresis**: Many gels often contract spontaneously on standing and exude some fluid medium. This effect is known as syneresis. The degree to which Syneresis occurs, increases as the concentration of gelling agent decreases.

**Ageing**: Colloidal systems usually show slow aggregation naturally. This process is known as ageing. In gels, ageing causes gradual formation of a denser network of the gelling agent.

**Structure**: The rigidity in a gel results due to the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the stress, straighten them out and decrease the resistance to flow.

**Rheology**: Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic in nature, i.e. follow Non-Newtonian flow behavior, characterized by a reduction in viscosity with increase in shear rate.

## 9. Formulation Design[22]

Topical gel may include the following components:

9.1.Gel forming agent or polymer

9.2.) Drug Substance

9.3.Penetration Enhancers

### 9.1. Gel forming agent or Polymer [23]

Polymers are used to give the structural network, which

is essential for the preparation of gels. Gel forming

Polymers are classified as follows:

**Natural Polymers:** [23, 24]

Proteins – Collagen, Gelatin

Polysaccharides – Agar, Alginate acid,

Sodium or Potassium carageenan,

Tragacanth, Pectin, Guar Gum, Cassia

tora, Xanthan, Gellum Gum

**Semisynthetic polymers cellulose derivatives:**

Carboxymethyl cellulose, Methylcellulose, Hydroxyethyl cellulose

Hydroxypropyl cellulose, Hydroxy propyl (methyl

cellulose),

**Synthetic polymers:**

Carbomer – Carbopol 940,

Carbopol 934

Polyacrylamide

Poloxamer

Polyvinyl alcohol

Polyethylene and its copolymers

**Inorganic substances:** [25]

Bentonite

Aluminium hydroxide

**Surfactants:**

Cebrostearyl alcohol

Brij – 96

The following criteria should be satisfied for a polymer to be used in a topical system.

- Molecular weight.

Chemical functionality of polymer must allow diffusion and release of the specific drug

The polymer should permit the incorporation of a large amount of drug.

The polymer should not react, physically or chemically with the drug.

The polymer should be easily manufactured and fabricated into the desired product and inexpensive. .

Polymers and its degradation products must be nontoxic

### 9.2. Drug Substance [8, 26]

Drug Substance plays a very important role in the successful development of a topical product. The important drug properties that effect its diffusion through gels as well as through skin are as follows.

- **Physicochemical properties**

Drug should have a molecular weight of less than 500 Daltons.

Drug should have adequate lipophilicity

Drugs highly acidic or alkaline in solution are not suitable for topical delivery.

A saturated aqueous solution of the drug should have a pH value between 5 and 9[8]

- **Biological properties**

The drug should not be directly irritated to the skin.

Drugs, which those degrade in gastrointestinal tract or are inactivated by hepatic first pass effect, are suitable for topical delivery.

Tolerance to the drug must not develop under the near zero order release profile of topical delivery.

The drug should not stimulate an immune reaction in the skin.[26]

### 9.3. Penetration Enhancer[26, 27]

An ideal penetration enhancer should have the following properties:

It should have pharmacologically and chemically inert, and chemically stable.

It should be non-toxic, non-irritant, noncomedogenic and non-allergenic.

It should have a rapid onset of action, predictable duration of activity, as well as a reproducible and reversible effect.

It should be odorless, tasteless, colorless, and inexpensive.

It should have pharmaceutically and cosmetically acceptable.

It should be non-toxic, non-irritating, and non- allergenic.

It should have a solubility parameter similar to that of skin[26]

It should have no pharmacological activity within the body, i.e., should not bind to receptor sites.

.It should have appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.

It should have cosmetically acceptable with an appropriate skin "feel."[27]

## 10. Application Of Gel[28]

As drug delivery systems for orally administered drugs.

To deliver topical drug applied directly to the skin, eye or mucous membrane.

As long acting forms of drug injected intramuscularly.

In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations.

## 11. Evaluation of gels[29, 30,31,32,33,34]

**pH Measurement:** The pH of various gel formulations are determined by using digital pH meter.1 g of gel is dissolved in 100 ml. freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

**Viscosity Measurement:** Brookfield digital viscometer can be used to measure the viscosity of prepared gel formulations. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted. The viscosity of gel is obtained by multiplication of dial reading with factor given in the Brookfield viscometer catalogues .[29]

**Spread ability:** Spread ability refers to the extent of area to which gel readily spreads on application. It is determined by wooden block and glass slide apparatus. The time in sec. taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load is expressed as spreadability. Lesser the time taken for the separation of two slides, better the spread ability. Spread ability is calculated by using the formula:

**S = M.L / T**

Where, S = Spread ability

M = Weight tide to the upper slide

L = Length of a glass slide

T = Time taken to separate the slide completely from each other.

**Homogeneity:** All developed gels are tested for homogeneity by visual inspection after the gels have been set in the container. They are tested for their appearance and presence of any aggregates.[30]

**Grittiness-** All the gel formulations are checked microscopically for the presence of any particulate matter.

**Extrudability-** The gel formulations are filled in collapsible tubes, after being set in the containers. The extrudability of gel formulations are determined in terms of weight required in grams to extrude 0.5 cm. ribbon of gel in 10 sec.[31]

**Stability test-** Stability study is carried out by freeze-thaw cycling. The product is subjected to a temperature of 40C for

one month, then at 25 0C for one month followed by 40 0C for one month. Syneresis is observed. Finally, the gel is exposed to ambient room temperature and the separating liquid exudates are noted.

**Drug content:** 1 g gel is dissolved in 100 ml. of suitable solvent. Absorbance is measured after suitable dilution at λmax nm using UV spectrophotometer.[32]

***In-vitro* Drug Diffusion Study:** In-vitro drug release studies are carried out by using a Franz diffusion cell. 0.5 g of gel is taken in cellophane membrane. Diffusion studies are conducted at 37 0C ± 1 0C employing 250 ml. phosphate buffer, pH 7.4 as the dissolution medium.. At time interval of 1 hr, 1 ml pg sample is collected and replaced with new buffer solution. Collected samples are analyzed by using suitable analytical method [33]

**10. Skin irritation test:** Ten healthy male and female volunteers were selected for skin irritation testing. 100 mg gel was applied on area of 2 cm for 6 hours, on the interior surface of upper arm and covered with cotton bandage. After 6 hr the sites were cleaned with acetone and readings are made according to the scale given by Draize. No irritation: 0 Slight irritation: 1 Irritation: 2[33]

**11**. ***In-vivo* Study:** Inhibition of carrageenan induced rat paw edema is studied in male wistar albino rats using mercury plethysmometer. The volume of unilateral hind paw of experimental animals is measured, before and after administration of carrageenan. % inhibition is noted.[30, 34]

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