International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 271-278 www.ijprajournal.com ISSN: 2249-7781

A Brief Review on Topical Drug Delivery System and Gel

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Submitted: 02-01-2022 Accepted: 12-01-2022

ABSTRACT:
Clinical evidence indicates that topical gels are the safest and most effective treatment option for use in the treatment of skin-related diseases and are used topically to reduce associated side effects. in relation to other conventional dosage forms. On-site drug delivery systems accommodate a variety of pharmaceutical dosage forms such as semi-solids, liquid preparations, sprays and solid powders.The most widely used semi-solid preparations for topical administration include gels, creams, and ointments. A gel is a network of cross-linked polymers that swell in a liquid medium. Its properties strongly depend on the interaction between the polymer in the solid state and the liquid component. The gel did not show steady-state flow. The interaction between the polymer and the liquid dispersion medium forms an interwoven three-dimensional network of dispersed phase particles. The increase in viscosity caused by intercalation and as a result internal friction is responsible for the semi-solid state. Topical gel formulations provide a consistent drug delivery system because they are less greasy and can be easily removed from the skin. The gel formulation offers better application properties and better stability than creams and ointments.

KEYWORDS: Topicaldrugdelivery system, Anatomy of skin, Percutaneouspenetration,drugdelivery,types of gel

INTRODUCTION:

Topical use can be introduced as an application of transdermal medicine to directly treat or cure skin disorders. These topical drug delivery systems are typically used for local skin infections such as fungal infections or when another route of administration is not suitable.1 The drug can penetrate deeper into the skin and thus allow better absorption. Topical application has no advantages over conventional dosage forms. In general, they are known to be more effective and less toxic than conventional formulations due to their composition and bilayer structure. In the formulation of topical dosage forms, attempts have been made to use drug carriers that ensure adequate localization or penetration of the drug into or through the skin to enhance local effects and minimize systemic effect, or to ensure adequate transdermal absorption. Anti-irritation of the gastrointestinal tract, blocking drug metabolism in the liver to increase bioavailability of the drug. Topical preparations give its effect directly at the site of action. The gel is a three-dimensional, cross-linked, two-component network made of structural materials. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, mainly polymers.3 U.S.P. Gel is defined as a semi-solid system consisting of a dispersion consisting of small inorganic particles or large organic molecules containing and interspersed by a liquid. The gel consists of a two-phase system in which the inorganic particles are not dissolved but simply dispersed throughout the continuous phase and the large organic molecules are dissolved in the continuous phase, coiling a randomly into flexible strings.

❖ Topical Drug Delivery System

A topical delivery system is defined as a carrier for a specific drug in contact and through the skin. The challenge with topical drug use is delivery across the skin barrier.
Topical use includes two basic types:
• Topical medication that is spread, sprayed, or dispersed over skin tissue to cover the affected area.
• Internal medicine to be applied to mucous membranes by mouth, vagina or anorectal tissues for local action. For the most part, topical preparations are used to have a local effect at the site of application due to drug penetration into the underlying layers of the skin. Although some unintentional absorption may occur, these are sub-therapeutic amounts and are usually minor concerns.

❖ ADVANTAGES[1,4]:

➢ The transdermal drug delivers the drug at regular intervals over a long period of time,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 1 Jan-Feb 2022, pp: 271-278 www.ijprajournal.com ISSN: 2249-7781

thereby avoid unwanted side effects and also avoid the frequent treatment failures associated with intermittent dosing.

- Alternative routes for patients who cannot tolerate oral dosage forms such as patients who are vomiting.
- Increase the therapeutic value of many drugs by avoiding specific drug-related problems, for example, gastrointestinal irritation, malabsorption and drug interactions with food, drink, and drugs other used drugs.
- Avoid first-pass metabolism.
- Self-administered and non-invasive, avoiding the inconvenience of parenteral therapy.
- They are easily and quickly identified in an emergency (eg, an unconscious, unconscious or comatose patient) because of their physical presence, characteristics and telltale signs.

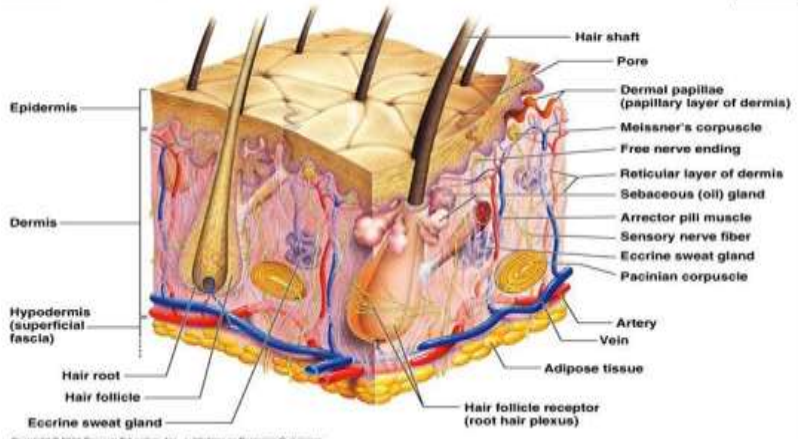
❖ **DISADVANTAGES:**

- Skin irritation or dermatitis may occur as a result of the drug or the excipients.
- Poor penetration of some drugs through the skin.
- Drugs with larger particle sizes cannot be easily absorbed through the skin.
- Possibility of allergic reactions 5
- Can only be used with drugs that require very low plasma concentrations to e effective
- Routes of administration are not suitable for drugs that cause skin sensitization or sensitization1,4,5

❖ **ANATOMYOF HUMEN SKIN**

Human skin is made up of three interdependent tissues:

Layered vascular tissue known as the "epidermis" · The dermis lies beneath the connective tissue : Hypodermis.[6](fig.1)[7]



Epidermis

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

- Stratumcorneum's(fig.2)[9]
- Stratumlucidum
- Stratumgranulosum
- Stratumspinosumand
- Stratumgerminativum

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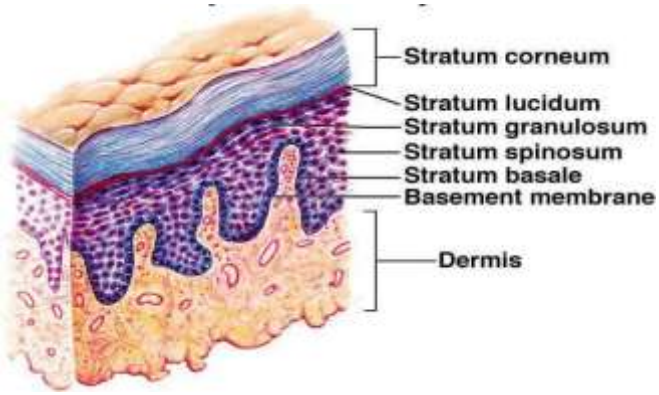
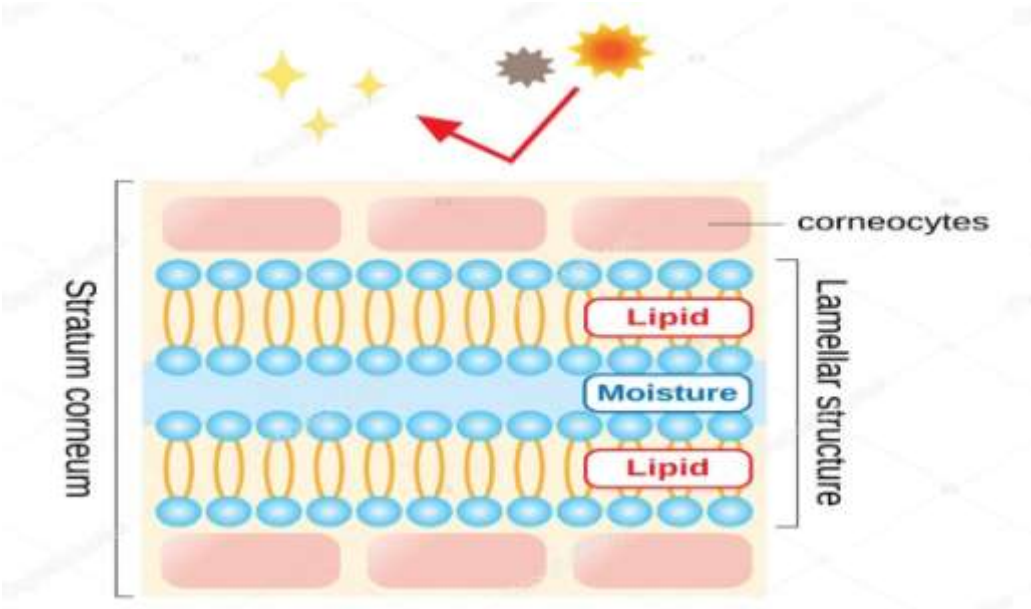


Figure2:EpidermalLayer



- **Dermis:**[11]

The next layer of skin in the dermis is a thick and elastic layer of fibrous tissue mainly composed of collagen elastin and fibrillin that gives the skin its suppleness and strength. The dermis contains nerve endings sweat glands sebaceous glands hair follicles and blood vessels9. The dermis is a collagen-rich vascular connective tissue containing mucopolysaccharides collectively known as the stroma.[11]

- **Hypodermis:**[12]

The dermis is the inner layer of the skin. It is the layer of contact between the skin and underlying body tissues such as muscles and bones. The sweat glands, sebaceous glands, and hair follicles enclose themselves in the epidermis, but they originate in the dermis. Sweat glands secrete a dilute salt solution onto the surface of the skin. The evaporation of this dilute salt solution cools the skin, which is important for regulating body and skin temperature. These routes are found throughout the body. The amount of (soft) diluent produced depends on the ambient temperature, the amount of heat generated by skeletal muscle activity, and various emotional factors. Sebum is an oily liquid that is secreted in the hair follicles and from there to the surface of the skin. Sebum protects hair and skin from drying out and provides a waterproof layer[12]

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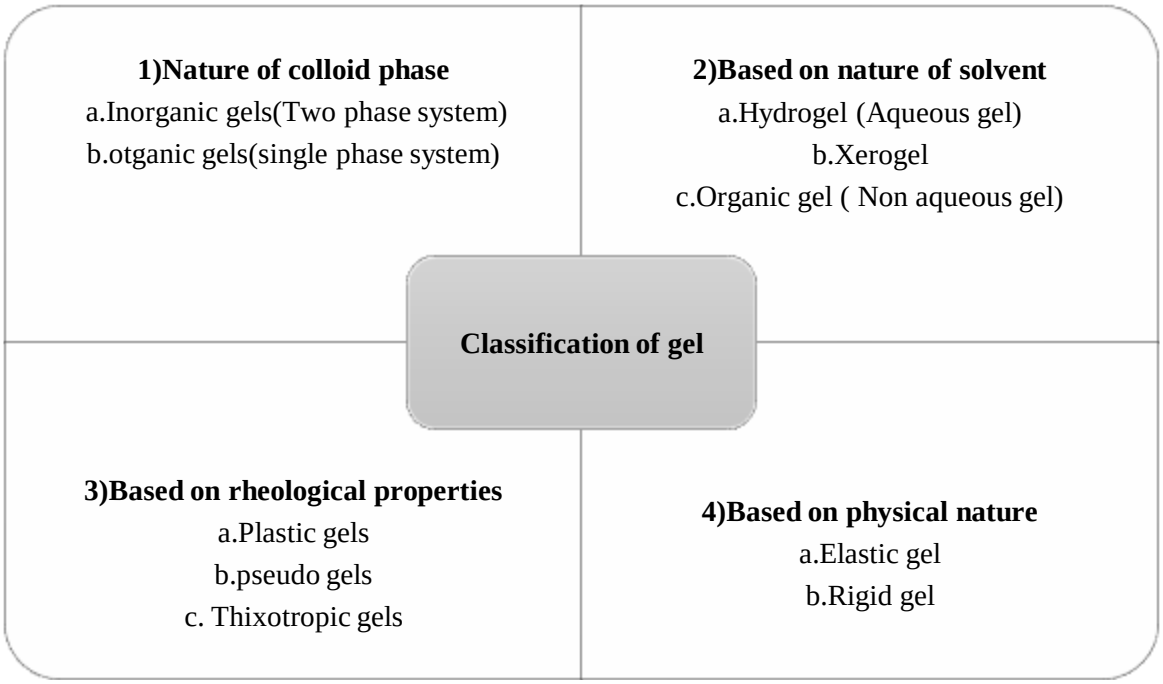
❖ FACTORS[13,14]

The factors that affect the topical absorption of drug are asfollows

Physiological	• Skin thickness • Lipid content • Density of hair follicles • Density of sweat glands • Skin pH • Blood flow • Hydration of skin • Inflammation of skin
Physiochemical	• Molecular weight • Partition coefficient

❖ CLASSIFICATION OF GELS [15,16]



❖ HYDROGEL[17]

The gel is made from a water-dispersible medium mixed with a suitable hydrophilic gelling agent known as a hydrogel. By definition, a hydrogel is a polymeric network with a three-dimensional configuration capable of absorbing large amounts of water or biological fluids. Their hydrophilic affinity is due to the presence of hydrophilic groups such as -OH, -CONH-, -CONH2- and -SO3H in the polymers forming the hydrogel structure. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to varying degrees, depending on the nature of the aqueous medium and the composition of the polymer.[17]

❖ TYPE OF HYDROGELS:[18]

- pH –Sensitive Hydrogel
- Temperature Sensitive Hydrogel
- Nanohydrogels
- Glucose Sensitive Hydrogel

❖ ORGANOGELS[19]

Organic substances can also be referred to as oil gels. They include both polar and non-polar groups, but the proportion of non-polar fractions is very high. They can contain 35% water because gels tend to swell in water. Organic substances are generally small, low-molecular-weight molecules capable of condensing in organic solvents into physical

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organic substances.[19]

❖ **PROPERTIESOFGELS[4,20]**

- Ideally, the gelling agent should be inert, safe, and unlikely to react with other ingredients in the formulation.
- The gelling agent must exhibit strong and sensitive properties during storage, and fragility when exposed

to shear.

- It must have the appropriate antibacterial agent. It should not be sticky.
- Ophthalmic gels must be sterile.
- The apparent viscosity or strength of the gel increases as the effective crosslinking density of the gel increases. However, an increase in temperature can increase or decrease the apparent viscosity, depending on the molecular interactions between the polymer and the solvent.

❖ **CHARACTERISTICSOFGELS[21,22]**

Swelling: When a gelling agent comes into contact with a liquid that melts it, a significant amount of the liquid is absorbed by the agent and the volume increases. This process is called swelling. This phenomenon occurs due to solvent penetration into the substrate.

Syneresis:Many gels usually contract spontaneously at rest and release some fluid. This effect is called fusion. The extent to which isomerization occurs increases as the concentration of the gelling agent decreases.

Ageing:Colloidal systems usually exhibit slow spontaneous aggregation. This process is called aging. In gels, aging causes the gradual formation of a denser gel-forming network.

Structure: The stiffness in the gel is the result of the presence of a network formed by the entanglement of the particles of the gelling agent. The nature of the particles and the stress straightens them out and reduces resistance to flow.

Rheology: Solutions of colloid and dispersions of coagulant solids are pseudoplastic in nature i.e. they obey non-Newtonian flow behavior which is characterized by a decrease in viscosity with an increase in shear rate.

❖ **FORMULATIONDESIGN[22]**

Topical gel may include the following components:

- Gelformingagentor polymer
- Drug Substance
- PenetrationEnhancers

- **GELFORMINGAGENTORPOLYMER[23]**

Polymers are used to give the structural network, whichis essential for the preparation of gels. Gel formingPolymersare classifiedasfollows:

Natural Polymers:[23,24]	✓ Proteins – Collagen, Gelatin ✓ Polysaccharides – Agar, Alginate acid, ✓ Sodium or Potassium carageenan,Tragacanth, Pectin, Guar Gum, Cassiatora,Xanthan,Gellum Gum
Semisyntheticpolymerscellulosederivatives:	✓ Carboxymethylcellulose,Methylcellulose,Hydroxyethylcellulose ✓ Hydroxypropyl cellulose, Hydroxy propyl (methylcellulose),
Synthetic polymers:	✓ Carbomer –Carbopol 94, ✓ Carbopol 934 ✓ Polyacrylamide ✓ Poloxamer ✓ Polyvinyl alcohol

- **DRUGSUBSTANCE[8,26]**

Pharmaceutical substances play a very important role in the successful development of a topical product. Important properties of the drug that affect its diffusion through the gel as well as through the skin are as follows.

- **Physicochemicalproperties**

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- ✓ The drug must have a molecular weight of less than 500 Daltons.
- ✓ Drugs must e appropriately lipophilic
- ✓ Drugs that are strongly acidic or alkaline in solution are not suitable for topical use.
- ✓ The saturated aqueous solution of the drug must have a pH between 5 and 9[8].

Biologicalproperties

- ✓ The drug should not cause direct irritation to the skin.
- ✓ Drugs that are degraded in the gastrointestinal tract or inactivated y primary action in the liver suitable for topical use.
- ✓ Tolerance is not developed below the near-zero release level when administered topically.
- ✓ The drug should not stimulate the immune response of the skin [26]

- **PENETRATIONENHANCER[26,27]**

- ✓ An ideal penetration enhancer should have the following properties:
- ✓ The substance should be pharmacologically and chemically inert and chemically stale.
- ✓ It must be non-toxic non-irritating non-comedogenic and hypoallergenic.
- ✓ It must have a rapid onset of action a predictable uptime as well as a reproducible and reversible impact.
- ✓ It must be odorless tasteless colorless and inexpensive.
- ✓ It must be used in pharmaceuticals and cosmetics. It must be non-toxic non-irritating and hypoallergenic.
- ✓ It must have a solubility profile similar to that of skin[26]
- ✓ It must not have any pharmacological activity in vivo i.e.; it must not find to receptor sites.
- ✓ It must be aesthetically acceptable with an appropriate feel on the skin[27].

❖ **APPLICATIONOFGEL[28]**

- ✓ As drug delivery system for oral drugs.
- ✓ For topical application to skin, eyes or mucous membranes.
- ✓ The long-acting form of the drug is administered intramuscularly.
- ✓ In cosmetic products such as shampoo, perfume, toothpaste, skin and hair care products.

❖ **EVALUATIONS[29-34]**

➢ **pH Measurement:** The pH of the different gel formulations was determined using a digital pH meter. one gm of gel was dissolved in 100 ml. freshly prepared distilled water stored for two hours. The pH measurement of formulation was performed in triplicate & the average values were calculated.

➢ **Viscosity Measurement:** The Brookfield Digital Viscometer can be used to measure the viscosity of prepared gel formulations. The gels were rotated at 0.3, 0.6 and 1.5 rpm. At each speed, the corresponding reading on the dial is recorded. Gel viscosity is obtained by multiplying the dial reading by the factor given in the catalog of the Brookfield viscometer..[29]

➢ **Spread ability:** Spreadability is the extent to which the gel spreads easily during application. It is determined by a device consisting of a block of wood and a slide. Weather in seconds. performed by two slides to slide the gel placed between the slides under the direction of a given load indicated by the spreading capacity. The less time separating the two slides, the better the chance of going viral. Spread is calculated according to the formula:

- o S=M.L/T
- o Where,S=Spreadability
- o M = Weight tide to the upper slideL=Lengthofaglassslide
- o T=Timetakentoseparatetheslidecompletelyfro meachother.

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

➢ **Grittiness:** All gel formulations are examined under a microscope for the presence of any particulate matter.

➢ **Extrudability:** Gel formulations are filled into collapsible tubes, after being placed into containers. The extrusion capacity of the gel formulation is determined by the weight required in grams to extrude 0.5 cm. duct tape for 10 seconds.[31]

➢ **Stabilitytest**-Stability studies were performed using the freeze-thaw method. The product is subjected to a temperature of 0°C. for one month, then 25°C. for a month followed by 0°C. for a month. Syneresis is observed. Finally, the gel was exposed at room temperature and exudates from the liquid were noted.

➢ **Drugcontent:**1 g of gel was dissolved in 100 ml. suitable solvent. Absorbance was measured after appropriate dilution to the maximum nm using a UV spectrophotometer.[32]

➢ **In-vitro Drug Diffusion Study:** In vitro drug

release studies were performed using Franz diffusion cells. 0.5 g of gel was obtained from the cellophane film. Diffusion studies were performed at 37°C. ±1°C. using 250 ml. phosphate buffer, pH 7. as the dissolution medium. Over a period of 1 h, 1 ml of pg sample was collected and replaced with fresh buffer. Collected samples were analyzed using an appropriate analytical method [33]

- **Skinirritationtest:** Ten healthy male and female volunteers were selected to test for skin irritation. 100 mg of gel is applied to a 2 cm area for 6 hours, on the inner surface of the arm and covered with a cotton bandage. After 6 h, the sites were cleaned with acetone and measurements were taken according to the scale given by Draize. No irritation: 0 Mild irritation: 1 Irritation:2[33]
- **In-vivoStudy:** Inhibition of carrageenan-induced rat leg edema was studied in male albino rats using a mercury pleurocentesis. The volume of the lateral hindfoot of experimental animals was measured, before and after the administration of carrageenan. % Inhibition was noted.[30,34]
- **Interaction studies:** Drugs and excipients must be compatible with each other to create a stable product. Drug and excipient interactions affect the bioavailability and stability of the drug. Although excipients are new and have not been used in formulations containing the active ingredient, compatibility studies played an important role in formulation and development. Interaction studies were performed by thermal analysis, FTIR, UV and chromatographic techniques by comparing their physicochemical properties such as dosage, melting point, wave number, absorption maxima[35-37]

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