ABSTRACT
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 forms. This review is concerned with all detail information regarding rational approaches to topical formulations, and their permeation.

Key words: Topical gel, topical formulations, side effects.

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 the human body for topical administration and is the main route of topical drug delivery system.

Topical preparations are applied to the skin for surface, local or systemic effects. In some cases, the base may be used alone for its therapeutic properties, such as emollient, soothing or protective action. Topically applied dermal and transdermal delivery systems could replace needles required to administer many of the new biologics-based drugs and vaccines, in addition to other significant advantages such as avoiding first-pass hepatic metabolism, gastrointestinal absorption such as food intake, stomach emptying, intestinal motility and transit time. However, the limited dermal and transdermal delivery of many small and large molecules is a significant challenge because of the unyielding barrier properties of the skin.

Topical preparations are used for both local and systemic effects. Systemic drug absorption should always be considered when using topical products if the patient is pregnant or nursing, because drugs can enter the fetal blood supply and breast milk and be transferred to the fetus or nursing infant.

TOPOCAL DELIVERY INCLUDES TWO BASIC TYPES OF PRODUCTS

- 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 a rectal tissue for local activity.

ADVANTAGES OF TOPICAL SYSTEMS
1. 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.
2. They eliminate the variables, which influence gastrointestinal absorption such as food intake, stomach emptying, intestinal motility and transit time.
3. Produces sustained and controlled level of drug in plasma thus reduces the chance of over or under dosing.
4. Reduces frequency of drug dosing.
5. Topical systems are easily retractable thereby termination of drug input, if toxic effects are observed.
6. Offers an alternative route when oral therapy is not possible as in case of nausea and vomiting.
7. Helps in achievement of more constant blood levels with lower dosage of drug by continuous drug input and by by-passing hepatic first metabolism and consequent degradation.
8. In certain circumstances, enzymatic may be used to improve permeability of certain...
hydrophilic drugs when applied to the skin in the form of pro drug.

**DISADVANTAGES OF TOPICAL SYSTEMS**

1. 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 percutaneous routes or by using penetration promoters, can be considered.
2. The route is not suitable for drugs that irritate or sensitize the skin.
3. The route is restricted by the surface area of delivery system and the dose that needs to be administered in the chronic state of disease.
4. Topical drug delivery systems are relatively expensive compared to conventional dosage forms. They may contain a large amount of drug, of which only a small percentage may be used during the application period.

**SKIN**

Skin is the largest organ of the body. It is not uniformly thick. At some places, it is thick and in some places, it is thin. The average thickness of the skin is about 1 to 2mm. In the sole of the foot, Palm of the hand and in the interscapular region, it is considerably thick, measuring about 5mm. All other areas of the body have got thin skin. It is thinnest over eyelids and penis measuring about 0.5mm only.

![Fig 1: Structure of Skin](image)

**SKIN IS MADE UP OF TWO LAYERS NAMELY:**

1. Outer epidermis
2. Inner dermis

**EPIDERMIS**

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

1. Stratum corneum
2. Stratum lucidum
3. Stratum granulosum
4. Stratum spinosum and
5. Stratum germinativum

The important feature of epidermis is that, it does not have blood vessels. The nutrition is provided by the capillaries of dermis.

1. Stratum corneum: It is also known as horny layer. It is the outer most layer and consists of dead cells which are called corneocytes. These cells lose their nucleus due to pressure and become dead cells. The cytoplasm is flattened with fibrous protein known as keratin. Apart from this, these cells also contain phospholipid and glycogen.
2. Stratum Lucidum: It is made up of flattened epithelial cells. Many cells have degenerated nucleus and, in some cells the nucleus is absent. As these cells exhibit shiny character, the layer looks like a homogenous translucent zone. So, the layer is called stratum lucidum (Lucid = clear).
3. Stratum Granulosum: This is a thin layer with 2 to 5 rows of flattened rhomboid cells. The cytoplasm contains keratohyaline granules. The protein keratohyaline is the precursor of keratin.
4. Stratum Spinosum: This layer is also known as prickle cell layer because; the cells of this layer possess some spine like protoplasmic projections. By these projections, the cells are connected to one another.
5. Stratum Germinativum: This is a thick layer made up of polygonal cells superficially and columnar or cuboidal epithelial cells in the deeper parts. Here new cells are constantly formed by mitotic division. The newly formed cells move continuously towards the stratum corneum. The stem cells are known as keratinocytes. From this layer; some projections extend down up to dermis. These projections provide anchoring and nutritional function.

The colour of the skin depends upon this layer which contains the pigment melanin.

**DERMIS**

Dermis of the skin is a connective tissue layer made up of dense stout collagen fibres, fibroblast and histiocytes. The collagen fibres, exhibit elastic property and are capable of storing or holding water. The collagen fibres contain the enzyme
collagenase, which is responsible for wound healing. Dermis is made up of 2 layers namely:

1. Superficial papillary layer and
2. Deeper reticular layer.

1. Superficial papillary layer: This layer projects into the epidermis. This contains blood vessels, lymphatic’s and nerve fibres. This layer also has some pigment containing cells known as chromatophores.

2. Reticular layer: This layer is made up of reticular and elastic fibres. These fibres are found around the hair bulbs, sweat glands and sebaceous glands.

Immediately below the dermis, subcutaneous tissue is present. It is a loose connective tissue, which connects the skin with the internal structure of the body. This serves as an insulator to protect the body from excessive heat and cold of the environment. Lot of smooth muscles called arector pili are also found in skin around the hair follicles. The hair follicles with hairs, nails, sweat, glands and sebaceous glands and even the mammary glands are considered as appendages of the skin.

FUNCTIONS OF THE SKIN [7]

Protection:
The skin forms a relatively waterproof layer, provided mainly by its keratinised epithelium which protects the deeper and more delicate structures. As an important non-specific defense mechanism it acts as a barrier against:

- Invasion by microbes
- Chemicals
- Physical agents, e.g. mild trauma, ultraviolet light
- Dehydration

The epidermis contains specialized immune cells called Langerhans cells. They phagocytose intruding antigens and travel to lymphoid tissue, where they present antigen to T-lymphocyte, thus stimulating an immune response.

Due to the presence of the sensory nerve endings in the skin the body reacts by reflex action to unpleasant or painful stimuli, protecting it from further injury. The pigment melanin affords some protection against harmful ultraviolet rays in sunlight.

Regulation of body temperature:
The temperature of the body remains fairly constant at about 36.8°C across a wide range of environmental temperature. In health, variations are usually limited to between 0.5 and 0.75°C, although it is raised slightly in evening, during exercise and in woman just after ovulation. When metabolic rate increases, body temperature rises and when it decreases body temperature falls. To ensure this constant temperature, a balance is maintained between heat produced in the body and heat lost to the environment.

Formation of Vitamin D:
7 dehydrocholesterol is a lipid-based substance in the skin, and ultraviolet light from the sun converts it to vitamin D. This circulates in the blood and is used, with calcium and phosphate, in the formation of maintenance of bone.

Cutaneous sensation:
Sensory receptors consist of nerve endings in the dermis that are sensitive to touch, pressure, temperature or pain. Stimulation generates nerve impulses in sensory nerves that are transmitted to the cerebral cortex. Some areas have more sensory receptors than others causing them to be especially sensitive, e.g. the lips and fingertips.

Absorption:
This property is limited but substances that can be absorbed include:

- Some drugs, in transdermal patches, e.g. hormone replacement therapy during the menopause, nicotine as an aid to stopping smoking
- Some toxic chemicals, e.g. mercury.

Excretion:
The skin is a minor excretory organ for some substances including:

- sodium chloride in sweat; excess sweating may lead to blood sodium levels (hyponatraemia)
- urea, especially when kidney function is impaired
- Aromatic substances, e.g. garlic and other spices.

ROUTES OF DRUG PERMEATION THROUGH SKIN [8]

There are three major routes by which Skin absorption may occur:

1) Primarily, the chemical moieties are transported through the keratin-packed corneocytes via partitioning into and out of the cell membrane (transcellular).
2) Secondly, the molecule is transported around the corneocytes in the lipid rich extracellular regions (intercellular).
3) Thirdly, the shunt transport supported by the sweat glands, sebaceous glands and hair follicles (transappendageal).

The permeation potential of a permeant through intercellular or transcellular routes is highly dependent on their relative ability and partitioning in each phase. Thus, the hydrophilic and lipophilic molecules follow separate pathway to transport across the skin layers. Further, the non-ionic and lipophilic compounds are easily permeated. Alternatively, skin appendages such as sebaceous gland, hair follicles and sweat glands act as a diffusional shunt through rate-limiting barriers, facilitating the absorption of topically applied molecules. Transappendageal absorption may be a dominant pathway of dermal permeation, in case of slowly diffusing molecules.

TRANSPORT MECHANISM
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. Diffusion process stops when the concentration gradient reaches zero. The following equation describes the drug flux following passive diffusion:

\[ J = \frac{DPA \Delta C}{h} \]

Where, \( J \) is the steady state flux across the stratum corneum, \( D \) is the diffusion coefficient /diffusivity of drug molecule (cm\(^2\)/sec), \( \Delta C \) is the concentration gradient of drug across the stratum corneum (g/cm\(^3\)), \( P \) is the partition coefficient of drug between skin and formulation, \( h \) is the thickness of stratum corneum (cm), \( A \) is the surface area of stratum corneum (cm\(^2\)). According to this equation, the rate of drug passage depends upon its aqueous solubility, directly proportional to its partition coefficient (oil/water), concentration of drug in formulation and the exposed surface area of the skin; and inversely proportional to the thickness of the skin. In reality, there is low concentration on the receiver side due to continuous blood stream. Thus, the donor sides have comparatively high drug concentration; equation becomes \( J = P_M AC \)

Where, \( P_M \) is the permeability constant, \( C \) is the concentration.

FACTORS AFFECTING SKIN PENETRATION
The penetration of substances through the skin surface depends upon different factors:

1. Age: penetration is more in newborn and children than in adults.
2. Skin condition: penetration is more on injured or abraded skin surfaces. Chemicals may cause injury and increase penetration.
3. Hydration of the skin: penetration is more in hydrated skin than dry skin. Hydration increases the permeability of the stratum corneum. Water is an effective penetration enhancer.
4. Fat content of the epidermis has no much effect on penetration.
5. Type of vehicles: vehicles may increase penetration and absorption of the drug from the skin surface. This depends on the type of vehicle and the condition of the skin. Certain vehicles that may cause injury to the skin even minimal injury predispose to more penetration of the drugs or other materials applied topically to the skin surface.
6. Hyperemia: vasodilatation of the blood vessels in response to different stimuli either local or generalized increases the penetration.
7. Physiological and pharmacological factors, the penetration in vivo of topically applied substances can be assessed by physiological or pharmacological signs or analyzed by chemical or histological techniques:
   - Vasoconstriction has been utilized for corticosteroids.
   - Vasodilatation for nicotinates.
   - Whealing for histamines.
   - Sweating for pilocarpine.
   - Anesthesia for local anesthetics.
8. Lipoid soluble substances facilitate penetration of substances applied to the skin surface. Steroid hormones and vitamin D, salts such as chloride and sulfate can penetrate the skin surface. Gases and volatile substances can pass through the skin.

GELS
Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substances and the liquid in the formulation, such as
Carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the product, and are easily washed off the skin with water.

Gel is two-component system of a semisolid nature rich in liquid. Although different authors emphasize various properties within their definitions, the one common feature that they identify as characteristic of a gel is the presence of some form of continuous structure, which provides solid-like properties. In a typical polar gel, a natural or synthetic polymer at a relatively low concentration (usually much less than 10%) builds a three-dimensional matrix throughout a hydrophilic liquid. The system may be clear turbid, because the gelling agent does not fully dissolve or because it forms aggregates which disperse the light. Typical polymers include the natural gums tragacanth, carrageen, pectin, agar, and Algic acid; semisynthetic material such as methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and the synthetic polymer Carbopol.

The cellulose derivatives from colloidal solutions in water, which gel at relatively high concentrations. These celluloses resemble the natural gum in many respects but are not as vulnerable to bacterial or fungal attack. Sodium carboxymethylcellulose, an anionic compound, stabilizes and thickens suspensions, lubricating jellies, and topical emulsions. Sodium alginate, which consists mainly of the sodium salt of Algic acid, produces aqueous solution that gel firmly on addition of small amounts of soluble calcium salts, e.g., gluconate, tartrate, or citrate. For example, in the presence of calcium citrate 3% solution yields a stable water-soluble jelly base.

Bentonite, a colloidal hydrated aluminum silicate, is insoluble in water but swells when mixed with 8 to 10 parts of water to generate a slightly alkaline gel resembling petrolatum.Veegum (colloidal magnesium aluminum silicate) and Laponite (a synthetic hectorite) behave somewhat similarly. Pharmaceutical and cosmetic manufacturers now extensively employ the synthetic polymer Carbopol to formulate gels; for example, the U.S preparation Topsyn gel and U.K preparation synalar Gel both use this polymer to gel a propylene glycol/water solution of a topical steroid.

The Carbopols (Carbomers), a group of carboxyvinyl polymers crossed linked with allyl sucrose, are hydrophilic colloidal materials, which thicken better than the natural gums. They disperse in water to form cloudy acidic solutions, which are neutralized by strong bases such as sodium hydroxide, by amines (e.g. triethanolamine), or by weak inorganic bases (e.g. ammonium hydroxide), thereby increasing the consistency and decreasing the turbidity.

**DESERABLE PROPERTIES OF GELS**[11]

1. It should be inert, compatible with other additives and non-toxic.
2. It should be stable at storage condition.
3. It should be free from microbial contamination.
4. It should maintain all rheological properties of gel.
5. Economical.
6. It should be washable with water and free from staining nature.
7. It should not affect biological nature of drug.
8. It should be convenient in handling and its application
9. It should possess properties such as thixotropic, greaseless, emollient, non-staining etc.

**GEL FORMING SUBSTANCES**[11]

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. **Natural polymer:**
   a. Proteins
      Collagen,
      Gelatin.
   b. Polysaccharides
      Agar,
      Alginic acid.
      Sodium or Potassium carrageenan,
      Tragacanth,
      Pectin,
      Guar Gum,
      Cassia tora,
      Xanthin,
      Gellum Gum.

2. **Semisynthetic polymers:**
   Cellulose derivatives,
   Carboxymethyl cellulose,
   Methylcellulose,
   Hydroxypropyl cellulose,
   Hydroxypropyl methyl cellulose,
   Hydroxyethyl cellulose,
3. Synthetic polymers:
a. Carbomer
   Carbopol -940,
   Carbopol -934,
   Carbopol -941,
b. Poloxamer
c. Polyacrylamide
d. Polyvinyl alcohol
e. Polyethylene and its co-polymers

4. Inorganic substances
a. Aluminium hydroxide
b. Bentonite

5. Surfactants
a. Cetostearyl alcohol
b. Brij – 96

CLASSIFICATION OF GELS

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 alginate exhibit an elastic behavior. 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 –COOH group then additional bonding takes place by salt bridge of type –COO-X-
COO between two adjacent strand networks. E.g. Alginate and Carbopol.

(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.

1.3.4 PREPARATION OF GELS \[12\]

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 behavior. 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.

CONCLUSION
Topical drug delivery systems offer several advantages over oral delivery systems. These delivery systems include patch, gel, cream, ointment and lotion. However it has been found so many side-effects were proved by the oral delivery system of fluconazole and here to over the side-effects of oral dosage form. The dosage form has been changed by formulation of fluconazole gel. Fluconazole is an imidazole derivative, used in the treatment of topical as well as systemic fungal infection. The bioavailability of fluconazole is 90%. In the present study, an attempt was made to formulate fluconazole gel for efficient delivery of drug to the skin.

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