Transdermal Gel: As a Novel Drug Delivery System

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Abstract

The objective of this paper is to study how the gel forms of drug becoming more popular due to ease of application and better percutaneous absorption. Topical therapy is an attractive choice for the treatment of the cutaneous infections due to its advantageous such as targeting of drugs to the site of infection and reduction of the risk of systemic side effects. 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. Gels are evaluated by following parameters such as pH, drug content, viscosity (Brookfield viscometer), spreadability, and extrudability, skin irritation studies, in-vitro release, in stability. Overall, the clinical evidence indicates that topical gel is a safe and effective treatment option for use in the management of skin related diseases. Different methods are used to enhance the permeability and bioavailability of topical gels that can be incorporated into a novel drug delivery system like emulgel, solid dispersion into gel, hydrogel, microemulsion gel, solid lipid nanoparticles into gel, liposomal gel. The objective of this article is to review the fundamental and present advances in topical gels including classification and method of preparation. In these study methods, advantages, gel forming substances, structure of gel, their properties, their absorption mechanism, evaluation and future perspective are discussed to improve the permeability and bioavailability of gels.

Key-Words: Topical delivery, Gel, Penetration enhancer

Introduction

Topical drug administration is 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 the main route of topical drug delivery system. Topical application of drugs offers potential advantages of delivering the drug directly to the site of action and acting for an extend period of time. The term gel are semi-solid, three dimensional, polymeric matrices comprising small amounts of solid dispersed in relatively large amount of liquid, yet possessing more solid like character. These system form a three dimensional, polymeric matrix in which a high degree of physical reticulation has been compromised. Numbers of medicated products are applied to skin or mucous membrane that either enhance or restore a fundamental function of a skin or pharmacologically alter an action in the underlined tissues. Such products are referred to as topical or dermatological products. Gel formulations provide better application property and stability in comparison to cream and ointments. The U.S.P. defines Gels as a semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules enclosing and interpenetrated by liquid. The inorganic particle forms a three-dimensional “house of card” structure. Gels consists 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. A gel is colloid that is typically 99% weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from small amount of a gelating substances present. Hydroxy propyl methyl cellulose (HPMC), Carbopol 934P, sodium alginate has been used as hydrophilic polymers topically in gel drug delivery system. A series of grades based on molecular fractions of these polymers are used at a concentration between 1 to 5% in topical gel formulation. Different methods are used to enhance of permeability and bioavailability of topical gels that can
be incorporate into a novel drug delivery system like emulgel, solid dispersion into gel, hydrogel, microemulsion gel, solid lipid nanoparticles into gel, liposomal gel.

**Drug permeation through 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. 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. Skin acts as a major barrier for permeation of any substance into the body and this is mainly due to the stratum corneum, which is its outer layer. In most of its areas, there are 10-30 layers of stacked corneocytes with palms and soles having the most. Each corneocyte is surrounded by a protein envelope and is filled with water-retaining keratin proteins. The cellular shape and orientation of the keratin proteins add strength to the stratum. 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. 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. 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.

**Route of penetration**

At the skin surface, drug molecules come in contact with cellular debris, microorganisms, and other materials, which effect permeation. The applied medicinal substance has three pathways to the viable tissue-

1) through hair follicles,
2) via sweat ducts and
3) across continuous stratum corneum between the appendages (hair follicles, sebaceous glands, eccrine, apocrine glands and nails).

Fractional appendageal area available for transport is only about 0.1% and is important for ions and large polar molecules. The intact stratum corneum is the main barrier and therefore many
enhancing techniques aim to disrupt or bypass this layer. Viable layers may metabolize a drug, or activate a prodrug. Usually, deeper dermal regions do not significantly influence absorption. For more than two decades, researchers have attempted to find a way to use the skin as a portal of entry for drugs in order to overcome problems associated with traditional mode of drugs administration. This route of drug delivery has gained popularity because it avoids first-pass effect, gastrointestinal irritation and metabolic degradation associated with oral administration.

**Classification of gel**

Gels are classified mainly by two methods based on:

1. **Nature of colloid phase**
   i) Inorganic gels (Two phase system)
   ii) Organic gels (single phase system)

2. **Based on nature of solvent**
   i) Hydrogel (Aqueous gels)
   ii) Organic gel (Non-aqueous gels)
   iii) Xerogel

3. **Based on rheological properties**
   Usually gels exhibit non-Newtonian flow properties. They are classified into,
   i) Plastic gels
   ii) Pseudo plastic gels
   iii) Thixotropic gels

4. **Based on physical nature**
   i) Elastic gel
   ii) Rigid gel

1. **Based on nature of colloidal phase**
   i) Inorganic gel

   **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 flocules 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 must become liquid on agitation.

   ii) Organic gel

   **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 waals forces.

2. **Based on nature of solvent**
   i) Hydro gels (water based)
   They contain water as their continuous liquid phase. E.g. bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.

   **Desired physicochemical properties of drug which required for formulation of topical hydrogels are**

   i) Drug should have a molecular weight of less than 500 Daltons.
   ii) Drug must have adequate hydrophilicity.
   iii) A saturated aqueous solution of the drug should have a pH value between 5 and 9.
   iv) Drug highly acidic or alkaline in solution is not suitable for topical delivery.

   **ii) 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.

   **iii) 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,

   i) Plastic gels
   ii) Pseudo plastic gels
   iii) Thixotropic gels

   **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 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.

4. **Based on physical nature**

   i) 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.
ii) Rigid gels – In this type of gel macromolecules in which the framework linked by primary valance bond e.g. Silica gel.

Properties of gels

1. Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.
2. The gelling agent included in the preparation should produce a reasonable solid-like nature during storage that can be easily broken when subjected to shear stress generated by shaking the bottle, squeezing the tube, or during topical application.
3. It should possess suitable anti-microbial to prevent from microbial attack.
4. The topical gel should not be tacky.
5. The ophthalmic gel should be sterile.

Characteristics of gels

1) Swelling: When a gelling agent is kept in contact with liquid that solvates it, then an appreciable amount of liquid is taken up by the agent and the volume increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel-gel interactions are replaced by gel solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages.

2) Syneresis: Many gels often contract spontaneously on standing and exude some liquid medium. This effect is known as syneresis. The degree to which syneresis occurs, increases as the concentration of gelling agent decreases. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out.

3) Ageing: Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as ageing. In gels, ageing results in gradual formation of a denser network of the gelling agent.

4) Structure: The rigidity of a gel arises from the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the stress, straightening them out and lessening the resistance to flow.

5) Rheology: Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. exhibiting Non-Newtonian flow behaviour, characterized by a decrease in viscosity with increase in shear rate. The tenous structure of inorganic particles dispersed in water is disrupted by applied shear stress due to breaking down of interparticulate association, exhibiting a greater tendency to flow. Similarly, for macromolecules the applied shear stress aligns the molecules in the direction of Organic (single phase system).

Gel forming substances

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 Polymers:
   - Proteins – Collagen, Gelatin
   - Polysaccharides – Agar, Alginate acid, Sodium or Potassium carageenan, Tragacanth, Pectin, Guar Gum, Cassia tora, Xanthan, Gellum Gum

2) Semisynthetic polymers cellulose derivatives:
   - Carboxymethyl cellulose, Methylcellulose, Hydroxypropyl cellulose, Hydroxy propyl (methyl cellulose), Hydroxyethyl cellulose

3) Synthetic polymers:
   - Carboxer – Carbopol 940, Carbopol 934
   - Poloxamer
   - Polycryliclamide
   - Polyvinyl alcohol
   - Polyethylene and its co-polymers

4) Inorganic substances:
   - Aluminium hydroxide
   - Bentonite

5) Surfactants:
   - Cebrostearyl alcohol
   - Brij – 96

Advantages

The topical administration of drug in order to achieve optimal cutaneous and percutaneous drug delivery has recently gain an importance because of various advantages:

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- They can substitute for oral administration of medication when that route is unsuitable.
- To avoid the first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzyme.
They are non-invasive and have patient compliance.
They are less greasy and can be easily removed from the skin.
Cost effective.
Reduction of doses as compare to oral dosage forms.
Localized effect with minimum side effects.
Improving drug bioavailability, reducing dose frequency.
Stabilizing drug delivery profiles.

Limitations
The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult.
Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin’s impermeability.
Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

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
\[
dQ / dt = Ps \left( Cd - Cr \right)
\]
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
- Skin integrity
- Hydration
- Temperature
- Anatomic location
- Age
- Disease

Formulation factors in percutaneous absorption
- Occlusivity
- Drug concentration
- pH
- Surfactant
- Solubility
- Penetration enhancer

Classification of penetration enhancer
- Terpenes (essential oils)
  E.g. Nerodilol, menthol, 18 cineol, limonene, carvone etc.
- Pyrrolidones
  E.g. N-methyl-2-pyrrolidone(NMP), azone etc.
- Fatty acids and esters
  E.g. Oleic acid, linoleic acid, lauric acid, capric acid etc.
- Sulfoxides and similar compounds
  E.g. Dimethyl sulfoxide(DMSO), N,Ndimethyl formamide
- Alcohols, Glycols, and Glycerides
  E.g. Ethanol, Propylene glycol, Octyl alcohol etc.
- Micellaneous enhancers
  E.g. Phospholipids, Cyclodextrins, Amino acid derivatives, Enzymes etc.

Methods of preparation
i) Dispersion method: In this method polymer is dispersed over water for 2 hours till all the polymer is soaked with water after that other chemical ingredients are mixed and stirred well until a homogenous mass is obtained
ii) Cold method: In this method all the ingredients are mixed together to form a homogenous mass, under low temperature at about 50C. In this polymer is mixed with permeation enhancer to form solution A, drug is mixed with solvent to form solution B. After that solution B is poured into solution A slowly with complete stirring.
iii) Chemical reaction: In the preparation of sols by precipitation from solution, e.g., Aluminum hydroxide sol precipitated by interaction in aqueous solution of an aluminum salt and sodium carbonate, increased concentration off reactants will produce a gel structure. Silica gel is another
example and is produced by interaction of sodium silicate and acids in aqueous solution.

**iv) Temperature effect:** As lower the temperature the solubility of most lyophilic colloids, e.g., gelatin, agar, sodium-oleate, is reduced, so that, if cooling a concentrated hot sol will often produce a gel. Similarly to hydrogen bonding with water. Increasing the temperature of these sols will break the hydrogen bonding and the reduced solubility will produce gelatine.

**Flocculation with salts and nonsolvents:**
Gelatin is a popular collagenic derivative primarily used in food, pharmaceutical, photographic and technical products. In foods, gelatin provides a meltsin- mouth function and to achieve a thermo-reversible gel property. Gelatin is produce by adding just sufficient precipitant to produce the gel structure state but in sufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentration of precipitants. Solutions of ethyl cellulose, polystyrene, etc, in benzene can be gelled by rapid mixing with suitable amount of a nonsolvent such as petroleum ether. The addition of salts to moderately sols such as aluminum hydroxide, ferric hydroxide and bentonite produces gels.

**Evaluation**

- pH
- Drug content
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- In vitro release
- In vivo study
- Stability
- Consistency

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

2. **Drug content**
1 g of the prepared gel is mixed with 100 ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance is measured. Drug content is calculated using the equation, which is obtained by linear regression analysis of calibration curve.

3. **Viscosity study**
The measurement of viscosity of the prepared gels done with a Brookfield Viscometer. 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 the gel is obtained by multiplication of the dial reading with factor given in the Brookfield Viscometer catalogues.

4. **Spreadability**
One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula:

\[ S = \frac{M \cdot L}{T} \]

Where M = wt. tied to upper slide
L = length of glass slides
T = time taken to separate the slides

5. **Extrudability study**
The formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

6. **Skin irritation study**
Guinea pigs (400-500 g) of either sex are used for testing of skin irritation. The animals are maintained on standard animal feed and had free access to water. The animals are kept under standard conditions. Hair is shaved from back of guinea pigs and area of 4 cm2 is marked on both the sides, one side served as control while the other side is test. Gel is applied (500 mg / guinea pig) twice a day for 7 days and the site is observed for any sensitivity and the reaction if any, is graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

7. **In vitro Diffusion studies**
The diffusion studies of the prepared gels can be carry out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) is taken in cellophane membrane and the diffusion studies are carried out at 37 ± 1°C using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample is withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample is replaced with equal volume of fresh...
dissolution medium. Then the samples are analyzed for the drug content by using phosphate buffer as blank.

8. Stability
The stability studies are carried out for all the gel formulation by freeze-thaw cycling. In this syneresis is observed by subjecting the product to a temperature of 4°C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted.

9. Consistency
The measurement of consistency of the prepared gels is done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The penetration by the cone is measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone is noted down after 10sec.

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<tr>
<th>Table 1: Required properties of pharmaceutical gels</th>
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<td>Pharmaceutical gel application</td>
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<td>Dental</td>
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<td>Dermatological</td>
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<td>Nasal</td>
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<td>Ophthalmic</td>
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<td>Surgical and medical Procedures</td>
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<td>Vaginal</td>
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<th>Table 2: General classification and description of gels</th>
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<td>Class</td>
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<td>Inorganic</td>
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<td>Organic</td>
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Conclusion
Transdermal drug delivery system is useful for topical preparation and give local action of the drug. The drugs which shows hepatic first pass effect and unstable in GI conditions are the suitable candidate for TDDS through gel. The principal advantage of topical drug delivery lies in targeting the drug action directly to the site of disorder by allowing accumulation of high local drug concentration within the tissue and around its vicinity for enhanced drug action. The gel formulation can provide better absorption characteristics and hence the bioavailability of drug.

Future Prospective
Expanding the use of novel permeation enhancement techniques with macromolecules and other conventional molecules for a wider range of indications is highly desirable for the transdermal industry. Physical enhancement methods afford substantial improvement in the rate of delivery of therapeutic agents across skin. Currently, a variety of them are undergoing extensive investigation and new device-based TDS can be expected in the near future.
References


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