



TOPICAL GEL:- A REVIEW

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ABSTRACT

Topical drug delivery is defined as the application of pharmaceutical dosage form to the skin for direct treatment of cutaneous disorder or the cutaneous manifestation of the general 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 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.

INTRODUCTION^[1,2]

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. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use. The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in pain management, contraception, and urinary incontinence.

Over the last decades the treatment of illness has been accomplished by administering drugs to human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical activities may or may not require intra-cutaneous penetration or deposition. 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.

Gels As Pharmaceutical Dosage Forms^[3]

The term 'Gel' was introduced in the late 1800 to name some semisolid material according to their physiological characteristics rather than molecular composition.

The 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 are a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. They consist of a two component semi-solid system rich in liquid. Their one characteristic feature is the presence of continuous structure providing solid like properties. 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.

Structure of Gels^[4]

A gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After application, the liquid evaporates leaving the drug entrapped in a thin film of the gel-forming matrix physically covering the

skin. The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkages determine the structure of the network and the property of the gel.

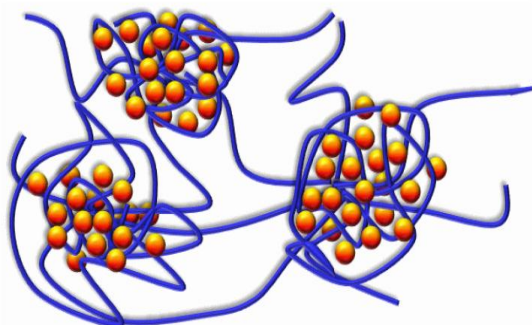


Figure 1: Structure of gels

Properties of Gels^[5]

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 forces 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^[6]

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 fluid 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 tenuous 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).

Advantages of Topical Drug Administration^[7]

- Avoids gastrointestinal (GI) drug absorption difficulties caused by GI pH, enzymatic activity and drug interactions with food, drink, and other orally administered drugs.
- A substitute for other routes of administration (e.g. oral administration, intravenous injection) when that route is unsuitable, as with vomiting, swallowing problems, resistant children and diarrhoea.
- Patient acceptability is better as this drug delivery system is non-invasive, avoiding the inconvenience of parenteral therapy.
- Avoids the first-pass effect, possibly avoiding the deactivation by digestive and liver enzymes.
- Reduction of doses as compare to oral dosage forms.
- Ability to dissolve a wide range of medications with different chemical properties, making combination therapy with one transdermal cream possible.
- Provides extended therapy with a single application, improving compliance.
- Drug therapy may be terminated rapidly by removal of the application from the skin surface.
- Less greasy and can be easily removed from the skin.

Classification of Gels^[8]

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) type of force that is responsible for the linkages determine the structure of the network and the properties of the gel.

- a) **Two phase system** If partial sizes of the dispersed phase are 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.

- b) **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^[9]

- a) **Hydro gels (water based)** Here they contain water as their continuous liquid phase E.g. bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.
- b) **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.
- c) **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 resulting 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 nonspherical 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 alginates 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 Carbapol.

- 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.

MATERIALS AND METHODS

Gel Forming Substances^[10]

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

- i. Gelatin
- ii. Collagen

b. Polysaccharides

- i. Alginic acid
- ii. Agar
- iii. Tragacanth
- iv. Sodium or Potassium carrageenan
- v. Pectin
- vi. Gellum Gum
- vii. Xanthin
- viii. Cassia tora ix. Guar Gum

2. Semisynthetic polymers

a. Cellulose derivatives

- i. Hydroxyethyl cellulose
- ii. Methylcellulose
- iii. Hydroxypropyl methyl cellulose
- iv. Hydroxypropyl cellulose
- v. Carboxymethyl cellulose

3. Synthetic polymers a. Carbomer

- i. Carbopol -941
- ii. Carbopol -940
- iii. Carbopol -934
- b. Poloxamer
- c. Polyvinyl alcohol
- d. Polyacrylamide
- e. Polyethylene and its co-polymers

4. Inorganic substances

- a. Bentonite
- b. Aluminium hydroxide

5. Surfactants

- a. Brij-96
- b. Cetostearyl alcohol

PREPARATION OF GELS^[11,12]

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 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.

3. Chemical reaction: In this method gel is produced by chemical interaction 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)hat cross-links the polymeric chain.

Evaluation Parameters of the Formulated Gel**Measurement of pH**

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours.

Then measurement of pH of each formulation was done in triplicate and average values are calculated.

Drug content^[13]

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

Viscosity study

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial reading with factor given in the Brookefield Viscometer catalogues.

Spreadability^[14]

It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic potency 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 which is placed in between the slides under the direction of certain load. Lesser the time taken for the separation of two slides, better the spreadability. It is calculated by using the formula:

$$S = M \cdot L / T$$

Where,

M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

Extrudability study^[15]

After the gels were set in the container, the formulations were filled in the collapsible tubes. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

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