AN OVERALL REVIEW ON TOPICAL PREPARATION - GEL

A.KRISHNA SAILAJA, R.SUPRAJA

1Associate Professor, RBVRR Women’s college of Pharmacy, affiliated to Osmania University, Hyderabad
2 M-Pharmacy student, RBVRR Women’s college of Pharmacy, affiliated to Osmania University, Hyderabad.Email:shailaja1234@rediffmail.com

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Abstract
Topical application has many advantages over the conventional dosage forms. In general, they are deemed more effective less toxic than conventional formulations due to the bilayer composition and structure. In the formulation of topical dosage forms, attempts are 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. Topical preparations avoid the GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action. In this review a detailed discussion was made on the properties, classification, characterization, preparation and applications of gel.

Key word: The properties, classification, characterization, preparation and applications of gel.

INTRODUCTION TO GEL
A gel is a two-component, cross linked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to form an infinite rigid network structure which immobilizes the liquid continuous phase within. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarily polymers. Cross links can be formed via chemical or physical interactions. This leads to gel classification into chemical and physical gel systems, respectively. Chemical gels are associated with permanent covalent bonding while physical gels result from relatively weaker and reversible secondary intermolecular forces such as hydrogen bonding, electrostatic interactions, dipole dipole interactions, Vander Waals forces and hydrophobic interactions.

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 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.

PROPERTIES OF GELS
Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.

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.

It should possess suitable anti-microbial to prevent from microbial attack.

The topical gel should not be tacky.

CHARACTERISTICS OF GELS
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.

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.

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.

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.

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).

CLASSIFICATION OF GELS
Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

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.

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.

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.

**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, carbopol, and poloxamer gel.

**Carbopol hydrogels**

Carbopol is made of carbomers. Carbomer polymers are cross-linked together and make a microgel structure that makes them optimal to be used as a drug vehicle for dermatological purposes. They can be used in cases when drug delivery in a controlled manner is desired. The microgel structure makes it possible for these systems to tolerate the physical movement of the body and shape themselves after the application area movement. Carbopol polymers are acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. These polymers are anionic polymers that need naturalization to become gelled. Organic amines like triethylamine can be used to naturalize these polymers in liquids.

Advantages with use of carbopol gels as vehicles are

- Good rheological properties resulting in long statement on the administration Site.
- Good alternative to oil-based ointment formulations
- Anionic hydrogels with good buffering capacity which contributes to maintenance of the desired pH
- High viscosity already at low concentrations
- Wide concentration interval and characteristic flow behavior
- Compatibility with many active ingredients
- Bio adhesive properties
- Good thermal stability
- Excellent organoleptic characteristics

**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 swell and can bereconstituted.

E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

**Based on rheological properties**

Usually gels exhibit non-Newtonian flow properties. They are classified into,

- Plastic gels
- Pseudo plastic gels
- Thixotropic gels.

**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.

**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.

**Thixotropic gels**

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. 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. This occurs in colloidal systems with non-spherical particles to build up a scaffold like structure.

Eg: kaolin, bentonite and agar.

**Based on physical nature**

**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.

**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.

**Methods of preparation of hydro-gels**

- Fusion method
- Cold method
- Dispersion method

Whether the scale of preparation is large or small, semisolid dosage forms are produced by one of two general methods. Either they are made at high temperature by blending the liquid or liquefied components and dispersing the solids (fusion method) or the drug is incorporated in the already semi-solid base (cold incorporation). Cold corporation is used with heat labile drugs, when a drug is to be added to already prepared semi-solid base or when the vehicle itself is heat labile as happens with plastibase. The preparation of gels may involve a fusion process or may require a special procedure, depending on the gelling agent involved. Tragacanth system must be prepared at low temperature due to the extreme heat liability of this natural gum. On the other hand, it is easier to disperse methyl cellulose in hot than in cold water. The carbopol are gelled by a unique procedure. The polymer is dispersed in an acidic medium. When the dispersion is uniform, gelation is induced by neutralizing the system with an inorganic base (aqueous system) or with an amine such as tri-ethanolamine. This ionize the acidic functional groups on the polymer, drawing the polymer into colloidal solution, in which state it forms the requisite structural matrix.

**Dispersion method**

Disperse the polymers in distilled water by continuous stirring. Warm the colloidal viscous dispersion to get a gel. Dissolve the drug in solvent and incorporate into gel by stirring followed by penetration enhancer. Add pH adjustifier to modify the buffering capacity of the gel, if necessary.

**GEL FORMING SUBSTANCES**

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

**Natural polymer**

- Proteins
  - Gelatin
  - Collagen
- Polysaccharides
  - Alginic acid
  - Agar
  - Tragacanth
  - Sodium or Potassium carrageenan
- Pectin
  - Gelum Gum
  - Xanthin
  - Cassia tora
  - Guar Gum
- Semisynthetic polymers
  - Cellulose derivatives
    - Hydroxyethyl cellulose
    - Methylcellulose
    - Hydroxypropyl methyl cellulose
    - Hydroxypropyl cellulose
    - Carboxymethyl cellulose
- Synthetic polymers
Carbomer 
(i) Carbopol -941 (ii) Carbopol -940 (iii) Carbopol -934
Poloxamers
Polyvinyl alcohol
Polyacrylamide
Polyethylene and its co-polymers

Inorganic substances

Bentonite
Aluminium hydroxide

Surfactants

Brij-96
Cetostearyl alcohol

Polymer Gels are cross-linked networks with a liquid Gels and have both liquid-like and solid-like properties. These Gels are transparent or semisolid preparation of solution or dispersion of one or more active ingredients in suitable hydrocolloidal substances known as gelling agent. Gels are not greasy exhibit pseudoplastic property due to gelling agent.

ADDITIVES USED IN GEL FORMULATION

Gelling agents

Gelling agents are hydrocolloids substances which gives thixotropic consistency to the gel. Gelling agents are organic in nature and are also known as solidifiers or stabilizer and thickening agent. Gelling agents are more soluble in cold water than hot water. Gelling agents like methylcellulose and poloxamers have better solubility in cold water while bentonite, gelatin and sodium carboxymethylcellulose are more water soluble in hot water. Gelling agents require a neutralizer or pH adjusting chemical to create the gel after the gelling agent has been wetted in the dispersing medium. Gelling agents are used in concentration of 0.5 up to 10% depending on the agent most gelling agents require 24-48 hours to completely hydrate and reach maximum viscosity and clarity. It is easier to add the active drug before the gel is formed if the drug does not interfere with the gel formation. The viscosity of the gelling agents in the gelling layer be within range of about 1000 cps to about 100,000 cps.

Humectant and cosolvents in gel

Humectant is a substance that absorbs or helps another substance retain moisture, as glycerol. A humectant is a hygroscopic substance. It is often a molecule with several hydrophilic groups, most often hydroxyl groups, but amines and carboxyl groups, sometimes esterifies, can be encountered as well; the affinity to form hydrogen bonds with molecules of water is crucial here.

Examples: Glycerine, propylene glycol (E 1520) and glyceryl triacetate (E1581). Others can be polysols like sorbitol (E420), xylitol Or polymeric polyols like polyvinyltriole (E 200) or natural extracts like quillia (E999), or lactic acid or urea. Lithium Chloride is an excellent humectant.

Stabilizers

Bases and medicaments sensitive to heavy metals are sometimes protected by chelating agent, such as E.D.T.A.(Ethylene diamine tetra acetic acid).

EVALUATION PARAMETERS OF GELS

Clarity

The clarity of formulation is determined by visual inspection under black and white background and it is graded as follows; turbid: +, clear: ++, very clear (glassy): +++.

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

Drug content

1 g of the prepared gel was mixed with 100 ml 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 Brookfield Viscometer catalogues.

Spreadability

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:

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

Where, S = Spreadability. 
M = Weight tide to upper slide.
L = Length moved on the glass slide.
T = Time taken to separate the slide completely from each other

Extrudability study

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.

Homogeneity

After the gels have been set in the container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.

Grittiness

All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence obviously the gel preparation fulfills the requirement of freedom from particular matter and from grittiness as desired for any topical preparation.

Skin irritation study

Guinea pigs (400-500 g) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4 cm² was mark done both the sides, one side served as control while the other side was test. Gel was applied (500 mg / guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, was 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.

In vitro Diffusion studies

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

Stability

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

Kinetic data analysis

The release kinetics is evaluated considering four different models including Zero order, Higuchi’s equation and Korsmeyer-Peppa’s equation and the selection is based on the comparison of relevant correlation coefficients and linearity test.
APPLICATIONS OF GEL

- As delivery systems for orally administered drugs.
- To deliver topical drug applied directly to the skin, mucous membrane or the eye.
- As long acting forms of drug injected intramuscularly.
- As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid and suppository bases.
- In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations.

REFERENCES


