MINI REVIEW

PHARMACEUTICAL GELS

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ABSTRACT
Gels are three-dimensional semisolid systems formed by the interlinking of gelling agent and dispersion medium. They are non-invasive, less greasy, non-toxic, and inert to food and drugs. They have minimum side effects, hence becoming a reason for increasing patient compliance and topic of interest over the last few decades. Various methods of preparations of gels have been designed by incorporating variety of polymers in dispersion mediums to meet the needs of different applications. This shows their flexibility in the formulation. Their structures, characteristics, properties, methods of preparation, components, classification and stability parameters have been discussed. Thus, gives an idea about the importance of gels in biomedical applications.

Keywords: Gels, hydrogels, organogels, preparation, stability.

1. INTRODUCTION

A gel is a three-dimensional network of constituent materials cross-linked and distributed in hefty amounts of liquid to form an absolute rigid structure which paralyzes the liquid dispersion medium inside (Fig. 1.). Gels can be classified into physical and chemical gel systems depending upon the type of cross links formed. Chemical gels are correlated with strong bonding i.e. covalent bond, while the latter is affiliated with comparatively weaker and reversible intermolecular forces such as hydrogen bonding, dipole-dipole forces, electrostatic interactions, van der Waals forces and hydrophobic interactions[1,2]. Gels can be defined as "A semisolid system consisting of dispersion made up of either small inorganic particles or large organic molecules encircled and interpenetrated by liquid. Gels consist of a 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, which are then coiled in stretchable chains"[3].

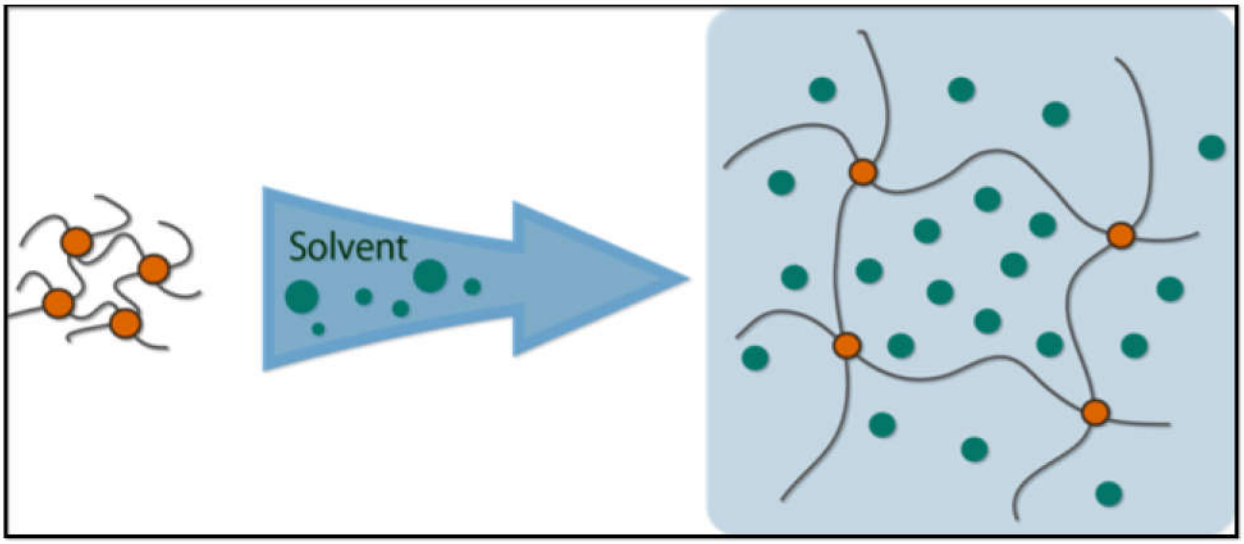

Fig. 1. Cross-linking of polymer in a solvent to form a gel matrix.

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2. STRUCTURE OF GELS

The toughness of a gel originates from the existence of a network formed by interlinking the fragments of gelling agent. The structure and properties of a gel mainly depends on the nature of particles and types of force responsible for the connection of these linkages. The force of attraction in coupling gelling agent entities may vary from strong valencies as in silicic acid gels to weak hydrogen bonds and van der Waals forces. The weak interactions show liquefaction in gels with a slight increase in temperature[4].

3. CHARACTERISTICS OF GELS

3.1. Syneresis

The exudation of fluid medium upon contraction of gels on standing is referred to as syneresis. As the concentration of gelling agent decreases, syneresis increases and vice versa which shows that the gel was thermodynamically unstable. The loosening of elastic stress developed during the formation of gels is linked to contraction. As the stresses are relieved, the space within the solvent is shortened thereby oozing the fluid out[5,6].

3.2. Swelling

When a gelling agent is kept in contact with a liquid that solvates it, an appreciable amount of the liquid is taken up that result in an increase in the volume, this is referred as swelling (Fig. 2.). This phenomenon occurs when the solvent penetrates the gel network. The extent of swelling depends upon the force of attraction between these linkages and the number of linkages present between the molecules of gelling agent[5,6].

3.3. Ageing

The progressive formation of a denser network of gelling agent is referred as ageing[5,6].

4. DESIRABLE PROPERTIES OF GELS

Some of the basic properties that a gel may possess may include[6]:

- The gelling agent should be non-toxic and should not react with other excipients present in the formulation.
- They should have an anti-microbial agent to protect it from microbial contamination and spoilage.
- They should be easy to use and should not be tacky.
- The ophthalmic gels should be sterile.
- The gels should be stable at the desired storage conditions.
- They should maintain all their rheological properties throughout the shelf-life.
- They should be economical.
- Staining is one of the worst properties of some dosage forms so it should be easily washable and free from staining.
- Biological nature of the drug should not be affected by the gel formation.
- The gelling agent should produce a solid-like mass during storage which can be easily broken when subjected to stress such as shaking the bottle, squeezing the tube during application.

5. ADVANTAGES OF GELS OVER OTHER DOSAGE FORMS

Some common advantages of gels over other dosage forms are as follows[7]:

- They have minimum side effects as they usually produce a local effect onto the site of application.
- In contrast to other topical preparations such as ointments and water-in-oil creams, they are less greasy hence can easily be washed away from skin.
- They increase patient compliance by being non-invasive in nature.

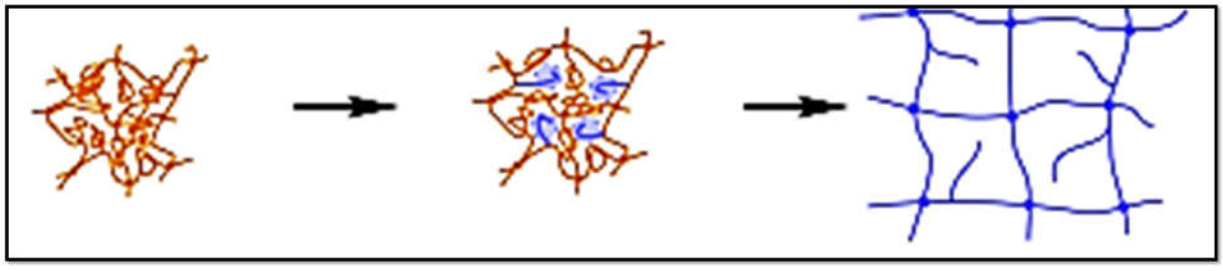

Fig. 2. Swelling of a gel.

- They avoid food-drug interactions as they do not cross gastrointestinal tract.
- They are not affected by the enzymes present in gastrointestinal tract as they do not confer first pass effect.

6. DISADVANTAGES

The disadvantages of gels have been described as[8]:

- There are chances of allergic reactions.
- If a gel contains a drug with a larger particle size, it cannot be absorbed easily through the skin.
- The skin also contains some enzymes so that there might be a possibility of denaturing of the drugs.
- Usually drugs that require high plasma concentration to produce action cannot be given in form of gels.

7. METHODS OF PREPARATION OF GELS

Different methods for the preparation of gels have been discussed[2,3,9-14], which includes:

7.1. Flocculation

In this method the gel is prepared by adding sufficient precipitant which can be a salt or a non-solvent to bring about the gel structure. For example, in case of gelatin the gel is produced by putting together ample amounts of precipitant to achieve the gel structure but is not sufficient enough to bring about complete precipitation as rapid mixing is essential to avoid high concentration of the precipitants. Another example is by the addition of a non-solvent such as petroleum ether to solution of ethyl cellulose in benzene.

7.2. Temperature Effect

Few substances like lyophilic colloids produce gels on reduction of temperature as their solubility is decreased and their hot concentrated solutions form gels easily on cooling. Examples include agar, sodium oleate, gelatin, etc.

7.3. Chemical Effect

Sometimes enormous amounts of reactants are added to produce precipitates which eventually form a gel structure. Aluminum hydroxide solution will produce a gel when ample amount of aluminum salt is allowed to interact with sodium carbonate.

7.4. Dispersion

In this method of gel preparation, a polymer is soaked in water for two hours until all of it gets wet completely. Then addition of remaining ingredients is done with frequent stirring till a uniform mass is obtained.

7.5. Cold Method

In this case a uniform mass of gel is obtained by reducing the temperature to about 5 °C. The polymer is then mixed with permeation enhancer to form a solution A whereas the drug is mixed with the solvent to produce a solution B. Finally the gel is produced when solution B is slowly poured into solution A with continuous stirring.

8. COMPONENTS OF A GEL

The basic components of a topical gel may include the following[10-12]:

8.1. Drug Substance

An antibacterial, antifungal, analgesic, anti-inflammatory agent, etc. are predominantly used as drug substances in gels. The most important aspect of drug incorporation is that it should diffuse easily through the skin.

8.2. Polymers

The structural network of the gels is formed by the addition of inorganic particles, organic molecules and polymer whereas the mechanism of drug release chiefly depends on the polymer used and the physicochemical properties of the drug. The polymers can be natural in origin or can be semisynthetic or synthetic in nature. Some common examples of such polymers are mentioned in Table 1.

8.3. Permeation Enhancers

These agents promote the permeability of drug across the skin by altering it as a barrier for the influx of the ligand. They are thought to be the integral part of the topical formulations as they have no pharmacological activity within the body. The examples may include water, essential oils, urea and its derivatives.

8.4. Preservatives

These are the chemical agents that provide protection against microbial contamination and degradation for e.g. methyl paraben, propyl paraben, etc.

8.5. Surfactants

They reduce interfacial tension and hence make the formulation more stable, for e.g. sodium lauryl sulfate, sodium glycolate, etc.

Table 1. Some examples of different types of polymers[2,3,12-14]

Natural Polymers	Polysaccharides Tragacanth Agar Dextran Pectin Guar gum Locust gum Hyaluronic acid Starch Xanthine Alginic acid Carrageenan Proteins Gelatin Collagen Casein Albumin
Semi-synthetic Polymers	Cellulose derivatives Methyl cellulose Hydroxymethyl cellulose Hydroxypropylmethyl cellulose Hydroxyethyl cellulose Carboxymethyl cellulose Ethylcellulose Hydroxypropyl cellulose Magnesium aluminum silicate
Synthetic Polymers	Poloxamer Acrylic acid (AA) Methacrylic acid (MAA) Chitosan Poly vinyl alcohol Polyethylene Polyacrylamide Polyethyleneglycol acrylate/methacrylate (PEGA/PEGMA) Polyethylene oxide Carbomers Carbopol-934 Carbopol-940 Carbopol-941
Inorganic Substances	Bentonite Aluminium hydroxide
Surfactants	Brij-96 Cetostearyl alcohol

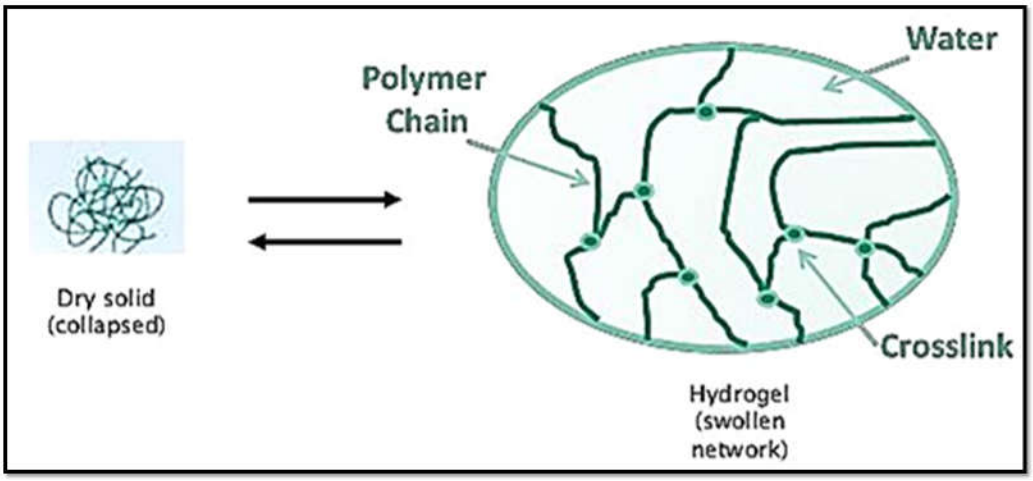

Fig. 3. Structure of a hydrogel.

9. CLASSIFICATION OF GELS

Gels can be classified as hydrogels, organogels and xerogels.

9.1. Hydrogels (Water Based)

It is a type of gel in which the polymeric material displays its ability to swell and retain abundant amount of water[2,13,15]. Hydrophilic functional groups attached to the backbone of polymer have this property of absorption and swelling with water. The structure of hydrogels can contain various amount of water, chiefly in the swollen state depending upon the characteristic of the polymer used as well as the nature and density of the matrix network (Fig. 3.) The weight content of water in a hydrogel is greater than that of the polymer[16].

9.2. Organogels (Non-Aqueous Liquid)

Various non-aqueous liquids are mentioned in Pharmacopoeias for the topical delivery of lipophilic drugs and incorporation of such liquids in a gel form is termed as organogel (Fig. 4.). These gels not only produce local effects but are also known to produce systemic effects via absorption through skin[17]. Because of their remarkable penetration capability, organogels are considered useful in the treatment of chronic diseases like osteoarthritis when the relevant analgesics are used[18].

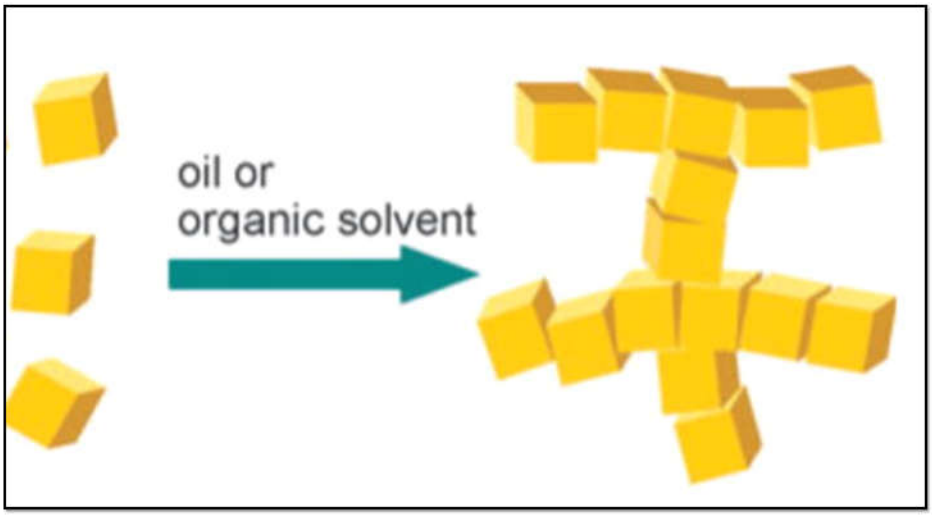

Fig. 4. Structure of an organogel.

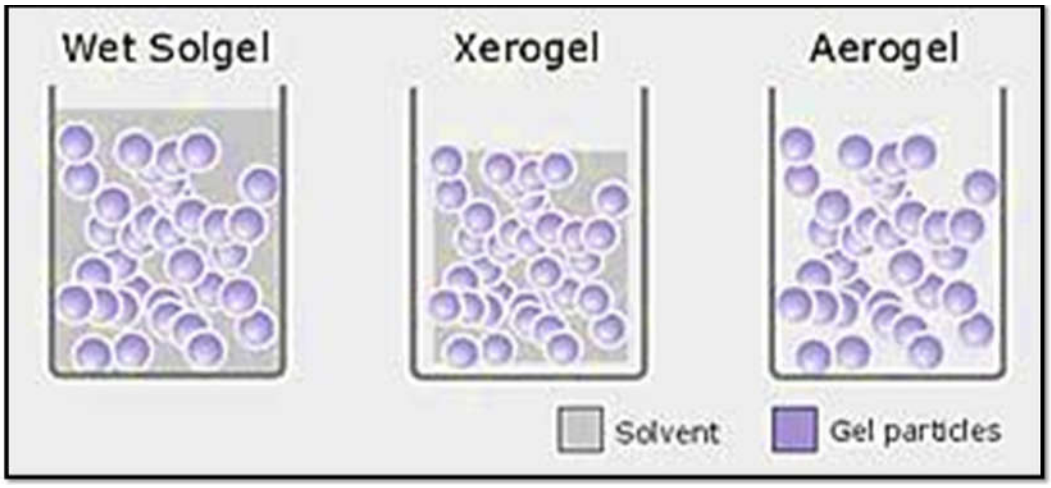

Fig. 5. Formation of xerogel.

9.3. Xerogels

When the solvent is removed from a gel via evaporation or freeze drying leaving behind a gel matrix with the fresh fluid is called as xerogel (Fig. 5). They have a low solvent concentration in them, hence they are more solid[2]. They can easily swell up and can be reconstituted (aerogels). Examples include tragacanth ribbons, polystyrene, dry cellulose, etc. Gels can also be classified as single and two phase systems[19]:

9.3.1. Single-phase system

They comprise of macromolecules which are organic in nature and are uniformly distributed within the dispersion medium in such a way that no separate boundaries exists between them. They can be made from natural gums or from synthetic polymers. Although water is mostly being used as their dispersion medium, alcohols and oils can also be used as continuous phase. They are frequently used in pharmacies because of their clarity, faster release of drug substances, independence of water solubility of drug, ease of application and removal over other semisolid dosage forms.

9.3.2. Two-phase system

If in a gel the particles of dispersed phase are distributed throughout the gel and appear as floccules rather than as large molecules then the gel structure is referred to as a two-phase system. This is because they become liquid on agitation and semisolids on standing.

10. TECHNOLOGIES ADOPTED IN GEL PREPARATION

A gel in simple words is a polymeric network cross-linked in some fashion to produce an elastic structure. The polymers are cross-linked to form gels in a number of ways[20]:

i. Linking polymer matrices through chemical reactions.
ii. Using ionizing radiation to generate main-chain free radicals which can recombine as cross-link junctions.
iii. Physical interactions such as entanglements, electrostatics, and crystallite formation.

11. MECHANISM OF DRUG RELEASE THROUGH GELS

Drug delivery to nasal or ocular mucosal membranes for either local or systemic action suffers many hurdles. Gel preparations can prolong the drug contact at the site of administration by its rheological and mucoadhesive properties thus making them sustained release drug delivery systems[21,22]. However, drug release from the gel must be sustained if benefits are to be gained from the prolonged contact time. Drug release from a gel includes the absorption of water and desorption of drug through a swelling controlled mechanism[23]. The rate factor mediating drug delivery is the resistance of the gelling agent to increase in volume and change its shape[24]. A glassy gel, on coming into contact with solvent medium, allows its penetration into free spaces on the surface

between the macromolecular chains. The presence of solvent in a polymer causes the development of stresses accommodated by an increase in end-to-end distance of polymer molecules, seen macroscopically as swelling[23]. Most of the time, drug release is observed during the swelling of the hydrogel. However, a few instances have been reported for drug release during syneresis of the hydrogel, as a result of a squeezing mechanism[25].

12. EVALUATION OF STABILITY OF GELS

Following parameters are considered important for the evaluation of stability of gels[26-32]:

12.1. Viscosity

The viscosity of a formulated gel may be quantified using a viscometer (e.g. Brookfield viscometer) by rotating them at 0.3, 0.6 and 1.5 revolutions per minute and the reading is then noted at each speed. Hence the viscosity can be calculated by multiplying the reading obtained with the factor mentioned in the catalogue of viscometer.

12.2. Spreadibility

One of the most important properties that determine the quality of a gel is its spreadibility. In order for a gel to be good, it should be easily spreadable onto the part on which it is applied and the area covered by it. Spreadibility is testified in terms of time taken by two slides in seconds to slip off from gel which is kept in between slides on application of some amount of load.

12.3. pH Determination

The pH of the gels can be determined by dissolving one gram of gel in 100 ml of distilled water and kept for two hours. The values are noted by using digital pH meter in triplicate of each gel and mean is calculated.

12.4. Drug Content

The assay of the active drug from gel formulations can be performed using any suitable technique like HPLC, UV-Vis spectrometry, etc. For e.g. in some cases a quantity of one gram of gel is incorporated in a suitable solvent and dilutions are made from filtered stock solution which is prepared in different concentrations from which absorbance are measured. The drug content is estimated by regression analysis of calibration curve.

12.5. Extrudability

The property of a gel by which it forces itself out of the collapsible tube is called extrudability. It is calculated by weight in grams needed to extrude a 0.5 cm ribbon of gel in 10 seconds.

12.6. Homogeneity

Homogeneity is determined by visually testing the gels for the presence of any aggregates after they have been set into the container in which they are to be inspected.

12.7. In Vitro Release

Franz diffusion cell is generally used for the evaluation of release of drug from gels through a membrane which can be of natural, synthetic or semisynthetic source. A suitable solution / solvent is placed in the receptor chamber which is used as the dissolution medium. A sample of gel is taken and placed on the donor chamber keeping it at a suitable temperature that can relate to the skin temperature of human body, i.e. 35±1°C. Appropriate amount of samples are withdrawn at different time intervals and are subjected to assay in order to calculate the in vitro release of the drug.

12.8. Microscopic Examination

The gels are observed under the microscope to indicate the presence of any particulate matter. The freedom of a gel from grits is the necessity of any topical dosage form.

12.9. Stability

The stability studies for gels are usually performed by freeze-thaw cycling. In this method, the product is exposed to a temperature of 4 °C for a month, then at 25 °C for a month and then at 40 °C for a month. For all three gels syneresis is noted visually. The gels are then brought to room temperature and the exudation of liquid is also observed.

12.10. Solubility

A small test tube is taken in which a specific amount of gel is allowed to dissolve in distilled water with continuous shaking.

12.11. Consistency

The evaluation of consistency of a gel can be carried out by dropping a cone which is attached to a rod holding it at a distance of 10 cm. The gel is completely filled in a cup and the cone is allowed to fall off the rod. The penetration of the cone into the gel is calculated by the tip of the cone from the surface to the inside.

13. APPLICATIONS OF GELS

Based on the different types their applications include[20,33]:

i. Incorporating drugs and applied to skin and mucous membrane or the eye.
ii. They can be applied in almost every route of administration.
iii. Used as binders in granulation of tablets, protective colloids in suspensions, thickeners in oral liquid and suppository bases.
iv. Used in cosmetics, dentifrices, skin and hair care preparations.
v. Used as a lubricant for catheters.
vi. Used in electrocardiography (e.g. sodium chloride gel).
vii. Used for dental care prophylaxis (e.g. sodium fluoride and phosphoric acid gels).

14. NOVEL APPLICATIONS OF GELS

Although the use of gels for various pharmaceutical, cosmetic and biomedical applications have increased tremendously in the recent past. Some of their novel applications may include[33,34]:

i. They are used as environment sensitivity detector.
ii. As scaffolds for the purpose of tissue engineering.
iii. Dressings for healing.
iv. In ECG electrodes.
v. In diagnosis of rectal drug delivery.
vi. Hydrogel-coated wells are also used in cell culture.
vii. In the preparation of contact lenses.

15. CONCLUSION

Gels are gaining more popularity nowadays because of their extended stability and controlled release unlike other semi solid dosage forms. They have better absorption characteristics because of their swelling nature thus increasing the bioavailability of the drug. The clinical evidences from its applications shows that pharmaceutical gel provides a safe and an effective treatment for skin related and other topical diseases.

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