RADS-JPPS Vol 4 (1), June 2016, 40-48

Pharmaceutical Gels: A Review

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ABSTRACT

There are different semisolid dosage forms that are used for topical applications among which gels formulations are becoming pre-eminent. The basic network of gel is a combination of a gelling agent and a solvent in which the drug molecules are embedded or entwined evenly. The nature of the solvent classify gels into two basic types i.e. organogels and hydrogels. This review highlights the basic advantages of gel formulations over other semisolid preparations as well as limitations of their use. Other aspects such as their classification, formulation, mechanism involved in the formation of gels and factors affecting their formulation have also been included.

Keywords: *Semisolids, organogels, hydrogels, cross-linking, gelling agent.*

INTRODUCTION

Gels are semisolid preparations intended for application on the skin or the accessible mucous membranes like oral cavity. Gels are composed of two interpenetrating systems where the colloidal particles, also known as the gelator or gallant, are uniformly distributed throughout a dispersion medium or solvent forming a three dimensional matrix known as the gel [1,2]. The gels are prepared by adding a gelling agent (gelator) which could be natural, synthetic or semi-synthetic polymer or low molecular weight small molecules, into an organic, inorganic or aqueous solvent or solvent systems (Fig. 1) [3–6]. The polymer in gels acts as the backbone of the gel matrix. The polymeric meshwork gives gel its structural strength, increased adherence to the surface where applied and decreased permeation of the larger molecules hence making the retention possible [7].

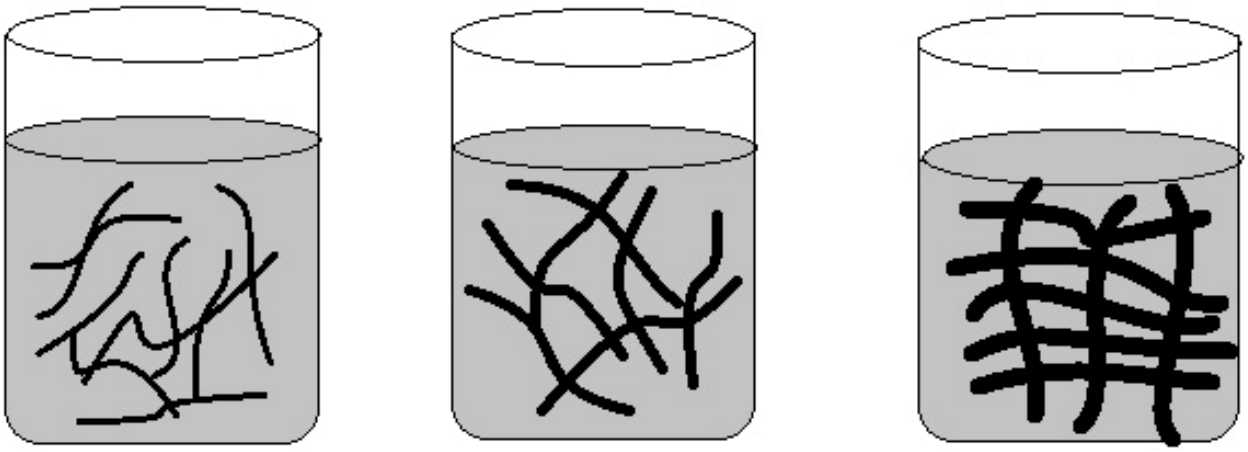

Fig. 1. Swelling of gelling agent in solvent.

Gels may be either reversible or irreversible

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based on the type of bonding. The reversible gels are generally hydrogen bonded systems whereas irreversible gels are usually covalently bonded. A gel may either appear as a single system with no apparent boundaries or as a two phase system with floccules of discrete particles [3,8]. During the gel formation, swelling occurs as a result of solvent penetration causing the polymer network to stretch and hold its shape and entwine the drug particles in them [7,9]. Viscosity plays an integral role in the formation of a gel. A gel, in its solution form, requires a specific concentration of polymer to increase the viscosity of the gel [9].

Advantages of Gel Formulations

Some of the major advantages of gel formulations over other semisolid dosage forms are as follows [4,7,9].

i) Gels are easy to formulate as compared to other semisolid dosage forms.
ii) A gel is an elegant non-greasy formulation.
iii) It can be used as controlled release formulation by entwining the polymer more than once.
iv) Gels have good adherence property to the site of application.
v) They are biodegradable and biocompatible.
vi) The retention time of gels is higher than other topical dosage forms.
vii) They have excellent tolerability to certain stress conditions.
viii) They form a protective layer on the application site.
ix) They are washable and nontoxic in nature.
x) They provide excellent spreadibility and cooling effect because of solvent evaporation.
xi) They have comparatively less long term stability issues.
xii) They can be used to administer both polar and non-polar drugs.

Disadvantages / Limitations of Gel Formulations

In spite of a number of advantages, gel formulations also have some disadvantages or limitations such as [4,7,9].

i) The effect of gels is comparatively slower and sustained.
ii) The additives or the gelators may induce irritation.
iii) The water content may increase the chances of microbial or fungal attack in gels.
iv) Syneresis (expulsion of solvent from the gel matrix) may occur in gels during storage.
v) Solvent evaporation from the formulation may result in drying of the gel.
vi) Covalent bonds present in some gels may render them unbreakable thus sealing the medicament inside the gel matrix.
vii) Flocculation in some gels may produce an unstable gel.
viii) Rheology of some gels may alter due to the effect of temperature, humidity and other environmental factors.
ix) The gelling agents may precipitate and result in salting out.
x) Some drugs may degrade in gel formulation due to the presence of polymers.

Classification of Gels

Based on the nature of solvent, its affinity and the physical state, gels are classified in two basic groups i.e. organogels and hydrogels.

Organogels

Organogels may also be referred as oleaginous gels. They are composed of both polar and non-polar groups but the ratio of the non-polar part is very high. They may contain 35% water as the gels tend to swell in water. Organogelators are usually low molecular weight small molecules that have the ability to thicken in organic solvents [5,6] in physical organogels has grown rapidly with the discovery and

synthesis of a very large number of diverse molecules, which can gel organic solvents at low concentrations. The gelator molecules immobilise large volumes of liquid following their self-assembly into a variety of aggregates such as rods, tubules, fibres and platelets. The many interesting properties of these gels, such as their thermoreversibility, have led to much excitement over their industrial applications. However, only a few organogels are currently being studied as drug/vaccine delivery vehicles as most of the existing organogels are composed of pharmaceutically unacceptable organic liquids and/or unacceptable/untested gelators. In this paper a brief overview of organogels is presented, followed by a more in-depth review of the gels that have been investigated for drug and/or vaccine delivery. These include microemulsion-based gels and lecithin gels (studied for transdermal delivery. Organogels are prepared with lipids like glycerol esters. The water is entrapped between the lipid bilayer in a 3-D matrix. At room temperature they appear as waxes. The presence of both polar and nonpolar entities enables the preparation to be used with both hydrophilic and hydrophobic drugs. Fig. 2 shows an organogel having a hydrophilic drug uniformly distributed in the polar solvent. The release of the active drug from these gels can be altered by changing the ratio of polar and non-polar parts of the gel.

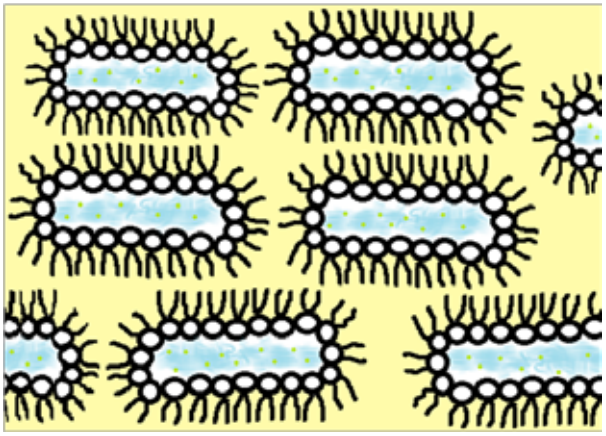

Fig. 2. Hydrophilic drug in polar solvent surrounded by an organic solvent.

These gels can sometimes completely displace the water content present in it thus resulting in dehydration of the gels. These dry gels are called as xerogels. The sheets of gelatin, tears of acacia and ribbon of tragacanth are prepared by removing the water from these gels [10]. Some examples of organogelators include sterol, derivatives of cholesteryl anthraquinones and disaccharides [11,12].

Hydrogels

Hydrogels, as the name indicates contain major portion of water which may be as much as 90% of the total gel content [7]. They are considered biocompatible and as the most beneficial and supportive option when it comes to implication as surface modifying systems [13]. The core of the hydrogel is a polymeric channel system which may be formed through physical or chemical cross-linking of homopolymers or copolymers, which when subjected to an aqueous surrounding result in swelling [14] as shown in Fig. 3. Hydrogels are three dimensional complex system where the core meshwork of polymer have the ability to soak up a large amount of water [15]. The predilection of polymer and the solvent, and the type and extent of cross-linking imparts the degree of swelling in hydrogels [7]. They are highly porous in nature which enhances their ability to hold the active drug and other substances [16], which are dispersed as colloids or may dissolve in water. With respect to the type and concentration of the polymer present, the hydrogels may vary in their thickness and rheology [3]. Many different physical forms of hydrogels can be devised such as hydrogel

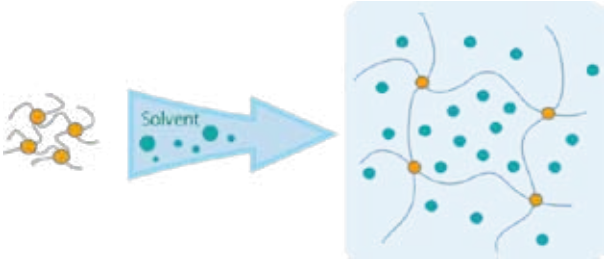

Fig. 3. Hydrogel swelling.

slabs, microparticles, nanoparticles, coatings and films [16].

FORMULATION OF GELS

Gel Formation

A gel is formed by creating a balance between the polymer and the solvent. A critical concentration yields the gel, also known as the gelling point, below this point the gel cannot be formed while above this point the viscosity increases greatly. The gelling point can be determined using the hydrophilic and lipophilic balance of the polymer, solvent and polymer interaction, uniformity in the structure, molecular weight of the polymer and flexibility of the polymer chain. The relationship between the flexibility and the gelling point is directly proportional. The gelling point can be increased or decreased by using solvents that alter the affinity towards that polymer [17].

Some gels require temperature manipulation for their formation. Heating the liquid and then incorporating the polymer in it with thorough mixing and then leaving it to cool down for settling is a basic procedure for their formation. In contrast to this method, some gels should be kept away from heating because increasing the temperature will disrupt the bonds (for e.g. hydrogen bonds).

Another technique to formulate gels can be through flocculation. This can be done by adding salts in the lipophilic solutions and hence forming the gel [17–19]. The example of such type includes mineral oil with fumed silica to form a gel by particle-particle interaction through hydrogen bonding [20]. Another example can be the formation of gel by adding benzene to ethyl cellulose and mixing vigorously to produce a uniform gel. It was also observed that the presence of electrolyte produces rheological changes and subsequently formation of gel, such as in Na^+–montmorillonite clay of smectite group (bentonite) and hydroxides of iron and magnesium [18,21]. Gels can also be prepared by chemical reactions like treating titanium with H_2O_2 / 0.1M HCl. This reaction produces a gel on the surface of titanium and the gel layer is increased in thickness with increase in H_2O_2 / 0.1 M HCl solution on the surface [22].

Mechanisms of Gel Formation

Gels can be formed via three types of cross-linking which are described as follows:

Chemical cross-linking

Sometimes dual or multifunctional monomers present in a polymer results in the formation of an unalterable chemical cross-linking with massive molecular mass (Fig. 4). These polymers are usually insoluble in the solvent but certain solvents, when incorporated, results

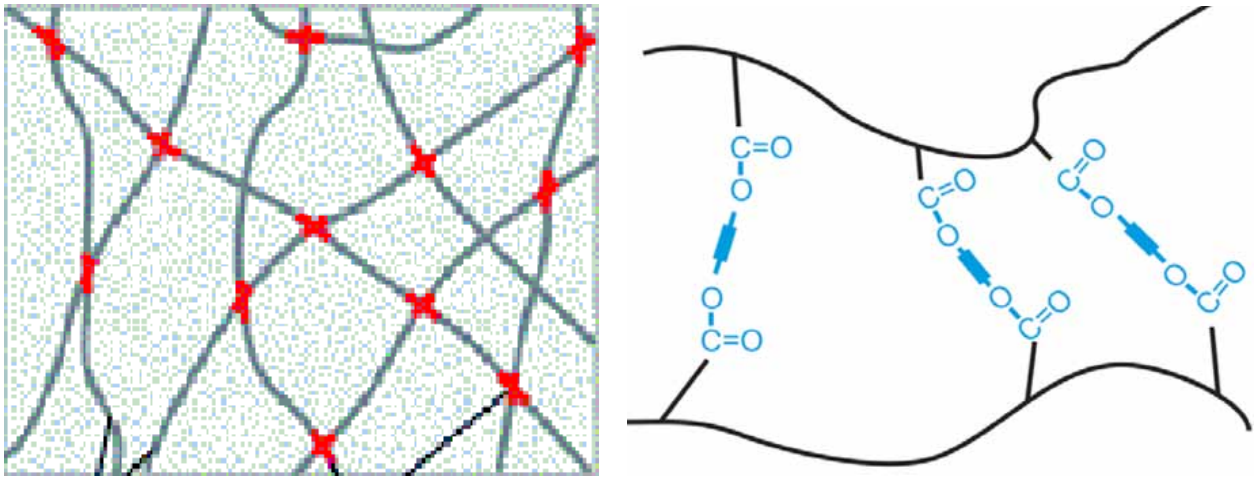

Fig. 4. Chemically cross-linked gel.

in only swelling and hence forming a gel, for e.g. polyacrylamide gels. These gels are covalently bonded and are irreversible in nature. Chemical cross-linking can also be obtained with polymers having un-bonded groups in their structure. A cross-linking compound when introduced in such polymers results in an irreversible chemical reaction between the free group and the added component. This irreversible reaction causes an increase in the viscosity and after attaining a certain concentration a gel is formed, for e.g. polyacrylic acid (with multiple carboxylic acid) and glycols (with hydroxyl groups) forms such kind of chemical cross-linking gels [7,10,23].

Physical cross-linking

In some cases, solution to gel transition can takes place by hydrogen bond formation, crystalline component solubilization, concentration variation, temperature variation transition or hydrophobic interactions. Examples of such gels include dextran gels, poly (N-isopropylacrylamide) gels, cellulose gels, etc. [7,23,24]. Physical cross-linking is shown in Fig. 5.

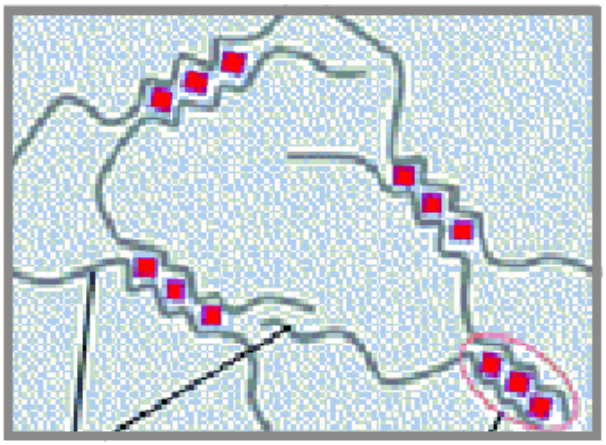

Fig. 5. Physically cross-linked gel.

Ionic cross-linking

Cross-linking can also be achieved by forming charges on polymer(s) or other molecules (solvent) that may attract each other to form a gel (Fig. 6). Ionic bonds are formed as a result of the charges on such molecules. For example, polysaccharide alginate in the presence of calcium ions produces a gel matrix which can encapsulate certain components (enzymes, etc.). Ionic gelation can also be attained by altering the pH of the medium (solvent). Changing the pH of such mixtures results in gelation, for e.g. pectin forms a gel when subjected to acidic pH in a suitable medium [7,10,23].

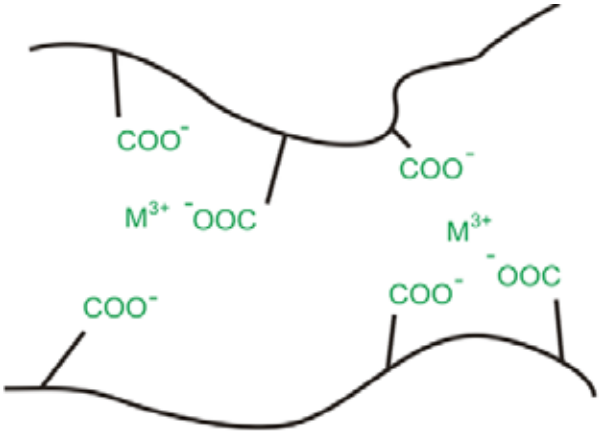

Fig. 6. Ionic cross-linking in gel.

Formulation Ingredients

In comparison to other semisolid formulations, like creams and ointments, gels are simple and easy to make. Besides the polymer and the solvent, the gels may contain stabilizers, dispersing agents, penetration enhancers and preservatives since they can be subjected to microbial contamination especially in case of hydrogels which contain enough amount of water to propagate the microbial growth [7,10].

Gelling agents

Gelling agents are selected according to the use and solvent affinity. Some commonly used gelling agents that are included in the official compendia are reported in the Table 1 [7,10,25].

Medium for gel preparation

The medium for formulation of a gel is selected according to its desired application. The medium could be one or more solvents depending upon the use of the gel. The solvents could be of hydrophilic, lipophilic or organic nature. The solvent(s) employed for the preparation of gels must be efficient and safe to use and should not

Table 1. Commonly used gelling agents and their salient features.

Name	Gelling Strength	Gelling Features
Alginic acid		• Insoluble in water. • Viscosity changes with changing molecular weight and concentration. • Calcium salts increases viscosity.
Bentonite	10–20%	• Available in crystalline state. • Increase in concentration, alkalinity and temperature increases viscosity.
Carbomer	0.5–2%	• Acidic in nature but neutralization increases their viscosity.
Carboxymethylcellulose calcium		• Addition of water increases their viscosity.
Carboxymethylcellulose sodium	3–6%	• High concentrations produce viscous gels. • Viscosity is stable in pH range between 4–10 and decreases beyond this range.
Carrageenan	0.3–2%	• Shows good gelling properties on increased temperature.
Colloidal silicon dioxide	2–10%	• Insoluble in water. • Viscosity is not affected by temperature. • Viscosity increases at acidic pH.
Ethylcellulose		• Insoluble in water and soluble in organic solvents (mixture of ethanol and toluene). • Viscosity increases with decrease in alcohol ratio and increase in concentration.
Gelatin	10–20%	• Soluble in water. • Gels are prepared by increasing temperature and then cooled to get the desired viscosity.
Guar gum	1–5%	• Viscosity is influenced by pH, particle size, rate of agitation, swelling time and temperature.
Hydroxyethyl cellulose		• Temperature and pH affects the gelling process. • Viscosity decreases at high temperature and improves in basic pH.
Hydroxyethylmethyl cellulose		• Viscosity increases with decrease in temperature and in pH range of 5.5–8.
Hydroxypropyl cellulose	2–5%	• Viscosity increases with an increase in concentration and mixing with anionic polymer. • pH other than neutral and temperature variation decreases viscosity.

Hydroxypropylmethyl cellulose	1–10%	• Gels are stable in pH range of 3–11. • Viscosity depends on concentration, solvent composition and molecular weight.
Glyceryl behenate	1–15%	• Insoluble in water and solubilize in organic solvents. • It increases the viscosity of silicon gels.
Glyceryl monooleate		• Insoluble in water. • Emulsifying grade with anionic surfactant results in swelling.
Magnesium aluminum silicate	5–15%	• It is insoluble in water but can swell in water. • Viscosity increases with increase in concentration, temperature and addition of electrolyte.
Methyl cellulose	1–5%	• Insoluble in hot water but swells in cold water. • Increase in temperature and decrease in pH reduces viscosity. • Increase in concentration increases viscosity.
Poloxamer	15–20%	• Soluble in water. • Increase in concentration increases viscosity. • Optimum pH range is 5–7%.
Polyethylene oxide		• Swelling can be achieved in water. • Viscosity increases with an increase in concentration and with addition of alcohol.
Polyvinyl alcohol	2.5–10%	• Temperature variation changes viscosity. • Addition of borax increases viscosity. • Optimum pH is from 5–8.
Povidone	2–20%	• Soluble in water. • Viscosity increases with an increase in concentration of viscosity grade povidone.
Propyleneglycol alginate		• Viscosity is based on concentration, temperature and pH (3–6).
Sodium alginate	10–20%	• They form viscous gels in water. • Viscosity increases with low concentrations of electrolyte, alcohol, glycerol, glycols and sugars. • Stable at pH 4–10. • Viscosity decreases in pH above or below this range.
Tragacanth	1–8%	• Viscosity is affected by temperature and pH variation (increases with an increase in temperature and maximum at pH 8 and starts increasing above 8). • Addition of glycols, glycerin and ethanol increases the quality of gel.
Polyacrylic acid		• Viscosity increases with addition of glycols or sugars. • Increase in concentration increases viscosity.

evaporate rapidly. Moreover, they should be compatible and have acceptable stability.

Most commonly employed medium for gel formulation is purified water. Other solvents can also be used either alone or in combination especially in case of insolubility. Examples of the solvents for preparing a gel besides water include glycerin, glycols, alcohols (ethanol), sucrose, toluene, mineral oils, etc. [7,10,20,23].

Mixing

The mixing order can be selected in accordance to the ingredients being used to formulate the gel. Their interactions and physicochemical properties should always be considered before mixing. A suitable solvent can be selected or co-solvency phenomenon can be employed if insoluble ingredients are present. One method is to produce the gel matrix with the solvent (with or without providing heat) and then incorporate the active pharmaceutical compound and other ingredients. The most preferred method to formulate a gel is through solubilizing all the ingredients in the solvent and then introducing the gelling agent to this mixture. Thorough mixing of the gel is very important to not only avoid lumps and bubbles but also to produce a uniform and consistent gel of desired viscosity [10]. All gels need some settling time ranging from 24–48 h which gives gel its final consistency and uniformity [10,19] .

Factors Affecting Gel Formulation

A number of factors are known to affect gel preparations. Some major factors have been enlisted as follows [7,10]:

i. Concentration of the gelling agent.
ii. Molecular weight of the gelling agent.
iii. Solubility and affinity of gelling agent to the solvent being used.
iv. Nature of the solvent.
v. pH of the solution.
vi. Ionic strength of the solution.
vii. Temperature at which the gel is being formulated.
viii. Humidity and other environmental conditions.

Uses

i. Some of the common uses of gel formulations are listed as follows [3,7–9]:
ii. Gels are used to produce sustained release dosage form.
iii. They are used as lubricants and as carriers for different pharmaceutical agents.
iv. Both polar and non-polar drugs can be formulated in a single gel.
v. They can be used to administer drugs through different routes like topical, intraocular, intranasal, vaginal, rectal, and in some cases parenteral and intramuscular.
vi. They are widely used in cosmetic industry and food industry.

CONCLUSION

Gels have gained considerable importance in the recent times due to their wide application and uses. Their preparation is easy and simple but requires considerable optimization between the drug and excipients for the manufacture of safe, effective and stable product.

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