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Review Article

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A Review on Pharmaceutical Gels

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Abstract The goal of this study was to compile the most recent research, with a particular focus on a logical approach to topical formulation and the fundamental components of topical drug delivery systems. Topical medication applications offer the benefit of delivering the drug directly to the site of action and acting for a longer time. The main route of topical medication delivery is through the skin, which is one of the most common and easily accessible organs on the human body for topical administration. Many commonly used topical treatments, such as ointments, creams, and lotions, have a number of drawbacks, such as being sticky and making the patient uncomfortable when administered. Furthermore, they have a lower spreading coefficient and must be applied by rubbing, as well as having a difficulty with stability. As a result of all of these characteristics, the use of gel has risen in both cosmetics and medicinal preparations. A gel is a colloid that is 99 percent liquid by weight and is immobilised by surface tension between it and a macromolecular network of fibres formed by a little quantity of gelatinous material.

Keywords Pharmaceutical gels; Terminologies; Characteristics; Classification; Preparation; Evaluation of Gels

Introduction

Gel Dosage form

A gel is a physical state in which two or more ingredients are mixed in a way that they form a semi-solid jelly like material which cannot flow in steady state [1-5]. Water and hydroalcoholic solutions are the most prevalent in medicinal applications. Between the gel state and the sol, which is the fluid phase containing the dispersed or dissolved macromolecule, many polymer gels show reversibility [6-10]. Because their chains are covalently connected, the production of certain polymer gels is irreversible. Several inorganic colloidal clays create the three-dimensional networks found in two-phase gels and jellies. These inorganic gels are reversible in their creation [11-13].

Mechanism of Gel Formation

There are three different methods of cross-linking that may be used to make gels:

Chemical cross-linking

When dual or multifunctional monomers are present in a polymer, an irreversible chemical cross-linking with large molecular mass can emerge. These polymers are normally insoluble in the solvent, however some solvents, such as polyacrylamide gels, cause only swelling and therefore formation of a gel when included [13-16]. These gels are irreversible since they are covalently linked. Polymers with un-bonded groups in their structure can also be chemically cross-linked. When a cross-linking ingredient is introduced into such polymers, the free group and the added component undergo an irreversible chemical reaction. This irreversible reaction increases viscosity, and after

reaching a particular concentration, a gel is generated; for example, chemical cross-linking gels are formed by polyacrylic acid (with multiple carboxylic acids) and glycols (with hydroxyl groups) [15-19].

Physical cross-linking

Hydrophobic interactions, hydrogen bond formation, crystalline component solubilization, concentration fluctuation, temperature variation transition, and other factors can all contribute to the transition from solution to gel. Dextran gels, poly (N-isopropylacrylamide) gels, cellulose gels, and other types of gels are examples of this kind [18-22].

Ionic cross-linking

Charges can be formed on polymer(s) or other molecules (solvent) to attract one other and create a gel. The charges on such molecules result in the formation of ionic bonds. For example, olysaccharide 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 [23-25].

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 [26-35]

Advantages of Gel Dosage Form:

1) Local action offers many advantages like
    a. Fast action & Long-lasting action (direct at site)
    b. Less side effects
    c. bypass problems of GI administration like bad taste, chances of interaction with other drugs/food/HCl, metabolism by liver or other organs
2) High Patient Compliance because of Easy Use (non invasive application or use)
3) Easy to formulate as compared with other dosage forms
4) Mostly gels are non-greasy & elegant formulations
5) This Dosage form is very suitable for
    a. Unconscious patients
    b. Patients with gastric problems
    c. Pediatric & Geriatric Patients
    d. Patients taking lot of Medications
    e. Skin Disorders
    f. Salts which have bitter taste [36-40]

Disadvantages of Gel Dosage Form:

1) Less Dosage accuracy
2) Drugs of big molecular size cannot be absorbed by skin so cannot be given in gel form
3) Less stable as compared to Solid Dosage forms
4) More chances of contamination at time of usage
5) May be greasy & patient may not like because of cleaning problem, staining of clothes etc
6) May cause irritation or allergy to patient
7) Mostly costlier & require more storage space as compared to solid dosage forms

8) Have chances of deactivation by enzymes present in Epidermis
9) Sterilization is required if to be inserted in eyes or any body cavity
10) More vulnerable to environmental factors like temperature, humidity [22, 36, 41-46]

Classification of Gels can be done on different bases

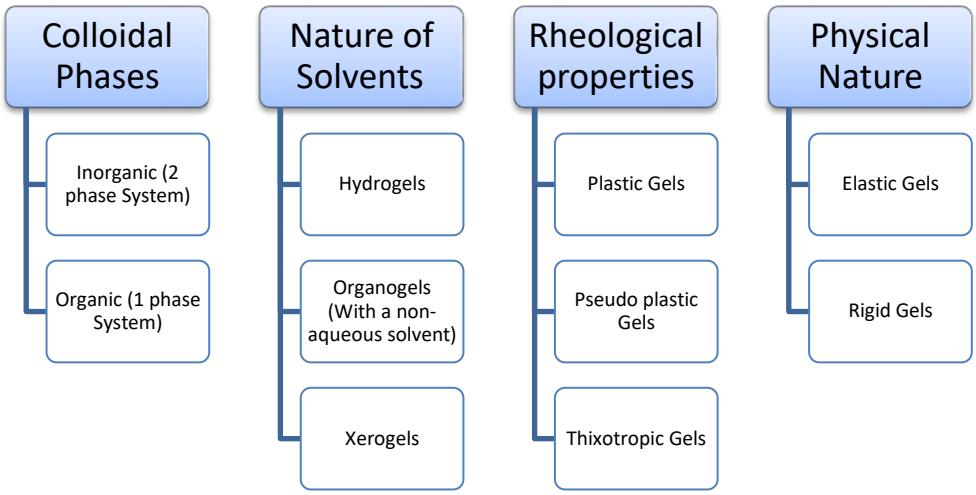

Figure 1: Classification of Gels

The idea behind development of Gel is attaining a substance that don't flow like a liquid in static form but retains characteristics of liquid to some extent in such way that one can dissolve a solid (medication) in this substance and easily apply on any surface (affected part) from where it can be absorbed & act locally to give fast action while minimizing wastage & side effects [47-49]. Gels are sometimes referred as "Jellies" [50].

Depending on the contents, certain gel systems are as transparent as water, while others are turbid. This is due to the fact that the ingredients may not be completely molecularly distributed (whether soluble or insoluble), or they may form aggregates that scatter light. With a few exceptions, the concentration of the gelling agents is usually ranging from 0.5 to 2.0% (less than 10%) [51-55].

Properties of Gels

1. It is a colloidal system with a liquid dispersed phase and a solid dispersion medium.
2. It is a semi-solid that is immovable.
3. The structure is honeycomb-like.
4. Swelling occurs in most gels as a result of the absorption of fluids.
5. Elastic Gels are made of organic substances and they give elastic solids on heating and on adding water gel form can be re-obtained. (reversible & lyophilic)
6. Non-Elastic (Rigid) Gels are made up of inorganic substances and they give powder on heating which cannot be converted into gel again by adding water (irreversible & lyophobic)
7. It is possible for gels to swell, absorbing more liquid and expanding in bulk.
8. Many gel systems contract when left standing, a phenomenon known as syneresis, which occurs as a result of the relaxation of elastic tensions created during the gel's setup.
9. In colloidal systems, such as gels, gradual aggregation is common and is referred to as "ageing."
10. Some gels are rigid due to the presence of a network produced by the interlinking of gelling agent particles.
11. Gelling agent solutions and flocculated solid dispersion are pseudo plastic in nature [56-61].

Components of Gels

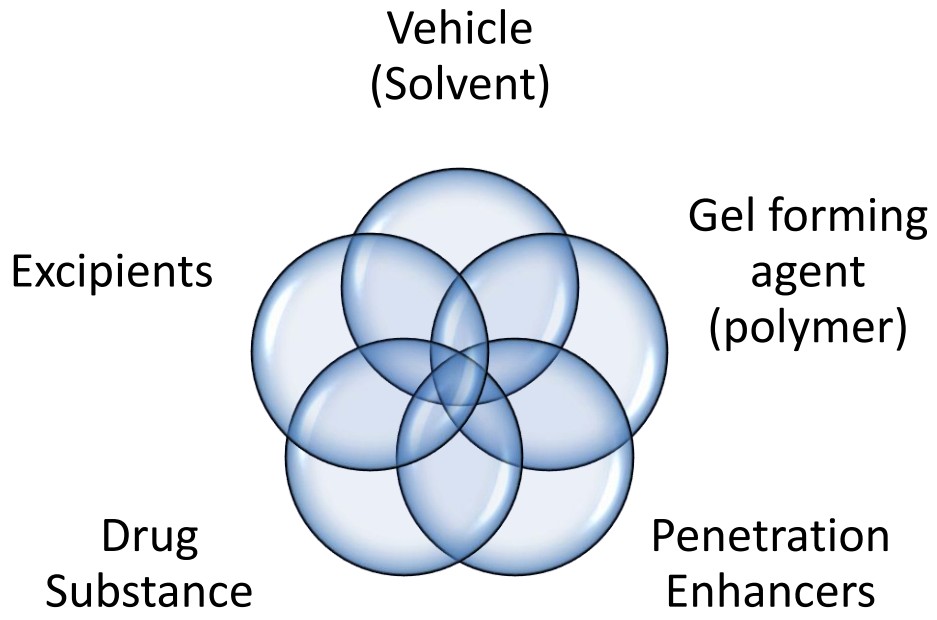

Figure 2: Components of Gels

Excipients may include:

a. Buffers
b. Preservatives
c. Anti-Oxidants
d. Flavors
e. Sweetening Agents
f. Stabilizers [62-67]

Choice of excipients depends on use of Gel i.e. oral/topical/ophthalmic etc.

Buffers are generally added to maintain the pH of the product (as per site of use) for example pH required for dermatological products for topical application is near 4.5 whereas pH required for ophthalmic products is near 7 [66-70].

Preservatives, Stabilizers and Anti-Oxidants are required to keep drug in gel dosage form in safe and usable form. Antioxidants are generally added in formulations which are prone to degradation due to oxidation ex E.g., Sodium metabisulphite, sodium formaldehyde sulfoxylate, etc. Drugs which are sensitive to heavy metals are sometimes protected with help of adding chelating agents such as E.D.T.A.(Ethlylene diamine tetra acetic acid)

Flavors and Sweetening agents are required in when gel is to be applied in oral cavity for treatment of Ulcers, infection or inflammation etc. In Such cases elegant taste is required so that compliance can be increased. Examples of different flavors used in gels are Cherry, Mint, Vanilla, Raspberry, Butterscotch, Citrus flavors etc. Examples of different sweetening agents used in gels are Glucose, Sucrose, Glycerol, Sorbitol, Saccharin sodium etc [62-70].

Desired properties of an Ideal Penetration Enhancer

An Ideal penetration enhancer should have following properties:

1. Inert (pharmacologically and chemically)
2. Chemically stable.
3. Non-toxic

4. Non-irritant
5. Non-comedogenic
6. Non-allergenic.
7. Odorless
8. Tasteless
9. Colorless
10. Inexpensive.
11. Pharmaceutically and cosmetically acceptable.
12. Pharmacologically inactive (should not bind to receptor sites)
13. Compatible with excipients and drugs [71-75]

Some Commonly Used Gel Forming Agents:

Alginic acid, Bentonite, Carbomer, Carboxymethylcellulose Calcium, Carboxymethylcellulose sodium, Carrageenan, Colloidal silicon dioxide, Ethylcellulose, Gelatin, Guar gum, Hydroxyethyl cellulose, Hydroxyethylmethyl cellulose, Hydroxypropyl cellulose, Hydroxypropylmethyl cellulose, Glyceryl behenate, Glyceryl monooleate, Magnesium aluminum silicate, Methyl cellulose, Poloxamer, Polyethylene oxide, Polyvinyl alcohol, Povidone, Propyleneglycol alginate, Sodium alginate, Tragacanth.

Different Gel Forming agents have different properties. Properties of some commonly used Gelling Agents is as given below:

a. Gelatin:

Gelling strength of Gelatin is 10–20%. It is soluble in water. Gelatin Gel is prepared by increasing temperature of mixture and then cooling to get the desired viscosity.

b. Guar Gum:

Gelling strength of Guar Gum is 1–5%. Viscosity of Guar Gum can be influenced by many factors like: temperature, swelling time, agitation rate, pH, particle size

c. Polyvinyl alcohol:

Gelling strength of polyvinyl alcohol is 2.5–10%. Optimum pH for making gel of Polyvinyl alcohol is 5-8. Adding Borax increases the viscosity of gel formed by polyvinyl alcohol. Temperature variation also changes viscosity of Gel formed using polyvinyl alcohol as Gelling Agent.

d. Tragacanth:

Gelling strength of Tragacanth is 1–8%. Viscosity of gel formed by Tragacanth increases with increase in temperature. Glycols, Glycerin and Ethanol can be added to increase the quality of gel formed by Tragacanth.

e. Methyl cellulose:

Gelling strength of Methyl cellulose is 1–5%. Methyl cellulose swells in cold water. Increasing the temperature or decrease in pH, decreases its viscosity.

f. Carbomer:

Gelling strength of Carbomer is 0.5-2%. Gel formed using carbomer as gelling agent is acidic in nature and neutralization increases it's viscosity.

g. Hydroxypropyl cellulose:

Gelling strength of Hydroxypropyl cellulose is 2-5%. Viscosity of gel formed by using Hydroxypropyl cellulose increases by mixing anionic polymer or increasing concentration whereas Viscosity of gel formed by using Hydroxypropyl cellulose decreases with variation in temperature or pH other than Neutral.

h. Hydroxypropylmethyl cellulose:

Gels formed using Hydroxypropylmethyl cellulose are stable in pH range between 3 to 11. Viscosity changes with changes in factors such as solvent composition and concentration.

i. Magnesium aluminum silicate:

Gelling strength of Magnesium aluminum silicate is 5-15%. It is not soluble in water but swells when it is in contact with water. Viscosity of gel formed by using Magnesium aluminum silicate increases by adding lectrolyte or with increase in temperature or concentration [6, 22, 36, 76-81].

Method of preparation of Gels:

1. Thermal Changes:

Many polymers are more soluble in hot water than in cold water, so solution is heated to solublize polymers and gel is formed when this solution is cooled down. E.g., Gelatin, Guar Gum, Agar, cellulose derivatives, etc

2. Flocculation:

In this method salt is added in limited quantity to form precipitate (to form gel) but this quantity is not sufficient to make full precipitates (solid) In this method quick mixing should be done to avoid local high concentration and formation of Solid. E.g., Solution of ethyl cellulose, polystyrene in benzene can be gelled by quick mixing with suitable amounts of a non-solvent such as petroleum ether.

3. Chemical Reaction:

Some solutes chemically interact with solvent to form gels. For example, an aluminium hydroxide gel can be made by combining an aluminium salt and sodium carbonate in an aqueous solution and increasing the concentration of reactants to generate a gel structure [6, 22, 36, 82].

Evaluation of Gels:

There are many methods available to evaluate gels which can be used as per need in different gel formulations. Some evaluation methods are discussed below:

a. pH:

Using a digital pH meter, the pH of various gel compositions is determined. 1 g of gel is dissolved in 100 mL of newly made distilled water and kept in the refrigerator for two hours. Each formulation's pH is measured three times and the average readings are calculated.

b. Drug Content:

In 100 mL of appropriate solvent, 1 g gel is dissolved. Using a UV spectrophotometer, absorbance is determined after an appropriate dilution at λmax.

c. Viscosity:

The viscosity of produced gel compositions can be measured with a Brookfield digital viscometer. The gels are rotated at three different speeds: 0.3, 0.6, and 1.5 revolutions per minute. The relevant dial reading is documented for each speed. The viscosity of the gel is calculated by multiplying the dial reading by the factor specified in the Brookfield viscometer catalogues.

d. Spreadability:

The extent to which gel spreads rapidly after application is referred to as spreadability. The wooden block and glass slide device are used to determine it. Spreadability is defined as the time it takes two slides to slip away from a gel placed in between them under the influence of a specific load in seconds. The spreadability improves as the time it takes to separate two slides decreases. Following formula is used to calculate spreadability:

$S = M.L / T$

Where, S denotes Spread ability, M denotes weight tide to the upper slide, L denotes glass slide's length, T denotes time taken to separate the slide completely from each other

e. Grittiness:

The presence of any particle matter is tested microscopically on all gel compositions.

f. Extrudability:

After being placed in the containers, the gel formulations are put in collapsible tubes. The weight required in gram to extrude a 0.5 cm. ribbon of gel in 10 seconds is used to test extrudability of gel formulations.

g. Homogeneity:

After the gels have been placed in the container, all generated gels are visually inspected for uniformity. They are examined for the appearance of aggregates and the presence of any.

h. Skin irritation:

Irritation is tested for all gel formulations. For skin irritation tests, some healthy male and female participants are chosen. On the internal surface of the upper arm or any other suitable site 100 mg gel is applied on a 2 cm area and covered with cotton bandage. After 6 hours, the site is cleaned with acetone and readings are taken using Draize's scale.

i. Stability:

Product is subjected to high & low temperatures (for ex say 40°C & 20° C) for some time (for ex say 1 Month). Syneresis is observed and finally, the gel is exposed to ambient room temperature and the separating liquid exudates are noted [23, 83-87].

Applications of gels

Gels are commonly used as

a. delivery systems for topical drug application (directly on skin, mucous membrane, eye)
b. binders in tablet granulation
c. protective colloids in suspensions
d. thickeners in oral liquid and suppository bases
e. In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations [6, 22, 23, 36, 88-90].

Conclusion

Gels are becoming increasingly popular as a result of their increased stability and ability to give controlled release over other semisolid preparations such as creams, ointments, pastes, and so on. The gel formulation may have improved absorption qualities, increasing the drug's bioavailability. A comprehensive examination of the gel formulation's stability properties over a long period of time may open the door to its therapeutic usage in patients. Because the polymer is water soluble, it forms a water washable gel and has a greater chance of being employed as a topical medication delivery dosage form. The primary benefit of topical drug delivery is that it allows for the accumulation of high local drug concentrations within the tissue and its vicinity for enhanced drug action. This is especially useful when drugs with a short biological half-life and a narrow therapeutic window are administered via this route. Clinical data suggests that topical gel is a safe and effective therapy option for the treatment of skin disorders. Gels have risen in prominence in recent years as a result of their vast range of applications and uses. Their preparation is straightforward, but it necessitates extensive adjustment between the drug and excipients in order to produce a product that is safe, effective, and stable.

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