Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Review Article

Gels as Topical Drug Delivery System: A Review

SREELAKSHMI M S, FELS SAJU*

Department of Pharmaceutics, Nirmala College of Pharmacy, Muvattupuzha, Kerala, India, 686 661

ARTICLE DETAILS

Article history:
Received on 19 November 2020
Modified on 16 December 2020
Accepted on 23 December 2020

Keywords:
Gel,
Gel Delivery System,
Topical Drug Delivery System,
Inorganic Gel,
Organic Gel.

ABSTRACT

Topical drug delivery systems are localized drug delivery systems for the treatment of cutaneous disorders in which the drug is delivered via skin. These systems are generally used for treating local skin infection. Many semisolid preparations including ointments, creams and lotions are available for treating skin ailments. Gels also belong to this category. But some of its properties make it more suitable dosage form than the others in this group. Gels are solid, jelly like materials formed from colloidal mixtures. The major property of a pharmaceutical gel is that it has a solid like consistency upon storage but is breakable through sheer force generated via shaking the bottle or squeezing the tube. Another property which makes it popular is that gels are less greasy and can be easily removed from the skin. Moreover, the gels have a better application property and stability in comparison to other topical formulations like creams and ointments which make it more acceptable in the pharmaceutical industry. In this review, a general overview of the gels are described including its chemistry, classes, formulation considerations, method of preparation and evaluation methods.

INTRODUCTION

Gels are solid, jelly-like materials formed from colloidal mixtures. They are composed of 2 phases: a solid continuous phase (Gelator) and a liquid dispersed phase (Solvent). The gelator is dispersed within the solvent due to which the gels are colloidal in nature [1]. As per the USP definition, gels are semisolid system containing either suspension made up of small inorganic particles or large organic molecules interpenetrated by a liquid. The gel mass is sometimes called as magma if the size of dispersed particle is relatively large [2]. When gels are used pharmaceutically it should posses some ideal properties which include, that they should be inert, safe and should not show any interactions with other ingredients of formulation. And another important property is that, when a gel is used in a formulation it should produce a sufficient solid like consistency upon storage but at the same time could be breakable with shear force generated by shaking the bottle, squeezing the tube or during topical application [3]. Also the gel should not be tacky and if it is used for ophthalmic preparation, it should be sterile [4].

Author for Correspondence:
Email: fels.academics@gmail.com

Chemistry of Gels

Coming to the chemistry of gels we have to discuss the term cross linking. If we take a polymer solution it can be concentrated or diluted depending on the amount of polymer dissolved in the solvent. And in a diluted solution, there is no interaction between the dissolved coils. But in the case of a concentrated solution number of molecules is large and they are forced to be close together so that they develop some kind of interaction upon each other. The summation of intermolecular forces cause the viscosity to increase drastically and thereby solution begins to exhibit a transition from a concentrated solution to a gel [5].

In this process the mixture containing water and soluble branched polymer is called a sol. With increasing dimension of the structure the solubility of the polymer decreases, and this "infinite polymer" is called the "gel" or "network" which is composed of several finite branched polymers. So, this process of transition from a system with finite branched polymer to infinite polymer is called "sol-gel transition" or

"gelation". And the point at which gel first appears is called the gel point [6].

Any substance capable of forming gel is called gelator. Usually the gel is composed of one or more gelling agents and a fluid which behaves as a visco-elastic material, due to the immobilisation of solvent molecules in a three dimensional network. This network result from the self assembly of the gelling agent into fibres via various interactions such as hydrogen bonding, Vander-Waal's electrostatic interactions and charge transfer [7]. Solvent interactions have a significant influence in the gel formation and the self assembly of the gelators is also important. Another factor which is significant is the modulation of the HLB in order to ensure that the 3D network imbibes the solvent within polymer network [8]. Depending on the bonding the gel can be reversible (hydrogen bonding) or irreversible (covalently bonded).

Classification of Gels [2, 9, 10]

Based on Colloidal Properties

1. Inorganic gels (Two phase system)
2. Organic gels (Single phase system)

Two Phase System

In this system, the particle size of dispersed phase is relatively large, and form three dimensional structure, throughout gel. This system consists of floccules of small particles rather than large molecules, and system is not always stable. They are thixotropic in nature, which upon standing become semisolid and liquid on agitation.

Single Phase System

It consists of large organic molecules called gel formers existing on the twisted strands dissolved in a continuous phase. Gel formers are either natural or synthetic polymers. They tend to entangle with each other by Vander Waal's forces or by their random motion.

Based on Nature of Solvent

1. Hydrogels
2. Organo-gels
3. Xerogels

Hydrogels

In hydrogels, water is the continuous phase, about 90% of the toatal gel content is water. The core of hydrogel is a polymeric channel system which is formed by physical or chemical cross-linking of homopolymers or copolymers. This is subjected to aqueous surrounding which cause swelling.

Organogels

It consists of polar and nonpolar groups. And as the name indicates nonpolar part is very high. Organo-gels have the ability to thicken in organic solvents. They immobilize large volume liquid and then self assemble into variety of aggregates such as rods, tubules, fibres, platelets etc

Xerogels

They are solid gels with low solvent concentration. The main step in their preparation is the evaporation of solvent or freeze drying upon leaving the gel framework on contact with fresh fluid they swells so that they can be reconstituted.

Based on Rheological Properties

1. Plastic gels
2. Pseudo plastic gels
3. Thixotropic gels

Plastic Gels

Eg: Bingham bodies, flocculated suspension of Aluminium hydroxide exhibit a plastic flow and when we plot a rheogram yield value of the gels above which the elastic gel disorts and begin to flow.

Pseudo-plastic Gels

Eg: Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. shows pseudo-plastic flow. That means viscosity of these gels decreases with increasing rate of shear. With increasing shear stress this disarranged molecules begin to align their long axis in the direction of flow with release of solvent from matrix.

Thixotropic Gels

They show gel-sol-gel transformation. It means due to weak bonds between particles these gels broken-down by shaking and then reverts back to normal by the collision of particles and linking together again. Eg: kaolin, Agar, Bentonite

Based on Physical Nature

1. Elastic gels
2. Rigid gels

Elastic Gels

In this molecules are linked at the point of junction by weak bonds such as hydrogen bonds and dipole attractions.

Eg: Gels of Agar, Pectin, Guar gum

Rigid Gels
These are gels in which the framework is linked by primary valence bond.
Eg: silica gel.

Formulation of Gels [2, 11, 12]
A gel is formed by creating a balance between polymer (gelator) and solvent. Gels form at a critical concentration also called gelling point. This point is very critical because below this point gel cannot be formed and above this point viscosity increases. The gel formulations have the advantages that it is non-greasy, efficacious, non- irritating, easily rubbed in by local administration leaving no visible residue. Also, non- staining of the skin or clothing is very important property which promotes the patient acceptance. The ingredients for formulation include polymer, solvent, stabilizers, dispersing agents, penetartion enhancers and preservatives.

Gelling Agent
Gelling agents are selected based on their use and affinity for solvent. Some commonly used gelling agents are; agar, alginate, carageenan, guargum, sodium carboxy methyl cellulose etc.

Medium for Gel Preparation
The medium can be one or more solvents depending upon the use of the gel and is selected according to its desired application.

- It can be hydrophilic, lipophilic or organic in nature.
- It should be efficient and safe to use.
- Should evaporate rapidly.

Most commonly purified water is used as the medium for gel formation. Other solvents include glycerin, glycols, alcohols, sucrose, toluene, mineral oils etc.

Buffers
In aqueous and hydroalcoholic based gels the pH of the formulation is controlled by adding buffers.
Eg: citrate, phosphate etc

Preservatives
In order to protect the gels from microbial activity preservatives are cooperated with the hydrophilic polymers.
Eg: Parabens, Phenolics etc.

Antioxidants
To improve the chemical stability of therpaeutic agents that are prone to oxidative degradation antioxidants are added to the formulation. Since, most of the gels are aqueous based, antioxidants used are water soluble in nature.

Flavours/ Sweetening Agents
If the gel is meant for oral administration then only flavours and Sweetening agents are included.

Flavours: Butterscotch, Vanilla, Cherry etc

Sweetening agents: Sucrose, Liquid glucose, Sorbitol

Mixing of the Ingredients
The order of mixing ingredients is based on the ingredients being used, their interaction and physicochemical properties. One method is to first prepare the gel matrix with solvent followed by incorporation of the active pharmaceutical ingredients. And the preferred method is, solubilizing all the ingredients in solvent and finally adding gelling agent to this mixture. The factors to be taken into care are to avoid any lumps and bubbles during mixing as well as to maintain uniformity and consistency of the gel.

Preparation Methods of Gels [10, 12]
In the industrial scale, gels are prepared under room temperature. Sometimes special treatment before processing is needed. Three methods are used;

1. Thermal changes
2. Flocculation
3. Chemical reaction

Thermal Changes
Solvated polymers are subjected to thermal changes to cause gelation. Most of the hydrogen formers are soluble in hot than cold water. Mechanism is that by reducing temperature degree of hydration reduces and gelation occurs. Eg: Gelatin, Agar, Sodium oleate etc. This is not a general method as this mechanism cannot be applied to some of the polymers.

Flocculation
In this, by addition of salt to precipitate, the gelation is produced. Rapid mixing should be ensured to avoid local high concentration of precipitant.

Eg: Solution of ethyl cellulose, Polystyrene in benzene can be gelled with suitable amounts of a non-solvent such a petroleum ether ensuring rapid mixing. The disadvantage of this method is;

- When salt is added to a hydrophobic solution only coagulation is observed and gelation rarely occurs.
- And with "salt out" effect the gelation doesn't occur.

Chemical Reaction
As the name indicates here the gels are produced by a reaction between a solute and solvent.
Eg: By interaction in aqueous solution of Aluminium salt and sodium carbonate Aluminium hydroxide gel can be prepared. Another example for gelation by chemical reaction includes PVA, Cyanoacrylates with glycidol ether; Methane diphenyl isocyanine (MDI) that cross links the polymeric chain.

Evaluation of Gels [2, 3, 4, 11, 12, 13, 14]
pH Measurement
1g of gel is dissolved in 100ml of freshly prepared distilled water and stored. After 2 days pH of each formulation is measured using digital pH metre and the average values are calculated.

Viscosity Measurement
Brookfield digital viscometer is used to measure the viscosity. The gels are rotated at different speeds say 0.3, 0.6 & 1.5 rotations per minute and corresponding dial readings are noted. Viscosity can be calculated by multiplying dial readings with factor given in the Brookfield viscometer catalogue.

Spreadability
It is the extent of area to which gel readily spreads on application which can be measured using wooden block and glass slide apparatus. The gel is placed between the two slides of the apparatus under the direction of some load. The time required by the slides to slip off from the gel in seconds is expressed as spreadability.

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

Where, S- Spreadability
M - Weight tide to the upper slide
L - Length of a glass slide
T - Time taken to separate the slide completely from each Other.

Less the value of T better the spreadability.

Homogeneity
After the gel has set in the container, homogeneity can be tested by visual inspection.

Drug Content
1g gel is dissolved in 100ml of solvent. Different concentration of gel are prepared by suitable dilution, filtered and absorbance measured spectrophotometrically. Drug content can be obtained from the calibration cure of drug by linear regression analysis.

Grittiness
All the prepared gel formulations are analysed microscopically for the presence of any unwanted matter.

Extrudability
After being set in the container the gel formulations are filled in collapsible tubes. Then extrudability is measured in terms of weight required in grams to extrude 0.5cm ribbon of gel just in 10 seconds.

Stability
Study is carried out by freeze thaw cycling. The product is subjected to a temperature of 4°C for one month followed by 25°C for one month and finally 40°C for one month. After that it is also exposed to ambient room temperature and the seperated liquid exudates are noted.

Centrifugation Test
10g of the formulation is added in a tapered test tube and subjected to a cycle of 3000rpm for 30 minutes at room temperature. The test is performed with centrifugation apparatus.

***In Vitro* Drug Diffusion Study**
Franz diffusion cell is used for the purpose. 0.5g of the gel formulation is placed in the cellophane membrane. And studies are conducted at a temperature of 37+-1°C, using 250ml phosphate buffer, pH 7.4 as dissolution medium. 5ml of each sample was withdrawn at regular time intervals 1,2,3,4,5,6,7 & 8 hours and replaced with same amount. The sample is analysed by using phosphate buffer as blank.

Skin Irritation Test
Guniea pigs weighing 400-500g of either sex can be used for the study. Hairs are shaved and an area of 4cm^2 is marked on both sides of their body. 500mg of gel is applied at the side twice daily for one week and observed for any reaction throughout the period. Reaction is graded as 0,1,2,3 which correspond to;
0 - No reaction
1 - Minnor patchy erythema

2 - Minor confluent or moderate but patchy erythema
3 - Severe erythema with or without edema respectively.

CONCLUSION

Pharmaceutical gel has been discussed in this review. Gels are considered to be an important topical drug delivery system. Its advantages like stability compared to other semi solid dosage forms such as ointments and creams make it more acceptable among the patients also. In this review various aspects of Gel including its chemistry, classification, formulation, preparation methods and evaluation are mentioned.

REFERENCES

[1] Lloyd, Gareth, Owen. Anion-Tuning of Supramolecular Gel Properties. Durham theses. 2010.
[2] Hemendrasinh J, Rashid, Mehta CP. A Review on Pharmaceutical Gel. International Journal of Pharmaceutical Sciences. 2015; 1(1): 33-47.
[3] Sharma B and Singh LR. Pharmaceutical Gels for Topical Drug Delivery:An Overview. International Journal of Research in Pharmacy and Pharmaceutical Sciences. 2018; 3(2): 19-24.
[4] Kaur LP, Guleri TK.Topical Gel:A Recent Approach for Novel Drug Delivery. Asian Journal of Biomedical & Pharmaceutical Sciences. 2013; 3(17): 1-5.
[5] Susana B.Grassino. Gel: A Short Word with A Long Meaning. https://www.pslc.ws/macrog/gel.htm.
[6] Redaelli F, Sorbona M, Rossi F. Synthesis and Processing of Hydrogel for Medical Applications. In: Giuseppe Perale and Jöns Hilborn. Bioresorbable Polymers for Biomedical Applications, 1st ed. 2017. 205-228.
[7] Desvergne JP. Organic Gelators and Hydrogelators. Beilstein Journal of Organic Chemistry. 2010; 6:846-847.
[8] Karoyo AH, Wilson LD. Physicochemical Properties and the Gelation Process of Supramolecular Hydrogels: A Review. Gels. 2017; 3:1.
[9] Nabi SAAU et.al. Pharmaceutical Gels: A Review. RADS-JPPS.2016; 4(1), 40-48.
[10] Santanu RC, Hussan SD, Rajesh G, Daljit M. A Review on Pharmaceutical Gel. Journal of Pharmaceutical Research and Bio-Science. 2012; 1(5):21-36.
[11] Basha BN, Prakashan K, Goli D. Formulation and Evaluation of Gel Containing Fluconazole-Antifungal Agent. International Journal of Drug Development and Research. 2011; 3(4):109-128.
[12] Ritter L, Suffer NY; Wyeth Holdings LLC. Stable Cosmetically Acceptable Topical gel Formulation and Method of Treatment for Acne. US Patent 5122519A. 1992 June 16.
[13] Dantas MGB, Reis SAGB, Damasceno CMD, Rolim LA, Neto PJR, Carvalho FO et al., Development and Evaluation of Stability of a Gel Formulation containing the Monoterpene Borneol. The Scientific World Journal. 2016.
[14] Guleri KT Preet K. Formulation and Evaluation of Topical Gel of Aceclofenac. Journal of Drug Delivery & Therapeutics. 2013; 3(6):51-53.