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Pharmaceutical gels for topical drug delivery: An overview

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Abstract
The topical routes, such as ophthalmic, rectal, vaginal and skin offer certain visible advantages for drug delivery like direct application of drug to the site of action and persistence of action for prolonged periods of time. Skin is one of the most readily accessible and main route for topical drug delivery. Many semisolid preparations, viz. ointments, creams and lotions are available for treating various skin ailments but they suffer from certain demerits like less spreading coefficient, uneasiness caused by sticky nature, less stability and difficulty in application leading to increasing use of gels in cosmetics and pharmaceutical fields. Gels represent semisolid dosage forms, intended for skin application or to some mucosal surfaces either for local action or for emollient properties. Gel is preferred for topical application due to more stability and better application property. The main objective of this article is to review all the information related to gels like structure, properties, characteristics, classification, uses, polymers, formulation, evaluation and future scope of gels.

Keywords: topical routes, drug delivery, emollient, local, evaluation

Introduction

The topical drug delivery denotes the application of drug onto the body employing ophthalmic, rectal, vaginal and skin as the route of administration [1]. Skin is one of the most readily accessible organs on human body for topical drug delivery and constitutes the chief route for topical application. For the local treatment of dermatological diseases as well as for cosmetic purposes, a number of preparations, ranging from solids to semisolids and liquid formulations are available to healthcare practitioners and patients. Within the category of semisolid preparations, transdermal gels offer great potential for use in cosmetic and pharmaceutical fields [2]. External application of gel at skin offers certain visible advantages like quick release of drug directly to the site of action, independent of water solubility of drug, as compared to creams and ointments [3, 4]. According to USP, gels (sometimes called jellies) are semisolid systems containing either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid. Many polymer gels exhibit reversibility between the gel and sol state. However, the formation of some polymer gels is irreversible because their chains are covalently bonded. The three-dimensional networks in two-phase gels and jellies are formed by several inorganic colloidal clays. The formation of these inorganic gels is reversible. Gels are generally more rigid than jellies because gels contain more covalent crosslinks, a higher density of physical bonds or simply less liquid. Gel-forming polymers produce materials that span a range of rigidities, beginning with a sol and increasing in rigidity to a mucilage, jelly, gel and hydrogel. The gel systems may be clear as water or turbid because the ingredients may not be entirely molecularly dispersed (soluble or insoluble) or they may produce aggregates, which disperse light. The concentration of the gelling agents is mostly less than 10%, usually in 0.5% to 2.0% range, with a few exceptions [5]. Different kinds of transdermal preparations like lotions, creams, ointments, patches, gels etc. are available; out of which gel is preferred due to more stability and better application property [2].

Structure of Gel **[6]:** The rigidity of a gel is attributed to the presence of a network formed by the interlinking of gelling agent particles. The nature of the particles and the kind of force involved in the linkages, determines the structure of the network and the properties of gel. The individual particles of hydrophilic colloid may consist of either spherical or an isometric aggregates of small molecules or single macromolecules. Possible arrangements of such particles in a gel network are depicted in (fig.1). In linear macromolecules, the network is composed of entangled molecules, the point of contact between which may either be relatively small or consist of several molecules aligned in a crystalline order, as shown in Fig.1(c) and (d). The force of attraction responsible for the bonding between gelling agent particles may range from strong primary valencies, as in silicic acid gels, to weaker hydrogen bonds and vander waals forces. The weaker nature of the latter forces is reflected by the fact that a slight increase in temperature often causes liquefaction of gel [7].

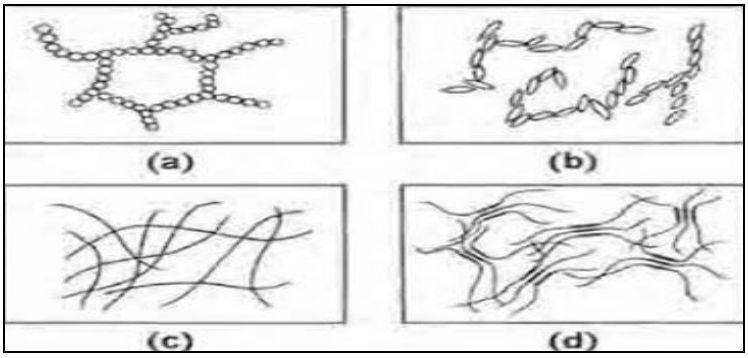

Fig 1: Representations of gel structures. (a) Flocculated particles in a two-phase gel structure. (b) Network of elongated particles or rods forming a gel structure. (c) Matted fibers as found in soap gels. (d) Crystalline and amorphous regions in a gel of carboxymethyl cellulose [5]

Properties of Gels [8]

1. Ideally, the gelling agent for pharmaceutical use should be inert, safe and should not react with other formulation ingredients.
2. The gelling agent incorporated in the formulation should produce a sufficient solid-like consistency during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube or during topical application.
3. It should possess suitable anti-microbial to prevent from microbial attack.
4. The topical gel should not be tacky.
5. The ophthalmic gel should be sterile [7].

Characteristics of Gels [8]:

a. Swelling: When a gelling agent is left in contact with a liquid that solvates it, then a considerable amount of liquid is absorbed by the agent and the volume increases. This process is called swelling. This phenomenon occurs as a result of solvent penetration into the matrix [7, 9].

b. 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.

c. Ageing: Colloidal systems usually show slow aggregation naturally. This process is known as ageing. In gels, ageing causes gradual formation of a denser network of the gelling agent.

d. Structure: The rigidity in a gel results due to the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the stress, straighten them out and decrease the resistance to flow.

e. Rheology: Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic in nature, i.e. follow Non- Newtonian flow behavior, characterized by a reduction in viscosity with increase in shear rate.

Classification of gels [8]: Gels can be classified depending upon colloidal phases and nature of solvent used, physical nature and rheological properties [9].

A. Based on colloidal properties

1. **Two phase system (Inorganic) –** In this type, the particle size of the dispersed phase is fairly large and forms the three dimensional structure throughout gel. They must be thixotropic, i.e. form semisolids upon standing and turn into liquid on agitation.
2. **Single phase system (organic) –** Single-phase gels comprise of organic macromolecules uniformly circulated within a liquid in such a way that no visible boundaries are found between the dispersed macromolecules and the liquid.

B. Based on nature of solvent used

1. **Hydro gel (water based) –** In hydrogels, water acts as a continuous liquid phase. E.g. gelatin, cellulose derivatives, poloxamer gel.
2. **Organic gels (with a non- aqueous solvent) –** They have non- aqueous solvent as their continuous phase. E.g. Plastibase olag gel and dispersion of metallic state in oils.
3. **Xerogels –** Xerogels represent solid gels with lesser concentration of solvent. They are produced by the evaporation of solvent leaving the gel framework behind, e.g. tragacanth ribbons, dry cellulose and polystyrene.

C. Based on rheological properties: Usually gels exhibit non-Newtonian flow properties. Based on rheological properties, they are classified into three types

a) Plastic gels
b) Pseudo plastic gels
c) Thixotropic gels.

a. Plastic gel –The plot of rheogram gives the yield value of gels above which the elastic gel distorts and begins to flow, e.g. flocculated suspensions of aluminium hydroxide, Bingham bodies, exhibit a plastic flow.

b. Pseudo plastic gel –There is a decrease in the viscosity of this type of the gel with an increase in rate of shear, with no yield value, e.g. liquid dispersion of tragacanth, sodium alginate, Na CMC etc. exhibits pseudo plastic flow.

c. Thixotropic gel- In this type of gel, the bonds between the particles are very weak and can be broken down by shaking. The resultant solution will reform gel due to the collision of particles and bonding together again (the reversible isothermal gel-sol-gel transformation), e.g. bentonite and agar.

D. Based on physical nature

1. **Elastic gel –**The fibrous molecules are joined together at the point of junction by relatively weak bonds, viz.

hydrogen bonds and dipole interaction. Gels of agar, pectin, guar gum and alginates exhibit an elastic behavior.

2. **Rigid gels –** These represent gel macromolecules in which the framework is bonded 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.

Bases or gel forming polymers

Gel forming bases or polymers are classified as follows: -

1. **Natural polymers –** These polymers are found naturally and can be synthesized by living beings, e.g. Proteins like collagen, gelatine etc and polysaccharides like agar, tragacanth, pectin and gum etc.
2. **Semi synthetic polymers –** These types of polymers are mostly formed from natural polymers by chemical modification, e. g. cellulose derivatives like carboxymethylecelulose, methylcellulose, hydroxypropyl cellulose and hydroxyethyle cellulose.
3. **Synthetic polymers –** The polymers which are prepared under in-vitro conditions are called synthetic polymers. These are also known as manmade polymers, e.g. Carbomer carbopol 940, carbopol 934, Poloxamer, Polyacrylamide, Polyvinyl alcohol and Polyethylene.
4. **Inorganic substances –** Aluminium hydroxide and Besitonite.
5. **Surfactants –** Sebrotearyle alcohol and Brij-96.

Following table denotes the general classification and various forms of gels used:

Table 1: General classification and description of gels [10]

Class	Description	Examples
Inorganic	Usually two-phase systems	Aluminium hydroxide gel, bentonite magma
Organic	Usually single-phase systems	Carbopol, tragacanth
Hydrogels	Contains water	Silica, bentonite, pectin, sodium alginate, methylcellulose, alumina
Organogels	Hydrocarbon type Animal / vegetable fats Soap- base greases Hydrophilic organogels	Petroleum, mineral oil / polyethylene gel, plastibase, lard, cocoa butter, aluminium stearate with heavy mineral-oil gel, carbowax bases (PEG ointment)
Hydrogels	Organic hydrogels Natural and synthetic gums Inorganic hydrogels	Pectin paste, tragacanth jelly, methylcellulose, sodium carboxymethylcellulose, bentonite gel

Uses of Gels [8, 9]: Gels or gelling agents are used:

1. As delivery systems for orally administered drugs.
2. To deliver topical drug applied directly to the skin, mucous membrane or the eye.
3. As long acting forms of drug injected intramuscularly.
4. As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid and suppository bases.
5. In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations.
6. NaCl gel for electrocardiography
7. Sodium fluoride and Phosphoric acid gel for dental care prophylactic
8. Bases for patch testing
9. Lubricant for catheters

Formulation Considerations for Pharmaceutical Gels [5, 11]

a. The choice of vehicle / solvent

Normally purified water is used as a solvent. To increase the solubility of the therapeutic agent in the dosage form and / or to enhance drug penetration across the skin, co-solvents may be employed, e.g., alcohol, glycerol, PG, PEG 400, etc.

b. Inclusion of buffer: Buffers may be involved in aqueous and hydroalcoholic-based gels to control the pH of the formulation, e.g., Phosphate, citrate, etc.

c. Preservatives: Addition of preservatives increases stability or shelf-life of gel, e.g., Parabens, phenolics, etc.

d. Antioxidant: It may be incorporated in the formulation to enhance the chemical stability of therapeutic agents that are susceptible to oxidative degradation. Water-soluble antioxidants are generally used as the majority of gels are aqueous-based, e.g., Sodium metabisulphite, sodium formaldehyde sulfoxylate, etc.

e. Flavors / Sweetening agents

Flavors (e.g. Butterscotch, apricot, peach, vanilla, wintergreen mint, cherry, mint etc.) and sweetening agents (e.g. sucrose, liquid glucose, glycerol, sorbitol, etc.) are only included in gels that are meant for administration into the oral cavity (e.g., for the treatment of infection, inflammation, ulceration, etc.).

It will not be out of scope to give details of concentrations for different gelling substances.

Table 2: Gelling Concentrations for Substances Used In Pharmaceutical Products [5, 12]

S. No.	Substance	Gel forming concentrations (Wt. %)	Required Additives
1.	Alginates	0.5-1 %	Ca^{2+}
2.	Agar	0.1-1	-
3.	Gelatin	2-15	-
4.	Collagen	0.2-0.4[a]	-
5.	K-Carrageenan	1-2	K^{+}
6.	Geelum gum	0.5-1	Ca^{2+}
7.	Guar gum	2.5-10	-

8.	Glycyrrhiza	2	-
9.	Hyaluronic acid	2	-
10.	Pectins	0.8-2	Ca^{2+}
11.	Starch	6	-
12.	Tragacanth gum	2-5	-
13.	Carboxymethyl cellulose	4-6	Na^{+}
14.	Hydroxypropyl cellulose	8-10	-
15.	Hydroxypropylmethyl cellulose	2-10	-
16.	Methyl cellulose	2-4	-
17.	Carbomer	0.5-2	-
18.	Polaxomer	15-50	-
19.	Polyacrylamide	4	-
20.	Polyvinyl alcohol	10-20	-
21.	Aluminium hydroxide	3-5	-
22.	Bentonite	5	-
23.	Laponite	2	Electrolytes
24.	Cetostearyl alcohol	10	Cetrimide
25.	Brij 96[b]	40-60	-

[a]Adjusted to pH > 4 and warmed to 37 ^{0}C

[b] Brij 30-99 surfactants are polyoxyethylene-alkyl-ethers

Favourable Properties of Dermatological gels [5]

The dermatological gels should be thixotropic, greaseless, easily removed, non-staining, water-soluble or miscible and compatible with a number of ingredients. They should also possess demulcent, emollient and good spreadability properties.

Preparation of gels [5, 8]

Generally, the gels in the industrial scale are manufactured at room temperature. Nevertheless, some polymers require unique treatment before processing. Gels are manufactured by the given below methods:

1. **Thermal changes:** Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelation. If the temperature is lowered, the degree of hydration of lipophilic colloids is reduced and gelation occurs, e.g. gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. On the other hand, increasing the temperature of solutions like cellulose ether will disrupt the hydrogen bonding and decrease solubility, which will cause gelation
2. **Flocculation:** In flocculation, gelation is produced by adding just enough quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is essential and ensure rapid mixing to avoid local high concentration of precipitant. e.g.: Solution of ethyl cellulose, polystyrene in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether.
3. **Chemical reaction:** In this method, gel is prepared by chemical reaction between the solute and solvent. e.g.: aluminium hydroxide gel is precipitated by interaction in aqueous solution of an aluminium salt and sodium carbonate. An increased concentration of reactants will produce a gel structure.

Evaluation of gels [13, 14]

1. **pH Measurement:** The pH of various gel formulations are determined by using digital pH meter.1 g of gel is dissolved in 100 ml. freshly prepared distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.
2. **Viscosity Measurement:** Brookfield digital viscometer can be used to measure the viscosity of prepared gel formulations. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted. The viscosity of gel is obtained by multiplication of dial reading with factor given in the Brookfield viscometer catalogues [15].
3. **Spreadability:** Spreadability refers to the extent of area to which gel readily spreads on application. It is determined by wooden block and glass slide apparatus. The time in sec. taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load is expressed as spreadability. Lesser the time taken for the separation of two slides, better the spreadability. Spreadability is calculated by using the formula:

   $$S = M.L / T$$

   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.
4. **Homogeneity:** All developed gels are tested for homogeneity by visual inspection after the gels have been set in the container. They are tested for their appearance and presence of any aggregates.
5. **Drug content:** 1 g gel is dissolved in 100 ml. of suitable solvent. The aliquots of different concentrations of gel are prepared by suitable dilutions, filtered and absorbance is measured spectrophotometrically. Drug content is determined from the linear regression analysis of calibration curve of drug.
6. **Grittiness-** All the gel formulations are checked microscopically for the presence of any particulate matter.
7. **Extrudability-** The gel formulations are filled in collapsible tubes, after being set in the containers. The

extrudability of gel formulations are determined in terms of weight required in grams to extrude 0.5 cm. ribbon of gel in 10 sec.

8. **Stability test-** Stability study is carried out by freeze-thaw cycling. The product is subjected to a temperature of 4^0C for one month, then at 25 ^{0}C for one month followed by 40 ^{0}C for one month. Syneresis is observed. Finally, the gel is exposed to ambient room temperature and the separating liquid exudates are noted.
9. ***In-vitro* Drug Diffusion Study:** In-vitro drug release studies are performed by using a Franz diffusion cell. 0.5 g of gel is taken in cellophane membrane. Diffusion studies are conducted at 37 ^{0}C ± 1 ^{0}C employing 250 ml. phosphate buffer, pH 7.4 as the dissolution medium.
10. **Skin irritation test:** For skin irritation study, guinea pigs (400-500 g; either sex) can be used. The animals are maintained at standard animal feed and are given free access to water. Hair are shaved from back of guinea pigs and an area of 4 cm.^{2} is marked on both sides. 500 mg. gel is applied twice daily for 7 days and the site of application is observed for any sensitivity or reaction, if any. Reaction is graded as 0, 1, 2, 3 for no reaction; minor patchy erythema; minor, confluent or moderate but patchy erythema; severe erythema with or without edema, respectively.
11. ***In-vivo* Study:** Inhibition of carrageenan induced rat paw edema is studied in male wistar albino rats using mercury plethysmometer. The volume of unilateral hind paw of experimental animals is measured, before and after administration of carrageenan. % inhibition is noted.

Some of the gels, available commercially in Indian market are enlisted in the following table:

Table 3: List of the important commercially available pharmaceutical gels in Indian market

S. No.	Brand of gel	Composition	Company	Use
1.	Persol A C	Benzoyl peroxide	Wallace Rivela	Anti-acne
2.	Voli gel	Diclofenac	Synthokind	Analgesic
3.	Volini	Diclofenac diethylamine Linseed oil Methyl salicylate Menthol Benzyl alcohol	Sun Pharma	Analgesic
4.	A-Ret Gel	Tretinoin	Menarini	Anti-acne
5.	Omini Gel	Linseed oil, Diclofenac Diethylamine, methyl salicylate, menthol	Cipla	Analgesic
6.	Laxanox Gel	Benzoyl peroxide	Macleods	Anti-acne
7.	Biosore Gel	Choline salicylate, lignocaine hydrochloride, benzalkonium chloride	Biochem	Analgesic
8.	Silverex Gel	Silver nitrate	Virchow Biotech	Anti-acne
9.	Clear gel	Clindamycin phosphate	Hedge & Hedge	Anti-acne
10.	Somagesic MR	Diclofenac, Thiocolchicoside, Linseed oil, methyl salicylate, menthol	Somatico Pharmacal	Analgesic
11.	Metro Gel	Metronidazole	Galderma	Antibacterial (Vaginal)
12.	Regranex Gel	Becaplermin	Smith & nephew	Diabetic neuropathic ulcers
13.	Crinone Gel	Progesterone	Serono	Progesterone Supplement, IVF, Infertility

Future scope of pharmaceutical gels

Majority of pharmaceutical gels available in Indian market are used either for analgesic or anti-inflammatory purpose. Others are mostly antimicrobial. For treating bacterial or fungal infections of skin, antiseptic creams, ointments or solutions are commonly used but in near future more number of antimicrobial gels are expected to be launched in Indian market. As a result, India has an opportunity to get an increasing number of gels patented. Transdermal prodrugs could also emerge in Indian market in coming years. Due to ever increasing use of novel penetration enhancement techniques, indications of gels for treatment of systemic diseases are expected to rise up in future. More focus may be directed towards herbal gels in future because of their freedom from all kinds of adverse effects, especially skin irritation reactions. Therefore, the gels hold a great promise as a topical drug delivery system; popularity and use of gels could further increase in future.

Conclusion

The present paper deals with the usefulness of gels in comparison to other pharmaceutical preperations used as topical drug delivery for various treating skin problems. Because gels offer numerous advantages, notably more stability, targeted drug delivery and easily washable, thereby gels are becoming increasingly popular, day be day.

References

1. Bhowmik D, Chiranjib, Chandira RM, Tripathi KK, Kumar KPS. Nanomedicine: An Overview. Int. J. Pharm. Tech. Res. 2010; 2(1):2143-2151.
2. Saroha K, Singh S, Aggarwal A, Nanda S. Transdermal Gels - An Alternative Vehicle For Drug Delivery. IJPCBS. 2013; 3(3):495-503.
3. Chien YW. Novel Drug delivery systems. Marcel Dekker Inc., New York, 1992, 449.
4. Jain NK. Controlled and novel drug delivery system. CBS Publisher and Distributors, New Delhi, 1997, 110-115.
5. Rathod HJ, Mehta DP. A Review on Pharmaceutical Gel. International Journal of Pharmaceutical Sciences. 2015; 1 (1):33-47.
6. Cooper Gunn. Disperse systems. In. Carter SJ, editor. Tutorial Pharmacy. CBS Publisher and Distributors, New Delhi, 2000, 68-72.
7. Carter SJ. Disperse system In: Cooper and Gunn's Tutorial Pharmacy. CBS Publishers and Distributors,

New Delhi, 2000, 68-72.
8. Kaur LP, Guleri TK. Topical Gel: A Recent Approach for Novel Drug delivery. Asian Journal of Biomedical and Pharmaceutical Sciences. 2013; 3(17):1-5.
9. Zatz JL. Kushla GP: Gels. In: Lieberman HA, Rieger MM, Banker GS. Pharmaceutical dosage form: Disperse system, New York: Marcel Dekker, 2005, 399-421.
10. Naik A, Potts RO, Guy RH. Mechanism of oleic acid induced skin penetration enhancement in humans. J. Cont. Rel., 1995; 37(3):299-306.
11. Jones D. Pharmaceutics-Dosage Form and Design. London: Pharmaceutical Press, 2008.
12. Ofner CM. *et al*. Encyclopedia of Pharmaceutical Technology. Informa Healthcare, 2007, 1875-1890.
13. Kaur LP, Garg R, Gupta GD. Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(3):43-47.
14. Goyal S, Sharma P, Ramchandani U, Shrivastava SK, Dubey PK. Novel Anti-Inflammatory Topical Herbal Gel Containing Withania somnifera and Boswellia serrata. International Journal of Pharmaceutical and Biological Archives. 2011; 2(4):1087-1094.
15. Jani R, Jani K, Setty CM. Preperation and evaluation of topical gel Valdecoxib, Dipti Patel, Inter. Journal Pharm. Sci. Research. 2010; 2(1):51-54.