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REVIEW ARTICLE

Topical Gel: A Recent Approach for Novel Drug delivery

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ABSTRACT

Gel formulation provides better application property and stability in comparison to cream and ointment. Topical gel drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the most extensive and readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Topical application of drugs offers potential advantages of delivering the drug directly to the site of action and acting for an extended period of time. Topical gels are intended for skin application or to certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action. Gels are evaluated by following parameters such as pH, homogeneity, grittiness drug content, viscosity, spreadability, extrudability, skin irritation studies, in-vitro release, in Stability

Keywords: Topical gel, percutaneous penetration, drug delivery.

INTRODUCTION

Topical delivery is an attractive route for local and systemic treatment. The delivery of drugs onto the skin is recognized as an effective means of therapy for local dermatologic diseases. It can penetrate deeper into skin and hence give better absorption[1]. Topical application has many advantages over the conventional dosage forms. In general, they are deemed more effective less toxic than conventional formulations due to the bilayer composition and structure. In the formulation of topical dosage forms, attempts are being made to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to ensure adequate percutaneous absorption[2]. Topical preparation avoids the GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action[3].

A gel is a two-component, cross linked three-dimensional network consisting of structural materials interspersed by an adequate but proportionally large amount of liquid to form an infinite rigid network structure which immobilizes the liquid continuous phase within. The structural materials that form the gel network can be composed of inorganic particles or organic macromolecules, primarily polymers. Cross links can be formed via chemical or physical interactions. This leads to gel classification into chemical and physical gel systems, respectively. Chemical gels are associated with permanent covalent bonding while physical gels result from relatively weaker and reversible secondary intermolecular forces such as hydrogen bonding, electrostatic interactions, dipole dipole interactions, Vander Waals forces and hydrophobic interactions[4]

The **U.S.P**. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels consist of 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, randomly coiled in the flexible chains[5].

ANATOMY OF SKIN:

The skin is the largest organ of the body. Its large surface area in direct contact with the environment presents tremendous opportunities for drug delivery. The human skin is organized into two distinct layers, namely the epidermis and dermis directly beneath (Fig 1). The highly vascular dermis is made up of a connective tissue matrix

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containing the nerves, hair follicles, pilosebaceous units and sweat glands. The epidermis is avascular and its outermost layer, the stratum corneum, consists of keratin-rich, dead epidermal cells called corneocytes embedded within a lipid rich matrix. The stratum corneum forms the primary barrier for drug permeation especially to water-soluble compounds. Consequently, drug delivery across the stratum corneum has become the essence in the design of many dermal delivery systems [6].

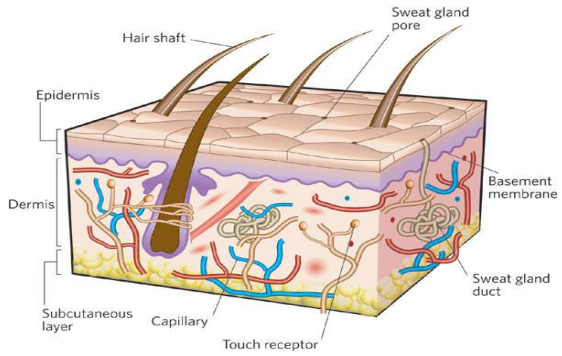

Fig 1: Human skin

STRUCTURE OF GELS:

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles gelling agent. The nature of the particles and the type of force that is responsible for the linkages, which 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 shown in (fig.2). In linear macromolecules the network is comprised 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.2(c) and(d). The force of attraction responsible for the linkage 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 these latter forces is indicated by the fact that a slight increase in temperature often causes liquefaction of gel [7].

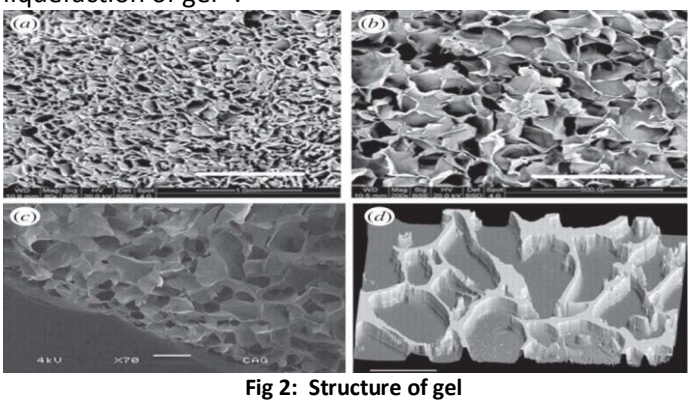

Fig 2: Structure of gel

PROPERTIES OF GELS:

1. Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.
2. The gelling agent included in the preparation should produce a reasonable solid-like nature 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:

A) Swelling

When a gelling agent is kept in contact with liquid that solvates it, then an appreciable amount of liquid is taken up by the agent and the volume increases. This process is referred to as swelling. This phenomenon occurs as the solvent penetrates the matrix. Gel-gel interactions are replaced by gel solvent interactions. The degree of swelling depends on the number of linkages between individual molecules of gelling agent and on the strength of these linkages[7, 8.]

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. The occurrence of syneresis indicates that the original gel was thermodynamically unstable. The mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels. As these stresses are relieved, the interstitial space available for the solvent is reduced, forcing the liquid out.

C) Ageing

Colloidal systems usually exhibit slow spontaneous aggregation. This process is referred to as ageing. In gels, ageing results in gradual formation of a denser network of the gelling agent.

D) Structure

The rigidity of a gel arises from the presence of a network formed by the interlinking of particles of the gelling agents. The nature of the particle and the stress, straightening them out and lessening the resistance to flow.

E) Rheology

Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. exhibiting Non-Newtonian flow behaviour, characterized by a decrease in viscosity with increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by

applied shear stress due to breaking down of interparticulate association, exhibiting a greater tendency to flow. Similarly, for macromolecules the applied shear stress aligns the molecules in the direction of Organic (single phase system)

USES:

- As delivery systems for orally administered drugs.
- To deliver topical drug applied directly to the skin, mucous membrane or the eye.
- As long acting forms of drug injected intramuscularly.
- As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid and suppository bases.
- In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care preparations[8].

CLASSIFICATION OF GELS:

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties.

1. Based on colloidal phases

They are classified into Inorganic (two phase system) type of force that is responsible for the linkages determine the structure of the network and the properties of the gel.

Two phase system

If partial sizes of the dispersed phase are relatively large and form the three dimensional structure throughout gel, such a system consists of floccules of smallparticles rather than larger molecules and gel structure, in this system is not always stable. They must be thixotropic-forming semisolids on standing and become liquid on agitation.

Single-phase system

These consist of large organic molecules existing on the twisted strands dissolved in a continuous phase. This larger organic molecule either natural or synthetic polymers are referred as gel formers, they tend to entangle with each other their random motion or bound together by Vander waals forces.

2. Based on nature of solvent

Hydro gels (water based)

Here they contain water as their continuous liquid phase
E.g. bentonite magma, Gelatin, cellulose derivatives, carpooler, and poloxamer gel.

Organic Gels (with a non-aqueous solvent)

These contain a non-aqueous solvent on their continuous phase. E.g. plastibase (low molecular wt. polyethylene dissolved in mineral oil & short Cooled) Olag (aerosol) gel and dispersion of metallic stearate in oils.

Xerogels

Solid gels with low solvent concentration are known as xerogels. These are produced by evaporation of solvent or freeze drying, leaving the gel framework behind on contact with fresh fluid, they swells and can be reconstituted. E.g. Tragacanth ribbons, acacia tear β-cyclodextrin, dry cellulose and polystyrene.

3. Based on rheological properties

Usually gels exhibit non-Newtonian flow properties.
They are classified into,
a) Plastic gels
b) Pseudo plastic gels
c) Thixotropic gels.

(a) Plastic gels

E.g. - Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.

(b) Pseudo-plastic gels

E.g. - Liquid dispersion of tragacanth, sodium alginate, Na CMC etc. exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value. The rheogram results from a shearing action on the long chain molecules of the linear polymers. As the shearing stress is increased the disarranged molecules begin to align their long axis in the direction of flow with release of solvent from gel matrix.

(c) Thixotropic gels

The bonds between particles in these gels are very weak and can be broken down by shaking. The resulting solution will revert back to gel due to the particles colliding and linking together again (the reversible isothermal gel-sol-gel transformation). This occurs in colloidal system with nonspherical particles to build up a scaffold like structure. E.g.: Kaolin, bentonite and agar.

4. Based on physical nature

(a) Elastic gels

Gels of agar, pectin, Guar gum and alginates exhibit an elastic behavior. The fibrous molecules being linked at the point of junction by relatively weak bonds such as hydrogen bonds and dipole attraction. If the molecule possesses free –COOH group then additional bonding takes place by salt bridge of type –COO-X-COO between two adjacent strand networks. E.g.: Alginate and Carbapol.

(b) Rigid gels

This can be formed from macromolecule in which the framework linked 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

PREPARATION OF GELS:

Gels are normally in the industrial scale prepared under room temperature. However few of polymers need special treatment before processing. Gels can be prepared by following methods.
1. Thermal changes
2. Flocculation
3. Chemical reaction

1) Thermal changes

Solvated polymers (lipophilic colloids) when subjected to thermal changes causes gelatin. Many hydrogen formers are more soluble in hot than cold water. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs.

(Cooling of a concentrated hot solution will produce a gel). E.g.: - Gelatin, agar sodium oleate, guar gummed and cellulose derivatives etc. In contrast to this, some materials like cellulose ether have their water solubility to hydrogen bonding with the water. Raising the temperature of these solutions will disrupt the hydrogen bonding and reduced solubility, which will cause gelation. Hence this method cannot be adopted to prepare gels as a general method.

2) Flocculation

Here gelation is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipitation. It is necessary to 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. The addition of salts to hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behaviour. Hydrophilic colloids such as gelatin, proteins and acacia are only affected by high concentration of electrolytes, when the effect is to "salt out", the colloidal and gelation doesn't occur.

3) Chemical reaction

In this method gel is produced by chemical interaction between the solute and solvent. E.g.: aluminium hydroxide gel can be prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate, an increased concentration of reactants will produce a gel structure. Few other examples that involve chemical reaction between PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates(TDI), methane diphenyl isocyanine (MDI)hat cross-links the polymeric chain[9].

GEL FORMING SUBSTANCES:

Polymers are used to give the structural network, which is essential for the preparation of gels. Gel forming polymers are classified as follows:

1. **Natural polymer**

a. Proteins

i. Gelatin ii. Collagen

b. Polysaccharides

i. Alginic acid ii. Agar iii. Tragacanth iv. Sodium or Potassium carrageenan v. Pectin

vi. Gellum Gum vii. Xanthin viii. Cassia tora

ix. Guar Gum

2. Semisynthetic polymers

a. Cellulose derivatives

i. Hydroxyethyl cellulose ii. Methylcellulose

iii. Hydroxypropyl methyl cellulose iv. Hydroxypropyl cellulose v. Carboxymethyl cellulose

3. Synthetic polymers

a. Carbomer

i. Carbopol -941 ii. Carbopol -940 iii. Carbopol -934

b. Poloxamer

c. Polyvinyl alcohol

d. Polyacrylamide

e. Polyethylene and its co-polymers

4. Inorganic substances

a. Bentonite

b. Aluminium hydroxide

5. Surfactants

a. Brij-96

b. Cetostearyl alcohol

EVALUATION PARAMETERS OF THE FORMULATED GELS:

Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

Drug content

1 g of the prepared gel was mixed with 100ml of suitable solvent. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve.

Viscosity study

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial reading with factor given in the Brookefield Viscometer catalogues[3].

Spreadability

It indicates the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic potency of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel which is placed in between the slides under the direction of certain load. Lesser the time taken for the separation of two slides, better the spreadability. It is calculated by using the formula:

$S = M. L / T$ where,

M = wt. tied to upper slide

L = length of glass slides
T = time taken to separate the slides

Extrudability study

After the gels were set in the container, the formulations were filled in the collapsible tubes. The extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

Skin irritation study

Guinea pigs (400-500 g) of either sex were used for testing of skin irritation. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions. Hair was shaved from back of guinea pigs and area of 4 cm^2 was mark done both the sides, one side served as control while the other side was test. Gel was applied (500 mg / guinea pig) twice a day for 7 days and the site was observed for any sensitivity and the reaction if any, was graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

***In vitro* Diffusion studies**

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) was taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample was replaced with equal volume of fresh dissolution medium. Then the samples were analyzed for the drug content by using phosphate buffer as blank.

Stability

The stability studies were carried out for all the gel formulation by freeze - thaw cycling. Here, by subjecting the product to a temperature of 4° C for 1 month, then at 25°C for 1 month and then at 40°C for 1 month, syneresis was observed. After this, the gel is exposed to ambient room temperature and liquid exudate separating is noted [10].

Homogeneity

After the gels have been set in the container, all developed gels were tested for homogeneity by visual inspection. They were tested for their appearance and presence of any aggregates.

Grittiness

All the formulations were evaluated microscopically for the presence of any appreciable particulate matter which was seen under light microscope. Hence obviously the gel preparation fulfils the requirement of freedom from particular matter and from grittiness as desired for any topical preparation [11].

DISCUSSION:

Topical formulations include creams, ointments, pastes, gels etc. Out of which gels are getting more popular now a days because they are more stable and also can provide controlled release than other semisolid preparations. The gel formulation can provide better absorption characteristics and hence the bioavailability of drug. It also provides the better information regarding to the formulation and evaluation parameters of the novel herbal gel for anti-inflammatory activity and to provide the better therapeutic effects to patient compliance.

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Conflict of Interest: None Declared

