INTERNATIONAL JOURNAL OF DECCAN PHARMA AND LIFE SCIENCES

www.ijdpls.com

(Review Article)

Received: 14-06-2012; Revised; Accepted: 10-07-2012

A REVIEW ON GEL

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Keywords:

Dermatological, protection, occlusion, adhesion, rectal tissue

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ABSTRACT

Delivery of drugs to the skin is an effective and targeted therapy for local dermatological disorders. Topical gel formulations provide a suitable delivery system for drugs because they are less greasy and can be easily removed from the skin. Gels comprise a body of products, which when applied to the skin or accessible mucous membranes tend to alleviate or treat a pathological condition or offer protection against a harmful environment. They have the property to cling to the skin or mucous membrane for a protracted period of time to exert their therapeutic effect through protection and occlusion. The adhesion is due to their plastic rheological behavior which allows semisolid to retain their shape and cling as film until acted upon by an outside force. Gels dosage forms usually are intended for localized drug delivery. In the past few years, however, these forms also have been explored for the systemic delivery of various drugs. They can applied topically to the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining.

1. INTRODUCTION:

1.1 General Consideration: The method by which a drug is delivered can have a significant effect on its efficacy. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Semisolids constitute a significant proportion of pharmaceutical dosage forms.

1.2 Definition: A gel is a solid or semisolid system of at least two constituents, consisting of a condensed mass enclosing and interpenetrated by a liquid. [1]

1.3 Advantages:

- Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH.
- Gels are having property to avoid enzymatic activity
- They can substitute for oral administration of medication when the route is unsuitable.
- They can avoid the first pass effect.
- They avoid systemic and portal circulation following gastrointestinal absorption.
- Gels are not deactivated by liver enzymes because liver is bypassed.
- They are non-invasive and have patient compliance.
- They are applied over skin for slow and prolonged absorption.
- They have localized effect with minimum side effects. [2, 3, 4]

1.4 Disadvantages:

- Gels have possibility of allergenic reactions.
- Enzyme in epidermis may denature the drugs of gels.
- Drugs of larger particle size do not absorb through the skin.
- They have poor permeability of some drugs through the skin.
- Selection of area to be examined carefully during application of gels.
- Gels which are used for the introduction into body cavity or the eyes should be sterilized.
- They may cause application side reactions.
- They may cause skin allergy during application. [3, 5, 6]

2.1 Classification of gels is following:

2.1.1 Controlled release gels: Drug delivery to nasal or ocular mucosa for either local or systemic action suffers from many obstacles. Gel formulations with suitable rheological and mucoadhesive properties increase the contact time at the site of absorption. However, drug release from the gel must be sustained if benefits are to be gained from the prolonged contact time. These gels were formed in simulated tear fluid at concentrations of polymer as low as 0.1%, the release depends on lipophilic interactions between the drug and the polymer and/or the micelles. Controlled-release formulations of charged drugs could be designed by mixing the drugs with oppositely charged surfactants in certain fixed ratios.

2.1.2 Organogels: Sorbitan monostearate, a hydrophobic nonionic surfactant, and numbers of organic solvents such as hexadecane, isopropyl myristate, and a range of vegetable oils are present. Gelation is achieved by dissolving/dispersing the organogelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel state. Cooling the solution/dispersion causes a decrease in the solvent-gelator affinities, an organogel is thus formed. Sorbitan monostearate gels are opaque, thermo reversible semisolids, and they are stable at room temperature for weeks. Such organogels are affected by the presence of additives such as the hydrophilic surfactant, poly sorbate 20, which improves gel stability.

2.1.3 Extended release gels: It is a controlled release technology consists of an agglomerated, hydrophilic complex that, when compressed, forms a controlled-release matrix. It consisting of xanthan and locust bean gums (two polysaccharides) combined with dextrose surrounds a drug core. In the presence of water, interactions between the matrix components form a tight gel while the inner core remains unwetted. The drug is encapsulated in the pores of the gel, and as the matrix travels through the patient's digestive system, the tablet swells and begins to erode. This erosion allows the drug to "back-diffuse" out through the gel-matrix at a controlled rate until the matrix erodes and a majority of the drug is released.

Advantage of Extended release gels:

- They have Predictable modified release profile like zero order or first order or initial immediate release kinetics.
- They can be manufacture on standard manufacturing equipment.
- They are Cheap.

2.1.4 Amphiphilic gels: Amphiphilic gels can prepared by mixing the solid gelator like sorbitan monostearate or sorbitan monopalmitate and the liquid phase like liquid sorbitan esters or polysorbate and heating them at 60°C to form a clear isotropic sol phase, and cooling the sol phase to form an opaque semisolid at room temperature. Amphiphilic gel microstructures consisted mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, forming a 3D network throughout the continuous phase.

2.1.5 Hydrophilic gels: Hydrophilic gels are composed of the internal phase made of a polymer producing a coherent three-dimensional net-like structure, which fixes the liquid vehicle as the external phase. Intermolecular forces bind the molecules of the solvent to a polymeric net, thus decreasing the mobility of these molecules and producing a structured system with increased viscosity. An important group of gels used in pharmacy are hydrophilic gels, usually made of hydrophilic polymers, which under certain conditions and polymer concentration, jellify.

2.1.6 Non aqueous gels: Ethylcellulose was successfully formulated as a nonaqueous gel with propylene glycol dicaprylate/dicaprate. The novel nonaqueous gel exhibited rheological profiles corresponding to a physically cross-linked three dimensional gel network, with suitable mechanical characteristics for use as a vehicle for topical drug delivery.

The gel matrices exhibited prominent viscoelastic behavior, yield stress and thixotropy. Rheological and mechanical properties showed significant upward trends with increased polymeric chain length and polymer concentrations.

2.1.7 Bioadhesive gels: Bioadhesive gels were formulated for nasal delivery of insulin. A nasal perfusion test was carried out to study the toxicity of four absorption enhancers like saponin,

sodium deoxycholate, ethylenediamine tetra-acetic acid (EDTA) and lecithin. The gels contained 4000 Iu/dl insulin, 2% or 4% of low and medium molecular weight of chitosan, and lecithin or EDTA.

2.1.8 Thermosensitive sol-gel reversible hydrogels: They are polymeric solutions which undergo reversible sol to gel transformation under the influence of environmental conditions like temperature and pH which results in insitu hydrogel formation.

2.1.8.1 Advantages over conventional hydro gels:

- They are easy to mix with pharmaceutical solution rather than semisolids.
- They are biocompatible with biological systems.
- They are convenient to administer.
- They release in a controlled fashion.
- They helps to deliver labile bio macromolecules such as proteins and genes.
- They causes immobilization of cells.
- They are used in tissue engineering.

2.1.9 Complexation gels: The goal of oral insulin delivery devices is to protect the sensitive drug from proteolytic degradation in the stomach and upper portion of the small intestine. In this work, the use of pH-responsive, poly (methacrylic-g-ethylene glycol) hydro gels as oral delivery vehicles for insulin were evaluated. Insulin was loaded into polymeric microspheres and administered orally to healthy and diabetic wistar rats. In the acidic environment of the stomach, the gels were unswollen due to the formation of intermolecular polymer complexes. The insulin remained in the gel and was protected from proteolytic degradation. In the basic and neutral environments of the intestine, the complexes dissociated which resulted in rapid gel swelling and insulin release. Within 2 hr of administration of the insulin-containing polymers, strong dose-dependent hypoglycemic effects were observed in both healthy and diabetic rats. These effects lasted for up to 8 hr following administration.

2.1.10 Hydrogels: Hydrogels are gel systems in which water immobilized by insoluble polymer. The elements of hydrogels are water and a polymeric substance that is hydrophilic, but not

water soluble. When exposed to water, the dry polymer swells and absorbs liquid. The polymer strands are cross-linked either chemically or by physical forces. For convenience, hydrogels may be defined by the type of polymer employed and/or the cross-linking mechanism. [7]

3.0 Classification of Hydrogels: [8]

3.1 Based on method of preparation:

A. Homopolymer Hydrogels, B. Co-Polymer Hydrogels, C. Multipolymer Hydrogels:.

3.2 Based on ionic charges:

A. Neutral hydrogels, B. Anionic hydrogels, C. Cationic hydrogels, D. Ampholytic hydrogels.

3.3 Based on structure:

A. Amorphous hydrogels, B. Semi crystalline hydrogels, C. Hydrogen bonded hydrogels.

4.0 Based on mechanism controlling the drug release from hydrogels:

A. Diffusion controlled release systems, **B.** Swelling controlled release systems, **C.** Chemically controlled release systems, **D.** Environment responsive systems.

5.0 Various properties of gels are following:

A. Physical properties

B. Physiological properties

C. Application properties

D. Hydrophilic properties

E. Rheological properties

A. Physical Properties:

- Smooth texture
- Elegant in appearance
- Non dehydrating
- Transparent and translucent
- Non greasy
- Semi solid in nature

B. Physiological Properties:

- Non irritating
- Do not alter membrane / skin functioning
- Miscible with skin secretion
- Have low sensitization index**.** [9]

C. Application Properties:

- Easily applicable with efficient drug release.
- High aqueous washability. [9]

D. Hydrophilic properties: The water absorbing capacity of oleaginous and water-in-oil bases may be expressed in terms of the water number, defined in 1935 by Casparis and Meyer as the maximum quantity of water that is held (partly emulsified) by 100g of a base at 20^{o}C.

The test consists of adding increments of water to the melted base and triturating until the mixture has cooled. When no more water is absorbed, the product is placed in a refrigerator for several hours, removed, and allowed to come to room temperature. The material is then rubbed on slab until water no larger exudes, and finally, the amount of water remaining in the base is determined.

E. Rheological properties: Gels exhibit different rheological properties. Do not flow at low shear stresses but undergo reversible deformation like elastic solids.

6.0 Ingredients used in preparation of gels are:

A. Antimicrobial preservatives
B. Antioxidant
C. Chelating agents
D. Humectants
E. Fragrances
F. Types of gelling agents
G. Permeation enhancer
H. Co solvent
I. Polymers
J. Adhesives
K. Adsorbents
L. Air displacement agents
M. Alkalizing agents
N. Anti caking agents
O. Antifungal preservative
P. Antistatic agents
Q. Bases
R. Binders
S. Buffering agents
T. Flocculating agents
U. Lubricating agents

A. Antimicrobial preservatives: Although some bases, e.g. clays and cellulose derivatives, resist microbial attack, all jellies, because of their high water contents, require antimicrobial preservatives, unless they are to be used immediately.

Examples are Methyl hydroxybenzoate, Propyl hydroxybenzoate, Chlorocresol, Benzoic acid, Phenylmercuric nitrate, Benzalkonium chloride solution, Chlorhexidine acetate [11].

B. Antioxidant: Ingredients employed to prevent or retard product spoilage from rancidity or by inhibiting oxidation (deterioration from reaction with oxygen).

Examples are Ascorbic acid, Propyl gallate, Butylated hydroxy anisole, Butylated hydroxy toluene.

C. Chelating agents: Ingredients that have the ability to complex with and inactivate metallic ions in order to prevent their adverse effects on the stability or appearance of products.

Chelation of ions, such as iron or copper, helps retard oxidative deterioration of finished products.

Examples are Ethylenediamine tetra acetic acid (EDTA), Altol, Citric acid, Maleic acid. [11]

D. Humectants: Loss of water can quickly lead to skin formation in gels and humectants may be added to retain water.

Examples are Glycerol, Propylene glycol or Sorbitol solution.[12]

E. Fragrances:

Examples of widely use fragrances are Lavender oil, Rose oil, Lemon oil, Almond oil.

F. Types of gelling agents:

Several compendial materials function as gelling agents, including Acacia, Alginic acid, Bentonide, Carboxymethyl cellulose sodium, Cetostearyl alcohol, Colloidal silicon dioxide, Ethyl cellulose, Povidone.

There are numerous gelling agents varying in gelling ability. Commonly used gelling agents are listed in table:

Table: Gelling agents

Material	**%**	**Brookfield Viscosity 'CP0'**
Carbomer 941resin NF	0.15	2900
Carbomer 941resin NF	0.25	6300
Carbomer 941resin NF	0.50	44000
Carbomer 941resin NF	1.00	81000
Sodium carboxymethyl cellulose	1.50	5000
Guar gum		
Methyl cellulose	1.50	8040
Locust bean gum	2.00	5200
Sodium alginate	2.50	22800
	2.50	10400

Sr. No.	Permeation Enhancer	Drugs Used
1.	Menthol, Carvacrol, Linalool	Propranolol hydrochloride
2.	Limonene	Indomethacin, ketoprofen
3.	Geraniol, Nerolidol	Diclofenac sodium
4.	Oleic acid	Piroxicam
5.	Lecithin	Hydrocortisone acetate, Heparin
6.	Propylene-glycol-dipelargonate	Heparin
7.	Cyclodextrins	Hydrocortisone

Table : Permeation enhancer used with drugs for pharmaceutical gels

G. Permeation Enhancer:

H. Co-Solvent: In addition to the use of permeation enhancers alone, their combination with co- solvent that deliver a drug in solubilized form has led to the achievement of higher drug permeability

Sr. No.	Permeation Enhancer	Co-solvent	Drugs Used
1.	Isopropyl myristate	Propylene glycol	Diclofenac sodium
2.	Cineole	Ethanol	TRH analogue p-Glu-3-methyl-His-Pro amide
3.	Ethanol	Propylene glycol	Aspirin

Table : Combination of Permeation enhancer and co-solvent for pharmaceutical gels.

I. Polymers: Polymers are used to give the structural network, which is essential for the preparation of gels.

Gel forming polymers are classified as follows:

A. Natural Polymers:

a) Proteins: Collagen, Gelatin

b) Polysaccharides: Agar, Alginate acid, Sodium or Potassium carageenan, Tragacanth, Pectin, Guar Gum, Cassia tora, Xanthan, Gellum Gum

B. Semisynthetic Polymers:

a) Cellulose derivatives: Carboxymethyl cellulose, Methylcellulose, Hydroxypropyl cellulose, Hydroxy propyl (methyl cellulose), Hydroxyethyl cellulose.

C. Synthetic Polymers:

a) Carbomer 910 , b) Carbomer 934 , c) Carbomer 934P , d) Carbomer 940 , e) Carbomer 941

D. Inorganic Substances:

a) Aluminium hydroxide, b) Besitonite

E. Surfactants:

a) Cebrotearyl alcohol, b) Brij – 96. [13]

J. Adhesives: Substances that tend to bind opposite surfaces to each other. Example is Hydroxypropyl methyl cellulose.

K. Adsorbents : Ingredients, usually solids, with a large surface area which can attract dissolved or finely dispersed substances from another medium by physical or chemical means. Examples are Bentonite, Cellulose.

L. Air Displacement Agents: Substances employed to displace air in a hermetically sealed container to enhance product stability. Examples are Nitrogen, Carbon dioxide.

M. Alkalizing Agents: Substances used to provide alkaline medium for product stability. Example is Diethanolamine.

N. Anticaking Agents: Ingredients used to prevent the agglomeration of a particulate solid into lumps or cohesive cakes. Examples are Calcium phosphate tribasic, Talc.

O. Antifungal Preservative: Substance used to prevent the growth of fungi.

The effectiveness of the parabens is usually enhanced when they are used in combination. Examples are Butylparaben, Ethylparaben.

P. Antistatic Agents: Ingredients that alter the electrical properties of materials or of human body surfaces (skin, hair, etc.) by reducing their tendency to acquire an electrical charge.

Q. Bases :

Agents used as a vehicle into which medicinal substances are incorporated. Examples are Polydextrose, Lanolin, Hard fat.

R. Binders: Ingredients added to provide adhesive qualities during manufacturing. Examples are Acacia, Gelatin.

S. Buffering Agents: Chemicals which have the property of maintaining the pH of an aqueous medium in a narrow range even if small amounts of acids or bases are added.

Buffering agents and pH adjusters are used to alter and to maintain a products pH at the desired level. Examples are Malic acid, Sodium citrate.

T. Flocculating Agents: Gelation is produced by adding just sufficient precipitant to produced the gel state but insufficient to bring about complete precipitation. Examples are Salts such as Aluminium hydroxide, Ferric hydroxide, Bentonite and Non-solvents such as Petroleum ether.[14]

U. Lubricating Agents: They are used in formulation of lubricating gels. Example is Tragacanth.[15]

7.0 Types of evaluations are following:

A. pH
B. Drug content
C. Viscosity
D. Spreadability
E. Extrudability study
F. Skin irritation studies
G. In vitro release
H. In vivo study
I. Stability

A. 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.

B. 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.

C. 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 Brookfield Viscometer catalogues.

D. Spreabability:

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy 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 and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula:

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

Where: M = Wt. tied to upper slide.

L = Length of glass slides.

T = Time taken to separate the slides.

E. Extrudability Study: The formulations were filled in the collapsible tubes after the gels were set in the container. 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.

F. 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 marked on 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.[16]

G. In Vitro Release Studies:

The principal in vitro technique for studying skin penetration involves use of some variety of a diffusion cell like

Franz cell and Flow through cell in which animal or human skin is fastened to a holder and the passage of compounds from the epidermal surface to a fluid bath is measured.

Hairless rats were sacrificed by an overdose of halothane anesthesia. The skin from the dorsal surface was excised, and the adherent fat and subcutaneous tissue were removed. The skin was mounted on Franz diffusion cells with the epidermis facing the donor compartment. The skin permeation studies were performed by the procedure as described under "release studies".

For the skin retention studies, the donor cell was removed, and the excess formulation was removed from the surface of the skin using a cotton swab. The skin was then washed with 50% ethanol: water and blotted dry with lint-free absorbent wipes. The entire dosing area (0.636 cm2) was collected with a biopsy punch. The epidermis was separated from the dermis, and the tissues were minced using a dissection blade. Where applicable, the stratum corneum (SC) was stripped 20 times using breathable medical tape and the stripped skin was used to conduct permeation and skin retention experiments. Active drug content of epidermis and dermis was extracted using a previously reported method. Briefly, the samples were homogenized and boiled for 10 minutes in solvent (xM). The samples were then centrifuged and the supernatant was collected for analysis of drug by HPLC. The experiments were repeated at least 3 times using the skins from different rats. (16)

H. In Vivo Studies:

Inhibition of carrageenan – induced rat paw odema – Three groups of 6 male wistar albino rats were used one for marketed sample (reference). Other for test formulation and one group for control. The volume of unilateral hind paw test animal were measured. On each paw, 100 mg of preparation was carefully rubbed twice at 1 and 2 h. before carrageenan administration. They were placed in cages with copography meshes. 0.1 ml of 1 % w/v carrageenan was injected subcutaneously into the paw and volume of hind paw measured at hourly interval for 5 hr using a mercury plethysmometer. Percentage of inhibition was calculated.[16]

I. Stability: The stability studies were carried out for all the gel formulation by freeze - thaw cycling. In this syneresis was observed by subjecting the product to a temperature of 4° C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted.[17]

8.0 SUMMARY AND CONCLUSION:

A pharmaceutical gel comes under the topical drug delivery system. Gels are semisolid preparation used for the application of drug to the skin disorders or the coetaneous symptoms of a disease. They effects at the site of their application by virtue of the drug penetration into the underlying layers of skin or mucous membrane. The main advantage of this form is bypass first pass metabolism.

These are used when after system of drug administration fails or these are mostly used in Acne, Psorasis, pain and are advanced technique while are coidely being to increase delivery through skin. They are also used to prevent various other skin allergies.

Pharmaceutical gels (semi-solid formulation) in all their diversity dominate the system for topical delivery of drug for better relief and treatment of infections.

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