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A REVIEW ON GEL AS A RECENT APPROACH FOR NOVEL DRUG DELIVERY

Shinde Nishiganda G.[1], Nagoba Shivappa N.[1]*, Sakhare R. S.[1] and Gaware R. G.[1]

Channabasweshwar Pharmacy College, Latur, Maharashtra, India.

***Corresponding Author: Dr. Nagoba Shivappa N.**
Channabasweshwar Pharmacy College, Latur, Maharashtra, India.

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ABSTRACT
Gel provides better application property and stability in comparison to cream and ointment. Topical drug administration is a localized drug delivery system any where 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, Penetration Enhancer, Classifications, Characteristics.

INTRODUCTION
Topical drug 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. Topical application has many advantages over the conventional dosage forms.

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. Topical preparations give its action directly at the site of action.[1]

Gels are defined as semi rigid systems in which the movement of the dispersing medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase.[2]

The USP defines gels (sometimes called jellies) as semisolid systems containing either suspensions made up of small inorganic particles, or large organic molecules interpenetrated by a liquid. Where the gel mass contains a network of small separate particles, the gel is classified as a two-phase system. In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass is sometimes called as a magma. Single-phase gels consist of organic macromolecules uniformly circulated throughout a liquid in such a way that no apparent boundaries occur between the dispersed macromolecules and the liquid.

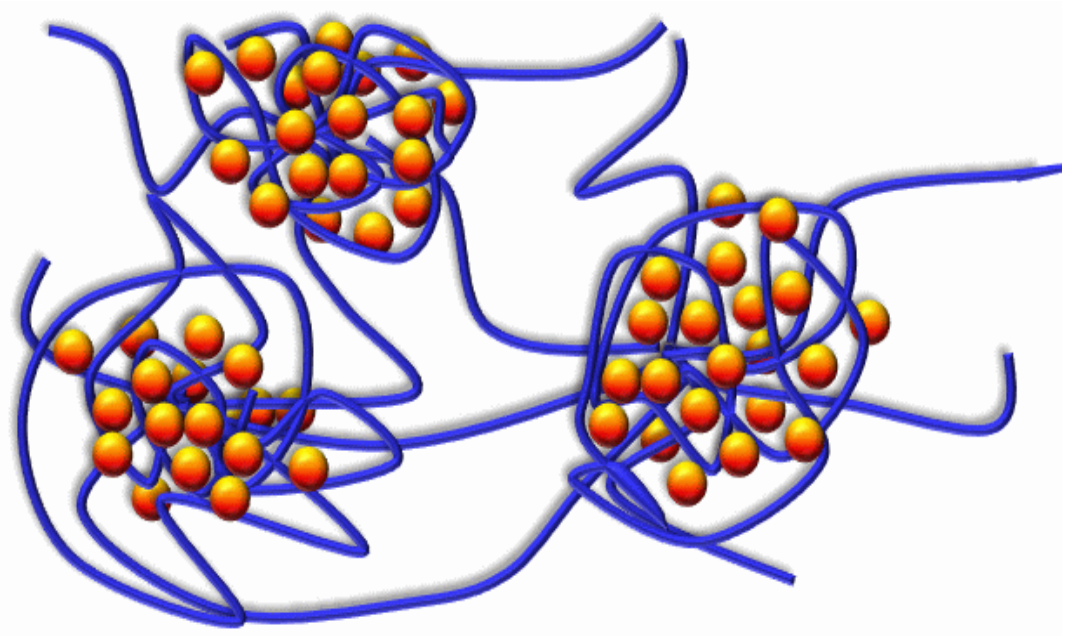
Gels are generally considered to be more rigid than jellies because gels contain more covalent crosslinks, a higher density of physical bonds, or simply less liquid. Gel-forming polymers produce materials that span a range of rigidities, beginning with a sol and increasing in rigidity to a mucilage, jelly, gel, and hydrogel.

Some gel systems are as clear as water, and others are turbid because the ingredients may not be completely molecularly dispersed (soluble or insoluble), or they may form aggregates, which disperse light. The concentration of the gelling agents is mostly less than 10%, usually in 0.5% to 2.0% range, with some exceptions.[1,2]

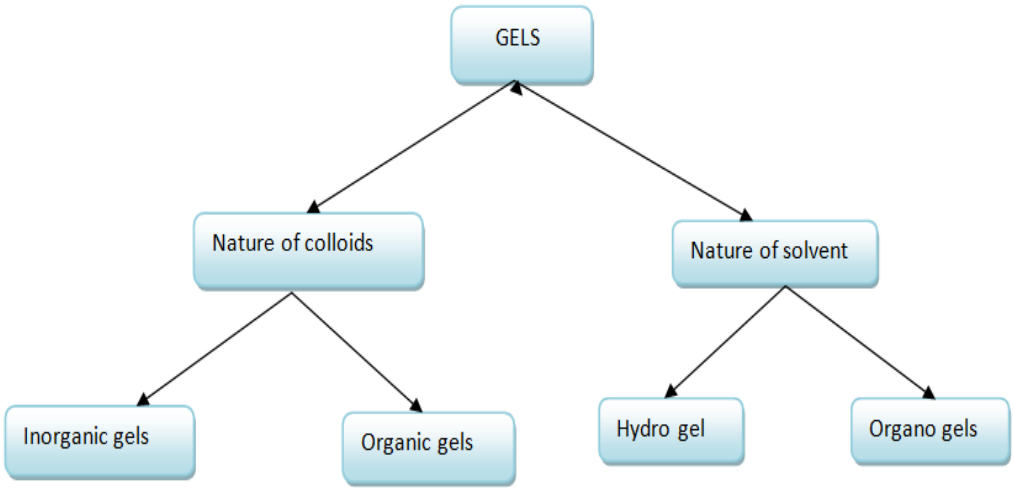
Structure of Gels
The gel consists of a natural or synthetic polymer forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After application, of the liquid evaporates leaving the drug entrapped in a thin film of the gel – forming matrix physically covering the skin.

The presence of a network formed by the interlocking of particles of the gelling agent gives rise to the rigidity of a gel. The nature of the particles and the type of form that is responsible for the linkages determine the structure of the network and the property of the gel.

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.[3]



Classification of Gels[4]



1. Based on colloidal phases[5]

They are classified into

- Inorganic (two phase system)
- Organic (single phase system)

Inorganic (Two phase system)

In two phase system, the partition size of dispersed phase is relatively large and form the three-dimensional structure throughout gel, such a system is consists of floccules of small particles rather than larger molecules and gel structure, in this system is not always stable. They must be thixotropic-forming semisolid on standing and become liquid on agitation.

Organic (Single phase system)

Single phase system; 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 walls forces.

Based On Nature of Solvent

Hydrogels (Water based)

A hydrogel is the network of polymer chains that are hydrophilic, infrequently found as a colloidal gel in which water is dispersion medium. These are highly absorbent natural or synthetic polymeric networks. They

also have a degree of flexibility likely to the natural tissue, due to their significant water content.

Uses for hydrogels

1. The hydrogel are Sustained-release drug delivery systems
2. Hydrogel used for the rectal drug delivery and diagnosis
3. Hydrogel-coated wells have been used for cell culture
4. It is used as scaffolds in tissue engineering
5. Itis environment sensitivity detector
6. Contact lenses (silicone hydrogels, polyacrylamides, polymacon)
7. ECG medical electrode
8. Dressing of healing

E.g., Bentonite magma, gelatin, cellulose derivatives, carpooler and poloxamer gel[2, 5].

Organogels (With a non-aqueous solvent)

Organogel is a non-crystalline, non-glassy thermo reversible solid material composed of a liquid organic phase trapped in a 3D cross-linked network. The liquidis can be, E.g., vegetable oil, an organic solvent or mineral oil. The solubility and particle sizes of the structurant are significant characteristics for the elastic properties and firmness of the organ gel. Frequently, these systems are based on self-assembly of the structurant molecules.

Xerogels

Is the solid formed from a gel by drying with unrestricted shrinkage. It is frequently retains high porosity (15-50) % and huge surface area (150-900 m2/g), along with very small pore size (1-10 nm). When solvent removed under supercritical conditions, the network doesn't shrink and a highly porous, low-density material known as an aerogel is produced.

E.g., Tragacanth ribbons, β-cyclodextrin, dry cellulose and polystyrene, gelatin sheets and acacia tears.

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

Plastic gels

E.g., The Bingham bodies, flocculated suspensions of the 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 the flow.

Pseudo-plastic gels

E.g., The Liquid dispersion of the tragacanth, sodium alginate, Na CMC, etc. Exhibits pseudo-plastic flow. The viscosity of these gels decreases with the increasing rate of shear, with no yield value. The rheogram results from the 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 the release of solvent from gel matrix.

Thixotropic gels

The bonds between the 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 a colloidal system with non-spherical particles to build up a scaffold like structure.

E.g., Kaolin, bentonite, agar, etc.

Based on physical nature

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 comparatively weak bonds like hydrogen bonds and dipole attraction.

Rigid gels

This can be formed from macromolecule in which the framework linked by primary valence bonds.

E.g., in silica gel, silica acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.

Characteristics of Gels[4]

A. Swelling

When a gelling agent is left in contact with liquid that solvates it, then a appreciable amount of liquid is takenup by the agent and the volume increases. This process is referred as swelling. This phenomenon occurs as thesolvent penetrates the matrix. Gel-gel interactions are replaced with 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.

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 mechanism of contraction has been related to the relaxation of elastic stress developed during the setting of the gels.

C. Ageing

Colloidal systems usually exhibit slowaggregation naturally. This process is referred to as ageing. In gels, ageing results in gradual formation of a denser network of the gelling agent. In gels, ageing gradual Formation of a denser network of the gelling agent. Theimer suggests that this process is similar to the original gelling process

and continues after the initial gelation, since fluid medium is lost from the newly formed gel.

D. Structure

The rigidity in 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.

E. Rheology

Solutions of the gelling agents and dispersion of flocculated solid are pseudo plastic i.e. follow Non-Newtonian flow behavior, characterized by a decrease in viscosity with increase in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by n gels, ageing results in gradual formation of a denser network of the gelling agent.

Anatomy of skin[5]

Skin is the largest organ in the body. It consists of three layers. The outer layer is called epidermis, the middle layer is dermis and the inner most layer is hypodermis. At some place it is thick and in some place it is thin. The average thickness of the skin about 1 to 2mm. In the sole of the foot, palm of the hand in the interscapular region, it is considerably thick, measuring about 5mm.

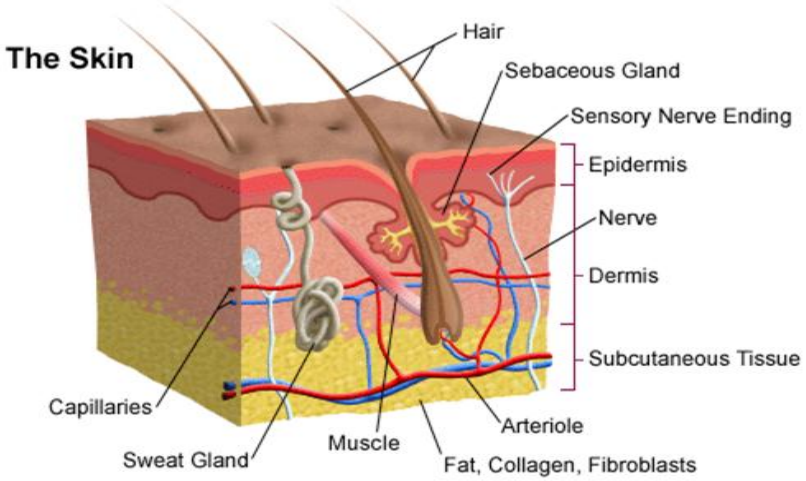


Fig. Longitudinal section of skin.

Skin Is Made Up of Two Layers Namely[6]

1. Outer epidermis
2. Inner dermis

Epidermis

The epidermis of the skin is formed by stratified epithelium, which is made up of 5 layers:

a. Stratum corneum
b. Stratum lucidum
c. Stratum granulosum
d. Stratum spinosum and
e. Stratum germinativum

1. Stratum corneum

The stratum corneum also known as horny layer. This is the outer most layer of skin and it consists of dead cell which are called corneocytes.

2. Stratum Lucidum

These made up of flattened epithelial cells. Many cells have degenerated nucleaus and in some cells the nucleus is absent. AS these cells shows shiny character, the layer looks like a homogenous translucent zone. So, the layer is called stratum lucidum**.**

3. Stratum Granulosum

This layer is very thin layer with 2 to 5 rows of flattened rhomboid cells. The cytoplasm contains keratohyaline granules. The protein keratohyaline is the precursor of keratin.

4. Stratum Spinosum

The cells of this layer possess some spine like protoplasmic projections due to this reason this layer also known as prickle cell layer. By these projections, the cells are connected to one another.

5. Stratum Germinativum

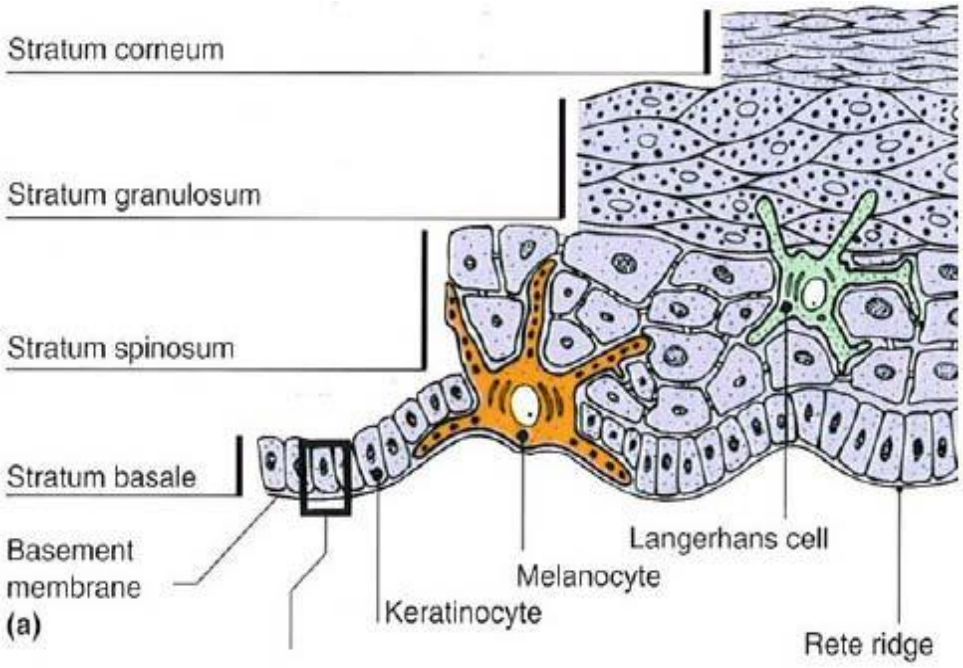
This is very thick layer which is made up of polygonal cells superficially and columnar or cuboidal epithelial cells in the deeper parts. Here new cells are constantly formed by mitotic division.

The colour of the skin depends on the the which contain the pigment of melanin.

Dermis

This is connective tissue layer made up of dense stout collagen fibres, fibroblast and histiocytes. The collagen fibers, exhibit elastic property and are capable of storing

or holding water. The collagen fibers contain the enzyme collagenase, which is responsible for wound healing.



Preparation of Gels[5]

Gels are normally 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. If the temperature is reducing, the degree of hydration is reduced and gelatin occurs. Many hydrogen formers are more soluble in hot than cold water (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

In this method 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 essential 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 in the hydrophobic solution brings about coagulation and gelation is rarely observed. The gels formed by flocculation method are Thixotropic in behavior. 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 made 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 chain9.

Gel Forming Substances[7]

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

Natural polymers	**A**	Proteins
		Gelatin
		collagen
	B	polysaccharides
		Pectin
		Gellum gum
		Alginic acid
		Agar
		Xanthin
		Cassia tora
		Tragacanth
		Guar gum
Semisynthetic polymers	A	Cellulose derivative
		Methylcellulose
		Hydroxyethyl cellulose
		Hydroxypropyl cellulose
		Carboxymethyl cellulose
		Hydroxypropyl methyl cellulose
Synthetic Polymers	**A**	Carbomer
		Carbopol-934
		Carbopol-940
		Carbopol-941
	B	Polyacrylamide
	C	Poloxamer
Inorganic substances	**A**	Bentonite
	B	Aluminium hydroxide
surfactants	**A**	Brij-96
	B	Cetostearyl alcohol
	C	Sodium lauryl sulphate
	D	Dodecyl pyridinium iodide

Formulation Considerations for Pharmaceutical Gels[8]

The choice of vehicle/solvent

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

Inclusion of buffers

Buffers may be involved in aqueous and hydroalcoholic-based gels to control the pH of the formulation. The solubility of buffer salts is reduced in hydroalcoholic-based vehicles. E.g., Phosphate, citrate, etc.

Preservatives

Preservatives cooperate with the hydrophilic polymers used to prepare gels, they reducing the concentration of free (antimicrobially active) preservative in the preparation. Therefore, to compensate for this, the initial concentration of these preservatives should be improved.

E.g. prabens and phenols.

Antioxidants

Antioxidants may be involved in the formulation to improve the chemical stability of therapeutic agents that are prone to oxidative degradation. Its choice is based on the nature of the vehicle used in the preparation of gel. Water-soluble antioxidants are generally used as the majority of gels are aqueous-based.

E.g., Sodium metabisulphite, sodium formaldehyde sulfoxylate, etc.

Flavors/Sweetening agents

Are only incorporated in gels that are designed for administration into the oral cavity (E.g., for the treatment of infection, inflammation, ulceration, etc.).

Sweeteners

Sucrose, liquid glucose, glycerol, sorbitol, saccharin sodium, aspartame, etc.

Flavors

Butterscotch, apricot, peach, vanilla, wintergreen mint, cherry, mint, anise, citrus flavors, raspberry.

Evaluation Parameters of The Formulated Gels[8,9]

Measurement of pH

The pH of various gel formulations was determined by using digital pH meter. Dissolve 1 gram of gel in 100 ml distilled water and stored for 2 hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

Drug content

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

Viscosity study

Viscosity measured by 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.

Spreadability

Spreadabilityindicates 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

For this Study Guinea pigs (400-500 g) 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 cm2 was mark done both the sides, one side served as control while the other side was test. Five ml of each sample was withdrawn periodically at 1,2,3,4,5,6,7 and 8h and each sample was replaced with an equal volume of fresh dissolution medium.

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.

Stability

It was carried out 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. Note the synersis.

Properties of Gel[10]

1. It should have suitable anti-microbial agent.
2. The topical gel must not be sticky.
3. The ophthalmic gel must be sterile.
4. The apparent viscosity or gel strength increases with an increase in the effective crosslink density of the gel. However, a rise in temperature may increase or decrease the apparent viscosity, depending on the molecular interactions between the polymer and solvent.
5. They exhibit the mechanical characteristics of the solid state.
6. Each component is continuous throughout the system.
7. There is high degree of attraction.

Application[11,12]

1. Gels are used to achieve optimal cutaneous and percutaneous drug delivery.
2. They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal ph.
3. Gels are having property to avoid enzymatic activity and drug interaction with food and drinks.
4. They can substitute for oral administration of medication when the route is unsuitable.
5. They can avoid the first pass effect, that is, the initial pass of drug substance through the human body.
6. They avoid systemic and portal circulation following gastrointestinal absorption.
7. Gels are not deactivated by liver enzymes because the liver is bypassed.
8. They are non-invasive and have patient compliance.
9. They are applied over skin for slow and prolonged absorption.

10. Gels have also been applied in pharmacy to some viscous suspension for oral use for example Aluminium hydroxide gel.
11. They have localized effect with minimum side effects.

Advantages[1,2]

a. Simple formulation and manufacturing so less investment and cost.
b. Improved patient compliance and comfort.
c. Reduced dosing frequency.
d. Reduced dose concentration improved local bioavailability.
e. Ease of administration.

Disadvantage[1,2,3]

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

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