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TOPICAL GEL: A HOMOGENOUS PREPARATION

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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.[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 macro-molecules in the dispersed phase. Physical and /or chemical cross-linking may be involved. The interlacing and consequential internal friction is responsible for increased viscosity and the semisolid state. Gels are evaluated by following parameters such as pH, homogeneity, grittiness drug content, viscosity, spreadability, extrudability, skin irritation studies, *in vitro* release, in Stability.[2]

Keywords: Topical gel, percutaneous penetration, drug delivery.

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INTRODUCTION

The field of pharmaceutical science has been developing steadily over the years, and has today become invaluable in helping to keep us healthy and prevent disease. An avenue of research that has progressed a great deal in the past few decades is the treatment of diseases via biomolecules such as drugs, proteins etc. Initially these could only be administered in limited manner, due to limitations of drug delivery through harmful environments in the body. Thus limited mobility reduced the effectiveness of administered drugs.[3]

Topical 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 readily accessible organs on human body for topical administration and is main route of topical drug delivery system. The skin of an average adult body covers a surface area approximately 2 mm and receives about one third of the blood circulating through the body. An average human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts on every square centimeter of the skin1. Although skin has been divided histologically into the stratum corneum, the living epidermis and the dermis, collectively it can be considered a laminate of barrier, permeation of this laminate can occur by diffusion via:

a. Transcellular penetration (across the cells)

b. Intracellular penetration (between the cells)

c. Transappendageal penetration (via hair follicles, sweat and sebum glands)

A myriad of medicated product are applied to the skin or readily accessible mucous membrane that in some way either augment or restore a fundamental function of a skin or pharmacologically modulate an action in the underlined tissues. Such products are referred as topical or dermatological product.[4, 5]

RATIONAL APPROACH TO TOPICAL FORMULATIONS

Topical formulation can be used to:

- Manipulate the barrier function of the skin, e.g., topical antibiotics and antibacterial help a damaged barrier to ward off infection, sun screening agents and the horny layer protect the viable tissues from U.V. radiation.

- Direct drugs to the viable skin tissues without using oral, systemic or other routes of therapy, e.g., anaesthetic, anti-inflammatory, antipruritic and antihistaminics drugs are to be delivered to viable epidermis and dermis.

- For skin appendage treatment, e.g., antiperspirants, exfolients and depilatories are to be delivered to the skin appendages.

- Deliver drugs for systemic treatment, e.g., transdermal therapeutic systems

provide systemic therapy for motion sickness, angina and hypertension.[5]

TOPICAL GELS

The word "gel" is derived from "gelatin", and both "gel" and "jelly" can be traced back to the Latin word gelu for "frost" and gelare, meaning "freeze" or "congeal". This origin indicates the essential idea of a liquid setting to a solid-like material that does not flow, but is elastic and retains some liquid characteristics.

The distinction between gel and jelly remains somewhat arbitrary, with some differences based on the field of application. The food industry uses the term ''gelatin jelly'' whereas the pharmaceutical industry uses the term ''gelatin gel.''

Gels are defined by the USP as: "semisolid systems consisting of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consist of a network of small discrete particles".

Gels are also 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 macro-molecules in the dispersed phase. Physical and /or chemical cross-linking may be involved. The interlacing and consequential internal friction is responsible for increased viscosity and the semisolid state.

Some gel systems are clear and others are turbid, since the ingredients involved may not be completely soluble or insoluble, or they may form aggregates, which disperse light. Gels can be used to administer drugs topically or into body cavities. The concentration of the gelling agents is generally less than 10% and usually in 0.5 to 2.0% range.

Most topical gels are prepared with organic polymers, such as carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the products and are easily washed off from the skin with water. The type of base used in formulating a topical dermatological product greatly influences its effectiveness. Bases containing large amounts of oleaginous substances provide an emollient effect to dry irritated skin. More importantly, bases made up of non-volatile oleaginous substances (e.g. hydrocarbon bases) can form an occlusive barrier on the skin that prevents escape of moisture from the skin into the environment. As a result, moisture accumulates between the skin and the ointment layer that cause hydration of the stratum corneum. Hydration of stratum corneum all 'opening up' of intra and inter-cellular channels and pathway for easier passage of drug molecules. Additionally, the moisture layer provides a medium for dissolution of the drug that is otherwise dispersed as fine particles in the ointment base. Since only the dissolved drug presented to the skin, as an individual molecular entity is able to enter the

stratum corneum, skin occlusion generally results in enhanced percutaneous drug absorption.[1]

CLASSIFICATION

Gels are also classified as:

a) Hydrogel

b) Organogel

c) Xerogel

Hydrogel

Hydrogel is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are highly absorbent (they can contain over 99.9% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. Common uses for hydrogels include-

- currently used as scaffolds in tissue engineering. When used as scaffolds, hydrogels may contain human cells to repair tissue.
- hydrogel-coated wells have been used for cell culture
- environmentally sensitive hydrogels which are also known as 'Smart Gels' or 'Intelligent Gels'. These hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
- as sustained-release drug delivery systems.
- provide absorption, desloughing and debriding of necrotic and fibrotic tissue.
- hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors, as well as in DDS.
- used in disposable diapers where they absorb urine, or in sanitary napkins
- contact lenses (silicone hydrogels, polyacrylamides)
- EEG and ECG medical electrodes using hydrogels composed of cross-linked polymers (polyethylene oxide, polyAMPS and polyvinylpyrrolidone)
- water gel explosives
- rectal drug delivery and diagnosis

Other, less common uses include

- breast implants
- now used in glue.
- granules for holding soil moisture in arid areas.
- dressings for healing of burn or other hard-to-heal wounds.
- Wound gels are excellent for helping to create or maintain a moist environment.
- reservoirs in delivery; particularly ionic drugs, delivered by iontophoresis.

Common ingredients are e.g. polyvinyl alcohol, sodium polyacrylate, acrylate polymers and copolymers with an abundance of hydrophilic groups.

Natural hydrogel materials are being investigated for tissue engineering; these materials include agarose, methylcellulose, hyaluronan, and other naturally derived polymers.

Organogels

An organogel is a non-crystalline, non-glassy thermoreversible (thermoplastic) solid material composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network. The liquid can be, for example, an organic solvent, mineral oil, or vegetable oil. The solubility and particle dimensions of the structurant are important characteristics for the elastic properties and firmness of the organogel. Often, these systems are based on self-assembly of the structurant molecules.

Organogels have potential for use in a number of applications, such as in pharmaceuticals, cosmetics, art conservation and food An example of formation of an undesired thermoreversible network is the occurrence of wax crystallization in petroleum.

Xerogels

A xerogel is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (15-50%) and enormous surface area (150–900 m^2/g), along with very small pore size (1-10 nm). When solvent removal occurs under hypercritical (supercritical) conditions, the network does not shrink and a highly porous, low-density material known as an *aerogel* is produced. Heat treatment of a xerogel at elevated temperature produces viscous sintering (shrinkage of the xerogel due to a small amount of viscous flow) and effectively transforms the porous gel into a dense glass.[6]

According to USP, gels are classified as:

- Single –Phase Gels
- Two-Phase Gels

Single-Phase Gels

Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase gels may be made from synthetic macromolecules or from natural gums. Although these gels are commonly aqueous, alcohols and oils can be used as the continuous phase. Single-phase gels are used more frequently in pharmacy for several reasons; semisolid state, high degree of clarity, ease of application, and ease of removal and use. The gels often provide a faster release of drug substances, independent of the water solubility of drug, as compared to creams and ointments.

Some gel formulation examples are provided below-

Carbomer 941 gel:

Carbomer 941	**0.5 (% w/w)**
Glycerine	10.0 (% w/w)
Triethanolamine	0.5 (% w/w)
Water	89.0 (% w/w)
Preservative	q.s.

Procedure: Water, glycerine, and preservative are mixed and the carbomer added by sprinkling on the surface while constantly mixing at high speed. Triethanolamine is added with slow agitation until a clear viscous gel forms.

Carbomer 934 alcoholic gel:

Carbomer 934 resin	**3.0 (% w/w)**
Glycerine	10.0 (% w/w)
Ethanol	40.0 (% w/w)
2-Ethylhexylamine	2.5 (% w/w)
Water	44.5 (% w/w)

Procedure: The carbomer is dispersed in the glycerine and water, and a solution of the 2-ethylhexylamine in ethanol is added to the water solution with mixing until a clear transparent gel is formed.

Two-Phase Gels

Two-phase gels containing bentonite may be used as a base for topical preparations such as plaster and ointment. Aluminum Hydroxide Gel, USP is an example of a two phase gel. The USP states that "Aluminum Hydroxide Gel is a suspension of amorphous aluminum hydroxide in which there is a partial substitution of carbonate for hydroxide." The gel is usually prepared by the interaction of a soluble aluminium salt, such as a chloride or sulphate, with ammonia solution, sodium carbonate, or bicarbonate.

The physical and chemical properties of the gel will be affected by the order of addition of reactants, pH of precipitation, temperature of precipitation, concentration of the reactants, the reactants used, and the conditions of aging of the precipitated gel.[2]

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. Collagen

ii. Gelatin

b. Polysaccharides

i. Agar

ii. Alginic acid

iii. Sodium or Potassium carrageenan

iv. Tragacanth

v. Pectin

vi. Guar Gum

vii. Cassia tora

viii. Xanthin

ix. Gellum Gum

2. Semisynthetic polymers

a. Cellulose derivatives

i. Carboxymethyl cellulose

ii. Methylcellulose

iii. Hydroxypropyl cellulose

iv. Hydroxypropyl methyl cellulose

v. Hydroxyethyl cellulose

3. Synthetic polymers

a. Carbomer

i. Carbopol -940

ii. Carbopol -934

iii. Carbopol -941

b. Poloxamer

c. Polyacrylamide

d. Polyvinyl alcohol

e. Polyethylene and its co-polymers

4. Inorganic substances

a. Aluminium hydroxide

b. Bentonite

5. Surfactants

a. Cetostearyl alcohol

b. Brij – 96[7]

Advantages of topical gel

The topical administration of drug in order to achieve optimal cutaneous and percutaneous drug delivery has recently gained an importance because of various advantages :

- To avoid gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks.
- To avoid the first pass effect, that is, the initial pass of drug substance through the systemic and portal circulation following gastrointestinal absorption, possibly avoiding the deactivation by digestive and liver enzymes.
- Non-invasive and have patient compliance.
- Less greasy and can be easily removed from the skin.
- Economic.
- Reduction of doses as compare to oral dosage forms.
- Localized effect with minimum side effects..

Desirable Properties of Gels

a) It should be inert, compatible with other additives and non-toxic.

b) It should be stable at storage condition.

c) It should be free from microbial contamination.

d) It should maintain all rheological properties of gel.

e) Economical.

f) It should be washable with water and free from staining nature.

g) It should not affect biological nature of drug.

h) It should be convenient in handling and its application.

i) It should possess properties such as thixotropic, greaseless, emollient, non-staining etc.

Desirable Properties of Gellants

a) It should be inert, compatible with addition and non-toxic.

b) It should produce gels at low concentration.

c) It should help gel formation.

d) It should be economical.

e) It should be free from microbial contamination.[8]

METHOD OF PREPARATION OF GEL

Chemical reaction: In the preparation of sols by precipitation from solution, e.g., aluminum hydroxide sol precipitated by interaction in aqueous solution of an aluminium salt and sodium carbonate, increased concentrations of reactants will produce a gel structure. Silica gel is another example and is prepared by the interaction of sodium silicate and acids in aqueous solution.

Temperature effect: As lower the temperature, the solubility of most lyophilic colloids, e.g., gelatin, agar, sodium oleate, is reduced, so that, if cooling a concentrated hot sol will often produce a gel. Similarly to this, some material such as the cellulose ethers shows their water solubility to hydrogen bonding with the water. Increasing the temperature of these sols will break the hydrogen bonding and the reduced solubility will produce gelatin.

Flocculation with salts and non-solvents: Gelatin is a popular collagen derative primarily used in food, pharmaceuticals, photographic and technical products. Gelatin is produced by adding just sufficient precipitant to produce the gel structure state but insufficient to bring about complete precipitation. The addition of salts to hydrophobic sols brings about coagulation and gelation is rarely observed.

STRUCTURE OF GEL

Elastic gels: Gels of agar, pectin and gelatin are elastic, the fibrous molecules bring at the points of junctions but relatively weak bond such as hydrogen bonds and dipole attraction.

Rigid gels: In contrast to elastic gels, rigid gel can be formed from macromolecules in which the framework is linked by primary valence bonds. e.g., Silica gel

Thixotropic gels: The term thixotropy describes the property of fluid passing from gel to sol state through agitation. The bond between particles in these gels is very weak and can be broken by agitation and shaking. The resulting sol will revert back to gel. This is termed as thixotropy.[9]

PRINCIPLES OF TOPICAL PERMEATION

Before a topically applied drug can act either locally or systemically, it must penetrate the stratum corneum - the skin permeation barrier. Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway). In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact stratum corneum becomes the primary pathway for topical permeation.

The release of a therapeutic agent from a formulation applied to the skin surface and its transport to the systemic circulation is a multistep process, which involves

- Dissolution within and release from the formulation
- Partitioning into the skin's outermost layer, the stratum corneum (SC)
- Diffusion through the stratum corneum, principally via a lipidic intercellular pathway, (i.e., the ratelimiting step for most compounds)
- Partitioning from the stratum corneum into the aqueous viable epidermis, diffusion through the viable epidermis and into the upper dermis, and uptake into the papillary dermis and into the microcirculation.[11,12]

KINETICS OF TOPICAL PERMEATION

Knowledge of skin permeation kinetics is vital to the successful development of topical systems. Topical permeation of a drug involves the following steps :

a. Sorption by stratum corneum

b. Penetration of drug through viable epidermis

c. Uptake of the drug by the capillary network in the dermal papillary layer

This permeation can be possible if the drug possesses certain physico-chemical properties. The rate ofpermeation across the skin (dQ/ dt) is given by:

$dQ / dt = Ps (Cd – Cr)$ Eq. 1

Where,

Cd = Concentration of skin penetrant in the donar compartment (e.g., on the surface of stratum corneum)

Cr = Concentration in the receptor compartment (e.g., body) respectively

Ps = Overall permeability constant of the skin tissue to the penetrant

Ps = (KsDss) / hs Eq. 2

Where,

Ks is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium.

Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues.

hs is the overall thickness of skin tissues.

As Ks, Dss and hs are constant under given conditions, the permeability coefficient (Ps) for a skinpenetrant can be considered to be constant.

From Eq.1 it is clear that a constant rate of drug permeation can be obtained only when Cd>>Cr i.e., the drug concentration at the surface of the stratum corneum (Cd) is consistently and substantially greater than the drug concentration in the body (Cr), then Eq. 1 becomes:

dQ / dt = PsCs Eq. 3

Permeability coefficient = (KsDss) / hs = 1 / resistance.[13, 16]

CONCLUSION

Topical formulations include creams, ointments, pastes, gels etc. Out of which topical gels are getting more popular now a days because they are more stable and also can provide controlled release than other semisolid preparations. The topical 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 opical gel for anti-inflammatory activity and to provide the better therapeutic effects to patient compliance.

Table 1: Example of topical gel

Active ingredient	Gelling agent	Route	Use
Acetic acid	Tragacanth, acacia	Vaginal	Restoration and maintenance of acidity
Becaplermin	Sodium CMC	Dermatologic	Promotes healing of diabetic ulcers of lower extremity
Benzoyal peroxide	Carbomer 940	Dermatologic	Acne vulgaris
Clindamycin	Carbomer 934P	Dermatologic	Acne vulgaris
Cyanocobalmin	Methylcellulose	Nasal	Hematologic
Metronidazole	Carbomer 934P	Vaginal	Bacterial vaginosis
Timolol maleate	Gellan gum	Ophthalmic	Treatment of elevated intraocular pressure
Progesterone	Carbomer 934P	Vaginal	Bioadhesive gel

Table 2: Formulation excipients:

S.NO.	EXCIPIENTS	
1.	Gelling agents	• Carbomers 934p/941 • HPMC • Sod. CMC • HPC • PVP • HEC • Chitosan • Guar gum • Gelatin
2.	Solvents	• purified water • Ethanol • glycerin • Olive oil • Paraffine oil • Polyethylene glycol
3.	Surfactants	• Tweens • Spans
4.	Preservatives	• Methyl parabeans • Propyl parabeans
5.	Flavour	• Mannitol

Table 3: Some examples of Carbopol group of gelling agents are-

Polymer Name	Viscosity*	Properties
Carbopol® 910	3,000 - 7,000	Effective in low concentrations and will provide a low viscosity formulation.
Carbopol® 934	30,500 - 39,400	Effective in thick formulations such as emulsions, suspensions, sustained-release formulations, transdermals, and topicals. Forms clear gels with water.
Carbopol® 934P	29,400 - 39,400	Same properties as 934, but intended for pharmaceutical formulations. "P" = highly purified product
Carbopol® 940	40,000 - 60,000	Effective in thick formulations, very good clarity in water or hydroalcoholic topical gels. Forms clear gels with hydroalcoholic systems.
Carbopol® 941	4,000 - 11,000	Produces low viscosity gels, very good clarity.

Table 4: Gelling concentrations for substances used in pharmaceutical products-[10]

Substance	Gel-forming concentrations (wt %)	Required additives
Proteins		
-Collagen	0.2-0.4	-
-Gelatin	2-15	-
Polysaccharides		
-Agar	0.1-1	
-Alginates	0.5-1	Ca^{+2}
-Pectins	0.8-2	Ca^{+2}

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