A REVIEW ON PHARMACEUTICAL GELS

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ABSTRACT:
Topical gels are semisolid solutions that have a liquid phase that is restrained within a three-dimensional polymeric matrix made of gum that is either natural or synthetic and has a high degree of physical or chemical cross-linking. Topical gels are an excellent contender for a wide range of applications because of their behaviour in the middle of solid and liquid components. Since topical gels are a subject that interests scientists working in industry, research and development, education, drug control administration, and professional fields, they have attracted a lot of attention in recent years. This article's goal is to discuss the fundamentals and most recent developments of topical gels, including their categorization and preparation techniques. The use of hydrogel in medication delivery systems is covered separately. Particular focus is placed on classification, method of preparation and evaluation parameters.

KEYWORDS*: Skin, characteristics of gels, preparation method and evaluation tests.*

I. INTRODUCTION

Topical medication delivery is the application of a substance on the skin with the purpose of treating or curing skin conditions. When alternative routes of administration are ineffective, such as in cases of localized fungal infections of the skin, these topical drug delivery methods are often utilized [1]. It can enter the skin more deeply, improving absorption. Topical application is not superior to traditional dose forms in any way. Because of the bilayer composition and structure, they are typically thought to be more effective and less harmful than traditional formulations. To promote the local and reduce the systemic effects of topical dose forms, efforts have been undertaken to use drug carriers that enable appropriate localization or penetration of the medication within or through the skin. It inhibits GI irritation and stops the liver from metabolizing the medication, increasing the medicine's bioavailability. Topical treatments respond immediately where they are applied [2,3].

The skin serves as a localized drug delivery route for topical medications, including ocular, vaginal, and rectal.

a. Skin

Skin is the largest organ in the body. It consists of three layers. The outer most layer is called epidermis; the middle layer is dermis and the inner most layer is hypodermis.

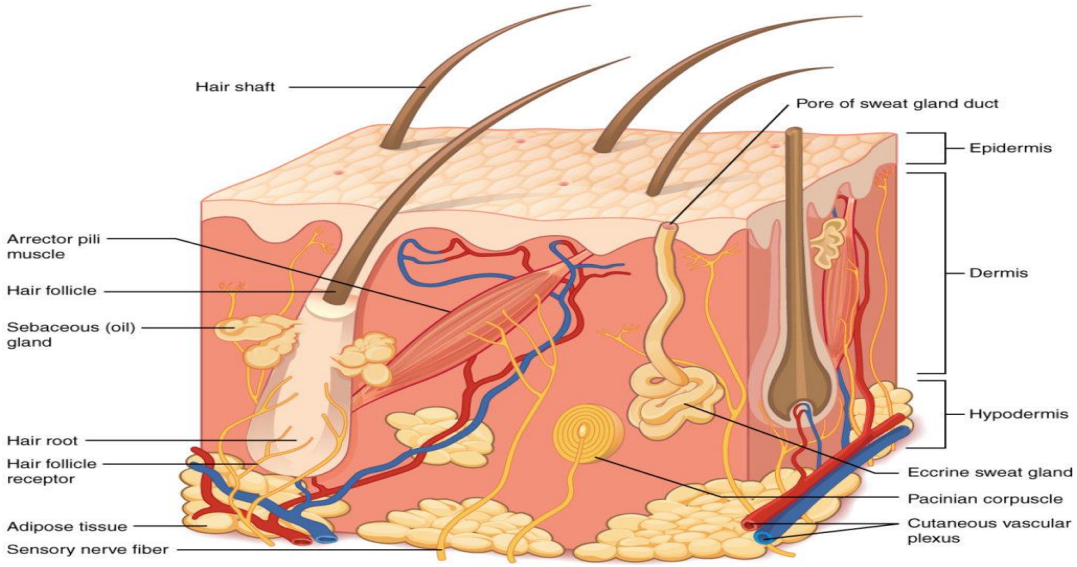

Figure -1 The structure of skin

a. Epidermis: Epithelial cells that forms the epidermis. Both live and dead cells can be detected among these cells. The older cells are pushed forward by the younger cells at the bottom of the epidermis, which divide quickly. There are no direct blood vessels that supply nutrients to the epidermis. It receives its nourishment from a dense circulatory network in the underlying dermis, which allows the required molecules to diffuse here. Desmosomes form a very tight connection between epidermal cells. Desmosomes and intracellular keratin filmates are in touch. Keratin is created by keratin filmates. During the maturation process, keratin cells

gather and crosslink with one another in the cytosol. This network of keratin fibroses produces a hard and rigid protective layer in the epidermis once the older cells die.

Cell types that exist in the epidermis are:

Keratinocytes: These are the main cell types in epidermis (95% of cells).

Melanocytes: These are producing pigment cells and found in the basal layers of epidermis.

Langerhans cells: These cells are important immunological cells and can be found in the mid dermis as well Merkel cells; these cells are found in the basal layer of epidermis and are one part of amine precursor and decarboxylation system [4,5].

Epidermis consists of five layers, namely from inside to outside;

- stratum germinativum (basal layer)
- stratum spinosum
- stratum granulosum
- stratum lucidum
- stratum corneum

- **Stratum corneum:** It is the skin's outermost layer, and it protects it mechanically. It serves as a barrier to prevent water loss. There are coenocytes in it. Due to the pressure, these cells lose their nuclei and become into dead cells. Keratin-A, a protein found in cells, hinders water from evaporating [6,7].

- **Stratum lucidum:** This consist of flattened epithelial cells. The cells exhibit shiny character. This is mostly found on palm and soles. The layer resembles lustrous zone so it is called stratum lucidum.
- **Stratum granulosum**: This is made up of granular cells which are thin layer 2-5 rows of compressed rhomboid cells [8]. Keratohyalin granules are found in cytoplasm. It prevents from water loss and mainly seen in palm and soles.
- **Stratum Spinosum**: This layer is also known as the prickle cell layer because it contains spinous cells that imitate spines. They include keratin filaments as well.
- **Stratum germinativum:** It has columnar or cuboidal epithelial cells in the deeper portions and polygonal cells on the edges. It has keratocytes that are undergoing mitosis, as well as glands and keratin structures, which are produced from these layers. [9,10]
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b. **Dermis**:

The dermis, which lies beneath the epidermis, is distinguished by a dense network of fibers that gives the skin its ability to stretch and a dense network of collagen that gives the skin its strength. Dermal blood vessels deliver nutrition to the dermis and epidermis. The dermis is crucial for monitoring body temperature. There are nerves that provide pressure and pain feelings. The dermis is 3 to 5 mm thick. Dermis is composed of elastin fibers, blood arteries, and nerves in addition to an interfibrillar gel of glycosaminoglycan, salt, and water, lymphatic cells, and sweet glands. Cell types found in dermis are:

- **Fibroblasts**: collagen producing cells
- **Macrophages**: scavenger cells

- **Mast cells**: responsible for immunological reactions and interactions with eosinophils [11].

Dermis plays an important role as connection to other skin layers also. Changes in the metabolism in dermis can influence growth integrity of the epidermis, hair follicles and skin glands.

c. Hypodermis:

The innermost layer of skin is known as the hypodermis. It is the layer of skin that has contact with the body's deeper tissues, such muscles and bone. Sebaceous glands, sweat glands, and hair follicles all originate in the dermis but are enclosed in the epidermis. A thin salt solution is delivered onto the skin's surface by sweat glands. In order to regulate body and skin temperatures, the evaporation of this solution cools the skin. The body contains sweet glands everywhere. The quantity of dilutions (sweet) generated is influenced by the ambient temperature, the level of heat-producing skeletal muscle activity, and a variety of emotional aspects. Produced by the sebaceous glands is sebum. Sebum is an oily substance that is released from hair follicles onto the skin.

II. ROUTES OF DRUG PERMEATION THROUGH SKIN: Three primary routes of skin absorption [12,13]

1) Primary Transcellular: The chemical moieties are transported all the way through keratin packed coenocytes into and out of cell membrane.

2) Secondary Intercellular: The molecules are transported around coenocytes in the lipid-rich extracellular region.

3) Thirdly Transappendageal: These transports are been supported by sweat glands, hair follicles and sebaceous glands.

III. GELS

Topical gels are homogeneous, semi-solid preparations used to cure and prevent skin conditions. Due to the hydrophilic nature of gels, the medicine or active component was released quickly. A gel is made up of two parts: a cross-linked, three-dimensional substance that contains a significant volume of liquid to create a sufficient, stiff network that immobilizes the liquid continuous phase. Both organic macromolecules and inorganic particles are employed to create the structural network of gel. Chemical gels have a permanent covalent bonding that binds the particles together, whereas physical topical gels have secondary intermolecular forces includes hydrogen bonds, electrostatic interactions, hydrophobic contacts, and Vander Waal forces that are weaker and reversible [14].

Figure-2 Gel

IV. STRUCTURE OF GELS

A gel consists of a natural or synthetic polymer forming a three-dimensional matrix throughout a dispersion medium or hydrophilic liquid. As soon as the liquid is applied, it evaporates, leaving the medication contained in a thin layer of the gel-forming matrix that physically covers the skin [15]. The flexibility of a gel is caused by the existence of a network created by the interlocking of gelling agent particles. The composition of the particles and the kind of forming narathat creates the links influence the network's structure and the gel's properties [16].

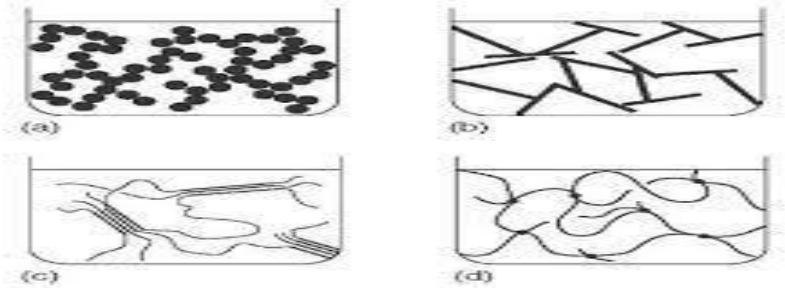


Figure-3 - Gel structures (a) Flocculated particles. (b) Network of stretched out particles or rods. (c) Matted fibers as found in soap gels. (d) Amorphous and Crystalline zones in a gel.

V. IDEAL PROPERTIES OF TOPICAL GEL [17]

- The gel should be clear and homogenous.
- The gel should be inert in nature.
- The gel should be non-sticky.
- The gel should not interact with any other formulation component.
- The gel should be stable.
- It should be non-irritate to the skin or any part where the gel is applied.
- The viscosity is should be optimum.
- It should have anti- microbial activity.

VI. ADVANTAGES OF GEL FORMULATIONS

Some main advantages of gel formulation over other semisolid dosage forms [18,19]

- Gels are effortless to prepare when compared to other formulations.
- Gel is elegant non-greasy formulation.
- Gels have excellent adherence property to application site.
- Gels are biocompatible and eco-friendly.
- Have magnificent tolerability to stress conditions.

VII. DISADVANTAGES OF GEL FORMULATION

In spite of several advantages. Gel formulations also have some disadvantages [20,21]

- Effect of gels is relatively sustained and slower.

- The gelators or additives may cause irritation.
- Water content increases possibility of fungal or microbial attack in gel.
- Solvent loss from the formulation dries of gel.
- Flocculation in some gel causes an unstable gel.

VIII. IDEAL CHARACTERISTICS OF GELS. [22,23]

Swelling: Gels have the ability to swell, absorbing liquid while expanding in size. This might be viewed as the beginning of the disintegration process. Gel-gel interactions are replaced by gel-solvent interactions as a result of solvent permeating the gel matrix. Normal cross-linking in the gel matrix, which inhibits complete disintegration, causes limited swelling. When the solvent combination has a solubility characteristic similar to that of the gellant, this gel swells significantly.

Syneresis: Upon standing, many gel systems shrink. The interstitial liquid is expressed and accumulates on the gel's surface. This method, known as syneresis, has also been seen in organogel and inorganic hydrogels in addition to organic hydrogels. Syneresis often intensifies with lowering polymer concentration.

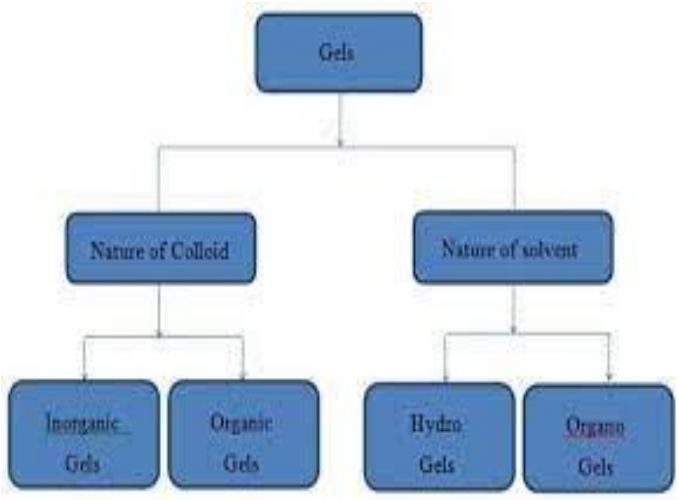
Ageing: Slow spontaneous aggregation is a typical feature of colloidal systems. Ageing is a term that describes this process. Ageing induces a thick network of the gelling ingredient to gradually accumulate in gels. Since the fluid medium is lost from the freshly created gel, the timer infers that this process is identical to the first gelling process and continues after the initial gelation.

Structure: The network developed by the interlinking of the gelling agent particles is what gives a gel its flexibility. The characteristics of the gel and the network's structure depend on the kind of particles used and the force used to create the links.

Rheology: Solutions of the gelling agents and flocculated solid dispersion display non-Newtonian flow characteristics, which is defined by a drop in viscosity with an increase in shear rate, and are hence considered pseudoplasticity, or pseudo-plastic solutions. By breaking down interparticle attachment, the fragile structure of inorganic particles distributed in water is disturbed and exhibits a stronger inclination to flow when shear force is applied. Similar to this, when shear stress is applied to macromolecules, the molecules align in the direction of the tension.

IX. CLASSIFICATION OF GELS

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties [24].



Based on colloidal phases

They are classified into:

a. Inorganic (Two phase system)

b. Organic (Single phase system)

Inorganic (Two-Phase System)

The system consist of floccules of tiny particles rather than larger molecules and the gel structure will be unstable if the dispersed phase partition size is especially large and develops a three-dimensional structure throughout the gel. They must be thixotropic, which means that when disturbed, they transform from a semisolid to a liquid. Gel made of aluminium hydroxide and bentonite magma are two examples.

Organic (Single Phase System)

On the twisted threads, there are large organic molecules that are continuously dissolved. The majority of organic gels are single-phase solutions made up of organic liquids such Plastic base and gelling agents like carbomer and tragacanthin.

Based on Nature of the Solvent

Hydrogels: (water based):

A hydrogel is a three-dimensional network of hydrophilic polymers that can grows in water and contain a significant quantity of water while maintaining their structural integrity due to the chemical or physical cross-linking of individual polymer chains. Hydrophilic colloids like silica, bentonite, tragacanth, pectin, sodium alginate, etc. provide an example. The hydrogel may be utilised as an ECG medical electrode, rectal medication delivery system, and sustained release drug delivery system.

Organogel: (With a non-aqueous solvent): A liquid organic phase is contained within a three-dimensional, cross-linked network in an organogel, a type of gel. The addition of a polar solvent causes the organogelling or gelation of lecithin solution in organic solvents.

Xerogels: Xerogels are solid-formed gels created by allowing materials to gently dry at room temperature while experiencing unrestricted shrinking. Viscous sintering takes place when a xerogel is heated over a certain point, thereby turning the porous gel into a thick glass. Examples include polystyrene, dry cellulose, and tragacanth ribbons. Gels are occasionally categorized as plastic gels, pseudo-plastic gels, and thixotropic gels because they display non-Newtonian flow.

Based on Physical Nature

Elastic gels: Agar, pectin, Guar gum, and alginates gels have an elastic property. At the point of junction, the fibrous molecules are joined by comparably weak connections such as hydrogen bonds and dipole attraction. If the molecule has a free -COOH group, a salt bridge of the type -COO-X-COO forms an extra bond between two adjacent strand networks. Eg.: Alginate and Carbopol.

Rigid gels: This can be made from macromolecules with primary valence bonds connecting the framework. Eg. Silic acid molecules are kept together in a silica gel by the Si-O-Si-O link, resulting in a polymer structure with a network of pores.

X. GELS CAN BE PREPARED BY FOLLOWING METHODS [25]

1) Thermal change: When the lipophilic colloids (solvated polymers) are exposed to thermal changes, gelatin results. In comparison to cold water, several hydrogen formers are more soluble in heat. When the temperature drops, the amount of moisture decreases and gelatin forms. (A gel will form when a concentrated hot solution is cooled). For examples, cellulose derivatives, gelatin, agar sodium oleate, and guar gum. Some substances, such as cellulose ether, on the other hand, have their water solubility due to hydrogen bonding with the water. These solutions' lower solubility and broken hydrogen bonds will result in gelation when the temperature is raised. As a result, this technique cannot be used as a standard for creating gels.

2) Flocculation: Here, gelation is created by adding just the right amount of salt to cause age state precipitation, but not enough to cause complete precipitation. In order to prevent a particular high concentration of precipitant, fast mixing must be ensured. For instance, ethyl cellulose and polystyrene solutions in benzene can be gelled by combining them quickly with the right quantity of a non-solvent, such petroleum ether. Salts cause coagulation and gelation when added to hydrophobic solutions, respectively. The gels created using the flocculation process behave in a thixotropic way. Hydrophilic colloids like gelatin, proteins, and acacia are only impacted by high electrolyte concentrations; typically, the colloidal state becomes "salted out," and gelation is prevented.

3) Chemical reaction: Using this technique, the solute and solvent interact chemically to form gel. A higher concentration of the reactants will result in a gel structure, as in the formation of aluminium hydroxide gel by interaction of an aluminium salt and sodium carbonate in an aqueous solution. A few more instances in which the polymeric chain has been cross-linked include PVA, cyanoacrylates with glycidol ether (Glycidol), toluene diisocyanates (TDI), and methane diphenyl isocyanine (MDI).

4) Fusion method: In this technique, the medication, vehicles, and gelling agents are all mixed together at high heat until a semi-solid texture is not produced.

5) Cold method: All the components, excluding the medication or active pharmaceutical ingredient, are heated and mixed concurrently in this approach. After lowering the formulation's temperature, the drug is added, and the blending process is repeated until the gel has not formed.

6) Dispersion method: In this technique, the medication is dissolved in the medium and mixed in while the gelling agent is agitated with water until it begins to swell. If required, add buffer solution to the gel to change the pH.

XL. MECHANISM OF GEL FORMATION:

Gels are formed via three types of cross-linking,

a) Chemical cross-linking

b) Physical cross-linking

c) Ionic cross-linking

a) Chemical cross-linking: Polymers containing bonded units in their assembly also exhibit chemical cross-linkage. Such polymers produce an irreversible interaction between the added chemical and the free group while cross-linkage compounds are bringing them together. In this kind of reaction, viscosity rises after reaching a particular concentration and causes gel formation. Consider polyacrylic acid (with multiple carboxylic acid)

b) Physical cross-linking: By establishing hydrogen bonds, solution to gel transitions may also be achieved in situations including concentration fluctuation, temperature transition, and the solubilization of crystalline components. Physical cross-linking is demonstrated, for instance, in cellulose and dextran gels [26].

c) Ionic cross-linking: In this case, gel is created by creating a charge on the polymer (S) or various particles (Solvent), which attract one another. Ionic charges come from charges on the molecules [27, 28].

XII. GELLING AGENT

Gelling agents are the polymers that are used to structural network or provide texture to the gels. Gelling agents are classified as follows:

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: [29,30]

Proteins – Collagen, Gelatin

Polysaccharides – Agar, Alginate acid

Sodium or Potassium carageenan, Tragacanth, Pectin, Guar Gum, Cassia Tora, Xanthan, Gellum Gum.

Semisynthetic polymers cellulose derivatives: Carboxymethyl cellulose, Methylcellulose, Hydroxyethyl cellulose Hydroxypropyl cellulose, Hydroxy propyl (methyl cellulose).

Synthetic polymers: Carbomer – Carbopol 940, Carbopol 934 Polyacrylamide Poloxamer Polyvinyl Alcohol Polyethylene and its copolymers.

Inorganic substances: [31] Bentonite Aluminum hydroxide

surfactants: Cebrostearyl alcohol, Brij – 96

The following criteria should be satisfied for a polymer to be used in a topical system.

Molecular weight: Chemical functionality of polymer must allow diffusion and release of the specific drug The polymer should permit the incorporation of a large amount of drug. The polymer should not react, physically or chemically with the drug.

- The polymer should be easily manufactured and fabricated into the desired product and inexpensive.
- Polymers and its degradation products must be nontoxic.

Drug Substance: [32]

A key factor in the effective creation of a topical medication is the drug substance. The crucial pharmacological characteristics that influence how efficiently it diffuses through gels and through skin.

Physicochemical properties:

Drug should have a molecular weight of less than 500 Daltons. Drug should have adequate lipophilicity Drugs highly acidic or alkaline in solution are not suitable for topical delivery. A saturated aqueous solution of the drug should have a pH value between 5 and 8.

Biological properties:

The skin must not be irritated by the medication directly. Topical application is appropriate for medications that either break down in the gastrointestinal system or are rendered inactive by the hepatic first pass effect. Under the near zero order release profile of topical delivery, drug tolerance must not form. Skin immunity shouldn't be triggered by the medication.

XIII. ADDITIVES USED IN GEL FORMULATION [33, 34,35]

Preservative: - Preservatives are used to make the gel long lasting and prevent them to spoil Eg. Methyl Paraben and Propyl Paraben etc.

Drug solubilizer: - Drug solubilizer is used in the case of drug having poor solubility. Some drugs are poorly soluble in medium so drug solubilizer helps to dissolve the drug in the medium. E.g., Triethyl-o-amine and PVP (Polyvinyl pyrrolidine) etc.

Stabilizers: - Some gels containing heavy metals and agents which is stabilized by chelating agent, such as EDTA (Ethylene diamine tetra acetic acid).

Penetration Enhancer [33,34]

An ideal penetration enhancer should have the following properties:

- It should have pharmacologically and chemically inert, and chemically stable.
- It should be non-toxic, non-irritant, noncomedogenic and non-allergenic
- It should have a rapid onset of action, predictable duration of activity, as well as a reproducible and reversible effect.
- It should be odorless, tasteless, colorless, and inexpensive
- It should have pharmaceutically and cosmetically acceptable. It should be non-toxic, non-irritating, and non- allergenic.
- It should have a solubility parameter similar to that of skin [34] It should have no pharmacological activity within the body, i.e., should not bind to receptor sites.
- It should have appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- It should have cosmetically acceptable with an appropriate skin “feel.” [35]

IVX. APPLICATION OF GELS

- Used in soft and hard gel pills.
- Gels are used to create continuous drug release formulation.
- Used for drug administration to various routes such as, tropical, intranasal, intraocular, vaginal, rectal and intramuscular and parenteral in some cases.
- They are widely used in food and cosmetic industry.
- Phosphoric acid and Sodium fluoride gel used in dental care.

XV. EVALUATION PARAEMETERS OF TOPICAL GELS [36,37,38,39,40,41]

pH measurement: A digital pH metre is used to measure the pH of different gel compositions. 100 ml of newly made distilled water are added to 1 g of gel, which is then allowed to dissolve for two hours. Each formulation's pH is examined three times, with the average readings being computed.

Measurement of Viscosity: The viscosity of produced gel formulations may be evaluated using a Brookfield digital viscometer. The rotation rates for the gels are 0.3, 0.6, and 1.5 per minute. The relevant dial reading is noted for each speed. By multiplying the dial measurement with a factor listed in the Brookfield viscometer catalogues, one may determine the viscosity of gel.

Spreadability:

The region that gel spreads to easily after application is referred to as its spreadability. Glass slide and wooden block measuring tools are used to evaluate it. Spreadability is measured in seconds and is the amount of time it takes for two slides to separate from a gel that is positioned in their interstices under the influence of a specific load. Better spreadability is achieved with shorter gap times between two slides. Spreadability is determined by applying the following formula:

$S = M.L / T$

S is the spread ability.

M = Weight of the top slide tide

L is the glass slide's length.

T is the amount of time needed to fully separate one slide from the others.

Homogeneity: Following development, all gels are examined visually to determine their homogeneity.

Grittiness: All gel formulations are microscopically examined to see whether any particle matter is present.

Extrudability: After being placed in the containers, the gel formulations are filled in collapsible tubes. The weight in grammes needed to extrude a 0.5 cm ribbon of gel in 10 seconds is used to gauge the extrudability of gel compositions.

Screening for stability: Freeze-thaw cycling is used to investigate stability. The product is heated to 40 degrees for one month, then 25 degrees for one month, then 40 degrees for one month. There is syneresis. The gel is then exposed to room temperature, and the exudates of separate liquid are observed.

Drug content: 1g of gel is added to 100 ml of a suitable solvent, which contains the drug. Utilizing a UV spectrophotometer, absorbance is determined following an appropriate dilution at max nm.

Drug Diffusion Study in Vitro: Franz diffusion cells are used to conduct drug release experiments in vitro. A cellophane membrane containing 0.5 g of gel is used. A 250 mg phosphate buffer with a pH of 7.4 is used as the dissolving media in diffusion experiments carried out at 37^0c to 10^oc. A 1-hour interval is used to collect a 1ml of sample and replace it with fresh buffer solution. Samples that have been collected are properly examined.

Skin irritation test: Ten healthy male and female volunteers were selected for skin irritation testing. 100 mg gel was applied on are of 2 cm for 6 hours, on the interior surface of upper arm and covered with cotton bandage. After 6 hr the sites were cleaned with acetone and readings are made according to the scale given by Draize. No irritation: 0 Slight irritation: 1 Irritation: 2

In-vivo Study: Inhibition of carrageenan induced rat paw edema is studied in male wistar arabino rats using mercury plethysmometer. The volume of unilateral hind paw of experimental animals is measured, before and after administration of carrageenan. % Inhibition is noted.

XVI. CONCLUSION:

The use of pharmaceutical gel getting more popular nowadays because they are more stable and also provide control release than other semisolid dosages forms. The topical gel improves the skin's capacity to absorb medication, increasing bioavailability. A topical administration system's main advantage is that it avoids first-pass metabolism. Additionally, it offers high patient acceptance. The majority of the time, when another method of medication administration has a lower bioavailability, topical distribution is preferred. Topical gel is a safe and effective therapy option for use in the management of skin-related illnesses, according to the clinical data.

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