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A REVIEW ON TOPICAL GEL

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ABSTRACT

Topical formulations, including gels, are designed for both systemic and local effects when applied to the skin. Topical gels are semisolid preparations where drugs are dispersed in a liquid medium, enhancing drug delivery. These gels consist of three-dimensional structures made from natural or synthetic polymers linked through physical, chemical, or ionic interactions. They are classified based on colloidal system nature, solvent system, rheological properties, and physical characteristics. The development of innovative formulations like hydrogels and emulgels has emerged alongside traditional gels. Various preparation methods include cold, chemical, dispersion, flocculation, and thermal techniques. This review covers classification, novel approaches, applications, gel formation mechanisms, preparation methods, and evaluation parameters.

KEYWORDS: Topical drug delivery; skin; gels; anatomy.

INTRODUCTION

For the topical treatment of dermatological diseases and skin care, clinicians and patients have access to a wide range of vehicles, including solids, semisolids, and liquid preparations. Among the semisolid formulations, the use of transparent gels has significantly increased in

both cosmetic and pharmaceutical contexts. A gel is a colloidal system that typically consists of 99% liquid, which is held in place by surface tension between the liquid and a macromolecular network formed by a small amount of gelling agent.[1]

Topical drug administration is a localized delivery system that can be applied through various routes, including ophthalmic, rectal, vaginal, and dermal applications. The skin is one of the most accessible organs for topical administration and serves as the primary route for these delivery systems.[2]

The material that brings a particular drug into contact with and through the skin is referred to as a topical delivery system. These topical drug delivery systems are typically used for localized skin infections, such as fungal infections, or in situations where other routes of administration are in effective.[3]

Topical application allows for deeper tissue penetration, enhancing drug absorption. This method offers several advantages over conventional dosage forms. Due to their bilayered composition and structure, topical formulations are generally more effective and less toxic than traditional options.

According to the United States Pharmacopoeia, gels are classified as semisolid systems composed of a dispersion of small inorganic particles or large organic molecules that are enclosed and interpenetrated by a liquid. Gels function as a two-phase system where inorganic particles are distributed within a continuous phase rather than dissolved, while large organic particles are dissolved in the continuous phase and arranged randomly in flexible chains.[4]

Anatomy of the Skin

The human body has two primary systems that safeguard it against harmful organisms from the environment. The internal defence system is responsible for eliminating microorganisms and bacteria that have already entered the body. Meanwhile, the external defence mechanism works to prevent these germs from getting in. The skin is the largest component of this external defence system. In addition to protecting the body's exterior, the skin serves several other functions, acting as a mechanical barrier that separates the body's internal processes from the external environment.[5]

Epidermis

The epidermis consists of epithelial cells and is composed of five distinct layers: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinatum.

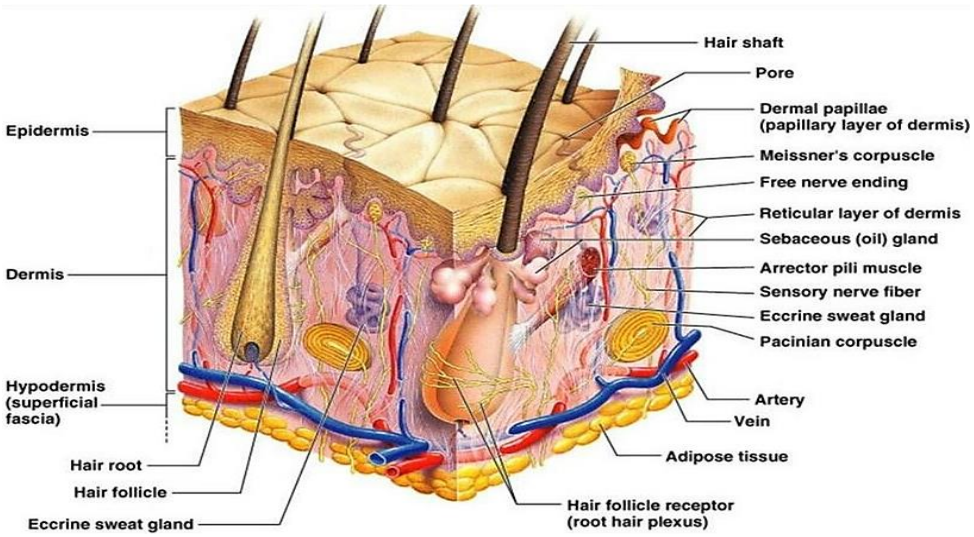
The stratum corneum, which is the outermost layer of the epidermis, has a thickness of 10-20 μm when dry and can reach up to 40 μm when wet and swollen.

The main cell types found in the epidermis include

Keratinocytes: These are the primary cells of the epidermis, accounting for about 95% of its composition.

Melanocytes: Located in the basal layers of the epidermis, these cells produce pigment.

Langerhans cells: These immune cells are found in the mid-dermis and are essential for immune response. Additionally, Merkel cells, situated in the basal layer, are involved in sensory perception.[6,7]



Structure of skin

Dermis

The dermis lies beneath the epidermis and is characterized by a high concentration of elastin fibers, which enable the skin to stretch, as well as a substantial amount of collagen that provides strength. Within the dermis, you can find nerve endings, sweat glands, oil glands, hair follicles, and blood vessels. [8] The dermis plays a crucial role in regulating body temperature. It also contains nerve endings that are responsible for sensing pressure and pain.[6]

Hypodermis

The hypodermis is the innermost layer of the skin, serving to connect the skin to the underlying tissues, including muscles and bones. While sweat glands, sebaceous glands, and hair follicles originate in the dermis, they are contained within the epidermis.

Drug Absorption from Topical Formulations

The total amount of active ingredients absorbed through topical applications can vary significantly due to several factors, including the application site, frequency of use, and the viscosity or thickness of the vehicle used. Other influences on drug absorption include the location of application, the individual's age, and the condition of the skin. An active ingredient is more likely to penetrate the dermis effectively if the skin is not keratinized.

Optimal topical formulations manage drug diffusion through the skin by ensuring that the drug is sufficiently soluble in the vehicle to allow for controlled release at the desired rate. This is achieved by ensuring that the entire drug is dissolved in water.

Gels: Represent a newer class of dosage forms created by encapsulating a significant volume of aqueous or hydro alcoholic liquid within a network of colloidal solid particles. Compared to ointments and creams, gel formulations generally offer faster drug release. Additionally, gels are often preferred for their superior patient acceptability and ease of use.[9]

Advantages of Topical Drug Delivery

- The initial rapid metabolism is bypassed.
- It is convenient and user-friendly.
- Medications can be easily discontinued when necessary.
- The delivery of medication targets a specific location with high precision.
- Gastrointestinal incompatibility is eliminated.
- Patient adherence to the treatment can be enhanced.
- It enables the use of medications that have a short biological half-life and a narrow therapeutic window.[10]

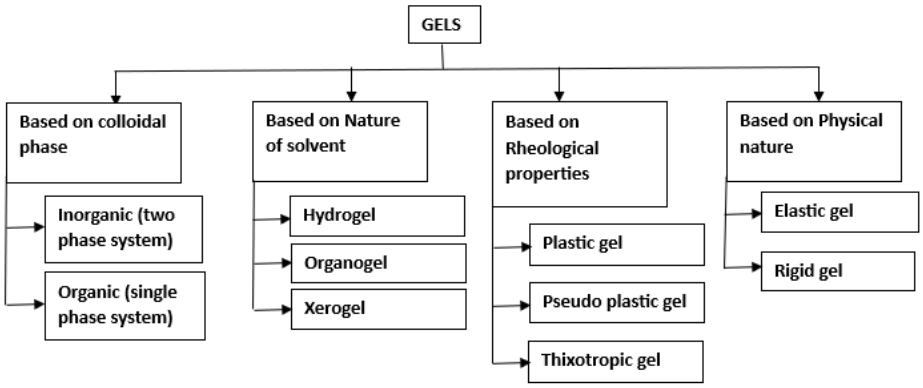
Disadvantages of Topical Drug Delivery

- Certain medications have low permeability through the skin.
- Drugs with larger particle sizes are more challenging to absorb through the skin.
- Allergic reactions can occur.

- Medications that irritate or sensitize the skin are unsuitable for this administration route.[10,11]

CLASSIFICATION OF GELS

Gels can be categorized according to various criteria, including colloidal phases, the type of solvent utilized, physical characteristics, and rheological properties, among others.



Classification of gels

Based on Colloidal Phases[12-15]

They are categorized into:

a. Inorganic (two-phase system)

b. Organic (single-phase system)

Inorganic (Two- Phase System)

If the dispersed phase partition size is very big and forms a three-dimensional structure throughout the gel, the system will consist of floccules of small particles rather than bigger molecules and the gel structure will be unstable. They must be thixotropic, meaning they form a semisolid on standing and turn liquid when agitated.

Examples are aluminium hydroxide gel and bentonite magma

Organic (Single Phase System)

These are large organic molecules that dissolve in a continuous phase along twisted strands. Most organic gels consist of single-phase solutions that include gelling agents such as carbomer and tragacanth, along with organic liquids like Plastibase.

Based on Nature of the Solvent

Hydrogels (water- based)

A hydrogel is a three-dimensional network of hydrophilic polymers formed through the chemical or physical cross-linking of individual polymer chains. This structure allows the hydrogel to swell in water and retain a significant amount of water while maintaining its integrity. Examples of hydrophilic colloids that can form hydrogels include silica, bentonite, tragacanth, pectin, and sodium alginate. Hydrogels have various applications, including sustained-release drug delivery, rectal drug administration, and ECG medical electrodes.

Organogels (With a non-aqueous solvent)

An organogel is a type of gel that consists of a liquid organic phase trapped within a three-dimensional, cross-linked network. The gelation of lecithin solutions in organic solvents occurs when a polar solvent is incorporated, leading to the formation of the organogel.

Example: Dispersion of metallic stearate in oils.

Xerogels

Xerogels are solid-formed gels that are made by slowly drying at room temperature with unconstrained shrinkage. When a xerogel is heated to a higher temperature, viscous sintering occurs, effectively transforming the porous gel into a thick glass. Example: Tragacanth ribbons, dry cellulose, and polystyrene.

Based on Physical Nature

Elastic gels

Gels made from agar, pectin, guar gum, and alginates exhibit elastic properties. At the junction points, the fibrous molecules are linked by relatively weak interactions, such as hydrogen bonds and dipole attractions. When a molecule contains a free -COOH group, it can form additional bonds between adjacent strand networks through salt bridges of the type -COO-X-COO. Examples of this include alginate and carbopol.

Rigid gels

This structure can be formed from macromolecules that are interconnected by primary valence bonds. For example, in silica gel, silicic acid molecules are linked together by Si-O-Si-O bonds, creating a polymer structure with a network of pores.

Based on their rheological properties, (follow Non-Newtonian flow characteristics)

a) **Plastic Gel**: These gels typically exhibit plastic flow. The rheogram indicates that the yield value of the gels changes above the elastic limit, affecting their flow properties.

Examples include Bingham bodies and flocculated suspensions of aluminium hydroxide.

b) **Pseudo-Plastic Gel**: These gels demonstrate pseudo-plastic flow, where the viscosity decreases as the rate of shear increases.

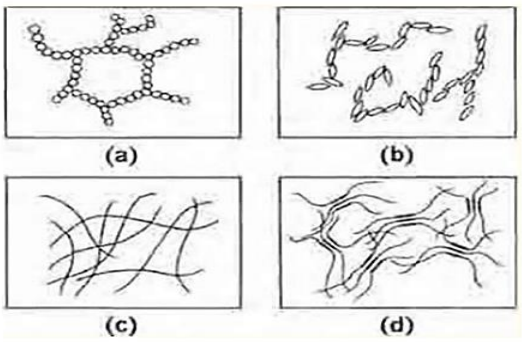
Examples include liquid dispersions of tragacanth, sodium alginate, and sodium carboxymethyl cellulose (CMC).

c) **Thixotropic Gel**: In these gels, the linkages between particles are weak and can break upon shaking. This behaviour is attributed to a reversible isothermal gel-sol-gel transformation, which occurs in colloidal systems containing non-spherical particles.

Examples include kaolin, agar, and bentonite.

Structure of gels

The interconnection of gelling agents forms networks that contribute to the rigidity of the gel.[16] If the polymeric particles are spherical or form isometric aggregates of small molecules or single macromolecules, their arrangements can be illustrated in Figure 2 (a, b). In contrast, if the macromolecules are linear, the networks formed arise from the entanglement of either relatively small molecules or multiple molecules arranged in a crystalline manner, as depicted in Figure 2 (c, d). The various forces responsible for interlinking include van der Waals forces, weak hydrogen bonds, and strong bonds. When the linkages are due to weaker forces, an increase in temperature often leads to the liquefaction of the gel.[14,17]



Crosslinking of gel structures; (a) Flocculated particles in a two-phase gel structure; (b) Network of elongated particles or rods forming gel structure; (c) Matted fibers as found in soap gels; (d) Crystalline and amorphous regions in a gel of carboxy methylcellulose.

A gel is a three-dimensional matrix created by a natural or synthetic polymer dispersed in a hydrophilic liquid or medium. The configuration of this network and the gel's properties are influenced by the presence of particles and the types of forces responsible for their linkages. The hydrophilic colloids can consist of spherical particles or isometric aggregates of small molecules or single macromolecules. The possible configurations of particles within a gel network are illustrated in Figure. In the case of linear macromolecules, the networks are formed through the entanglement of molecules, with each contact point potentially being small or comprising several molecules arranged in a crystalline structure, as shown in Figure.[18]

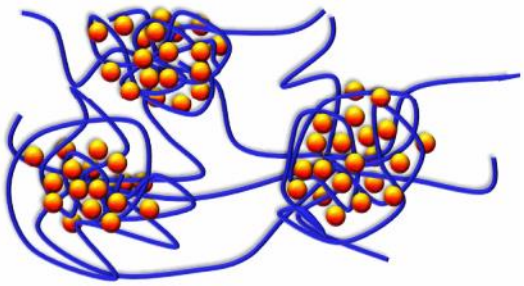


Fig. Structure of gels.

Uses of gel[19,20]

1. Gels are utilized as topical drug delivery systems for direct application to the skin, mucous membranes, or the eyes.
2. They serve as tablet granulators, protective colloids in suspensions, and thickeners in oral liquids and suppository bases.
3. Gels can be formulated for use in shampoos, dentifrices, and skin and hair care products.
4. They act as lubricants for catheters.
5. Sodium chloride gel is used in electrocardiography.
6. Phosphoric acid gel and sodium fluoride are included in dental care products.

Characteristics of gel[21-25]

1. **Structure:** The rigidity of a gel arises from the formation of networks created by the interlinking of gelling agents. The properties of the gel and the structure of the network are determined by the nature of the particles and the types of forces involved.
2. **Rheology:** The dispersion of flocculated solids and solutions of gelling agents exhibit pseudo-plastic behavior, demonstrating Non-Newtonian flow characteristics. The weak

structure of inorganic particles dispersed in water is disrupted when shear stress is applied, leading to a breakdown of inter-particulate associations and an increased tendency to flow.

3. **Syneresis:** Many gels tend to contract spontaneously and release the fluid medium, a phenomenon known as syneresis. This occurs due to the relaxation of elastic stresses that develop during gel formation. When these stresses are alleviated, the available interstitial spaces for the solvent decrease, resulting in fluid exudation. This effect is primarily observed in organogels and inorganic hydrogels but is absent in hydrogels. The degree of syneresis increases as the concentration of polymer decreases.
4. **Swelling:** When a gelling agent is placed in contact with a solvent, it absorbs a significant amount of liquid, leading to an increase in volume, which acts as an initial phase of dissolution. This process is referred to as swelling. During swelling, the solvent penetrates the gel matrix, replacing gel-gel interactions with gel-solvent interactions. However, this swelling process is limited by the degree of cross-linking, which prevents complete dissolution.
5. **Aging:** Colloidal systems generally exhibit a slow rate of aggregation, a phenomenon known as aging. This process leads to the gradual development of a denser network of the gelling agent.

Properties of gels[26-28]

- The gelling agent should be inert, non-toxic, and compatible with other ingredients.
- It must be easy to handle and apply.
- The gel should maintain its rheological properties during storage.
- It should be non-greasy while possessing emollient and thixotropic properties.
- The topical gel should not have a gummy texture.
- The incorporated gelling agent should provide a solid-like consistency during storage but should easily break down when subjected to shear forces from shaking or squeezing the container.

Formulation design[29]

The topical gel may consist of the following components:

a) Gel forming agent or polymer
b) Drug substances
c) Penetration enhancer

a) **Gel Forming Agent or Polymer**: Polymers are essential for creating the structural network required for gel preparation. Gel-forming polymers can be classified as follows:

➢ **Natural Polymers**

- **Proteins**: Examples include gelatin, collagen, and xanthan gum.
- **Polysaccharides**: Examples include agar, alginic acid, tragacanth, pectin, and guar gum.

➢ **Semi-Synthetic Polymers**

- **Cellulose Derivatives**: Examples include carboxymethyl cellulose, methylcellulose, hydroxypropyl methylcellulose, and hydroxyethyl cellulose.

➢ **Synthetic Polymers**

- **Carbomer**: Examples include Carbopol-934, Carbopol-940, Carbopol-941, poloxamer, polyacrylamide, polyvinyl alcohol, polyethylene, and its copolymers.

➢ **Inorganic Substances**: Examples include aluminum hydroxide and bentonite.

➢ **Surfactants**: Examples include sodium lauryl sulfate and cetosteryl alcohol.

b) Drug Substances

During the formulation of a topical product, drug substances play a crucial role. The key properties of drugs that affect their diffusion through gels and the skin include

➢ **Physicochemical Properties**

- The drug should have a molecular weight of less than 400 daltons.
- Highly acidic or alkaline drugs are not suitable for topical drug delivery.
- The drug should possess adequate lipophilicity.
- Ideal pH for drug candidates should range between 5 and 9.

➢ **Biological Properties**

- The drug must not irritate the skin.
- Drugs that degrade in the gastrointestinal tract are suitable for topical delivery.
- The drug should not provoke an immune reaction in the skin.

c) Penetration enhancers

Penetration enhancers, also known as accelerants or sorption promoters, are substances that facilitate the penetration of drugs into the skin. An ideal penetration enhancer should possess the following characteristics:

- It must be pharmacologically and chemically inert.

- It should be non-toxic, non-irritating, and non-allergenic.
- The enhancer should be odorless, colorless, tasteless, and cost-effective.
- It should have a rapid onset of action and a predictable duration of activity.

Formulation Consideration for Pharmaceutical Gel[30]

Choice of Vehicle or Solvent:

Water is a widely used solvent for various dosage forms. To enhance solubility for transdermal absorption, co-solvents such as alcohol, glycerin, and PEG-400 may be utilized.

Inclusion of Buffers

Buffers can be added to the gel formulation to regulate its pH. However, the solubility of buffer salts tends to decrease in hydroalcoholic vehicles. Common examples of buffers include phosphate and citrate.

Preservatives

Preservatives are incorporated into pharmaceutical gel formulations to inhibit decomposition caused by microbial growth or undesirable chemical changes. Examples of preservatives include methyl paraben, propyl paraben, and phenolic compounds.

Antioxidants

Antioxidants are utilized to enhance the chemical stability of therapeutic agents that are susceptible to oxidative degradation. Typically, water-soluble antioxidants are preferred in the formulation of pharmaceutical gels. Examples include sodium metabisulfite and sodium formaldehyde.

Sweetening Agents/Flavors

Sweetening agents and flavorings are added to gels specifically designed for use in the oral cavity, such as those intended for treating mouth ulcers, inflammation, or infections.

Application of Gels[31]

- To provide localized action, gels are applied directly to the skin, mucous membranes, or eyes.
- Gels are utilized in a variety of cosmetic products, including shampoos, fragrances, dentifrices, and skin and hair care treatments.
- Gels present significant potential as a vehicle for the topical administration of drugs.

- Gels can serve as long-acting formulations for drugs that are injected intramuscularly or implanted within the body.

Examples of gels

Sl No.	Active Ingredients	Proprietary	Gelling Agent	Route & Use
1	Acetic acid	Aci-jel	Tragacanth, acacia	Vaginal: restoration and maintenance of acidity [32]
2	Becaplermin	Regranex Gel	Na CMC	Dermatologic [33]
3	Benzoyl peroxide	Desquam-x Gel	Carbomer940	Acnevulgaris [34]
4	Clobetasol	Termovate Gel	Carbomer934	Antipruritic [35]
5	Cyanocobalamin	Nascobal	Methyl Cellulose	Nasal: Hematologic [36]
6	Desoximetasone	Topicort Gel	Carbomer940	Anti-inflammatory; antipruritic [37]
7	Metronidazole	Metro-Gel	Carbomer	Vaginal:Bacteria[38]
8	Progesterone Supplement	Crinone-Gel	Carbomer	Progesteron[39]

Preparation of gel[27,28,40]

Gels can be produced on a large scale using five different methods:

1. **Cold Method:** In this approach, all ingredients are mixed at a low temperature of approximately 5 °C to create a homogeneous mass. The polymer and penetration enhancers are combined to form solution A, while the drug is mixed with the solvent to create solution B. Solution B is then added to solution A while stirring.
2. **Dispersion Method:** Here, the polymer is fully dispersed in water for about 2 hours. Afterward, the other excipients are added gradually while stirring until a homogeneous mass is achieved.
3. **Thermal Changes:** This method involves subjecting lipophilic colloids to thermal changes, where cooling a concentrated hot solution results in gel formation. As the temperature decreases, the degree of hydration reduces, leading to gel formation. Examples include agar, sodium oleate, gelatin, cellulose derivatives, and guar gum. However, some materials like cellulose ether may lose solubility in water as temperature rises due to disrupted hydrogen bonds, making them unsuitable for gel preparation using this method.

4. **Chemical Reaction:** Gels can be formed through the chemical interaction between solute and solvent molecules. By increasing the concentration of the reactants, a gel structure can be achieved. For example:

a) Aluminum hydroxide gel is produced by the reaction between aluminum salt and sodium carbonate in an aqueous medium.

b) Silica gel is created through the chemical interaction between sodium silicate and acids in an aqueous environment.

2. **Flocculation Method:** In this method, gels are formed through precipitation caused by the addition of an appropriate amount of salt, which leads to a gel state without achieving complete precipitation. Rapid mixing helps prevent locally high concentrations of the precipitant. For instance, a solution of ethyl cellulose and polystyrene in benzene can be gelled by quickly mixing in a non-polar solvent like petroleum ether. The addition of salts to hydrophobic substances can lead to coagulation, resulting in gels that often exhibit thixotropic behavior. Conversely, when salts are added to hydrophilic substances such as gelatin, acacia, or proteins, gel formation does not occur due to the salting-out effect.

Evaluation of Gels[41-46]

Physical Examination: The prepared gels should be evaluated for their organoleptic characteristics, washability, and occlusiveness.

Determination of pH: The pH of the prepared gel will be measured using a digital pH meter. One gram of the gel will be dissolved in 100 ml of distilled water and stored at 4 °C for approximately 2 hours. The electrode will then be immersed in the diluted gel to record the readings. Measurements will be taken in triplicate, and average values will be noted.

Viscosity: The viscosity of the gels will be assessed using a viscometer. The gels will be rotated at speeds of 0.3, 0.6, and 1.5 RPM, with readings recorded at each speed. The viscosity will be determined by multiplying the dial reading by the factor provided in the Brookfield Viscometer catalog.

Extrudability Study: Gel formulations are filled into collapsible tubes after being set in the container. Extrudability is assessed by measuring the weight in grams required to extrude a 0.5 cm ribbon of gel within 10 seconds.

Homogeneity: The prepared gels are evaluated for homogeneity through visual inspection once they have set in the container. This assessment includes checking their appearance and identifying any presence of aggregates.

Drug Content: One gram of the prepared gel should be mixed with 100 ml of an appropriate solvent and then filtered. Aliquots of various concentrations will be prepared through suitable dilutions of the stock solution, and the absorbance will be measured. The equation derived from linear regression analysis of the calibration curve will be used for this assessment.

Drug content = $\frac{absorbance}{slope} \times$ dilution factor $\times \frac{1}{1000}$

Spreadability: Spreadability refers to the extent to which a gel can easily spread upon application to the skin or affected area. This property is typically evaluated using a glass slide method. The time, measured in seconds, taken for two glass slides to slip apart from the gel placed between them under a specified load is used to express spreadability. A shorter time for the separation of the slides indicates better spreadability. It can be quantified using the formula:

Spreadability S =M×L\T

Where:

- S = Spreadability
- L = Length of the glass slides
- T = Time taken to separate the slides

Grittiness: Grittiness will be assessed microscopically using a light microscope. The absence of any particulate matter indicates that the prepared gel is free from grittiness.

Consistency: The gel will be placed in a glass cup. A cone attached to a holding rod will be dropped from a height of approximately 10 cm towards the center of the glass cup. The depth of penetration by the cone will be measured from the surface of the gel to the tip of the cone that is submerged in the gel. The distance traveled by the cone will be recorded after 10 seconds.

Percentage Yield: The weight of the empty container will be measured, and then it will be filled with the gel formulation. The practical yield will be calculated by subtracting the weight of the empty container from that of the filled container. The percentage yield can be determined be the formula.

$$\%\ yield = \frac{practical\ yield}{theoritical\ yield} \times 100$$

In-vivo Study: The inhibition of carrageenan-induced rat paw edema is assessed in male Wistar albino rats using a mercury plethysmometer. The volume of the unilateral hind paw of

the experimental animals is measured before and after the administration of carrageenan, and the percentage inhibition is recorded.

Skin Irritation Test: For the skin irritation study, guinea pigs (weighing 400-500 grams; either sex) are used under standard conditions. The fur is shaved from their backs, and 5 ml of each sample is withdrawn periodically at intervals of 1, 2, 3, 4, 5, 6, 7, and 8 hours, with each sample being replaced by an equal volume of fresh dissolution medium. The samples are then analyzed for drug content using a phosphate buffer. A 4 cm area of skin is marked on both sides, with one side serving as the control and the other for testing. The gel (500 mg per guinea pig) is applied twice daily for 7 days, and the application site is observed for any sensitivity or reactions. Reactions are graded as follows: 0 (No Reaction), 1 (Minor patchy erythema), 2 (Minor but confluent or modest but patchy erythema), and 3 (Severe erythema with or without edema).

In Vitro Diffusion Studies: The diffusion studies will be conducted using a Franz diffusion cell equipped with a cellophane membrane. The donor compartment will contain a fixed amount of the formulation, which will be immersed in the receptor compartment filled with phosphate buffer (pH 7.4) maintained at 37 ± 1 °C. Samples will be periodically withdrawn from the receptor compartment at specified time intervals. After each sample withdrawal, an equal volume of fresh medium will be added to maintain the volume. The drug content in the samples will be determined spectroscopically, using phosphate buffer as a blank.

Stability: Stability studies for the prepared formulation will be conducted using freeze-thaw cycles. The product will be subjected to varying temperatures: 4 °C for 1 month, 25 °C for 1 month, and 40 °C for 1 month, as well as exposure to room temperature.

Kinetic Study: The release kinetics will be evaluated using zero-order kinetics, Higuchi's equation, and Korsmeyer-Peppas equation. Selections will be made based on the comparison of correlation coefficients and linearity to interpret the data effectively.

CONCLUSION

The increasing popularity of pharmaceutical gels can be attributed to their stability and controlled release properties, which surpass those of other semisolid dosage forms. Topical gels enhance skin absorption, thereby improving bioavailability. A significant advantage of topical delivery systems is their ability to bypass first-pass metabolism, leading to better

therapeutic outcomes. Additionally, these gels are well-accepted by patients, making them a preferred choice when other drug administration methods yield lower bioavailability. Clinical evidence confirms that topical gels are a safe and effective option for managing skin-related diseases, reinforcing their role in modern therapeutic practices.

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