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TOPICAL GELS AS ADVANCED DRUG DELIVERY SYSTEMS: FORMULATION, CHARACTERIZATION AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Topical gels are semisolid formulations characterized by a significant degree of either chemical or physical cross linking that confines a fluid phase within a three-layer matrix made of artificial or natural polymers gum. Topical gels' intermediate nature between materials that are liquid and solid makes them an excellent choice for a variety application. In recent decades, topical gels have drawn a lot of attention from individuals working in the pharmaceutical sector, research and development, instruction, and the management of drug control, and other fields. This article's goal is to discuss the basics and current developments in topical gels, including categorization and preparation techniques. Hydrogel's use in drug delivery systems is covered separately. Particular attention is paid to its categorization, preparation process, and assessment criteria.

KEYWORDS: Topical gels, Hydrogel, Drug delivery system, Semisolid formulation.

INTRODUCTION

As efficient substitutes for traditional drug administration systems, topical and transdermal (TT) drug delivery channels have drawn a lot of interest. Avoiding hepatic first-pass metabolism, extended and regulated drug release, less systemic side effects, and increased patient compliance are only a few benefits of these methods.[1] Topical medication products, such as sunscreens, keratolytic agents, local anesthetics, antiseptics, and anti-inflammatory preparations, are primarily meant for external application and are intended to generate localized therapeutic effects on any or all skin layers.[2]

1.1 Topical Formulations' Drug Absorption:

Numerous physiological and formulation-related variables affect the extent to which topical formulations of medicine are absorbed, which varies greatly. The size of the application area, the frequency and technique of use, as well as the physicochemical characteristics of the formulation, such as the vehicle's thickness and viscosity, are important factors.[3]

Drug penetration is also greatly influenced by other parameters, including age, skin condition, and the anatomical place of administration. For example, due to lower barrier resistance, non-keratinized or moist skin areas are more permeable than keratinized skin.[3]

By keeping the medication in a sufficiently soluble condition inside the vehicle, an ideal topical formulation ensures regulated medication absorption via the skin. Sufficient solubility promotes effective medication release and subsequent epidermal layer penetration. To increase its thermodynamic activity and improve diffusion, the medication should ideally be present in a dissolved form.[3]

Additionally, the formulation vehicle should be able to increase the stratum corneum's permeability, which is the main obstacle to medication absorption. The addition of appropriate excipients and penetration enhancers can accomplish this.

When creating topical formulations, a number of crucial elements must be taken into account to guarantee patient acceptance, stability, and efficacy:

1. The medicinal ingredient's stability
2. Excipient and adjuvant stability
3. Aesthetic appeal and visual appearance
4. Features of color and smell
5. Rheological characteristics (spreadability, extrudability, and viscosity)
6. Water and other volatile component loss
7. Dispersed phase particle size distribution
8. pH of the mixture
9. Application-related texture and feel (such as tackiness, greasiness, and smoothness)
10. microbial contamination
11. release/bioavailability

Even while a tiny portion of the medication from topical formulations could enter the bloodstream, it usually stays at subtherapeutic levels and has no appreciable systemic effects. But in certain groups, such those who are pregnant or nursing, even a little amount of systemic exposure may be clinically significant, therefore care may be needed.[2]

1.1.1 Vehicles on the Top

The performance and therapeutic effectiveness of dermatological formulations are significantly influenced by topical vehicles. These vehicles often operate as carriers that hold the active pharmaceutical ingredient at the application site, allowing drug release and subsequent absorption, rather than penetrating the skin very deeply.[4]

Because it directly affects drug availability, penetration, and overall bioactivity, choosing the right vehicle is essential. One of the main factors affecting the vehicle selection is the drug's thermodynamic activity in the formulation. The driving power for drug diffusion from the vehicle into the epidermal layers is determined by this parameter.[4]

Another important factor is the vehicle's pH, particularly for drugs with weak bases or acids. The release and penetration properties of feebly uncomplicated medications are affected by their increased activity in alkaline settings, conversely, weakly acidic medications work better in acidic environments.[4]

The drug's solubility in the medium has a major impact on diffusion rates as well. Because the thermodynamic driving force for diffusion may be diminished by high solubility, moderately soluble drugs often show greater release rates than highly soluble drugs.

It is also necessary to take into account the possibility of complex formation between the medicine and vehicle components. These interactions have the potential to lower the drug's activity coefficient, which will eventually restrict its availability for penetration and therapeutic efficacy.[4]

1.1.2 Topical Drug Product Design:

Topical dermatological formulations come in a variety of physical forms, ranging from liquids to solid powders. However, because of their convenience of administration, improved patient compliance, and capacity to produce localized therapeutic effects, semisolid dosage forms are the most popular.[5]

Based on their physical consistency, topical formulations can be roughly categorized as liquids, solids, or semisolids:

Topical Liquids

These consist of tinctures (like iodine tincture), aqueous solutions, hydroalcoholic solutions, and organic solvent-based preparations like collodions (like salicylic acid collodion). When situations call for a rapid beginning of action or coverage over a vast surface area, liquid formulations are typically employed for speedy application.[5]

Solid Powders

Powders, both medicated and non-medicated, are used topically to offer antibacterial, absorbent, and protecting properties. Because they assist absorb skin secretions and lessen friction, they are especially helpful in situations when there is an excessive amount of moisture.[5]

Preparations for Semisolid

The most often used topical systems are semisolid dosage forms, which include ointments, creams, and gels:

Ointments

The main ingredients of ointments, which are viscous, transparent concoctions, are oleaginous bases such vegetable oils or hydrocarbons like petrolatum and beeswax. They are appropriate for dry and scaly skin disorders because to their superior occlusive and emollient properties.[5]

Creams

Creams are emulsion-based systems made up of phases of water and oil. While water-in-oil (w/o) creams are more occlusive and hydrating, oil-in-water (o/w) creams are non-greasy and simple to wash. Hydrous lanolin and

cold cream are two examples. Drug release and skin hydration characteristics are greatly influenced by the kind of emulsion used.[5]

Gels

Large volumes of aqueous or hydroalcoholic liquid are trapped inside a three-dimensional network of colloidal particles to create gels, which are comparatively more recent semisolid systems. Compared to ointments and creams, they have a number of benefits, including quicker medication release, non-greasy texture, simplicity of administration, and better patient acceptance.[5]

1.1.3 Justification for Gels as opposed to Transdermal Patches

Transdermal medication delivery devices have been widely used by the pharmaceutical sector, especially patches, because of their capacity to give regulated and prolonged drug release. Nevertheless, despite their benefits, a number of drawbacks have raised interest in topical gel formulations as substitute delivery methods.[6]

The fact that transdermal patches are intended to administer the whole dosage across a very limited surface area of the skin is one of their main drawbacks. especially in people who are susceptible to occlusive materials or adhesives., this targeted distribution of high medication concentrations may cause skin discomfort. In individuals who are older or have reduced skin integrity, these effects may be more noticeable.[6]

Furthermore, Patches must adhere to the skin for an extended period of time, frequently hours or days. This might lead to poor patient compliance, particularly in elderly or mentally ill patients who might inadvertently remove the patch.

Additionally, the adhesive components themselves may result in skin damage, hypersensitivity responses, or pain.[6]

Transdermal patches' reliance on a concentration gradient to promote medication diffusion is another significant drawback. Drug distribution may become erratic when the gradient diminishes over time, and a sizable amount of the medication may stay in the patch unused. In addition to decreasing treatment efficacy, this poses questions about safe disposal, especially for strong or restricted drugs.[6]

Topical gels, on the other hand, provide a number of benefits, such as simpler administration, increased patient acceptance, a lower chance of irritation, and more affordable production. By offering consistent medication distribution across a greater surface area and reducing problems with adhesion and drug waste, absorption-enhanced gel formulations can get around many of the drawbacks of patches.[6]

1.1.4 Topical vs. Transdermal Drug Administration

The design goals and therapeutic results of Transdermal and topical medication delivery methods are considerably different. The main objective of transdermal administration is to minimize medication retention and metabolism inside the epidermal layers while maximizing drug flow over the skin to achieve systemic circulation.[7] In order to sustain therapeutic plasma concentrations, this method of treating systemic diseases need effective percutaneous absorption.

Topical medication distribution seeks to limit the pharmacological activity to the skin or underlying tissues, however. As a result, the formulation is made to minimize systemic absorption and optimize medication retention at the application site.[7] This approach is very effective for treating localized symptoms of systemic disorders and dermatological issues.

Despite these variations, the medicine must pass through the stratum corneum, the skin's outermost layer, in order for both delivery methods to work. In contrast to topical systems, where medication activity is mostly limited to superficial or intra-cutaneous layers, transdermal systems need deeper penetration into systemic circulation.[7]

1.2 Gels used topically

The term "gel" was first employed in the late 19th century to describe semisolid systems based on their physical characteristics rather than their molecular composition. Gels are characterized as semisolid systems where a liquid phase is confined in a three-dimensional polymeric network made of highly cross-linked natural or synthesized polymers.[8]

Synthetic polymers like carbomers, which have a clear, aesthetically pleasing look and are readily removed from the skin, are frequently used in the formulation of topical gels. Drug release and therapeutic efficacy are significantly influenced by the base selection. On the surface of the skin, non-volatile hydrocarbon bases can form an occlusive barrier, reducing moisture loss and improving skin hydration, bases with oleaginous components offer emollient qualities.[9]

Increased drug penetration is made possible by the stratum corneum's expansion and loosening of the intercellular lipid matrix. Furthermore, moisture facilitates the drug's disintegration and presents it in a molecularly distributed state, which is necessary for efficient epidermal barrier penetration.[9]

Gels are regarded as semi-rigid systems where a three-dimensional network of linked polymer chains or solvated macromolecules limits the dispersion medium's mobility. Viscoelastic qualities, such is the ability to withstand deformation to regain shape upon stress reduction, are imparted to gels by this structural structure.[10]

The interactions between polymers and solvents determine the integrity and functionality of gel systems. Three types of solvent states inside the gel matrix are described by classical gel theory:
(i) free solvent, which is very mobile; (ii) bound solvent, which is bonded to polymer chains by hydrogen bonds; and (iii) entrapped solvent, It is part of the network architecture.[11]

Polymer attentiveness in addition to solvent affinity affect the relative fraction of various solvent types, which in turn controls the creation of cross-links, entanglement, and polymer chain growth.

Drug release and penetration characteristics are largely determined by the physicochemical features of gels, such as their structural organization, hydration behavior, and polymer interactions. enhanced percutaneous medication absorption is largely attributed to enhanced hydration and better polymer networks.[11,12]

1.2.1 Topical Gel Classification

The kind of colloidal phase, solvent system, and gel microstructure may all be used to systematically categorize topical gels. This categorization aids in comprehending their drug release characteristics, formulation features, and physicochemical behavior.[12–16]

A. Considering the Colloidal Phase's Nature

Depending on the kind of dispersed phase, topical gels can be classified as either organic or inorganic:

Inorganic Hydrogels

Usually, they are biphasic systems made up of inorganic particles scattered over an aqueous media. Bentonite magma and aluminum hydroxide gel are typical examples. Because of its swelling and gel-forming qualities, In concentrations ranging from 10% to 25%, bentonite magma is too commonly utilized as an ointment base.[12–16]

Organic Gels

Generally speaking, Organic gels are single-phase systems composed of organic polymers, either natural or manufactured. like tragacanth and carbomers. As demonstrated by formulations like Plastibase, which offer the desired consistency and durability, these gels may also incorporate organic liquids.[12–16]

B. In accordance with the Solvent System

Hydrogels and organogels are two general categories of gels based on the dispersion medium:

Hydrogels

Water serves as the main solvent in hydrogels, which consist of hydrophilic polymers that dissolve or disperse in water. Inorganic substances like bentonite and silica, as well as man-made and organic polymers such pectin, sodium alginate, methylcellulose, and sodium carboxymethyl cellulose (CMC). These substances create semisolid systems with superior hydration and biocompatibility at greater concentrations.[12–16]

Organogels

Hydrocarbons, vegetable oils, or fatty bases are examples of non-aqueous solvents that make up the liquid phase of organogels. Among these are blends like Plastibase, which blends high mass hydrocarbons with mineral oil. When it comes to administering lipophilic medications and offering improved stability in non-aqueous conditions, organogels are very helpful.[12–16]

C. Gel Microstructure-Based

Gels can also be classified according to their internal network structure, using Flory's classification:

Covalently Bonded Gels

These gels are made up of networks of polymers that are permanently cross-linked by covalent connections. Usually made using artificial hydrophilic polymers, these systems are irreversible. Nonlinear copolymerization utilizing multifunctional monomers creates the gel network, which has a highly disordered yet stable three-dimensional structure. These gels have limited reversibility and good mechanical strength because of their strong cross-linking.[12–16]

Table 1: Applications of Hydrogels.

Pharmaceutical gels applications	Advantageous characteristics
Dental	Extremely thixotropic, water soluble, orally digested, adheres to the enamel surface, and the ideal viscosity for filling fissures
Dermatological	Thixotropic, spreadable, greaseless, readily removable, emollient, demulcent, non-staining, and compatible with a variety of excipients (miscible or water soluble)
Nasal	Permeable to water, odorless, non-irritating, and tenacious

Ophthalmic	Optically transparent, sanitary mucomimetic lubrication or non-sterile, water-soluble or miscible.
Surgical & medical	lubricating, sticking to the surface of the instrument, and making the most contact with mucous
Vaginal	It is greaseless, lubricating, slow to dissolve, adherent, acid stable, and does not melt at body temperature.

Classification Continued: Gel Microstructure

Gels that are physically bonded

Reversible systems known as Non-covalent interactions like hydrogen bonds and van der Waals forces produce physically linked gel networks, and ionic interactions. Temperature, pH, and ionic strength are examples of outside factors that may have an impact the sol–gel transitions seen in these systems.

These gels are often made from semi-synthetic polymers and natural polymers. In the sol state, Random coils make up polymer chains; during gelation, they undergo conformational changes to produce organized structures like single, double, or triple helices. Such gels are suitable for controlled drug delivery applications because of their reversible nature, which enables them to react dynamically to environmental circumstances.[12–16]

Structures of Well-Ordered Gel

Usually, inorganic elements like silica, alumina, and clay minerals create well-ordered gel systems. These substances may create stiff gel structures called lyogels under the right circumstances.

When hydrated, clays of the smectite group (such as bentonite and hectorite) experience interlayer and osmotic swelling, which results in gel formation. Electrostatic repulsive forces and electrical double-layer interactions solidify the arrangement of the plate-like particles into a three-dimensional "card-house" structure. The gel system is made hard and stable by its well-organized structure.[12–16]

1.2.2 Substances that Form Gel

Because they offer the structural framework necessary for gel formation and stability, polymers are crucial ingredients in gel formulation. The following categories apply to gel-forming agents.[17]

1. Natural Polymers

Proteins: gelatin and collagen

Polysaccharides: gellan gum, guar gum, xanthan gum, tragacanth, pectin, carrageenan, alginic acid, and agar

2. Semisynthetic Polymers

Carboxymethyl cellulose (CMC), methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxyethyl cellulose are cellulose derivatives.

3. Synthetic Polymers

Poloxamers, polyacrylamide, polyvinyl alcohol, polyethylene, carbomers (Carbopol 940, 934, 941), and their copolymers.

4. Inorganic Materials

Bentonite and aluminum hydroxide

5. Surfactants

Brij-96, cetostearyl alcohol

1.2.3 Topical Gel Benefits

Topical gel formulations have grown in significance due to several benefits:

1. Preventing drug-food interactions and gastrointestinal deterioration
2. Hepatic first-pass metabolism elimination
3. Better patient compliance through non-invasive delivery
4. Easy to remove from the skin and non-greasy
5. Economical manufacturing and formulation
6. Lower dosage requirements in comparison to oral dosing types
7. Drug activity that is localized and has little systemic adverse effects[15]

1.2.4 Topical Gel Drawbacks

Topical gels have various drawbacks despite their benefits:

1. Restricted use to medications with appropriate physicochemical characteristics
2. Limited permeability as a result of the skin's barrier function
3. Drug absorption variation brought on by physiological variables including age and skin condition[15]

1.2.5 Desired Gels' Properties

The following qualities should be present in the perfect topical gel:

1. Excipient compatibility, non-toxicity, and biocompatibility
2. Stability both chemically and physically while being stored
3. No microbiological contamination
4. Suitable rheological characteristics (thixotropy, viscosity)
5. Cost-effective and simple to produce
6. Easily clean and non-staining
7. No disruption of medication action
8. Patient acceptance and ease of use
9. Desired sensory qualities include smooth texture and non-greasiness

1.2.6 Desired Gelling Agent Properties

1. Compatible with formulation ingredients, non-toxic, and inert
2. The capacity to gel at low concentrations
3. Effective gel-forming capacity
4. Affordable and easily accessible
5. Devoid of microbiological contamination

1.3 Topical Permeation Principles

The stratum corneum, which serves as the main barrier to drug absorption, must be penetrated for a topically administered medication to have a therapeutic impact. Passive diffusion is the primary method of percutaneous being absorbed, which is possible by transfollicular or transepidermal channels.[18]

Drug molecules may first diffuse through appendages like sweat glands and hair follicles (shunt route). Diffusion over the intact stratum corneum, however, takes over as the primary penetration pathway under steady-state circumstances.[18]

The process of drug transfer via the skin involves several steps, including:

1. Drug release from the mixture
2. Dividing into the corneum stratum
3. The rate-limiting stage of diffusion via the lipid-rich intercellular matrix
4. Dividing into the living epidermis
5. Systemic absorption after diffusion into dermal layers

1.3.1 Topical Permeation Kinetics

Designing topical formulations that work requires an understanding of penetration kinetics. The following procedures are involved in drug permeation:

a. Infiltration of the stratum corneum
b. The viable epidermis's diffusion
c. Intake into the network of cutaneous capillaries

Both drug qualities and formulation parameters affect the pace and degree of permeation, which in turn affects therapeutic effectiveness.[18–20]

Topical Drug Delivery Permeation Kinetics

Only when a medication has the right physicochemical characteristics—such as the right molecular size, lipophilicity, and solubility—can percutaneous drug penetration take place. Fick's law of diffusion, which governs The speed at which drugs enter the body through the skin, may be represented as follows[18–20]:

Equation 1 states that dQ/dt = Ps (Cd – Cr).

Where

Cd is the amount of medication in the stratum corneum's donor compartment.

Cr stands for drug meditation in the systemic circulation's receptor compartment. Ps is the skin's permeability coefficient.

An further definition of the permeability coefficient (Ps) is:

$$Ps = (Ks \times Dss) / hs. \quad \text{(Eq. 2)}$$

Where

Dss is the drug's diffusion coefficient through the skin at steady state, hs is the thickness of the skin barrier, and Ks is the drug's partition coefficient between the formulation and the skin.

For a particular medication and system, The coefficient of permeability (Ps) may be regarded as constant since Ks, Dss, and hs stay mostly constant under constant physiological circumstances.

A steady-state flux, or constant rate of drug penetration, is reached when the drug concentration in the donor compartment is much higher than that in the receptor compartment (Cd >> Cr).. Under such conditions, Eq. 1 simplifies to:

Equation 3 states that dQ/dt = Ps × Cs.

This implies a direct relationship between the frequency of drug penetration and the drug quantity at the skin's surface. The permeability coefficient may also be seen as the reciprocal of the diffusional resistance of the skin barrier Ps = 1/Resistance

1.3.2 Physiological Elements Influencing Percutaneous Absorption:

Drug penetration is greatly influenced by physiological aspects of the skin. Among them are:

- Skin integrity (intact or damaged skin)
- Hydration level
- The temperature of the skin
- Anatomical location of use
- The patient's age
- The existence of pathogenic disorders or skin illnesses

1.3.3 Factors Associated with Drugs

The drug's physicochemical characteristics are a major factor in how well it penetrates the skin:

- Molecular size (ideally less than 500 Da)
- Polarity and chemical nature
- Lipophilicity, or partition coefficient
- Attachment affinity to skin constituents
- The skin's metabolic stability
- The drug's thermodynamic action

1.3.4 Elements of Formulation

Drug release and penetration are significantly influenced by formulation characteristics:

- Dosage form type
- The concentration of drugs
- The formulation's pH
- The drug's solubility in the vehicle
- The existence of surfactants
- The use of penetration enhancers
- The formulation's occlusivity

1.3.5 Fundamental Elements of Topical Gels

Lone of the main components of relevant gel formulations is polymers.

Polymer

Polymers are the primary structural components that provide origin to the three-dimensional gel network. They regulate the formulation's viscosity, consistency, and drug release profile. The physicochemical characteristics of the drug and the polymer, such as molecular weight, cross-linking density, and polymer–drug interactions, influence the process of drug release from gels.[20,21]

Table 2: Beneficial Biomaterials for Dermal Gel.

Natural polymers	Semi synthetic polymers	Synthetic polymers
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. Xanthan ix. Gellum Gum	**a. Cellulose derivatives** i. Carboxymethyl cellulose ii. Methylcellulose iii. Hydroxypropyl cellulose iv. Hydroxypropyl methylcellulose v. Hydroxyethyl cellulose v. Pectin vi. Guar Gum vii. Cassia tora viii. Xanthan ix. Gellum Gum	**a. Carbomer** i. Carbopol-940 ii. Carbopol-934 iii. Carbopol-941 **b. Poloxamer** i. Carbopol-940 ii. Carbopol-934 iii. Carbopol-941 **c. Polyacrylamide** **d. Polyvinylalcohol** **e. Polyethylene and its co-polymers**

Criteria for Selecting Polymers for Topical Gels

The ideal polymer for topical gel formulation must satisfy many essential criteria in order to ensure effective drug delivery and formulation stability:

1. The polymer needs to have the right molecular weight and glass transition temperature in order to facilitate efficient drug diffusion and release, and chemical activity. Additionally, it should make it possible to incorporate an adequate amount of medication.
2. It must not negatively interact with the medication and must be chemically and physically compatible.
3. The polymer should be inexpensive, simple to create, and straightforward to process.
4. It must not degrade while medicine is present, excipients, excessive humidity, or physiological temperature while being stored.
5. The polymer and the byproducts of its breakdown must be biocompatible and non-toxic.[17]

Excipients are frequently used in formulation techniques to alter characteristics since no single polymer satisfies all of these needs. To increase medication solubility and boost formulation efficacy, cosolvents such ethanol, propylene glycol, and polyethylene glycol (PEG 400) are frequently used.

Several methods may be utilized to change the characteristics of polymers:

Cross-linked Polymers

A more compact polymer network is produced by increased cross-linking density, which slows the release rate and decreases drug diffusion.

Blends of polymers

Drug loading, hydration behavior, breakdown rate, and mechanical strength may all be optimized by blending various polymers in certain ratios, improving formulation performance overall.

Selection of Drug Substances

Selecting the right drug is essential to the development of topical formulations. To guarantee efficient penetration and therapeutic activity, the medication must have particular

Physicochemical and biological properties

Physicochemical Characteristics

- A molecular weight of fewer than 500 Daltons is ideal.
- Sufficient lipophilicity to partition into the stratum corneum
- Appropriate pH range (usually 5–9)
- Highly acidic or alkaline medications are often inappropriate for topical administration.

Biological Characteristics

- The skin is not irritated or sensitized.
- Avoid causing allergic or immunological responses.
- Appropriate for medications that undergo first-pass metabolism or are broken down in the digestive system
- Long-term usage shouldn't cause tolerance.
- Appropriate for medications with negative systemic effects or long-term treatment[17]

Enhancers of Penetration

The penetration accelerators are substances that temporarily alter the stratum corneum's barrier characteristics to facilitate medication penetration through the skin. They are essential for reaching therapeutic drug concentrations, especially in topical and transdermal systems.[18]

In order to lower diffusional resistance and improve medication flow, these compounds interact either directly with the skin or with the formulation.

Qualities of the Perfect Penetration Enhancers

1. Take specified, reversible action for a predetermined amount of time.
2. Inert pharmacologically
3. Non-allergic, non-irritating, and non-toxic
4. Offer regulated and reversible improvement
5. Do not result in the loss of vital biomolecules or bodily fluids
6. Harmonious with medications and excipients

7. After removal, permit a quick return to normal skin barrier function.
8. Colorless, odorless, and aesthetically pleasing

The mechanism of action is

Drug penetration is increased by penetration enhancers via a numeral of mechanisms:

- The arrangement of their stratum corneum is disrupted
- Denaturation of proteins and swelling of keratin
- Intercellular lipid fluidization and disarray
- Enhanced drug partitioning and solubility in the skin

While lipophilic enhancers work by removing epidermal lipids and boosting medication partitioning into the skin, hydrophilic enhancers promote penetration by improving solvent characteristics and promoting drug transport.

By lowering surface tension, enhancing wetting, and promoting medication dispersion, surfactants further improve penetration. When compared to less hydrophilic compounds, hydrophilic surfactants often interact with keratin more strongly, enhancing permeability.

Penetration enhancers are categorized as follows:

- Water
- Sulfoxides, such as dimethyl sulfoxide
- Pyrrolidones
- Alcohols and fatty acids
- Azone and its byproducts
- Anionic, cationic, and non-ionic surfactants
- Urea and its byproducts
- Glycols and alcohols
- Terpenes and essential oils
- Mixtures that work well together[18]

FORMULATION AND EVALUATION

Method of Preparation of Topical Gels

Depending on the kind of medicine, polymer, and excipients, topical gels can be made in a number of ways. The often used techniques consist of:

1. The fusion technique
2. The cold approach
3. The technique of dispersion

Semisolid dosage forms are generally produced using moreover fusion or inclusion methods. *The fusion method* produces the final result by heating all ingredients until they melt, mixing them evenly, and then chilling the mixture. Thermostable medications and excipients can be used using this technique.

The medication is integrated into a prepared semisolid basis using the *cold technique* (cold incorporation) without the application of heat. For medications that are heat-labile or sensitive to temperature, such plastibase, this technique is very helpful.

In gel formulation, the *dispersion method* is frequently employed, in which the polymer is dispersed in an appropriate solvent, then hydrated and swelled to create a gel matrix.

The gelling agent employed determines the preparation method. For instance, tragacanth must be treated at a low temperature since it is sensitive to heat, but methylcellulose is better disseminated in hot water and then cooled. Gels based on carbopol must be dispersed in an acidic solution and then neutralized with an amine like triethanolamine or an alkaline agent like sodium hydroxide. Ionization of functional groups brought on by neutralization causes polymer expansion and the creation of a three-dimensional gel network.

Assessment of Topical Gels

To guarantee quality, stability, and effectiveness, the manufactured gel compositions are assessed using a variety of physicochemical and performance metrics:

1. Uniformity

After preparation, gels are examined visually for consistency, appearance, and aggregate absence.

2. Grittiness

To verify smooth texture and topical application appropriateness, formulations are microscopically inspected for the presence of particle matter.

3. Extrudability

The force required to protrude gel from collapsible tubes is tested to determine extrudability. The weight (in milligrams) required to emerge a specific length of gel (e.g., 0.5 cm of ribbon in 10 seconds) indicates its ease of application).[22,23]

4. Skin Irritation Research

Animal models, such as albino mice, are hand-me-down to assess skin irritation. To evaluate safety, the formulation is smeared to shaved skin, and over a certain amount of time, erythema and edema are monitored.

5. Measuring pH

A digital pH meter is used to measure the pH of gel compositions. To guarantee precision, measurements are usually made in triplicate after dissolving 1 g of gel in 100 mL of distilled water.[24]

6. Drug Content

To guarantee that the active ingredient is distributed uniformly throughout the formulation, spectrophotometric analysis is used to assess the drug content.

7. Viscosity

A Brookfield viscometer is used to test viscosity at various rotating rates, such as 20 and 30 rpm. This parameter represents the gel's consistency and flow characteristics.[25–27]

8. Spreadability

Spreadability, which directly affects therapeutic efficacy, is a measure of how easily the gel distributes across the skin's surface. The formula below is used to compute it.

$$S = (M \times L) / T$$

where

M is the weight attached to the higher slide. L = glass slide's length.

T is How long does it take to separate the slides.

Better spreadability is indicated by lower time values.[28, 29]

9. Diffusion Studies in Vitro

Diffusion cells like the Keshary–Chien diffusion cell with an appropriate membrane (such as cellophane membrane) are employed to evaluate drug release in vitro. The receptor compartment is filled with phosphate buffer and maintained at 37 ± 0.5°C. Samples are taken out at scheduled intervals to determine the medication release profile and subjected to spectrophotometric analysis. To guarantee repeatability, the investigation is usually conducted in triplicate.[30–32]

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