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Review Article

Formulation and Evaluation of Topical Gel: Comprehensive Review

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ABSTRACT

Topical drug delivery refers to the transfer of a substance to the skin for the aim of treating or curing skin problems. Gels, creams and ointments are the most often used semisolid formulations for the delivery of topical drugs. In recent years, gels have been popular in cosmetics and topical medicinal treatments because of their favorable features such as being greaseless, easily spreadable and fast removable. Gel compositions have more application characteristics and stability in comparison with creams and ointments. A gel is a cross-linked polymer network, that swells in a liquid media. Gels are homogeneous, viscous, jelly-like compositions containing one or more solutions or dispersions of medicines in suitable hydrophilic or hydrophobic bases. Clinical studies suggest that topical gels are the most safe and effective therapy alternative for skin related disorders and are used topically to reduce the associated unwanted effects as compared with other traditional dosing forms. The purpose of this article is to describe the ideas and latest improvements of topical gels such as classification, production procedures, characteristics, evaluation parameters and applications.

INTRODUCTION

Topical delivery means applying a drug-containing formulation to the skin for treating skin diseases (such as acne) or skin signs of a systemic disease (such as psoriasis). The skin is one of the most accessible routes for drug administration and topical drug delivery methods are among the most used. From simple solutions and ointments to multiphase nanotechnology-based products are available as topical medical medicines. The gel is a semisolid preparation of small and large molecules dispersed in liquid aqueous carriers. Gels are semi-solid systems in which the colloidal particles interact (physical or covalent) in a liquid carrier. Topical/transdermal (TT) drug delivery is associated with many advantages such as high patient compliance, continuous drug delivery, less side effects and bypassing the hepatic first pass effect compared to other drug delivery routes. In topical drug delivery systems, percutaneous absorption is an important consideration to achieve

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and maintain consistent, systemic, therapeutic levels throughout the duration of use [1].

The topical/transdermal (TT) route of drug administration has many advantages over other routes, which include the avoidance of hepatic first pass effect, continuous drug delivery, fewer side effects and improved patient compliance [2]. Topical drug products are for topical use only. They are intended for local action on one or more layers of the skin (e.g. Sun screens, keratolytic agents, local anesthetics, antiseptic and anti-inflammatory). Although some of the medication from these topical products may inadvertently reach systemic circulation, it is generally at subtherapeutic concentrations and does not exert effects of any major concern except possibly in special situations, such as pregnant or nursing patient [3].

Research has made possible the treatment, prevention and eradication of many of these diseases that plague man. The treatment of diseases through biomolecules such as drugs, proteins etc. Has come a long way in the last few decades. These carriers enable the release of drugs at previously inaccessible sites. In the intervening years these carriers have been made from ceramics, natural and artificial materials. Three dimensional matrices were used as carrier materials considering the integrity, biocompatibility and durability. Gels is a term used to describe a class of materials. These 3D polymer matrices can soak up large quantities of water and biological fluids. This property has led to a wide range of applications for gels such as food additives, pharmaceuticals and medicinal applications [4].

Drug Absorption from Topical Formulations

The total amount of active ingredient absorbed with topical treatments varies greatly and is dependent on several parameters, such as the size of the application region, the frequency and vigor of the application, and the viscosity or thickness of the vehicle employed. Age, skin condition, and the application site are other factors that impact drug absorption. Non-keratinized dermis will be more easily penetrated by the active substance. By making the medication just sufficiently soluble in the medium to promote drug release at the intended pace, the ideal topical formulations regulate drug diffusion through the skin. To achieve this, make sure the medication is fully dissolved. [5]

Additionally, the vehicle's parts should encourage stratum corneum penetration.

When creating topical treatments, the following factors are crucial:

1. Stability of the active ingredient
2. Stability of the adjuvant
3. Visual appearance
4. Viscosity, extrudability, spreadability
5. Loss of water and other volatile vehicle components
6. Particle size distribution of dispersed phase
7. Ph
8. Texture, feel upon application (stiffness, grittiness, greasiness, tackiness)
9. Microbial contamination
10. Release/bioavailability

Topical vehicles

In order to facilitate drug absorption, topical carriers typically merely retain the active substance on the skin rather than penetrating it. Care should be used while selecting a vehicle because it may have an impact on how well the medication is absorbed through the skin. The drug's activity in the vehicle is the most crucial factor to take into account when selecting a topical delivery method. For example, if the medicine is a weak acid or weak base, the vehicle's ph may be significant since weak basic drugs are more active in basic vehicles and weak acidic drugs are more active in acidic vehicles. The drug's solubility in the vehicle must also be taken into account. A drug will diffuse out of a less soluble vehicle more quickly than a highly soluble one. The potential for complexes to develop between the active substance and the vehicle is another important issue. Complexing may reduce the drug's diffusion by lowering the activity coefficient [6].

Design of Topical Drug Products

The most widely used dermatological products are semi-solid preparations, while they come in a variety of formulations and consistencies, from liquid to solid powder.

a) ***Topical liquids:*** Aqueous solutions, hydroalcoholic solutions, tinctures (like iodine tincture), organic solvent-based collodions (like salicylic acid collodion), etc. Are examples of topical liquids.

b) ***Solid powders:*** Both medicated and non-medicated powders are typically applied to the skin to absorb skin secretions or to prevent sepsis.

Semisolid preparations include

a) **Ointments:** Transparent materials are employed in the ointment form. Traditionally, oleaginous bases have been used for ointments. They contain vegetable oils or hydrocarbons (beeswax, petrolatum).

b) **Creams**: Compared to ointments, creams are easier to apply to the skin since they are emulsions of oleaginous substances and water. Oil-in-water (o/w) creams, as opposed to water-in-oil (w/o) creams, are water-washable. Hydrous lanolin and cold cream lack emulsions. They have a restricted capacity to absorb water. Water can be absorbed by the bases of o/w emulsions like Dermabase® and Unibase®, but as water is absorbed into the continuous phase of the emulsion, the consistency starts to thin.

c) **Gels:** Gels are a relatively recent class of dosage forms made by trapping a significant volume of hydroalcoholic or aqueous liquid in a network of colloidal solid particles. Compared to ointments and lotions, the gel formulation releases the medication more quickly. They are better in terms of patient acceptability and use [7].

The Rationale for Gels Versus Patches

When it comes to delivering medications through the skin, the pharmaceutical industry has overwhelmingly favored transdermal patches over gels. However, patch designs need that the full medication be administered through a very tiny skin area. Many people, especially those who are sensitive to adhesives, may find it extremely irritating to have such concentrated amounts of medication applied over a few square centimeters of skin. Sensitive and aging skin may be traumatized by this. When administering medication to elderly patients with changed mental states, patches also present a challenge. The majority of patches that must remain in place for hours or days are frequently torn off by patients

with mental illnesses. The majority of patches use a medication concentration gradient in the matrix or reservoir to push the active ingredient through the skin. Because of this, when delivery is halted or slowed, a large portion of the dose may be retained. In an institutional context, disposing of such patches can be a serious issue, particularly if the medicine that is not administered is a narcotic. Lastly, compared to gels, patches are more costly and need more procedures to develop. Thus, the resolution of numerous patch-related issues in absorption-enhanced gels [8].

Transdermal versus Topical

Transdermal product design aims to reduce drug retention and metabolism in the skin while maximizing the drug's flux through the skin into the systemic circulation. The formulation of topical medications, on the other hand, is intended to increase the drug's retention in the skin while decreasing its flow over the surface. However, the stratum corneum, the skin's outermost layer, must be penetrated by both topical and transdermal therapies. Applying a medication to treat a systemic illness is known as transdermal delivery. It is geared toward the attainment of systemically active doses of medicines. Here it is a necessary to have a percutaneous absorption with a large systemic administration of the medicine. Ideally there is no local build-up of medicine which is pushed through the relatively tiny diffusional window which is determined by contact area of patch. Topical delivery can be defined as the application of drug containing formulation to the skin for the direct treatment of cutaneous disorders or the cutaneous manifestation of general disease with the intent to confine the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical actions may or may not be linked to intra-cutaneous penetration and deposition [9].

Topical Gels

Around the end of the 1800s, the term "gel" was coined to refer to certain semisolid materials based more on their physiological properties than their molecular makeup.

A liquid phase is trapped in a three-dimensional polymeric matrix of natural or synthesized gums with a high degree of physical or chemical cross linking in gels, which are semi-solid systems [10].

The majority of topical gels are made with organic polymers like carbomers, which give the products a clear, glossy, and aesthetically attractive look and make them simple to remove from the skin with water. The efficacy of a dermatological topical product is significantly influenced by the type of base employed in its formulation. On dry, irritated skin, bases high in oleaginous compounds have an emollient effect. More significantly, bases containing non-volatile oleaginous compounds (like hydrocarbon bases) can create an occlusive barrier over the skin that stops moisture from escaping into the surrounding environment. The stratum corneum becomes hydrated as moisture builds up between the skin and the ointment layer. Drug molecules can more easily travel through intracellular and intercellular channels and pathways when the stratum corneum is hydrated. Additionally, the medicine that would normally be scattered as tiny particles in the ointment base dissolves in the moisture layer. Skin occlusion typically results in greater percutaneous medication absorption because only the dissolved drug as a single molecular entity exposed to the skin can enter the stratum corneum [11].

Gels are semi-rigid systems in which the interpenetration of a three-dimensional network of particles or solvated macromolecules of the dispersed phase limits the dispersing medium's movement. The rise in viscosity brought on by the

interlacing and the ensuing internal function results in the semi-solid state. After being distributed in an appropriate solvent, the gelling agents entangle or aggregate to create a three-dimensional colloidal network structure. The network's structure also explains a gel's viscoelastic characteristics and resistance to deformation. Certain gels' elasticity may be attributed to their double helix structure, which also affects each studied polymer's rheological profile and water absorption capacity [12].

The integrity of the gel is determined by the type of polymer solvent affinity.

Three types of solvents are distinguished by classical gel theory:

1. Free solvent that is very mobile.
2. Solvent attached as a layer of salvation, typically through hydrogen bonding.
3. Liquid trapped inside the structure of the network.

The concentration of the polymer determines the ratio of the three types of solvent in a particular gel. The solvent's affinity for the polymer regulates the random coil's extension. The coils enlarge and entangle with other coils to create crosslinks as the solvent affinity increases [13].

The majority of topical gels are made with organic polymers, such as carbomers, which give the products a clear, glittering appearance that is both visually pleasant and easily removed from the skin with water. The efficacy of a dermatological topical product is significantly influenced by the type of base employed in its formulation. On dry, irritated skin, bases high in oleaginous compounds have an emollient effect. More significantly, bases containing non-volatile oleaginous compounds (like hydrocarbon bases) can create an occlusive barrier over the skin that stops moisture from escaping into the surrounding environment. The stratum corneum becomes hydrated as a result of moisture being trapped between the skin and the ointment layer. Drug molecules can more easily travel through all intracellular and intercellular channels and routes when the stratum corneum is hydrated.

The medicine, which would otherwise be distributed as tiny particles in the ointment base, dissolves in the moisture layer. Since only the dissolved drug can enter the stratum corneum as a single molecular entity, skin occlusion typically improves percutaneous drug absorption [13, 14].

Classification of Topical Gels

A. Based on the Nature of Colloidal Phase

a) **Inorganic hydrogels**, such as bentonite magma and aluminum hydroxide gels, are typically biphasic systems. In quantities of roughly 10–25%, bentonite magma has also been utilized as an ointment basis.

b) **Organic gels**, are often single-phase systems that include organic liquids like Plastibase as well as gelling agents like tragacanth and carbomer.

B. Based on Solvent System

a) **Hydrogels**, are made up of substances that are soluble in water or dispersible as colloids, such as organic hydrogels, synthetic and natural gums, and inorganic hydrogels. For instance, at high concentrations, hydrophilic colloids including silica, bentonite, tragacanth, pectin, sodium alginate, methylcellulose, sodium CMC, and alumina create semisolid gels.

b) **Hydrocarbons,** vegetable and animal fats, soap base greases, and hydrophilic organogels are among them. With a molecular weight of roughly 1300, Jelene is a Plastibase, a blend of heavy hydrocarbon waxes and mineral oils.

C. On the Basis of Gel Microstructure

The Flory scheme can be used to categorize the microstructure of the network of medicinal gels.

a) Covalently bonded structures

Networks of covalently cross-linked gels are irreversible systems. They are made from one or more synthetic hydrophilic polymers. One of the preparation techniques involves the nonlinear co-polymerization of two or more monomer species, at least one of which is trifunctional, to create infinite gel networks. Each polymer chain grows randomly in both position and direction throughout the process. This gel's ultimate microstructure is entirely disorganized.

Table 1 Applications of Gels

Pharmaceutical gels applications	Favorable properties
Dental	Highly thixotropic, optimal viscosity for filling fissure, adherent to enamel surface, optically clear, water soluble, orally digestible
Dermatological	Thixotropic, spreadability, greaseless, easily removable, emollient, demulcent, non-staining, compatible with number of excipients (water soluble or miscible)
Nasal	Adherent, odorless, non-irritant, water-soluble
Ophthalmic	Optically clear, sterile mucomimetic, lubricating or non-sterilizing, water soluble or miscible
Surgical & medical	Lubricating, adherent to instrument surface, maximal contact with mucous
Vaginal	Acid stable, adherent, does not liquefy at body temperature, slow dissolving, lubricating, greaseless

b) Physical Structure Bonded

Gel networks that are physically coupled are reversible systems. Temperature and ion additions can cause a transition between the sol and gel phases. These gels are mostly made from semi-synthetic cellulose derivatives and natural organic polymers, such as proteins and polysaccharides. The majority of the polymer chains in the sol are in a random coil state before undergoing a conformational shift to gel. Large organized sections of one or more chains that fold into a single, double, or triple helix may be involved in this transition.

c) Well-Ordered Gel Structure

Certain silica, alumina, and clay soils can create stiff gels or lyogels under the right circumstances. When certain smectite-class clays, like bentonite, hectorite, and loponite, come into contact with water, they spontaneously swell through interlayer swelling and osmotic swelling, resulting in a gel. The "cubic cardhouse" is an orderly structure formed by the plate-like clay particles. Repulsive forces from the interacting electrical double layer stabilize the structure [14–18].

Gel Forming Substances

The structural network needed to prepare gels is imparted by polymers. The following categories apply to gelling polymers:

1. Natural Polymer

a) **Proteins-** Collagen, Gelatin

b) **Polysaccharides-**Agar, alginic acid, sodium or potassium carrageenan, pectin, guar gum, cassia tora, xanthin, and gellum gum are examples of polysaccharides.

2. Semisynthetic Polymers

Carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and hydroxyethyl cellulose are cellulose derivatives.

3. Synthetic Polymers

Poloxamer, Polyacrylamide, Polyvinyl Alcohol, Polyethylene, Carbomer (Carbopol -940, Carbopol -934, Carbopol -941), and co-polymers

4. Inorganic Substances

Aluminum hydroxide and bentonite

5. Surfactants

SLS, Cetostearyl alcohol [19]

Advantages

For the best cutaneous and percutaneous drug distribution with a number of benefits, topical medication administration is becoming more and more crucial.

1. Prevent the gastrointestinal tract's pH, enzymatic activity, and drug interactions with food and beverages from causing problems with drug absorption.
2. Prevent the first pass effect, which is the drug's initial entry into the portal and systemic circulation following gastrointestinal absorption, perhaps preventing the deactivation caused by liver and digestive enzymes.
3. Patient cooperation and non-invasiveness.
4. Easily removed from skin and less oily.
5. Less than oral dosage types.
6. Localized activity with few adverse effects.
7. Steer clear of first-pass metabolism
8. A reduction in intravenous therapy hazards and consequences, as well as variations in absorption brought on by pH levels, enzyme presence, and stomach emptying time.
9. Steer clear of gastrointestinal incompatibilities.
10. Making drugs with short biological half-lives and limited therapeutic windows easier to utilize.
11. Greater adherence to treatment by patients.
12. For therapeutic efficacy, a lower total daily dosage is administered continuously [20].

Disadvantages

1. The drug is not appropriate for this delivery system because of its wide range of cutaneous fluxes and large variety of solubility in vehicle components.

2. The delivery route is limited to a small drug population due to skin barrier characteristics and dose size.

3. A number of factors that affect the skin, including age and physical condition, can impact the system's reliability in delivering medication [20].

Properties of Gels

For pharmaceutical or cosmetic applications, the gelling agent should ideally be safe, inert, and not react with other ingredients in the formulation. When stored, the preparation's gelling ingredient should have a fairly firm consistency that is easily disrupted by shear forces from shaking the container, squeezing the tube, or topical administration. To prevent microbial attack, it should have the appropriate antimicrobial. There should be no stickiness in the gel that is applied to the skin [21].

Properties of Gellants

1. It needs to be non-toxic, inert, and compatible with addition.
2. At low concentrations, it ought to gel.
3. It ought to improve the creation of gels.
4. It needs to be economical.
5. There shouldn't be any microbiological contamination.

Principles of Topical Permeation

A topically administered medication must first pass through the stratum corneum, the skin's permeation barrier, in order to have a local or systemic impact. The passive diffusion of substances through the skin is known as percutaneous absorption. Either diffusion through shunts, particularly those supplied by the very extensively dispersed hair follicles and eccrine glands (trans follicular or shunt pathway), or transit through the epidermis itself (trans epidermal absorption) can be the mechanism of permeation. Drug molecules can enter the skin through sweat ducts or hair follicles during the early transient diffusion phase, where they are subsequently absorbed by the sebaceous glands and follicular epithelium. Diffusion through intact stratum corneum was the main pathway for topical penetration once steady state was attained [22].

Dissolution within and release from the formulation are two steps in the process of releasing a therapeutic drug from a formulation applied to the skin's surface and transporting it to the systemic circulation.

1. Stratum corneum (SC), which divides into the skin's outermost layer
2. The lipidic intercellular pathway, which is the rate-limiting step for most substances, is the main route of diffusion through the stratum corneum.
3. Diffusion through the viable epidermis and upper dermis, absorption into the papillary dermis and microcirculation, and partitioning from the stratum corneum to the aqueous viable epidermis.

Kinetics of Topical Permeation

The effective development of topical solutions requires an understanding of skin penetration kinetics. The following steps are involved in a drug's topical penetration:

1. Sorption of the stratum corneum
2. Drug penetration through healthy epidermis
3. Drug entry via the dermal papillary layer's capillary network

If the medication possesses certain physico-chemical characteristics, such penetration may be feasible.

The formula for the rate of skin penetration

(dq/dt) is dq/dt = Ps (Cd – Cr)... (1)

where **Cd** is the concentration of skin penetrant in the donor compartment (i.e., on the stratum corneum surface).

Cr stands for concentration in the receptor compartment (body, for example).

Ps = Skin tissue's overall permeability constant to penetrant

Ps = ($k_s d_{ss}$) / h_s(2) where hs is the total thickness of skin tissues, Dss is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues, and **Ks** is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium.

Because **K, Ds**, and hs remain constant under specific circumstances, a skin penetrant's permeability coefficient **(Ps)** can be regarded as constant.

It is evident from Eq. 1 that only when **Cd>>Cr**, or the drug concentration at the stratum corneum surface (Cd) is continuously and significantly higher than the drug concentration in the body (Cr), can a constant rate of drug permeation be attained. In this case,

Eq. 1 becomes:

Dq / dt = $p_s c_s$ (3) (ksdss) / hs = 1 / resistivity is the permeability coefficient [23].

Drug Factors in Percutaneous Absorption

The characteristics of the barrier itself are physiological considerations. Among the crucial elements are: Hydration, temperature, and skin integrity Age-related disease and anatomical location.

Physiological Factors in Percutaneous Absorption

The following variables influence the percutaneous absorption of medications: The drug's molecular size, chemical makeup, partition coefficient, skin binding, metabolism, and thermodynamic activity in the donor.

Formulation Factors in Percutaneous Absorption

The parameters of skin penetration are greatly influenced by the type of dose form. Occlusives, drug concentration, pH, solubility, surfactant, and penetration enhancer are some of the formulation parameters.

Fundamental Elements of Topical Gels

An essential part of pertinent gel compositions is polymers.

Polymer

The three-dimensional gel network's primary structural elements are polymers. They regulate the formulation's viscosity, consistency, and drug release profile. The physicochemical characteristics of the drug and polymer, such as molecular weight, cross-linking density, and polymer-drug interactions, have an impact on drug release from gels [24].

Table 2 Polymers for Topical Gel

Natural polymers	Semi synthetic polymers	Synthetic polymers
a. Proteins	a. **Cellulose derivatives**	a. **Carbomer**
i. ollagen	i. Carboxymethyl cellulose	i. Carbopol-940
ii. Gelatin	ii. Methylcellulose	ii. Carbopol-934

b. Polysaccharides *i. Agar* *ii. Alginic acid* *iii. Sodium or Potassium carrageenan* *iv. Tragacanth* *v. Pectin* *vi. Guar Gum* *vi Cassia tora* *viii. Xanthin* *ix. Gellum Gum*	iii. Hydroxypropyl cellulose iv. Hydroxypropyl methyl cellulose v. Hydroxyethyl cellulose	iii. Carbopol-941 b. **Poloxamer** c. **Polyacrylamide** d. **Polyvinyl alcohol** e. **Polyethylene and its co-polymers**

The polymer must meet the following requirements in order to be used in a topical system:

1. The molecular weight, glass transition temperature, and chemical functionality of the polymer must permit the release and diffusion of a particular medication. A significant amount of medication should be able to be incorporated into the polymer.

2. The medication and the polymer cannot interact chemically or physically.

3. The polymer should be inexpensive and simple to produce and build into the intended product.

4. The polymer should be stable and not break down when the medicine and other formulation excipients are present, when humidity levels are high, or when the body temperature is high.

5. Polymers and their breakdown products ought to be non-toxic.

Certain excipients can be added to change some of these characteristics; for example, cosolvents like ethanol, propylene glycol, or PEG 400 can be added to improve drug solubility. Useful polymers for topical gel are shown in Table 2.

Different methods have been used to modify medication release rates and polymer characteristics.

1) **Polymers with cross-links** Drug molecules diffuse more slowly in polymers with higher levels of cross-linking.

2) **Polymer blends:** To obtain the combined advantages of distinct polymers, the polymers have been combined in various ratios. Polymer blends provide benefits in terms of simple device manufacture, drug incorporation modification, and other device features like hydration, degradation rate, and mechanical strength.

Drug Substance

The careful choice of medication is essential to the development of a topical product. The following are significant drug characteristics that affect the drug's diffusion via the device and through the skin**:**

A. Physico-chemical qualities

1. The drug's molecular weight needs to be under 500 Daltons.

2. The drug should be lipophilic.

3. A saturated aqueous solution of the medication should have a pH between 5 and 9.

4. Drugs that are extremely acidic or alkaline in solution should not be used topically.

B. Biological traits

1. The medication shouldn't directly irritate the skin.

2. The medication shouldn't cause the skin to react immunologically.

3. Topical distribution is appropriate for medications that are broken down in the digestive system or rendered inactive by the hepatic first pass effect.

4. The near zero order release profile of topical delivery should prevent the development of medication tolerance.

5. Topical distribution can also be used for medications that must be given for extended periods of time or that negatively impact non-target tissue.

Penetration Enhancers

These substances alter the skin to act as a barrier to a desired penetrant's flux. Promoting skin permeability is regarded as a crucial component of the majority of topical formulations. The stratum corneum's resistance to drug diffusion must be decreased in order for drug molecules to pass through the skin and sustain therapeutic blood levels. By interacting with the skin or the applied formulation, they can change the skin's barrier to penetration.

The following requirements should be satisfied by the best penetration enhancers:

1. The capacity to operate with precision, reversibility, and predictability.

2. The absence of pharmacological activity

3. It is not annoying, allergic, or poisonous.

4. Enhance reversible and regulated action.

5. No bodily fluids, electrolytes, or other endogenous materials may be lost.

6. Compatibility both chemically and physically with the medications and other pharmaceutical excipients it is used with.

7. As soon as the enhancer is removed, the stratum corneum's normal barrier function should be fully restored.

8. Affordable, odorless, colorless, and aesthetically pleasing.

Enhancers increase penetrant solubility and disturb the structure of the stratum corneum, the skin's outermost layer, to improve permeant penetration. Both extracellular and intracellular structure may be impacted by chemical disturbance. Protein denaturation, intercellular lipid fluidification and randomization, or intercellular delamination and expansion can all cause disruption. The accelerants reduce diffusional resistance and increase medication penetration into the skin by causing keratin to expand and leach out of vital structural material from the stratum corneum. Improved topical penetration of a water-soluble medication in a hydrophilic topical penetration enhancer due to solution characteristics and solvent miscibility.

Lipophilic enhancers improve the percutaneous absorption of both oil-soluble and water-soluble medications. The enhancer's partial leaching of the epidermal lipids appears to be the cause of the

improvement in oil-soluble medication absorption, which improves skin conditions for topical and trans follicular penetration as well as wetting.

The physical state of water in the skin may be altered by surfactant action, allowing charged hydrophilic substances to move through the skin with more freedom. Their influence on lowering surface tension, which improves skin wetting and facilitates medication distribution, is responsible for their permeation-promoting activity. Furthermore, compared to less hydrophilic surfactants (long chain alcohols), more hydrophilic surfactants were observed to interact with keratin more strongly and alter permeability.

Classification of Permeation Enhancers

Water, sulphoxides (particularly dimethylsulphoxide) and their analogues, pyrrolidines, alcohols and fatty acids, azone and its derivatives, anionic, cationic, and nonionic surfactants, urea and its derivatives, alcohols and glycols, essential oils, terpenes and derivatives, and synergistic mixtures [25].

FORMULATION AND EVALUATION

Pharmaceutical literature has detailed a number of preparation techniques for topical gel formulations. The most popular technique for creating cutaneous gels is the polymer dispersion technique [26].

1. Polymer Dispersion Method

The most popular approach for preparing gels is the polymer dispersion method. This process involves dispersing the necessary amount of polymer, such as sodium carboxymethyl cellulose, HPMC, or Carbopol, in filtered water and letting it fully hydrate. Polymer hydration results in swelling and the creation of a three-dimensional network that serves as the gel's foundation. The medication is dissolved separately in an appropriate solvent, such as ethanol or propylene glycol. Next, while continuously stirring, the drug solution is added to the hydrated polymer base. Lastly, the pH is adjusted and the polymer dispersion is transformed into a gel structure by adding a neutralizing agent such triethanolamine [27, 28].

2. Cold Method of Gel Preparation

The cold method is frequently employed in recipes that contain heat-sensitive ingredients. In this method, the polymer is continuously stirred while being gently dispersed in cold water. The mixture is allowed to stand long enough for the polymer to fully hydrate [29, 30]. The medication is dissolved separately and added to the polymer dispersion along with additional excipients such as humectants, preservatives, and penetration enhancers. Constant stirring guarantees homogenous gel formation and consistent mixing [31, 32].

3. Hot Method of Gel Preparation

When certain polymers require heating in order to dissolve properly, the hot technique is used. This process involves heating the aqueous phase to a particular temperature and then gradually adding the polymer while continuously stirring. Polymers like hydroxypropyl methylcellulose and methyl cellulose can be dissolved by heating. The solution is gradually chilled when it has completely dissolved. Next, while continuously stirring, the medication and additional excipients are added to the gel base [33, 34].

EVALUATION PARAMETER

To guarantee quality, stability, and therapeutic efficacy, topical gel compositions must be evaluated. When developing a formulation, a

number of physicochemical experiments are carried out.

1. Organoleptic Evaluation

Visual observation was used to examine the organoleptic characteristics of the gel composition. This involves evaluating homogeneity, color, odor, and appearance. It should be an excellent gel formulation. Easy. No lumps. Uniform in appearance. These factors are crucial because they have an impact on the topical product's esthetic appeal and patient acceptance.

2. Viscosity measurement

The consistency and thickness of the gel formulation are determined by its viscosity. Typically, a Brookfield viscometer with the proper spindle at a regulated temperature is used to test the gel must have the right viscosity to be stable and easily applied to the skin's surface.

3. Spreadability Test

One of the key factors that determines how easily the gel spreads on skin is spreadability. Two glass slides can be used to take the unique weight. The time it takes for the upper slide to pass over the bottom slide indicates how spreadable the formulation is.

Typical formulas:

$$\textit{Spreadability is} = M \times L / T.$$

Where:

M is the weight on the upper slide.

L is the slide's length.

T is the separation time of the slides.

4. Drug Content Determination

Halcinonide is distributed uniformly throughout the gel formulation. UV spectrophotometry or HPLC are used to analyze a known quantity of gel that has been dissolved in an appropriate solvent. For therapeutic efficacy, the drug's content must be within acceptable bounds.

5. Extrudability Test

The ease with which the gel can be forced out of the tube or container is known as extrudability. The amount of gel released from a collapsible tube using a certain force is often measured as part of the test [35].

6. In-Vitro Drug Diffusion Study

To determine the rate of drug release from the gel formulation, in vitro diffusion tests are carried out. A Franz diffusion cell apparatus is typically used for this investigation. Animal skin or a dialysis membrane work well as a barrier between the donor and receptor compartments. At predetermined intervals, the amount of a medication that diffuses into the receptor media is assessed [36, 37].

7. Skin irritation Test

Studies on skin irritation are used to assess the topical gel formulation's safety. Under carefully monitored circumstances, the gel is administered to the skin of human or animal volunteers, and any indications of redness, swelling, or irritation are noted.

8. Stability Studies

Stability studies determine the gel formulation's physical stability and shelf life. The formulation is kept under several settings, including room temperature, refrigeration, and accelerated stability conditions (40°C ± 2°C, 75% RH). Ph,

viscosity, appearance, and medication content are parameters that are tracked throughout time.

9. Homogeneity Test

Testing for homogeneity guarantees that the gel formulation has a consistent texture and is free of lumps or particles. The gel is examined visually once it has solidified in the container. The gel's homogeneity is a sign that the medication was properly mixed and dispersed throughout the polymer matrix.

10. Washability Test

The washability test establishes how simple it is to use water to remove the gel from the skin's surface. Compared to ointments, topical gels should be easier to wash, which enhances patient comfort and hygiene.

11. Rheological Studies

Gels' rheological behavior is crucial to comprehending spreadability and flow properties. Rheological analyses determine if the gel exhibits Newtonian or non-Newtonian flow characteristics. The majority of pharmaceutical gels have pseudoplastic flow, which means that as shear stress increases, viscosity decreases.

12. Calculating pH

A digital pH meter is used to determine the gel formulation's ph. To prevent irritation or harm to skin tissues, topical medicines should have a pH that is near to the natural pH of skin, which is often between 5 and 7. Before testing, a small amount of gel is usually dispersed in distilled water [38].

CONCLUSION

Topical gel formulations have a number of benefits, such as enhanced cosmetic acceptability, increased patient compliance, and effective medication delivery to epidermal layers. A promising dosage form for the treatment of inflammatory skin conditions is halcinonide topical gel. Topical gel drug release behavior is significantly influenced by polymer selection, penetration enhancers, and viscosity control. The use of polymers like Carbopol and HPMC to create stable dermatological gels with good spreadability has been validated by multiple investigations. Ph, viscosity, spreadability, medication content, and in vitro diffusion can all be used to assess the topical gels' quality and effectiveness. Compared to other gel bases, carbopol-based gels frequently offer improved spreadability and regulated drug release, according to numerous studies. Stability tests further demonstrate that in order to preserve the formulation's chemical and physical stability, the proper pH and storage conditions must be maintained. This study is helpful for future investigations and the creation of better topical gel formulations of halcinonide. New delivery methods for enhanced skin penetration and stability of corticosteroid formulations may be the subject of future research.

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