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(REVIEW ARTICLE)

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A review on "Topical gels: an emerging drug delivery system"

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Abstract

Topical drug distribution is the application 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 topical medicine administration. Gels have been popular in cosmetics and topical medicinal treatments in recent years due to their advantageous properties such as being greaseless, easily spreadable, and quickly detachable. In compared to creams and ointments, gel formulations have greater application properties and stability. A gel is a network of cross-linked polymers that expand in a liquid media. Gels are homogenous, semisolid preparations that typically consist of one or more medicament solutions or dispersions in appropriate hydrophilic or hydrophobic bases. Clinical research suggests that topical gels are the safest and most effective treatment choice for skin-related disorders, and that they are used topically to lessen associated adverse effects when compared to other traditional dose forms. The purpose of this article is to discuss the concepts and recent advancements in topical gels, such as classification, techniques of manufacture, characteristics, evaluation factors, and applications.

Keywords: Topical drug delivery system; Structure of skin, Gels; Hydrogel; Emulgel; penetration Enhancer

1. Introduction

Topical delivery is defined as the application of a drug-containing formulation to the skin to treat cutaneous illnesses (like acne) or cutaneous symptoms of a systemic disease (like psoriasis)[1]. The skin is one of the most accessible routes for medication administration, and topical drug delivery methods are among the most widely used [2]. Simple solutions and ointments to multiphase nanotechnology-based products are accessible as topical medical medicines [1].

The gel is a semi-solid preparation of tiny and big molecules dispersed in aqueous liquid carriers. Gels are semi-solid systems in which colloidal particles interact (physically or covalently) inside a liquid carrier. When compared to alternative drug administration techniques, the topical/transdermal (TT) route provides several advantages, such as increased patient compliance, continuous drug delivery, fewer adverse effects, and avoidance of the hepatic first pass effect [3]. Percutaneous absorption is an important component to address in topical drug delivery systems in order to attain and maintain consistent, systemic, therapeutic levels during the course of use [4].

Topical drug delivery systems are often employed when other methods of medication administration fail, or they are primarily utilised in pain treatment, contraception, and acne [5]. Overall, topical gels provide a convenient and effective method of delivering drugs and other therapeutic agents to the skin, with minimal systemic absorption and fewer side effects compared to other routes of administration [6].

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2. Topical drug delivery system

Topical drug delivery systems are defined as carrying specific drugs upon contact with and across the skin. The challenge with topical medications is that they cross the skin barrier [7].

Topical drug include two basic types of products, internal and external. Internal topical preparations for local action on mucous membranes, applied orally, vaginally, or to anorectal tissues. Topical medications are sprayed, sprayed, or otherwise distributed onto skin tissue to cover the affected area [2].

2.1. Advantages of topical drug delivery systems:[4]

- Avoid primary metabolism.
- Easy to use and easy to apply.
- Easy to stop medication.
- Drugs are selectively delivered to specific sites.
- Avoid gastrointestinal intolerance.
- Allow the use of drugs with short biological half-lives and narrow therapeutic windows.
- Better patient compliance.
- Self-medication.

2.2. Challenges of Topical Drug Delivery System:[7]

- The drug or excipients may cause skin irritation or dermatitis.
- Some drugs may not penetrate the skin effectively.
- Larger particle size drugs may not be easily absorbed through the skin.
- Allergic reactions may occur.
- Only drugs that require very low plasma concentrations can be used.
- Routes of administration may not be suitable for drugs that cause skin sensitization.

3. Structure of skin

The skin is the body's largest organ, composed of three distinct layers: the outermost epidermis, the intermediate dermis, and the innermost hypodermis [8].

- **Epidermis**: The epidermis, which is the outermost layer of skin, function as essential tissue barrier [9]. It is made up of stratified epithelium consisting of five layers: The stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale [7,10].
- **Dermis**: The dermis is a layer that is approximately 3 to 5mm thick and consists of a connective tissue matrix. This matrix contains blood vessels, lymph vessels, and nerves [11]. Positioned beneath the epidermis, the dermis is characterized by an abundance of elastin fibers, which enable the skin to stretch, and a significant amount of collagen, which provides strength. Within the dermis, one can find nerve endings, sweat glands, oil glands, hair follicles, and blood arteries [8].
- **Hypodermis**: The hypodermis is the inner layer. It is the layer that connects the skin to the underlying tissues, such as muscles and bones [8]. This layer provides food support, mechanical protection and helps in temperature regulation. It connects major blood vessels and nerves to the skin and may contain pressure sensitive organs [11].

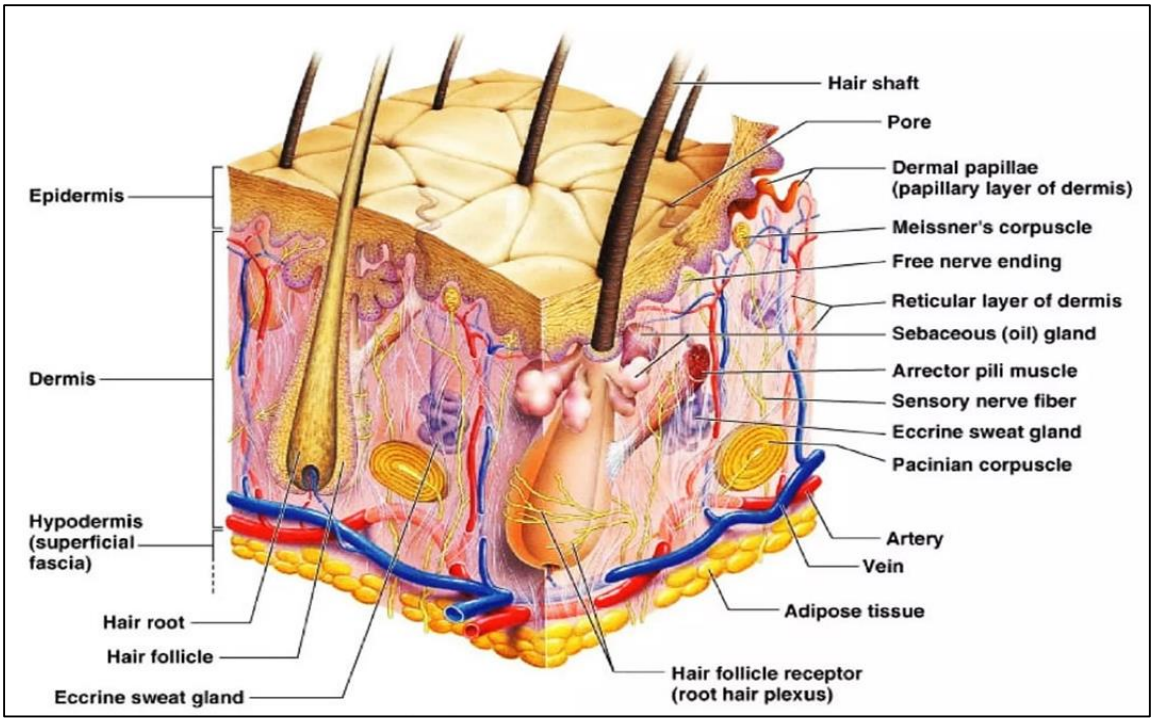

Figure 1 Anatomy of skin [7]

4. Gels

Topical gels are homogeneous semi-solid preparations used for the treatment and prevention of skin diseases [12]. The U.S.P. defines gels as a semi-solid system consisting of a dispersion consisting of small inorganic particles or large organic molecules, surrounded by liquid and penetrated by liquid. Gels consist of a two-phase system in which inorganic particles are not dissolved but only dispersed in the continuous phase, while large organic particles are dissolved in the continuous phase and randomly entangled in flexible chains [13]. Chemical gels have permanent covalent bonds that hold the particles together, whereas physically localized gels have secondary intermolecular forces, including hydrogen bonds, electrostatic interactions, hydrophobic contacts, and van der Waals forces, which are weaker and reversible [1].

Figure 2 Gel [12]

4.1. Gel structure

Gels consist of natural or synthetic polymers that form a three-dimensional matrix in a dispersion medium or hydrophilic liquid. After application, the liquid evaporates, trapping the drug in a gel-forming matrix film that physically covers the skin [14]. The stiffness of the gel is achieved through gelling agents as the particles interlock and form a network [5].

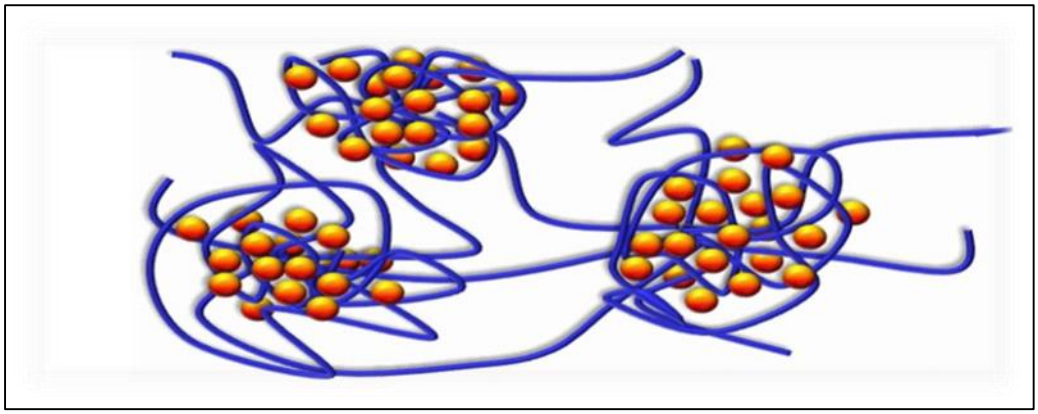

Figure 3 Structure of gel [8]

4.2. Desirable properties of topical gel: [15,5]

- The gel should have inert ingredients.
- The gel must not be sticky.
- Do not irritate skin or area where gel is applied.
- Should be inert, non-toxic and compatible with other additives.
- The gel should be easy to use.
- It should have appropriate antimicrobial agents to prevent the occurrence of microbial attacks.

4.3. Optimal Features of Gels:

- **Swelling:** Upon contact with a liquid, the gelling agent undergoes a process known as swelling, absorbing water and increasing in volume [5]. Gels exhibit the capacity to absorb liquids, expanding in size. Gel-gel interactions shift to gel-solvent interactions as the solvent permeates the gel matrix. The typical cross-linking within the gel matrix restricts complete disintegration, resulting in controlled swelling. Significant gel swelling occurs when the solvent combination shares a solubility characteristic with the gallant [12].
- **Syneresis:** Several gel systems experience contraction over time, leading to the expulsion of interstitial liquid, which accumulates on the gel surface. This phenomenon, known as syneresis, is observed in both organic and inorganic hydrogels, not exclusive to organic hydrogels [3]. It indicates an insufficient amount of gelling agent or a decrease in the concentration of the gelling agent. Ideally, a gel should be free from syneresis [16].
- **Ageing:** Colloidal systems undergo slow, spontaneous aggregation, a phenomenon known as ageing. In gels, ageing contributes to the gradual formation of a thick network of the gelling agent over time [8]. This process leads to the development of a denser network of the gelling ingredient within the gel [14].
- **Structure:** A gel's rigidity is conferred by the interlinking of gelling agent particles, forming a network. The character of these particles and the forces responsible for their linkages determine the property and structure of the gel [5]. The careful selection of the gelling agent is a crucial aspect of achieving the desired gel properties [6].
- **Rheology: G**elling agent solutions and dispersions of flocculated solids display pseudoplastic behavior, demonstrating non-Newtonian flow characteristics with a decrease in viscosity as shear rate increases. The applied shear stress disrupts the elongated structure of inorganic particles dispersed in water, breaking inter particulate bonds and enhancing their propensity to flow [3].

4.4. Classification of gels

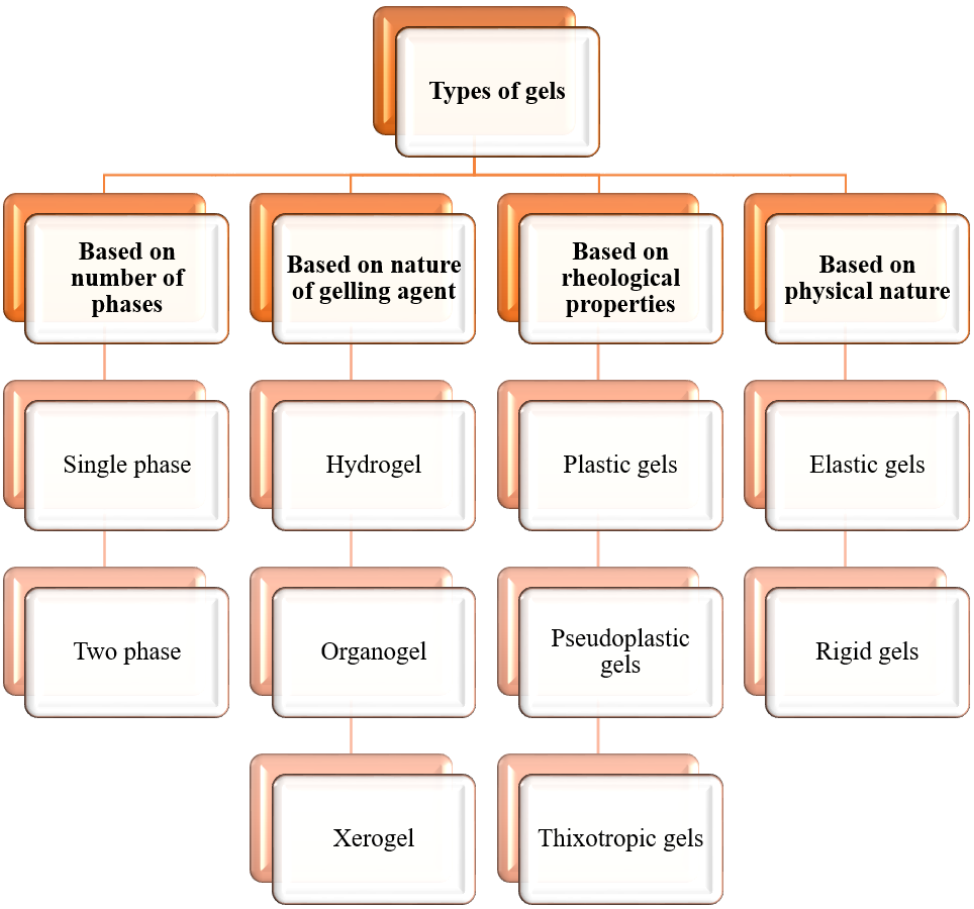

Figure 4 Classification of gels [3]

4.4.1. Based on number of phases:

Colloid Phase: Divided into two system:

- **Inorganic (Two-phase) System:** This system comprises floccules of small particles instead of larger molecules. The gel structure becomes unstable if the dispersed phase partition size is notably large, forming a three-dimensional structure throughout the gel. These gels must exhibit thixotropic behavior, transitioning from a semisolid to a liquid when disturbed. Examples include gels made of aluminum hydroxide and bentonite magma [12].
- **Organic (Single-phase) Systems:** Twisted threads in this system host large organic molecules that remain continuously dissolved. The majority of organic gels belong to single-phase solutions, incorporating organic liquids such as plastic base and gelling agents like carbomer and tragacanth [12].

4.4.2. Based on the nature of gelling agent:

- **Hydrogel (Water-based):** A hydrogel is a three-dimensional structure composed of hydrophilic polymers with a high capacity to interact with and retain significant amounts of water and biological fluids. This capability is attributed to various functional groups (e.g., amino (–NH2), carboxylic acid (–COOH), hydroxyl (–OH), amide (–CONH), sulfo groups (–SO3H)) present in the polymer chains [16]. The polymer undergoes hydration to varying degrees, influenced by the nature of the aqueous medium and the polymer's composition [7].
  - **Types of Hydrogels: [17]**
    - pH-Sensitive Hydrogel
    - Temperature-Sensitive Hydrogel
    - Nano Hydrogels
    - Glucose-Sensitive Hydrogel

- **B. Organogels (With a Non-aqueous Solvent):** Organogels, also known as oleaginous gels, consist of both polar and non-polar groups, with a notably high proportion of the non-polar component. They may incorporate up to 35% water, as these gels tend to swell in water. Organogelators, typically low molecular weight molecules, possess the ability to thicken in organic solvents [18]. Organogels are thermodynamically stable, clear, viscoelastic, biocompatible, and isotropic gels composed of phospholipids and a suitable organic and polar solvent [19].
- **C. Xerogel:** A xerogel is a dehydrated solid gel that undergoes indefinite shrinkage. It generally maintains high porosity (15-50%) and a large surface area (m2/g). Examples include strips of gum tragacanth, beta-cyclodextrin, dry cellulose and polystyrene, gelatin sheets, and acacia tears [3].

4.4.3. Based on rheological properties

Gels typically demonstrate non-Newtonian flow properties and can be classified into:

- **Plastic Gels:** For instance, Bingham bodies and flocculated suspensions of aluminum hydroxide exhibit plastic flow. The rheogram plot provides the yield value, above which the elastic gel distorts and begins to flow.
- **Pseudoplastic Gels:** Examples include liquid dispersions of tragacanth, sodium alginate, and Na CMC, which exhibit pseudoplastic flow. The viscosity of these gels decreases with an increasing rate of shear, without a yield value.
- **Thixotropic Gels:** Gels in this category have weak bonds between particles that can be broken down by shaking. The resulting solution reverts back to a gel as particles collide and link together again. Examples include kaolin, bentonite, and agar [20].

4.4.4. Based on physical nature:[12]

- **Elastic Gels:** Gels like agar, pectin, guar gum, and alginates possess elastic properties. Fibrous molecules are connected at junction points through relatively weak interactions like hydrogen bonds and dipole attraction. If the molecule contains a free -COOH group, an additional bond in the form of a salt bridge (-COO-X-COO) forms between two adjacent strand networks. Examples include alginate and Carbopol.
- **Rigid Gels:** These gels are formed from macromolecules with primary valence bonds connecting the framework. For instance, silicic acid molecules in a silica gel are held together by Si-O-Si-O links, resulting in a polymer structure with a network of pores.

4.5. Method of preparation of gels: [21]

There are three methods for the preparation of gels:

- **Fusion Method:**- In this method, vehicles, gelling agents, additives, and the drug are blended at high temperatures until a semi-solid texture is formed.
- **Cold Method:**- In this approach, all components except the drug or active pharmaceutical ingredient are heated and blended simultaneously. The temperature of the formulation is then lowered, the drug is added, and blending continues until the gel is formed.
- **Dispersion Method:** - In this approach, the gelling agent is stirred with water until it swells up. The drug is then dissolved in the medium and incorporated into the swollen gelling agent. If necessary, a buffer solution is added to adjust the pH of the gel.

4.6. Formulation design: [22]

Topical gel components typically include:

- Gel forming agent or polymer
- Drug Substance
- Penetration Enhancers

4.7. Gel forming agent or polymer

These agents increase the viscosity of a liquid substance without substantially altering other properties like taste [21]. The addition of a gelling agent to certain formulations results in a gelled structure [23]. Various polymers are also employed to create the essential structural network in the gel system [24].

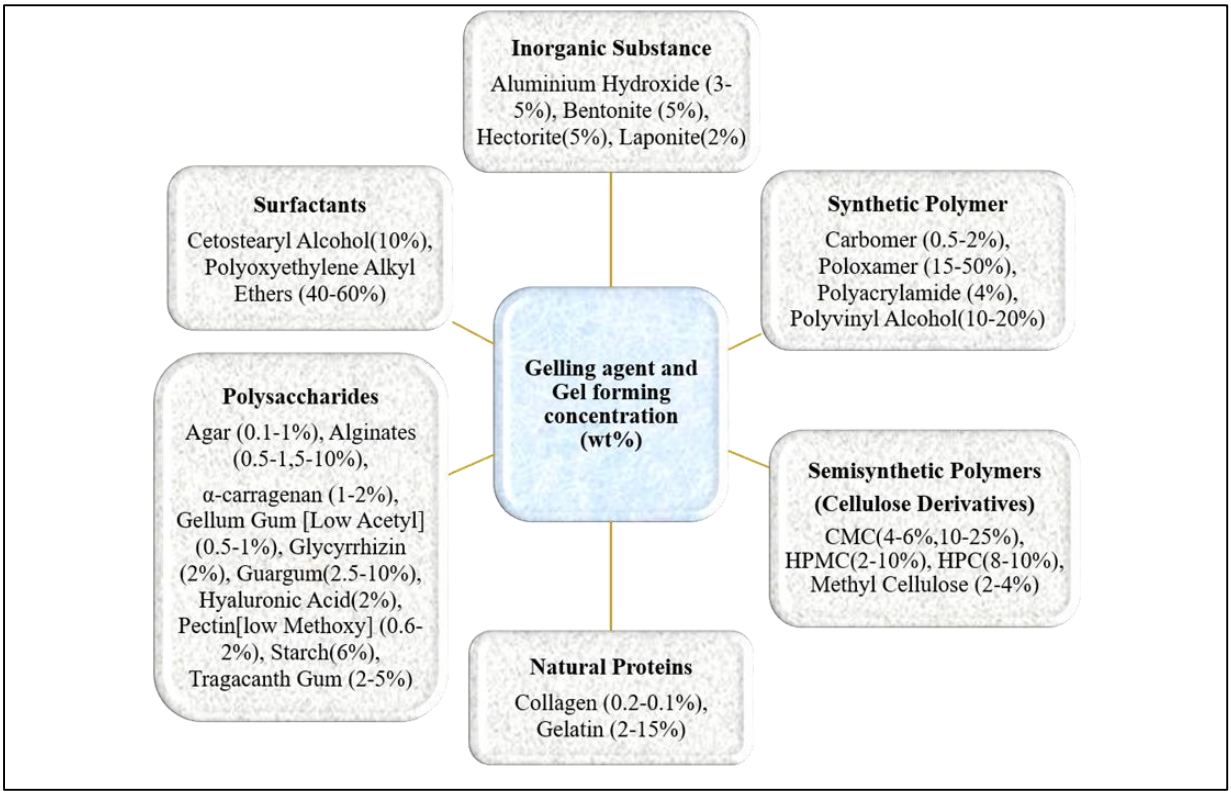

Figure 5 Gelling Concentration for substances used in pharmaceutical products [24]

4.8. Drug Substance

Physicochemical Properties:

- The drug should possess a molecular weight of less than 1000 Daltons.
- It should exhibit an affinity for both lipophilic and hydrophilic phases.
- The drug is ideally characterized by a low melting point.

Biological Properties

- The drug should exert a potent effect at a daily dose of several mg/day.
- The drug's half-life (t1/2) should be short, and it should not cause skin irritation or allergic reactions.
- Drugs susceptible to degradation in the gastrointestinal tract or inactivated by first-pass effects in the liver are suitable candidates for topical administration.
- Tolerance should not develop below the level of release close to topical administration.
- Drugs requiring prolonged use or causing undesired effects in non-target tissues can be formulated for topical administration [25].

4.9. Penetration Enhancer

Penetration enhancers are substances designed to enhance the drug's ability to penetrate the skin. Formulations often include ingredients that temporarily disrupt the highly ordered structure of the stratum corneum skin barrier. These enhancers may fluidize the lipid channels between corneocytes, alter the partitioning of the drug into skin structures, or employ other mechanisms to enhance delivery into the skin, promoting drug absorption through the skin barrier [23].

Properties of Permeation Enhancer:[26,14]

- Permeation enhancers must be non-toxic, non-irritating, and non-allergenic.

- They should be suitable for formulation into various topical preparations, compatible with both excipients and drugs [26].
- Ideally, permeation enhancers should be odorless, tasteless, colorless, and cost-effective [14].
- They should exhibit no pharmacological activity within the body, meaning they should not bind to receptor sites [14].

4.10. Evaluation of gels

- **pH Measurement:** - The pH of different gel formulations is determined using a digital pH meter. 1 g of gel is dissolved in 100 ml of freshly prepared distilled water and stored for two hours. pH measurements for each formulation are conducted in triplicate, and average values are calculated [13].
- **Homogeneity:**- All formulated gels undergo testing for homogeneity through visual inspection after being poured into the container. The gels are assessed for their appearance and the presence of any impurities [22].
- **Grittiness:**- Microscopic examination is conducted on all gel formulations to check for the presence of any particulate matter [22].
- **Stability:** - The stability of gels is assessed through freeze-thaw cycling. In this method, the sample is kept at 4°C for 1 month, then at 25°C, and finally at 40°C for another month to examine for syneresis [21].
- **In vitro Dissolution Studies:** - In-vitro dissolution studies are carried out using the USP paddle apparatus. The dissolution medium (900ml) maintained at 37°C ± 0.5°C and stirred at 50 rpm. Samples (5ml) are withdrawn at specified time intervals (10, 20, 30, 40, 50, 60, 90, 120 min), and sink conditions are maintained by replacing fresh media. These withdrawn samples are then analyzed using a UV spectrophotometer. Now, the percentage of drug release is calculated based on the absorbance values obtained from the UV spectrophotometer [21].
- **Drug Content:** - To assess drug content, 1g of the gel or jelly sample is taken and mixed in a suitable solvent. Different concentrations are prepared by suitable dilutions after filtering the stock solution, and absorbance is measured. The drug concentration is then determined using an equation obtained through linear regression of a calibration curve. Alternatively, it can be evaluated by spectroscopy using a UV spectrophotometer [21].
- **Skin Irritation Test:** - For the skin irritation test, the Swiss albino mice strain and Guinea pigs (400-500gm) of either sex are employed as animal models. Hairs are removed using a skin removal cream, and the skin is cleaned with spirit. In this test, three mice are used where normal saline, blank gel, and the formulated gel are applied to check for irritation in animals [27].
- **Spreadability:** - To assess spreadability, 0.5 g of the gel is applied within a pre-marked circle of 2 cm diameter on a glass plate. A second glass plate is then placed over it, and a weight of about 500 g is rested on the upper glass plate for 10 minutes. The increase in diameter due to gel spreading is noted [27].
- **Viscosity:**- The viscosity of the gel is measured using the Brookfield Viscometer [27,28].

4.11. Applications of Gels

Gel applications include the pharmaceutical and cosmetic sectors.

- Gels are administered directly to the skin, mucous membrane, or eye to provide local action.
- They serve as long-acting drug implants or intramuscular injections.
- Cosmetic gels are found in a variety of goods such as shampoos, deodorants, dentifrices, and skin and hair care products [15].

4.12. Recent approaches in topical gels

4.12.1. Emulgel

An emulgel is a mixture of gel and emulsion. Both oil-in-water and water-in-oil emulsions are utilised as vehicles to deliver different medications to the skin. They have a high penetration rate into the skin [29]. Emulgels are thixotropic, emollient, and readily removable, have a long shelf life, are bio-friendly, have a beautiful, translucent look, and are greaseless [30]. Because Emulgel has both aqueous and non-aqueous phases, it may transport both hydrophilic and lipophilic medicines. They have recently been employed as a control release formulation. These are biphasic systems with increased drug loading capacity and stability [31]. Emulsified gel is a preferable carrier for medications that are poorly water soluble or hydrophobic. The main disadvantage of this gel, despite its many advantages, is in the delivery of hydrophobic medicines. To circumvent this limitation, an emulsion-based strategy is being developed, allowing even a hydrophobic medicinal moiety to benefit from the special features of gels [32].

4.12.2. Method of preparation

- STEP 1: Emulsion formulation (o/w or w/o)
- STEP 2: Gel base formulation
- STEP 3: Incorporate emulsion into gel base while stirring continuously [33].

4.13. In-Situ Gel

The "in situ gel" drug delivery technology has emerged as one of the most promising innovative drug delivery systems. Because of its unique transition from "Sol to Gel," the in-situ gel drug delivery system aids in the prolonged and regulated release of medications, as well as increased patient compliance and comfort. Before entering the body, an in situ gelling system is a formulation that is in solution form, but will convert to gel form under certain physiological conditions [34]. The sol-gel phase transition behaviour of in situ gelling formulations is influenced by one or more stimuli, such as pH change, temperature modulation, solvent exchange, UV irradiation, and the presence of particular ions or molecules [35]. By prolonging the release of a drug, such that it is attached and absorbed in gel form, in situ gel creates a continuous plasma drug profile in the body and is known to prolong the life of the drug in the mucosa. Oral, buccal, subcutaneous, transdermal, intraperitoneal, ophthalmic, nasal, rectal, vaginal, and parenteral routes may be employed for in situ gels [36]. Natural polymers utilised for in situ gelling systems include pectin, gellan gum, chitosan, alginic acid,guar gum, carbopol, xyloglucan, xantham gum, HPMC, poloxamer, and others [37].

4.13.1. Importance of an in-situ gelling system:

- Dosing accuracy and controlled drug release from in-situ gels result in no drug buildup and no adverse effects.
- Significant gains in drug bioavailability and dosage reduction.
- The drug's longer residence duration and greater interaction with tissue as a result of gel formation.
- Unlike typical gel formulations, in situ gels provide for accurate and repeatable dosage delivery [38].

4.14. Solid lipid nanoparticle gel

Solid lipid nanoparticles (SLNs) are considered the most effective lipid-based colloidal carriers and were introduced in the early 1990s. It is composed of a matrix of soluble lipophilic molecules and a solid lipid core [39] that remain solid at room and body temperature [40]. It is one of the most popular approaches to improve the oral bioavailability of poorly soluble drugs in water [41]. SLNs are the most popular designs because they can deliver strong and stable nanoparticles, have a good delivery system, and can be modified with various lipid matrices, emulsifiers, base materials, and production methods [42]. Nanoparticle gels are three-dimentional, nanoscale, chemically or physically cross linked polymer networks [43].

4.14.1. Advantages of SLN:

- It demonstrates the potency of drug targeting and controlled drug release.
- Improving medication stability is conceivable.
- This carrier's medication loading capability outperforms that of other carriers.
- It can transport both hydrophilic and lipophilic medicinal molecules [44].

4.15. Liposome based gel

Liposomes are self-assembled (phospho) lipid-based drug vesicles that form a bilayer (uni-lamellar) or a concentric sequence of several bilayers (multilamellar) encircling a central aqueous compartment [45] Liposomes range in size from 30 nm to micrometres, with the phospholipid bilayer being 4-5 nm thick [46]. Because liposomes have a greater diffusivity in the skin than most bare medicines, liposomal formulations are commonly employed as topical drug delivery systems [47,48]. Liposomes are small, spherical artificial vesicles comprised of cholesterol and natural phospholipids. Liposomes' hydrophobic and hydrophilic characteristics, as well as their biocompatibility, making them attractive drug delivery platforms [49, 50].

4.15.1. Benefits of Liposomes: - [49]

- High solubility
- Capture both hydrophilic and lipophilic drug molecules
- High chemical, biological, and colloidal stability

- Limit macrophage absorption
- Increasing the therapeutic effectiveness of an encapsulated drug.

4.16. Microsphere based gel

Microspheres are free-flowing powders composed of biodegradable protein or synthetic polymers with sizes ranging from 1 μm to 1000 μm [51].

4.16.1. Advantages: [52]

- Microspheres provide a consistent and long-lasting therapeutic impact.
- Convert the liquid to a solid and hide the unpleasant flavour.
- Reduces dose frequency, improving patient compliance.
- Because of their spherical form and lower size, they may be injected into the body.
- It provide a medication with sustained or delayed release [53].

5. Conclusion

The topical gel improves skin absorption and thereby enhances bioavailability. Furthermore, it has high patient acceptance. According to clinical evidence, topical gel is a safe and effective therapy choice for the treatment of skin-related disorders. Because of improved patient compliance, topical medication delivery systems have been increasingly popular in recent years. The whole study concludes that gels are a potential semisolid topical treatment that may be extensively employed.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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