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Emulsion based gel technique: A novel approach for Topical drug delivery system

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ABSTRACT: Compared to other semisolid preparations, gels have become more prevalent in cosmetics and pharmaceuticals. Emulgel is a term that refers to the combination of gel and emulsion. For the delivery of hydrophobic medicines, Emulgel is a potential drug delivery technology. Emulgel is an emulsion that has been gelled by adding a gelling agent. Gels offer several benefits, but their delivery of hydrophobic medicines is one of them. As a result, an emulsion-based technique is employed to circumvent this constraint. Emulgel is a unique topical medication delivery technology since it contains both a gel and an emulsion release control mechanism. Emulgels are thixotropic, greaseless, readily spreadable, easily removable, emollient, nonstaining, have a long shelf life, are clear, and have a nice look for dermatological application. As a result, emulgels are a superior topical drug delivery mechanism to current technologies. This study provides information on emulgel, including its features, benefits, formulation considerations, and recent research breakthroughs.

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INTRODUCTION:

Topical drug administration is a localized drug delivery technique that may administer drugs to any part of the body through ophthalmic, rectal, vaginal, and cutaneous channels. These employ a broad range of aesthetic and dermatological treatments for healthy or damaged skin. The physicochemical character of these formulations ranges from solid to semisolid to liquid. Drugs are seldom given alone but usually as part of a formulation with one or more non-medicated chemicals that perform various specialized pharmacological functions. Drugs are applied topically to impact the application site or to have systemic effects. If the drug ingredient is in solution, has a favorable lipid/water partition coefficient, and is a non-electrolyte, drug absorption via the skin is

improved. Pharmaceutical preparations applied to the skin, for the most part, are designed to have a local effect and are made to offer extended local contact with limited systemic drug absorption. Antiseptics, antifungal agents, skin emollients, and protectants are some of the drugs administered to the skin for local action. The primary benefit of a topical administration method is that it bypasses first-pass metabolism. Topical formulations also benefit from avoiding the hazards and hassles of intravenous treatment, as well as a variety of absorption variables such as pH fluctuations, enzyme presence, and stomach emptying time. The topical drug delivery system is often utilized when other methods of medication administration fail or when a fungal infection is present (Fig 1). Human skin is a specially designed organ that allows for terrestrial existence by controlling heat and water loss while blocking the intrusion of harmful chemicals and microbes. It is the biggest organ in the human body, accounting for around 10 % of the typical person's body mass and covering an average area of 1.7 m^2. While such a vast and readily accessible organ seems to provide excellently and many locations for administering therapeutic chemicals for both local and systemic effects, the human skin is a highly effective self-repairing barrier intended to keep the insides in and the outsides out [1].

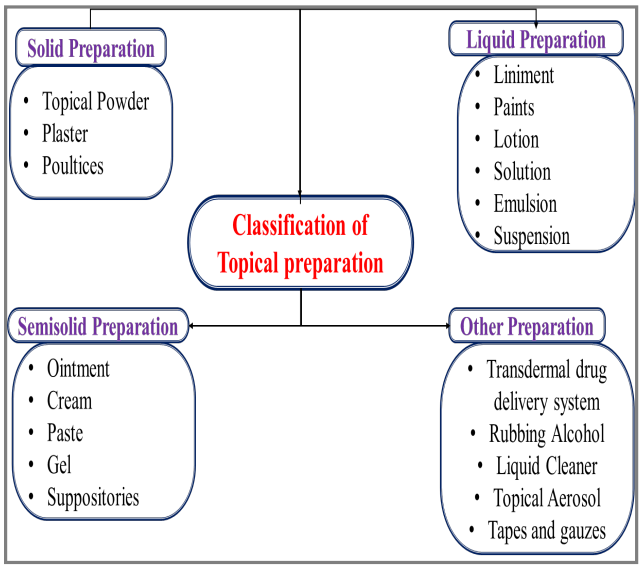

Fig 1. Classification of topical preparation.

Gels are a kind of dosage form made by trapping significant volumes of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may be made of inorganic substances like aluminum salts or organic polymers of natural or synthetic origin. When opposed to an ointment or cream base, they contain a more prominent aqueous component, which allows for more drug solubility and easy drug migration via a vehicle that is practically a liquid. In terms of ease of use and patient acceptance, they are better. Despite the numerous benefits of gels, one significant drawback is the delivery of hydrophobic medicines. As a result, emulgels are created and employed to bypass this barrier, allowing even a hydrophobic medicinal moiety to benefit from the unique features of gels. Adding a gelling ingredient to the water phase transforms a traditional emulsion into an emulgel. Various medications are delivered to the skin using both oil-in-water and water-in-oil emulsions.

Thixotropic, greaseless, easily spreadable, readily removable, emollient, non-staining, extended shelf life, bio-friendly, clear, and appealing look are only a few of the benefits of emulgels dermatological application. The elements that impact percutaneous absorption must be understood when using topical medications. Molecules may enter the skin through three pathways: the intact stratum corneum, sweat ducts, or sebaceous follicle. More than 99 % of the entire skin surface is accessible for percutaneous medication absorption on the stratum corneum's surface. Percutaneous absorption is limited by its ability to pass through this outermost layer. The creation of a concentration gradient, which provides the driving force for drug movement across the skin, the release of drug from the vehicle (partition coefficient), and drug diffusion through the layers of the skin are the primary phases in percutaneous absorption (diffusion coefficient). Low molecular mass (600 Da), good solubility in oil and water, and a high partition coefficient are desirable properties for topical medicines. Water-soluble ions and polar molecules cannot permeate intact stratum corneum save for extremely minute particles. Topical formulations can manipulate the skin's barrier function; for example, topical antibiotics and antibacterial can help a damaged barrier resist infection, sun screening agents. The horny layer can protect viable tissues from UV radiation, and emollient preparations can restore flexibility to a desiccated horny layer [2].

The requirement and effectiveness of the selected preservative must be proved to the satisfaction of the competent authority during the creation of semi-solid preparations for a cutaneous application whose composition comprises an antimicrobial preservative. In the effectiveness of antimicrobial preservation, an appropriate test technique and criteria for determining

the preservative qualities of the formulation are presented. Sterile semi-solid preparations for cutaneous application are made using ingredients and processes that maintain sterility while preventing the entrance of impurities and microbial development. The active element of the practice, the formulation in which it is included, or the container and closure utilized may all affect the efficiency of an antimicrobial preservative. The preparation for topical usage should be microbiologically sound and sterile, as determined by a sterility test. A total viable aerobic count of 102 microorganisms (aerobic bacteria + fungus) per gram is recommended. It should include no more than 101 enterobacteria per gram and certain other gram-negative bacteria and be free of Pseudomonas aeruginosa and Staphylococcus aureus. This study shows that the material and procedure employed do not cause microbiological contamination and that the methylparaben 0.2 % utilized is adequate to keep the product sterile [3]. Emulgels emerged as an exciting drug delivery system, with two release control systems, gel, and emulsion. The important purpose behind this is the delivery of hydrophobic drugs to the systemic circulation through the skin. Many hydrophobic drugs are applied to the oily base and are presently delivered to the skin using emulgel. Emulgel has a few desirable features skin uses such as thixotropic, colorless, non-greasy, easy to spread, long shelf life, emollient, easily removable, transparent, and pleasing look. Implementation of this emulgel-based program as drug delivery vehicles are updated, emphasis on recent developments and future trends.

The objective of the review is to present updated information on emulsion-based gel technology.

RATIONALE OF EMULGEL AS A TOPICAL DRUG DELIVERY SYSTEM:

Many commonly used topical treatments, such as ointment, cream, and lotion, have drawbacks. When administered, they are very sticky, creating discomfort in the sufferer. They also have a lower spreading coefficient and must be applied by rubbing. They also have difficulty with stability. The usage of transparent gels in cosmetics and medicinal preparations has increased due to all of these variables within the principal category of semisolid preparations. A gel is a colloid that is 99 % water by weight and is immobilized by surface tension between it and a macromolecular network of fibers formed by a little quantity of a gelatin material. Despite the numerous benefits of gels, one significant drawback is the delivery of hydrophobic medicines. To address this constraint, an emulsion-based technique is being employed to effectively integrate and transport even a hydrophobic medicinal component via gels [4].

PHYSIOLOGY OF HUMAN SKIN:

Most topical preparations are meant to be applied to the skin (Fig 2). Hence, a basic knowledge of the skin and its physiology function is essential for designing topical dosage forms. The skin of an average adult body covers a surface area of approximately 2 m^2 and receives about one-third of the blood circulating through the body. An average human skin surface is known to contain 40 to 70 hair follicles and 200 to 300 sweat ducts on every square centimeter of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have three distinct layers of tissue [5].

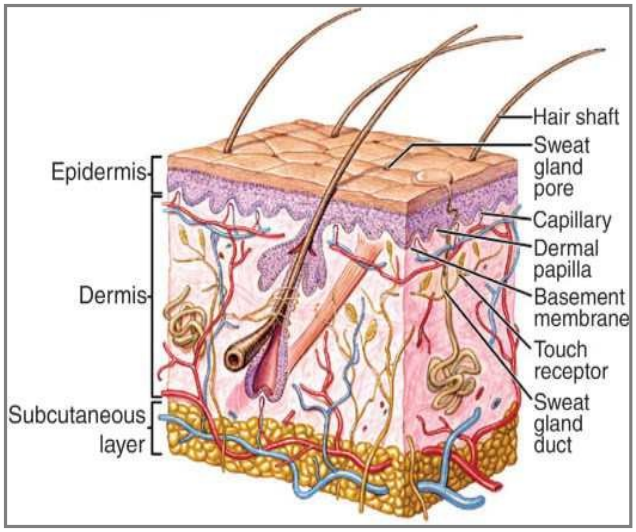

Fig 2. Structure of human skin.

Epidermis:

The stratum corneum is the outermost layer of skin, which is the physical barrier to most substances that come into contact with the skin. The stratum corneum is 10 to 20 cell layers thick over most of the body. Each cell is a flat, plate-like structure – 34 to 44 µm long, 25 to 36 µm wide, and 0.5 to 0.20 µm thick with a surface area of 750 to 200 µm stocked up to each other in a brick-like fashion. Stratum corneum consists of lipid (5 to 15 %) including phospholipids, glycosphingolipid, cholesterol sulfate, and a neutral lipid, protein (75 to 85 %) which is mainly keratin [6].

The layers of the Epidermis are *Stratum germinativum* (Growing layer), Malpighian layer (pigment layer), *Stratum spinosum* (Prickly cell layer), *Stratum granulosum* (Granular layer), *Stratum lucidum* (false layer), and *Stratum corneum* (horny layer).

Stratum germinativum/ Stratum basal:

It is known as the growing layer because the cell of this layer has a high mitotic index and constantly renews the epidermis. Healthy skin balances the loss of dead horny cells from the skin surface.

Malpighian layer:

It is known as the pigment layer. The basal cell includes melanocytes that produce melanin granules to the keratinocytes required for pigmentation, a protective measure against UV radiation.

Stratum spinosum:

The cell of the layer is produced by morphological and histochemical alteration of the basal layers as they move upward. The cells flatten, and their nuclei shrink. Fine prickles interconnect them, known as the prickly cell layer. These links maintain the integrity of the epidermis.

Stratum granulosum:

This layer is above the keratinocytes because of keratinohylline granules, known as the granular layer. This keratogenous zone is a region of intense biochemical activity and morphological change.

***Stratum lucidum*:**

It is a thin, transparent layer of dead skin cells in the epidermis. It is readily visible by light microscopy only in the areas of thick skin, which are found on the palm and sole of the feet, and immediately forms a thin translucent layer. The cells are non-nuclear. It is composed of three to five layers of dead, flattened keratinocytes. The keratinocytes of the stratum lucidum do not feature distinct boundaries, and it is an intermediate form of keratin. The thickness of the lucidum is controlled by mitosis.

Stratum corneum:

It is the superficial layer of the epidermis. It is the physical barrier to most substances that contact the skin. The thickness of the stratum corneum is 10 to 20 cells. Each cell is a flat, plate-like structure and 34 to 44 µm long, 25 to 36 µm wide, and 0.5 to 0.20 µm thick with a surface area of 750 to 1200 µm stocked up to each other in a brick-like fashion. It consists of lipid (5 to 15 %), including phospholipids, glycosphingolipids, cholesterol sulfate, and protein (75 to 85 %), mainly keratin. The cell of this layer contains mainly keratin, so these cells are also known as Coreanocytes [7].

Dermis:

Just beneath the viable epidermis is the dermis. It is structural fibrin, and very few cells like it can be found histologically in normal tissue. Dermis thickness ranges from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphophile's ground substance [8].

Subcutaneous connective tissue:

The subcutaneous tissue or hypodermis is not considered a genuine part of the structured connective tissue, composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretary pores of the sweat gland, and cutaneous nerves. Most investigators consider the drug is permeating through the skin and entering the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug [9].

DRUG DELIVERY ACROSS THE SKIN:

The epidermis is a very thick layer of skin, composed of stratified keratinized squamous epithelium that varies in thickness throughout the body. The elastic fibers make it thicker. The deeper and more fragile skin layers are protected by a waterproof layer made of leather. Beneath the epidermis, there are numerous blood vessels. A continuous venous plexus filled with blood from the skin capillaries is essential. The skin acts as a two-dimensional barrier, preventing water absorption and electrolyte loss. Absorption of topical drugs is divided into transcellular, intercellular, and follicular. Many drugs roam the abrasive pathway past the corneocytes and through the lipid bilayer to reach the active layers of the skin. Chemical penetration rates through the separated stratum corneum and the rest of the skin are almost comparable, indicating that the barrier is located on the outer layer of the epidermis, the stratum corneum. For years, scrubbed creams and gels have been used to bring pain medication and anti-infection medications to the affected area of the body. Gel and vaginal yeast creams, skin lotion creams, and arthritic pain relievers are some examples. Thanks to new technologies, some drugs may now be absorbed through the skin (transdermal). These may be used to treat the entire body, not just the damaged parts (The skin) [10].

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUGS [11,12]:

Physiological factors:

The physiological factors that are affecting the topical absorption of the drugs are the thickness of the skin, the content of lipids, hair follicle density, the number of sweat glands in the body, the pH of the skin, flow of blood, hydration of the skin, and skin inflammation.

Physiochemical factors:

The physiochemical factors that are affecting the topical absorption of the drugs are the coefficient of partition, molecular weight (< 400 Daltons), ionization degree (only unionized drugs get absorbed well), and vehicle impact.

FACTORS TO BE CONSIDERED WHEN CHOOSING A TOPICAL PREPARATION [13]:

- Vehicle effect, an occlusive vehicle, boosts the penetration of the active component and its effectiveness. The vehicle's cooling, drying, emollient, or protecting properties are possible.
- Select the appropriate preparation for the lesions. For acute weepy dermatitis, for example, stay away from oily ointments.
- Choose a method of preparation that is appropriate for the location. (For hairy regions, use a gel or lotion.)
- Potential for irritation or hypersensitivity ointments and w/o creams is often less irritating, while gels are. Ointments are not for you if you have an allergy to preservatives or emulsifiers.

Method to enhance drug penetration and absorption:

The methods that are used to enhance the drug permeation absorption are chemical enhancement, physical enhancement, biochemical enhancement, and supersaturation enhancement [14].

EMULGELS:

They are a hybrid of gel and emulsion, as the name implies. Emulsions of the oil-in-water and water-in-oil types are used to deliver medications to the skin. They're also quite good at penetrating the skin. A traditional emulsion becomes an emulgel when the gelling ingredient is present in the water phase (Fig 3). Thixotropic, greaseless, easily spreadable, readily removable, emollient, non-staining, water-soluble, extended shelf life, bio-friendly, translucent, and pleasant look are only a few of the benefits of emulgel for dermatological application. Molecules may enter the skin through three pathways: the intact stratum corneum, sweat ducts, or sebaceous follicle. More than 99 % of the entire skin surface is accessible for percutaneous medication absorption on the stratum corneum's surface. Percutaneous absorption is limited by its ability to pass through this outermost layer. The creation of a concentration gradient, which provides the driving force for drug movement across the skin, the release of drug from the vehicle (partition coefficient), and drug diffusion through the layers of the skin are the primary phases in percutaneous absorption [15].

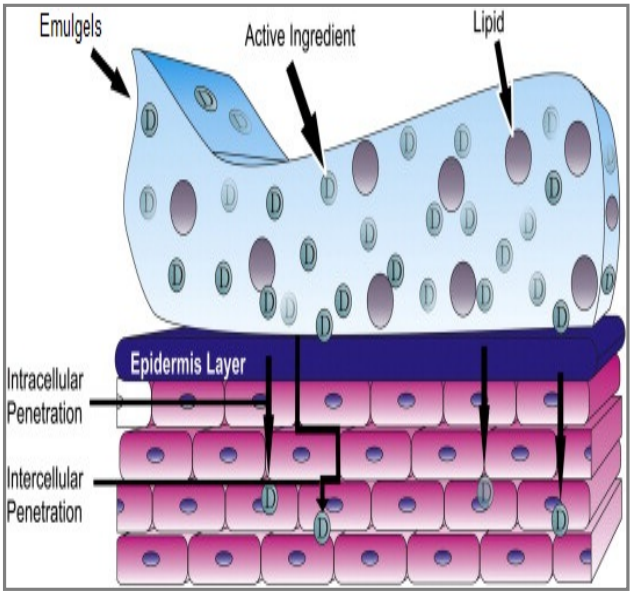

Fig 3. Emulgel structure.

Advantages of emulgel [16]:

Hydrophobic drugs:

Using D/O/W emulsions, hydrophobic medicines may be readily absorbed into gels. Because solubility acts as a barrier, most hydrophobic medication cannot be incorporated directly into gel bases, and problems develop during drug release.

Emulgel aids in the integration of hydrophobic medicines into the oil phase, followed by the dispersion of oily globules in the aqueous phase, resulting in an o/w emulsion. This emulsion may also be added to a gel basis. This will provide better drug stability and release than merely integrating medicines into a gel foundation.

More stable than other transdermal preparations:

Emulgels are more durable than transdermal preparations. Creams display phase inversion or breaking, while ointment indicates rancidity owing to the oily basis, much like powders.

Increased loading capacity:
Other innovative techniques, such as Noisome and Liposomes, are nanoscale and may leak owing to vesicular features, resulting in lower trapping efficiency. On the other hand, Gels have a higher loading capacity due to their extensive network.

***Manufacturing feasibility and cheap preparation costs*:**
Emulgel preparation consists of simple and quick procedures, boosting production feasibility. Emulgel manufacture does not need the use of specialist equipment. As a result, the cost of producing emulgels is reduced.

No severe sonication:
Vesicular molecule production requires extensive sonication, which might lead to drug downfall. However, since emulgels do not need sonication, this issue does not arise.

Controlled release:
Emulgels may be used to extend the duration of action of medications with a shorter half-life.

Disadvantages of emulgel:
Nowadays, emulgel is utilized to circumvent this constraint. As a result, its disadvantage is mitigated. Hydrophobic medications may benefit from the particular features of gels in this manner. The drug's big particle size prevents it from passing through the skin; permeability is low; skin allergy or contact dermatitis may develop; and when emulgel is administered, a bubble may emerge [17].

RATIONALE OF EMULGELS AS NEW FORMULATION [18,19]:
Pharmaceutical topical preparations, such as ointments and creams, have significant drawbacks, such as poor spreadability, penetration, and patient compliance owing to stickiness or the necessity to apply by rubbing, among other things. Gels, too, have the problem of being unable to distribute hydrophobic medicines. Previously, many infections were treated with ointment, creams, and lotions. Emulgels were explored in cosmetics and medicinal preparations for various reasons and limits. As a result, the problem of drug solubility is solved, and the problem of drug penetration. Because emulgel medicines' globules may permeate soft tissues, they need fewer dosages and generate more excellent pharmacological activity. In addition, several additional excipients may aid pharmacological action in some manner. Moisturizers, creams, ointments, and other topical dosage forms have several disadvantages. Stickiness and greasiness are two of them, and they make it difficult for patients to apply them. It also wreaks havoc on the stability of hydrophilic medication formulations. Despite all these focuses, delivering hydrophobic medicines remains a significant challenge. Emulgel has the advantages of both an emulsion and a gel. Emulgel promotes medication absorption via the skin. Topically applied emulgel, on the other hand, provides several benefits over ointment and gels.

Important components of emulgel preparation [20-29]:
Aqueous material:
This is what makes up the emulsion's aqueous phase. Water and alcohol are often utilized, agents.

Oils:
These substances are responsible for the emulsion's oily phase. Mineral oils, either alone or in combination with soft paraffin or hard paraffin, are commonly employed as the drug's carrier, and their occlusive and sensory properties in topically administered emulsions. Non-biodegradable mineral and castor oils, which have a local laxative effect, are often used in oral preparations, as are fish liver oils or different fixed vegetable oils (e.g., Arachis oil, Cottonseed oil, and Maize oil) as nutritional supplements.

***Emulsifiers*:**
Emulsifying compounds are used to enhance emulsification throughout the manufacturing process and maintain stability during a shelf life that may range from days for impromptu emulsions to months or years for commercial preparations. Examples like Polyethylene glycol, stearate, Sorbitan monooleate (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, Sodium stearate, etc.

***Thickening Agent*:**
Gelling agents enhance the consistency of any dosage form and may also be employed as a thickening agent. Examples like Carbopol-934, Poloxamer 407, Sodium CMC, etc.

Permeation Enhancers:
These substances partition into skin components and interact with them to provide a transient and reversible increase in skin permeability. Examples like Oleic acid, Lecithin, Urea, Clove oil, Eucalyptus oil, Menthol, Linoleic acid, Chenopodium oil, etc.

The properties of penetration enhancers are given below;

- They should be non-toxic, non-irritating, and non-allergenic.
- They must have no pharmacological action in the body, which means they must not bind to receptor sites.
- The penetration enhancers should function one-way fashion, allowing therapeutic materials to enter the body while preventing endogenous material from being lost.
- The penetration enhancers should be suitable for incorporating into various topical formulations and hence compatible with excipients and medicines.
- They should have a natural skin "feel" and be aesthetically acceptable.

Vehicle:

The vehicle has the following properties;

- Effectively and evenly distribute the medication on the skin.
- Allow the medicine to move to the site of action readily.
- Deliver the medicine to the desired location.
- Maintain a therapeutic medication concentration in the target tissue for long enough to have a pharmacologic impact.
- explicitly formulated for the anatomical place to be treated.
- The patient finds it satisfactory in terms of appearance.
- The quantity of topical medicine that passes through the stratum corneum is often modest due to the efficacy of the epidermal barrier. The rate and amount of absorption vary based on the vehicle's properties, but the active agent also regulates it.

EMULGEL PREPARATION [30,31]:

Carbopol 934 and Carbopol 940 are disseminated in purified water with continual stirring at a moderate speed, and the pH is then adjusted to 6 to 6.5 using Triethanolamine (TEA). The oil component of the emulsion is made with Span 20 dissolved in light liquid paraffin, while the liquid phase is completed with Tween 20 dissolved in filtered water. The parabens were dissolved in propylene glycol, while the medicine was dissolved in ethanol, and the aqueous phase was mixed with both solutions. The oily and aqueous phases will be heated separately from 70 to 80 °C. The oily phase will be introduced to the aqueous phase and constantly agitated until the mixture reaches room temperature. During the mixing process, add Glutaraldehyde in a 1:1 ratio to the gel and emulsion to form the emulgel [30]. The emulgel preparation is given in Fig 4.

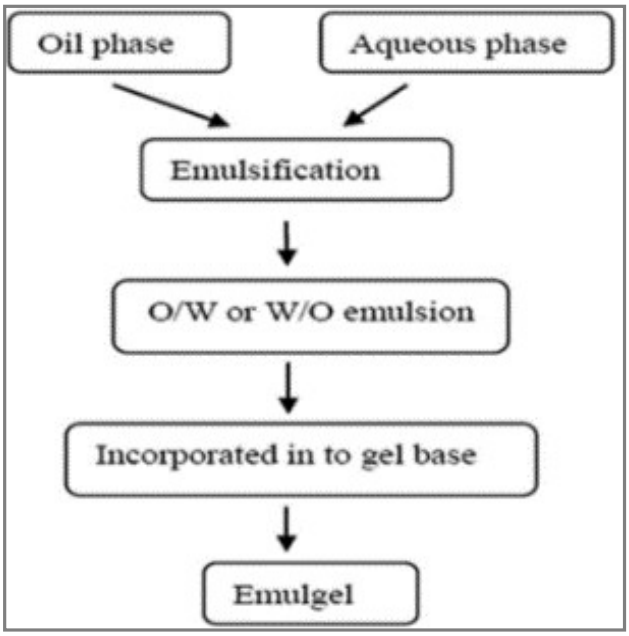

Fig 4. Emulgel preparation technique.

CHARACTERIZATION OF GELLIFIED EMULSION [32-38]:

Physical appearance:

Color, homogeneity, consistency, and pH of the produced Emulsion compositions were visually evaluated. A pH meter was used to determine the pH of 1 % aqueous solutions of the produced Jellified Emulsion.

Spreadability:

Mutimer, *et al.*, 1956 proposed equipment for determining spreadability, adapted in the lab and utilized for the investigation. It is made of a wooden block with a pulley attached to one end. Spreadability is assessed using this approach based on the emulgels 'Slip' and 'Drag' qualities. On this block is a ground glass slide. This ground slide has an excess of emulgel (approximately 2 g) under observation. The emulgel is then sandwiched between this slide and a second glass slide with the same dimensions as the fixed ground slide and a hook. For 5 mins, a 1 kg weight is put on top of the two slides to release air and produce a consistent emulgel coating between the slides. The excess emulgel is scraped away from the edges. After that, an 80 g pull is applied to the top plate. The time (in seconds) taken

for the top slide to travel a distance of 7.5 cm should be recorded with the assistance of a string tied to the hook. A shorter interval indicates better spreadability. The formula was used to determine spreadability.

Extrudability study:

It's a standard empirical test to determine how much force is necessary to extrude material from a tube. The technique used to determine the applied shear in the rheogram area corresponds to a shear rate more significant than the yield value, resulting in plug flow. The method used to assess emulgel formulation extrudability in this research is based on the percentage of emulgel and emulgel extruded from a lacquered aluminum collapsible tube using the weight in gram necessary to extrude at least a 0.5 cm ribbon of emulgel in 10 s. Extrudability improves as the amount extruded increases. Each formulation's extrudability is measured three times, and the average figures are reported. The extrudability is then calculated by using the following formula:

Extrudability = W/A ……(1)

Where W is applied weight in g to extrude emulgel from the tube and A is the area in cm^2.

Globule size and its distribution:

Zetasizer was used to assess the size and distribution of globules. A 1.0 g sample was dissolved in filtered water and stirred to achieve homogenous dispersion. The sample was injected into the zetasizer photocell. The average globule diameter and distribution were calculated.

Rheological Study:

A cone and plate viscometer with spindle 52 attached to a thermostatically controlled circulating water bath is used to evaluate the viscosity of the various emulgel compositions at 25 °C.

Swelling Index (SI):

About 1 g of manufactured topical emulgel is put on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH to estimate the swelling index. After that, samples were taken from beakers at various time intervals and placed in a dry area before being reweighed. The swelling index is calculated as follows:

SI (%) = [(Wt – Wo) / Wo] × 100 …..(2)

Where, (SI) % = Equilibrium percent swelling, Wo = Original weight of emulgel at zero time after time t, Wt = Weight of swollen emulgel.

***Ex-vivo* bioadhesive strength measurement of topical emulgel:**

The bioadhesive strength is measured using the modified outlook. Cut the fresh skin into pieces and wash it in 0.1 N NaOH. Two pieces of skin were linked to two glass slides, one of which was fastened to the wooden part and the other tied to the balance on the right-hand side. The right and left pans were balanced by putting more weight on the left-hand pan. Extra weight from the left pan is removed to sandwich the two pieces of skin, and some pressure is applied to remove the presence of air. 1 g of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two parts of the skin. For 5 mins, the balance is maintained in this posture. Weight is steadily added to the left-hand pan at a 200 mg/min rate until the patch separates from the skin surface. The bioadhesive strength was determined by the weight (gram force) needed to separate the emulgel from the skin surface. The bioadhesive strength (BS) is calculated by using the following:

BS = Weight required (in g) / Area (cm^2) ….(3)

Drug content determination:

A spectrophotometer was used to determine the drug concentration in the jellified emulsion. The drug content of Jellified Emulsion was determined by sonication of a known amount of jellified emulsion in a solvent (methanol). In a UV-Visible spectrophotometer, absorbance was measured after appropriate dilution.

***In-vitro* release study:**

The drug release investigations were conducted using a Franz diffusion cell (effective diffusion area 3.14 cm^2 and cell volume 15.5 ml). Jellified Emulsion (200 mg) was equally administered to the egg membrane's surface. Between the donor and the receptor chamber of the diffusion cell, the egg membrane was clamped. The receptor chamber was filled with freshly made phosphate buffer saline (pH 5.5) solution to solubilize the medication. A magnetic stirrer was used to agitate the receptor chamber. At appropriate intervals, the samples (1.0 ml aliquots) were collected. After proper dilutions, samples were tested using a UV-Vis spectrophotometer for drug content. To determine the overall quantity of medication released each time, cumulative adjustments were made. The total amount of drugs released through the egg membrane was calculated as a function of time.

Drug release kinetics:

To analyze the mechanism of drug release from the topical gel, the release data were fitted to the following equations:

Zero-order equation: $Q = k0\ t$ ……(4)

Where, Q is the amount of drug released at time t, and k0 is the zero-order release rate.

First-order equation: $\ln (100 - Q) = \ln 100 - k1\ t$ ….(5)

Where, Q is the percent of drug release at time t, and k1 is the first-order release rate constant.

Higuchi's equation: $Q = k2\sqrt{t}$ ……..(6)

Where, Q is the percent of drug release at time t, and K2 is the diffusion rate constant.

Microbiological assay:

The method of ditch plates was applied. It's a method for determining a compound's bacteriostatic or fungistatic activity. It's primarily used in semisolid formulations. Sabouraud's agar-dried vessels that had been previously prepared were employed. In a trench made in the dish, 3 g of jellified emulsion are put. From the ditch to the plate's border, freshly made culture loops are streaked over the agar at a right angle. The fungal growth was examined after 18 to 24 h of incubation at 25 °C, and the % inhibition was calculated.

Skin irritation test:

A 0.5 g sample of the test product was then introduced beneath a double gauze layer to an area of skin measuring 1" × 1" for each location (two sites per rabbit) (2.54 × 2.54 cm^2). The jellified emulsion is applied to rabbit skin. The animals were put back in their cages. The jellified Emulsion is removed after a 24 h exposure. To eliminate any leftover test article residue, the test locations were cleaned with tap water.

Accelerated stability studies of gellified emulsion:

Stability tests were carried out as per ICH recommendations. The formulations were kept in a hot air oven for three months at 37±2, 45±2, and 60±2 °C. The samples were tested for drug content every two weeks using a UV-Visible spectrophotometer. The change in pH of the gel was measured at regular intervals throughout the stability.

Packaging of emulgels:

Emulgels are typically packaged in a membrane-sealed lacquered aluminum tube with an inner coating of phenoxy-epoxy-based lacquer and a propylene screw cap or in an aluminum laminated tube with a molded seal and a propylene screw cap. Boxes are made of laminated material. Foil laminates provide light, air, and moisture barriers. All plastic laminates have a chemical-resistant barrier [39,40].

MARKETED EMULGELS:

Globally, manufacturers have developed Emulgel products and are into market circulations (Table 1) [41-43].

REVIEW OUTCOME:

Many formulations are utilized in topical medication delivery systems, but each has its own set of drawbacks. The majority of these drawbacks are mitigated by emulgel preparation. The emulgel is the most convenient, better, and effective delivery technique throughout the project. Incorporating emulsion within the gel becomes a dual control release system that addresses issues such as phase separation, emulsion creaming, and improved stability. Emulgel, like emulsion and gel formation, requires ingredients. The production of emulgel consists of three steps: emulsion preparation, gel preparation, and the combination of the two. Every formulation requires a thorough examination. As a result, roughly twenty-five different determination methodologies are available, including photomicroscopy, spreadability, rheological studies, *in-vitro* drug release studies, etc. The emulgel is commonly used nowadays. Miconaz-H emulgel, Isofen emulgel, Diclon emulgel, and other emulgels are routinely used. Typically, emulgel are used to treat inflammation.

FUTURE PERSPECTIVES:

Hydrophobic behavior of drugs is one of the most common problems faced during the formulation and development of any new formulation. This behavior is responsible for poor water solubility and the bioavailability of drugs. Many numbers of medicines are hydrophobic. Their delivery to the biological system has been challenging. Different delivery systems such as ointments, lotion, creams, and pastes are applied for topical delivery of drugs. These topical formulations generally include many greasy bases such as petrolatum, beeswax, or vegetable oils. Those themselves are hydrophobic that do not allow the inclusion of water or aqueous phase. It makes them an excellent emollient but retards the release of drugs and makes the product thick and greasy. Whereas gel provides an aqueous environment to the drug, favors its dissolution, and offers quicker drug release compared to other topical delivery systems. The emulsion-based gel offers a suitable medium for delivering hydrophobic medicines

Table 1. Marketed Emulgel products [41-43].

Brand Name	Active ingredient	Manufacturer	Uses
Accent Gel	Aceclofenac	Intra Labs India Pvt. Ltd.	Anti-inflammatory
Avindo gel	Azithromycin	Cosme Pharma Lab Ltd.	Anti-bacterial
Cataflam Emulgel	Diclofenac Diethylammonium	Novartis	Anti-inflammatory
Clina Gel	Clindamycin phosphate, Allantoin	Stiefel Pharma Ltd.	Anti-bacterial
Cloben Gel	Clotrimazole, Betamethasone	Indoco Remedies	Anti-fungal
Denacine Emulgel	Clindamycin phosphate	Beit Jala Pharmaceuticals	Anti-acne
Diclon Emulgel	Diclofenac Diethylammonium	Medpharma	Anti-inflammatory
Excex Gel	Clindamycin, Adapalene	Zee Laboratories Ltd.	Anti-bacterial, Anti-acne
Kojivit Gel	Kojic acid, Dipalmitate arbuti	Micro Gratia Pharma Ltd.	Sunscreen
Miconaz-H Emulgel	Miconazole nitrate, Hydrocortisone	Medical Union Pharmaceuticals	Topical Corticosteroid, Anti-fungal
Nadicin cream	Nadifloxacin	Psycho Remedies	Anti-bacterial
Pernox Gel	Benzoyl peroxide	Cosme Remedies Ltd.	Anti-acne
Topinate Gel	Clobetasol propionate	Systopic Pharma	Skin care
Voltarol Emulgel	Diclofenac Diethylammonium	Novartis	Anti-inflammatory
Zorotene Gel	Tazarotene	Elder Pharmaceuticals	Total skin care

where such drugs can be incorporated into their oily phase and returned to the skin. All such advantages of emulgel over other topical delivery systems make them more efficient and productive. These properties will be used to deliver more topical drugs in the form of emulgel [44,45].

CONCLUSION:

Emulgel is a recently discovered topical drug delivery approach best suited for hydrophobic pharmaceuticals and is a superior strategy for drug delivery of hydrophilic and lipophilic medications. The emulgel method may make a hydrophobic drug formulation since it contains oil and an aqueous phase, but hydrogels are not suited for hydrophobic pharmaceuticals. As compared to other topical delivery systems gel provides quick drug release as they provide an aqueous environment for drugs. Many hydrophobic drugs are incorporated in an oily base and are delivered to the skin by using an emulgel. Topical medicine administration will be widely employed to improve patient compliance. As a result of emulgel capacity to improve spreadability, adhesion, viscosity, and extrusion, this innovative drug delivery formulation will become well-known in the future.

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