Emulgel: An Imminent Technology for Topical Drug Delivery Systems

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Abstract: Pharmaceutical researchers are currently interested in emulgel systems because of their significant potential to serve as drug delivery systems by combining a variety of therapeutic compounds. These are either water-in-oil emulsions or oil-in-water mixtures that have been gelled by adding a gelling agent. Gel becomes a dual control release mechanism and more stable when emulsion is added to it. In comparison to other topical drug delivery systems, it exhibits improved drug release due to the absence of insoluble excipients and excessive oily bases. Due to non-greasy due to the gel phase's existence, which encourages good patient compliance. This paper provides a general overview of the optimal features, production, and characterisation of emulgels in order to better comprehend their potential as delivery vehicles. Review of the utilisation of emulgel-based systems as drug delivery vehicles is done with a focus on recent advancements and potential future prospects.

Index Terms: emulgel, hydrophobic, emulsion, gel, topical.

I.INTRODUCTION

In the past, many administration methods—including sublingual, oral, rectal, topical, parenteral, inhalation were employed to treat various illnesses. The topical medication delivery strategy is typically utilised when other drug administration methods are ineffective or is mostly utilised in fungal infections. The human skin is a specially designed that allows for terrestrial existence by controlling loss of water and heat from the body while guarding against the entry of harmful substances or germs. It is also the largest organ in the human body, making up 10% of the average person's body weight and occupy an area of 1.7 m^2[1]. Topical delivery, in which the required drug is applied to the skin, is chosen when a person has cutaneous disorders including acne, psoriasis, eczema etc. Although this mode of administration has a long history, new techniques and technologies are being researched and developed in order to improve patient comfort [2]. The topical administered route is the most effective choice for cutaneous applications since the skin is the typically accessible organ and makes drug delivery easier and more effective than other routes [3, 4]. The most frequent local application of topical medicines is for localised effects at the application site [5].The capacity to distribute drugs more precisely to a particular spot and the prevention of gastro-intestinal incompatibility are two benefits of topical drug delivery systems.[6]Additionally, topical deliveries that skip first pass metabolism offer a higher bioavailability and consistent delivery over a longer time frame [7,8].

In topical treatment, the drug diffuses to the site of action from the delivery system, where it is absorbed in place of the skin.[9] Increasing the drug's rate of release from the dosage form can help percutaneous absorption [10] The varied physical and chemical features of the carrier and the medicine used directly affect the release rates of pharmaceuticals from topical formulations. [11,12] Drugs that are applied topically work in two different ways. Penetration of the drug through the skin membrane is increased if it has a favourable o/w partition coefficient or in the form of a solution and if it is a nonelectrolyte. Pharmaceutical products applied topically to the skin are often meant to have a local effect; as a result, their formulations are created to give extended local contact with the least amount of systemic drug absorption. Antiseptics, skin emollients, antifungal agents, and protectants are drugs that are applied topically for their local effects.[7,8]

II. Different types of topical drug delivery systems

Solid: powders, plasters, etc.
Semi-solid: ointments, creams, poultices, gels, pastes, etc.
Liquid: tinctures, emulsions, paints, lotions, etc.
Miscellaneous: topical aerosol, gauzes, rubbing alcohols, liquid cleansers, tapes, etc. [13].

Large quantities of hydroalcoholic or aqueous liquid are trapped in a colloidal solid particles network to generate gels, a more recent family of dosage forms. Related to traditional creams and ointments, gel formulations typically offer quicker medication delivey. Despite numerous One of the gel's significant drawbacks is how challenging it is to distribute hydrophobic medications. Emulgels are created as a result to get off this restriction, which allows hydrophobic drugs to enjoy the the special qualities of gels. Emulgels are the dosage forms that are used when gels and emulsions are combined. In reality, when a gelling ingredient is present in the water phase a traditional emulsion becomes an emulgel.

III.EMULGEL

Water in oil or oil in water are the two types of emulgels. By adding a gelling material, these are made gelled [14]. Various emulgels are frequently utilised in the pharmaceutical sector to deliver different medications topically to the skin [15]. They own their ability to readily enter the skin makes them distinctive [16]. Emulgel is a formulation that incorporates an ingredient in the water phase.[17]. Emulgel is the term used when a traditional gel and an emulsion are joined [18]. Since they have the characteristics of both gels and emulsions They have a high level of patient acceptability [19]. They frequently transport different medications to the skin due to their dual characteristics [20]. Emulgels may alternatively be referred to as creamed gels or gelled emulsions [21]. Some of the key advantages of emulgels include their bio-friendly, thixotropic, readily removable, long shelf-life, emollient, attractive,

greaselessness, translucent appearance, [22].Emulgels are a less widely advertised product even though they are thought to be in a developing industry. Emulgels are now a attractive and difficult dosage form to concentrate on because of this [23]. There are several benefits since emulgel is thought to be applied topically delivery. The dispersed phase and the two immiscible phases in emulsions Using an emulsifying agent for improved stability, the two phases are the discrete and continuous [24]. They are either O/W or W/O in Identifying the drug particles stuck in the internal phase goes through the exterior phase before progressively delivers a regulated action when absorbed into the skin [25].

The USP definition of gel states that it is a semi-solid dispersion consisting of either large organic molecules or small inorganic particles that are encased in liquid. It comprises a significant volume of aqueous or hydro-alcoholic liquid in the form of the cross-linked network where drug particles are trapped, maintaining a controlled release effect continually [26]. The liquid phase produces physical or chemical cross-linking, resulting in the three polymeric matrix structure. Its continuous structure results in homogeneous, unambiguous behaviour that resembles that of a solid. Both the emulsion and the gel are necessary for the regulated drug release from the system [27].

There are two different kinds of gels; the first is created using a solvent and is known as an organic, hydrophobic, or organogel, while the second is created using water and is known as a hydrophilic or hydrogel [28]. The most common type of gel is made of base fluid paraffin combined with polyethylene or greasy oils and colloidal silica, aluminium, or zinc cleansers, while the alternate type has propylene as the basis [29]. Although gels have numerous benefits, they also have significant drawbacks when it comes to the delivery of hydrophobic medications. The emulgel hypothesis, which combines hydrophobic medications in an emulsion before mixing them into the gel, was introduced as a remedy for these restrictions and to enjoy the dispersion of drugs in the gel formula [30].

A strategy by which Both the advantages of gel and emulsions are well known as an emulgel where there is an increase in the twin measured release impact.The emulsion, which is incorporated into the gel base, is either oil in water or vice versa. Emulgels can be simply described as gel-based emulsions [31]. In an emulsion, the drug particles are suspended in Consolidated inside the stage, serving as a calm source from the place where the sedative travels through the outdoor stage and to theskin and swallowed [32].

Emulgel is a superior option when it comes to Class II medications of the BCS classification because it has a poor solubility and high permeability [33]. They are emollient, non-staining water solvent, thixotropic, greaseless, efficiently spreadable, easily removable, bio appealing, and have a pleasing look that increases awareness of merit [34]. Emulgels are used all over the world to treat various anti-inflammatory activity and other skin-related viral, bacterial, and infectious contaminations [35].

IV.Drug delivery across the skin

The epidermis, the layer of skin that is closest to the surface, is made up of stratified keratinized squamous epithelium, which varies in thickness depending on where on the body it is located. On fibres with little stretch, it is thickest. The deeper and more fragile structures are shielded by the relatively waterproof covering that the skin creates. There are many blood vessels all over the skin. A continuous venous plexus that receives blood supply from skin capillaries is particularly significant. Blood is also given to the plexus directly from the tiny arteries in the body's most exposed regions—the hands, feet, and ears—through highly muscular arteriovenous anastomoses. Skin can be directly accessed for diagnosis and therapy, which is a distinctive feature of dermatological pharmacology.

The skin functions as a two-way barrier to stop the absorption and loss of electrolytes and water. Topical medication absorption mostly occurs through three mechanisms: transcellular, intercellular, and follicular. The majority of medications navigate the difficult trip around corneocytes and through the lipid bilayer to reach the skin's viable layers. The pilosebaceous route is the second most typical (and possibly under-appreciated in the clinical setting) method of distribution. As shown by about identical rates of chemical penetration through isolated stratum corneum or whole skin, the barrier is located in the epidermis' uppermost layer, the stratum corneum. Since many years ago, painkillers and antibiotics have been applied topically to damaged areas of the body using creams and gels. Among these are topical creams for skin infections, creams to relieve arthritis pain, and gels and creams for vaginal yeast infections. Other medications can now be absorbed through the skin thanks to new technologies (transdermal). These can be used to treat the entire body as well as the problematic parts (such the skin, for example). (systemic)

V.Factors Affecting Topical Absorption of Drug[36,37]

Physiological Factors

1. Skin thickness.
2. Lipid content.
3. Density of hair follicles.
4. Density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.
8. Inflammation of skin

Physiochemical Factors

1. Partition coefficient.
2. Molecular weight (<400 Dalton).
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles

VI.Considerations to Make When Selecting a Topical Preparation [38,39]

1. The effect of the vehicle, such as how an occlusive vehicle increases the active ingredient's penetration and increases effectiveness The vehicle's own actions could be cooling, drying, emollient, or protecting.

2. Align the preparation type with the kind of lesions. For acute weepy dermatitis, for instance, stay away from greasy ointments.
3. Align the preparation method with the location. (Example: gel or lotion for places with hair)
4. The potential for irritation or hypersensitivity Ointments and creams without alcohol are typically less irritating, whereas gels are irritating.
If a person has a preservative or emulsifier allergy, ointments are not recommended.

VII. Method to Enhance Drug Penetration and Absorption. [40]

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancement

VIII. ADVANTAGES [41,42]

1. O/W emulsions make it simple to introduce hydrophobic medicines into gels. Most hydrophobic medications cannot be added directly to gel bases because their solubility acts as a barrier and causes issues with drug release. In order to create an oil-water emulsion, hydrophobic medicines must first be incorporated into the oil phase. Emulgel aids in this process. This emulsion can also be incorporated into a gel base.Compared to just incorporating drugs into a gel base, this may demonstrate superior drug stability and release.
2. Better stability: Emulgels are more stable than other transdermal preparations, which are often less stable. Similar to how creams exhibit phase inversion or breaking and ointments exhibit rancidity because of their oily base, powders are also hygroscopic.
3. Greater loading capacity: Other cutting-edge methods, such as niosomes and liposomes, are nanosized and may leak due to vesicular features, which lowers trapping efficiency. However, gels have a considerably higher loading capacity due to their extensive network.
4. Production feasibility and cheap preparation costs: Emulgel preparation involves only a few straightforward procedures, which improves production feasibility. The creation of emulgels does not require any specialist equipment. Additionally, the materials are inexpensive and readily available. reduces the price of making emulgels as a result.
5. No intensive sonication: Vesicular molecules require intensive sonication for production, which could cause medication degradation and leakage. However, because sonication is not used in the manufacturing of emulgels, this issue is not present.
needed.
6. Emulgels can be used to extend the effects of medications with shorter half-lives (t1/2). Both hydrophobic (without emulgel) and hydrophilic (without emulsion) medications can be administered using it.

IX. Important Ingredients in the Preparation of Emulgel

1. **Aqueous Material**: This contributes to the emulsion's aqueous phase. Alcohols and water are often used agents.[43]
2. **Oils**: These substances contribute to the emulsion's oily phase. Mineral oils are frequently utilised for topically applied emulsions, both as the drug's delivery system and for their occlusive and sensory properties. They can be used alone or in combination with soft or hard paraffins. Widely used oils in oral preparations include fish liver oils and different fixed oils of vegetable origin (such as arachis, cottonseed, and maize oils) as dietary supplements as well as nonbiodegradable mineral and castor oils that have a local laxative effect. [44,45]
3. **Emulsifiers:** Emulsifying compounds are used to control stability during a shelf life that can range from days for impromptu made emulsions to months or years for commercial preparations. They are also used to enhance emulsification at the time of creation. Stearic acid [46], Sodium stearate, Polyethylene glycol [47] stearate, Sorbitan monooleate [48] (Span 80), Polyoxyethylene sorbitan monooleate (Tween80) [49][50]
4. **gelling agents:**

These substances are used to make dose forms more consistent and can also be employed as thickeners [51,52].

5. **permeation enhancers**

These substances cause a brief and reversible increase in skin permeability by partitioning into and interacting with skin constituents [53]

X. METHOD OF FORMULATION

There are several ways to make Emulgel, using different types of ingredients.
Mohamed (2004) documented one approach in his research paper (optimization of chlorphenesin in Emulgel), which involves first creating an emulsion (o/w or w/o), then adding a gelling agent to create Emulgel. Here, the aqueous phase of the emulsion is formed in the first step. Tween 20 is first dissolved in clean water to create the aqueous phase of the emulsion, and then methyl and propyl paraben are dissolved in propylene glycol to create the solution for the emulsion, which is then combined and left aside. In order to make the gel phase of Emulgel, HPMC or Carbopol are dissolved in water. In contrast to Carbopol gel, which may be made by simply scattering HPMC in clean water for an overnight soak, When both the emulsions and the gel are ready, they are combined in a 1:1 ratio with moderate swirling to create the Emulgel [54].
Perioli et al. (2008) reported on a different approach in their research on the development and characterisation of Emulgel for buccal delivery. Here, the creation of Emulgel requires three steps: neutralising the polymeric aqueous dispersion, neutralising the polymer dispersion in water, and emulsifying the oil phase. Three different TR-1 percentages, namely 0.3, 0.4, and 0.5%, w/v, are needed for the first phase. Using a mechanical stirrer with three blade helical impellers, the first stage entails suspending the polymer in deionized water for 20 minutes at room temperature. The slurry is then neutralised with NaOH solution (18% w/v) to the desired pH 5.5, 6.0, and 6.5 as values. Clear, stable gels are produced as a result of the distension of polymer chains during the neutralisation process. Now, polymer gels must be kept at 4 °C for 24 hours before the addition of oil phase in order to hydrate completely. Following the completion of the gel's hydration, various amounts of oil phase in three o/w ratios (w/w) of 0.5, 1.0, and 1.5 are added while being stirred at 800 rpm (80 °C). After cooling, the pH of the mixture is then determined. [55]

Shahin et al. (2011) developed Emulgel for the delivery of clotrimazole using a new methodology. With the help of a magnetic stirrer, the drug and span 60 are dissolved in the oily phase of the emulsion at a temperature of 75 °C. After cooling, the oily phase is next mixed with carbopol. Secondly, Brij-35 is dissolved in propylene glycol to create the aqueous phase. Triethanolamine, a gelling agent, and/or HPMC are added to the emulsion using an overhead mixer at 200 rpm for 45 minutes in order to gel it. This process also entails correcting the pH of the formulation including Carbopol to 5.5-6.5 using TEA.[56]

XI. CHARACTERIZATION OF EMULGELS [57-65]

Physical appearance: The prepared emulsion formulations' colour, homogeneity, consistency, and pH were all visually assessed. Using a pH metre, the pH values of 1% aqueous solutions of the gelatinized emulsion were determined (Digital pH metre DPH 115 pm).

Spreadability: Spreadability is assessed using Mutimer et al. (1956)-recommended equipment that has been appropriately adjusted for use in the study. It is made up of a wooden block that has a pulley at one end. This method bases the measurement of spreadability on the emulgels' "Slip" and "Drag" properties. On this block is fixed a ground glass slide. On this ground slide, extra emulgel (approximately 2 gm) is being studied. The emulgel is then sandwiched between this slide and another glass slide \shaving the dimension of fixed ground slide and equipped with the hook. To remove air and create a consistent emulgel coating between the slides, a 1 kg weight is placed on top of the two slides for five minutes. The edges are scraped clean of extra emulgel. A pull of 80 grammes is then applied to the top plate. With the use of a thread fastened to the hook, record the amount of time (in seconds) needed for the top slide to travel 7.5 cm. Better Spreadability is indicated by a shorter interval. Spreadability was determined using the following formula:

$$S = M.L/T$$

Where,
S = spreadability,
M = Weight tied to upper slide,
L = Length of glass slides
T = Time taken to separate the slides completely from each other.

Extrudability study:

This common empirical test determines the amount of force needed to extrude the substance from a tube. The technique used to determine the amount of applied shear in the area of the rheogram where the yield value is exceeded and plug flow is as a result. The method used in the current study to assess an emulgel formulation's extrudability is based on the amount of emulgel and emulgel extruded from a lacquered aluminium collapsible tube on application of the weight in grammes required to extrude at least 0.5 cm of emulgel ribbon in 10 seconds. Extrudability is improved by greater extrusion volume. Each formulation's extrudability is measured three times, and the average results are given.

The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (in gm.) / Area (in cm2).

Globule size:

Malvern Zetasizer was used to calculate the distribution and size of the globules in the emulgel. For homogenous dispersion, a 1gm sample was dissolved in filtered water and stirred. A sample was inserted into the zetasizer's photocell. The distribution and mean globule diameter were determined.

Rheological Study:

Using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories) coupled to a thermostatically controlled circulating water bath, the viscosity of the various emulgel compositions is assessed at 25°C.

Swelling Index:

To calculate the topical emulgel's swelling index, 1 gramme of gel is placed on a piece of porous aluminium foil and then placed separately in a 50 ml beaker with 10 ml of 0.1 N NaOH. After then, samples were taken out of the beakers at various intervals and placed on a dry surface for a while before being reweighed. Swelling index is determined as follows:

$$\text{Swelling Index (SW)} \% = [(Wt - Wo) / Wo] \times 100.$$

Where, (SW) % = Equilibrium percentage 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 modified approach is employed to gauge the bioadhesive strength (MICE SHAVEN SKIN). The new skin is sliced into pieces and rinsed with 0.1 N NaOH. Separately, two pieces of skin were fastened to two glass slides; one glass slide was secured to a wooden piece, while the other was fastened to the balance on the right side. By placing more weight on the left-hand pan, the right and left pans were brought into balance. The two slides containing the hairless skin pieces are sandwiched with 1 g of topical emulgel, additional weight from the left pan is removed, and pressure is applied to remove any air pockets. For five minutes, the balance is held in this posture. Weight is gradually added to the left-hand pan at a rate of 200 mg/min until the patch separates from the skin's surface. The bioadhesive strength was determined by the mass (gramme force) needed to pull the emulgel away from the skin's surface. The following formulas are used to compute the bioadhesive strength:

Bioadhesive Strength = Weight required (in gm) / Area (cm2)

Drug Content Determination:

A spectrophotometer was used to calculate the drug content in the gelified emulsion. Gellified Emulsion's drug content was determined by sonicating a known quantity of the emulsion into a solvent (methanol). After an appropriate dilution, absorbance was measured using a UV/VIS spectrophotometer.

Invitro diffusion studies:

For the drug release studies, a Franz diffusion cell (15.5 ml cell volume, 3.14 cm2 effective diffusion area) was employed. A uniform coating of gelatinized emulsion (200 mg) was applied to the egg membrane's surface. Between the donor and the receptor chamber of the diffusion cell, the egg membrane was clamped. To solubilize the medication, newly made PBS solution (pH 5.5) was added to the receptor chamber. Magnetic stirrer was used to stir the receptor chamber. At appropriate intervals, the samples (1.0 ml aliquots) were collected. After the proper dilutions, samples were examined for drug content using a UV visible Spectrophotometer. To determine the overall amount of drug release at each time period, cumulative adjustments were done. A function of time was used to calculate the total amount of medication released across the egg membrane.

Microbial assessment:

The ditch plate method was employed. This method is employed for evaluation of a substance's bacteriostatic or fungistatic potential compound. It is mostly used for compositions that are semisolid.The Sabouraud's agar dried plates were previously produced. A ditch is filled with three grammes of the gellified emulsion. plate has been cut. Culture loops that have just been made are streaked from the ditch to the edge of the agar, straight across the dish. 18 to 24 hours of incubation at 25°C results in the fungi were found to be growing, and the amount of inhibition as follows was measured.

$$\% \text{ inhibition} = L2 / L1 \times 100$$

Where L1 = total length of the streaked culture

L2 =length of inhibition.

Test for skin irritability:

A 0.5 gm sample of the test substance was then introduced under a double layer of gauze to each location (two sites per rabbit), measuring approximately 1" × 1" (2.54 x 2.54 cm2). On the skin of the rabbit, the gellified emulsion was applied. The creatures were put back in their cages. The Gellified Emulsion is removed after a 24-hour exposure. To get rid of any last bits of test article residue, the test locations were cleaned with tap water.

Accelerated stability studies of emulgel:

Stability tests were carried out in accordance with ICH recommendations. For three months, the formulations were kept in a hot air oven at 37°, 45°, and 60°. Every two weeks, samples were examined using a UV-visible spectrophotometer to determine their drug content. Gel's pH change was monitored at regular intervals of time as part of a stability study.

Study of Drug Release Kinetics

The release data were fitted to the following equations in order to analyse the mechanism of drug release from the topical gel.

- **Zero – order equation:**

$$Q = K\,0t$$

Where Q is the amount of drug released at time t, and K0 is the zero – order release rate.

- **First – order equation:**

$$\text{In}\,(100 - Q) = \text{In}\,100 - K1t$$

Where Q is the percentage of drug release at time t, and K1 is the first – order release rate constant.

- **Higuchi's equation:**

$$Q = K2\sqrt{t}$$

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

XII.Stability studies:

The prepared emulgels were placed in aluminium collapsible tubes (5 g) and subjected to stability tests over a three-month period at 5°C, 25°C/ 60% RH, 30°C/ 65% RH, and 40°C/75% RH. At intervals of 15 days, samples were taken out and examined for their physical characteristics, pH, rheological characteristics, drug content, and drug release profiles.

XIII. Marketed formulations:

Voltaren Emulgel is a topical analgesic gel that is sold commercially and relieves back and shoulder pain while also reducing edoema. Voltaren Emulgel is a white, odourless gel that is non-greasy and supplied in a 100g tube and contains the active component diclofenac diethylamine at 1% w/w sodium. Diclomax Emulgel, made by Torrent Pharma, is another emulgel used to treat inflammation of the tendons, ligaments, muscles, and joints. Medical Union Pharmaceuticals makes the Miconaz H emulgel, which has an active component. Both hydrocortisone and miconazole nitrate have bactericidal, fungicidal, anti-inflammatory, and antipruritic effects.

XIV.Conclusion

This article effectively explored the topic of emulgels because it addressed all the important concerns and aspects while emphasising their significance. The majority of medications are available in hydrophobic form, making the formulation of these medicines a difficult task. When we think about administering these medications topically, we are thinking about using traditional dose forms, such as creams, ointments, lotions, emulsions, etc. Drug's hydrophobic properties cause stability and bioavailability problems in a variety of dosage formulations. A contemporary formulation, ideal emulgels is provided as the remedy, where the medication is dissolved in the emulsion's oil phase. Combining the oil and aqueous phases produces the controlled release effect. Additionally, it improves the drug's bioavailability. Emulgel is a fantastic complement to dermatological pharmacotherapy and a highly helpful topical dose form. Emulgels improve patient compliance since they have a variety of spreadability, viscosity, adhesion, and other qualities. When used with hydrophobic medications, they will work more effectively and have less adverse effects. Emulgels will be extremely important in the next years for the delivery of hydrophobic medications because to the benefits discussed above in this article.

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