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Research

Emulgel: A Promising Tool For Improve Skin Permeability And Stability

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Abstract

Emulgel is a versatile pharmaceutical formulation designed to deliver hydrophobic and hydrophilic drugs topically. Comprising a combination of hydrophilic gelling agents and lipophilic substances, emulgels offer unique advantages such as enhanced drug solubility, prolonged drug release, improved skin permeation, and increased stability compared to conventional gels or creams. The formulation process involves creating a stable emulsion of oil and water phases, which is then thickened using gelling agents like carbomers or cellulose derivatives. This results in a semi-solid, easily spreadable gel with a smooth texture. Emulgels can accommodate a wide range of active pharmaceutical ingredients, making them suitable for various therapeutic applications including anti-inflammatory, analgesic, antimicrobial, and dermatological treatments. The biphasic nature of emulgels allows for efficient incorporation of both lipophilic and hydrophilic drugs, enabling targeted delivery to the site of action while minimizing systemic side effects. Additionally, emulgels can be tailored to control drug release kinetics, offering sustained or controlled release profiles based on specific therapeutic requirements. This review provides an overview of emulgel, its advantages, and disadvantages, drug delivery mechanism, material used for formulation, and evaluation techniques of emulgel, as well as their potential applications in drug delivery.

Keywords: Emulgel, Carbomers, Lipophilic, Hydrophilic

INTRODUCTION

Topical drug delivery systems offer several advantages, including targeted delivery to specific sites and the prevention of gastrointestinal incompatibilities [1]. Furthermore, they enhance bioavailability and ensure consistent delivery over an extended period by bypassing first-pass metabolism [2, 3]. In such systems, drugs diffuse out of the delivery vehicle and are absorbed through the skin, reaching their site of action [4]. Enhancing

percutaneous absorption can be achieved by increasing the drug release rate from the dosage form. The release rates of medications from topical preparations are directly influenced by the physical and chemical properties of both the carrier and the medication itself [5,6]. The emergence of gels as a contemporary dosage form stems from their ingenious construction, wherein copious amounts of aqueous or hydroalcoholic liquids are ensnared within a meshwork of colloidal solid particles. These particles, composed of inorganic substances like aluminum salts or organic polymers of natural or synthetic origin, facilitate the dissolution and easy migration of drugs due to the substantial aqueous component, surpassing traditional bases like ointments or creams in drug dispersion and patient preference [8]. However, despite their myriad advantages, gels encounter a significant drawback in delivering hydrophobic drugs effectively [9]. To address this limitation, the concept of emulgels arises, bridging the gap by allowing hydrophobic therapeutic agents to harness the unique benefits of gels. By incorporating a gelling agent into the water phase, a conventional emulsion transforms into an emulgel, presenting a versatile platform for delivering diverse drugs to the skin, whether through oil-in-water or water-in-oil emulsions [10].

Emulgel

Emulgel is considered an advanced leading form of topical drug delivery system. It possesses the quality of a dual control drug mechanism for drug release as it holds the properties of both gel as well as emulsion.

Types of emulgel

Emulgel possesses the capability to transport both hydrophilic and lipophilic medications by accommodating both aqueous and non-aqueous phases. Over recent years, it has gained prominence as a controlled-release formulation, presenting as a biphasic system with enhanced drug loading capacity and stability [11,12]. Its myriad favorable attributes include excellent spreadability, non-greasiness, thixotropic behavior, prolonged shelf life, absence of odor, and an aesthetically pleasing appearance, surpassing conventional topical formulations. Operating as a dual-controlled release system, emulgel seamlessly integrates the properties of both gels and emulsions to optimize drug delivery efficacy [13].

Macroemulsion gel

Emulgel with emulsion having particle sizes greater than 400 nm is known as macroemulsion gel. They are physically invisible, but the individual droplets can be seen clearly under a microscope. Macroemulsions are thermodynamically unstable, but surface-active agents can help to stabilize them. [14]

Microemulgel

Micro-emulsions are transparent and thermodynamically stable as their droplet size ranges from 100 to 400 nm and they do not coalesce. Microemulsions are composed of oil, surfactant, co-surfactant, and water in particular ratios. [16,17,]

Nanoemulgel

When Nano-emulsion are incorporated into a gel, it is called Nano-emulgel Nanoemulsion are thermodynamically stable transparent dispersion of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a globule size of less than 100 nm [18].

Submicron emulgel

When submicron-emulsion are incorporated into a gel it is called as submicron-emulgel. Submicron emulsion (SE) possesses a dispersed phase mean droplet diameter under 1 μm and is also referred to as mini emulsion, ultrafine emulsion, and nanoemulsion. SE can be given by a variety of routes such as parenteral, topical, ophthalmic, and nasal delivery and as a vehicle in cosmetics. [18]

Advantages of emulgel [19, 20]

- Increased patient acceptability.
- Provide targeted drug delivery.
- Easy termination of the therapy.
- Improve bioavailability and even the low doses can be effective in comparison with other conventional semi-solid preparations.
- Stable formulation by decreasing surface interfacial tension increasing viscosity of aqueous phase, more stable than Transdermal preparations that are comparatively less stable, powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
- The hydrophobic drug can be incorporated in emulgel using emulsion as the drug carrier that is finally dispersed in the gel.
- Provide the controlled effect that enhances the prolonged effect of the drug with a short half life.
- Easy and cost-effective preparation.

- Drug loading capacity is better than other novel approaches like niosomes and liposomes.

Disadvantages of Emulgel [19,20]

- The drug and/or excipients can lead to skin irritation in people with contact dermatitis.
- Some medications have low permeability through the skin.
- Possibility of allergenic reactions.
- Larger-particle-size drugs are not easily incorporated into the skin

Drug delivery across the skin

Drug penetration through the stratum corneum predominantly occurs via passive diffusion, while a limited amount undergoes active transport through several sequential stages: initial dissolution of the drug in its vehicle, followed by diffusion from the vehicle to the skin surface, and ultimately, penetration through the various layers of the skin [7]. Active transport involves passage through the lipophilic stratum corneum into the viable epidermis, then continuing passively into the hydrophilic dermis, ultimately reaching the dermal-epidermal junction where systemic circulation carries it via blood vessels. Topical drugs serve diverse functions, typically falling into three categories. Firstly, epidermal formulations address surface-level needs such as disinfection, insect repellency, and cosmetic enhancement. Secondly, endodermal formulations are tailored to penetrate deeper into the skin, targeting the viable epidermis and dermis. Thirdly, the transdermal application aims for systemic drug action. Drug penetration through the stratum corneum can occur via two routes: transepidermal passage and passage through pores.

The transepidermal route comprises two main pathways: the transcellular and the intercellular routes. The transcellular route represents the most direct path, as the drug traverses both the lipid structures of the stratum corneum and the cytoplasm of the deceased keratinocytes. However, this route faces considerable resistance due to the necessity of crossing both lipophilic and hydrophilic structures. In contrast, the intercellular route, which is more common, involves the drug passing between corneocytes. Historically, the contribution of skin appendages (such as glands and hair follicles), which occupy only 0.1% of the total human skin surface, was presumed to play a minor role in the pore route.

However, for highly lipophilic molecules and large compounds (as well as certain electrolytes), skin appendages and other diffusion shunts may also exert a significant influence. The follicular apparatus within hair follicles, sweat glands, and microlesions within the interfollicular horny layer have been posited as potential vertical pathways for percutaneous penetration (see Fig. 1). Lipophilic drugs, which readily traverse the stratum corneum, often experience slowed diffusion upon encountering the hydrophilic epidermis, leading to temporary deposition known as the reservoir effect. Substances with small molecular sizes and balanced lipid-aqueous solubility typically exhibit the most efficient permeation. Electrolytes present a challenge for absorption when applied in aqueous solutions due to their creation of a stable hydration field, which enlarges the diffusing component. The permeability coefficient of drugs is contingent upon factors such as solute size, lipophilicity, and the length of the diffusion path. While Fick's law initially describes penetration as being reliant on skin thickness, subsequent studies suggest a greater dependency on the lipid composition of the skin [21-24].

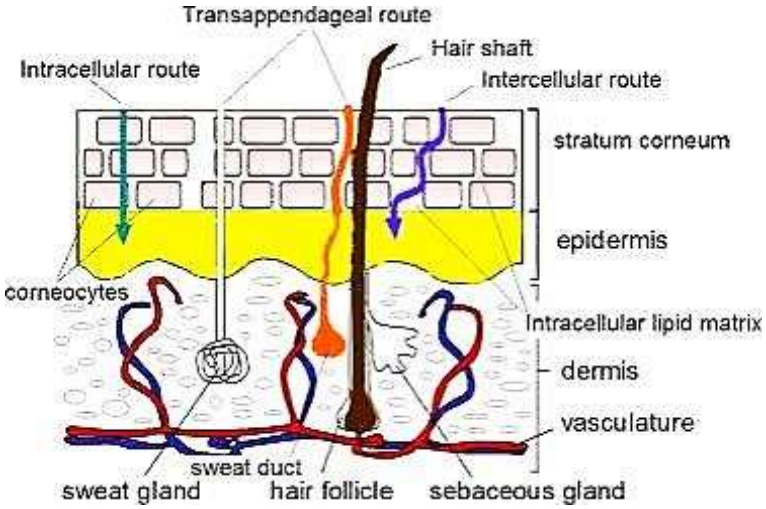

Fig 1: Drugs enter through the skin

Table 1: Ideal properties of a drug candidate to formulate emulgel [25]

S.NO	DRUG CANDIDATE
1.	Drug dose should be low
2.	Molecular weight should be 600dalton or less
3.	Molecular size should be low
4.	Half-life of drug 10 hr or less
5.	Partition coefficient i.e Log P 0.4-0.8
6.	Drugs should be non-irritant and non-sensitizer having a less polarity.

Various excipients used for emulgel formulation

Aqueous material: This forms the aqueous phase of the emulsion. Generally, water is used.

Oils: They are responsible for the oily phase of the emulsion. The oil phase has great importance in the formulation of emulsion /microemulsion/nanoemulsion as physicochemical properties of oil (e.g., molecular volume, polarity, and viscosity) significantly govern the spontaneity of the emulsification /micro-emulsification/nanoemulsification process, the droplet size of the respective emulsion, drug solubility. Usually, the oil, which has the maximum solubilizing potential for the selected drug candidate, is preferred as an oily phase for the formulation of emulsion/microemulsion/nanoemulsion. This helps to attain the maximal drug loading. Hence, the choice of the oily phase is often a compromise between its tendency to solubilize the drug and its capability to facilitate the formation of the respective emulsion with desired characteristics. For example: castor and mineral oils, which have laxative effects, are the most commonly used oils for oral and topical preparations [26].

Emulsifiers: Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. e.g. polyethylene glycol 40 stearate, sorbitan monooleate (span 80), polyoxyethylene sorbitan monooleate (tween 80), stearic acid, sodium stearate [27].

Gelling Agents: Gelling agents are used to form a gel base by incorporating emulsion to form an emulgel. These are also known as thickening agents which expand the consistency of any dosage form by swelling in the aqueous phase and forming a gel-like structure. The incorporation of a gelling agent into a system makes it thixotropic. HPMC-based Emulgel was found to be superior to Carbopol-based Emulgel since it showed a better drug release rate [28].

pH adjusting agent: These agents are used to maintain the pH of the formulation[14]. Examples: triethylamine, NaOH, etc.

Preservatives: Preservatives are used to inhibit the growth of micro-organisms and are added to emulgel to avoid spoilage of the formulation from micro-organisms. E.g., Propylparaben, methylparaben, Benzalkonium chloride, Benzoic acid, Benzyl alcohol, etc.

Penetration Enhancer [29]: Vehicles frequently contain penetration-enhancing components that temporarily interfere with fluidizing the lipid channels between corneocytes, protect the skin barrier affect the drug's distribution into skin structures, or otherwise, improve skin penetration. Oleic acid 1%, Lecithine 5%, Urea 10%, Isopropyl myristate 5% , Linoleic acid 5% ,Clove oil 8% ,Menthol 5% , and Cinnamon 8%

Properties of penetration enhancers [30]

They should be non-toxic, non-irritating, and non-allergenic. They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.

- They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
- The penetration enhancers should work unidirectional i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations and, thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin feel.

Mechanism of penetration enhancers

Penetration enhancers operate by modifying any of the three pathways. To alter the polar pathway, the key is to induce solvent swelling or provoke conformational changes in proteins. Fatty acid enhancers increase the fluidity of the lipid-protein segment of the stratum corneum. Some enhancers affect both non-polar and polar

pathways by modifying the multi-laminate pathway for penetration. Permeation enhancers can also enhance drug diffusivity through skin proteins. The choice of enhancer significantly influences product development and design. Terpenes, for instance, induce lipid domain reorganization and barrier disruption, thereby enhancing drug diffusion by extracting lipids from the stratum corneum [31- 33].

Formulation of emulgel: The following steps are involved in the formulation of emulgel.

Step 1: Formulation of O/W or W/O emulsions

The initial step of emulsion formulation involves the dissolution of oil-soluble substances in the oil vehicle (e.g. dissolving span 20 in liquid paraffin) and the dissolution of the water-soluble substances in the aqueous vehicle (e.g. dissolving tween 80 in purified water). Both phases were mixed under turbulent mixing conditions to ensure the dispersion of the two phases into droplets. In the laboratory, the preparation of emulsions involves the use of a mechanical stirrer, whereas the emulsification of industrial manufacturing is generally performed using mechanical stirrers, ultrasonicators, homogenizers, or colloid mills.

Step 2: Formulation of gel base

To begin, the water-soluble substances or excipients are dissolved in the aqueous vehicle using mechanical stirring in a mixing vessel. To avoid aggregation, the hydrophilic polymer is slowly added to the stirred mixture, and stirring is continued until the polymer has dissolved while the pH remains within the desired range. Superfluous stirring of pharmaceutical gels may result in the entrapment of air, so the mixing rate must be at a moderate pace.

Step 3: Addition of emulsion into gel base with continuous stirring

The emulsion is mixed into the gel to get emulgel [34] as shown in Fig. 2

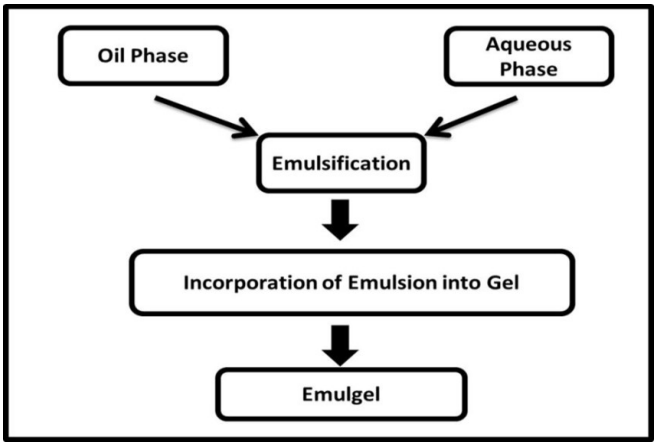

Fig 2: Method of preparation of emulgel

Evaluation of emulgel

Physical appearance

The prepared Emulsion formulations were inspected visually for their color, homogeneity, consistency, and pH. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter DPH 115 pm) [35,36].

Spreadability

Spreadability is determined by the apparatus suggested by Mutimer et al (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured based on the Slip‟ and „Drag‟ characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2gm) under study is placed on this ground slide. The emulgel is then sandwiched between this slide and another glass slide having the dimension of the fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges [35, 36]. The top plate is then subjected to a pull of 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Spreadability was calculated by using the 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 from each other

Extrudability

Here the weight required to extrude a 0.5 cm ribbon of emulgel in 10 sec from the lacquered collapsible aluminum tube is determined. The test was repeated and the average values were used for the calculation [37].
Formula for extrudability calculation
Extrudability = weight applied to extrude emulgel from tube (gm)/Area (cm^2)

Viscosity

Viscosity was determined by using a cone and plate type of Brookfield viscometer (Brookfield viscometer RVT) with spindle No.7. The maximum shear rate was 100 RPM while the minimum shear rate was 10 RPM [38].

Swelling Index

Formulation with maximum swelling index indicates its tendency to absorb extrudates from a wound. the swelling index is calculated by placing 1gm of emulgel on porous aluminum foil and then it was placed in a Petri dish containing 10 ml 0.1 N Sodium Hydroxide. Then samples were removed from a dish at different time intervals and put in a dry place for some time after it was reweighed. The swelling index was calculated using a formula [39].

$$\textbf{Swelling Index (SW) \% = [(Wt-Wo)/Wo] ×100}$$

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

Globule size and its distribution in emulgel

Globule size and distribution is determined by the Malvern zeta sizer. A 1.0 gm sample is dissolved in purified water and agitated to get homogeneous dispersion. The sample was injected into a photocell of zeta sizer. Mean globule diameter and distribution are obtained [40].

Skin Irritation Test (Patch Test)

The emulgel is applied on the properly shaven skin of rats and its adverse effects like color change, and change in skin morphology should be checked up to 24 hours. A total set of 8 rats can be used in the study. If no irritation occurs the test is passed. If the skin irritation symptom occurs in more than 2 rats the study should be repeated [35, 36].

In Vitro Release Study

Franz diffusion cell (with an effective diffusion area of 3.14 cm2 and 15.5 ml cell volume) is used for the drug release studies. A gellified Emulsion of approximately (200 mg) is applied onto the surface of the egg membrane. The egg membrane is clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber is filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber is stirred by a magnetic stirrer. The samples (1.0 ml aliquots) are collected at suitable time intervals. Samples are analyzed for drug content by UV visible Spectrophotometer after appropriate dilutions. Cumulative corrections are made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the egg membrane is determined as a function of time [35, 36].

Microbiological assay

The ditch plate technique is used. It is a technique used for the evaluation of the bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar-dried plates are used. Three grams of the Gellified Emulsion are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth is observed and the percentage inhibition is measured as follows [35, 36].

$$\textbf{\% inhibition = L2 / L1 × 100}$$

Where, L1 = total length of the streaked culture, and
L2 =length of inhibition.

Drug Content Determination

A spectrophotometer is used to determine the drug concentration in the emulsion. The drug content of an emulsion is determined by sonicating a known amount of emulsion in a solvent (methanol). In a UV/VIS spectrophotometer, absorbance is measured after appropriate Dilution [41].

Stability Studies

The optimized emulgel formulation was selected for the stability study. A sufficient quantity of emulgel formulation was sealed in a 10 gm collapsible tube in triplicate, and subjected to stability studies at 5°C, 25°C,/ 60%RH, 30°C 65%RH, and 40°C/ 75%RH for 3 months. The samples were analyzed at predetermined time intervals for pH, physical appearance, rheological properties, and drug content [42].

CONCLUSION

Emulgels emerge as a compelling alternative to other semi-solid preparations, offering versatility in both local and systemic treatments. Beyond their attributes such as viscosity, spreadability, extrudability, drug release, and stability, emulgels exhibit commendable penetration characteristics. With a high loading capacity and efficient drug delivery, emulgels facilitate effective penetration of drugs through the skin, attributed to their small particle size. This feature not only enhances patient compliance but also boosts drug bioavailability in specific target areas. In conclusion, emulgels represent a promising frontier in drug delivery systems, offering a multitude of advantages. Their versatility and efficacy make them a preferred choice for topical pharmaceutical formulations spanning various medical disciplines. Emulgels stand poised to address the evolving needs of modern medicine, providing a reliable and efficient platform for delivering therapeutic agents effectively and safely to targeted sites within the body.

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Conflicts of interest

There are no conflicts of interest regarding the publication of this article to disclose.

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