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An Overview on Emulgel and Natural Permeation Enhancers

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Abstract
Gels appear to be a more favorable formulation to use in both medicinal and cosmetic applications when compared to other semisolid formulations. Emulgel is the term for the combination of gel and emulsion applications. pharmaceutical arrangements. Emulgel is the term for the combination of gel and emulsion applications. The most promising medication delivery method for hydrophobic medicines is emulgel. Emulgel is an intriguing topical drug delivery method that possesses both a gel and an emulsion dual release control system. Emulgel has a number of benefits, including being transparent, emollient, readily spreadable, and easily removed. The main drawback of this approach is that the stratum corneum, or outermost layer of skin, acts as a barrier to protect the underlying tissues from the external environment, making it difficult for the medications to pass through the skin. A transdermally delivered medication can only be effective if it can pass through the transdermal barrier and enter the systemic circulation. Penetration enhancers are substances that make the skin more permeable, which in turn keeps the drug level in the blood stable. Chemical, natural, and physical penetration enhancers are the three different types available. This review discusses natural permeation enhancers that can be used to improve medication transdermal penetration.

Keywords: Gels, Emulsion, Permeation Enhancers, Essential oils, Emulgel.

Introduction

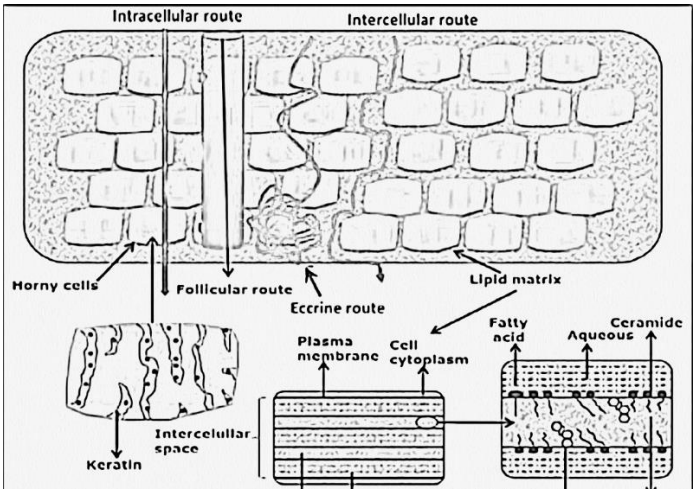
When a medicine is delivered topically, it is transferred from a topical product to a localized area that is targeted and has dermal circulation throughout the body and deeper tissues. Nevertheless, distribution through the skin can be challenging because of the skin's barrier function. [1] Compared to oral delivery, topical drug administration may have a number of benefits, including the ability to avoid first-pass metabolism, improve patient acceptance (i.e., non-invasiveness), allow for immediate treatment withdrawal, and maintain a steady supply of medication to maintain plasma profiles, especially for medications with short biological half-lives.[2,3] Topical agents such as ointments, creams, and lotions are used in topical drug delivery; nevertheless, their sticky nature sometimes causes uneasiness in the patient during application. They also require rubbing when applied and have a lower spreading coefficient. They also show the instability issue. Transparent gels are being used more often in pharmaceutical preparations

as well as cosmetics to address these issues. [4] Emulgels are the term for dosage forms that are created by combining gels with emulsions. A gel is a colloid, usually composed of 99% liquid by weight, that is kept immobile by surface tension acting between the gel and a network of macromolecules made of gelatin fibers. Large volumes of aqueous or hydroalcoholic liquid become trapped in a network of colloidal solid particles to form gels. Generally speaking, gel formulations offer faster medication release than ointments and creams. [5,6] Novel polymers with complex functions have attracted a lot of attention as emulsifiers and thickeners in recent years because of their gelling capacity, which lowers surface and interfacial tension while simultaneously raising the viscosity of the aqueous phase to form stable emulsions and creams. Actually, an emulgel is created when a gelling ingredient is present in the water phase of a traditional emulsion. Lipophilic medications are encapsulated in a direct (oil in water) system, while hydrophilic pharmaceuticals are encapsulated in a reverse (water in oil) system. [7] Gels have many benefits, but one significant drawback is their inability to evenly distribute drugs that are hydrophobic. In order to get over this restriction, emulgels are made and applied, enabling even a hydrophobic medicinal moiety to benefit from the special qualities of gels. Emulsions are elegant to a certain extent and remove from the skin with ease. Additionally, they have a high degree of skin penetration. Thixotropic, greaseless, easily spreadable, readily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, translucent, and aesthetically pleasant are just a few of the advantageous qualities of emulgels for dermatological application. [8,9]

Drug Penetration Routes

The diagrammatic presentation of the transepidermal and transappendegeal channels represents the two potential routes of drug entry through intact skin (Figure1). Molecules penetrate the stratum corneum multilayered, multicellular barrier with a variable architectural style as part of the transepidermal pathway. Another word for transepidermal penetration is intra- or intercellular [10] Hydrophilic or polar solutes can be transported intracellularly through corneocytes, which are terminally differentiated keratinocytes. Diffusion of lipophilic or non-polar solutes through the continuous lipid matrix is made possible via transport through intercellular gaps. The transappendegeal pathway entails molecules traveling through hair follicles and sweat glands. [11,12]

Figure1: Diagrammatic presentation of the transepidermal and transappendegeal channels represents the two potential routes of drug entry through intact skin



Factors affecting topical absorption of drug

A. **Physiochemical properties of drug** [13,4]

1) Size of drug molecules and molecular weight
2) Partition coefficient and solubility
3) Drug concentration
4) pH conditions

B. **Formulation characteristics** [14, 15]

1) Release rate of the drug
2) Ingredients of formulation
3) Presence of permeation enhancers

C. **Skin physiology and pathology** [16, 17, 18]

1) Hydration of skin
2) Skin temperature
3) Skin age
4) Blood flow
5) Pathology of the skin
6) Regional Site of skin
7) Skin flora and enzymes

Considerations for Selecting a Topical Preparation [19,20]

1. Effect of the vehicle e.g. An occlusive vehicle increases the active ingredient's penetration and boosts its effectiveness. The vehicle itself may act as a drying, emollient, cooling, or protective agent.
2. Match the preparation type with the lesions type. For example, avoid greasy ointments for acute weepy dermatitis.
3. Match the type of preparation with the site. (e.g., gel or lotion for hairy areas)
4. Potential for irritation or hypersensitivity. In general, gels are irritating, whereas ointments and w/o creams are less so. If an allergy to preservatives or emulsifiers be concern, ointments don't contain these ingredients.

Method to Enhance Drug Penetration and Absorption [21]

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

Pathway of Transdermal Permeation [22]**:**

Permeation can occur by diffusion via

- Transdermal permeation, through the stratum corneum.
- Intercellular permeation, through the stratum corneum.
- Transappendaged permeation, via the hair follicle, sebaceous and sweat Glands.

Since various compounds can enter the skin through the intercellular micro route, many skin-enhancing methods try to interfere with or bypass the molecular architecture of the skin.

Constituents of Emulgel Preparation

1. **Aqueous Material**: which makes up the emulsion's aqueous phase. Alcohols and water are often used agents. [23]
2. **Oil:** Mineral oils are commonly employed in topically applied emulsions, either by themselves or in conjunction with soft or hard paraffins, for their occlusive and sensory properties as well as the drug's vehicle. Nonbiodegradable mineral and castor oils, which have a local laxative effect, as well as fish liver oils and other fixed oils derived from vegetables (such as arachis, cottonseed, and maize oils) are frequently employed in oral formulations as nutritional supplements. [24,25]
3. **Emulsifiers:** Emulsifying agents are used to control stability during a shelf life that can range from days for spontaneously formed emulsions to months or years for commercial preparations. They are also used to enhance emulsification during the manufacturing process. Examples include Sodium stearate [30], Polyethylene glycol 40[26] stearate, Polyoxyethylene sorbitan monooleate (Tween 80) [28], Sorbitan monooleate (Span 80) [27], and Stearic acid [29].
4. **Gelling Agent:** These can also be used as thickening agents. They are used to improve the consistency of any dosage form [31,32]
5. **Permeation Enhancers:** These substances cause a transient and reversible increase in skin permeability by partitioning into and interacting with skin components. [33]

In the pharmaceutical sector, natural penetration enhancers are a relatively new class of penetration enhancer. Owing to its benefits, which include low cost and a better safety profile, further study is required in this area to create stable transdermal formulations with natural permeation enhancers (NPEs) that can be scaled up for transdermal medicinal products sold commercially. [34]

Table 1: Natural penetration enhancers used in emulgel formulation.

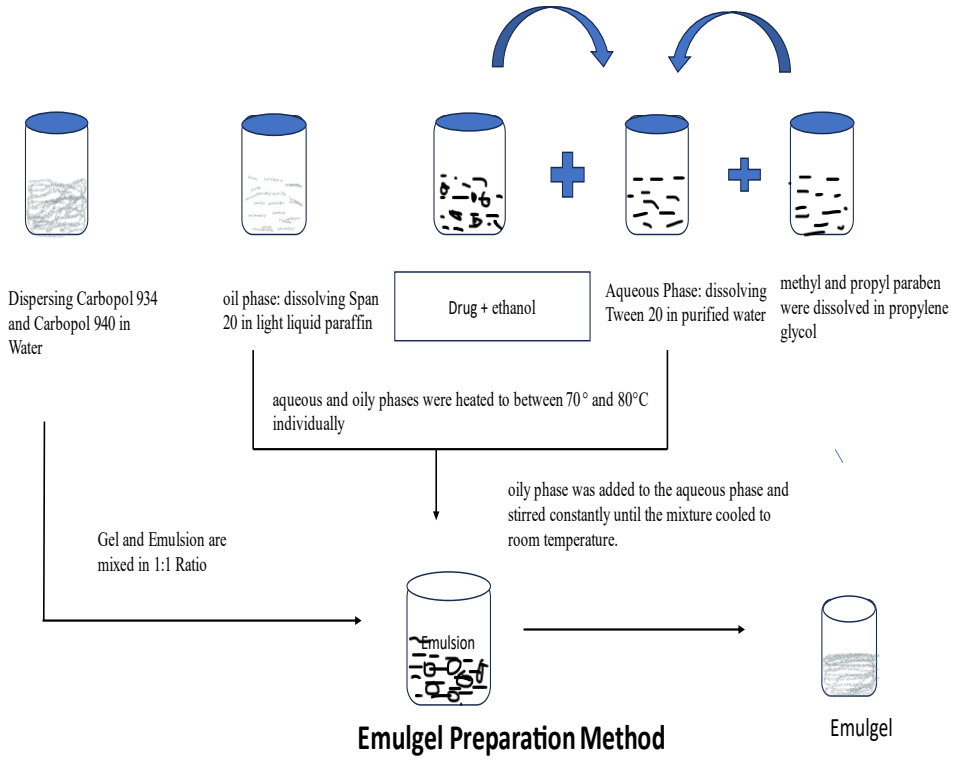
Essential Oils	Drug	Quantity	Reference
Eucalyptus oil	1,8-cineol, α-pinene	10 %	35, 36
Niaouli oil	1,8-cineole, α-pinene, α-terpineol and d- limonene	10%	37
Fennel oil	Trans-anethole, phenylpropanoid	10 %	38
Black cumin oil	Thymoquinone, o-cymene, β-thujene	5 %	39, 40
Almond oil	oleic acid , linoleic acid, stearic acid, behenic acid, lignoceric acid and ecosenoic acid	3 %	41
Basil oil	methyl cinnamate, linalool, β-elemene, camphor	10%	42
Alpinia oxyphylla oil	Estragol, germacrene B	5%	43
Turpentine oil	alcohol terpinene-4-ol, α-pinene, limonene, *p*-cymene	3%	35,44
Clove oil	Eugenol, eugenyl acetate, β caryophyllene and α-humulene	8%	45
Rosemary oil	bornyl acetate, verbenone, camphor, ,8-cineole, *α*-pinene, α-terpineol, *β*-pinene	1%	46

Cardamom Oil	α-terpinyl acetate and 1,8-cineole	1%	43
Peppermint Oil	Menthone, 1,8-cineole, pulegone	5.0%	43
Lemongrass Oil	Farnesol	0.25%	41

Emulgel Preparation:

The preparation of emulgel was done slightly differently from the technique described by Muhammad et al. (2004). The Gel used in the formulations was made by dispersing Carbopol 934 and Carbopol 940 in filtered water and stirring continuously at a moderate speed. Tri ethanol amine (TEA) was then used to adjust the pH to 6 to 6.5. The aqueous part of the emulsion was made by dissolving Tween 20 in purified water, while the oil phase was made by dissolving Span 20 in light liquid paraffin. While the medication was dissolved in ethanol, methyl and propyl paraben were dissolved in propylene glycol. Both solutions were then combined with the aqueous phase. The aqueous and oily phases were heated to between 70° and 80°C individually. After that, the oily phase was added to the aqueous phase and stirred constantly until the mixture cooled to room temperature. And to create the emulgel, add glutaraldehyde in a 1:1 ratio while the gel and emulsion are being mixed. [47]

Figure 2: Flow chart of emulgel preparation



Characterization of Gellified Emulsion

Physical examination: This involves examining the color, homogeneity, consistency, and phase separation. [48]

Spreadability: The "slip" and "drag" properties of emulgel serve as a check on spreadability. A pulley at one end powers the device, which consists of a wooden block, to measure spreadability. A ground glass

is fixed in the block. After spreading 2 g of emulgel over it, a second glass slide is used to cover it like a sandwich. It is weighted with one kilogram, and the spreadability is examined.

pH determination: A digital pH meter is used to measure pH. Three times, the pH is measured after dipping the pH meter into the emulgel. [49]

Rheological study: At 25 ºC, the viscosity is measured in a rheological study. Cone and plate viscometer is the instrument utilized. [20]

Study of drug release in vitro: This is done with a Franz diffusion cell. It facilitates figuring out the medication release.

Microbiological assay: The ditch plate technique is employed in this procedure. This technique is used to assess the fungistatic or bacteriostatic activity.

Accelerated stability analyses: According to ICH rules, it is done. For three months, the stability test is conducted in a hot air oven at 37 ± 2 ºC, 45 ± 2 ºC, and 60 ± 2 ºC. [50]

Drug content: UV spectroscopy analysis is used to determine the drug content. The formula that is applied is,

Drug content = (Concentration × Dilution factor × Volume taken) × Conversion factor

Malvern Zetasizer is the tool used to determine the size and distribution of globules in emulgel. To find the value, the emulgel is put into the equipment, agitated, and dissolved in water.

Centrifugation study: This technique is employed to determine emulgel stability. Only after a week of preparation is it finished. For 30 minutes, a minicentrifuge operating at 3000 rpm was used for this investigation.

Swelling index: In a 50 ml beaker with 10 ml of 0.1 N NaOH, one gram of emulgel is taken and placed separately in a porous aluminum foil container. After that, the samples are taken out at various intervals and weighed again.

Swelling index is determined by the equation; Swelling index (SW) % = [(Wt-Wo)/Wo] × 100

Where, Wt = Weight of swollen emulgel after time t, Wo = Original weight of emulgel at zero time.

Test for skin irritation: Because the preparation is topical, this test is crucial. The animal's skin is used for the test. The animals are placed back in their cages once the emulgel has been administered to their skin. The animals are evaluated 24 hours later. After that, the emulgel is taken out of the area and cleaned with tap water.

Stability studies: The emulgel was placed in collapsible metal tubes, kept in harsh environments, and its stability was examined.

Conclusion

Topical medicine delivery will play a major role in improving patient compliance in the upcoming years. Emulgel is a relatively new topical drug delivery method that works well with hydrophobic medications. Considering that it can also improve extrusion, adhesion, viscosity, and spreadibility. They'll gain popularity as a medication administration method. They will also be used as a means of loading hydrophobic medications into a gel basis that is soluble in water. Only if a drug is able to cross the transdermal barrier and enter the systemic circulation will it be effective when applied topically. Penetration enhancers are compounds that increase the skin's permeability, maintaining a consistent medication level in the blood. Penetration enhancers come in three major varieties: chemical, natural, and physical. Natural permeation enhancers that can be utilized to increase medicine transdermal penetration are included in this review.

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