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Emulgel: A Comprehensive Review For Topical Delivery of Antifungal Drugs

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ABSTRACT

Emulgel is a promising novel formulation for the topical delivery of antifungal drugs. Emulsions and gels synergize to deliver effective treatment solutions. The formulation of this type improves drug solubility, stability, and controlled release, which is effective in the treatment of fungal infections. Emulgels act as both emulsions and gels, thus improving bioavailability through dermal delivery. Such formulation enhancements ensure drug deposition in the target location, diminishing systemic absorption and reducing the eventual side effect profile. It is a distinctive gel-emulsion-based delivery system that combines the benefits of both gels and emulsions, providing double release control. Because of its thixotropic properties, non-greasy texture, easy application and removal, emollient activity, and longer shelf-life, this preparation has proven to be a very useful topical delivery system that also offers superior organoleptic properties. However, specific factors, formulation strategies, characterization parameters, and the consequences of different excipients on both stability and effectiveness in emulgels have been described in this review. This review compiles the advances in antifungal drug-loaded emulgels with an emphasis on recent developments, as well as challenges and opportunities to establish a realistic benchmark for further development in the optimized formulation of emulgels that can attain clinical application.[1]

Keywords: Emulgel, Microemulsion, Topical delivery, Antifungal drugs, Sustained release.

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INTRODUCTION

The easiest way of local administration as a single application is topical drug delivery, which includes different routes such as rectal, vaginal, and dermal.[2] On the other hand, in the case of topical drug delivery systems, the medication is released through the skin and then reaches the site where the medicinal effect occurs.[3] The dissolution rate of a drug from the topical formulation can be influenced by the physicochemical properties of the drug or the excipients used. Topical drug delivery bypasses first-pass metabolism and eliminates the need for intravenous therapy, which carries risks and is often uncomfortable. It also circumvents the fluctuating conditions characteristic of absorption, such as pH, enzyme activity, and gastric emptying time.[4]

Skin diseases are commonly treated with topical drug delivery systems, which include creams, ointments, emulsions, and lotions, among others.[5] unfortunately; these systems suffer from limitations concerning stickiness, spreadability, and stability issues, which can decrease patient compliance. The conventional topical systems had many limitations, which were overcome by the development of clear gels for dermatological and cosmetic applications, providing better spreadability as well as good patient compliance.[6] However, gels, which are created by entrapping liquids inside a solid particle network, struggle with delivering hydrophobic compounds. To overcome these limitations, a new formulation known as emulgel has been developed. Emulgels are a type of emulsion either water-in-oil (w/o) or oil-in-water (o/w), thickened with a gelling agent. They are an efficient approach to delivering hydrophobic drugs. The favorable properties of Emulgels, such as dual-mode release and an improved skin permeation profile, make them ideal for antifungal activity.[7]

Physiology of Skin

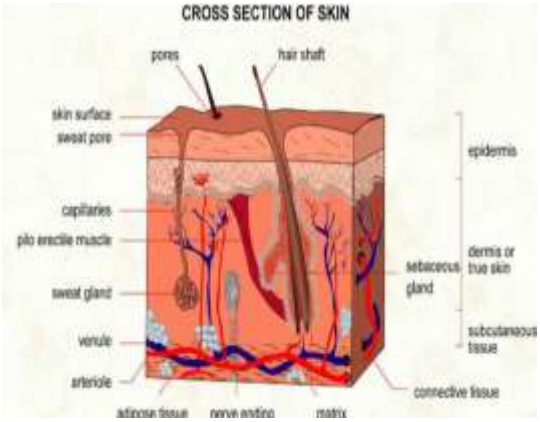

Figure 1: Physiology of Skin[42]

To treat numerous skin conditions, topical formulations are directly applied to the surface layer.

In order to develop topical dosage forms, a basic idea of the working and function of the skin is necessary. The skin of an average human covers about 2 square meters and is approximately responsible for one-third of the blood circulation. Human skin has around 200-300 sweat ducts and as many as 40-50 hair follicles in each square centimetre. The skin normally falls within a pH range of 4.7-5.7.[8]

PHYSIOLOGICAL FACTORS

Lipid Content: Higher lipid content in stratum corneum corresponded with reduced penetration of substances through the skin, despite its primary role as a water barrier.[9]

Thickness of the Skin: The skin thickness varies from outer epidermal to deeper subcutis, with an average size over 100–150 micrometres in length.

Hair follicle density: The infundibulum in the hair follicles has 10 times greater storage capacity than that of stratum corneum.

Skin pH: A rise in skin pH levels is a direct result of increased sweating and release of fatty acids.

Skin Temperature: The higher skin temp accelerates permeability in an alarming rate.

Enhanced Skin Hydration: Higher level of moisture in the skin enhances drug penetration.

Inflammation of the Skin: A damaged stratum corneum becomes more permeable.[10]

TOPICAL DELIVERY OF ANTIFUNGALS VIA SKIN

Through the development of topical delivery systems, localized fungal infections can be treated by direct application, thus reducing systemic side effects. Emulgels are a combination of emulsions and gels, and seem to be a favourable formulation for improving the topical delivery of antifungal drugs. Emulgel systems are oil-in-water emulsions thickened with a gelling agent that impart a semi-solid consistency. The incorporation of antifungal agents, like clotrimazole or miconazole, in this formulation allows for controlled release at the infection site. The presence of surfactants in emulgels may additionally improve skin permeation by interacting with the stratum corneum barrier and promoting higher penetration of the antifungal drug into the epidermal layers.

Emulgels are also excellent at holding moisture, which is useful when treating common conditions such as tinea and candidiasis. In addition to this, emulgels can help reduce itch and irritation that is experienced by many patients with these fungal infections due to the cool feeling they provide during application.[11]

FACTORS AFFECTING TOPICAL ABSORPTION OF THE DRUG

Both physiological and physicochemical factors strongly modulate the process of skin drug

absorption. Physiological parameters for skin such as pH, thickness, hydration, density of sweat glands, blood flow changes and inflammation etc since all these properties effect overall retention. On the other hand, drug characteristics like molecular weight, partition coefficient and ionization state of a drug also influences penetration across skin.[12]

INTRODUCTION TO EMULGEL

Emulgel is a topical formulation prepared by gelling an emulsion with a suitable gelling agent. It serves as a powerful and durable way to deliver water-insoluble drugs into the body. It is a dual-phase system that consists of both the Emulsion and Gel.[13] While some of the benefits are offered by gels, they have difficulty in loading and delivering hydrophobic drugs effectively. The combination of emulsion and gel addresses this problem and allows it to work using more complex systems. The presence of oil and water phases allows it to deliver hydrophilic as well as lipophilic drugs.[14] In the few past years, emulgels have been utilized in controlled release formulations because of better drug loading capacity and stability in these biphasic systems. Emulgel has several advantages over conventional topical formulations, being easy-to-use, non-greasy, thixotropic in nature with good shelf-life and without any Odor, making it ideally suitable for application and visually appealing.[15]

TYPES OF EMULGEL

Microemulsion

They are thermodynamically stable and visually clear, and consist of a surfactant-stabilized oil-in-water (o/w) system, which is referred to as microemulsions. Microemulsions have droplet sizes of 10–100 nm and do not coalesce. Conventional oil-in-water systems are known simply as emulsions, which include a specific ratio of oil and water in the aqueous phase.[16] They are characterized by low interfacial tension, a large interface area, and the ability to solubilize both hydrophilic and lipophilic compounds. The components of microemulsions may reduce the diffusion barrier, thereby enhancing drug permeation. It has low viscosity and limited skin retention. So, Microemulsions are often modified with gelling agents like Carbopol 940, or guar gum etc to create microemulsion-based gels which is suitable for topical use.[17]

Nanoemulgel

Nanoemulsion refers to a transparent or translucent oil-in-water dispersion, which are integrated and stable systems (typically thermodynamically stable systems) stabilized with surfactants and cosurfactants, having globule sizes ranging from 1–100 nm. Then as soon as a gel incorporating this kind of emulsion is formed, it is referred to as a nanoemulgel. Nanoemulsions are superior to traditional formulations, including emulsions and gels, in terms of transdermal permeation. Both

in vitro and in vivo studies demonstrate that nanoemulsions improve transdermal as well as dermal delivery. This is mainly due to their high loading capacity and small globule size, which in turn enables efficient drug permeation through the skin, providing a rapid therapeutic effect.[18]

Macroemulsion gel

Emulgels containing emulsion droplets of size larger than 400 nm are not visible physically, although the individual units (droplets or micelles) can be observed under a microscope. Because macroemulsions are thermodynamically unstable, the addition of surfactants is a means to stabilize them and enhance their shelf-life.

Rationale of Emulgel

There are several semisolid and other preparations on the market that have emerged to address skin essential activities or pharmacological effects in subcutaneous tissue. Lotions, ointments and creams usually have problems of stickiness, poor spreadability or stability. These gels are therefore often used in pharmaceutical and cosmetic applications, especially for clear formulations. This technique allows for the encapsulation and release of hydrophobic pharmaceuticals within gels. The emulgel incorporates hydrophobic drugs by preparing drug/oil/water emulsions. Incorporation of most drugs directly into gel bases is difficult owing to solubility considerations; hence, drug release may be affected. The method is an oil-in-water emulsion where the hydrophobic drug is dissolved in the oil phase. This emulsion could then be mixed with a gel base, possibly enhancing drug stability and release as opposed to directly including the drug in the gel.[19]

KEY COMPONENTS IN EMULGEL FORMULATION

Oils

The oily phase in emulsions is usually comprised of mineral oils, either alone or in combination with soft paraffin or hard paraffin. Examples of these include mineral oil and castor oil, which are not biodegradable in oral preparations but have laxative properties. Fish liver oil and various fixed oils derived from plants are also frequently utilized. Rachis oil, wheat germ oil, jojoba oil, and castor oil are a few examples of such oils.[20]

Table 1: Oil Quantities for Preparing Gels, Emulgels, and Emulsions

Ingredients	Percentage Range	Used In
Light Liquid Paraffin	7.5%	Emulsion, Emulgel
Isopropyl Myristate	7-7.5%	Emulgel
Isopropyl Stearate	7-7.5%	Emulgel
Isopropyl Palmitate	7-7.5%	Emulgel
Propylene Glycol	3.5%	Gel

Aqueous vehicles

This forms the aqueous phase of the emulsion. Generally, water and alcohol are used.[12]

Emulsifiers

For better stability of shelf life, an emulsifier is used to improve the emulsification of the formulation. Examples of emulsifying agents include Tween 80, Span 80, and Tween 20.[21]

Gelling Agents

The gelling properties and consistency can be improved by introducing different thickening agents. The concentration of the gelling agent is usually negatively correlated with the drug release rate. Carbopol and HPMC are among the commonly used gelling agents in emulgels.[12]

Table 2: Gelling agents and their quantities in the preparation of gels and emulgel.

Gelling Agent	Quantity	Formulation
Carbopol-934	1%	Emulgel
Carbopol-940	1%	Emulgel
HPMC-2910	2.5%	Emulgel
HPMC	3.5%	Gel
Gel Sodium CMC	1%	Gel

Permeation Enhancers

Permeability enhancers are chemicals that enhance the ability of drug molecules to cross the skin. They interact with substances in the skin, which temporarily changes its chemistry. Some examples are oleic acid, clove oil, methanol etc.[22]

pH Adjustment

These are used to stabilize the pH of the formulation. Triethanolamine, sodium hydroxide are specific examples.[23]

Preservatives

Most of these chemicals inhibit or retard the growth of microbes, thereby enhancing stability in order to prevent spoilage. Common preservatives include propylparaben, methylparaben, benzalkonium chloride, benzoic acid, benzyl alcohol and others.[24]

STEPS INVOLVED IN THE PREPARATION OF EMULGEL

Step 1: Preparation of o/w or w/o emulsions

The initial step is to dissolve the oil-soluble components in liquid paraffin, which acts as the oil phase, such as span 20, and water-soluble ingredients in purified water, which serve as the aqueous phase of O/W (W/O) emulsion, for example, tween 80. The two phases are then combined vigorously to form a droplet suspension.[25] In the laboratory, emulsions are prepared with a mechanical stirrer, like the rotary stirrer, and in industrial production, various devices are used, such as mechanical stirrers, ultrasonicators, homogenizers, and colloid mills.[26]

Step 2: Preparation of gel base using gelling agent.

Carbopol 940 (1% w/w) was weighed and a suitable quantity was taken; it is thereafter dispersed in warm distilled water with stirring. After the mixing, it was allowed to hydrate for 1-2 hours. Then, propylene glycol (10% w/w) and glycerol (10% w/w) were added to the aqueous dispersion with stirring.[27] Optimum levels of the drug (1% w/w) were added and uniformly dispersed. The pH of the liquid phase was adjusted to 6 using triethanolamine, and its weight was adjusted with distilled water. The gel was sonicated for 5–15 minutes, until there were no bubbles, and then allowed to settle overnight.[28]

Step 3: Incorporation of the emulsion into gel base

The emulsion is gradually incorporated into the gel base while stirring continuously to form an emulgel.

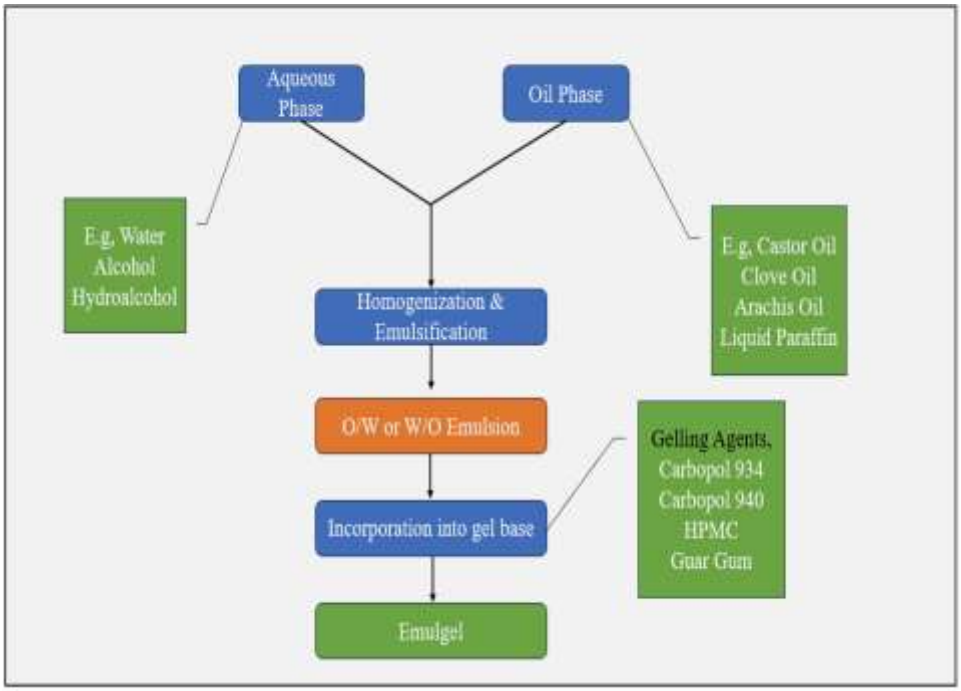

Figure 2: Formulation methods of Emulgel[43]

CHARACTERIZATION OF EMULGEL

Physical Appearance

The prepared emulgel formulations are examined for their visual characteristics (color, homogeneity, consistency, and pH). The pH of 1% aqueous solutions of the gellified emulsions is determined using a digital pH meter.[29]

pH

The pH of the prepared emulgels is measured using a digital pH meter. The pH meter is calibrated using a standard buffer solution prior to each use.[30] A uniform suspension of the

formulation is prepared by dissolving one gram in distilled water, and allowing it to stand for two hours. After this, the glass electrode is immersed in the suspension and the pH is noted.[31]

Emulgel globule size and distribution

The size and distribution of the globules were determined by an optical microscope. The globules were visualized at a 40x magnification using a compound microscope. The micrometer lenses were calibrated with a stage micrometer prior to observation and stabilization was ensured. The average globule size was determined as well.[20]

Drug Content

The drug content is estimated by dissolving a measured quantity of emulgel in a suitable solvent. The drug content is then quantified after filtration, and the absorbance value is recorded by a UV spectrophotometer.[32]

Spreadability

It is determined by the diameter of the circular area formed when a given amount of an emulgel is placed between two glass plates under some fixed weight. A quantity of 350 mg of emulgel is applied to one glass plate and then another glass plate is allowed to fall from a height of 5 cm. The diameter of the spread emulgel is measured to determine its spreading behavior.[33]

Swelling Index

The gel (1 g) was placed on a porous aluminum foil and kept in a beaker containing 10 ml of 0.1 N NaOH to determine the swelling index of the emulgel. Different time intervals were fixed, and samples from the beakers were dried; each sample was weighed again. The formula for the swelling index is represented as:

Swelling Index (SW) % = [(Wt – Wo)/ Wo] × 100

Where,

Wo= Initial weight of the emulgel at time zero

Wt= Weight of the swollen emulgel after time t

SW%= Percent swelling index.[34]

Rheological Studies

The viscosity of the emulgel is measured at 25°C using a cone and plate viscometer equipped with spindle 52, which is connected to a thermostatically controlled circulating water bath.[35]

Extrudability

An empirical test performed to determine the force required for cream extrusion from a collapsible tube. This was then filled in the tube with the cream, which was locked and sealed, and the weight of the initial amount was also taken. Then a 500g weight was placed over the

tube, and the cream that extruded was collected and weighed. The percentage extruded of the cream was then calculated.[36]

Skin irritation test

Skin irritation tests are often performed on human volunteers, following the receipt of written consent. The formulation is applied to the skin of the forearm or another suitable area and observed for any adverse effects.[37]

In vitro release study

In vitro drug release studies of emulgels are done in a modified diffusion cell with a dialysis membrane. The emulgel is spread uniformly over the dialysis membrane, and the receptor compartment contains phosphate buffer in a beaker. The receptor compartment is in direct contact with the donor and is kept under agitation. The percent cumulative drug release of these samples is determined by spectrophotometric analysis.[38]

Ex vivo skin permeation study

An ex vivo skin permeation study can be carried out using male rats. Full-thickness abdominal skin is excised, hydrated for 1 hour and mounted on a Franz diffusion cell. The emulgel is applied onto the skin, and it is secured on the Franz diffusion cell. A receptor compartment is filled with adequate medium and stirred throughout the entire period of the experiment. Samples withdrawn at regular time intervals are analysed spectrophotometrically.[39]

Kinetics Modeling

Drug release kinetics were estimated from ex-vivo permeation studies by fitting the data into various mathematical models such as zero-order, first-order, and Higuchi models. The best-fitting model was selected by scrutinizing the R^2 value, where a larger R^2 suggested a better fit. Hence, the model that yields a value of R^2 closer to 1 is better seen as representing the drug release profile.[40]

Zeta Potential

The zeta potential of the emulgel formulation was determined by using a zetasizer. The tests were performed using a single-use zeta cell into which the formulations are poured for the test. The cuvettes were cleaned with methanol before any experiment and filled with the sample for analysis.[41]

PRODUCTS AVAILABLE IN THE MARKET

Table 3: Different marketed emulgel formulations along with their manufacturers

Brand Name	Active Ingredient	Manufacturer
Voltaren Emulgel	Diclofenac diethyl ammonium	Novartis Pharma
Diclomax Emulgel	Diclofenac Sodium	Torrent Pharma
Miconaz-H-Emulgel	Miconazole Nitrate, hydrocortisone	Medical union pharmaceutical
Excex Gel	Clindamycin, Adapalene	Zee Laboratories
Topinate Gel	Clobetasol Propionate	Systopic Pharma
Cataflam Emulgel	Diclofenac potassium	Novartis
Avindo Gel	Azithromycin	Cosme Pharma Lab
Lupigyl Gel	Metronidazole, Clindamycin	Lupin Pharma
Clinagel	Clindamycin Phosphate, Allantoin	Stiefel Pharma
Pernox Gel	Benzoyl Peroxide	Cosme Remedies Ltd.
Kleraderm Gaia 480	Diclofenac sodium	Kleraderm Pharma
Isofen Emulgel	Ibuprofen	Beit Jala Pharmaceuticals

CONCLUSION

Amongst pharmaceutical dosage formulations, emulgels are considered a growing platform for the topical delivery of antifungals that have proven to be an excellent alternative in overcoming many common challenges associated with the hydrophobic nature of most active agents used topically, such as poor solubility and limited bioavailability. Effective delivery of these drugs via the skin is vital to effectively treating fungal infections. However, conventional topicals such as creams, ointments, and lotions, while useful for their emollient actions, frequently impair drug release characteristics because of their oleaginous bases. In contrast, emulgels offer rapid drug release due to the presence of an aqueous phase and also allow the incorporation of hydrophobic antifungal agents in oily phases. One approach to improving this is by adding gold nanoparticles (NPs), which can further accelerate the release rate and enhance skin penetration, ultimately improving therapeutic efficacy. Emulgels are a favorable choice for topical fungal therapy due to their improved release profile, simplicity in formulation, and effective delivery of hydrophobic antifungal drugs. In the future, these benefits are expected to promote the increased use of emulgels for delivering more antifungal drugs.

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