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A Comprehensive Review of Antifungal Emulgel as a Topical Drug Delivery System: A Review

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Abstract: Emulgels are the prominent topically active drug delivery systems having a dual controlled drug release mechanism, which comprises the properties of both gel and emulsion. These systems can be either W/O or O/W emulsions, with the addition of gelling agents resulting in the formation of an emulgel. The incorporation of the emulsion into a product will improve its properties. It has unique properties to treat fungal infections. Emulgel has many characteristics, including improved permeability, dual control, and sustained release and thermodynamically stable. It helps improve bioavailability and patient compliance. The final preparation was assessed for various parameters like viscosity, zeta potential, particle size, drug content, skin irritation test, stability tests, etc.

Keywords: Topical drug delivery, Emulgel, Gelling agent, Emulsifying agent

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Introduction

The system that delivers drugs locally to any part of the body such as the ocular, rectal, vaginal, and skin via topical routes is known as the Topical Drug Delivery system. These substances are used in a wide range of formulations for both dermatological and cosmetic use, applicable on both healthy and diseased skin. These formulations have different physical and chemical properties and exist in different phases, ranging from solid to semi-solid (Mathew *et al*., 2016). The drug is used topically for its local application effect or for its systemic effect. The absorption of the drug through the skin is improved if the drug substance is in solution form, if it has a lipid

partition coefficient/ water which is favourable as a nonelectrolyte. The purpose of formulation was to produce a local effect and, as such, are prepared to give site-specific exposure for a long period of time with systemic absorption of the drug in a minimum. Protectants, antiseptic drugs, emollients and antifungal drugs are some of the medications which have topical effects on the skin. The major benefit of the on-site delivery system is that it bypasses the first-pass conversion process. Other advantages of topical preparations include avoidance of the risk and inconveniences associated with intravenous therapy and of absorption-related complications which include pH changes, presence of enzymes, gastric emptying time (Satya Lakshmi *et al*., 2021).

Topical drug delivery system is often used when other drug delivery systems are affected like fungal infections. The skin is designed in such a way that enables us to survive by controlling heat and water loss from the body and at the same time preventing microbes and chemicals from entering into the body. The human skin is a large, easily acceptable organ and also a self-repairing barrier specifically designed to maintain the internal environment of the body. It seems to give many suitable sites for drug delivery for both local and systemic effects. Gels are a recent type of dosage form formed by entrapping a large quantity of water-based (aqueous) or hydroalcoholic liquids in a framework of colloidal solid particles, which may include inorganic substances like aluminium salt. Gels have a higher water content, allowing the drug to be more soluble and also allowing the drug to more easily move through the carrier, which is essentially a liquid, compared to ointments or foundations (Sharma *et al*., 2014).

The conventional emulsion is transformed into an emulsion due to the presence of a gelling agent in the aqueous phase. Oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulgel used for dermatological purposes has some ideal properties which include thixotropic, fat-free, easy to spread, easy to remove, softening, non-staining, long shelf life, bio-friendly, transparent and pleasant appearance (Anand *et al*., 2019)

Antifungal Properties

An antifungal drug, more commonly referred to as an antimycotic medicine, may kill the fungi (fungicidal) or may inhibit growth and multiplication of fungi (fungistatic) and predict mycosis. The increased resistance to antifungal drugs could be a potential risk to human health worldwide. These formulations exist in different forms like Gels, powders, creams, ointments, lotions, ointments, shampoos, sprays and tinctures are some of the existing forms (Anand *et al*., 2019)

Emulgel

Emulgel is an emerging area of topical drug delivery, with few products currently available in the market, so focusing on this field is both exciting and challenging. Before focusing much on emulsions, knowing the advantages of both emulsion and gel for topical drug delivery is very essential. Emulsions are controlled release systems which consists of two phases which are immiscible. One phase is dispersed (inner or discontinuous phase) in the other (outer or continuous phase) using an emulsifying agent. Drug particles obtained in the inner phase pass through the outer phase, then is gently absorbed into the skin to produce a conditioning effect. Emulsions are oil-in-water or water-in-oil.

According to the USP, a gel is a semi-solid system containing and permeated with a liquid and consisting of dispersions of small inorganic particles or large organic molecules. The gel encloses small drug particles and maintains regulated drug release by containing a huge quantity of water or alcohol liquid in an interconnected system of colloidal solid particles. The liquid phase forms a three-dimensional polymer matrix, which is then physically or chemically cross-linked. The continuous structure creates solid, consistent, and transparent behaviour (Hyma *et al*., 2014).

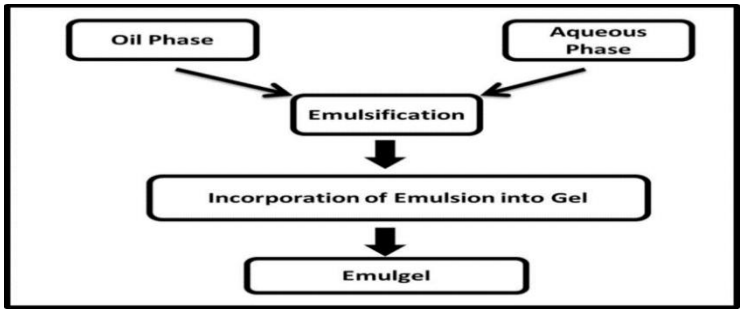

Fig. 1: Preparation of Emulgel (Ahmed *et al*., 2022).

Gels and emulsions both regulate the controlled release of the drug from the system. Both, hydrophilic water-based hydrogel and hydrophobic, organic solvent-based gels or organic gels are classified as gels. The first is based on liquid paraffin with polyethene or fatty oil gelled with colloidal silica, aluminium or zinc soap, while the second is based on water, glycerol or propylene glycol. Although gels have many advantages, they have limitations in delivering hydrophobic drugs. To overcome this limitation and benefit from hydrophobic drug delivery in gel form, the emulsion concept has been developed, in which hydrophobic drugs are incorporated into the emulsion and then gelled.

Advantages of emulgel (*Yadav et al., 2017*)

- Hydrophobic drugs are included.
- Improved loading capacity and stability.
- Controlled release is a term used to describe when something is released in a controlled manner
- There will be no intensive sonication.
- Avoiding the first-pass metabolic process.
- Keeping gastrointestinal incompatibility to a minimum.
- More focused on a single location.
- Patient compliance has improved.
- Convenient and simple to use.

Disadvantages of emulgel (*Jain et al., 2019*)

- Skin irritation due to contact dermatitis.
- Allergic reactions are a possibility.
- Low skin permeability of some medications.
- Drugs with large particles are difficult to absorb via the skin.
- A bubble might be formed during the formulation of the emulgel.

Important Constituents of Emulgel Preparation (*Singh et al., 2014*)

Aqueous Substances:

Aqueous substances form the aqueous phase of the emulsion. The most used agents for this aqueous phase are water and alcohols.

Oils:

Mineral oils are the components that form the oily phase of the emulsion (Fig. 1). They can be used on their own or can be mixed with paraffins. Non-biodegradable mineral and castor oils are mostly used in oral formulations owing to their local laxative effects. Fish liver oils and other fixed vegetable oils such as maize, Arachis, and cottonseed oil are used as dietary supplements.

Examples include Propylene glycol, Isopropyl stearate, Light Liquid Paraffin, Isopropyl myristate, and Isopropyl palmitate (Khare *et al*., 2021).

Emulsifying agents:

Emulsifiers, which are commonly known as emulsifying agents, help to regulate and improve stability of the emulsification process. As

emulsions have thermodynamic instability, their stability can be enhanced through the use of an appropriate emulsifier. Surfactants like nonionic surfactants (tweens, spans) which having high Hydrophilic-Lipophilic Balance (HLB) results in improved stable compound as compared to the separate systems.Sodium stearate, Stearic acid, Tween 80,Span 80 are examples of emulsifying agents/emulsifiers.

Permeation Enhancers:

These agents temporarily increase the permeability of the skin by partitioning into skin constituents and interacting with them. This is a reversible process. Examples of such agents include Oleic acid, Lecithine, Urea, Linoleic acid,Clove oil and Menthol (Dhawas *et al*., 2020).

Factors Influencing Topical Absorption of Medicine Physiological Factors (*Sanjay et al., 2007*)

1. Thickness of the skin .
2. Lipid content
3. Hair follicle density
4. Density of sweat glands
5. pH of skin
6. Blood flow
7. Skin hydration
8. Skin inflammation

Physicochemical Factors (*Ashara et al., 2014*)

1. Partition coefficient.
2. Molecular weight (less than 400 daltons).
3. Ionization degree (only drugs which are unionizable are well absorbed).
4. Effect of vehicles.

Method of Preparation of Emulgel (*Mohammed et al., 2013*)

Step I: Preparation of Emulsion can be formed in either O/W or W/O type.

Step II: Preparation of gel base.

Step III: Emulsion are added into the gel base with continuous stirring.

Evaluation of Emulgel

Spreadability: According to Mutimer *et al*. (1956), a specific laboratory apparatus was developed to assess spreadability. This device consists of a wooden board equipped with a pulley system. Slip and Drag are the important strategy used in measuring the spreadability. A fixed amount of emulgel is placed in squares around the ground glass slide. Another identical slide is placed on top with 1 kg weight on both slides for 5 min to get a steady emulgel coating in-between slides. The excess emulgel is scratched off the corners. An 80 g of Drug is connected to best slide plate after this. The total time required for the best slide to cover a separate of 7.5 cm must be noted down. The shorter the time it takes, the better the spreadability (Light and Karboune, 2022).

$$S=MLT/T$$

Where S- spreadability; M- weight tied to upper slide; L- length of glass slides; T- time taken to detach the slides

Extrudability study:

It's a common experiment to determine the amount of force is required to expel fabric out of a container. When the shear rate is more prominent than the surrender esteem, the strategy for deciding the sum of connected shear within the rheogram zone which occurs is laminar flow is applied. This study depends on the speed at which the emulgel is expelled in a coated Al- collapsible tube, that mass needed discharge within 10 sec at leastat 0.5 cm strand. Average value of each formulation's extrudability is calculated after it is tested 3 times and normal values are detailed. Subsequently, the extrudability is determined using the following equation (Arora *et al*., 2017).

Extrudability= weight used to extrude emulgel from tube (in g)/ area (in cm^2)

Rheological studies: The rheological properties of the various emulgel formulations are assessed using a Brookfield viscometer equipped with

spindle no. 18, operating at 100 rpm, at the highesttemperature (Sah *et al*., 2017).

Swelling Index: 10 ml of 0.1 N NaOH was taken in a beaker along with prepared gel on Aluminium foil. The samples are periodically removed from the beakers, left to dry, and then reweighed at different time intervals (Sah *et al*., 2017).

$$SW\% = [wt-Wo/Wo]x\ 100$$

Where SW%-equilibrium per cent swelling; Wt- swollen weight emulgel after time t; Wo-initial weight of emulgel at time zero.

Skin irritation- In this, the hairless rabbit used 0.5gm of gel on the skin and was under observation for 72 h whether the redness persisted (Single *et al*., 2012)

Stability study- Aluminium collapsible tubes (15 grams) are used to store emulates after that they are placed for 4 weeks at different temperatures and relative humidity to see the changes occur according to the guideline. Samples collected monthly and assessed by ICH guidelines for physical appearance, pH, rheological properties, drug content, and drug release profile, among other parameters (Single *et al*., 2012).

Dilution test- By introducing Continuous phase to a 50 to 100 times aqueous dilution of emulgel, phase separation and clearness were visually verified.

Determination of pH- It was determined by using a digital pH meter (Single *et al*., 2012).

Drug Content Determination- 1 g of emulgel is required. It should be mixed in a suitable solvent. To achieve a clear solution, filter it and then measure its absorbance using a UV spectrophotometer. In the same solvent, a standard drug plot is made. Using the same standard plot, the concentration and active drug content can be measured by plugging the absorption value into the standard plot equation (Single *et al*., 2012).

Drug content=(concentration x Dilution factor x Volume taken) x Conversion factor

In Vitro release study:

The medicate discharge examinations are conducted utilizing the Franz dissemination cell. Emulgel is equally set on the surface of the egg film. Between the giver and the dissemination cell's receptor chamber, the egg film is secured. To solubilize the medicine, the receptor chamber is at that point filled with recently made PBS (pH 5.5) arrangement. A attractive stirrer is utilized to mix the receptor chamber. The 1.0 ml aliquots of the emulgels must be collected at suitable time interims, and the accurately weakened tests must at that point be analyzed for medicate substance employing a UV unmistakable spectrophotometer. Total alterations are utilized to decide the in general sum of pharmaceutical discharged at each time period. Time is utilized as a function to calculate the full sum of pharmaceutical discharged over the egg film (Panwar and Jain, 2011).

The arrangement and assessment of a home-grown eucalyptus emulgel include an orderly definition handle and thorough testing to guarantee it is compelling, steady, and secure for utilize. The combination of eucalyptus oil's normal antifungal properties with the progressed emulgel definition offers a promising treatment for parasitic contaminations with the included benefits of moisturizing and relieving the skin.

Author Contributions

All authors contributed to the conceptualization, literature review, analysis, drafting, and critical revision of the manuscript ensuring its accuracy and completeness. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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