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A REVIEW ON: MICROEMULGEL FOR TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT

A topical drug delivery system is a localized method of administering drugs to specific areas of the body through routes such as ophthalmic, skin, vaginal, and rectal. It is primarily used to provide a local effect at the site of action and bypasses first-pass metabolism. Microemulgel is a combination dosage form that combines the properties of a microemulsion and a gel. It exhibits desirable characteristics like spreadability, thixotropy, transparency, biocompatibility, emollient properties, and an elegant experience. With its dual release control system, incorporating both hydrophilic and hydrophobic drugs is possible. Microemulgels are prepared by incorporating a microemulsion into a gel matrix and evaluated for various parameters such as spreadability, pH, rheological properties, swelling index, and *in-vitro* release studies. Due to its micron-sized particles, microemulgels have excellent penetration through the stratum corneum. In summary, microemulgels represent a promising approach for topical drug delivery and hold potential for future applications in dermal care due to their dual release control system and enhanced therapeutic activity compared to microemulsions.

Keywords: Microemulgel, Microemulsion, Gel, Novel topical drug delivery

INTRODUCTION:

Microemulgel is considered a highly promising technology among innovative drug delivery systems due to its dual mechanism involving both emulsion and gel components. To prepare microemulgels, screening of oil, surfactant, and co-surfactant is necessary, based on the solubility profile of the active pharmaceutical ingredient (API). The presence of oil in microemulgels allows

deeper penetration of the API into the skin, while the creation of small-sized droplets in microemulsions provides a high interfacial area for drug absorption and helps maintain the drug's solubilized state **[1]**.

Topical formulations are used for localized effects at the application site, allowing the drug to penetrate into deeper layers of the skin or mucous membranes. While gels have several advantages, they have limitations in delivering hydrophobic drugs. However, by employing a microemulsion-based technique, these limitations can be overcome, enabling hydrophobic drugs to benefit from the unique properties of gels **[2]**.

The skin plays a vital role in the body's defense against external factors and in maintaining overall well-being. Topical drug delivery systems that provide local effects while avoiding first-pass metabolism, gastrointestinal degradation, and discomfort associated with oral treatments are employed for treating topical infections. Microemulgels, created by transforming a liquid microemulsion into a semisolid gel, serve as dual drug delivery systems and are considered highly promising in novel drug delivery technologies due to their dual mechanism involving both emulsion and gel **[3]**.

When both microemulsion and gel components are used in combination dosage forms, the formulations are referred to as microemulgels. These formulations combine the advantages of both emulgels and microemulsions. They can incorporate drugs that are hydrophilic or hydrophobic, providing a significant surface area for drug absorption **[4]**. The oil component in microemulgels enhances drug permeability and bioavailability.

Advantages of Microemulgels in Topical Drug Delivery:

1. *Integration of Hydrophobic Drugs:* Microemulgels allow for easy incorporation of hydrophobic medications into gels using oil-in-water (o/w) microemulsion. This expands the range of drugs that can be effectively delivered topically.
2. *Enhanced Loading Capacity:* Microemulgels have a higher capacity for drug loading compared to conventional gel formulations. This means that a larger amount of the active ingredient can be incorporated into the formulation, potentially leading to improved therapeutic efficacy.
3. *Cost-Effective and Feasible Production:* The production of microemulgels is economically viable and can be set up using inexpensive equipment and processes. This makes them a practical option for large-scale manufacturing.

4. *Controlled Drug Dispersion:* Microemulgels offer controlled dispersion of the drug, ensuring a uniform distribution within the gel matrix. This promotes consistent and predictable drug release over time.
5. *Reduced Need for Intensive Sonication:* Microemulgels can be prepared without the need for intensive sonication, which is a common requirement in traditional microemulsion formulations. This simplifies the manufacturing process and reduces production time and costs.
6. *Precise Drug Targeting:* Microemulgels enable more precise administration of drugs to specific localized areas, allowing targeted therapy and minimizing systemic exposure.
7. *Avoidance of Gastrointestinal Incompatibility:* Topical drug delivery bypasses the gastrointestinal tract, avoiding potential issues of drug degradation or incompatibility in the stomach or intestines.

Limitations of Topical Drug Delivery Systems:

1. *Physicochemical Composition***:** The physicochemical properties of the drug must be favourable for penetration through the stratum corneum (outermost layer of the skin). If the drug's properties are not suitable, transdermal drug delivery becomes challenging, especially if high daily doses are required for therapeutic benefit.
2. *Potential for Skin Irritation:* The use of certain drugs, excipients, and enhancers to promote percutaneous absorption can cause skin irritation or contact dermatitis in some individuals. This limits the suitability of topical drug delivery for certain patients.
3. *Variability in Skin Barrier Function:* The barrier function of the skin can vary across different anatomical sites within an individual, among different individuals, and with age. As a result, the rate of drug delivery may differ depending on the application site, leading to inconsistencies in therapeutic outcomes.

PHYSIOLOGY OF THE SKIN AND PENETRATION OF THE TOPICAL MEDICATIONS:

The skin, which is the largest organ in the body, serves as both a protective barrier and a defence mechanism against the external environment. It acts as a physical barrier, separating the internal body from the outside world.

The surface area of an average adult's skin is approximately two square meters, and it receives about one-third of the body's total blood circulation. On average, there are around 200-300 sweat ducts and 40-70 hair follicles per square centimetre of the skin's surface. The pH of the skin's surface ranges between 4 to 5.6, making it mildly acidic. The pH is influenced by the release of sweat and fatty acids.

The skin is composed of three main layers: the epidermis, dermis, and subcutaneous connective tissue. The epidermis is the outermost layer and provides protection, while the dermis is located beneath the epidermis and contains blood vessels, nerve endings, and other structures. The subcutaneous connective tissue, also known as the hypodermis, is the deepest layer and consists of fat cells that help insulate the body and provide cushioning.

Overall, the skin plays a crucial role in maintaining the body's integrity, regulating temperature, and protecting against physical, chemical, and microbial threats from the environment **[5]**.

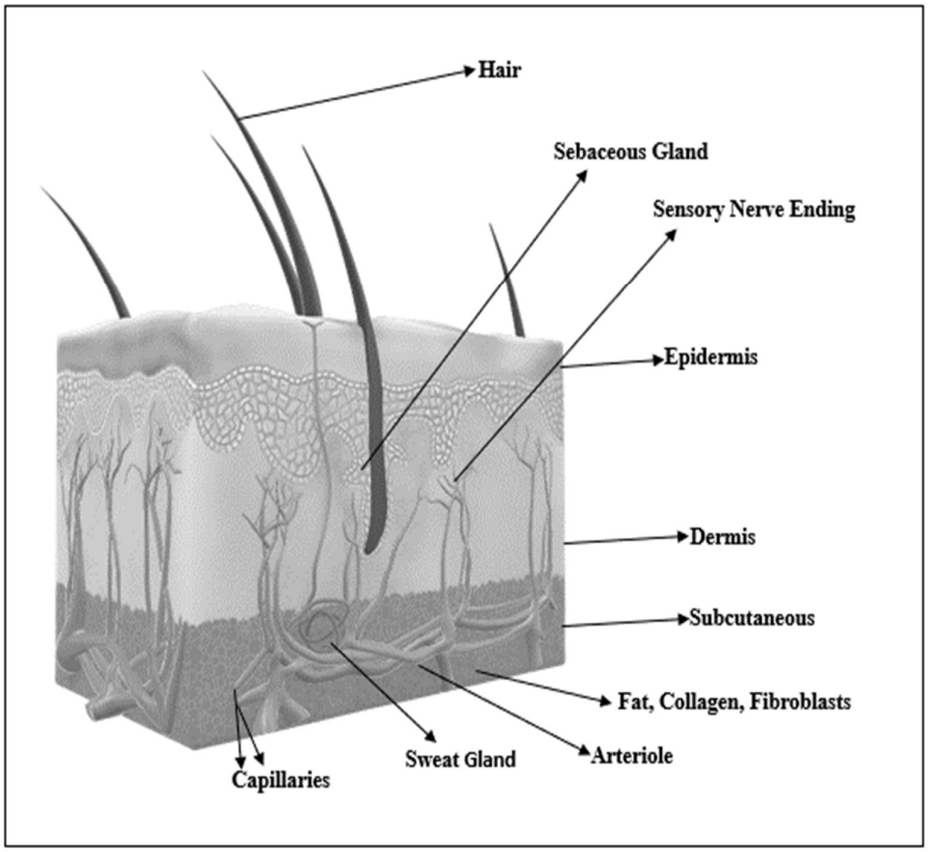

Figure 1: Structure of skin

FACTORS AFFECTING TOPICAL ROUTE OF DRUG ABSORPTION

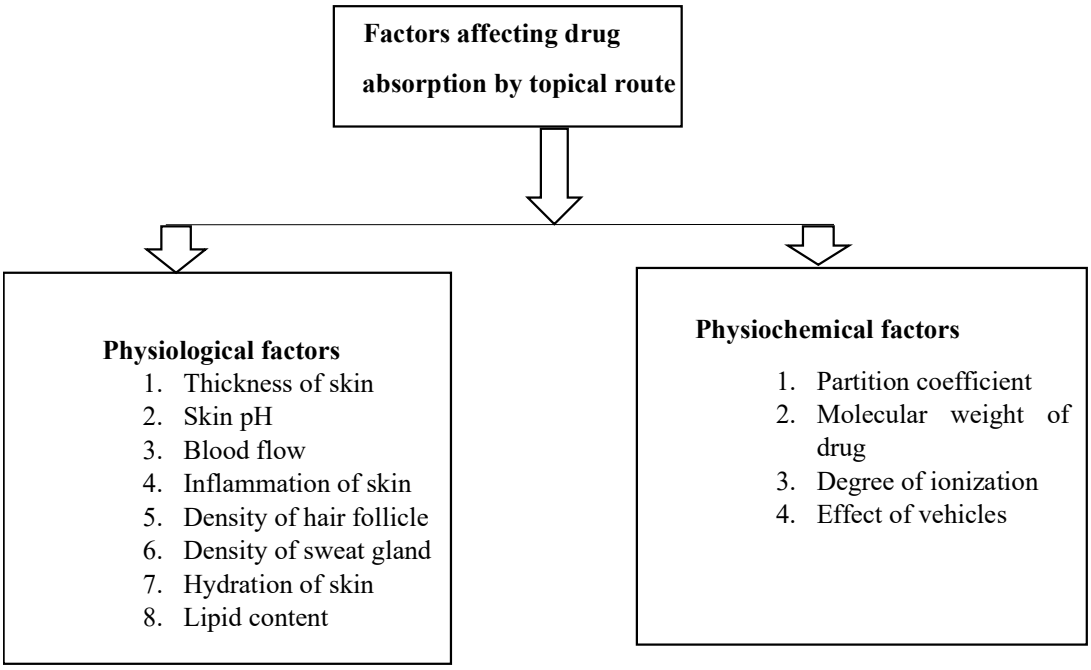

Figure 2: Flow chart for factors affecting topical drug absorption

FORMULATION CONSIDERATION:

a. Selection of oil phase: The oil phase in microemulsion-based gel formulations is chosen based on the solubility of the lipophilic bioactive. Low molecular weight oils, such as triglycerides, are preferred over high molecular weight oils as they can penetrate the interfacial film and aid in its development with the desired curvature. Additionally, microemulsions are thermodynamically stable systems, eliminating the need for ripening inhibiting agents to prevent instability phenomena like Ostwald ripening.

b. Selection of aqueous solvents: Water and alcohols are commonly used as the aqueous phase in emulsion formulations.

c. Selection of emulsifiers: Emulsifying agents, such as polyethylene glycol 40 stearate, sorbitan monooleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid, and sodium stearate, are employed to ensure stability during the shelf life of the formulation **[6]**.

e. Selection of surfactants: Surfactants are active compounds that possess both hydrophilic and lipophilic domains. They enable the dispersion of two immiscible phases and create a flexible film that surrounds the droplets with the ideal

curvature. Nonionic, zwitterionic, cationic, or anionic surfactants can be used to stabilize the microemulsion system. Examples of nonionic surfactants include Span 80, Tween 20/80, and Briji 35.

f. Selection of co-surfactants: Short-chain and medium-chain alcohols, such as ethanol, isopropanol, isopropyl myristate, and propylene glycol, are commonly used as co-surfactants in microemulsion formulations. They assist in reducing interfacial tension and promoting the formation of small droplets **[7]**.

g. Selection of gelling agents: Gelling agents are added to create a gel structure in the formulation. They can be of natural or synthetic origin. Gelling agents provide thixotropic properties to the formulation. Thickeners are used in oil-in-water microemulsions and nanoemulsions to balance the density of the oil phase with the surrounding liquid phase and prevent settling or creaming. Texture modifiers are also often employed. Preservatives are typically added to water-based systems to prevent microbial growth, although the addition of essential oils (EOs) can serve as a natural antimicrobial agent, reducing the need for additional preservatives in EO-based systems.

Overall, the selection of these components in microemulgel formulations plays a crucial role in achieving stability, solubility, and desired drug release properties for effective topical drug delivery **[8]**.

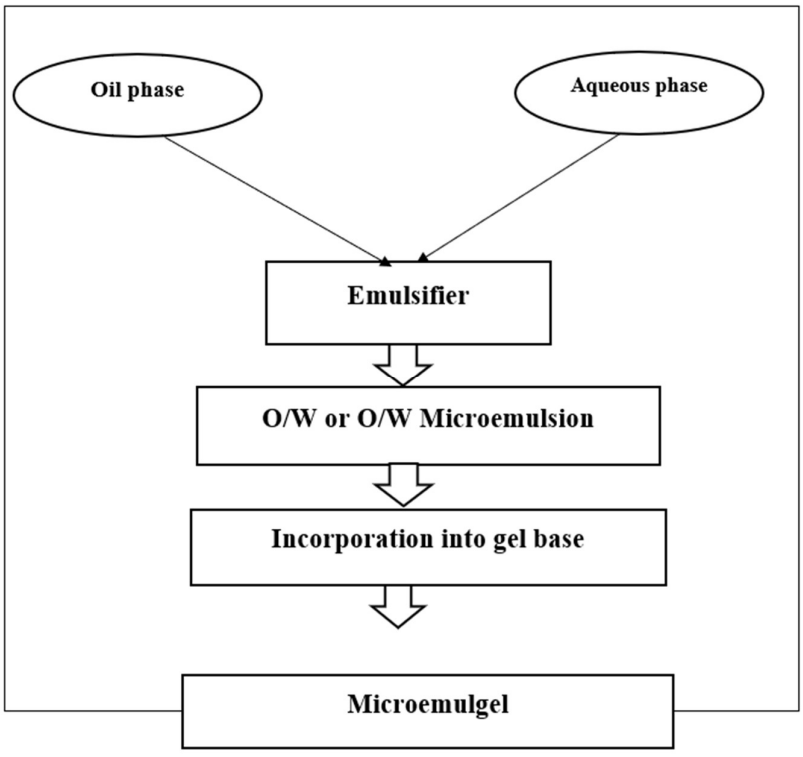

Figure 3: Schematic diagram for preparation of microemulgel

Table 1: Review of microemulgel formulation

Formulation	API	References
Formulation and evaluation of microemulsion based luliconazole gel for topical delivery	Luliconazole	[1]
Formulation and evaluation of topical microemulgel containing terbinafine hydrochloride	Terbinafine HCL	[3]
Formulation design and evaluation of microemulsion and microemulgel of itraconazole for topical application	Itraconazole	[7]
Design, development and evaluation of microemulgel containing Econazole nitrate	Econazole nitrate	[8]
Transdermal delivery of kojic acid from microemulgel	Kojic acid	[9]
Mcroemulgel formulation of kapok banana peel extract (*Musa paradisiaca* L) as an antioxidant	kapok banana peel extract (*Musa paradisiaca* L)	[10]

EVALUATION OF MICROEMULGEL:

1. **pH determination:**

   1% aqueous solution of the prepared microemulgel is made by dissolving 1gm of formulation in 100ml distilled water and kept it a side for 2 h after stabilization of the pH formulation is measured using digital pH meter in triplicate manner at a room temperature **[11]**.

2. **Determination of viscosity:**

   To determine the viscosity 20gm of microemulgel is filled in a 25ml beaker is subjected to Brookfield viscometer assembled with spindle number S6 **[12]**.

3. **Spreadability:**

   Spreadability is determined using a modified apparatus based on the method suggested by Multimer *et al*. in 1956. The apparatus consists of a wooden block with a pulley at one end. A ground glass slide is fixed onto this block. An excess of the microemulgel formulation being studied (approximately 2 grams) is placed on the ground slide. Another glass slide with the same dimensions as the fixed ground slide, equipped with a hook, is used to sandwich the microemulgel between the two slides. A 1 kg weight is placed on top of the slides for 5 minutes to ensure the expulsion of air and the formation of a uniform film of the microemulgel. Excess microemulgel is carefully removed from the edges. The top slide is then subjected to a pull force of 80 grams. By measuring the time (in seconds) taken for the top slide to cover a distance of 7.5 cm using a string attached to the hook, the spreadability can be determined. A shorter time interval indicates better spreadability. The spreadability (S) is calculated using the formula:

$$S = M \times L/T$$

Where,

S - spreadability,

M - weight tied to the upper slide,

L - length of the glass slide, and

T - time taken for the slides to separate completely from each other **[13]**.

4. **Rheological study:**

The viscosity of the prepared microemulgel is determind by using Brookfield viscometer (Brookfield LV, spindle no. 64). A glass container is filled with microemulgel sample and the spindle of the viscometer is allowed to rotate at predetermined speeds (5, 10, 20, 30, 40, 50, 60 and 100 rpm). For each speed of the viscosity was recorded after 30seconds **[14]**.

5. **Drug content determination:**

One gram of microemulgel sample is dispersed in 100ml phosphate saline buffer pH 7.4 and sonicated for 2 h. The sonicated mixture is filtrated using 0.45 µm Millipore filter and analyzed by using UV Spectrophotometric method **[15]**.

6. **Swelling index:**

The swelling index of the formulated microemulgel is determined by following a specific procedure. First, 1 gram of the microemulgel is carefully placed onto a piece of porous aluminum foil. Then, the aluminum foil with the microemulgel is placed separately into a beaker containing 50 ml of 0.1N NaOH solution. This NaOH solution serves as the swelling medium. The microemulgel is allowed to soak in the NaOH solution for a designated period of time.

At different time intervals, samples are taken from the beaker and carefully removed from the NaOH solution. These samples are then placed on a dry surface and allowed to dry completely. Once dried, the samples are reweighed to determine their final weight after swelling.

The swelling index is calculated using the following formula:

Swelling index (SI) % = [(Wt-Wo) / Wo] × 100

Where,

SI% - swelling index percentage,

Wo -initial weight of the microemulgel before swelling, and

Wt - weight of the microemulgel after swelling.

By measuring the change in weight, the swelling index provides an indication of the extent of swelling exhibited by the microemulgel formulation over time **[16]**.

7. **Centrifugation Study:**

The centrifugation study is conducted to evaluate the stability of the microemulgel formulation. This study is typically performed after one week of preparation. The following procedure is followed: After the specified period of one week, the microemulgel sample is prepared for centrifugation. A minicentrifuge is used for this study, set to a rotational speed of 3000 rpm. The microemulgel sample is placed in suitable containers, such as

centrifuge tubes or vials. The containers are carefully loaded into the centrifuge, ensuring proper balancing to avoid any disruption during centrifugation. The centrifuge is operated at the predetermined speed of 3000 rpm for a duration of 30 minutes. After the centrifugation process is complete, the containers are removed from the centrifuge. The stability of the microemulgel is assessed by observing any phase separation, creaming, or other changes in appearance or consistency. Any significant changes in the microemulgel after centrifugation may indicate instability or lack of homogeneity. The centrifugation study helps determine the ability of the microemulgel formulation to maintain its stability and prevent phase separation under centrifugal forces **[17]**.

9. Zeta potential measurement:

Zeta potential measurement is employed to identify the charge carried by the droplets in a microemulsion. In conventional emulsions, oil droplets typically carry a negative charge due to the presence of free fatty acids. The zeta potential of a microemulsion can be determined using a zeta sizer, such as the one provided by Malvern Instruments Ltd. (UK).

The zeta potential measurement involves the following steps:

- A sample of the microemulsion is prepared and made suitable for analysis according to the instrument's guidelines.
- The prepared sample is loaded into the zeta sizer instrument.
- The zetasizer applies an electric field to the sample, causing the particles within the microemulsion to move.
- As the particles move, their velocity is measured and analyzed.
- Based on the measured velocity, the zetasizer calculates the zeta potential, which represents the electrical potential at the shear plane surrounding the particles.
- The zeta potential value provides information about the surface charge of the microemulsion droplets.
- A higher magnitude of zeta potential indicates stronger repulsion between particles, leading to increased stability of the microemulsion.

By determining the zeta potential, it becomes possible to understand the electrostatic forces within the microemulsion and evaluate its stability based on the charge carried by the droplets **[18, 19]**.

8. *In Vitro* drug release study:

The drug release studies are conducted using a Franz diffusion cell with an effective diffusion area of 3.14 cm^2 and a

cell volume of 15.5 ml. In these studies, a 200 mg sample of the microemulgel is evenly applied onto the surface of an egg membrane. The egg membrane is securely clamped between the donor and receptor chambers of the diffusion cell. The receptor chamber is filled with a freshly prepared PBS solution at pH 5.5, which served to stabilize the drug. To facilitate mixing and enhance dissolution, the receptor chamber is stirred using a magnetic stirrer. At suitable time intervals, 1.0 ml aliquots of the sample are collected from the receptor chamber. These samples are then appropriately diluted and analysed for drug content using a UV-visible spectrophotometer. Cumulative corrections were made to determine the total amount of drug released at each time interval.

By measuring the cumulative amount of drug released across the egg membrane as a function of time, the drug release profile of the microemulgel formulation can be assessed **[20, 21]**.

CONCLUSION:

Microemulgel is considered one of the best approaches for topical drug delivery systems, especially for hydrophobic drugs. It possesses several desirable characteristics, including thixotropy, easy removal, emollient properties, high spreadability, water solubility, transparency, longer shelf life, good bioavailability, and an appealing appearance.

Microemulgel exhibits specific properties that make it suitable for controlling the release rate of drugs with a prolonged shelf half-life. While many drugs are highly effective when administered orally or parenterally, they often come with unwanted side effects. Therefore, alternative routes of administration, such as topical, ophthalmic, vaginal, or buccal, are required.

Since most drugs fall under BCS (Biopharmaceutics Classification System) Class IV, they face challenges related to solubility and permeability when attempting to penetrate the skin. The selection of appropriate oil, emulsifier, and co-emulsifier components in microemulgel formulation is crucial, as it can help overcome solubility and permeability issues. Additionally, the oil component of microemulgel can provide therapeutic benefits and further enhance drug permeability.

Microemulgel facilitates the enhanced disposition of drug molecules at the site of action, thereby enhancing their pharmacological action.

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