A Review on Microemulgel for Topical Drug Delivery System

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Abstract- Microemulgel formulations represent a promising advancement in the topical drug delivery system, combining the advantages of microemulsions and gels to enhance drug permeability and retention on the skin. Microemulsions, being thermodynamically stable, transparent systems, provide a suitable vehicle for the solubilization of both hydrophilic and lipophilic drugs. When incorporated into a gel matrix, microemulsions form a microemulgel that combines the superior permeation abilities of microemulsions with the desirable consistency of gels, facilitating easier application and improved patient compliance. This unique formulation has shown effectiveness in delivering drugs across the stratum corneum while prolonging drug release and enhancing bioavailability. The microemulgel system's stability and efficacy make it particularly suitable for treating localized skin disorders and conditions requiring controlled drug delivery. The review explores the composition, preparation techniques, evaluation parameters, and applications of microemulgel in dermatology and transdermal drug delivery, highlighting its potential as a carrier for various drugs.

Keywords: controlled release, dermatological applications, drug bioavailability, gel matrix

INTRODUCTION

In recent years, disease has been treated by giving drugs to the human body via a variety of routes, including oral, sublingual, rectal, and parental. The topical drug delivery system is commonly employed when other methods of medication administration fail, or it is primarily used in local skin infections such as fungal infections. Topical drug delivery refers to the application of a drug-containing preparation.[1,2]

Nowadays, pharmaceutical research is focused on meeting the therapeutic demands of patients. The majority of active pharmaceutical compounds generated are hydrophobic in nature, therefore using micro-emulsions to build new drug delivery systems has a positive impact on the successful delivery of hydrophobic medications [3,4]. Most commonly used medications have negative effects when administered orally, such as gastric discomfort, nausea, and gastrointestinal bleeding. One possible strategy for minimizing such side effects and systematic toxicities while still achieving superior therapeutic results is to inject drugs through the skin, often known as a topical drug delivery system.[5]

A liquid microemulsion is transformed into a semisolid gel to create the dual drug delivery device known as microemulgel. It is thought to be one of the most promising novel drug delivery technologies because of its dual mechanism of emulsion and gel. Additionally, it was shown that adding gel to the emulsion increased its stability. While gel can maintain drug release and offer a long drug residence time, microemulsion technology was selected due to its high solubility and skin penetration. [6–9]

The microemulgel drug delivery method is the best choice for skin-related conditions since it is more effective and uses less medication. The challenges of conventional topical delivery systems can be addressed by Microemulgel, which offers a wide interfacial area for drug absorption while keeping the medication in a solubilized state and generating droplets [10–12].

ANATOMY AND PHYSIOLOGY OF SKIN

The average adult's skin has a surface area of around 2 m^2 and receives roughly one-third of the blood that circulates throughout the body. The average human skin surface has between 40 and 70 hair follicles and between 2 and 300 sweat ducts per square meter.

The skin's pH ranges from 4 to 5.6. The pH of the skin is influenced by sweat and fatty acids released by sebum. Nonviable epidermis, viable epidermis, viable dermis, and subcutaneous connective tissues are the four separate tissue layers that make up the skin (Figure1) [13–15].

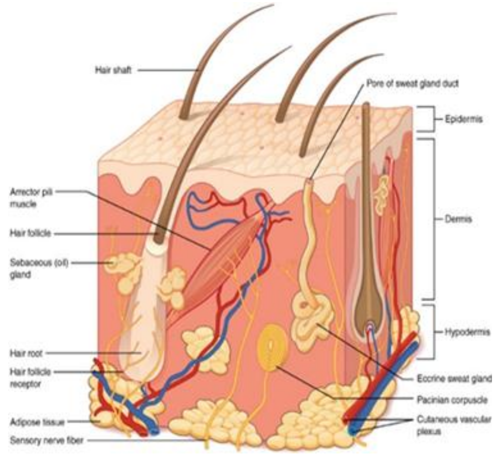

Fig 1: Anatomy and physiology of Skin

TOPICAL DRUG DELIVERY SYSTEM:

External topicals and internal topicals are the two primary categories of topical medication delivery agents. Whereas the internal topicals are given to mucosal membranes orally, vaginally, or on the rectal tissues for local activity, the exterior topicals are distributed, sprayed, or otherwise dispersed on the tissue to cover the diseased area. Among the primary benefits of topical drug delivery systems are the avoidance of first-pass metabolism, the avoidance of gastrointestinal incompatibilities, specific site selection, enhanced patient compliance, the possibility and ease of self-medication, the use of medications with short half-lives and narrow therapeutic indices, and the ability to quickly stop medication when needed.[16]

BASIC PRINCIPLE OF PERMEATION:

There are three main ways that substances typically enter the skin: through the stratum corneum between the corneocytes (intercellular route); through these cells and the lipids that are between them (intracellular route); or through the skin's appendages, like sweat glands and hair follicles. Skin penetration is possible for molecules that have a molecular weight less than 0.6 kDa, a log of the oil/water partition coefficient between 1 and 3, and sufficient solubility in both water and oil. Therefore, only hydrophobic and low-molecular-weight medications can be applied topically. The stratum corneum is difficult for anticancer medications to enter because they are hydrophilic, have a low oil/water partition coefficient, high molecular weights, and ionic characteristics. Ficks' second law describes how drugs penetrate the stratum corneum;

$$J = \frac{DmCvP}{L}$$

Where, J is the flux, Dm is the diffusion co-efficient of the drug in the membrane, Cv is the drug concentration in the vehicle, P is the drug partition co-efficient and L is the stratum corneum thickness.[17,18]

FACTORS AFFECTING TOPICAL ABSORPTION OF THE DRUG: [19,25]

Physiological Factors:

1. Skin thickness

2. pH of skin

3. Lipid content

4. Blood flow

5. Hydration of skin

6. Density of hair follicles

7. Inflammation of skin

8. Disease condition

9. Density of sweat glands

Physiochemical Factors:

1. Effect of vehicles

2. Partition co-efficient

3. Molecular weight (<400 Dalton)

4. Degree of ionization (Only unionized drugs get absorbed well)

ADVANTAGES OF MICRO-EMULGEL:[7,12-17]

1. Greater stability: The gel based on microemulsion is more stable than other transdermal preparations. Creams exhibit phase inversion or breaking, ointments exhibit rancidity because of their oily foundation, and regular topical emulsions exhibit a creaming action, much like powders are hygroscopic. The microemulsion-based gel provides superior stability and exhibits none of the aforementioned issues.

2. Greater loading capacity: Other cutting-edge strategies, such as liposomes and niosomes, are nanoscale and may leak and have lower trapping efficiency because of their vesicular architecture. However, gels have a relatively higher drug loading capacity because of their extensive network.

3. Manufacturing feasibility and low preparation cost: The manufacturing of microemulsion-based gel is made more feasible by the shorter and easier procedures involved in its preparation. The creation of microemulsion-based gel does not require any specialist equipment. Additionally, the materials are less expensive and readily available. Consequently, the costof producing microemulsion-based gel is reduced.

4. Incorporation of hydrophobic pharmaceuticals: The majority of hydrophobic drugs, primarily class VI drugs, cannot be directly incorporated into the gel base due to their solubility acting as a barrier and causing issues during drug release. Hydrophobic medications can be incorporated into the oil phase with the use of microemulsion-based gel. The resulting o/w emulsion is then produced by dispersing oily globules in the aqueous phase.

5. Absence of intense sonication: The production of vesicular molecules necessitates intense sonication, which could cause drug leakage and degradation. However, as sonication is not required when producing microemulsion-based gel, this issue is not observed.

6. To prevent the drug material from being deactivated by liver and digestive enzymes, which is known as the first pass effect. This is the first time the drug substance enters the systemi and partial circulation after gastrointestinal absorption.

7. Controlled release: Drugs with a shorter half-life can have their effects extended using a gel based on microemulsions.

DISADVANTAGES OF MICRO-EMULGEL:

1. The larger particle size drugs not easy to absorb through the skin.

2. Poor permeability of some drugs through the skin.

3. Can be used only for drugs which require very small plasma concentration for action.

4. Possibility of allergenic reactions.

5. An enzyme in the epidermis may denature the drugs. (22,26-31)

Application of microemulsion based gel [37]

1. Compared to traditional formulations like solutions, gels, or creams, greatly increase the transdermal penetration of medications.
2. They can also improve the penetration of lipophilic medications (estradiol, finasteride, ketoprofen, meloxicam, felodipine, triptolide, etc.) and hydrophilic medications (such as 5-fluorouracil, apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, methotrexate, etc.).
3. The high solubilizing capability allows for the incorporation of a considerable amount of medication into the formulation.
4. boost thrmodynamic activity towards the skin. Since a drug's affinity for the internal phase of a microemulsion may be readily altered to favor partitioning into the stratum corneum, this may boost the drug's rate of penetration from the microemulsion.
5. By functioning as penetration enhancers, the surfactant and co-surfactant in the microemulsions may lower the diffusional barrier of the stratum corneum by using a different internal phase and altering its portion in the microemulsion.
6. If the water content in the microemulsion is high enough, the stratum corneum's hydration action will also boost the drug's percutaneous absorption.

FORMULATION CONSIDERATIONS

Selection of Oil Phase:

The oil phase may include the lipophilic bioactive ingredient dispersed in a carrier oil Compared to high molecular weight oils (such as triglycerides), low molecular weight oils are preferred in microemulsion formulation because they can penetrate the interfacial film and help create the ideal curvature of the film. Furthermore, because microemulsions are thermodynamically stable systems, they do not experience instability phenomena like Ostwald ripening; so, the use of oil as a ripening inhibitor is not necessary. When creating an oil phase for a microemulsion-based gel, the oil that exhibits the highest solubility of the medication is chosen. These lipids might have anything from a liquid-like mobility to a high.

Selection of Surfactants:

The second criterion for selecting surfactants was their capacity to create a microemulsion with a specific lipid that had the best medication solubility . Both a hydrophilic and a lipotropic domain are present in the molecular structure of surfactants, which are unit active molecules . Surfactants' amphiphilic properties allow two incompatible phases to disperse, reducing surface tension and preparing a sufficiently versatile film to deform around the droplets with the optimal curvature . They are rapidly absorbed into the interface during the emulsification process, which prevents the droplets from aggregating . Such systems are stabilized with cationic, anionic, zwitterionic, or non-ionic surfactants. The microemulsion area is the extent to which ionic and non-ionic surfactants are effective.

Selection of Co-surfactants

Co-surfactants, such as ethanol, isopropanol, isopropyl myristate, and propylene glycol (PG), are often short- and medium-chain alcohols and polyglycerol derivatives. Low irritancy co-surfactants have also been made with nonionic surfactants . The interfacial tension is reduced to a temporary negative value by using cosurfactants in conjunction with surfactants. The interface expands at this negative value, forming fine droplets, and more surfactant or co-surfactant is adsorbed on the surface until the bulk condition is sufficiently depleted to restore a positive interfacial tension. Because the connection between main surfactant molecules reduces the polar head group interaction and the hydrocarbon chain interaction, co-surfactant of short-medium chain length alcohols also guarantees that the interfacial layer is flexible enough to bend easily around droplets

Selection of Gelling agent:

The gel phase is added to the mixture to provide the gel structure. There are two types of natural and artificial. A formulation becomes thixotropic when a gel phase is added . In O/W microemulsions and nanoemulsions, thickening agents are used to balance the density of the oil component with that of the surrounding liquid component. As a result, they may slow down the occurrence of deposit or creaming phenomena by focusing on the effects of attraction forces Additionally, texture modifiers are also frequently utilized. In order to prevent the growth of microbes, water-based systems typically need to include a preservative. Since EOs are naturally occurring antimicrobials, preservatives are usually added in excess in the particular instance of EO-based systems. According to the study, the utilized EOs-based microemulgel.[36]

METHODS OF PREPARATION OF MICRO-EMULGEL [32]:

1. Phase Titration Method:

The spontaneous emulsification method, also known as the phase titration method, is used to create microemulsions, which can be illustrated using phase diagrams. A helpful method for examining the intricate sequence of interactions that may arise when several components are combined is to construct a phase diagram. Depending on the chemical makeup and concentration of each component, microemulsions and different association structures (such as emulsions, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) are generated. Delineating the phase boundaries and comprehending their phase equilibrium are crucial components of the research. The pseudo ternary phase diagram is frequently created to identify the various zones, including the microemulsion zone, where each corner of the diagram represents 100% of the specific component, because the quaternary phase diagram (four component system) is time-consuming and challenging to interpret (1). By merely taking into account the composition—that is, whether it is water-rich or oil-rich—the region can be divided into w/o or o/w microemulsions. In order to exclude metastable systems, rigorous observations must be undertaken.

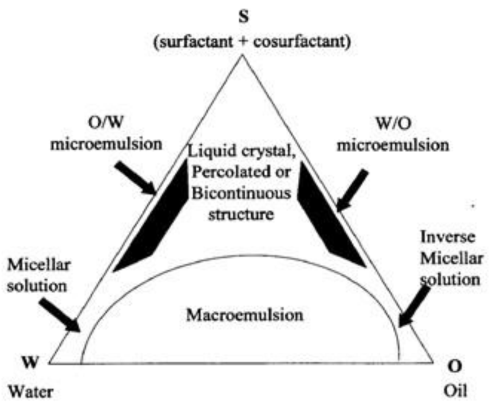

Fig 2 : Phase Titration Method

2. Phase Inversion Method:

When too much of the dispersed phase is added, or when the temperature changes, the microemulsion undergoes phase inversion. Significant physical changes, such as modifications in particle size, take place during phase inversion and can impact drug release in vitro and in vivo. These techniques utilize altering the surfactant's spontaneous curvature. This can be accomplished for non-ionic surfactants by altering the system's temperature, which will force a transitional phase inversion—the change from an o/w microemulsion at low temperature to a w/o microemulsion at high temperature. A point of zero spontaneous curvature and low surface tension is crossed by the system during cooling, which encourages the development of finely distributed oil droplets. Phase inversion temperature (PIT) is the name given to this technique. Other parameters, such the pH level or salt concentration, could be taken into account in place of the temperature. Altering the water volume fraction can also result in a change in the spontaneous radius of curvature. Water droplets are first created in a continuous oil phase by gradually adding water to oil. The surfactant's spontaneous curvature shifts from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus as the water volume percent is increased. At the o/w interface, short-chain surfactants create flexible monolayers, which at the inversion point produce a bicontineous microemulsion.

METHOD OF PREPARATION OF MICRO-EMULGEL:

STEP 1: Formulation of microemulsion either O/W or W/O.

STEP 2: Formulation of gel base.

STEP 3: Incorporation of microemulsion into gel base with continuous stirring.

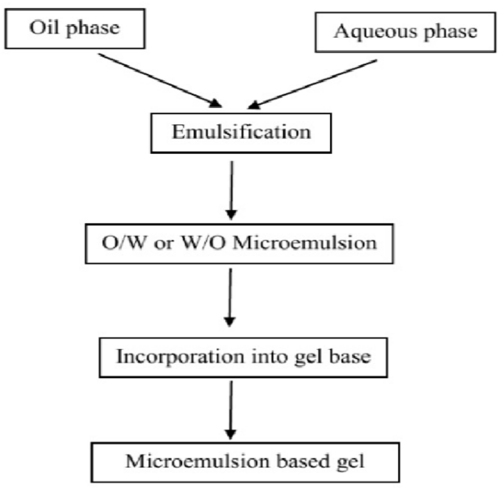

Fig 3: Method of Preparation of Microemulgel

CHARACTERIZATION OF MICRO-EMULGEL

1. The viscosity:

The rheological characteristics of formulations are ascertained by measuring the viscosity. Brookfield viscometer The viscosity is measured using the rotational r type. Three duplicates of the results are obtained, and the average is taken into account.

2. The pH :

A digital pH meter is used to measure the pH, and the results are recorded in triplicate seven times before the average is taken into account. Measurement of the micro-emulsion's pH is also necessary since variations in pH can impact the zeta poantial, which in turn can impact the products' stability.

3. Drug content :

The UV visible spectroscopic approach is used to measure the drug content [33].

4. The ability to conduct :

A digital conductometer is used to measure the micro-emulsion's electric conductivity at room temperature. Three copies of the results are obtained, and an average is then calculated [34].

5. The test of dilution :

The micro-emulsion won't break or separate into phases if a continuous phase is added. The micro-emulsion is diluted 50–100 times in water and visually inspected for phase separation and clarity. Three copies of the results are obtained, and an average is then calculated [35].

CONCLUSION

By combining the benefits of microemulsions and gels, microemulgels provide a novel and efficient method of topical drug administration that improves patient compliance, prolongs release, and improves drug penetration. High solubilization of hydrophilic and lipophilic active substances is made possible by the special structure of microemulgel, which also makes effective distribution through the epidermal barrier possible. This technique has great promise for improving transdermal medicine delivery and addressing localized skin diseases. Microemulgels stand out as a flexible and promising choice for creating more potent topical and transdermal medicinal applications thanks to developments in formulation processes. The microemulgel technique may be further improved by future studies, which would increase stability, optimize drug release rates, and broaden its applicability in a variety of dermatological and pharmaceutical fields.

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