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A REVIEW ON : MICROEMULGEL AS A TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT:
Topical drug delivery is the potential route to deliver the drug producing low side effect in comparison with any other dosage forms. There are many conventional dosage forms for topical applications as ointment, cream, gel, but they show fluctuation in bioavailability of drugs and are associated with other limitation as gel is limited to deliver the hydrophilic drugs. The new approach in the field of topical drug delivery is introduced to deliver the hydrophilic drug that can enjoy the gelling property and whose rate can be controlled named microemulgel. It is simply where Micro-emulsion of the drug .is prepared using oils, surfactants and co-surfactants, and incorporated in the gelling agents forms microemulgel. Microemulgel with its micron sized globule has better penetration which delivers the drug directly to systemic circulation, and also enhances improved bioavailability of the drug and improved patient compliance . Currently many drugs of antimicrobial, antifungal and non steroidal anti inflammatory drugs (NSAIDs) are studied for their topical delivery through microemulgel formulation. The Microemulgel for dermatological & Cosmetic use have different desirable properties such as good consistency, being thixotropic, easily spreadable, Non-staining, emollient, bio-friendly, clear, transparent & elegant appearance, & these Microemulgel based formulations enhances the skin deposition of API , thereby ultimately enhancing its therapeutic activity.

KEYWORDS : Topical delivery , microemulsion , gel , microemulgel

INTRODUCTION :

TOPICAL DRUGDELIVERYSYSTEMS:

Topical therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin deliver the drug, through the skin at a controlled rate to the systemic circulation. Thus, it is anticipated that topical drug delivery system can be designed to deliver drug at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port of entry of drugs.

Topical drug delivery offers numerous advantages over other routes of delivery including its accessibility and non-invasiveness allowing for ease and convenience of administration. This approach results in direct entry of bioactive molecules into the systemic circulation, thereby avoiding first-pass metabolism, efflux transporters, as well as metabolizing/digestive enzymes and unfavorable conditions associated with other routes of administration such as oral route.

ADVANTAGES OF TOPICAL DRUG DELIVERY OVER THE CONVENTIONAL DOSAGE FORMS: -

The perceived advantages for transdermal drug delivery are as follows:

- Avoids vagaries associated with gastrointestinal absorption due to pH, enzymatic activity, drug-food interactions etc.
- Substitute's oral administration when the route is unsuitable as in case of vomiting, diarrhea.
- Avoids hepatic "first pass"effect.
- Avoids the risks and inconveniences of parenteral therapy.
- Reduces frequency of doses, thus improves patient compliance.
- Extends the activity of drugs having short plasma half-life through the reservoir effect and controlled release characteristics.
- Rapid termination of drug effect by removal of drug application from the surface of the skin.
- Rapididentificationofthemedicationinemergencies.(E.g.Non-responsive,unconscious.
- Enhances therapeutic efficacy, reduced side effects due to optimization of the blood concentration-time profile and elimination of pulse entry of drugs into the systemic circulation.
- Provides predictable activity over extended duration of time and ability to approximate zero-order kinetics.

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- Improves control of the concentrations of drug with small therapeutic indices.
- Minimizes inter and intra patient variation.
- Allows self-administration.

LIMITTIONS OF TDDS:

- The drug must have some desirable physicochemical properties for penetration through stratum corneum. If the drug dosage required for therapeutic value is more than 10mg/day, the transdermal delivery becomes very difficult.
- Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age. Hence rate of drug delivery may vary from site to site.

DESIRABLE PROPERTIES FOR TRANSDERMAL CANDIDATE:

1. The drug should have a molecular weight less than 500daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases.
3. The drug should have a low melting point.
4. The drug should be potent with a daily dose of the order of a few mg/day.
5. The half life ($t_{1/2}$) of the drug should be short.
6. Oral bioavailability , therapeutic index and polarity should be less.
7. The drug must not induce a cutaneous irritation or allergic response.
8. Drugs which degrade in the G.I. tract or /are inactivated by hepatic first-pass effect are suitable candidates for transdermal delivery.

Physiology of Skin and Penetration of Topical Medications :

Skin is the biggest organ in the body and it is considered as a external defense system .It covers the outside of the body a has other functions beside the defense mechanism it serve as a mechanical barrier between the inner part of the body and the external world.

The skin of an average adult body covers a surface area approximately 2m2 and receives about one third of the blood circulating through the body .An average of every square centimeters of the human skin surface is known to contain, on the average 40-70 hair follicles and 200-300 sweat ducts . Skin surface is slightly acidic and the pH of the skin varies from (4 to 5.6). Sweat and fatty acid secretions influences the pH of the skin surface

The skin can be considered to have three distinct layers of tissue that is epidermis, dermis and subcutaneous connective tissue as shown in figure. (1)

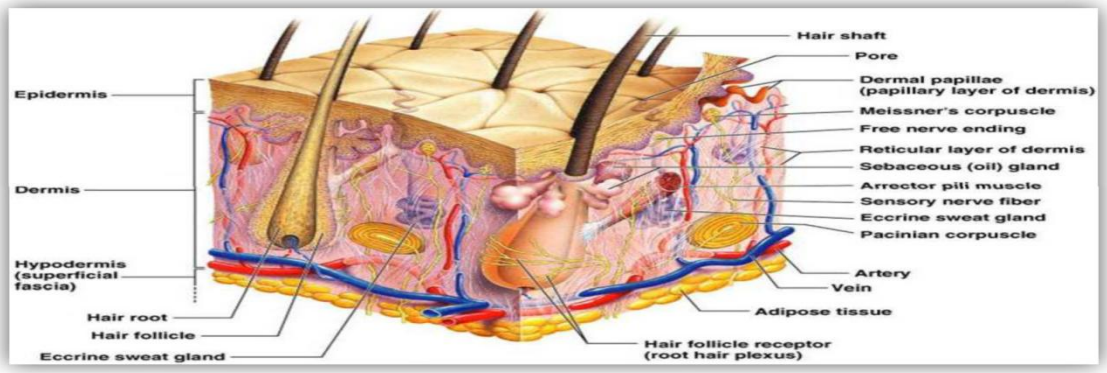

fig 1 : structure of skin

Factors Affecting Topical Absorption of Medications :

A-Physiological Factors of Skin :

- Skin thickness
- Lipid content and part of skin.
- Density of sweat glands.
- Skin pH.
- Blood flow.
- Hydration of skin.
- Disease state and inflammation of skin.

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B-Physiochemical Factors of Drug -

- Distribution coefficient.
- Molecular weight (<400Dalton).
- Degree of ionization (unionized drugs gets absorbed well).
- Effect of excipients

Introduction to Microemulsions :

In 1943, Hour and Schulman visualized the existence of small emulsion- like structures by electron microscopy and subsequently coined the term "microemulsions". Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 10-100 nm. whereas the diameter of droplets in a kinetically stable emulsions>500nm. Because the droplets are small , microemulsion offers advantages as a carrier for drugs that are poorly soluble in water. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity.

Rationale of microemulgel as a Topical Drug Delivery System :

When gel and microemulsion are used in combination form, the dosage form is referred to as "microemulgel". microemulgel is having major advantages on novel vesicular systems as well as on conventional systems in various aspects:

Being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance.microemulgeldosageformisusedforsome antibioticsanditwas extended to analgesics and antifungal drugs.

Topical agents such as ointment, cream, lotion have many disadvantages. They are sticky and causing uneasiness to the patients, also have lesser spreading coefficient, and need to be applied sometimes with rubbing. They exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gel has expanded both in cosmetics and in pharmaceutical preparation . However, despite of offering several benefits, gels a colloid system shows major limitations like delivery of hydrophobic drugs. In order to overcome this problem an microemulsion-based approach is being used so that even hydrophobic therapeutic moiety can be successfully incorporated and delivered through gel mixtures. Microemulgel structure was showed in **figure (2)**

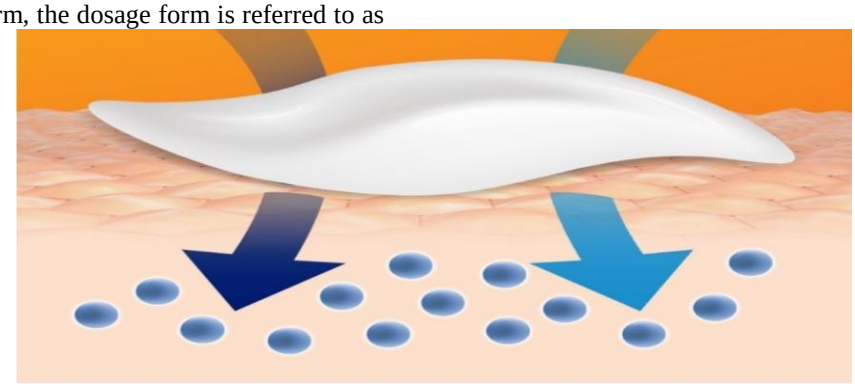

fig 2 : Microemulgel structure

Important constituents of Microemulgel dosage form :

1 Aqueous Material -

This forms the aqueous phase of the micro-emulsion. Commonly used agents
are water, alcohols.

2 Oils -

oils used in the microemulsion preparation will be used as a penetration enhancer.

3 Emulsifiers -

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared microemulsions to months or years for commercial preparations.

4 Gelling agents -

Gelling agents used to form gel base to incorporate microemulsion in it to prepare microemulgel. Gelling agents are the agents which increase the consistency of any dosage form by swelling in aqueous phase and forming jelly like structure . They used as thickening agent in microemulgel.

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Preparation of Microemulsion

A predetermined amount of drug was weighed accurately and dissolved in oil by stirring on a magnetic stirrer. Water and surfactant were mixed together. This mixture was added drop-wise to an oily solution of drug and mechanically stirred to form an emulsion. Co-surfactant was added drop-wise to the emulsion. Formation of the transparent solution indicated the formation of microemulsion.

Method of preparation of Microemulgel :

Gelling agents were presoaked separately in aqueous phase (water) for 24 hours. The prepared oil phase i.e,microemulsion was then added to the gel phase to form microemulsion based gel and mixed until the smooth, elegant microemulgel was obtained.

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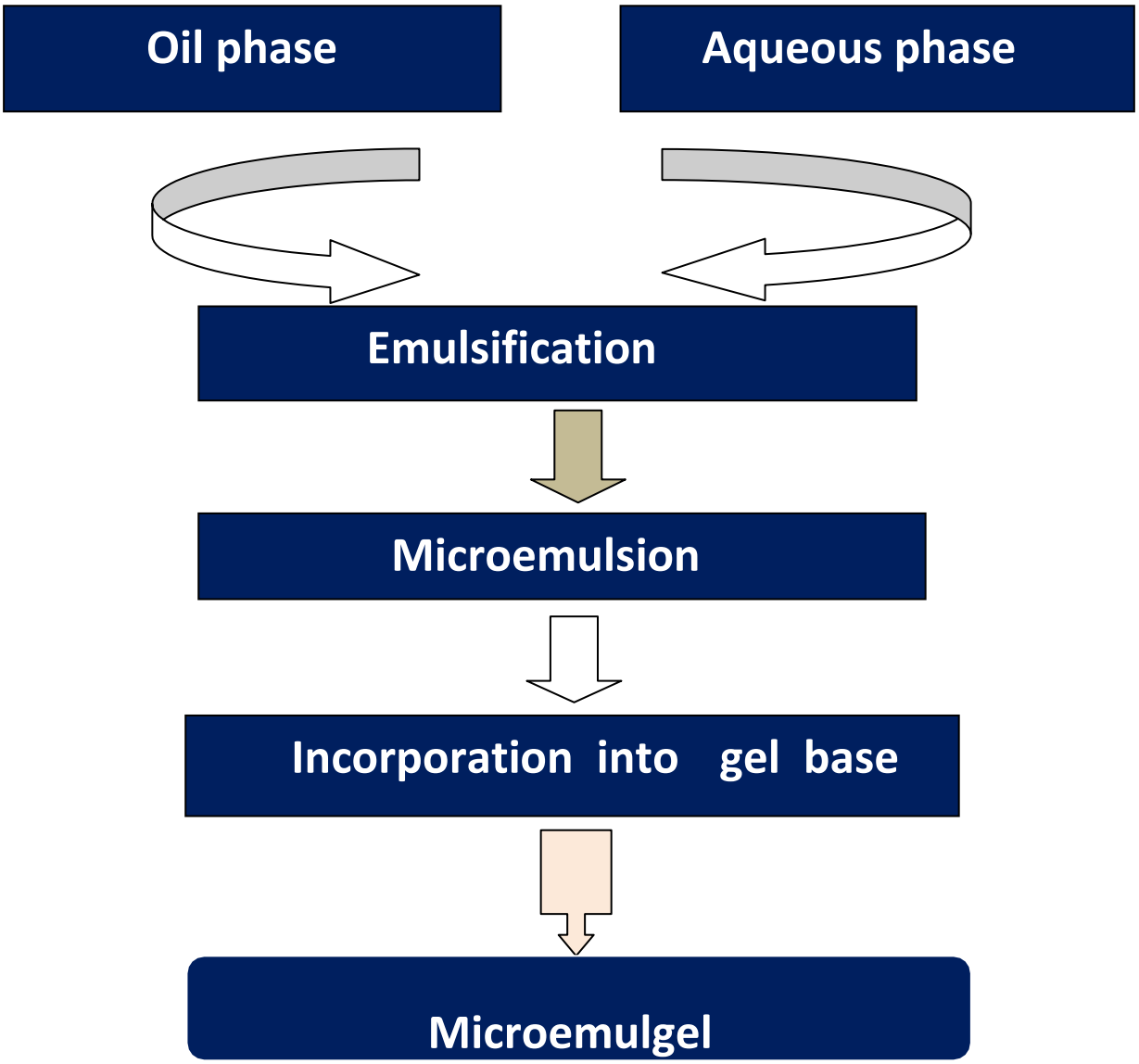

Fig 3 : Formation of Microemulgel

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Evaluation of Microemulsion :

1) % Transmittance Measurement–
Microemulsion was diluted 100 times with distilled water. % transmittance of formulation was measured using UV Visible spectrophotometer at 560 nm wavelength against continuous phase (Distilled water) as blank**.**

2) Particle Size Measurements –
Particle size determination: Particle size of optimized microemulsion formulations were determined by dynamic light scattering Malvern Zetasizer . Sample preparation was done by diluting 0.1ml of microemulsion in distilled water i.e. dispersion medium

3) Zeta Potential Measurement -
Zeta potential of microemulsion was determined by Zetasizer (Malvern). Samples were placed in clear disposable zeta cell and results were recorded.

4) Dilution Test -
This test was carried out to find out which type of microemulsion was formed. The prepared microemulsion was diluted with water which was external /continuous phase.

5) Electro conductivity measurement
Electrical conductivity of MEs was measured with a conductivity meter for testing microemulsion type using conductivity cells with a cell constant of 1.0 and consisting of two platinum plates separated by desired distance and having liquid between the platinum plate acting as a conductor.

6) pH–
The pH meter was calibrated with standard buffer solution having pH 4 and 7 before use. And then prepared Microemulsion formulations was dissolved in distilled water and stirred until it forms uniform suspension, kept it aside for 2 hr. The volume made up to 100 ml and pH of the suspension can be measure with the digital pH meter. The measurements of pH of each formulation were performed in triplicate

7) Density–
Density was measured using a specific gravity bottle (density bottle). Weight of empty specific gravity bottle was noted as W1 , weight of specific gravity bottle with distilled water noted as W2 and weight of specific gravity bottle with microemulsion was noted down as W3.It can be calculated by the formula ,

$$\text{Specific gravity of liquid} = \frac{\text{Mass of liquid}}{\text{Mass of equal volume of water}}$$

8) Viscosity–
Brookfield programmable DVII+ Model pro II type viscometer was used for viscosity studies. The prepared microemulsion formulations in ml , were placed in a beaker and were allowed to equilibrate for 5 minutes before measuring the dial reading using spindle No. 62 at a speed of 50 rpm.

9) Centrifugation -
This parameter was measured to evaluate the physical stability of microemulsion. The prepared microemulsion was centrifuged at ambient temperature at 5000 rpm for 10 minutes to evaluate the system for creaming or phase separation. The microemulsion was observed visually for appearance.

10) Drug Content-
The drug content was determined by dissolving amount of the formulation equivalent to required mg of active drug in 100ml of phosphate buffer pH 5.5. The volumetric flasks were kept for 2 hour over a rotary shaker to mix it properly. The solution was filtered and drug content was measured spectrophotometrically in UV

11) **In-vitro drug release studies**
The in vitro drug release studies were performed by using Franz diffusion cell with cellophane paper. The water jacketed recipient compartment had total capacity of 25 ml and it had 2 arms, one for sampling and another for thermometer. The donor compartment had internal diameter of 2 cm. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The receptor compartment contained phosphate buffer (pH 5.5) that was maintained at 37°C ± 1°C. The membrane was equilibrated

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before application of the microemulsion equivalent to required quantity of drug onto the donor side. ml of Samples were periodically withdrawn from the receptor compartment, replacing with the same amount of fresh Phosphate buffer pH 5.5 solution, and assayed by using UV.

Evaluation of Microemulgel

1. Physical Examination

The prepared microemulgel formulations were examined visually for their color, appearance, consistency, grittiness, phase separation and homogeneity Consistency, grittiness and phase separation.

2. Extrudability test

It is an test peformed to determine the force required to extrude the material from tube . The formulations were filled in the collapsible tubes. The extruability of the formulation was determined in terms of weight required to extrude 0.5 cm ribbon of microemulgel in 10 second When more quantity is extruded, extrudability is considered to be better . The percentage of gel extruded was calculated and recorded.

3. Syneresis Measurement

After microemulgel was visually inspected , it was tested for any possible phase separation. Upon standing, gel sometimes shrinks and little liquid is pressed out. This phenomenon is called syneresis. It is expressed as percent syneresis. This test involves the use of a centrifuge machine. The formulation was added in a cylindrical tube which had a perforated bottom which was covered with Whatman filter paper. The tube was placed in the centrifuge and centrifuged for 15 minutes. Tube and liquid separated from microemulgel were weighed. Percent syneresis was calculated using formula.

$$\% \text{ syneresis} = \frac{\text{weight of liquid separated from microemulgel}}{\text{Total weight of microemulgel before centrifugation}} * 100$$

4. pH

The pH value can be measured by using pH meter (Digital pH meter). The pH meter was calibrated with standard buffer solution having pH 4 and 7 before use. And then the 1% aqueous solution of the prepared Microemulgel can be made. Required quantity of formulation was dissolved in distilled water and stirred until it forms uniform suspension, kept it aside for 2 hr. The volume made up to 100 ml and pH of the suspension can be measure with the digital pH meter. The measurements of pH of each formulation were performed in triplicate.

5. SpreadabilityTest

To determine the spreadability of microemulsion based gel, 0.5 g of gel was placed within a circle of 1 cm diameter pre-marked on a glass plate, over which a second glass plate was placed. A weight of 500g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to gel spreading was noted.

6. Rheological Study

Viscosity of microemulgel was determined by using Brookfield's viscometer.

7. Drug content determination

Drug content in microemulgel will be measured by dissolving 1gm of microemulgel in solvent by sonication. Absorbance will be measured after suitable dilution at λ_{max} nm using UV spectrophotometer.

8. In-vitro Diffusion Study

Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5ml cell volume) is used for the drug release studies. Microemulgel is applied on to the surface of cellophane membrane. The cellophane membrane is clamped between donor and receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared PBS (pH 5.5) solution to solubilise the drug. The receptor chamber is stirred by magnetic stirrer. The samples are collected at suitable time interval sample are analyzed for drug content by UV visible spectrophotometer at respected wave length after appropriate dilutions. Cumulative corrections are made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the cellophane membrane is determined as a function of time.

Release Kinetics :

Drug release from all the batches of the microemulgel was evaluated for best fit model. Various kinetic models are zero order, first order, Higuchi, and Korsmeyer Peppas.

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Stability study :
Stability study for the optimised batch was carried out as per ICH guidelines. Short term accelerated stability of gel was carried at 40°C ± 2°C /75% ± 5% RH for 3 months.The microemulgel formulation were tested and checked at regular intervals for changes in Physical appearance , consistency , pH ,viscosity , Spreadability , and drug content.

CONCLUSION

Microemulgel is one of the best approaches for topical drug delivery of hydrophobic drugs, as microemulgel has several favorable properties Such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Microemulgel have properties of both emulsion and gels and thus can be used for controlling release rate of drugs with short half-life. various advantages and future prospective micro-emulgels offer a wide utility in derma care. Mostly drugs are poorly water soluble, so have the problem of penetrating through the skin. Selection of oil, emulsifiers and co-emulsifiers for preparation are based on solubility of it in them, so the problem of solubility would be overcome. Oil portion has more or less pharmacological action and itself enhances penetration. Microemulgel enhances deposition of drug moieties at the site, so have increased therapeutic activity.

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