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A NOVEL APPROACH OF MICROEMULSION BASED HYDROGEL FOR TOPICAL DELIVERY

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ABSTRACT

Topical drug delivery is a potential route to deliver the drugs that produce few side effects when compared with any other dosage form. There are wide range of conventional dosage forms for topical applications such as ointments, creams, gels, but they show variation in drug bioavailability and are associated with other limitation as gels are limited to deliver the hydrophilic drugs. New approach in the field of topical drug delivery is introduced that is microemulsion based hydrogel (MBH) which deliver the hydrophilic and lipophilic drug that can take advantage of gel forming property and rate can be controlled. Microemulsion - based approach is used, so that even the hydrophobic therapeutic moiety can be effectively combined and delivered by hydrogels. Microemulsions are prepared using oils, surfactants and co-surfactants and incorporated in gelling agents to form a microemulsion based hydrogel (MBH). MBH with its micron-sized spheres has better penetration which directs the drug to systemic circulation and prolongs drug release and retention of dosage form on the skin, thus reducing fluctuation in concentration of drug, reducing drug toxicity and improving patient compliance by prolonging dosage application intervals. Currently, many drugs of antibacterial, anti-fungal and non-steroid anti-inflammatory drugs (NSAIDs) studied for topical administration by MBH formulation. MBH formulation is used to improve API deposition in the skin, this ultimately improve its therapeutic activity.

KEYWORDS: Microemulsion, hydrogel, surfactant, anti-fungal.

INTRODUCTION

Topical systems are defined as discrete, self-contained dosage forms that when applied to intact skin, deliver the drug through skin at a controlled rate to the systemic circulation. Therefore, it is anticipated that topical drug delivery systems can be designed to deliver drugs in appropriate levels to maintain adequate plasma drug concentration for effective level of treatment using skin as drug entry point. Topical drug delivery offers many benefits over other delivery routes, including its accessibility and non-invasiveness allowing for easy and convenient administration. This approach that leads to direct penetration of biologically active substances in the systemic circulation, thereby avoiding first-pass metabolism, efflux transporter, as well as metabolic/digestive enzymes and adverse conditions related to other routes such as oral route.[1]

Microemulsion is isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactants, which often used in combination with co-surfactants, with droplet sizes usually in the range of 10-100 nm, while the diameter of the droplets in a kinetically stable emulsion >500 nm. Because the droplets are small, the microemulsion offers advantage for poor water-soluble drugs. The microemulsion components may function as permeation enhancers, which may reduce the diffusional barrier of the stratum corneum and increase the drug permeation rate through the skin. Moreover, the microemulsion's hydration effect on the stratum corneum may affect the permeability of medication formulations. 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. To overcome this disadvantage, various gelling agents are added into the microemulsion to form microemulsion-based hydrogels (MBHs).[2,3]

Hydrogels are three-dimensional (3D) polymeric networks, which have a hydrophilic structure that enables them to absorb a lot of water (thousands of times their dry weight). Due to their longer lifespan, greater capacity to absorb water, excellent mechanical qualities, and finely-tuned breakdown, hydrogels made of synthetic polymers are currently attracting more interest than those made of natural polymers. They are important candidates for biomedical applications such as drug delivery, tissue engineering, 3D cell cultures, *in vitro* diagnostics, and stem cell research due to their distinctive properties, which include reliable biocompatibility, tunable mechanical and degradation

features, sensitivity to different stimuli, and the ability to be easily conjugated with hydrophilic and hydrophobic therapeutic compounds.[4]

Microemulsion-based hydrogel (MBH) formulations have generated considerable interest as a potential topical delivery system. Both hydrophilic and lipophilic materials can be solubilized because a single-phase solution contains microdomains with various polarities.[5] Microemulsion based hydrogels with a suitable viscosity and good biocompatibility can prolong the retention time of drug on the skin and reduce the risk of skin irritation after their topical application.[6]

Physiology of Skin

Skin is the largest organ in the body which is considered as external defence system. It covers outside of the body and has other functions besides the protection mechanism, it serves as mechanical barrier between the inner part of body and the outside world. The skin of an average adult body covers the surface area of about $2m^2$ and receives about one third of the blood circulating in the body. An average per square centimetre of human skin surface is known to contain, on average 40-70 hair follicles and 200-300 sweat ducts. The surface of the skin is slightly acidic and the pH of skin ranges from 4 to 5.6. Sweat and fatty acids secretion affect the pH of the skin surface. Skin can be considered as three separate tissue layers that are the epidermis, dermis and subcutaneous connective tissue as shown in figure.[7,8]

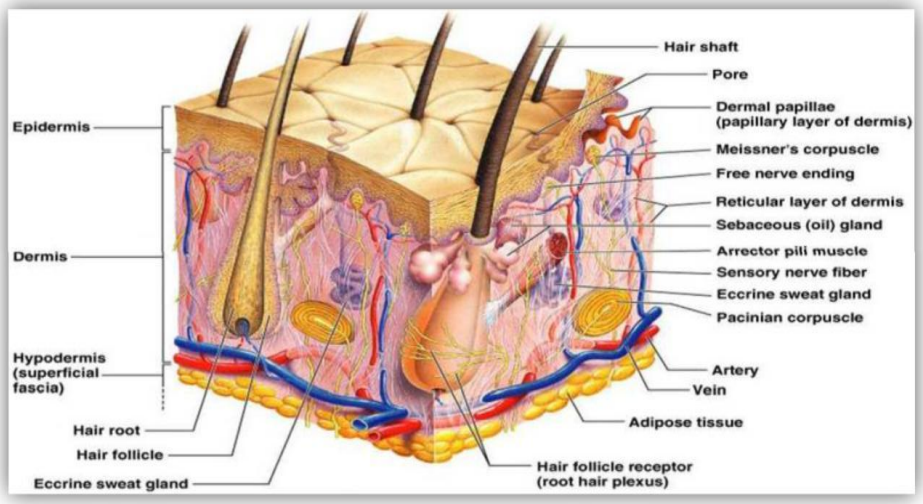

Fig. 1: Structure of skin.

Mechanism of Drug Absorption[9]

Permeation of a drug involves the following steps:

1. Sorption of a penetrate molecule on surface layer of stratum corneum.
2. Diffusion through it and viable epidermis and finally reach to dermis.
3. The molecule is taken up into the microcirculation for systemic distribution.

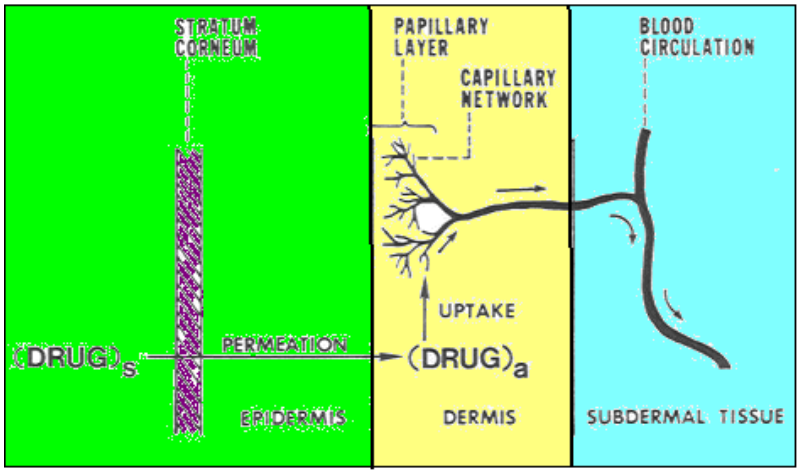

Fig. 2: A multilayer skin model showing sequence of skin permeation of drug.

Permeation pathways[10]

A molecule may use three diffusional routes to penetrate normal intact skin.

1. Penetrates through the skin, through the stratum corneum.
2. Intercellular permeation, through the stratum corneum.
3. Trans appendageal permeation, through the hair follicle, sebaceous and sweat glands.

The skin acts as a great barrier for the penetration of any substances into the body and this is mainly due to stratum corneum, which is its outermost layer. In most of its area, there are 10-30 layers of corneocytes with palms and soles having the most. Each corneocytes is surrounded by a protein coat and filled with the water-retaining keratin proteins. The cell shape and orientation of keratin protein adds a strength to the stratum corneum. When a formulation is applied to the skin, several gradients are established across it and the drug, up to a certain level, are able to cross the stratum corneum.

There has been a constant effort to understand structural barrier and stratum corneum properties. The drug penetration through hair follicles and stratum corneum is widely discussed. Moreover, it is reported that the follicular pathway is more favourable for the permeation of polar molecules as their influx through stratum corneum is difficult. There are specific factors which determine the efficacy of the drug through skin. The physicochemical nature of the drug, its site and skin conditions, formulations and their effect on the properties of the stratum corneum are also important.

Factors Affecting Topical Absorption of Drug[11,12]

Physiological Factors

- Skin thickness
- Lipid content
- Density of hair follicles
- Density of sweat glands
- Skin pH
- Blood flow
- Hydration of skin
- Inflammation of skin

Physiochemical Factors

- Partition coefficient
- Molecular weight (<400 daltons)
- Degree of ionization (only unionized drugs gets absorbed well)
- Effect of vehicles

BASIC CONSTIUENTS OF MICROEMULSION BASED HYDROGEL(MBH) FORMULATIONS

Oil phase[13]

The choice of oil is based on the nature of the drug as well as the route of administration. There are two main factors that must be taken into consideration before choosing the proper oil phase because it determines the selection of the other ingredients for the micro emulsion. First, the oil's ability to dissolve the chosen substance must be considered. Next, the substance should be selected so that the area for microemulsion formation is enhanced. Compared to oils with long hydrocarbon chains, those with shorter hydrocarbon chains are simpler to micro-emulsify. A substance's capacity to dissolve lipophilic groups is inversely correlated with the length of its molecular chain. Therefore, the chosen oil should be able to solubilize the API and facilitate the formation of microemulsions with the desired properties.

Aqueous phase[14]

The aqueous phase may contain hydrophilic active ingredients and preservatives. Water is most commonly used as the aqueous phase. Due to its significant effect on the microemulsion's phase behaviour, the pH of the aqueous phase must always be adjusted. Commonly used agents are alcohol, water etc.

Surfactants[15]

The selected surfactant must be able to reduce the surface tension to a very low value that facilitate the dispersion process when preparing micro-emulsions and provides a flexible film that can easily deforms around the droplets. In the composition of microemulsions, the concentration of surfactants usually varies from 30% to 60% w/w. High values of HLB (>12) in the surfactant favours the rapid formation of o/w droplet.

Co-surfactants[16]

In most cases, single-chain surfactants alone are unable to reduce surface tension sufficiently to form a microemulsion. Due to its amphiphilic nature, the co-surfactant accumulates significantly at the interface layer, which increase the fluidity of the interfacial film by penetrating into the surfactant layer. Short to medium chain alcohols often added as a co-surfactant to increase fluidity of the interface. Among the short-chain alkanols, ethanol is widely used as permeation enhancer. The ratio of surfactant and co-surfactant is key factor for phase properties.

Table 1: Surfactants and co surfactants ratio to form best microemulsions.[17,18,19,20]

Surfactant	Co-surfactant	Ratio of surfactant and co-surfactant
Tween 80	Ethanol	2:1
Tween 80	Propylene glycol	2:1
Cremophor RH40	Ethanol	1:2
Tween 80	Polyethylene glycol 200	1:1

Hydrogel matrix[17]

Hydrogels are polymeric materials that exhibit the ability to swell and retain a significant amount of water in its structure, but insoluble in water. Due to hydrophilic functional groups attached to the polymeric backbone, hydrogels have capacity to absorb water, while their resistance to dissolution arising from cross-links between network chains. Various polymers such as Poloxamer 407, Carbopol 934, Carbopol 930, Methyl cellulose, Carboxy methylcellulose, Hydroxypropyl methylcellulose, and Pluronic F- 127 can be used in the formation of hydrogel.

Table 2: Components of microemulsion based hydrogel.

Components	Examples
Oil	Ethyl oleate, Mineral oil, Isopropyl myristate, Decanol, Oleic acid, Vegetable oils (coconut oil, sunflower oil, soyabean oil, olive oil)
Surfactant	Polysorbate (Tween 80 and Tween 20), Lauro macrogol 300, Lecithin, Decyl poly glucoside (Labrafil M 1944 LS), Polyglyceryl-6- di-oleate
Co-surfactant	Sorbitan mono oleate, Sorbitan mono stearate, Propylene glycol, monocaprylate (Capryol 90), 2-(2-ethoxyethoxy) ethanol (Transcutol P)
Hydrogel agents	Poloxamer 407, Carbopol 934, Carbopol 930, MC, CMC, HPMC, and Pluronic F-127

PREPARATION OF MICROEMULSION BASED HYDROGEL

Methods of preparation of microemulsion

Microemulsion can be prepared by two different methods, they are Phase titration method and phase inversion method.

Phase Titration Method[21,22]

The microemulsion can be prepared by phase titration method (spontaneous emulsification method). Microemulsions can be depicted with the help of phase diagram. Quaternary phase diagram is time consuming process and also difficult to intercept. Thus, we use pseudo ternary phase diagram to prepare microemulsion. These have various zones, including microemulsion zones and shows 100% of the particular component. In this phase titration method, oil, water, surfactant and Co-surfactant blend are used by fixed weight ratio. This phase diagram is responsible for the mixing of ingredient. All these mixtures were stirred at room temperature, then the monophasic / biphasic phase system will be confirmed by visual inspection. In the separation phase, the sample which shows turbidity should be considered as two phases because one phase is clearly displayed and the mixture is transparent after constant stirring. The obtained points must be marked in the phase diagram.

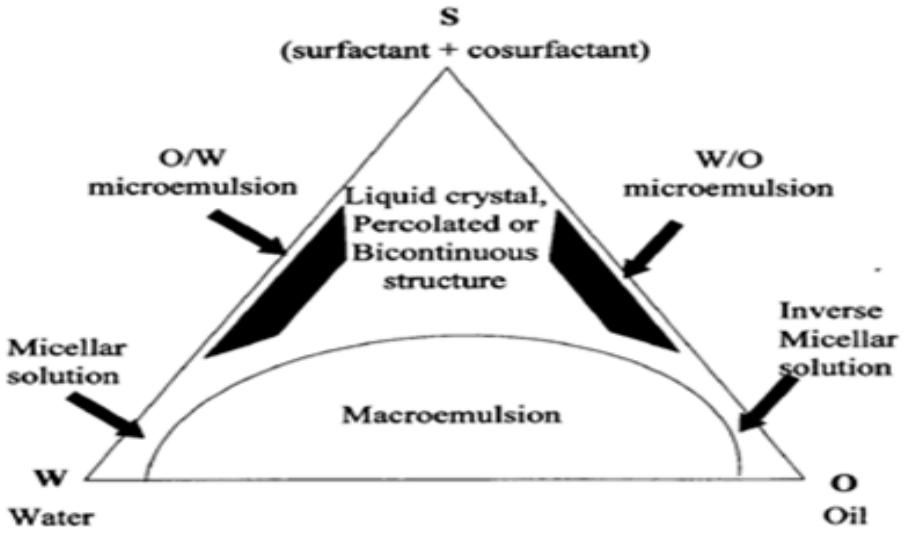

Fig. 3: Hypothetical phase regions of microemulsion system of oil (O), water (W), and surfactant + co-surfactant (Smix)

Phase Inversion Method[23,24]

The phase inversion of the microemulsion is carried out on addition of excess dispersed phase or in response to temperature. During the phase reversal method, possible physical changes, as well as changes in particle size occur, which they may ultimately affect the release of the drug in *in vitro* and *in vivo*. For non-ionic surfactants, this can be achieved by the temperature variation of the system, forcing a transition from an o/w microemulsion at low temperature into w/o microemulsion at higher temperatures (transitional phase inversion). During the cooling process, the system passes a zero spontaneous

curvature and minimal surface tension, and also there is increase in the formation of finely dispersed oil droplets. This method is also known as phase inversion temperature method (PIT). Other than temperature, other parameters such as pH value or salt concentration can be considered more effectively. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. The spontaneous curvature of the surfactant is changed from originally stabilizing a w/o microemulsion to an o/w microemulsion at the inversion point by raising the water volume percentage.

Preparation of Microemulsion[25]

A predetermined amount of the drug is accurately weighed and dissolved in oil by stirring on a magnetic stirrer. Surfactant and co-surfactant are mixed in fixed ratio and this mixture is added into oily solution of the drug. Finally, an appropriate amount of water is added to the solution mixture drop by drop to get microemulsion. The clear solution shows the formation of microemulsion.

Preparation of Hydrogel and Microemulsion based hydrogel (MBH)[26]

Hydrogel can be prepared by using various polymers such as Carbopol 934p, HPMC K15M and Xanthan gum. Polymer is hydrated in fixed amount of water for at least 4h to swell for the formation of hydrogel.

The previously formulated microemulsion is gradually added to the above solution with continuous stirring until a clear viscous solution is obtained. Finally, the fixed amount of triethanolamine is added to obtain microemulsion based hydrogel (MBH).

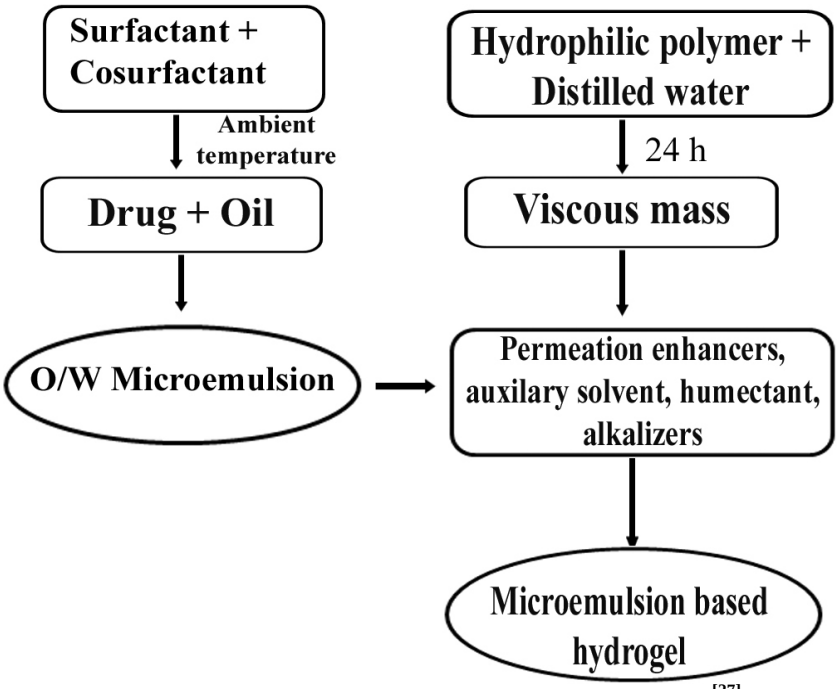

Fig. 4: Formulation of microemulsion based hydrogel.[27]

CHARACTERIZATION OF MICROEMULSION

Viscosity[28]

The viscosity of Microemulsion based hydrogel (MBH) is determined by using Brookfield viscometer. For this hydrogel is filled in a beaker and the viscosity is measured by using suitable spindle number.

pH[28]

pH can be determined by using digital pH meter. 1g of formulation is mixed in 10 ml distilled water. Electrodes are then immersed in the developed gel solution and readings are recorded.

Zeta potential and globule size analysis[29]

Zeta potential and globule size analysis can be detected by using Malvern zeta sizer.

Drug content[30]

Drug content is determined by dissolving a specific amount of formulation in suitable solvent, stirred constantly for 10 min. From this 1 ml of solution is diluted to 10ml with solvent. The resultant solution is filtered and analyzed by U.V spectrophotometer**.**

Drug content can be calculated by using following formula:

Amount of drug = [Concentration/1000] × Dilution factor

Electrical conductivity[31]

Electrical conductivity of formulated microemulsion can be measured using conductometer at a constant frequency of 1Hz.

Centrifugation[32]
To measure the microemulsion's physical durability, this parameter is evaluated. The prepared microemulsion is centrifuged for 10 min at 5000 rpm at room temperature to test the stability of formulation (Phase separation or cream formation). The appearance of the microemulsion is carefully assessed.

% Transmittance[33]
% Transmittance of microemulsion can be measured by UV spectrophotometer.

***In vitro* drug release studies**[34]
The *in vitro* drug release studies are performed by using Franz diffusion cell with cellophane membrane. The membrane is clamped between the donor and the receptor chamber. The receptor compartment contains buffer that is maintained at 37± 10ºC and the microemulsion formulation is placed in the donor compartment. At predetermined time interval samples are periodically withdrawn from the receptor compartment, replacing with the same amount of fresh buffer solution and analysed for drug content, using a UV spectrophotometer at specific wavelength.

CHARACTERIZATION OF MICROEMULSION BASED HYDROGEL (MBH)

Physical parameter[35]
Gel formulations are tested for visual color, uniformity, consistency, texture and feel on application such as graininess, stickiness and softness.

Viscosity[35]
A Brookfield viscometer can be used to determine the viscosity of MBH.

Extrudability study[36]
The standard capped collapsible aluminium tubes were filled with the prepared MBH formulations and were sealed by crimping to the end. The weights of the tubes were recorded. The tubes are placed between two glass slides and weight of 1kg is placed over the slides and then the cap is removed. The quantity of the extruded gel is recorded.

***In vitro* diffusion studies**[37]
The *in vitro* drug release studies are performed by using Franz diffusion cell with cellophane paper. The membrane is clamped between the donor and the receptor chamber of Franz diffusion cell. Then, formulation is placed in the donor compartment. The receptor chamber is filled with buffer. The receptor medium is set at 37 ± 0.5 ºC and stirred at 600 rpm throughout the experiment. Samples are periodically withdrawn from the receptor compartment, replacing with the same amount of fresh buffer solution, and assayed by a UV spectrophotometer.

Spreadability[37]
The spreadability of the gel formulation is determined by taking two glass slides of equal length. A weighed quantity of gel is taken on one glass slide. To another glass slide, weights (125g) are added and the time in seconds require to separate the slides is taken as a measure of spreadability.

The spreadability is calculated by using the following formula:

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

Where S =Spreadability; M=weight kept on upper slides; L= length of glass slide and; T = time taken in seconds to separate the slides.

pH[38]
The pH of microemulsion based hydrogel is determined using digital pH meter.

Drug content[39]
One gram of gel is dissolved in a 100 ml of suitable solvent, stirred constantly for 10 min. From this 1 ml of solution is diluted to 10ml with solvent. The resultant solution is filtered and analyzed by U.V spectrophotometer**.**

Drug content can be calculated by using following formula:
Amount of drug = [Concentration/1000] × Dilution factor

***Ex vivo* permeability studies**[40]
Ex vivo skin permeation study is determined by using Franz diffusion cells. The rat skin is clamped between the donor and the receptor compartment with the stratum corneum facing the donor compartment. Then, 1g of MBH is placed on the donor compartment. Buffer is filled in receptor compartment and maintained temperature of 37℃ with stirring at 100 rpm. At predetermined time intervals, 1ml receptor medium is withdrawn and the same volume of pure medium is added to the receptor compartment. Filtered samples are analysed spectrophotometrically.

Drug release kinetics[41]
By using a variety of kinetic model equations, the drug release kinetic study can be carried out to identify pattern of drug release process. Hixon Crowell's zero-order, first-order, Higuchi plot and Korsmeyer Peppas are tested.

CONCLUSION

The MBH formulation can be used to improve solubility and skin permeability of the drug. MBH can be successfully formulated using suitable gelling agents to impart viscosity as well as to sustain the action of the drug by increasing the residence time. Topically applied microemulsions have been shown significant increase in the absorption of drugs through skin. Potential strategies

for improving percutaneous penetration includes modification of the skin physiology and formulation modification to influence the distribution, diffusion or solubility of the drug. Safe and effective MBH formulation provides increased drug absorption, reduced frequency of drug administration and maintain drug release for desired duration.

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