REVIEW ARTICLE

MICROEMULSION SYSTEM IN ROLE OF EXPEDIENT VEHICLE FOR DERMAL APPLICATION

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ABSTRACT:

Ever since the discovery of microemulsions, they have attained increasing impact in the field of both research and industry. Industrial applications of microemulsions have escalated in the last 40 years following an increased understanding of formation, stability and the role of surfactant molecular architecture. For the reason of having diverse advantages such as thermodynamic stability, increased solubility, simplistic method of preparation and low cost, these have been explored. In recent times investigation has been spurted in direction of microemulsions for transdermal drug delivery as very low surface tension associated with massive increase in interfacial area persuades drug permeation across the skin. The basic components of microemulsion are oils, surfactants and cosurfactants. The transdermal drug delivery prospective of microemulsion is basically dependant on two factors, one is applied components and the other is internal structure of the phases. The present article confronts microemulsions system as dermal drug delivery carrier highlighting the assortment of components which will augment the drug permeation across the skin.

Keywords: Microemulsions, oils, permeation, surfactants, transdermal.

INTRODUCTION

Advancements in drug delivery strategies are taking place at much prompt pace than the last decade. Currently 74% of drugs are taken orally but not found to be as effective as desired because of various obstacles coming in path of oral drug delivery. Today transdermal drug delivery system is one of the most capable modes of drug application. Drug delivery via skin to achieve systemic effect of drug is commonly referred to as transdermal drug delivery. Dermal application of drugs offer many advantages as increased patient acceptability, avoidance of gastrointestinal disturbances[1], bypass of first pass hepatic metabolism[2] and sustained delivery of drugs and reduced systemic side effects[3]. Recent attention has been sharply focused on microemulsions which in addition to aforesaid advantages reveal superior stability. Microemulsions represent versatility as novel vehicle having potential of increasing percutaneous delivery of both hydrophilic and lipophilic drugs[4]. The review explores microemulsions in relation to their use to modify penetration rate of drug across skin and dermal tolerability of vehicles. The components, composition and structure of microemulsions are also discussed.

Microemulsions

The microemulsion concept was introduced by Hoar and Schulman in early 1940s who created single clear phase solution by titrating milky emulsion with hexanol and the term microemulsion was coined by Schulman and coworkers in 1959. Microemulsions are thermodynamically stable, isotropically clear mixture of oil, water and surfactant frequently in combination with cosurfactant[5]. These homogenous systems have gained wide acceptance because of their enhanced drug solubilization, longer shelf life due to thermodynamic stability, easy formation because of zero interfacial tension, ability to be sterilized by filtration, massive surface area[6].

In some respects, microemulsions can be considered as small scale version of emulsions i.e. droplet type dispersions. Such a description however lacks precision since there are significant differences between emulsions and microemulsions. In particular, in emulsions, the average drop size grows continuously with time so that phase separation ultimately occurs under gravitational force, i.e. they are thermodynamically unstable and their formation requires input of work. The drops of the dispersed phase are generally large (> 0.1 μm) so that they take a milky appearance[7]. On the other side, for microemulsions, once the conditions are right, spontaneous formation occurs they are clear or translucent in size range of 20-200 nm. Microemulsions are vibrant systems in which interface is continuously fluctuating. According to the structure they are divided into oil in water (o/w), water in oil (w/o) and bicontinuous microemulsions. In all these microemulsions interface is stabilized by appropriate combination of surfactant and cosurfactant[6,7].

Role of microemulsion in skin permeation

The skin is incredible organ of body which is competent to perform various vital functions. It is an effectual communicator between the outside environment and brain. Skin makes upto 12-15% of adult's body weight. Each square centimeter has 6 million cells, 5000 sensory points, 100 sweat glands and 15 sebaceous glands. The skin is composed primarily of three layers: the epidermis, the dermis and the hypodermis[8].

Epidermis: It is the outermost layer of skin. It forms waterproof defensive wrap upon body's surface and formed up of stratified squamous epithelium underlying basal lamina. It contains no blood vessels and is nourished by diffusion from dermis and has role in regulation of body's temperature. It is further divided into 5 sublayers: Stratum corneum, Stratum lucidum, Stratum granulosum, Stratum spinosum and Stratum germinativum

Dermis: It is the layer of skin underneath the epidermis that consists of connective tissue and mitigates the body from stress and strain. It is rigidly connected to epidermis by basement membrane. It contains hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. The dermis is structurally segregated into two areas; a superficial area called as papillary region and the reticular region.

Hypodermis: Its rationale is to attach the skin to underlying bones and muscles. It consist loose connective tissue and elastin.

The great hindrance for transdermal drug delivery is the stratum corneum that forms primary rate restrictive barrier to permeation of drugs across the skin. It consists of dead flattened cells filled with keratin that are entrenched in lipid matrix. The stratum corneum has been illustrated as hydrophilic protein bricks embedded in hydrophobic lipid mortar. Diffusion of drug in dermal vasculature includes contact of skin with dosage form from which the active constituent must partition, followed by diffusion of compound to external strata to dermis. Partitioning is governed to large extent by thermodynamic activity of the drug in the vehicle and this aspect is of major importance in controlling the degree of penetration. It is relevant to note that transdermal delivery potential of microemulsions is dependent not only on constituents of vehicle but also on internal structure of the phases. Several plausible mechanisms of skin permeation enhancement property have been proposed. A large amount of active principle can be incorporated in the formulation due to high solubilizing capacity that might increase thermodynamic activity towards the skin. The surfactant and co-surfactant in the microemulsion may lessen the diffusional barricade of stratum corneum by operating as penetration enhancers. The percutaneous absorption of the active agent will also augment due to hydration effect of stratum corneum if the water content in microemulsion is high enough. The nanosized droplets provide superior adherence to skin and have large surface area thereby providing high concentration gradient and improved active constituent permeation. The permeation rate of drug from microemulsion can be increased as the empathy of drug to internal phase in microemulsion can be easily modified to favor partitioning into stratum corneum using different internal phase, changing its portion in microemulsion[8,9].

If the endeavor is at providing sustained release of lipophilic active constituent then it is integrated into inner oil phase in o/w microemulsions so that active agent will partition from inner compartment to outer aqueous compartment and then it is released into skin. Some microemulsions act as supersolvent of highly lipophilic compounds due to having capacity of incorporating large amount of it. When the aim is towards immediate absorption and short duration of action then w/o type can be formulated. The condition shall be reversed if the active constituent is hydrophilic. Due to presence of both hydrophilic and lipophilic domains, it can be suggested that microemulsions are able to interact with both lipid (nonpolar) and the protein (polar) pathway by entering stratum corneum via intercellular route. The drug dissolved in lipid domain can directly partition in lipids of stratum corneum thereby destabilizing its bilayer eventually leading to increased permeability[9]. On the other side hydrophilic domain hydrates the stratum corneum which facilitates percutaneous uptake of drug.

Outline of theories of microemulsion formation

Microemulsions are formed simultaneously when interfacial tension between oil and water is reduced close to zero. The formation and as well as stability of microemulsion can be affected by various factors such as nature of surfactant, molecular weight of surfactant, alcohol chain length, temperature *etc.*

Three approaches have been used to explain microemulsion formation[7]:

(i) Interfacial or mixed film theory: It states film at the interface is assumed to be dual film and the type of microemulsion (o/w or w/o) depends on bending or curvature of interface.
(ii) Solubilization theory: It states that oil is solubilized by normal micelles and water is solubilized by reverse micelles.
(iii) Thermodynamic theory: It states that free energy of formation must be negative to form thermodynamically stable microemulsion.

COMPONENTS OF MICROEMULSION

The components of microemulsion formation as oils and surfactants are largely present but due to their toxicity, irritancy and unclear mechanism of action retards their use. For mild microemulsions to form, biocompatible, clinically acceptable, non toxic components should be screened. Therefore greater emphasis is laid upon use of generally regarded as safe (GRAS) excipients

Oil phase

The selection of oil is based on the nature of the drug as well as the route of administration. The screened oil should have solubilization potential for the drug. The oil influences the curvature and has the capability to swell the tail group of surfactant. Saturated and unsaturated fatty acids have penetration enhancing activity of their own. The fatty acids increase the permeability of by disrupting densely packed lipids and filled up in extracellular spaces of stratum corneum. Amongst unsaturated fatty acids, oleic acid is an effective skin penetration enhancer. Also penetrating effect of fatty acids is selective of individual drug. Out of fatty acid esters, isopropyl palmitate is popular.

Recent trend is towards use of semisynthetic oils that are more stable than their natural counterparts. Poorly aqueous soluble drugs need to have solubility in dispersed oil phase to form efficient o/w microemulsion system. Even with increase in oil content in o/w microemulsions leads to increase in droplet size. Excipients that are commonly used as oil phase in transdermal formulations is isopropyl palmitate, isostearylic isostearate, ethyl oleate and alcohols such as octanol, decanol and benzyl alcohol[10].

Surfactant

Surfactants are the molecules which when present in low concentration will adsorb to the surface of interfaces of a system and alter the interfacial energies of the system. The interfacial energy is the work required to create unit area of an interface. The actual purpose of surfactant is to lower the interfacial tension to negligible value facilitating the

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process of dispersion during preparation of microemulsion. It presents the microemulsion with pertinent lipophilic character to furnish accurate curvature. This adsorption behavior can be attributed to solvent nature and to the chemical nature of surfactant that combines both polar and non polar group in a single molecule. Due to their dual nature these amphiphiles "sit" at interfaces so that their hydrophobic moiety is repelled from strong solvent interactions. Surfactant screening can be done with help of HLB (Hydrophilic lipophilic balance) value. The HLB provides a numerical value that suggests whether o/w or w/o emulsion will form. It relates molecular structure to interfacial packing and film curvature[11]. The HLB concept was introduced by GRIFFIN. The accepted fact is that generally low HLB surfactants are favorable for w/o microemulsion and high HLB surfactants are suited best for o/w microemulsions. Surfactants with HLB greater than 20 require co-surfactants in order to reduce the HLB value within the range entailed by microemulsion to form.

Table1: Showing HLB ranges and the typical application of surfactant related to it

HLB Value	Application
1- 3.5	Antifoams
3.5- 8	Water in oil emulsion
7 -9	Wetting and spreading agents
8 – 16	Oil in water emulsions
13 – 16	Detergents
15 – 40	Solubilizers

Skin permeation enhancement is magnificent function of surfactants and the magnitude of permeation enhancement is largely dependent on physicochemical properties and nature of vehicle[13]. Non ionic surfactants are good replacement for naturally occurring surfactants. Tweens have been investigated for their minimal toxicity. Surfactants such as sorbitan fatty acid esters, polysorbates, pegylated fatty alcohols and poloxamers are recurrently used. Microemusions are highly dynamic structures, it is plausible that monomer surfactants can diffuse to the skin surface and act as enhancers facilitating diffusion through barrier phase or by increasing the solubility of drug in the skin[11,12].

Co-surfactants

In most of the cases, single chain surfactants alone are incapable to reduce o/w interfacial tension sufficiently to form microemulsion. Owing to its amphiphilic nature, a co-surfactant accumulates substantially at interface layer, increasing the fluidity of interfacial film by penetrating into surfactant layer. Short to medium chain length alcohols are generally added as co-surfactants helping in to increase the fluidity of interface[12]. Amongst short chain alkanols, ethanol is widely used as permeation enhancer. In medium chain alcohols 1- butanol was reported to be most effective enhancer. The surfactant and co-surfactant ratio is a key factor for phase properties.

Aqueous phase

Most commonly, water is used as aqueous phase. The pH of aqueous phase always needs to be adjusted due to its considerable impact on phase behavior of microemulsions[11,12]. As in case of microemulsions used for parenteral administration aqueous phase should be isoosmotic to blood which is adjusted by sodium chloride, glycerol, dextrose and sorbitol.

PHASE BEHAVIOUR

The relationship between the phase behavior of mixture and its composition can be confined with the support of phase diagram. The phase behavior of simple microemulsion systems comprising oil, surfactant and co-surfactant can be studied with the aid of ternary phase diagrams in which each corner of the diagram represents 100% of the meticulous component[14]. However, almost always in case of microemulsions, they contain an additional component as cosurfactant and/or drug. In the case where four or more components are involved, pseudoternary diagrams are constructed where a corner represents binary mixture of two components as surfactant/co-surfactant, water/drug or oil/drug.

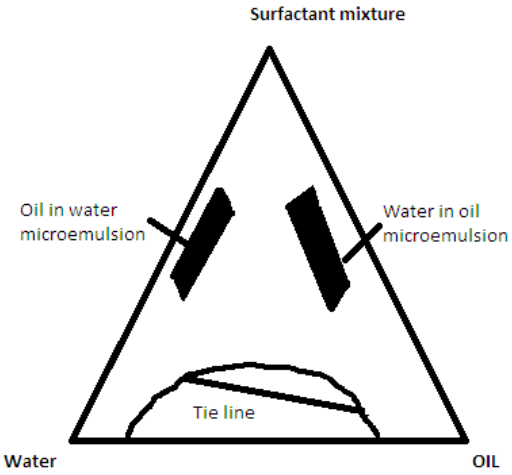

Figure 1: This represents a pseudoternary phase diagram

Phase rule: The phase rule enables identification of the number of variables depending on system compositions and conditions. It is depicted as

$$F = C - P + 2$$

Where, F is the number of possible independent changes of state or degrees of freedom, C the number of independent chemical constituents and P the number of phases present in system. The F value determines the system to be invariant, monovariant, bivariant *etc* depending on its value whether zero, 1, 2 or so on. At low surfactant concentration, there is series of equilibria between phases, referred as winsor phases

Winsor I: The microemulsion phase (o/w) is in equilibrium with the upper excess oil. The surfactant rich water phase coexists with oil phase where surfactant is only present as monomers at small concentration.

Winsor II: The upper microemulsion phase (w/o) is in equilibrium with excess of water. The surfactant rich oil phase coexists with surfactant poor aqueous phase.

Winsor III; The middle microemulsion phase (o/w plus w/o called bicontinuous) is in equilibrium with excess oil and lower excess water. Surfactant rich middle phase coexists with both excess water and oil surfactant poor phase

Winsor IV: Here oil, water and surfactant are homogenously are mixed to form isotropic single phase micellar solution.

Inter-conversion between these phases can be produced by adjusting the proportions of components. Phase transitions are brought by increasing either electrolyte concentration in case of ionic surfactants or increasing temperature in case of non ionic surfactants[15]. Various investigators have explored on interactions in adsorbed interfacial film to explain the direction and extent of curvature. Bancroft gave a rule stated as "that phase will be external in which the emulsifier is most soluble" i.e. oil soluble emulsifiers will form w/o emulsion and water soluble emulsifiers will form w/o emulsions. The R- ratio was first proposed by winsor to account for influence of amphiphiles and solvents on interfacial curvature. The R- ratio compares tendency for amphiphile to disperse in oil, to its tendency to dissolve in water. The R- ratio of cohesive energies coming from interaction of interfacial layer with oil , divided by energies resulting from interactions of water determines the preferred interfacial curvature. A balanced interfacial layer is represented by R=1.

METHOD OF PREPARATION

Phase titration method:

Microemulsions are prepared by spontaneous emulsification method[16] which is illustrated with help of phase diagrams. Phase diagram construction is practical approach to study complex series of interaction which occurs when different components are mixed. The aspect of the phase diagram is phase eqilibria and demarcation of phase boundaries. Most often pseudo-ternary phase diagrams are constructed to figure out microemulsion zone as quaternary phase diagram is time consuming and difficult to interpret[14].

Phase inversion method:

Phase inversion of microemulsion happens upon addition of excess of dispersed phase. Phase inversion leads to radical physical changes as change in particle size that alter drug release[16]. During cooling, this system crosses the point of zero spontaneous curvature and minimal surface tension, prompting the formation of finely dispersed oil droplets[17]. Microemulsions can be prepared by controlled addition of lower alkanols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either o/w or w/o or colloidal dispersions. The lower alkanols are called co-surfactants. They lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation.

Overview of research work on transdermal drug delivery with microemulsion system

Many studies have been conducted on incorporation of various drugs in microemulsion systems. Microemulsions based transdermal gel of lacidipine was formulated and characterized for reducing hypertension in rabbits and compared with oral suspension of drug[18].The bioavailability as well as permeability was found to be increased 3.5 times. Researchers have keenly explored potential application, examples of some of which are quoted in table 2

DERMAL DRUG DELIVERY POTENTIAL OF TOPICAL MICROEMULSION FORMULATION

The considerable amount of work on dermal drug delivery has been published during past few years, where attracting facet is application of vehicle which has increased the attention for pharmaceutical formulation[7]. Various potentials have been explored in view to describe prospective efficacy of microemulsions used cutaneously. But, the studies have not been consecutive and moreover many studies get confined to *in vitro* studies, only few put upto *in vivo* studies[33]. This has impeded general conclusions between properties of microemulsion and drug delivery rate.

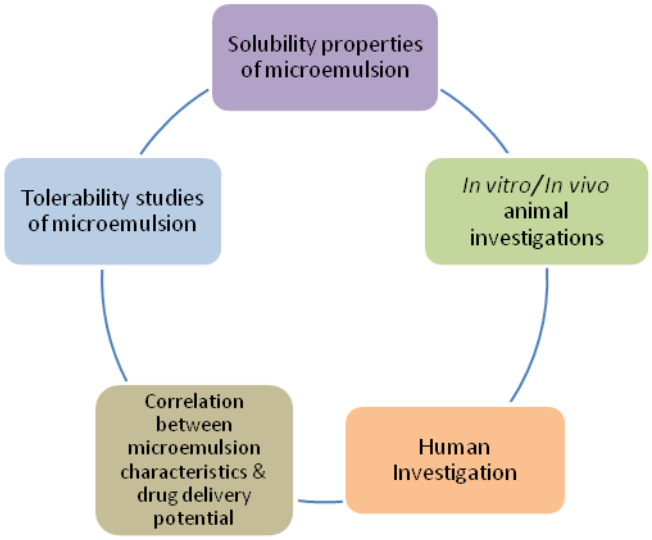

Figure 2: The figure represents potential of dermal drug delivery of topical microemulsion

Skin tolerability studies of microemulsions

It is utmost important point to consider the skin irritation and toxicological reactions which can be the result of topical application of the formulation. It was reported that the prepared soyabean lecithin microemulsion (Mygliol 812N, soybean lecithin, and water) and oleic acid microemulsion (Mygliol 812N, soybean lecithin, oleic acid, and water) containing ketoprofen and tested skin acceptability of these formulations along with conventional w/o and o/w emulsions and hydrophilic gel on human volunteers[25]. An occlusive patch bearing the formulation was applied to the upper outer arm for 23 h. One hour after removal, skin sites were assessed for signs of skin irritation. After assessment, an identical fresh patch was applied to the same skin area for a further 23 h. One hour after patch removal, skin sites were again assessed. The values of scoring assigned were as follows: vesicles, 5; edema, 4; erythema, 3; flakiness, 2; dryness, 1; wrinkling, 1; and glazing, 1. Microemulsion formulations showed the highest skin tolerability. Wrinkling (2) and glazing (2) were observed with soybean lecithin microemulsion, whereas flakiness (1), dryness (1), wrinkling (2), and glazing (1) were observed with soybean lecithin microemulsion. No edema or erythema was seen. The authors concluded that these microemulsions made up of biocompatible constituents (high percutaneous effect and low human skin irritation) prompt their use as topical

delivery systems both in pharmaceutical and cosmetic fields.

For the skin irritancy test, a single dose of 10 µL of the optimized microemulsion (4% oleic acid, 20.5% labrasol, 20.5% transcutol, and 55% water) was applied to the left ear of the mouse with the right ear as a control[17]. The development of erythema was monitored daily for 6 days. The authors concluded that the microemulsion can be considered to be safe for the transdermal delivery of levobunolol.

Table 2: This represents examples of drugs formulated in microemulsions

DRUG	MICROEMULSION COMPONENTS			Ref
	Oil phase	Surfactant/cosurfactant	Aqueous phase	
5- Florouracil	IPM	AOT	Water	19
Aceclofenac	Labrafil M1944CS	Tween80, span 80, 1,2-octanol, cremophor ELP, ethanol	Water	20
Celecoxib	IPM	Caprylic/ capric mono-/ diglycerides,polysorbate 80	Water	21
Cyproterone	Eucalyptus oil	Brij 30, ethanol	Water	22
Diclofenac	IPM	Lecithin	Water	23
Estradiol	Epikuron 200, oleic acid, IPM	Tween 80, span 20/ ethanol, isopropanol	Water	24
Flurbiprofen	IPM, ethyl oleate	Aerosol OT, span 80	Water	25
Ketoprofen	Mygliol 812	Lecithin, n- butanol	Water	26
Methotrexate	Decanol	Lecithin, benzyl alcohol	Water, PW	27
Nifedipine	Benzyl alcohol	Tween 80, taurodeoxycholate	Water	28
Sucrose	Ethyl oleate	Labrasol, Plurol isostearique	Water, 154 mM Nacl	29
Tetracaine	IPM	Lecithin, n- propanol	Water	30
Valdecoxib	Oleic acid	Labrasol, transcutol	Water	31
Voriconazole	Paraffin, Jojoba	Tween 80, Brij 97, Glycerol, sorbitol	Water	32

CONCLUSION

The skin is evolved to be a defensive barricade. It performs this function extraordinarily well and presents, therefore, an alarming confrontation to the drug delivery experts. Transdermal route of administration is perhaps one of the most successful controlled release technologies available today. Microemulsions are currently the object of extensive research worldwide. They represent interesting, promising and potential transdermal drug delivery systems. Microemulsion, that are made up of oil, surfactant, co-surfactant and water have unique properties as drug carriers and garnering more attention due to their solubilization capacity, transparencies, high stability and simplicity in manufacturing. Many *in vitro* and *in vivo* studies have examined the significance of microemulsions by topical and transdermal route. Microemulsion when applied in the form of gel or liquid shall obviate this issue and will be more acceptable. Concerted research efforts directed toward evaluating their systemic and local toxicity, as well as their mechanism of action, shall further help in ascertaining their efficacy and safety.

It is important to prudently choose the surfactants and their concentration, as a large amount of surfactant is required for microemulsion formation to fulfill the criterion of lowering of interfacial tension. More research work is required for the production of safe, efficient and more compatible microemulsion constituents which will further enhance the utility of these novel vehicles. A considerable amount of work still needs to be performed to characterize the physiochemical behavior of the microemulsions. It appears that prospect work will contemplate on the

expansion of new and sophisticated analytical tools for the microemulsion structure. More organized studies are needed for the evaluation of their full potential as they can be formed over a wide range of composition. It seems that proper selection of the microemulsion components for the formulation is a key factor in the enhancement of transdermal potential. The studies that have been conducted so far demonstrate that the microemulsion system has terrific potential as a novel transdermal drug delivery tool. Based on this review, it could be assumed that as a result of these developments, new products based on these novel formulations will emerge in the close outlook.

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