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MICROEMULSION: A NOVEL APPROACH FOR DRUG DELIVERY

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ABSTRACT

The dispersions of nanometer-sized droplets of an immiscible liquid within another liquid are known as Microemulsions. The addition of surfactants cosurfactants facilitated the Droplet formation. Nevertheless, the cosmetic researchers still try to understand and develop the most acceptable cosmetically eloquent and functional products possible. Aesthetically appealingproducts can be formulated as transparent o/w or w/o dispersions called microemulsions. "A microemulsion is a system of water, oil and an amphiphile which is a single optically isotropic and thermodynamically stable liquid solution". Microemulsions are considered as small-scale versions of emulsions, i.e., droplet type dispersions either of water-in-oil (w/o) or of oil-in-water (o/w), having a size range in the order of 5−50 nm in drop radius. 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 the input of work. The drops of the dispersed phase are generally large (> 0.1 μm) so that they often take on a milky, rather than a translucent appearance. Schulman et al were use The term "microemulsion". in 1959 to describe a multiphase system consisting of water, oil, surfactant, and alcohol, which forms a transparent solution. There has been much debate about the word "microemulsion" to describe such systems. Although not systematically used today, some prefer the names "micellar emulsion" or "swollen micelles".

KEYWORD: Microemulsion, Surfactant, Co-surfactant, Phase diagram.

INTRODUCTION

Transdermal drug delivery is a better drug delivery route over other administration routes: for example, avoidance of hepatic metabolism, convenient administration for the patient, and easy withdrawal of treatment if necessary. Despite extensive studies of transdermal drug delivery, only a few drug formulations are commercially available.[1] One of the reasons for this is the permeation barrier by the stratum corneum to exogenous substances. Skin penetration enhancement can be achieved using appropriate physical and chemical means to overcome the skin's barrier function. Chemical penetration enhancers such as fatty acids, fatty esters, surfactants, and terpenes have received considerable attention due to their low cost,ease of use, safety, and efficacy.[2] In search of safe and effective therapy, the developmentof new drugs has been the common practice historically. However, it involved a long gestation period in terms of time, efforts, and huge cost. Distribution can affect the efficacyand safety of the drug within the biological system, as there is an appreciable deviation from the desired site of action, i.e., the target site. Therefore the alternate approach of drug delivery, wherein the carrier systems were used to deliver the drug to the specific sites without afflicting the normal tissues and organs of the body. The fundamentals lie in hosting the drug in carefully designed carriers to bring favorable change(s) in its surrounding microenvironment, and consequently, it is delivery. It is the modification(s) in physicochemical characteristics of the molecules and in the barrier properties of the biological membranes at various locations, which lead to improved transportation of drugs toward the diseased locations.[3]

The dispersions of nanometer-sized droplets of an immiscible liquid within another liquid are known as Microemulsions. The addition of surfactants cosurfactants facilitated the Droplet formation. Nevertheless, the cosmetic researchers still try to understand and develop the most acceptable cosmetically eloquent and functional products possible. Aesthetically appealing products can be formulated as transparent o/w or w/o dispersions called microemulsions.[4] "A microemulsion is a system of water, oil and an amphiphile which is a single opticallyisotropic and thermodynamically stable liquid solution". Microemulsions are considered as small-scale versions of emulsions, i.e., droplet type dispersions either of water-in-oil (w/o) orof oil-in-water

(o/w), having a size range in the order of 5−50 nm in drop radius. 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 an input of work. The drops of the dispersed phase aregenerally large (> 0.1 μm) so that they often take on a milky, rather than a translucent appearance. For the spontaneous formation of microemulsions, the right conditions are required. As for simple aqueous systems, microemulsion formation is dependent onsurfactant type and structure.[5]

Microemulsions were not recognized until the work of Hoar and Schulman in 1943, who reported a spontaneous emulsion of water and oil on the addition of a strong surface-active agent.[6] Schulman et al were use The term "microemulsion".[7] in 1959 to describe a multiphase system consisting of water, oil, surfactant, and alcohol, which forms a transparent solution. There has been much debate about the word "microemulsion" to describe such systems.[8] Although not systematically used today, some prefer the names "micellar emulsion".[9] or "swollen micelles".

Theory of Formation

A simple picture for describing microemulsion formation is to consider a subdivision of the dispersed phase into very small droplets. Then the configurational entropy change, ΔS, can Conf be approximately expressed as.[11]

$$\Delta S_{conf} = -n k_B \left[\ln\phi + \{(1-\phi)/\phi\}\ln(1-\phi)\right]$$

Where n is the number of droplets of the dispersed phase, kB is the Boltzmann constant and φ is the dispersed phase volume fraction. The associated free energy change can be expressed as a sum of the free energy for creating a new area of the interface, ΔAγ12, and configurational entropy in the form.[12]

$$\Delta G_{form} = \Delta A\gamma_{12} - T\Delta S_{conf}$$

$$d\gamma_{o/w} = -\sum_i (\Gamma_i d\mu_i) \approx -\sum_i (\Gamma_i RT d\ln C_i)$$

Where ΔA is the change in interfacial area A (equal to 4πr per droplet of radius r) and γ is 12 the interfacial tension between phases 1 and 2 (e.g., oil and water) at temperature T (Kelvin). Substituting Eq. 1 into 2 gives an expression for obtaining the maximum interfacial tension between phases 1 and 2. On dispersion, the droplet number increases, and ΔS is positive. If conf the surfactant can reduce the interfacial tension to a sufficiently low value, the energy term in Eq. 2 (ΔAγ) will be relatively small and positive, thus allowing a negative (and hence 12 favorable) free energy change, that is, spontaneous microemulsification. In surfactant-free oil−water systems, γ o/w-1 is of the order of 50 mN m, and during microemulsion formation, the increase in interfacial area, ΔA, is very large, typically a factor 4 5 of 10 to 10. Therefore in the absence of surfactant, the second term in Eq. 2 is of the order of 1000 k T, and to fulfill the condition $\Delta A\gamma \leq T\Delta S$, the interfacial tension should be B 12 conf -1 very low (approximately 0.01 mN m). Some surfactants (double chain ionics,[13,14] and -2 -4 some non-Ionics,[15]) can produce extremely low interfacial tensions − typically 10 to 10 -1 mN m − but in most cases, such low values cannot be achieved by a single surfactant since the CMC is reached before a low value of γ is attained. An effective way to further o/w decrease γ is to include a second surface-active species (either a surfactant or medium- o/w chain alcohol), that is a co-surfactant. This can be understood in terms of the Gibbs equation extended to multicomponent systems.[16] It relates the interfacial tension to the surfactant film composition and the chemical potential, μ, of each component in the system, i.e., where C is the molar concentration of component i in the mixture, and Γ the surface excess I i-2 (mol m). Assuming that surfactants and co-surfactants, with concentration C and C s corespectively, are the only adsorbed components (i.e., Γ = Γ = 0), Eq. 3 becomes: Water oil.

$$d\gamma_{o/w} = -\Gamma_s RT d\ln C_s - \Gamma_{co} RT d\ln C_{co}$$

$$\gamma_{o/w} = \gamma^{\circ}_{o/w} - \int_0^{C_s} \Gamma_s RT d\ln C_s - \int_0^{C_{co}} \Gamma_{co} RT d\ln C_{co}$$

Integration of Eq. 4 gives

Eq. 5 shows that is lowered by two terms, both from the surfactant and co-surfactant (of surface excesses Γow/oγs and Γco respectively) so their effects are additive. It should be mentioned, however, that the two molecules should be adsorbed simultaneously and should not interact with each other (otherwise they lower their respective activities), i.e., are of completely different chemical nature, so that mixed micellization does not occur.

Figure 3.1 shows typical low interfacial tensions found in microemulsions, in this case -3 -1 spanning ~ 1 to 10 mN m. The effect of salt concentration is consistent with changes in the phase behavior, which are discussed in more detail in Section 3.3 and Figure 3.2 below.[17,18]

Type of microemulsion

A well-known classification of microemulsions is that of Winsor,[19] who identified four general types of phase equilibria:

- Type I: the surfactant is preferentially soluble in water and oil-in-water (o/w) microemulsions form (Winsor I). The surfactant-rich water phase coexists with the oil phase where the surfactant is only present as monomers at a small concentration.
- Type II: the surfactant is mainly in the oil phase and water-in-oil (w/o) microemulsions form. The surfactant-rich oil phase coexists with the surfactant-poor aqueous phase (Winsor II).
- Type III: a three-phase system where a surfactant-rich middle-phase coexists with both excess water

and oil surfactant-poor phases (Winsor III or middle-phase microemulsion).
- Type IV: a single-phase (isotropic) micellar solution, that forms upon addition of a sufficient quantity of amphiphile (surfactant plus alcohol).

MATERIAL AND METHODS

Materials

There are a different number of oil and surfactants are available but due to their toxicity, irritation potential them they are not permitted to use them in the formulation of the microemulsion.

Therefore only those oil and surfactant are used which are biocompatible, nontoxic, and much clinically accepted. The use of emulsifier concentration should be appropriate.

There are the following materials that are used in the preparation of microemulsion-

Oil phase

This is one of the most important components of the emulsion system. They penetrate and swell the tail region of the surfactant monolayer. The oil penetrates the greater extent of the tail region of surfactant as compared to the long-chain alkanes.

The various oils which are used in the preparation of microemulsion are given as follows- Saturated fatty acids: Lauric acid, myristic acid, capric acid, etc.

Unsaturated acids: oleic acid, linoleic acid, linolenic acid, etc.Vegetable oils: Cumin oil, soybean oil, etc.

The oil should be selected based on the excess solubility of the drug into it.

Surfactant

These are the chemical substance which is used in the emulsion for the purpose to reduce the interfacial tension, therefore, the dispersion process facilitates during the formulation process.

The used surfactant must possess the lipophilic character to provide the best curvature at the interfacial region. To achieved w/o microemulsion the low HLB value of surfactant was used. And to achieved o/w type microemulsion high HLB value surfactant was used. The surfactant which is used in the microemulsion is Polysorbate (Tween 80 & Tween 20), PEG-8, etc.

Cosurfactants

They are used in microemulsion due to the following reason-
- They permit the interfacial film to get flexible to make different curvatures required to form a microemulsion.
- To reduce interfacial tension.
- To reduce the HLB value of Surfactant.

The used Co-surfactants are sorbitan, propylene glycol, etc.
The other excipients like a preservative, moisturizer, coloring agent also are used to enhancethe stability and the acceptance of formulation.

Method

There are the following methods which are used for the formulation of microemulsion-(Fig-1)

i. Phase titration method
ii. Phase inversion method

Phase titration method

The microemulsion is formulated by the phase titration method with help of the phase diagram. The pseudo ternary phase diagram is used to justify the appropriate quantity of the oil, S_{mix}(Surfactant & Co- surfactant), and water phases. The oil phase containing the drug is heated separately on a water bath at 70^0C. In another container, the aqueous phase is prepared to have the same temperature. Mix the oil phase with the water phase and vortex for 15-30 min to achieved microemulsion.

Phase inversion method

This method of the microemulsion is done by the addition of an excess of the dispersed phase or in response to temperature. The physical changes are shown during the phase inversion process like particle size which can ultimately affect the bioavailability of the drug. In the case of a non-ionic surfactant, this process achieves by a change in temperature, at low temperature the o/w phase is converted into w/o phase on high-temperature w/o to o/w microemulsion.[20]

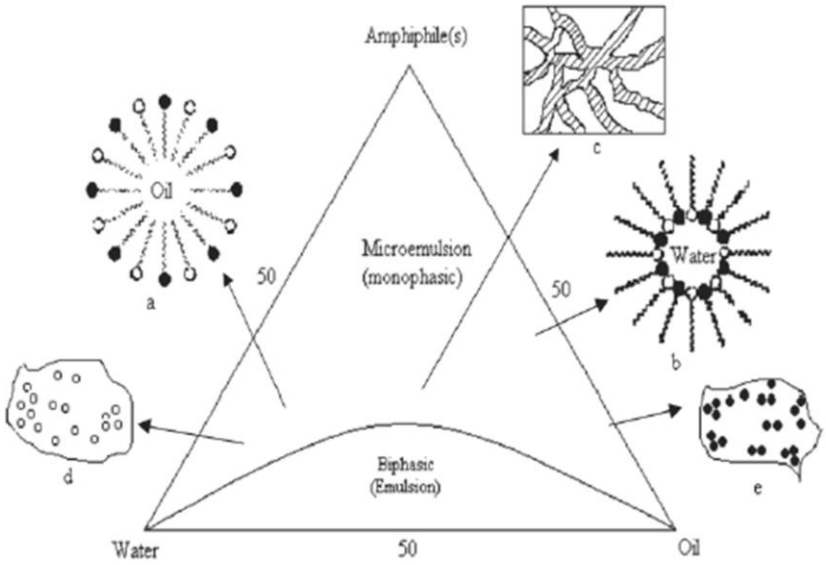

Fig. 1: A ternary phase diagram portraying various structures a) o/w microemulsion; b) w/o microemulsion; c) bicontinuous microemulsion; d) and e) various dispersions.) (Fig 2. A diagrammatic presentation of Formulation of microemulsion)Characterization of Microemulsions

It is difficult to work to characterizes the microemulsion due to their complexity, different structures, and components involved in this system as well as limited techniques. there are the following techniques that are used to characterizes the microemulsion.

Scattering Techniques for Microemulsions Characterization

The various scattering techniques such as small-angle neutron scattering (SANS), Small- angle X-ray scattering (SAXS), and static as well as dynamic light scattering are widely used to characterized microemulsion. This method is widely used for obtaining quantitative information on the size, shape, and dynamics of the components. This technique has a drawback because in this technique there is a need to dilute the sample before testing therefore the change in the structure and the composition of the phases of an emulsion. To obtain information about droplet size and shape the SAXS has been used.[21]

Nuclear Magnetic Resonance Studies

The NMR is used to study the structure and the dynamics of the microemulsion. The Fourier transform pulsed-gradient spin-echo techniques uses magnetic gradient on the samples and it allows simultaneous and rapid determination of the self-diffusion coefficients (in the range of 10-9 to 10-12 m2s-1), of many components.[22,23]

Viscosity Measurements

To check the presence of a worm-like reverse micelle the viscosity measurement should be done. Measurement of viscosity is to be done for the determination of the hydrodynamic radius of droplets, and the droplet-droplet interaction and deviation from spherical shape by fitting obtained data to suitable models. The Brookfield viscometer is widely used to determine the viscosity of the formulation.[24]

Electron Microscope Characterization

TEM is the widely used technique to determine the microstructure of the formulated microemulsion, directly produce high-resolution images, and capture co-existent structure and transitions of microstructures.

Applications of microemulsion in delivery of drug

In recent years the use of microemulsion is increased for the delivery of active components to the body due to its thermodynamic stability, ease of penetration, and suitability in the application. the importance of this novel drug delivery is discussed below.

In oral delivery

This is always a challenging task for the researchers to discover an effective oral delivery system for a drug because the potency and activity of the drug are inhibited by the poor solubility or instability into the GI-Tract. The microemulsion has the capability to increases the solubility of the poorly soluble drug to achieve the therapeutic effect. They have both hydrophobic and hydrophilic properties therefore they easily solubilize the varying solubility of drugs. the drugs are incorporated inside the micelle so they are protected from oxidation, degradation, and other chemicals inside the body. Collectively they increase the bioavailability of the drugs.

Parenteral delivery

The development of dosage forms having hydrophilic and lipophilic drugs intended for parenteral uses is a challenging task. So the microemulsion of o/w type is effective in the parenteral delivery of slightly soluble drugs. they also exhibit higher physical stability in plasma than liposomes or other vehicles and the internal

oil phase is more resistant against drug leaching.[25]

Topical delivery

The topical delivery of a drug is more advantageous over the other delivery systems due to the severe reasons one of them is they avoided the first pass metabolism therefore the drug is prevented from any type of incompatibilities by GI-fluid or toxicity. At this time the different studies are going on to drug penetration into the skin. Microemulsions have able to hold both hydrophilic and lipophilic types of drugs.[26]

Ophthalmic delivery

Till the conventional ophthalmic dosage forms, the aqueous solutions (have the water-soluble drugs) and suspension and ointments (have water-insoluble drugs) are used. These delivery systems show low bioavailability in the corneal region and a lack of efficiency in the posterior portion of the ocular tissues. Microemulsion serves as a promising dosage form for ocular use. Chloramphenicol, an antibiotic used in the treatment of trachoma and keratitis, inthe common eye drops hydrolyzes easily. Lv *et al*. investigated the microemulsion composed of Span 20, Tween 20, isopropyl myristate, and water as potential drug delivery systems for eye drops.[27]

Nasal delivery

Recently, it has been studied that the greater absorbance of a drug from the nasal mucosa by the use of novel drug delivery system microemulsion. By the use of mucoadhesive polymer, the residence time of the drug on the mucosa should be increased. the effect of diazepam on the emergency treatment of status epilepticus was investigated by Lianly et al. they confirm that the absorption of diazepam is going to rapid and reached maximum plasma concentration within 2 min after the dosing of 2 mg/kg^{-1}.[28]

Drug targeting

Drug targeting can also be done by the use of microemulsions that have a specific type of surfactant or polymer. tumor targeting of lipophilic antitumor antibiotic aclainomycin A (ACM) was reported by Shiokawa *et al by the use of microemulsion formulation.*

CONCLUSION

The microemulsion is the appropriate drug delivery system for delivery of the both hydrophobic and hydrophilic types of drugs.

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Abbreviations

GI – Gastro Intestinal fluid.ACM – Aclainomycin
O/w – Oil in WaterW/o – Water in Oil
SANS- Small-angle neutron scattering SAXS- Small-angle X-ray scattering S_{mix}.Surfactant & Co-surfactant HLB Hydrophilic lipophilic Balance.

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