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Microemulsion: New Approach for protection of Pleasant Smell in Pharmaceuticals

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Abstract

Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. Since the discovery of microemulsions, they have attained increasing significance both in basic research and in industry. They are capable of solubilizing both hydrophilic and lipophilic ingredients with relatively higher encapsulation. There is growing recognition of their potential benefits in the field of cosmetic science in addition to the drug delivery. They are now being widely investigated for preparing personal care products with superior features such as having improved product efficiency, stability or appearance. These smart systems are suitable for perfuming purposes where minimum amount of organic solvents is required, such as for perfuming skin or hair. While microemulsions are used in several fields, this article focuses on the reported investigations for preservation and stabilization of fragrances in cosmetics, and pharmaceutical preparations.
Keywords: Perfume, Fragrance, Microemulsion, Surfactant.

Contents

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1. Introduction

Emulsion preparation in conventional food industries involves the application of energy to mixtures of oil, water, and emulsifier that stabilizes the interfacial layer between the dispersed and continuous phases. These macroemulsions are turbid, having droplet sizes ranging from 0.2 to 10 /m and may remain kinetically stable. Microemulsions, on the other hand, are thermodynamically stable, transparent isotropic solutions with particle sizes ranging from 5 to 100 nm, and form spontaneously. Application of microemulsions in foods is limited by the types of surfactants which are used. Many surfactants are not permissible in foods or may be added at low levels. Microemulsions can be considered as delivery systems as they can solubilize simultaneously hydrophilic, lipophilic and amphiphilic substances. Many studies in the pharmaceutical and cosmetic fields reported enhanced solubilization of poorly soluble compounds and improved bioavailability following incorporation into microemulsions. A similar case could be the solubilization of compounds with bioactive capability isolated from varying food sources. The cosmetic industry is constantly seeking new and pioneering products that will combine both proven biological activity and an efficient delivery system. Although conventional formulations are the primary cosmetic products seen on the market, numerous advances have been made in the development of newer and innovative techniques for cosmetic delivery systems. There is an ever growing and expanding market segment requiring specialty cosmetic products. Despite increased price structure, demand particularly for skin care, hair care and sun care products have shifted away from conventional products towards value added products. This highlights the fact that consumers are willing to pay higher prices for quality and additional benefits. Today more than ever, cosmetic formulator is being challenged to develop superior and clearly distinctive formulations.

Perfume and Fragrances

The uses of perfumes and products which contain fragrance have increased tremendously over the past few decades. Historically, fragrance has been for luxury and special occasion use. Since, the fragrance has become a part of our daily life. Fragrances may be either essential oils or fragrance oils(perfume oils) are presently employed in industry in a wide range of products, either as principal functional components (e. g. in perfumes) or as adjuncts to impart a sensorial dimension to the quality of other products such as in laundry compositions, deodorants, cleaning agents and toiletries. They are also used in Food Products as well as in Pharmaceutical Formulations. Fragrance improves the aesthetic value of the product and masks the undesirable odor of the other components of the formulations.

Drawbacks associated with Perfume and Fragrances

Major difficulties arise from the fact that many fragrance oils are labile and/or volatile (and so fugitive) because they undergo various chemical reactions such as polymerization, oxidation or decomposition. Hence such materials are not able to impart odour properties as long as desirable. Alcohol is traditionally used to solubilize perfume concentrates of lipophilic nature in a single homogeneous and transparent phase. Alcohol containing fragrances are the most commonly used vehicle in preparing fine perfumes. Alcohol is a material that has a fast evaporation rate and a strong lift of the fragrance after application to skin. Alcohol is a traditionally used to solubilize perfume concentrates of lipophilic nature. But there are numerous disadvantages to the use of alcoholic fragrances such as:-

- The fragrances are labile and/or volatile; the quality of product is reduced due to evaporation of oils. Hence there is a problem in the stability of the product containing fragrance.
- Fragrance oils tend to undergo oxidation during their shelf life and hence the quality of the product as well as customer satisfaction is decreased.
- Alcohol is skin irritant as it dehydrates the skin by removal of the hydrolipid film, covering and protecting the skin surface; it is also eye, nose, and throat irritant. Causes headaches and allergic symptoms.
- It tends to promote dandruff formation in contact with the hair, dulling the hair, furthermore, and making it dry and brittle by disorganizing the cuticle and removing the protective sebaceous coating.
- Use of alcohol is objected by environmentalist groups and persons concerned with infant safety as well as some countries based on religious grounds.
- Use of alcohol also increases the cost of final product.
- Because of volatile nature of alcohol the quantity on shelf is reduced which hampers final product's market value.

Nowadays, there is a worldwide incentive to reduce the use of volatile organic chemical (VOC). The market of alcohol free fragrances constitutes a new segment of activity which has an important growth potential in the future. Therefore, a non-alcoholic, aqueous microemulsion based perfuming product which is transparent and stable, safe to use, very well tolerated by the skin and virtually non-toxic is desired. Efforts are being made towards the development of water based fragrances and perfumes. One approach to prepare water based perfume formulations has resulted in the development of microemulsion technology which is capable of yielding a clear to opalescent and low viscosity solution.

Microemulsion

Recently, microemulsions have emerged as prospective delivery systems to overcome the limitations of the existing conventional formulations, such as macro emulsions which are thermodynamically unstable and have a very limited shelf life.[1] There has been a revolution in the last two decades in the utilization of microemulsion systems in a variety of chemical and industrial processes. Microemulsions have shown a wide range of applications starting with enhanced oil recovery in the 70's, expanding to a wide range of chemicals and entering the pharmaceutical and cosmetic formulation area a decade ago.

The microemulsion concept was introduced as early as the 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol.[3, 4 5 6] Schulman and coworkers (1959) subsequently coined the term microemulsion and it has since been defined and indeed redefined on many occasions. They defined Microemulsion as a transparent solution obtained by titrating a normal coarse emulsion with medium-chain alcohols. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a cosurfactant and with a droplet size usually in the range of 10-200 nm.[1, 8 9] .They can be classified into three types: oil-in-water (o/w), bicontinuous, and water-in-oil (w/o) depending on the ratio of the components. Fig. 1 shows schematic representations of the three types of microemulsions which are most likely to be formed depending on composition.

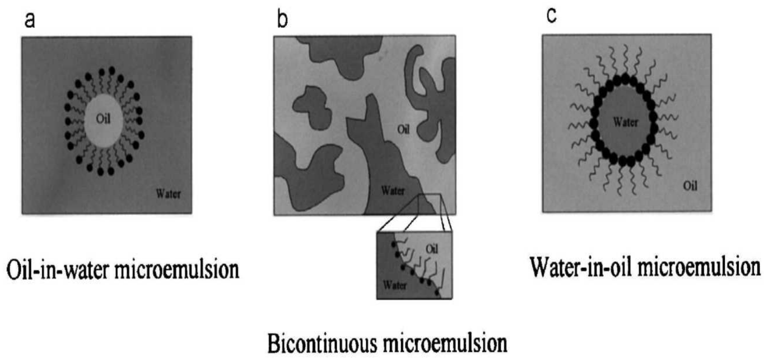

Fig. 1 Schematic representation of the three most commonly encountered microemulsion microstructures: (a) oil-in-water, (b) bicontinuous, and (c) water-in-oil microemulsion.

Microemulsions are the systems in which two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low. Therefore microemulsions form spontaneously, with an average droplet diameter of 10 to 140 nm.[10] They have been widely explored for drug delivery.The main difference between macroemulsions and microemulsions lies in the size and shape of the particles dispersed in the continuous phase: these are at least an order of magnitude smaller in the case of microemulsions (10-200 nm) than those of conventional emulsions (1-20 um). Macroemulsions consist of roughly spherical droplets of one phase dispersed into the other whereas microemulsions constantly evolve between various structures ranging from dropletlike swollen micelles to bicontinuous structures, making the usual "oil in water" and "water in oil" distinction sometimes irrelevant. Microemulsions show improved appearance, elegance, stability, ease of application and allow for controlled or sustained release of the active agent. They are formed spontaneously or with a little input of energy. Therefore, they are simple to prepare and are not process dependent i.e. the order of addition of starting materials or speed/type of mixing is not critical to the preparation of the microemulsions. This is attractive from manufacturing point of view. The key differences between ordinary emulsions (macro emulsions) and microemulsions are shown in Table 1.

Table I. Comparison of microemulsion with conventional emulsion (macroemulsion)

Sr.no.	Property	Microemulsion	Emulsion
1	Appearance	Transparent (or translucent)	Cloudy
2	Optical Isotropy	Isotropic	Anisotropic
3	Interfacial tension	Ultra low	High
4	Microstructure	Dynamic (interface is continuously and spontaneously fluctuating)	Static
5	Droplet size	20-200 nm	> 500 nm
6	Stability	Thermodynamically stable, long shelf-life	Thermodynamically unstable (kinetically stable), will eventually phase separate
7	Phases	Monophasic	Biphasic
8	Preparation	Facile preparation, relatively lower cost for commercial production	Require a large input of energy, higher cost
9	Viscosity	Low viscosity with Newtonian behaviour	Higher viscosity

Microemulsion's utility lies from the fact that they can incorporate a large amount of lipophilic cosmetic actives in the inner oil phase which are otherwise difficult to formulate. The existence of polar, nonpolar and interfacial domains allows encapsulation of ingredients with varying solubility.[14-15] Due to the small droplet size and large amount of inner phase, the density of droplets and their surface area are assumed to be high. Therefore, droplets improved drug permeation. Moreover, low surface tension ensures good contact to the skin. The surfactant andcosurfactant in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration enhancers thereby facilitating cutaneous penetration. The relationship between the phase behaviour of a mixture and its composition can be captured with the aid of a phase diagram. The phase behaviour of simple

microemulsion systems comprising oil, water and surfactant can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component.
The relative weight ratios are plotted with the help of Gibb's triangle. More commonly, however, and almost always in the case of microemulsions in pharmaceutical applications, the microemulsion will contain additional components such as a co surfactant and/or drug. In the case where four or more components are investigated, pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / co surfactant, water /drug or oil / drug. The number of different phases present for a particular mixture can be visually assessed. Micro structural features can also be investigated with the aid of a wide variety of techniques. A highly

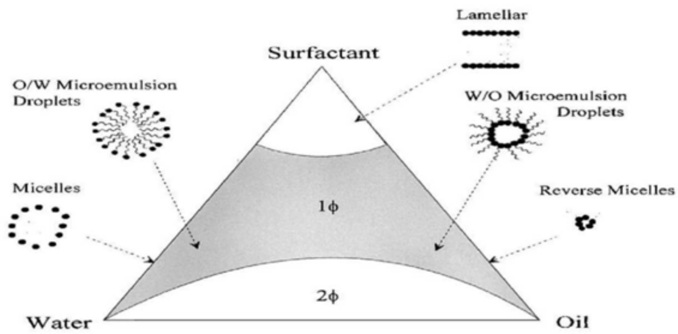

Figure. 2 A hypothetical pseudo-ternary phase diagram of an oil /surfactant /water system with emphasis on microemulsion and emulsion phases.

Ternary and quaternary phase diagrams can describe the phase manifestations and are essential in the study of microemulsions. The knowledge on the phase manifestations of the pseudo-ternary (water /amphiphile/ oil) or explicitly quaternary (water / surfactant / cosurfactant / oil) mixtures has been systematized. At low surfactant concentration, there is a sequence of equilibria between phases, commonly referred to as Winsor phases[19], they are Winsor I: with two phases, the lower (oil/water, o/w) microemulsion phase in equilibrium with the upper excess oil; Winsor II: with two phases, the upper microemulsion phase (water/oil, w/o) in equilibrium with excess water; Winsor III: with three phases, middle microemulsion phase (o/w plus w/o, called bicontinuous) in equilibrium with upper excess oil and lower excess water; Winsor IV: in single phase, with oil, water and surfactant homogeneously mixed. Inter-conversion among the above mentioned phases can be achieved by adjusting proportions of the constituents.

Microemulsion Formulation Components
The challenges in formulating topical microemulsions are:
1. Determining systems that are non-toxic, non-irritating, non-comedogenic and non sensitizing.
2. Formulating cosmetically elegant microemulsions.

The microemulsion formulation must have low allergic potential, good physiological compatibility and high biocompatibility. The components involved in the general formulation of microemulsions include (a) an oil phase (b) an aqueous phase containing hydrophilic active ingredients [preservatives and buffers may be included] (c) a primary surfactant [anionic, non-ionic or amphoteric] (d) secondary surfactant or cosurfactants.

Oil Phase
The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail group region to a greater extent than long chain alkanes, and hence swell this region to a greater extent, resulting inincreased negative curvature (and reduced effective HLB)[20]. Saturated (for example, lauric, myristic and capric acid) the upper microemulsion phase (water/oil, w/o) in equilibrium with excess water; Winsor III: with three phases, middle microemulsion phase (o/w plus w/o, called bicontinuous) in equilibrium with upper excess oil and lower excess water; Winsor IV: in single phase, with oil, water and surfactant homogeneously mixed. Inter-conversion among the above mentioned phases can be achieved by adjusting proportions of the constituents.

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Surfactants

The surfactant chosen must be able to lower the interfacial tension to a very small value which facilitates dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. It is generally accepted that low HLB surfactants are favoured for the formulation of w/o microemulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation. Quaternary ammonium alkyl salts form one of the best known classes of cationic surfactants, with hexadecyltrimethyl- ammonium bromide (CTAB),[21,,23] and the twin- tailed surfactant didodcecylammonium bromide (DDAB) amongst the most well known.[24] The most widely studied anionic surfactant is proably sodium bis-2-ethylhexylsulphosuccinate (AOT) which is twin-tailed and is a particularly effective stabiliser of w/o microemulsions.[25-29]

Cosurfactants

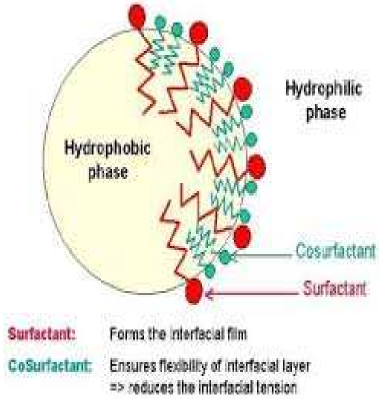
In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form.[30] The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition.[31] If a single surfactant film is desired, the lipophilic chains of the surfactant should be sufficiently short, or contain fluidising groups (e.g. unsaturated bonds). Short to medium chain length alcohols (C3- C8) are commonly added as cosurfactants which further reduce the interfacial tension and increase the fluidity of the interface. A large amount of surfactant is required for microemulsion formation which is undesirable. Surfactant may exhibit unwanted effects like skin irritation, allergy, etc. when used at high levels. Therefore, one must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsions. For these reasons, the generally regarded as safe (GRAS) excipients are being increasingly preferred. As a general guideline, nonionic and zwitterionic surfactants are less toxic than the ionic ones. The field of existence of microemulsion is generally narrow and their temperature stability, particularly of nonionic surfactant containing microemulsions, can be limited.

Table 2. Some of the Examples of the Microemulsion Excipients

Microemulsion Raw Material	Origin	Examples
Oils	Natural	Olive oil, soybean oil, corn oil, coconut oil, castor oil, jojoba oil
	Synthetic	Isopropyl myristate, isopropyl palmitate, ethyl laurate, oleic acid, cetyl behenate
Surfactants	Natural	Lecithin, sugar surfactants such as alkyl glucosides and alkyl esters
	Synthetic	Anionic: Sodium dodecyl sulfate, sodium lauryl sulfate
		Nonionic: Tweens, Spans, Poloxamers, Brij, cetyl alcohol, cocamide MEA
		Cationic: Quaternary ammonium alkyl salts e.g. cetyl trimethyl ammonium bromide
		Zwitterionic (Amphoteric): Dodecyl betaine, cocamidopropyl betaine
Cosurfactants	Natural	Phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol and their derivatives
	Synthetic	Ethanol, isopropanol, propanol (short chain alcohols), transcutol, polyethylene glycol, propylene glycol, etc.

Method of Preparation Phase Titration Method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary-phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component. Observations should be made carefully so that the metastable systems are not included. The methodology has been comprehensively discussed by Shafiq-un-Nabi *et al.*



Particle size	Description	Characteristics
300-1000 nm	Emulsion	Blue-white, milky liquid, reasonable physical stability. Particles reside on skin surface → transdermal delivery.
100-300 nm	Sub-micron Emulsion	Bluish, translucent liquid. Enhanced physical stability. Particles reside on skin surface → enhanced transdermal delivery.
10-100 nm	Microemulsion	Translucent-transparent liquid. Excellent physical stability. Particles reside on skin surface → enhanced transdermal delivery.

Characterization of Microemulsions

Characterization of microemulsions involves the physical and chemical tests e.g., assay, uniformity of content, stability of the active (impurities), appearance, pH, viscosity, density, conductivity, surface tension, size and zeta potential of the dispersed phase, etc. with respect to the effect of the composition on physical parameters.[33] Additionally, differential scanning calorimetry (DSC) provides information on the interactions of different components and polarization microscopy using crossed polarizers can be employed to confirm isotropicity of the formulation.[34] Size of the dispersed phase in o/w microemulsions can be measured by photon correlation spectroscopy (PCS) and total-intensity light scattering (TILS) techniques. The use of scattering techniques, e.g., static light scattering (SLS), dynamic light scattering (DLS), and small-angle neutron scattering (SANS), for dispersed phase size measurement requires correction for non-ideality of the hard sphere model arising from interparticle interactions in concentrated microemulsions.[35] Structural features of microemulsions can be studied using self-diffusion nuclear magnetic resonance (SD NMR)[36] and small-angle X-ray scattering (SAXS).[37]

Current & Future Developments

Cosmetic industry is facing new and unfamiliar challenges. These may affect the profitability and, indeed, the survival of some highly successful products. These constraints may be related to health hazards, environmental concerns and product functionality. The commitment to innovation is essential, not only to allow the companies to maintain their global competitiveness, but, more importantly, to improve the performance, safety and environmental impacts of products. Microemulsions represent an effective formulation approach for the delivery of cosmetic agents. They allow mixing of immiscible ingredients into single formulation with improved stability and enable the regulation of rheological properties by changing the relative proportions or the degree of dispersion of the various phases over wide ranges. Cosmetic microemulsion formulations can increase the product efficiency and performance considerably. Emulsion technology continues to expand and the introduction of new w/o emulsifiers which give elegant products without the inherent greasy feel, etc. is of interest to the whole industry. Modified carbomer copolymers are being introduced which produce products with interesting rheology and provide improved skin moisturization. Silicone copoly-mers have also been employed which give high cosmetic properties. Microemulsions are highly convenient and acceptable for formulating skin care products including sunscreen products. They are able to achieve high SPF and also have the ability to penetrate the skin's horny layer thus increasing their efficacy and time of operation. Skin moisturizers and antiperspirants and deodorants based on microemulsion have shown superior properties. The use of hair care preparations employing microemulsion technology has led to the realization of desirable properties which were lacking earlier with the conventional preparations. Moreover, clear microemulsions are advantageous with regard to consumer appeal since an opaque, pearlescent, or cloudy appearance is not always pleasing particularly if the product is used as a base for personal care items where a very fresh, clean and clear look is desired, such as skin hydrating moisturizers, antiperspirants, etc. With strict emphasis on reduction on the use of volatile organic chemical (VOC), microemulsion technology has emerged as one of the useful approaches to prepare water based alcohol free perfumes and fragrances which are more environmental freindly. The market will continue to grow as new and more effective cosmetic active ingredients are developed. Novel microemulsion preparations with unique properties will ensure a buoyant marketplace for the cosmetic manufacturers.

3. Conclusion

It is important to improve the performance, safety and environmental impacts of pharmaceutical and cosmetic products. Microemulsions represent an effective formulation approach for the preservation of fragrances in pharmaceutical and cosmetic products. They allow mixing of immiscible ingredients into single formulation with improved stability and enable the regulation of rheological properties by changing the relative proportions or the degree of dispersion of the various phases over wide ranges. Cosmetic microemulsion formulations can increase the product efficiency and performance considerably. The large variety of applications as well as the steadily increasing number of research workers engaged in studies on microemulsions due to their unique properties, have made significant contributions to many branches of chemistry and technology, and suggest that the potential of microemulsions as novel compartmentalized liquids will be even more significant in future.

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