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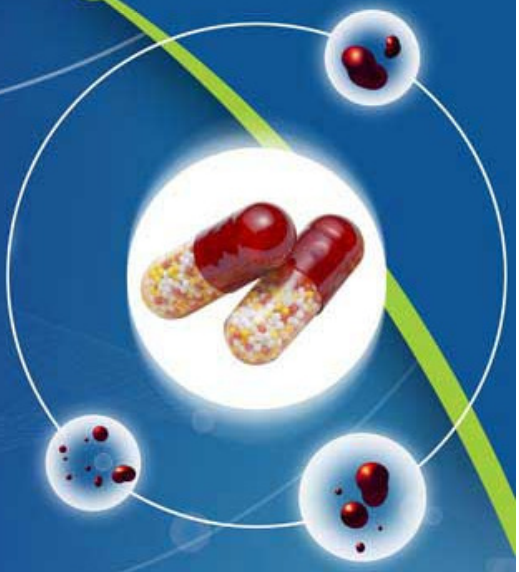

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Review Article

MICROEMULSION: A REVIEW

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ABSTRACT

Microemulsions have emerged as novel vehicles for drug delivery which allow sustained or controlled release for percutaneous, peroral, topical,transdermal, ocular and parenteral administration of medicaments. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, improved drug solubilization of hydrophobic drugs and bioavailability. This article focuses on types of microemulsion, composition of microemulsion, preparation & evaluation of microemulsion,While microemulsions are used in several fields, this article focuses on the reported investigations for different applications.

Keywords : *Microemulsion, Co-surfactant, Surfactant,Parentral,Phase Diagram,CPP Method.*

INTRODUCTION

The first Commercial microemulsion was used by Radawald in 1928. Then microemulsion was recognized as special kind of colloidal dispersion before the work of Schulman in 1943. Nevertheless,the opinion persists that microemulsions are true dispersions of one liquid within another and that their formation is not the same process as the solubilization of the oil phase be the interior of the micelles.Extensive investigations of the phase equilibria and structures in ternary reveal that the phenomena of micelle formation and solubilization may be have a common mechanism. The formulation are broadly reffered to as lipid based delivery system.more specifically these are reffered to as '*Self (Micro) Emulsifying Drug Delivery System' (SMEDDS).*

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Microemulsion is defined as microemulsion are clear, transparent, thermodynamically stable dispersions of oil and water, stabilized by an interfacial film of surfactant frequently in combination with a co-surfactant. Alternative names for these systems are often used, such as transparent *emulsion, swollen micelle, micellar solution,* and *solubilized oil***.** [1,2, 3]

TYPES OF MICROEMULSIONS [1,2, 3]

Microemulsions are thermodynamically stable, but are only found under carefully defined conditions.Characterizing the systems by whether the domains are in droplets or continuous ,results in three types of microemulsions:

Oil-In- Water Microemulsion

Oil-in-water microemulsions are droplets of oil surrounded by a surfactant (and possibly co-surfactant) film that forms the internal phase distributed in water, which is the continuous phase. This type of microemulsion generally has a larger interaction volume than the w/o microemulsions .

The monolayer of surfactant forms the interfacial film that is oriented in a "positive" curve, where the polar head-groups face the continuous water phase and the lipophilic tails face into the oil droplets.

Water-in-oil microemulsions

Water-in-oil microemulsions are made up of droplets of water surrounded by an oil continuous phase. These are generally known as "reverse-micelles", where the polar headgroups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil phase. A w/o microemulsion used orally or parenterally may be destabilized by the aqueous biological system. The biological system increases the phase volume of the internal phase, eventually leading to a "percolation phenomenon" where phase separation or phase inversion occurs.

Bicontinuous Microemulsion

When the amount of water and oil present are similar, a bicontinuous microemulsion system may result. In this case, both water and oil exist as a continuous phase. Irregular channels of oil and water are intertwined, resulting in what looks like a "sponge-phase" . Transitions from o/w to w/o microemulsions may pass through this bicontinuous state. Bicontinuous microemulsion, may show non-Newtonian flow and plasticity. These properties make them especially useful for topical delivery of drugs or for intravenous administration, where upon dilution with aqueous biological fluids, form an o/w microemulsion.

COMPOSITION OF MICROEMULSION [1,2, 4,5,6,7,8,9,10,11]

Oil Phase[2]

Oil is defined as any liquid having low polarity and low miscibility with water. The examples of such phase are toulene, cyclohexane , mineral oil & vegetable oil.

Surfactant[1,2,4,6,7,8,9,10,11]

The term surfactant (short for surface-active-agent) designates a substance which exhibits some superficial or interfacial activity & used to lower the surface or interface tension. This would imply that surface activity is strictly equivalent to tension lowering, which is not absolutely general, although it is true in many cases. It has affinity for polar & nonpolar solvents. Surfactants are molecules that typically contain a polar head group and an a polar tail. Surfactant molecules self-associate due to various inter- and intra-molecular forces as well as entropy considerations. All of these serve to optimize the free-energy overall. For example, when surfactant is mixed with oil and water, they accumulate at the oil/water interface, because it is thermodynamically favorable. The surfactant molecules can arrange themselves in a variety of shapes. They can form spherical micelles, rod-shaped micelles, a hexagonal phase (consisting of rod-shaped micelles), lamellar (sheet) phases, reverse micelles, or hexagonal reverse micelles. At low concentrations of dispersed (internal) phase, spherical, isolated droplets are present in the microemulsions. The surfactant used to stabilize the micro emulsion system are

Non-ionic surfactant

Nonionic Surfactants come as a close second with about 45% of overall industrial production. They do not ionize in aqueous solution, because their hydrophilic group is of non-dissociable type, such as alcohol, phenol, ether, ester, or amide. A large proportion of these nonionic surfactants are made hydrophilic by the presence of a polyethylene glycol chain,obtained by the polycondensation of ethylene oxide. They are called polyethoxylated nonionics. e.g polyoxyethylene eg. Brij 35 or Span-80.

Anionic surfactant

Anionic Surfactants are dissociated in water in an amphiphilic anion , and a cation ,which is in general an alkaline metal (Na , K) or a quaternary ammonium. They are the most commonly used surfactants. Anionic surfactants account for about 50 % of the world production.Alkali alkanoates, also known as soaps, are the most common anionic surfactants. The anionic charge in these surfactants comes from the ionized carboxyl group. This type is the most well understood surfactant when it comes to their structure and function .

Dioctyl sodium sulfosuccinate (DOSS) is the most widely studied anionic surfactant. Other important classes of anionic surfactants include alkyl sulfates, alkyl ether sulfates, alkyl sulfonates, aryl sulfonates, methylester sulfonates, and sulfonates of alkylsuccinates. The three most important

anionic groups in all of these surfactants being the carboxylate, sulfate, and sulfonate groups.

Cationic surfactant

Cationic Surfactants are dissociated in water into amphiphilic cation and anion,most often of halogen type. A very large proportion of this class corresponds to nitrogen compounds such as fatty amine salts and quaternary ammoniums, with one or several long chain of the alkyl type, often coming from natural fatty acids.Alkylammonium halides and tetra-alkylammonium halides are the most numerous in this class. Alkyl ammonium halides are excellent hydrogen bond donors and interact strongly with water. The most well known examples from the cationic surfactant class are hexadecyltrimethyl-ammonium bromide (CTAB) and didodcecylammonium bromide (DDAB). These surfactants are in general more expensive than anionics, because of the high pressure hydrogenation reaction to be carried out during their synthesis.

Zwitterionic surfactant

Zwitterionic surfactants, which contain both negatively and positively charged groups, form microemulsions upon the addition of co-surfactants. Phospholipids, such as lecithin, obtained naturally from soybean or egg are common zwitterionic surfactants. Unlike other ionic surfactants, which are somewhat toxic, lecithin which contains diacylphosphatidylcholine as the major constituent show excellent biocompatibility. Another important class of zwitterionic surfactants to note is the betaines, such as alkylbetaines, amidoalkylbetaines, and heterocyclic betaines .Some other examples are natural substances such as aminoacids and phospholipids.

Selection of Surfactant [1,2,5,7,8]

HLB Method:

The hydrophilic-lipophilic balance (HLB) of surfactant can be used as a starting point in the selection of Surfactant that will form micro emulsion.It is generally accepted that a surfactant with HLB from 3-6 will favor the formation of water-in-oil (w/o) micro emulsions, whereas surfactants with HLB from 8-18 are preferred for formation of oil-in-water (o/w) micro emulsions .

CPP Method:

CPP is a measure of the surfactant's preferred geometry, and can be used to predict the type of structure that possibly will be formed. The CPP can be calculated by dividing the partial molar volume of the hydrophobic part of the surfactant by the product of the optimal headgroup area and length of the surfactant tail.CPP values close to one tend to form worm-like micelles or lamellar structures. Values of CPP greater than one indicate that the headgoups are much larger, resulting in w/o microemulsion systems. The opposite is true for CPP values less than one. Values for CPP around one indicate the possible formation of lamellar phases .The amount of surfactant required can be estimated from the surface area of the droplets and the cross sectional area of surfactant molecules.

Cosurfactant[4]

One surfactant, whether nonionic or ionic, is not sufficient to form balanced microemulsions without the addition of another component. These additives are required because the head group of the ionic surfactants are generally substantially more hydrophilic than poly(ethylene oxide) moieties. The salts or co-surfactants shift the overall HLB into the optimal range for microemulsion formulation.Combinations of surfactants or sometimes co-surfactants are required for the optimal formation of a microemulsion. The term "Co-surfactant" can refer to a second surfactant being used, but may also refer to a low-molecular-weight amphiphile, such as an alcohol. Short and medium chain alcohols,such as butanol, pentanol, ethanol, isopropanol, or propylene glycol, are commonly added as "co-surfactants". These co-surfactants help to further reduce the surface tension and fluidize the surfactant film, which increases the entropy of the system leading to its thermodynamic stability. The requirement of a medium-chain alcohol as a co-surfactant may cause other problems such as

Can be irritating to the biological system, especially with chronic use

Toxicity issues with these chemicals

Solubility Problem: Most alcohols tend to be more soluble in the aqueous phase of o/w systems

than the primary surfactant. Because of this, as the system is diluted, the co-surfactant partitions more in the water-phase and reduces the amount of co surfactant present at the interface. This destabilizes the droplets, and ultimately the microemulsion system itself.

METHODS OF PREPARATION OF MICROEMULSION [1,2,3,8]

Microemulsion are formed only when Interfacial tension at the oil/water interface is brought to very low level

Interfacial layer is kept highly flexible and fluid Concentration of surfactant must be high enough to provide the number of surfactant molecules needed to stabilize the microdroplets to be produced by an ultra low interfacial tension

There are mainly two methods by which we can formulate microemulsion, which are as follows:

Titration Method

A mixture of fatty acid and oil is added to a caustic solution to produce a microemulsion, which is then titrated with a cosurfactant, an alcohol, until the system turned clear. It is found that as the chain length of the surfactant increased, microemulsions with significant transmittances by visible spectrum can be formed with oils of longer chain lengths.It is also found that different alcohols affect the formation of microemulsions in different ways. The best results, in terms of the greatest percent transmittance coupled with the widest range of oil (dispersed in water) concentration, are obtained from short or branched alcohols.

Agitation Method

The drug is dissolved in the lipophilic part of the microemulsion i.e. Oil and the water phases can be combined with surfactant and a cosurfactant is then added at slow rate with gradual stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules .

THEORIES OF MICROEMULSION [1,2, 7,9]

Various theories concerning microemulsion formation, stability and phase behavior have been proposed

Thermodynamic Theory[2,7]

Microemulsion formation and stability can be explained on the basis of simplified thermodynamic rationalization. The free energy of microemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil–water interface and the change in entropy of the system such that,

$DG_f = \gamma DA - T\,DS$

where DG_f = Free Energy of formation,

γ =Surface Tension of the oil–water interface,

DA = Change in interfacial area on microemulsification,

DS = Change in entropy of the system which is effectively the dispersion entropy, and

T = Temperature.

It should be noted that when a microemulsion is formed the change in DA is very large due to the large number of very small droplets formed. It is must however be recognized that while the value of γ is positive at all times, it is very small (of the order of fractions of mN/m), and is offset by the entropic component. The dominant favourable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of small droplets. However, favourable entropic contributions also arise from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus a negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favourable entropic change. In such cases, microemulsification is spontaneous and the resulting dispersion is thermodynamically stable.

Reason for Combining Two Surfactants[6]

Single surfactants do lower the interfacial tension γ, but in most cases the critical micelle concentration (c.m.c.) is reached before γ is close

to zero. Addition of a second surfactant of a completely different nature (i.e. predominantly oil soluble such as an alcohol) then lowers γ further and very small, even transiently negative, values may be reached.The two surfactant molecules should adsorb simultaneously and they should not interact with each other, otherwise they lower their respective activities. Thus, the surfactant and cosurfactant molecules should vary in nature, one predominantly water soluble (such as an anionic surfactant) and the other predominantly oil soluble (such as a medium-chain alcohol). In some cases a single surfactant may be sufficient to lower g far enough for microemulsion formation to become possible, e.g. Aerosol OT (sodium diethyl hexyl sulphosuccinate) and many non ionic surfactants.

Interfacial or Mixed Film Theory [7,9]

Schulman made interface mixed-film theory i.e a negative interfacial tension theory, the theory states that the micro-emulsion has been able to form spontaneously and instantaneous generate a negative interfacial tension in the surfactant and cosurfactant in working together. The film, which may consist of surfactant and cosurfactant molecules, is considered as a liquid ‘‘two-dimensional’’ third phase in equilibrium with both oil and water. Such a monolayer could be a duplex film, i.e. giving different properties on the water side and oil side. The initial ‘‘flat’’ duplex film has different tensions at the oil and water sides. This is due to the different packing of the hydrophobic and hydrophilic groups. According to the duplex film theory, the interfacial tension γT is given by the following expression

$$\gamma T = \gamma(O/W) \text{ --- } \pi$$

where γ(O/W)a = Interfacial Tension(reduced by the presence of the alcohol). γ(O/W)a is significantly lower than γ(O/W) in the absence of the alcohol; for example,for hydrocarbon/water is γ(O/W) reduced from 50 to 15–20 mNm---1 on the addition of a significant amount of a medium-chain alcohol such as pentanol or hexanol.

Contributions Contributions to π are considered to be due to crowding of the surfactant and cosurfactant molecules and penetration of the oil phase into the hydrocarbon chains of the interface.

According to above Eq. if π > γ(O/W) , γT becomes negative and this leads to expansion of the interface until gT reaches a small positive value. Since γ(O/W)a is of the order of 15–20 mNm--1, surface pressures of this order are required for γT to approach zero.

The theory in explaining the formation and stability of the microemulsion is a reasonable, but such a negative interfacial tension difficult to determine, so it's automatic emulsifying microemulsion in the interpretation of the phenomenon of lack of strong evidence and the fact that a number of double-stranded-ionic surfactant active agents, such as AOT and the ionic surfactant can also be joined to form microemulsions without cosurfactant, so the theory, there are some limitations.

Solubilisation Theory [8]

The formation of microemulsion is oil soluble phase and water phase by micelles or reverse micelles in micellar gradually become larger and swelling to a certain size range results.

FACTORS AFFECTING MICROEMULSION FORMATION[6,7,8]

Packing Ratio[7,8]:

HLB of surfactant determines the type of microemulsion through its influence on packing and film curvature.The analysis of film curvature for surfactant association`s leading to the formation of microemulsion.

Critical packing ratio is given by V/(a X l)

Where V= volume of surfactant molecule

a=head group surface area

l= length

If CPP is between 0-1, interface curves towards water(positive)

If CPP is greater than 1, interface curves towards oil(negative)

If CPP is equal to 1, then either bicontinuous or lamellar structure

Role of Surfactant [6,8]:

Surfactant contains two group hydrophilic and lipophilic groups.Hydrophilic single chain surfactants such as cetylethylammonium bromide

dissociate completely in dilute solution and has a tendency to form o/w microemulsion.When high concentration of surfactant is used or when the surfactant is in presence of salt, degree of dissociation of polar groups becomes lesser and resulting system may be w/o type.

Property of Oil Phase [8]:

Oil phase also influence curvature by its ability to penetrate & Swell the tail group region of the surfactant monolayer,Swelling of tail results into an increased negative curvature to w/o microemulsion.

Temperature [8]:

Temperature plays important role in determining the effective head group size of nonionic surfactant.At low temperature, they are hydrophilic & form normal o/w microemulsion where as at high temperature,they are lipophilic & form normal w/o microemulsion and at an intermediate temperature, microemulsion coexist with excess water and oil phase and form bicontinuous structutre. Chain length, Type and nature of cosurfactant:Addition of shorter chain cosurfactant (eg ethyl alcohol) gives positive curvature effect as alcohol swells the head region more than tail region so, it becomes more hydrophilic and o/w type is favoured. Addition of longer chain cosurfactant(eg gcetyl alcohol) favours w/o type by alcohol swelling more in tail region than head region.

ADVANTAGES [1,2,3,8,9]

- Increase the rate of absorption
- Eliminates variability in absorption
- Helps solublize lipophilic drug
- Provides a aqueous dosage form for water insoluble drugs
- Increases bioavailability
- Various routes like tropical, oral and intravenous can be used to deliver the product
- Rapid and efficient penetration of the drug moiety
- Helpful in taste masking
- Provides protection from hydrolysis and oxidation as drug in oil phase in O/W
- micro emulsion is not exposed to attack by water and air.
- Liquid dosage form increases patient compliance.
- Less amount of energy requirement
- Ease of manufacturing and scale up
- This system is reckoned advantageous because of its wide applications in colloidal drug

DISAVANTAGES [1,2,3, 8,9]

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Limited solubilizing capacity for high-melting substances
- The surfactant must be nontoxic for using pharmaceutical applications
- Micro emulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon micro emulsion delivery to patients.
- High cost of surfactant
- Narrow range of surfactant, co-surfactant, solvents
- Dilution is not possible for percolated and bicontinuous structure
- Formulation containing several components become more challenging to validate
- The precipitate tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.

EVALUATION OF MICROEMULSION [1, 6, 7, 8,9,14,15]

Optical birefringence [9]

The formulations are examined by polarized light microscopy in order to determine the optical

isotropy of the samples.Placing a polarizer in front of the condenser lens of a microscope produces plane-polarized light. This type of light vibrates in one plane only. The direction of polarization does not change when reflected from an optically isotropic surface, which has no birefringence. Polarizing light microscopy can distinguish between isotropic and anisotropic materials. It can be used to differentiate between microemulsions and liquid crystals, since birefringence is not found in microemulsions, which are isotropic systems.

Electrical conductivity[9]:

Conductivity is the ability of a material to conduct an electric current through it.Conductivity (G), the inverse of resistivity (R), is determined from the voltage (E) and current (I) values according to Ohm's Law, which is illustrated in Equation. G= 1/R=I/E

where I=amps E=volts

Conductivity is useful in the determination of which phase is continuous in the microemulsion. The conductance is very different in o/w, w/o and bicontinuous microemulsion systems.When water is the continuous phase, conductivity approaches that of the aqueous media,Conductivity, on the other hand, is very low in w/o microemulsions, due to the fact that the water, which is a better conductor than oil, is in droplets while the oil is continuous.When compared to w/o microemulsions, bicontinuous systems possess significantly higher conductivity. In this case, the charge carriers are transported through the continuous "channels" that are formed in a way similar to an aqueous electrolyte solution.

Rheology *[*7,9]

Rheology is less precise but simpler way to identify anisotropic aggregates in the system. Microemulsions being isotropic (spherical) systems offer less resistance to flow and exhibit low viscosity.Rheological properties can provide information about the microstructure of microemulsions.Both o/w and w/o microemulsions exhibit Newtonian flow, where as Bicontinuous formulations may exhibit non-Newtonian flow behavior and plasticity, which can be fairly complex.

Determination of pH[9]

The pH of microemulsion is measured on digital pH meter standardized using pH 4.0 and 7.0 standard buffers before use at 20±1°C.

Determination of permeability coefficient and flux [2,9]

Excised human cadaver skin from the abdomen can be obtained from dead who have undergone postmortem not more than 5 days ago in the hospital. The skin is stored at 40C and the epidermis separated. The skin is first immersed in purified water at 60 0c for 2 min and the epidermis then peeled off. Dried skin samples can be kept at -20 0c for later use. Alternatively the full thickness dorsal skin of male hairless mice may be used. The skin shall be excised, washed with normal saline and used. The passive permeability of lipophilic drug through the skin is investigated using Franz diffusion cells with known effective diffusional area. The hydrated skin samples are used. The receiver compartment may contain a complexing agent like cyclodextrin in the receiver phase, which shall increase the solubility and allows the maintenance of sink conditions in the experiments. Samples are withdrawn at regular interval and analyzed for amount of drug released.

In Vivo Studies [2,9]

Bioavailability studies: Skin bioavailability of topical applied microemulsion on rats

Male Sprague–Dawley rats (400–500 g), need to be anesthetized (15 mg/kg pentobarbital sodium i.p.) and placed on their back. The hair on abdominal skin shall be trimmed off and then bathed gently with distilled water. Anesthesia should be maintained with 0.1-ml pentobarbital (15 mg/ml) along the experiment. Microemulsions must be applied on the skin surface (1.8 cm2) and glued to the skin by a silicon rubber. After 10, 30 and 60 min of in vivo study, the rats shall be killed by aspiration of ethyl ether. The drug exposed skin areas shall be swabbed three to four times with three layers of gauze pads, then bathed for 30 s with running water, wiped carefully, tape-stripped (X10 strips) and harvested from the animals.

Determination Of Residual Drug Remaining In The Skin On Tropical Administration

The skin in the above permeation studies can be used to determine the amount of drug in the skin. The skin cleaned with gauze soaked in 0.05% solution of sodium lauryl sulfate and shall bathed with distilled water. The permeation area shall be cut and weighed and drug content can be determined in the clear solution obtained after extracting with a suitable solvent and centrifuging.

Pharmacological Studies

Therapeutic effectiveness can be evaluated for the specific pharmacological action that the drug purports to show as per stated guidelines.

Estimation of Skin Irritancy

As the formulation is intended for dermal application skin irritancy should be tested. The dorsal area of the trunk is shaved with clippers 24 hours before the experiment. The skin shall be scarred with a lancet. 0.5 ml of product is applied and then covered with gauze and a polyethylene film and fixed with hypoallergenic adhesive bandage. The test should be removed after 24 hours and the exposed skin is graded for formation of edema and erythema. Scoring is repeated 72 hours later. Based on the scoring the formulation shall be graded as 'non-irritant', 'irritant' and 'highly irritant'.

Interfacial Tension:

The formation and the properties of microemulsion can be studied by measuring the interfacial tension.Spinning-drop apparatus can be used to measure the ultra low interfacial tension. Interfacial tensions are derived from the measurement of the shape of a drop of the low-density phase, rotating it in cylindrical capillary filled with high-density phase.

Spreadability:

An apparatus used to determine spreadability of the formulation, consists of a wooden block to which a pulley is attached to one end.A rectangular ground glass plate is fixed on the same end. An excess of microemulsion (3g) under study is placed on ground glass plate. The microemulsion is than sandwiched between glass plate and another glass plate having a hook to which a pan is attached at one end with the help of string. The top glass plate was subjected to a weight of 50gm by putting weight in the pan and the time (in sec) required by the top plate to travel a distance of 10cm is noted. A shorter time interval indicates better Spreadability.

Predicting Microemulsion Type[9]

A well-known classification of microemulsions is that of Winsor 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 surfactant is only present as monomers at 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).

Simple Tests[9]

Dye Solubilization

A water soluble dye is solubilized within the aqueous phase of the W/O globule but is dispersible in the O/W globule. A oil soluble dye is solubilized within the oil phase of the O/W globule but is dispersible in the W/O globule.

Dilutability Test

O/W micro emulsions are dilutable with water whereas W/O are not and undergo phase inversion into O/W micro emulsion.

Electron Microscope Characterization [2]:

Transmission Electron Microscopy (TEM) is the most important technique for the study of microstructures of microemulsions because it directly produces images at high resolution and it can capture any co-existent structure and micro-

structural transitions. There are two variations of the TEM technique for fluid samples i.e cryo-TEM (samples are directly visualized after fast freeze and freeze fructose in the cold microscope)and Freeze Fracture TEM technique (a replica of the specimen is images under RT conditions).

Statistical analysis:

All studies are performed in triplicate and the values are expressed as mean ± SD The data are analysed by one way analysis of variance (ANOVA) followed by Dunett test. A value of P< 0.05 is considered as significant.

QUALITY CONTROL OF MICROEMULSION [1, 7, 8, 9]

Determination Of Globule Size And Particle Count

One of the most important characterizations of microemulsions is particle size and shape. Small-angle X-ray scattering (SAXS), small-angle neutron scattering (SANS), and static as well as dynamic light scattering are widely applied techniques in the study of microemulsions. These methods are very valuable for obtaining quantitative informations on the size, shape and dynamics of the components. The major drawback of this technique is the dilution of the sample required for the reduction of interparticular interaction. This dilution can modify the structure and the composition of the pseudophases. Microemulsions as a definition have particle sizes of less than 100 nm. DLS is a reliable method to detect particle sizes in this range. It is a very sensitive instrument, though, and samples must be free of all impurities. To eliminate the possibility for incorrect readings due to impurities that are present, microemulsion samples can be centrifuged, without phase separation. This separates out the unwanted particles while leaving the microemulsion droplets to continue to diffuse throughout the solution. DLS is best applied to systems with a narrow particle size distribution such as microemulsions.

Viscosity measurement[2,9]

Viscosity measurements can indicate the presence of rod-like or worm-like reverse micelle. The viscosities of microemulsions are measured using a Brookfield rotational viscometer. The measurement is performed at ambient temperature and in triplicate.Viscosity describes the interactions between microstructures in microemulsions.Viscosity of o/w microemulsions is usually close to that of water, even at high droplet concentration, probably due to reversible droplet coalescence.In w/o systems, the increase in viscosity with rising water concentration has been attributed to the clustering and shape changing of the internal phase droplets into channels of bi continuous nature.

DETERMINATION OF PHASE SEPARATION/STABILITY STUDIES[9]:

Temperature For The Stability Testing

The reaction rate doubles for every 100 C rise in temperature. Thus high temperature testing is used as a predictor of long-term stability.Conventional wisdom says that if a product is stored at 450C for three months (and exhibits acceptable stability) then is should be stable at room temperature for two years.But When the temperature rises to 500 C then there is approaching the melting point of the fatty alcohols (cetyl and stearyl) that are used to stabilize microemulsion and the microemulsion may exhibit product instability prematurely. In actuality, the microemulsion may have a shelf life of two or even three years but “failed” the 500C test.

Cycle Testing

The product should pass three cycles of temperature testing from -100 C to 250 C. Place the product at -100 C for 24 hours and place it at room temperature (250 C) for 24 hours. This completes one cycle. If the product passes three cycles then you can have a good degree of confidence in the stability of the product.

Centrifuge Testing

As we know microemulsions always contain materials of differing specific gravities. Thus the internal/dispersed phase (of an oil-inwater microemulsion) has a tendency to separate/agglomerate and rise to the top of the emulsion forming a layer of oil droplets called creaming. Creaming is one of the first signs of impending microemulsion instability and should be taken quite seriously.A good test method to predict creaming is centrifugation. Heat the

emulsion to 500 C and centrifuge it for thirty minutes at 3000 rpm and then inspected for signs of creaming. None of the microemulsion systems showe signs of phase separation on centrifugation at 3000 rpm for 30 minutes. This result provides a rapid and full proof identification of the stability of microemulsion.

Package Testing

While the formula may indeed be stable (have an adequate shelf life) if sold in a glass container with a tight fitting cap and a good liner, it may have an unacceptable stability in the actual package that is offered for sale. For this reason all testing should be done in glass and the commercial packaging. In this way we can determine if the cause of product failure is the formula or the package. Weight loss evaluation is one of the most important tests that must be conducted. This testing (performed in the commercial package with the cap torqued to 100% of target torque) is done at room temperature and at 450 C for a period of three months. The weight loss should not exceed 1%/month for the package to be considered acceptable. A variation of this test involves the torque testing of the package. Run the weight loss study with packages adjusted to 75%, 100% and 125% of the target cap torque.

Light Testing

All too often we forget that our formula and package can also be sensitive to the ranges of UV. All products should be placed, in glass and the commercial package, in the window and if its available a light box that has a broad-spectrum output. All too often we will see significant discoloration of the product and sometimes of the package also. This discoloration may be due to the fragrance or some other sensitive ingredient. Usually all that is needed is the addition of a UV absorber designed for this purpose. The Benzophenones seem to work particularly well in this regard, at use levels as low as 0.1%.

APPLICATIONS [1, 2,7, 8,9,12 ,13,14,15]

Pharmaceutical Applications [1,2,8]

Parenteral Delivery:

Both O/W and W/O microemulsion can be used for parenteral delivery. The literature contains the details of the many microemulsion systems, few of these can be used for the parenteral delivery because the toxicity of the surfactant and parenteral use

Oral Delivery:

Microemulsion formulations offer the several benefits over conventional oral formulation including increased absorption, improved clinical potency,and decreased drug toxicity. Therefore, microemulsion have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic and antibiotics.

Topical Delivery:

Topical administration of drugs have advantages like avoidance of hepatic first pass metabolism of the drug and targetability of the drug to affected area of the skin or eyes.The use of lecithin/IPP/water microemulsion for the transdermal transport of indomethacin and diclofenac has also been reported.

Ocular and Pulmonary Delivery:

For the treatment of eye diseases, drugs are essentially delivered topically. O/W microemulsions have been investigated for ocular administration, to dissolve poorly soluble drugs, to increase absorption and to attain prolong release profile.

Microemulsions in biotechnology :

Many biocatalytic and enzymatic reactions are conducted in aquo-organic or pure organic as well as in biphasic media .Their use is seriously limited because they can inactivate or denature the biocatalysts. Recently, interest on micro-emulsions is being focused for various applications in biotechnology, viz, enzymatic reactions, immobilization of proteins and bioseparation.

Other Applications[7,8,9,12,13,14,15]

Microemulsions in enhanced oil recovery:

The understanding of the mechanisms of enhanced oil recovery (EOR) using surfactant and microemulsion can help in obtaining unrecoverable underground oil. If the interfacial tension between the crude oil and reservoir brine can be reduced to around 10-3 mN/m, a substantial fraction of the residual oil in the porous media in which it is trapped can be mobilized. Low

interfacial viscosity of the system is also advantageous.

Microemulsions as fuels :

Interesting feature of microemulsion-based fuel is their capacity to increase the octane number of gasoline and the corresponding octane number for diesel oils. Octane number improvers include formamide, glycols, urea, etc. In diesel fuels, many problems are overcome due to the high combustion temperatures (160–325C). It is normal that diesel microemulsions contain watersoluble cetane number improvers . Microemulsions in fuels are also found to improve air–fuel contact and increase the flash point of fuel.

Microemulsions as lubricants, cutting oils and corrosion inhibitors :

Microemulsions are in use as lubricants, cutting oils and corrosion inhibitors for several decades The presence of surfactant in microemulsion causes corrosion inhibition and the increased water content compared to pure oil leads to higher heat capacity. On one hand the corrosive agents, because of solubilization in microemulsion cannot react with the metal surface hence the metal surface is protected by the adsorbed hydrophobic surfactant film. In microemulsions, water with much higher thermal conductivity, imparts higher heat capacity to the system. Such formulations can be used in cutting oil; the oil lubricates the cutting surface, and the water helps to remove the frictional heat generated during the cutting process.

Microemulsions as coatings and textile finishing:

The coating application area is a very promising and rapidly-growing field of microemulsion technology, because the microemulsified resins overcome many of the shortcomings of the more traditional water-based systems without creating the health and pollution problems and flammability hazards of the solvent-based coatings. Paint formulations using microemulsions have shown higher scrub resistance, better colour intensity and more stain resistance than those prepared by emulsions.

Microemulsions in detergency :

Due to their characteristic properties, microemulsions are promising systems for detergency purposes over traditionally-used organic solvents, as they can solubilize polar (e.g., salt, pigment, protein) and non-polar soil components (e.g., grease, oil). Various additives such as synthetic zeolites improve the properties, e.g. viscosity and secondary washing performance.The middle phase microemulsion is a better medium for detergency. Microemulsions are effective in soil removal from textile fabrics, in wool scouring, and in skin degreasing.

Microemulsions in cosmetics:

It is believed that microemulsion formulation will result in a faster uptake into the skin. Cost, safety, appropriate selection of ingredients are key factors in the formulation of microemulsions.Unique microemulsions as hair care products contain an amino-functional polyorganosiloxane and an acid and/or a metal salt. Solubilization of fragrance a

Microemulsions in agrochemicals :

Microemulsions have a variety of applications in agrochemical industry, of which pesticide-containing systems are relatively old. The ease of handling and lower requirement of smelly solvents go in favour of the use of micro emulsions. Microemulsions formulated with a hydrotope solubilizing the herbicide can be promising.The much finer droplet size of the microemulsion leads to higher penetrability, much larger contact area of the active substance to the treated surface and a much more even distribution during application.

Microemulsions in analytical applications :

Applications of microemulsions in the field of analytical techniques, are chromatography, laser-excited photoionization spectroscopy, etc. The characterization of solute hydrophobicity by microemulsion electrokinetic chromatography (MEEKC) has been attempted , which provides a quick and reproducible method to obtain hydrophobic parameters for solvents.

Microporous media synthesis (microemulsion gel technique) :

The unique properties of microemulsions have been utilized to produce microemulsion-gel glasses and microporous media with high surface area.These gels are reported to be obtained by the traditional sol/gel method with an increase in the

viscous and elastic response by several orders of magnitude at gelation.

***Microemulsions as liquid membranes* :**
Microemulsions of Winsor I (o/w) and Winsor II (w/o) types can be used as liquid membranes that can facilitate the transfer of solutes across it by trapping them in the microdroplets for convenient uptake and subsequent release.

Microemulsions in food :
The fruit coated with the microemulsions of caranauba wax maintains a better appearance than other coatings after washing and drying. Microemulsions have also been used to produce glycerides for application in food products. An important application of microemulsion is to provide improved antioxidation effectiveness because of the possibility of a synergistic effect between hydrophilic and lipophilic antioxidants.

***Microemulsions In Environmental Remediation And Detoxification*:**
A microemulsion intensifies the advantages of surfactant solution, such as decreasing interfacial tension and increasing wettability of soil and acting as an excellent solvent for polar and nonpolar organic substances. Further, the wettability of the soil particles is substantially increased due to the very low interfacial tensions provided by microemulsions, so that the fine grain fraction also becomes accessible for washing.Other uses of microemulsions in remediation include detoxification of mustard compounds.

***Influence of microemulsions on chemical reactions*:**
Due to varied consistencies and microstructures, microemulsions have been considered as useful reaction media for a variety of chemical reactions. These chemical reactions include Synthesis of nanoparticles , Polymerization, Photochemical, electrochemical & electrocatalytic reaction and Organic reactions.

***Novel Crystalline Colloidal Arrays As Chemical Sensor Materials*:**
Microemulsions as novel compartmentalized liquids have wide applications. Scientists are also in search of other novel self-organizing colloidal systems for important physico-chemical applications. The crystalline colloidal arrays (CCA) are new findings in this direction, which are prospective novel chemical sensors.

Use Of Microemulsions As Reaction Media:
Is compatible With the simultaneous use of other catalysts.Oil-in-water microemulsions based on a nonionic surfactant have been used as reaction media to oxidize aqueous azodyes.Addition of phase transfer agents enhance catalytic efficiency of microemulsions in the reaction of lipophilic epoxide with sodiumsulfite.

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