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ARE SMEDDs AND SNEDDs SAME? A GIMMICK OR PHARMACEUTICALLY RELEVANT

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ABSTRACT

From the last two decades, the area of pharmaceutically research is highly being diversified for generating newer and better self emulsifying system; from micron to nano size. The applications are wide and generally oriented towards an increase in the bioavailability of drugs, solubilized—due to their submicron size and great (kinetical or thermodynamical) stability of the suspensions—into the oil droplet core. In most of the articles and in litratutres the micro and nanoemulsions are being described indiscriminately. Although this misconception appears to be common, these two systems are fundamentally different, based on very different physical and physicochemical concepts. Their differences result in very different stability behaviors, which can have significant consequences regarding their applications and administration as nano medicines. In this article the attempt is being made to solve this misconception which will be beneficial to the formulation scientists and students. Finally, an illustration is given; how to clear up this misconception using simple experiments.

Key words: : *Microemulsion, Nanoemulsion, SEDDs, SMEDDs, SNEDDs*

INTRODUCTION

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists(1). Most of the drugs that are emerging from contemporary drug discovery programs are poorly water-soluble often present formulators with considerable technical challenges. The absorption of such compounds when presented in the crystalline state to the gastrointestinal tract is typically dissolution rate-limited, and the drugs are typically BCS class II or class IV compounds. The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, but care needs to be taken with formulation design to ensure consistent bioavailability(2). Essentially the options available involve either reduction of particle size (of crystalline drug) or formulation of the drug in solution, as an amorphous system or lipid formulations. The performance of amorphous or lipid formulations is dependent on their interaction with the contents of the gastrointestinal tract, therefore, a formulation exercise should involve the use of techniques which can predict the influence of gut physiology. A major consideration is the fate of metastable supersaturated solutions of drug, which are formed typically after dispersion of the formulation and its exposure to gastrointestinal digestion. A better understanding of the factors which affect drug crystallization is required, and the introduction of standardized predictive in vitro tests would be valuable (1-3). Lipid based formulation has offered variety of options like solutions, suspensions, solid dispersions and self emulsifying drug delivery systems. Amorphous formulations, such as 'solid dispersions' may allow drugs to disperse as supersaturated solutions, at least temporarily, but eventually the drug will relax into its most thermodynamically favourable crystalline state. At present the kinetics of crystallization cannot be predicted for an individual drug, which presents the formulator with some technical problems. In some cases crystallization takes place in minutes but in others the supersaturated system may be stable for many hours. It would be useful to establish an *in vitro* protocol which would serve to predict the fate of the formulation in the gut(4, 5).

Self-emulsifying drug delivery(SEDDs):

SEDDSs are isotropic mixtures of oils and surfactants; sometimes it contains co-solvents, and it can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SEDDSs emulsify spontaneously to produce fine oil-in- water emulsions when introduced into an aqueous phase under gentle agitation(1). SEDDS can be administered orally in soft or hard gelatin capsules. Self-emulsifying formulations spread readily in the gastrointestinal tract (GIT), and the GI motility of the stomach and the intestine provide the necessary agitation for self-emulsification. These systems

have the advantage that the drug is in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. SEDDSs typically produce emulsions with a droplet size between 100–300 nm however it may be from coarse to micron size while self-micro-emulsifying drug delivery systems (SMEDDSs) form transparent microemulsions with a droplet size of less than 50 nm. SEDDSs and self-nano-emulsifying drug delivery(SNEDDs) contains nanoemulsion with low quantity of surfactants(5). These are physically stable formulations that are easy to manufacture, but when compared with emulsions, which are sensitive and metastable dispersed forms. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. The process of self-emulsification proceeds through formation of liquid crystals (LC) and gel phases. Release of drug from SEDDSs is highly dependent on LC(liquid crystal) formed at the interface, since it is likely to affect the angle of curvature of the droplet formed and the resistance offered for partitioning of drug into aqueous media(6, 7). In short, SEDDs is a broad term which includes both SMEDDs and SNEDDs.

Microemulsion and SMEDDS

The Microemulsion concept was introduced as early as 1940s by Hoar and Schulman who generated a clear single-phase solution by titrating a milky emulsion with hexanol(8). Schulman and co-worker (1959) subsequently coined the term microemulsion(9). The microemulsion definition provided by Danielson and Lindman in 1981 will be used as the point of reference. Microemulsions are thermodynamically stable dispersions of oil and water stabilized by a surfactant and, in many cases, also a cosurfactant with globule diameter : 10-140 nm**.** Microemulsions can have characteristic properties such as ultralow interfacial tension, large interfacial area and capacity to solubilize both aqueous and oil-soluble compounds. "Microemulsions are dispersions of nanometer-sized droplets of an immiscible liquid within another liquid. Droplet formation is facilitated by the addition of surfactants and often also co surfactants." They can be known as Modern colloidal drug delivery system(10). The formulation of micro-emulsions corresponds to a thermodynamic equilibrium between all the compounds of the studied system (generally water, oils, and nonionic or ionic amphiphile molecules, with the optional addition of a co-solvent). In this respect, micro-emulsions are formed spontaneously, but a lot depends on the thermodynamic variables such as temperature and composition (and also, theoretically, pressure). Micro-emulsions exhibit a large range of structures, which involve the formation of one, two or three

phases in equilibrium in the flack. Each one of these phases can exhibit very different types of nanometric scaled morphologies of very different geometries which are, for example, worm-like, bicontinuous sponge-like, liquid crystalline, or hexagonal, spherical swollen micelles(11). Stable self-emulsifying water-in-oil (w/o) microemulsions of extremely small particle size (5-30 nm) and consisting of an oil, a blend of a low and high HLB surfactants and an aqueous phase, have been developed using commercially available and pharmaceutically acceptable components(12). A self microemulsifying drug delivery system (SMEDDS) is an anhydrous system of microemulsions. It has also been referred to as microemulsion preconcentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes from stomach and intestinal motility(13, 14). The nanosized droplets have very high surface to volume ratios which are able to efficiently solubilize the drug. The drug is released in a more reproducible manner which will become less dependent on the GI physiology and the fed/fasted state of the patient. Their formation was monitored by the corresponding pseudo-ternary phase diagram. To understand why a micro-emulsion is formed spontaneously, it is important to first consider the binary phase diagrams between each compound presented in Fig. 1.

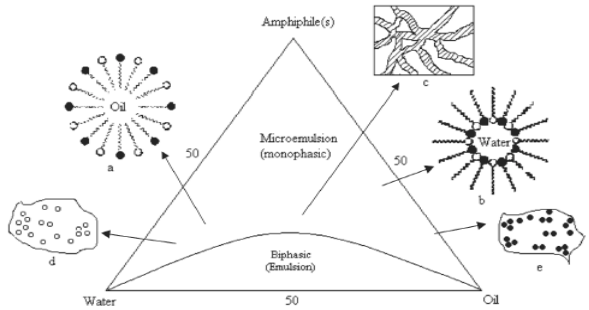

Fig. A ternary phase diagram portraying various structures a) o/w microemulsion; b) w/o microemulsion; c) bicontinuous microemulsion; d) and e) various dispersions.

Figure 1: Ternary phase diagram

Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating. Structurally, they are divided into oil-in-water (o/w), water in oil (w/o) and bicontinuous microemulsions. The formation of microemulsion is dependent on the temperature and the solubility of surfactant in both the phases(15). The oil phase contained long- or medium-chain triglycerides, and mono-/diglycerides or sorbitan esters (low HLB surfactants). Polysorbate 80 (Tween 80) was used as a high HLB surfactant, Microemulsions were readily prepared by admixing appropriate quantities of the various components with gentle hand-mixing or stirring to ensure thorough mixing. In the case of microemulsions incorporating long-chain glycerides and/or sorbitan esters, high temperature (40-60°C) was used to reduce viscosity and solubilize all components during the formation of microemulsions. Limited levels of aqueous phase (< 10%, w/w) can be solubilized within w/o microemulsions incorporating long-chain glycerides and/or sorbitan esters. Microemulsions containing medium-chain glycerides (mono-/di-/triglycerides) can be formulated at ambient temperature and can solubilize aqueous phase up to 40% (w/w)(16).

Nanoemulsion and SNEDDs

Nanoemulsions are submicron sized emulsions that are under extensive investigation as a drug carrier for improving drug delivery(17). Nano-emulsions consist of very small emulsion droplets, commonly oil droplets in water, exhibiting sizes lower than ~300 nm. These emulsions are easily produced in large quantities by mixing water-immiscible oil phase into an aqueous phase with a high stress(18). Like conventional emulsions (with sizes > µm),with thermodynamic point of view nanoemulsion exhibit non-equilibrium state. However, the kinetics of destabilization of nano-emulsions is so slow (~months) that they are considered kinetically stable. This is mainly due to their very small size, resulting in the prevention of droplet flocculation and coalescence: the Ostwald ripening alone governs the destabilizing process(18-20). Each type of the nanoemulsions serves as a template for preparing polymer latex particles, nanoporous polymeric solids etc. Apart from this, the nanoemulsions with pharmaceutically accepted ingredients are utilized in the development of drug formulations for oral drug delivery. Nanoemulsions are also referred as miniemulsions, ultrafine emulsions and submicron emulsions(11). The main application of nanoemulsion is the preparation of nanoparticles using a polymerizable monomer as the disperse phase (the so-called miniemulsion polymerization method) where Nanoemulsion droplets act as nonreactors. Another interesting application which is experiencing an active development is the use of Nanoemulsions as formulations, namely, for controlled drug delivery and targeting. The main application of nanoemulsions is the preparation of nanoparticles using a polymerizable monomer as the disperse phase where nanoemulsion droplets act as nonreactors(21). Nano-emulsions are generally formulated through the so-called “high-energy” methods, using specific devices (like ultrasound generators or high pressure homogenizers) able to supply enough energy to increase the water/oil interfacial area for generating submicronic droplets(17, 22). “Low-energy” methods also allow the formulation of nano-emulsions, but by spontaneous emulsification without requiring any device or energy(19, 23). This low-energy spontaneous emulsification is in fact an efficient method enabling the formation of kinetically stable and potentially concentrated emulsion droplets ranging in size from 10 nm to 300 nm. it is in fact the simplicity of the formulation process (simply mixing two liquid phases) which induces the confusion between nano-emulsions and micro-emulsions(24). The research project was done to develop SNEDDs for the noninvasive delivery of protein(25, 26). Solid self-nano-emulsifying drug delivery has solved the stability and leakage problem associated with the SNEDDs(27).

Difference between SMEDDs and SNEDDs

The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmes are poorly water-soluble(28). The problem is even more intense for drugs such as itraconazole and carbamazepine, as they are poorly soluble in both aqueous and organic media, and for drugs having a log P value of 2(29). Such drugs often have an erratic absorption profile and highly variable bioavailability because their performance is dissolution rate limited and is affected by the fed/fasted state of the patient. If a drug candidate has reasonable membrane permeability then often the rate-limiting process of absorption is the drug dissolution step(1). Much of the researches are being diversified to address such issue. Over the last decades, much research has been done on self-emulsifying systems generating nano-droplets. The applications are wide and generally oriented towards an increase in the bioavailability of drugs, solubilized—due to their submicronic size and great (kinetical or thermodynamical) stability of the suspensions—into the oil droplet core(24). The industrial scaling-up of the formulation process is very easy due to its simplicity(30). Research has also been done on the surface functionalization of such nano-particulate systems with different objectives, such as (a) increasing their stealth properties by grafting specific hydrophilic polymers onto the nanoparticle surfaces (i.e. inducing their persistence in the blood pool) or (b) tailoring their surface properties to receptors of specific sites or to a specific environment in order to perform, respectively, active or passive targeting(23, 31, 32). Mainly these emulsions are used as template and found application in therapeutics and diagnosis. There is often a mix-up between thermodynamically stable systems called micro-emulsions and thermodynamically unstable (but kinetically stable) systems called nano-emulsions. In a strict sense microemulsion is a one phase system while nano-emulsion is pure emulsion (terminology point of view). A microemulsion,

one of the pharmaceutical interests for new drug delivery, is normally composed of oil, water, surfactant, and cosurfactant. Hoar and Schulman were the first to introduce the word microemulsion, which they defined as a transparent solution obtained by titrating a normal coarse emulsion with medium-chain alcohols. The short to medium-chain alcohols are generally considered as cosurfactants in the microemulsion system. The presence of surfactant and cosurfactant in the system makes the interfacial tension very low. Therefore, the microemulsion is thermodynamically stable and forms spontaneously, with an average droplet diameter of 1 to 100 nm(9). These two systems are basically different in terms of thermodynamic stability. They differ notably in their behavior towards dilution or temperature fluctuations. Concretely, the nano-structures (morphology type and size) of microemulsions are strongly affected and even broken-up by temperature changes and/or dilutions, whereas nanoemulsion droplets will remain stable in such conditions of stress. This could have significant consequences on the target applications, notably inducing thermodynamic changes in function of the route of administration(33). Now, in the case of parenteral administration, thermodynamic variables will undergo significant changes, since the samples are diluted into the bloodstream. There will also be changes in potential temperature, pH and osmolarity: in this case, only nano-emulsions are suitable for use, since the droplets will remain stable in such environmental changes. Still you will find the article of parenteral microemulsions which generates confusion. These are basically nanoemulsion. For example, Corswant et al. (1998) were amongst the first to report development of parenteral microemulsions based on Solutol® HS 15, Soybean lecithin, ethanol, PEG 400 and MCT(34).

The physical degradation of nano-emulsions is due to the spontaneous trend toward a minimal interfacial area between the dispersed phase and the dispersion medium. Minimizing the interfacial area is mainly achieved by two mechanisms: first coagulation possibly followed by coalescence and second by Ostwald ripening. Coalescence is often considered as the most important destabilization mechanism leading to coursing of dispersions and can be prevented by a careful choice of stabilizers. The molecular diffusion of solubilizate (Ostwald ripening), however, will continuously occur as soon as curved interfaces are present. Mass transfers in emulsion may be driven not only by differences in droplet curvatures, but also by differences in their compositions. This is observed when two or more chemically different oils are emulsified separately and the resulting emulsions are mixed. Compositional ripening involves the exchange of oil molecules between emulsion droplets with different compositions. The stability of the electrostatically- and sterically stabilized dispersions can be controlled by the charge of the electrical double layer and the thickness of the droplet surface layer formed by non-ionic emulsifier. In spite of the similarities between electrostatically- and sterically-stabilized emulsions, there are large differences in the partitioning of molecules of ionic and non-ionic emulsifiers between the oil and water phases and the thickness of the interfacial layers at the droplet surface. The thin interfacial layer (the electrical double layer) at the surface of electrostatically stabilized droplets does not create any steric barrier for mass transfer. This may not be true for the thick interfacial layer formed by non-ionic emulsifier. The interactive sterically-stabilized oil droplets, however, can favor the transfer of materials within the intermediate agglomerates. The stability of electrosterically-stabilized emulsion is controlled by the ratio of the thickness of the non-ionic emulsifier adsorption layer (delta) to the thickness of the electrical double layer (kappa(-1)) around the oil droplets (delta/(kappa(-1))) = (deltakappa). The monomer droplet degradation can be somewhat depressed by transformation of coarse emulsions to nano-emulsion (miniemulsion) by intensive homogenization and by the addition of a surface active agent (coemulsifier) or/and a water-insoluble compound (hydrophobe). The addition of hydrophobe (hexadecane) to the dispersed phase significantly retards the rate of ripening. A long chain alcohol (coemulsifier) resulted in a marked improvement in stability, as well, which was attributed to a specific interaction between alcohol and emulsifier and to the alcohols tendency to concentrate at the o/w interface to form stronger interfacial film. The rate of ripening, according to the Lifshitz-Slyozov-Wagner (LSW) model, is directly proportional to the solubility of the dispersed phase in the dispersion medium. The increased polarity of the dispersed phase (oil) decreases the stability of the emulsion. The molar volume of solubilizate is a further parameter, which influences the stability of emulsion or the transfer of materials through the aqueous phase. The interparticle interaction is expected to favor the transfer of solubilizate located at the interfacial layer. The kinetics of solubilization of non-polar oils by ionic micelles is strongly related to the aqueous solubility of the oil phase (the diffusion approach), whilst their solubilization into non-ionic micelles can be contributed by interparticle collisions. In short the kinetically stable nanoemulsions are thermodynamically unstable which gives idea as well as provides proof that it is a biphasic system[35].

Another difference which is based on formulation and which surely provides immunity to this scientific context is order of mixing. nano-emulsions are only formed if surfactants are first mixed with the oily phase. If they are first mixed with water before adding the oily phase, only a “macroscopic” emulsion will be generated. Micro-emulsions, on the other hand, will be strictly identical whatever the order in which the compounds are mixed (after equilibration time). This point is very important and constitutes a preliminary test for characterizing the nature of the dispersion obtained. Furthermore, the method commonly used to characterize nano-systems can also strongly affect the structural properties of the samples. For example, dynamic light scattering (DLS, providing the size distribution of the dispersions) often requires a sample dilution prior to measurement. As mentioned above, this dilution, in the case of micro-emulsions, results in a modification of the size of the swollen micelles, which simply invalidates the characterization and can even lead to the destruction of the micelles. In the case of nano-emulsions, such a dilution does not have any influence on the droplet size and size distribution[24].

This confusion between nano-emulsions and micro-emulsions is due to several reasons. The first one is from the very similar structural and visual aspects of these two systems in specific experimental conditions. The second one concerns the formulation processes which can also be very similar between spontaneous nano-emulsification and the self formation of nano-emulsions. Finally, the third reason which has allowed this confusion to thrive is the lack of knowledge of the two latter points24.

Following the above discussion, some experimental procedures can be followed to definitively clarify the nature of the formulated system: (a) the dilution of the sample with the continuous phase (water here) should decrease the size measured by DLS in the case of micro-emulsions, up to the complete solubilization of oil in water; conversely, dilution will have no influence on nanoemulsion droplet size, varying the temperature can strongly affect the structures and measured size of micro-emulsions, which can even cross a phase boundary when the temperature is raised; however, temperature increase has no immediate effect on the structure of nano-emulsions (it can accelerate their destabilizing process). Lastly and more generally, when the work carried out is truly with micro-emulsions, the phase diagram established should be coherent with the theory presented in Fig. 1.

CONCLUSION

In this article, an attempt is made to clarify the recurrent confusion found in the literature concerning research on self-emulsifying drug delivery systems. The formulation scientists are generally not familiar with the physical definition and physicochemical behaviors of the ternary systems forming nano-emulsions and micro-emulsions. This results in phenomenological problems in the characterization of the formulated systems, as much as in their applications. This article is grafted to clarify the confusion between nano-emulsions and a microemulsion appears in the literature and how most professed micro-emulsion systems are actually nano-emulsions. In both the system drug is given in solubilized form where micro system is one phasic with swollen micells while nanoemulsion is true emulsion.

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