

Nano-emulsions and Micro-emulsions: Clarifications of the Critical Differences

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ABSTRACT Much research has been done over the past years on self-emulsifying drug delivery systems, their main interest being the simplicity of the formulation processes, the great stability of the systems and their high potential in pharmaceutical applications and industrial scaling-up. Self-emulsifying drug delivery systems are generally described in the literature indiscriminately as either nano-emulsions or micro-emulsions. 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 nanomedicines. This paper aims at clarifying the problem, first by reviewing all the physical and physicochemical fundamentals regarding these two systems, using a quantitative thermodynamic approach for micro-emulsions. Following these clarifications, we show how the confusion between nano-emulsions and micro-emulsions appears in the literature and how most of the micro-emulsion systems referred to are actually nano-emulsion systems. Finally, we illustrate how to clear up this misconception using simple experiments. Since this confusion is well established in the literature, such clarifications seem necessary in order to improve the understanding of research in this important field.

KEY WORDS emulsion · micro-emulsion · nano-emulsion · SEDDS · self-emulsifying drug delivery system

SCIENTIFIC CONTEXT

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. The many advantages of these systems lie in the self-emulsifying features of the processes themselves, which not only stem from their simplicity (as we will see below), but also from the very low energetic yields involved, thus showing great potential for use in industrial scaling-up (1,2). Research has also been done on the surface functionalization of such nanoparticulate systems with different objectives (5,14,15,22), 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. To this aim, the study of these nanoparticulate systems, so-called *templates*, and their generating processes, appears of fundamental importance since it should precede research on applications such as therapeutics and diagnosis. Such research on applications requires an understanding of the mechanisms of nano-droplet generation and their structural stability and thermodynamic behaviors. In the literature, these latter points appear somewhat confused. There is often a mix-up between thermodynamically stable systems called *micro-emulsions* and

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thermodynamically unstable (but kinetically stable) systems called *nano-emulsions*.

Apart from the terminology itself, these two systems are basically different in terms of thermodynamic stability. They differ notably in their behavior towards dilution or temperature fluctuations. Concretely (see below for details), the nano-structures (morphology type and size) of micro-emulsions are strongly affected and even broken-up by temperature changes and/or dilutions, whereas nano-emulsion 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 (16). For example, 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.

Examples of this misconception abound in the literature of the past 30 years, especially in research works published in pharmaceutical journals and dealing with nanopharmaceutics and nano-particulate formulations. The problem no doubt originates from the fact that in particular experimental conditions, with certain compositions and temperatures, micro-emulsions can strongly resemble nano-emulsions, exhibiting a very similar morphology in the form of spherical “nano-droplets” dispersed in a continuous phase, the so-called *swollen micelles* configuration. This often leads to a misinterpretation of the properties of the systems generated, resulting in inappropriate objectives and methods used to characterise the systems (*e.g.* building up ternary phase diagrams with a nano-emulsion system—a pointless and erroneous practice often carried out—see below for details and illustrations).

Bearing in mind this context, this review aims at highlighting this problem and providing clarification, giving the reader the keys to understand its origins, why it still persists in the literature, and also and above all, how the formulation processes can be analyzed with simple experimental procedures in order to grasp the nature of the nano-systems formed. In a first part, nano-emulsion and micro-emulsion systems are thoroughly examined from a quantitative thermodynamic point of view, illustrated by the model systems encountered in literature. The extent to which micro-emulsions exhibit the nano-emulsion-like droplets (*i.e.* swollen micelles) is presented, along with the impact of the composition and thermodynamic changes on their morphology, size, and stability. Finally, in this part, we also deal with the consequences on the formulation procedures.

Following these clarifications, based on illustrations provided by the literature regarding these “self-emulsifying

drug delivery systems,” the second part of the paper focuses on why and how this misconception has become commonly accepted and how it can be simply detected—by analyzing the texts, the experimental protocol, or the phase diagrams. Simple experimental procedures are also proposed in order to easily differentiate the two systems.

THE SELF-NANO-EMULSIFYING SYSTEMS

Nano-emulsions

Nano-emulsions consist of very small emulsion droplets, commonly oil droplets in water, exhibiting sizes lower than ~300 nm. Like conventional emulsions (with sizes > μm), nano-emulsions are, from a thermodynamic point of view, in a 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 (1,2,6,18–20).

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 (3,4).

“Low-energy” methods also allow the formulation of nano-emulsions, but by spontaneous emulsification without requiring any device or energy (1,2,20). Low-energy methods take advantage of the intrinsic physicochemical properties of the components in order to generate submicronic droplets. In short (1), the process only consists in mixing two liquid phases at room temperature, one containing a lipophilic phase into which a hydrophilic surfactant is solubilized to form a homogeneous liquid (plus potentially a solvent, polymer, or drug) and the other an aqueous phase, which can be pure water. Once these two liquids are brought into contact, the hydrophilic species contained in the oily phase (*i.e.* surfactants) is rapidly solubilized into the aqueous one, inducing the demixtion of the oil in the form of nano-droplets, immediately stabilized by the amphiphiles. The droplet size of nano-emulsions is easily controllable in function of the oil/surfactant weight ratio.

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. As discussed further in this work, 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.

Micro-emulsions

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 flask. Each one of these phases can exhibit very different types of nanometric-scaled morphologies (10) of very different geometries which are, for example, worm-like, bicontinuous sponge-like, liquid crystalline, or hexagonal, spherical swollen micelles. These systems share a common size range of the geometrical structures which are exclusively in the nanometric range, giving them a bluish and translucent aspect.

In this paper, we will limit the demonstration to a simple model composed of a polar protic solvent (*e.g.* water), a nonpolar oil (*e.g.* alkane), and a short-chain nonionic amphiphile (*e.g.* alkylpolyglycoether C_iE_j), since it can be described exactly in a three-dimensional temperature-composition diagram (8–11,13). The generation of micro-emulsion using ionic amphiphiles, or electrolytes, involves other dimensions due to the presence of additional compounds. In order to simplify the discussion, we will not deal with such cases here, but they are described in detail in the literature (7–12).

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 (top part). The nonionic surfactants present two solubility gaps with oil and water in function of the temperature, denoting that (a) the solubility of the amphiphiles changes considerably with the temperature and (b) a partial miscibility of the amphiphiles between water and oil at the interplay between the two binary gaps, gives rise to the micro-emulsion structures and notably the separation into three phases.

Now, the phase behaviors of the ternary mixture, reported in Fig. 1, clearly highlight the physical origins of the micro-emulsion nano-structures. Let us first consider a given system (called S_1 in Fig. 1) on the Water–Oil binary diagram and take as an example a temperature noted T_1 higher than the cloud point in oil or critical point, cp_α . This system S_1 presents in the flask of course an equilibrium between the two non-miscible phases which are pure water and pure oil. Then, nonionic amphiphiles are added to S_1 , still at constant temperature T_1 , giving a ternary system named S_2 in Fig. 1. Since at T_1 the surfactants are hydrophilic, they are naturally solubilized by the aqueous

phase. Above the critical micellization concentration (CMC), thermodynamic phenomena cause the surfactant self-association to form—in the simpler case we have chosen to illustrate here—spherical micelles. These micelles present a hydrophobic core able to solubilize a small amount of oil, which they actually do in S_2 . Thus, the oil causes the micelles to “swell,” creating “swollen micelles” in the aqueous phase, still in equilibrium with the oil excess. These swollen micelles generally range in size below 100 nm (10,13). This aqueous phase is what is known as micro-emulsion (the global system S_2 is called Winsor I). Now, if a given amount of oil in S_2 is removed to reach the point S_3 (still at a constant temperature), the whole system becomes a one-phase micro-emulsion system solely composed of spherical swollen micelles dispersed in water (called Winsor IV since it is a one-phase system). Understanding these S_3 -like systems is of fundamental importance in the present article, since it is precisely this sort of micro-emulsion that is structurally identical to the nano-emulsion described in section “Nano-emulsions,” and thus the origin of the confusion between the two systems.

In addition, as the surfactant amount is increased in the ternary system, the Winsor IV micro-emulsions can “disperse” higher amounts of oil in water than those of S_3 , lowering the solubility gap. In this case, however, the micro-emulsion structures are no longer in the form of spherical oil-swollen micelles in water, but can adopt various configurations, as for instance worm-like, bicontinuous sponge-like, liquid crystalline, hexagonal (named “structured phases in water,” S_4 at T_1 in Fig. 1).

This phase behavior also depends on the temperature, which can change the affinity of nonionic amphiphiles. Nevertheless, the behavior described above for T_1 remains true up to the critical end point cep_β . Thus, between cep_β and cep_α , the amphiphile affinities for the aqueous and oily phases are similar, and the micro-emulsions formed are in equilibrium with both water and oil excesses (as shown in S_5 at T_2). Next, as the temperature is increased, the surfactants become more lipophilic and may, for instance, form water-swollen micelles in oil (S_6 at T_3) at temperatures higher than cep_α .

Research in nano-pharmaceutical formulation is generally focused on simple systems exhibiting spherical-shaped oil-swollen micelles dispersed in water, *i.e.* S_3 . The examples presented above were therefore deliberately chosen to illustrate the drastic thermodynamic limits conditioning the stability of such an S_3 system. To summarize, the S_3 -like micro-emulsion-forming domains are reported as squared areas in Fig. 1. There are two possible ways to induce the break-up of S_3 -like systems: The first occurs when a change in composition and/or temperature makes the system cross a phase frontier in the phase diagram, resulting in a phase separation. The micro-emulsions are in equilibrium with oil

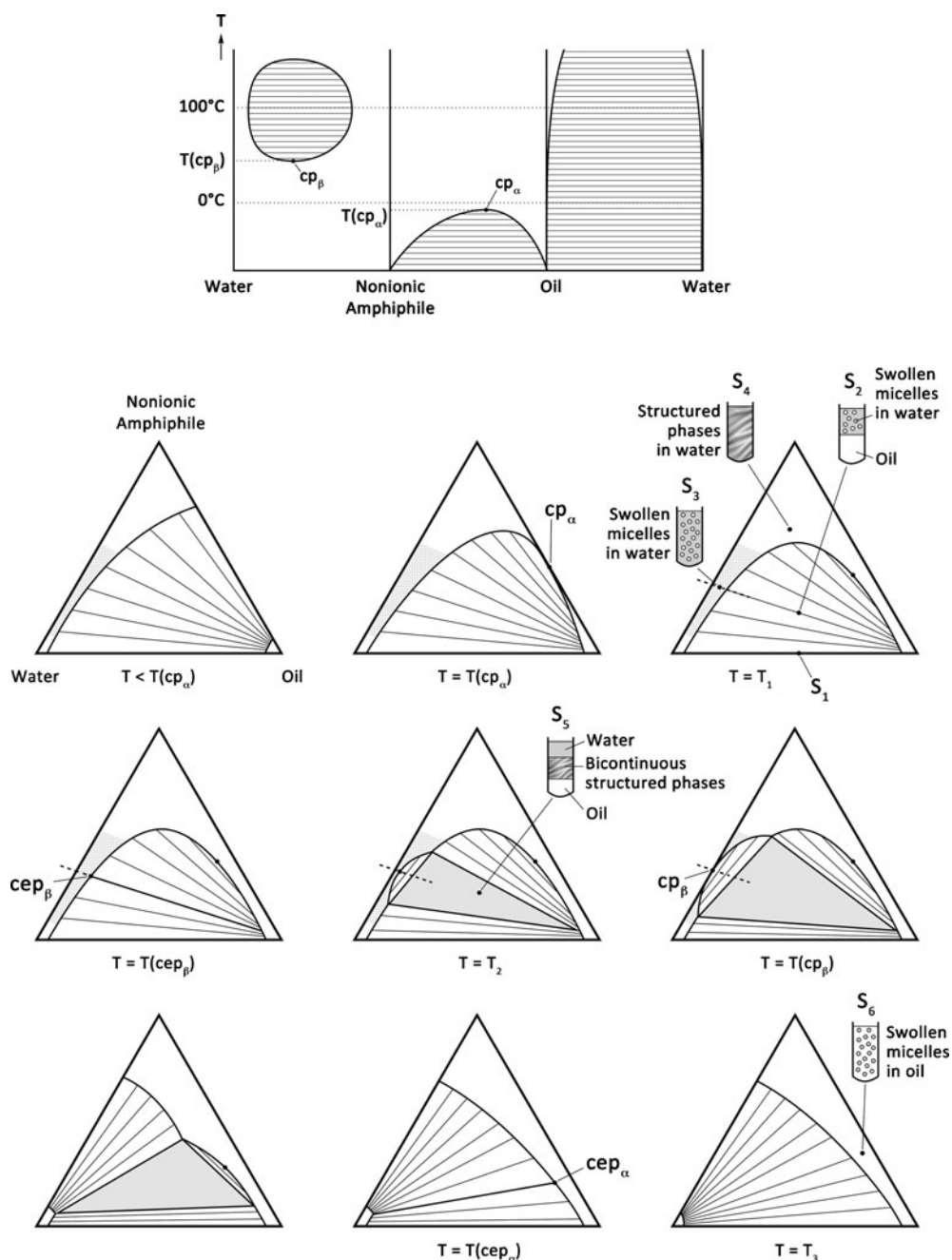


Fig. 1 Schematic phase behavior of a water/oil/nonionic surfactant ternary system with raised temperature (see details in the text).

(Winsor I, *e.g.* S_2), water (Winsor II, *e.g.* S_3 but at T_2 or T_3), or both (Winsor III, *e.g.* S_5). The second possibility induces the destabilization of S_3 -like systems and is illustrated with the passage from S_3 to S_4 . The one-phase Winsor IV aspect of the samples is preserved, but the spherical-shaped structure of the swollen micelle microemulsion itself is broken-up.

The region of interest in nano-pharmaceutical formulation, whereby spherical-shaped one-phase micro-emulsions are formed, appears rather limited, surrounded by (a) the changing composition and/or temperature to reach phase

frontiers and (b) the change in morphology, as seen above. Moreover, compared to nano-emulsions which can form concentrated nano-dispersion of oil in water (up to 70–80 wt.% for instance), the oil concentration in the S_3 -like systems does not exceed a small percentage of oil dispersed in water. In order to appreciate the effect of temperature on the micro-emulsion-forming domain, let us consider the vertical section through the water-rich corner, in Fig. 2 (a), corresponding to the dashed lines in the ternary phase diagrams of Fig. 1 from $T = T_1$ to $T = T(cp_\beta)$. This figure clearly shows and confirms the limited stability conditions

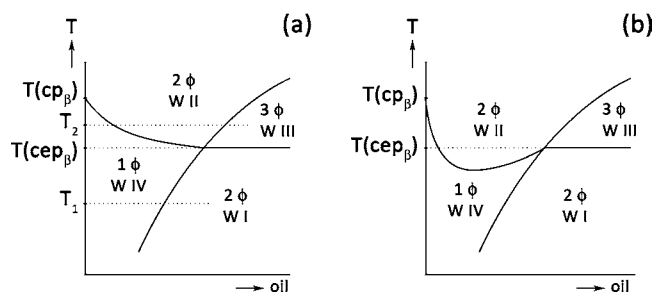


Fig. 2 Vertical section through the water-rich corner of the ternary system phase behavior at fixed amphiphile concentration, corresponding to the *dashed lines* in the ternary phase diagrams of Fig. 1.

of the (macroscopically) homogeneous S_3 -like oil-in-water micro-emulsions. Our presentation has focused on short-chain nonionic amphiphiles. However, long-chain amphiphiles even further restrict the forming S_3 -like micro-emulsion domain, as shown in Fig. 2 (b). The solubility limit arises below $T = T(\text{cep}_\beta)$. This behavior of course also depends on the nature of the aqueous and oily phases, as described in the works of Kahlweit *et al.* (12). This case is of fundamental importance since it also reflects numerous cases encountered in the literature, in research focused on self-emulsifying nano-pharmaceutics (*e.g.* (1,17,21,23)), notably the formulations intended for parenteral administration. Manufacturers propose a wide range of purified long-chain surfactants, recognized for their self-emulsifying properties (forming nano-emulsions or micro-emulsions), but also for specific stealth properties induced by their hydrophilic parts (*e.g.* PEG).

Finally, even when the ternary system is placed into the S_3 -like micro-emulsion-forming domain presented above, the morphology, size and shape of the swollen micelles themselves can change in function of the temperature and/or the composition, as described in detail in the works of Kahlweit *et al.* (13). This shows that the stability of such systems is both relative and quite sensitive to weak fluctuations or variations in temperature and composition. To illustrate this, let us consider the use of such micro-emulsions in the administration of drugs. For instance, using the parenteral route, drugs are solubilized in oil within the micelles. In this case, injecting the micro-emulsion into the bloodstream intravenously could have multiple consequences, since it involves a change in temperature as well as an aqueous dilution of the sample. These environmental variations can result in (a) reaching the limit of the micro-emulsion stability domain in case of an increased temperature as illustrated in Fig. 2 or (b) lowering the relative concentrations of oil and surfactant in the case of diluting the sample. The micelle size can be lowered to reach the CMC and then simply destroyed. Consequently, the potentially encapsulated drugs will precipitate, inducing embolism and/or a loss in the

required targeting properties. When administered orally, drug precipitation in the intestinal tract can considerably decrease its absorption. Compared to micro-emulsions, nano-emulsions can undergo temperature changes and dilution without such rapid destabilization: they are fairly robust systems, adapted, for instance, to the conditions imposed by parenteral administration.

The Confusion Between the Formulation Processes of Nano-emulsions and Micro-emulsions

The confusion between nano-emulsions and micro-emulsions is, in fact, as much a result of their formulation processes as of their structural (macroscopical and molecular) aspects, both being to some extent very close.

However, one fundamental point often neglected in the literature when it comes to determining whether the systems in question are nano-emulsions or micro-emulsions is the influence of the order in which the different compounds are mixed during formulation. In fact, in nano-emulsion formulation, this order is very important (see section “Nano-emulsions”), and 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.

Bearing in mind these clarifications and for all the physical reasons presented in the above sections, we will see that most examples referred to as “micro-emulsions” in the literature are actually “nano-emulsions.”

More worryingly, some of the experiments given in the literature are carried out with the premise of dealing with micro-emulsions, whereas they are in fact using nano-emulsions. They therefore lose their meaning, and the subsequent results are erroneous. Take, for example, the establishment of ternary phase diagrams supposedly formulated using micro-emulsions. The titration method

which consists in fixing the {oil + surfactant} amount in the formulation and gradually adding water is particularly problematic, as the procedure carried out is exactly identical to the one used for nano-emulsion formulation. Therefore, when work is done with the actual aim of forming nano-emulsions, using a very limited amount of water, very concentrated, opaque, milky nano-emulsions are generated, which can even contain heterogeneous phases. Increasing the amount of water towards the water-rich corner will only result in the dilution of the already formed droplets, forming translucent and transparent samples. This transition between milky, opaque, concentrated nano-emulsions and bluish, translucent, diluted nano-emulsions is often wrongly interpreted as a phase transition, and based on this misinterpretation, authors build “ternary phase diagrams” which are in fact not phase diagrams at all. Such errors are often found in the literature and can easily be disclosed in cases where these “diagrams” have no link with the global theoretical aspects, as presented above in Fig. 1. This is a major source of confusion and a problem that needs to be addressed.

The literature reports a plethora of publications dealing with self-emulsifying lipid nano-dispersion solubilizing a given bioactive molecule. Generally, the authors briefly present their formulation, the processes involved, the characterization (DLS), but here again build a “pseudo-ternary” diagram (see above) and then present the potential applications, for instance, in terms of drug delivery, *in vitro* or *in vivo* assays, *etc.* This article certainly does not call into question the validity of the applications and biological evaluations of the results obtained in the above-mentioned research, but aims rather at pinpointing the multitude of terms indiscriminately used, as much as the inappropriate characterization of the formulations. For example, these systems can be called “self-emulsifying drug delivery systems” (SEDDS), “self-micro-emulsifying drug delivery systems” (SMEDDS), “self-nano-emulsifying drug delivery systems” (SNEDDS), *etc.* and are presented as forming either emulsion droplets, micro-emulsions, or nanoglobules, a further lack of clarity that fosters confusion. Even, the term “self-micro-emulsifying drug delivery systems” is meaningless, since, by definition, micro-emulsions are formed spontaneously. It would appear that the problem lies in a certain lack of awareness of the basic underlying physics involved in micro-emulsion formation, as for instance the quantitative approach presented here. This fundamental problem helps perpetuate the confusion.

This tendency to confuse the two systems has previously been underlined in the literature, but has not been treated in-depth. That is, although micro-emulsion systems are well distinguished from nano-emulsions obtained by low-energy nano-emulsification, the low-energy nano-emulsification described in the literature is, in fact, restricted to the phase

inversion temperature method (PIT method). This PIT method follows an experimental procedure which is not really comparable to the self-generation of micro-emulsions or self-emulsification described in section “Nano-emulsions,” since it involves playing on temperature in a specific way in order to generate nano-emulsion droplets (1). Let us not forget that both nano-emulsions and micro-emulsions can be spontaneously formed, and, in this case, the formulation process and characteristics are so close they may be confused. As previous literature did not address this aspect, limiting the discussion to “self-emulsification” of microemulsions on the one hand and the PIT method on the other, this confusion has continued to thrive. In light of our recent works on the understanding of low-energy nano-emulsification processes (1), the “self-emulsification” described earlier may also include low-energy nano-emulsification processes other than the PIT method (*e.g.* the ones described in section “Nano-emulsions”). This is exactly where there is considerable misunderstanding in the literature concerning these formulation processes themselves. In fact, the PIT method as well as the spontaneous nano-emulsification method (forming nano-emulsions) are governed by a unique mechanism giving rise to exactly the same nano-emulsion systems (1).

Finally, the literature also provides a raft of articles, including recent publications, illustrating this misconception and thus highlights the urgent nature of the situation. A typical example can be found in the formulation of micro-emulsions called SMEDDS, used for instance as a nano-vehicle (size < 100 nm) for lipophilic anti-malarial delivery. The results obtained are interesting, but the study is subject to the conceptual problem presented above, and the nano-systems are very likely to be nano-emulsions rather than the micro-emulsions they are professed to be. As mentioned above, the ambiguity is due to the formulation process, described in two steps, first mixing oil, surfactant and co-surfactant and then adding water to this mixture (a process that corresponds as much to the formulation of nano-emulsions as to that of micro-emulsions). Further, the problem comes from the experimental procedure used to determine the “mean globule size.” In certain cases, samples were diluted prior to performing measurements, which for micro-emulsions is pointless. In these cases, according to the phase diagram, this dilution with water should have resulted in crossing the phase separation frontier, giving rise to a dephasing (Winsor I) between swollen micelles and excess oil. The system described seems very likely to be forming nano-emulsions rather than micro-emulsions. Exactly the same problem can be found in a number of other papers, in which these two concepts are commonly confused. For instance, a self-emulsification process was presented, characterized by the establishment of equilibrium phase diagrams after the SEDDS formula-

tion (by adding distilled water to a mixture of oil, surfactant and drugs), which is coherent if the SEDDS are micro-emulsions, but the authors referred to their system as one for nano-emulsions and used it as such, by measuring the “mean emulsion droplet diameter” after water dilution (1,333 times), which is not coherent if the SEDDS are micro-emulsions.

In another example, the titration method was used, and the “droplet” sizes analyzed by dynamic light scattering after diluting in 1,000 times the sample with water (which is not compatible with a micro-emulsion). Likewise, the phase separation boundary was established by simple observation, discerning the “turbid” samples from the “nonturbid” ones, thus corroborating our earlier remark on the titration method, which could correspond exactly to the dilution of nano-emulsions. Our aim here is not to single out any particular research group (which explains why no references are provided), but to focus on the problem itself and, in citing these examples taken from the literature, to highlight the extent of the confusion as well as the urgent need to address the issue.

To summarize, this confusion between nano-emulsions and micro-emulsions is due to several reasons. The first one stems from the very similar structural and visual aspects of these two systems in specific experimental conditions, as presented in detail in this paper. 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 points.

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 (see above and Ref. (13)), up to the complete solubilization of oil in water; conversely, dilution will have no influence on nano-emulsion droplet size; (b) as presented in Fig. 2, 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 Figs. 1 and 2.

CONCLUSION

In this article, we have endeavoured to highlight a recurrent confusion found in the literature concerning

research on self-emulsifying drug delivery systems. The problem stems from the fact that pharmaceutical formulators 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. In this article, we first review all the physical and physicochemical fundamentals regarding these two systems, notably through a quantitative thermodynamic approach for micro-emulsions. Then, following these clarifications, we show how the confusion between nano-emulsions and micro-emulsions appears in the literature and how most professed micro-emulsion systems are actually nano-emulsions. We suggest simple experiments to help clear up this misunderstanding. Given that the confusion between these two systems is unfortunately well-established in the literature, we feel that the clarifications proposed here are more than necessary to improve the understanding of future research in the interesting field of self-emulsifying drug delivery systems.

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