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OPINION

Nanoemulsions versus microemulsions: terminology, differences, and similarities

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Colloidal delivery systems based on microemulsions or nanoemulsions are increasingly being utilized in the food and pharmaceutical industries to encapsulate, protect, and deliver lipophilic bioactive components. The small size of the particles in these kinds of delivery systems ($r < 100$ nm) means that they have a number of potential benefits for certain applications: enhanced long-term stability; high optical clarity; and, increased bioavailability. Currently, there is considerable confusion about the use of the terms “microemulsions” and “nanoemulsions” in the scientific literature. However, these are distinctly different types of colloidal dispersions: a microemulsion is thermodynamically stable, whereas a nanoemulsion is not. It is therefore important to distinguish between them since this impacts the methods used to fabricate them, the strategies used to stabilize them, and the approaches used to design their functional attributes. This article reviews the differences and similarities between nanoemulsions and microemulsions in terms of their compositions, structure, fabrication, properties, and stability. It also attempts to highlight why there has been so much confusion in this area, and to clarify the terminology used to refer to these two kinds of colloidal dispersion.

1. Introduction

There has been considerable interest within the food, pharmaceutical, agrochemical and other industries in using colloidal dispersions to encapsulate, protect, and deliver bioactive lipophilic components, such as nutraceuticals, drugs, vitamins, antimicrobials, and antioxidants.^{1–7} Colloidal dispersions generally consist of a suspension of small particles distributed within a liquid medium. For certain applications, it is desirable to utilize colloidal dispersions containing very small particles (radius < 100 nm) since they have a number of potential advantages over systems containing larger particles. First, they usually have better stability to particle aggregation and gravitational separation.⁶ Second, they contain particles that only scatter light waves weakly, and so they are

suitable for incorporation into products that need to be optically clear or only slightly turbid.^{5,7,8} Third, they can often be designed to have novel rheological properties, *e.g.*, high viscosity or gel-like characteristics.^{5,6,9} Fourth, they may be able to increase the bioavailability of certain types of bioactive lipophilic substances encapsulated within them.^{4,10} A great deal of recent research has therefore been devoted to fabricating, characterizing, and utilizing colloidal dispersions containing very fine particles as delivery systems.

In this article, we focus on those colloidal dispersions that can be fabricated from oil, water, and surfactants, which are widely used as delivery systems in a range of different industries. The two most common types of colloidal dispersions that can be created from these components are *microemulsions* and *nanoemulsions*. There are many structural similarities between these two kinds of colloidal dispersion, but there are also some important differences.¹¹ Nevertheless, there has been great confusion about

the precise nature of these different systems, and there have been widespread errors in the classification of colloidal dispersions reported in the scientific literature. For example, some researchers have clearly prepared microemulsions but referred to them as nanoemulsions, and *vice versa*. It is important to accurately specify the kind of colloidal dispersion used in a particular study because this influences the most appropriate methods used to fabricate them, the major factors impacting their stability, and their physicochemical and functional properties. The purpose of the current article is to review the similarities and differences between microemulsions and nanoemulsions, to clarify the terminology used to describe them, and to suggest practical methods of distinguishing them from each other. This article covers some of the same ground as a recent article that discussed the critical differences between nanoemulsions and microemulsions in pharmaceutical applications, with special emphasis on understanding the phase diagrams of surfactant–oil–water

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systems.¹¹ Nevertheless, the current article presents a different approach for distinguishing between nanoemulsions and microemulsions based on free energy diagrams that highlight the importance of both thermodynamic and kinetic effects. In addition, it highlights some of the difficulties in developing practical methods of experimentally distinguishing nanoemulsions from microemulsions, and possible methods to overcome them.

Commercially nanoemulsions and microemulsions are commonly developed to encapsulate lipophilic components so that they can be dispersed into an aqueous medium, and so we restrict ourselves to consideration of oil-in-water (O/W) type systems in this article. However, it should be stressed that it is also possible to prepare water-in-oil (W/O) type nanoemulsions and microemulsions, and that these colloidal dispersions also have important applications in certain industries.

1.1. Terminology

Initially, we begin by describing and clarifying some of the terminology commonly used to refer to microemulsions and nanoemulsions.

1.1.1. Microemulsions. The term “microemulsion” is generally usually used to refer to thermodynamically stable isotropic liquids formed by mixing oil, water, and surfactants together.^{12,13} Mixtures of oil (O), water (W), and surfactant (S) can form a variety of different systems depending on their composition and the environmental conditions (particularly temperature). They may form one, two, three or more separate phases that are in equilibrium with each other. These phases may be water-continuous, oil-continuous, or bi-continuous depending on the concentrations, nature, and arrangements of the molecules present. The structures within these phases may be spheroid (*e.g.*, micelles or reverse micelles), cylinder-like (such as rod-micelles or reverse micelles), plane-like (*e.g.*, lamellar structures), or sponge-like (*e.g.*, bicontinuous).¹² Appropriate analytical methods are required to accurately identify the structures formed within a SOW system under a particular set of conditions, such as microscopy (*e.g.*, light, electron, or

atomic force), scattering methods (*e.g.*, light, X-ray, or neutrons), electrical conductivity, nuclear magnetic resonance, and rheology. When using the term “microemulsion” one must therefore clearly state which kind of microemulsion system is being considered. In this manuscript we are primarily concerned with delivery systems that can be used to encapsulate lipophilic components in a form that can be conveniently dispersed into aqueous media, and so we focus on *oil-in-water microemulsions* that consist of small spheroid particles comprised of oil and surfactant molecules dispersed within water. This type of colloidal dispersion has also been referred to as a “droplet microemulsion” or a “swollen micelle system”.¹⁴ The following definition is proposed to describe this type of oil-in-water microemulsion:

- An oil-in-water microemulsion is a thermodynamically stable colloidal dispersion consisting of small spheroid particles (comprised of oil, surfactant, and possibly co-surfactant) dispersed within an aqueous medium.

The surfactant molecules in an oil-in-water microemulsion are organized so that their non-polar tails associate with each other forming a hydrophobic core (Fig. 1), since this reduces the thermodynamically unfavorable contact area between non-polar groups and water. The hydrophilic head groups of the surfactant molecules protrude into the surrounding aqueous phase. Oil molecules may be incorporated into the hydrophobic interior of a micelle as a separate core or between the surfactant tails (Fig. 2). If the oil molecules have some polar groups, then they may be incorporated into the micelle in such a way that these groups interact with polar groups on the surfactant head groups or protrude some distance into the water.

Although the final system used to encapsulate a lipophilic component may be an oil-in-water microemulsion, it is possible to encapsulate a lipophilic component within other kinds of microemulsion system first (*e.g.*, W/O or bi-continuous) and then dilute them to the final O/W form using a suitable solution. This is the basis of the self-micro-emulsifying drug delivery systems (SMEDDS) developed for utilization within the pharmaceutical industry.¹⁵ In this case, it is particularly important to understand the

phase behavior of the surfactant-oil-water system, so as to identify the optimum composition of the initial system and the optimum method to dilute it.

1.1.2. Nanoemulsions. A nanoemulsion can be considered to be a conventional emulsion that contains very small particles.^{5,6} Nanoemulsions may be of the oil-in-water (O/W) or water-in-oil (W/O) types depending on whether the oil is dispersed as droplets in water, or *vice versa*. As mentioned previously, we are primarily concerned with colloidal dispersions suitable for encapsulating lipophilic components in aqueous environments, and so we focus on *oil-in-water nanoemulsions* that consist of small particles comprised of oil and surfactant molecules dispersed within an aqueous medium. The following definition is proposed to describe oil-in-water nanoemulsions:

- An oil-in-water *nanoemulsion* is defined as a thermodynamically unstable colloidal dispersion consisting of two immiscible liquids, with one of the liquids being dispersed as small spherical droplets ($r < 100$ nm) in the other liquid.

In principle, a nanoemulsion could be formed from oil and water without using a surfactant. In practice, this system would be highly unstable to droplet coalescence and a surfactant is needed to facilitate the formation of the nanoemulsion and to ensure its kinetic stability during storage.¹⁶ Sometimes a combination of surfactants rather than a single surfactant are used to form and stabilize nanoemulsions. A nanoemulsion is therefore usually prepared using the same components as a microemulsion: oil, water, surfactant and possibly a co-surfactant. The structure of the particles in a nanoemulsion are also very similar to those found in a microemulsion: the non-polar tails of the surfactant molecules protrude into the hydrophobic core formed by the oil phase, while the polar head groups of the surfactant molecules protrude into the surrounding aqueous phase (Fig. 1). The major distinction between a nanoemulsion and a microemulsion is therefore their thermodynamic stability: nanoemulsions are thermodynamically unstable, whereas microemulsions are thermodynamically stable (see Section 2).

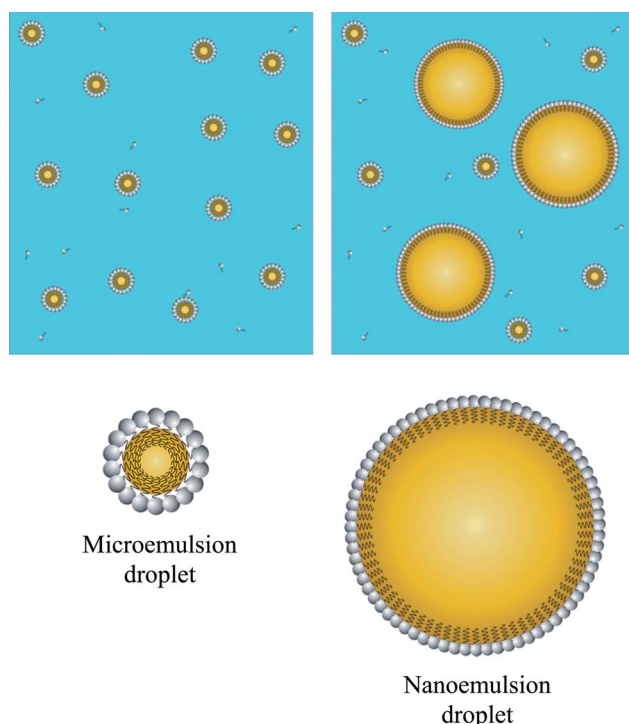


Fig. 1 Schematic diagram of microemulsions and nanoemulsions fabricated from oil, water and surfactant. The structure of the particles in both types of colloidal dispersion is fairly similar—a hydrophobic core of oil and surfactant tails and a hydrophilic shell of surfactant head groups.

2. Stability: thermodynamics and kinetics

The most fundamental way of distinguishing nanoemulsions and microemulsions is in terms of their thermodynamic stabilities: nanoemulsions are thermodynamically unstable, whereas microemulsions are thermodynamically stable. This difference between the two systems is shown schematically in Fig. 3, which compares the free energy of the colloidal dispersions to the free energy of the separate phases from

which they were prepared (*i.e.*, oil and an aqueous surfactant solution). In this example, it is assumed that the water phase consists of surfactant molecules dispersed within water in the form of either monomers or micelles depending on the total concentration and critical micelle concentration (CMC) of the surfactant.

2.1. Thermodynamic stability

2.1.1. Free energy diagrams. For a nanoemulsion, the free energy of the colloidal dispersion (droplets in water) is

higher than the free energy of the separate phases (oil and water), which means that a nanoemulsion is thermodynamically unstable (Fig. 3). A nanoemulsion can be made to be kinetically stable (metastable) by ensuring that there is a sufficiently large energy barrier between the two states (see Section 2.2).

For a microemulsion, the free energy of the colloidal dispersion (droplets in water) is lower than the free energy of the separate phases (oil and water), which means that a microemulsion is thermodynamically stable (Fig. 3). Nevertheless, there may still be an activation energy separating the two systems whose height determines the rate at which the separate phases form a microemulsion after the SOW components are brought into contact (see Section 2.2).

2.1.2. Mathematical model of thermodynamic stability. In this section, we consider the molecular basis for the difference in the thermodynamic stabilities of microemulsions and nanoemulsions. This difference can be understood by developing a simple mathematical model to calculate the free energy of their formation from the separate components. Consider a system that exists in equilibrium between a colloidal dispersion (nanoemulsion or microemulsion) and the separate phases (oil and an aqueous surfactant solution). To a first approximation, the free energy change associated with forming a colloidal dispersion from the separate phases consists of an interfacial free energy term (ΔG_I) and a configuration entropy term ($-T\Delta S_{\text{config}}$).¹⁷

$$\Delta G_{\text{formation}} = \Delta G_I - T\Delta S_{\text{config}} \quad (1)$$

At constant temperature, pressure and interfacial chemical potential, the interfacial free energy term is equal to the increase in contact area between the oil and aqueous phases (ΔA) multiplied by the interfacial tension (γ) at the oil–water interface:

$$\Delta G_I = \gamma\Delta A \quad (2)$$

The interfacial free energy term is always positive because the increase in contact area and interfacial tension are positive. Hence, this term always *opposes* the formation of colloidal dispersions.

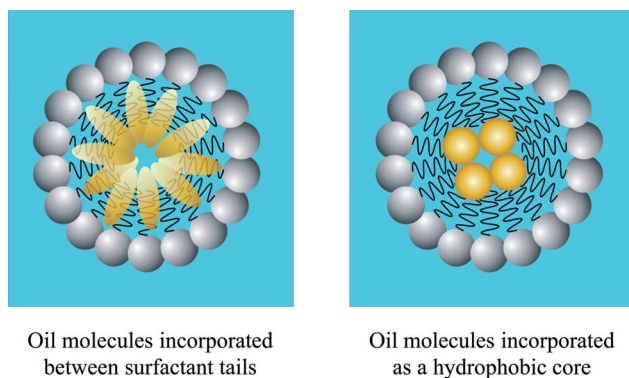


Fig. 2 Oil-in-water microemulsions consist of surfactant micelles with oil molecules incorporated within them. The oil molecules may be incorporated between the surfactant tails and/or within the core of the micelle.

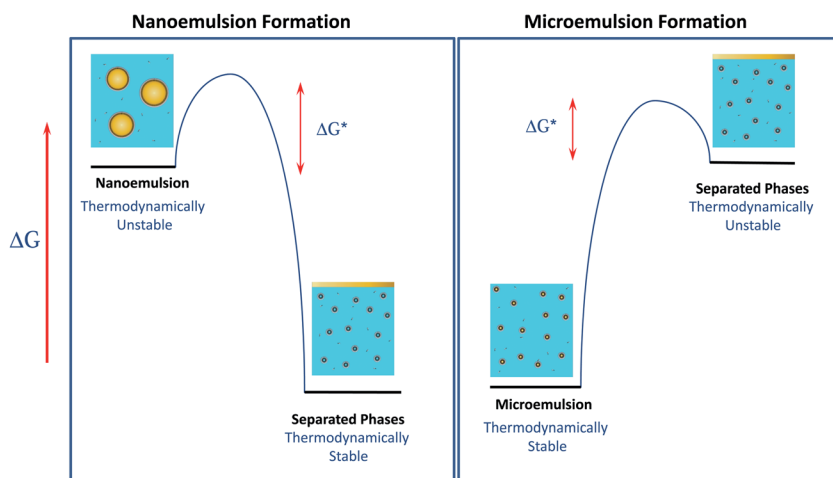


Fig. 3 Schematic diagram of the free energy of microemulsion and nanoemulsion systems compared to the phase separated state. Microemulsions have a lower free energy than the phase separated state, whereas nanoemulsions have a higher free energy. The two states are separated by an activation energy ΔG^* .

The configuration entropy term depends on the number of different ways that the oil phase can be arranged within the system. The configuration entropy term is always negative because the number of arrangements accessible to the oil phase in an emulsified state is much greater than in a non-emulsified state, and therefore it always *favours* the formation of colloidal dispersions. An expression for the configuration entropy can be derived from a statistical analysis of the number of configurations oil droplets can adopt in the colloidal dispersion and separated states:¹⁷

$$\Delta S_{\text{config}} = -\frac{nk}{\phi} (\phi \ln \phi + (1 - \phi) \ln(1 - \phi)) \quad (3)$$

Where, k is Boltzmann's constant, n is the number of droplets in the colloidal dispersion, and ϕ is the disperse phase volume fraction.

The above analysis assumes that the interfacial tension of a surfactant monolayer around an oil droplet is the same as that at a planar oil–water interface. However, the interfacial tension is known to depend on the curvature of a surfactant monolayer—decreasing as the monolayer approaches its optimum curvature, which depends on the molecular geometry of the surfactant molecules present.^{14,18,19} We use a simple phenomenological description of the dependence of interfacial tension on droplet curvature to model this effect:

$$\gamma = \gamma_0 + (\gamma_\infty - \gamma_0) \frac{(R_0 - R)^2}{R_0^2 + R^2} \quad (4)$$

Here γ_∞ is the interfacial tension at a planar oil–water interface, γ_0 is the (ultralow) interfacial tension when the surfactant monolayer is at its optimum curvature, and R_0 is the radius of the droplet when the surfactant monolayer is at its optimum curvature. The dependence of the interfacial tension on droplet size calculated using this equation is shown in Fig. 4, which demonstrates that there is a minimum value around the optimum curvature.

2.1.3. Free energy calculations for nanoemulsion and microemulsion formation. The dependence of the free energy of colloidal dispersion formation on droplet size was calculated using the equations given in the previous section. Initially, we calculated the interfacial (ΔG_I), configuration ($-T\Delta S_{\text{config}}$), and total (ΔG_T) free energies for the formation of a colloidal dispersion assuming that the interfacial tension was always the same as that measured at a planar oil–water interface (Fig. 5a). The interfacial free energy contribution becomes increasingly positive (unfavorable to the formation of a colloidal dispersion) with decreasing particle size due to the increase in interfacial area, whereas the configuration free energy becomes increasingly negative (favorable) with decreasing particle size due to the increase in the number of different ways the droplets can be organized. Nevertheless, the overall free energy change becomes increasingly positive with decreasing particle size,

since the interfacial free energy term dominates the configuration entropy term. These calculations suggest that the formation of a nanoemulsion becomes increasingly thermodynamically unfavorable as the particle size decreases for systems where the interfacial tension is similar to that at a planar interface. Nanoemulsions formed by amphiphilic biopolymers (e.g., proteins and polysaccharides) are likely to fall into this category.

The interfacial, configuration, and total free energies was then calculated for the formation of a colloidal dispersion assuming that the interfacial tension depended on the curvature of the surfactant monolayer (Fig. 5b). In this case the interfacial free energy contribution has a more complex dependence on droplet size. As the droplet radius decreases from 1000 nm there is initially an increase in the interfacial free energy, but once the size decreases below a certain value the free energy decreases to a minimum, before increasing again when the droplet size is decreased further. The overall free energy change is still dominated by the interfacial free energy contribution, so it has a minimum value that is close to the optimum curvature of the surfactant monolayer. These calculations show that a thermodynamically stable colloidal dispersion may form when the particle size is close to the optimum particle size ($R = R_0$), since this leads to an ultralow interfacial tension, and hence the interfacial free energy (ΔG_I) that normally opposes the formation of a colloidal dispersion is appreciably reduced.

It should be noted that the optimum curvature of a particular system also depends on the nature of the oil phase and the presence of any co-surfactants, since these substances can penetrate between the surfactant chains and thereby change their molecular packing.²⁰ The optimum particle radii of a number of commonly used surfactants have recently been measured, e.g., the radius of lemon oil swollen micelles have been reported to be 15 nm for sucrose monopalmitate²¹ and < 10 nm for Tween 80.²²

The above calculations assume that there is sufficient surfactant present to stabilize all of the oil molecules present. In practice, the formation of

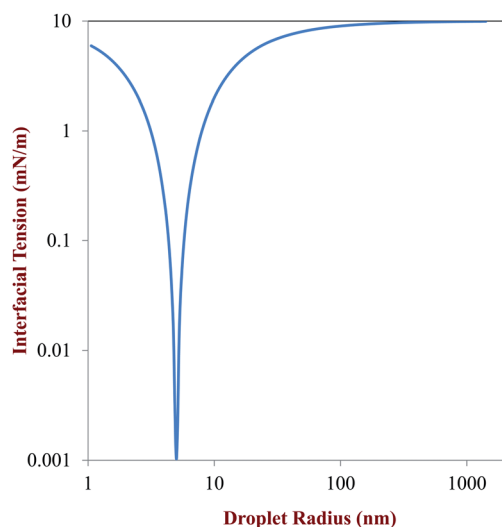


Fig. 4 Predicted influence of the droplet radius on interfacial tension for a surfactant monolayer that has an optimum particle radius of 5 nm.

a microemulsion or nanoemulsion depends on the relative amounts of oil and surfactant present. The maximum amount of oil that can be incorporated into a given amount of surfactant is characterized by a saturation concentration: C_{sat} . Oil molecules will be incorporated into surfactant micelles until the micelles become saturated leading to the formation of a microemulsion. Any further addition of oil molecules will lead to the formation of a separate oil phase. This separate oil phase may form a layer on top of the saturated surfactant solution, or it may be distributed as oil droplets (nanoemulsions or emulsions) within a surfactant solution if sufficient disruptive energy is applied (see Section 3).

2.2. Kinetic stability

The thermodynamic stability of a particular state (in this case a colloidal dispersion) is determined by the difference in free energy between it and an appropriate reference state (in this case the separate oil and water phases). A system will always tend to revert to the state with the lowest free energy under some specified conditions (e.g., composition, temperature). However, a system will persist in a metastable state for a considerable period of time if it is “kinetically stable”. In general, the kinetic stability of a metastable state is governed by two major factors:

- **Energy barriers:** If there are any energy barriers (activation energies) separating

the two states these will slow down the conversion of one state to another.

- **Mass transport phenomena:** The rate at which a system changes from one state to another state is determined by the speed at which the materials present can rearrange themselves into the new configuration. This structural reorganization of the system depends on diffusion and convection processes that determine how fast components can move.

A microemulsion is thermodynamically stable under a particular range of conditions, and hence it should form spontaneously when the surfactant, oil, and water components are brought together, and then it should remain stable indefinitely provided the initial conditions remain unaltered. In practice, a microemulsion may not form spontaneously due to the presence of kinetic energy barriers and/or slow mass transport processes (Fig. 3). Consequently, it may be necessary to mechanically agitate or heat the system in order to prepare a microemulsion from surfactant, oil, and water ingredients. The physicochemical origin of the energy barrier in microemulsion systems is not well understood, but it may be related to the free energy associated with moving a non-polar molecule from an oil phase to a water phase. When a non-polar molecule comes into contact with water there is a thermodynamic penalty associated with the hydrophobic effect, which increases as the contact area between the non-polar groups and water increases. The magnitude of this term will partly determine the water solubility of the oil molecules: the larger the free energy penalty, the lower the water solubility. Large oil molecules have very low water-solubilities and therefore their transport across the water phase will be very slow. The kinetics of microemulsion formation also depends on the speed that oil molecules move from the oil phase, through the water phase, and into the micelles, which will be governed by their translational diffusion coefficients. Larger oil molecules will tend to move more slowly through water than smaller ones.

A nanoemulsion is a thermodynamically unstable system so it will always breakdown given sufficient time. The rate of this breakdown depends on the

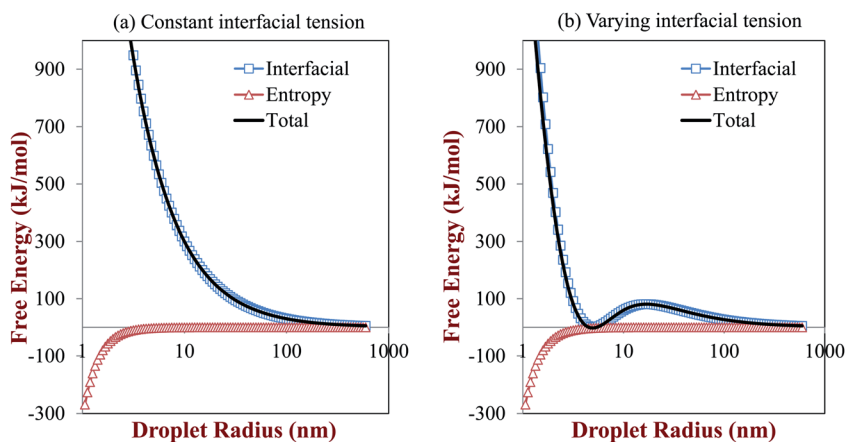


Fig. 5 Predicted influence of the particle size on the free energy change associated with the formation of a colloidal dispersion from the separate phases. Calculations were carried out assuming a constant interfacial tension and assuming an interfacial tension that varies with particle size (optimum curvature at a radius of 5 nm) as shown in Fig. 4.

height of any energy barriers between the nanoemulsion and separated states, as well as on the specific mass transport processes involved (Fig. 3). The height of the energy barrier determines the kinetic stability of a nanoemulsion: the higher the energy barrier, the longer the nanoemulsion will persist. Typically, the energy barrier should be >20 kT to produce nanoemulsions with good long-term stability.¹⁶ The height of the energy barrier is mainly determined by physicochemical phenomena that prevent the droplets from coming into close proximity, such as repulsive hydrodynamic and colloidal (*e.g.*, steric and electrostatic) interactions operating between droplets. The rate at which a nanoemulsion reverts back to the separated phases is also determined by the frequency that the oil droplets come into contact with each other, which depends on the primary mechanism responsible for particle–particle contacts, such as Brownian motion, applied shear, or gravitational forces. A discussion of these factors is beyond the scope of the current article, but has been reviewed elsewhere.^{16,17,23}

3. Nanoemulsions versus microemulsions: similarities and differences

In this section, similarities and differences between the composition, structure, preparation, and properties of nanoemulsions and microemulsions are highlighted. In addition, the origin of some of the confusion around the usage of the terms “microemulsions” and “nanoemulsions” is identified based on the similarities in their properties.

3.1. Composition

Nanoemulsions and microemulsions typically require fairly similar ingredients to fabricate them: an oil phase, an aqueous phase, a surface active agent, and possibly a co-surfactant. Indeed, it is possible to prepare both types of colloidal dispersion from exactly the same ingredients, but used in different ratios. Typically, a greater surfactant-to-oil ratio (SOR) is required to prepare a microemulsion than a nanoemulsion. An appreciation of this fact can be gained by considering an experiment

where increasing amounts of an oil-in-water emulsion are titrated into an aqueous surfactant micelle solution (Fig. 6). Prior to titration, the aqueous surfactant solution contains a dispersion of surfactant micelles distributed throughout the water phase. The initial size and shape of these micelles is determined by the molecular geometry and packing of the surfactant molecules, *i.e.*, their effective head group and tail group dimensions. Usually, the curvature of the surfactant monolayer is not at its optimum value when micelles are formed, and the system can be said to be in a “frustrated” state.²⁴ When relatively low concentrations of oil droplets are titrated into the surfactant solution, all of the oil molecules will move out of the droplets and be incorporated within the hydrophobic interiors of the surfactant micelles. One of the main driving forces for this process is that the surfactant monolayer can move towards its optimum value when the micelle size grows by incorporating oil molecules.^{18,24} As a result of this process, the oil droplets dissolve and disappear, whereas the surfactant micelles grow. As more oil droplets are added to the surfactant solution, the micelles eventually become saturated with oil and cannot incorporate any more, and so any additional oil droplets titrated into the system remain as oil droplets.²⁵ The system then consists of a mixture of saturated micelles and oil droplets (Fig. 6). The maximum amount of oil that can be incorporated into the surfactant micelles depends on the characteristics of the oil molecules (*e.g.*, molar volume, geometry, polarity), the characteristics of the surfactant molecules (*e.g.*, head group, tail group), and the environmental conditions (*e.g.*, temperature, pH, ionic strength).

The maximum amount of oil that can be incorporated into a given mass of surfactant can be characterized by a *saturation concentration* (C_{sat}^*), which is the number of grams of oil solubilized per gram of surfactant under specified environmental conditions. Above the critical micelle concentration (CMC) of a surfactant, the maximum amount of oil that can be incorporated into the micelles (C_{sat}) is approximately linearly related to the total surfactant concentration (C_{Tot}): $C_{\text{sat}} =$

$C_{\text{sat}}^* \times (C_{\text{Tot}} - \text{CMC})$.[†] If the total amount of oil present in the system is below this value, then all of the oil molecules will be solubilized and a microemulsion will be formed consisting of swollen micelles dispersed in water. On the other hand, if the total amount of oil present in the system is above this value, then it cannot all be solubilized by the micelles and any additional oil droplets added to the system will remain intact. However, the droplet size may change during storage due to flocculation, coalescence and/or Ostwald ripening phenomenon. In addition, the droplet size might change if mechanical energy was applied to the system to disrupt the droplets, *e.g.*, by passing the system through a homogenizer.

For colloidal dispersions fabricated from surfactant, oil, and water, it is therefore difficult to distinguish between microemulsions and nanoemulsions based solely on the type of ingredients used. One would also need to know the saturation concentration for the surfactant, and the total amount of oil and surfactant present.

In general, nanoemulsions can be made from a wider range of surface active agents than microemulsions. Typically, only small molecule surfactants can be used to prepare microemulsions because only they are capable of generating ultralow interfacial tensions at particular monolayer curvatures. On the other hand, small molecule surfactants, proteins and polysaccharides can be used as surface active agents to form nanoemulsions. Thus, if a colloidal dispersion containing small particles ($r < 100$ nm) is stabilized by a protein or a polysaccharide then it is highly likely that it will be a nanoemulsion rather than a microemulsion. One of the main reasons for this phenomenon is that monolayers of surfactants can adopt a curvature that gives an ultralow interfacial tension, whereas proteins and polysaccharides cannot.

3.2. Particle dimensions

A major reason for the confusion between microemulsions and nanoemulsions is due to the prefixes used to denote them.

[†] It should be noted that this expression will not be true if the surfactant concentration is so high that liquid crystals or other association colloids are formed.

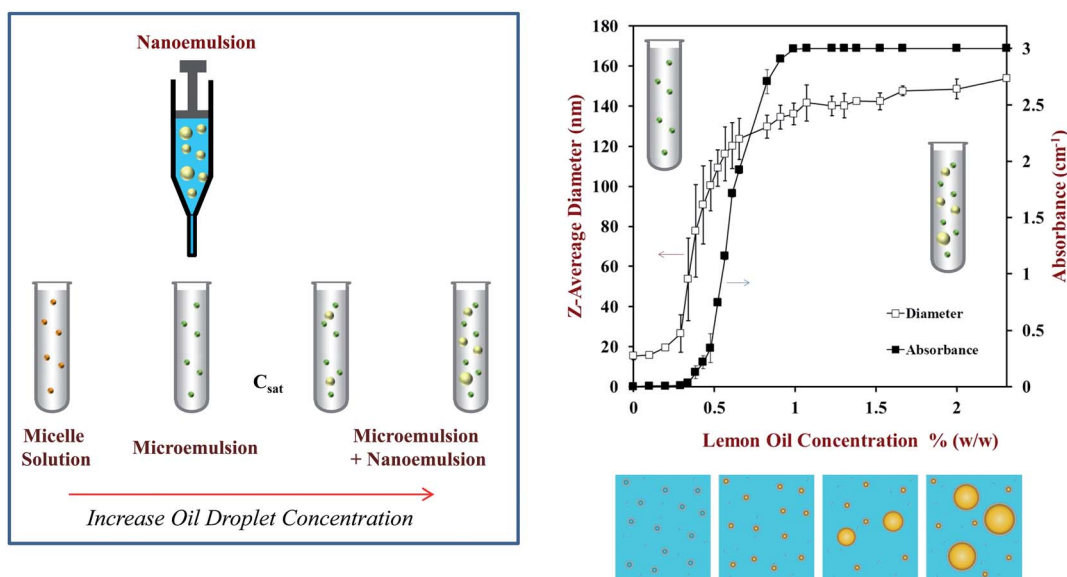


Fig. 6 Schematic representation of an experiment where increasing amounts of nanoemulsion droplets are titrated into an aqueous surfactant solution. Initially, the oil is solubilized within surfactant micelles to form microemulsion droplets. Above a critical oil concentration, the micelles become saturated with oil and any further droplets added remain. The experimental data are for lemon oil droplets titrated into a 1 wt% non-ionic surfactant solution (Tween 80).

The term “micro-” usually means 10^{-6} , while the term “nano-” usually means 10^{-9} , which would imply that nano-emulsions contain particles that are smaller than those in microemulsions. In practice, the opposite is usually the case – the particles in a microemulsion are smaller than those in a nanoemulsion. The reason for this confusing terminology is a result of the historical development of the field of colloid science. An on-line literature search using “Web of Knowledge” (Thomson Reuters) in October 2011 found that the first article appearing in the database that used the term “microemulsion” was published in 1961,²⁶ whereas the first article using the term “nanoemulsion” appeared in 1996.²⁷ Thus, the term “microemulsion” had become well-established among researchers in the field of colloid science well before the term “nanoemulsion” was introduced. Indeed, the utilization of the term “nanoemulsion” has only become popular during the past 10 years (Fig. 7), which can be at least partly attributed to the growing interest in the field of nanotechnology. Nevertheless, colloidal dispersions that would now be called nanoemulsions were certainly prepared long before this time, when they were referred to by other names, such as ultrafine emulsions, submicron emulsions, or mini-emulsions. It is clear that

the utilization of the terms “micro-emulsion” and “nanoemulsion” became widespread before they were clearly defined or distinguished from one another.

There has also been much disagreement about the critical particle size that should be used to distinguish a nanoemulsion from a conventional emulsion. Upper particle size limits for nanoemulsions of 500 nm,^{28,29} 200 nm,^{1,30} and 100 nm^{21,31} have all been proposed in the recent literature. It should be noted that many authors who propose such limits do not specify whether they mean particle *radius* or particle *diameter* as the most appropriate size to use. In reality, there is no distinct change in the physicochemical or thermodynamic properties of an oil-in-water emulsion when one reduces the droplet size from the micrometre range to the nanometre range. Nevertheless, there are some changes in overall system properties that could potentially be used as a basis for making a distinction between nanoemulsions and conventional emulsions:

- **Optical properties.** The appearance of a colloidal dispersion tends to become translucent or transparent when the particle radius falls below about 30 nm.⁸

- **Gravitational stability.** The stability of a colloidal dispersion to gravitational separation (creaming or sedimentation)

tends to increase appreciably when the particle radius falls below about 90 nm, since then Brownian motion dominates gravitational forces.³

- **Bioavailability.** There is some evidence that the bioavailability of lipophilic components increases appreciably when the radius of the droplets containing them falls below about 100 nm, which is at least partly attributed to the steep increase in the water-solubility of lipophilic components below a critical particle size due to an increased Laplace pressure.⁴ This effect increases the local concentration of the solute in the aqueous phase in close proximity to the droplet surface.

There is therefore no single particle size that can be used as a definitive cut-off point to distinguish a nanoemulsion from a conventional emulsion based on the physicochemical properties of the system. The author believes that a convenient definition of a nanoemulsion is that the mean particle *radius* of the system should be less than 100 nm. Even then, one still has to decide which mean particle radius to use, *e.g.*, Z-average, number-weighted average (r_{10}), surface-weighted average (r_{32}), or volume-weighted average (r_{43}). These mean values can be quite different for polydisperse emulsions. The strictest definition would be that the volume-weighted average radius be used since this tends to give the highest value of the

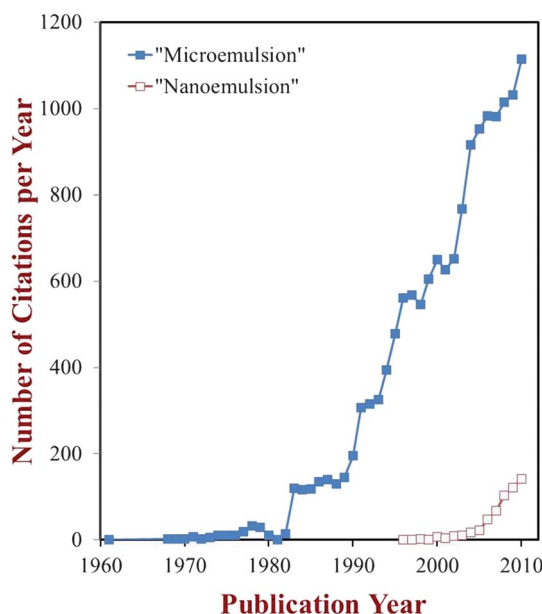


Fig. 7 Number of publications per year including the word “nanoemulsion” or “microemulsion” identified using an on-line literature search using “Web of Knowledge” (Thomson Reuters) in October 2011.

common mean values used. In some applications it may be more important to know the percentage of droplets that fall within the nanoemulsion size range, *e.g.*, the percentage of particles with radii less than 100 nm. For example, if it was found that small particles behaved differently than large particles in the gastrointestinal tract, and that this had potential detrimental effects on human health (toxicity), then it would be better to know the percentage of particles that fell within this size range, rather than the mean value.

There are also similar issues related to clearly defining the upper particle size limit for an oil-in-water microemulsion. A surfactant monolayer has an optimum curvature (where the interfacial tension is ultralow) that depends on its molecular geometry (packing parameter).^{12,23} In principle, oil-in-water microemulsions could therefore be formed with a wide range of different particle sizes corresponding to differences in surfactant optimum curvatures. In practice, once the droplets in a microemulsion exceed a particular size they become very unstable to coalescence, and a multiple emulsion, lamellar structure, or bicontinuous structure may be favored.²⁴ The critical particle size where this process happens depends on the mobility of the surfactant monolayer. If a surfactant monolayer has an ultralow interfacial

tension, then it is prone to large fluctuations in its surface topology due to thermal energy, which can lead to the formation of “holes” that promote droplet coalescence.²⁴ It is convenient to define the upper limit for the particle size of a stable oil-in-water microemulsion to be similar to that of a nanoemulsion, *i.e.*, radius < 100 nm.¹¹

One possible means of distinguishing between microemulsions and nanoemulsions is the shape of their particle size distribution (PSD). Oil-in-water microemulsions tend to have a single narrow peak, whereas nanoemulsions may have single or multiple peaks that may be narrow or broad. Thus, if the PSD of a colloidal dispersion is measured and it is found to have a single narrow peak then it may be either a microemulsion or nanoemulsion, but if it contains multiple peaks or broad peaks then it is probably a nanoemulsion.

3.3. Particle structure

Another important factor that has contributed to the confusion in distinguishing nanoemulsions from microemulsions is due to the great similarities in their structures (Fig. 1). Oil-in-water nanoemulsions and microemulsions both consist of small (approximately) spherical particles consisting of oil and surfactant

molecules dispersed within an aqueous medium. The particles consist of a hydrophobic core made up of oil molecules and surfactant tails, and a hydrophilic shell made up of surfactant head groups. Nevertheless, there may be some structural differences between the two systems that can be used to distinguish them. The particles in nanoemulsions tend to be spherical because the interfacial tension (γ) is relatively high and the particle radius (r) is relatively low and so there is a relatively large Laplace pressure ($\Delta P_L = 2\gamma/r$) favoring a reduction of the interfacial area: a sphere has the lowest interfacial area for a given volume of material.²³ On the other hand, the particles in microemulsions may be spherical or non-spherical depending on the optimum curvature of the surfactant monolayer and the amount of oil incorporated into the system.¹² This is because the interfacial tension of the surfactant monolayer is relatively low for microemulsion systems and so there is less of a penalty for having a non-spherical shape. Hence, oil-in-water microemulsions may contain particles that are spheroid or worm-like since this allows the surfactant molecules to adopt their optimum packing. It may therefore be possible to distinguish between microemulsions and nanoemulsions by measuring the shape of the particles present *e.g.*, using microscopy or scattering methods.

3.4. Fabrication methods

In principle, microemulsions can be formed spontaneously by simply bringing oil, water and surfactant together at a particular temperature without supplying any external energy, since they are thermodynamically stable systems. In practice, it is often necessary to apply external energy (in the form of stirring or heating) to facilitate the formation of a microemulsion because there are kinetic energy barriers that must be overcome or mass transport limitations retarding their spontaneous formation (Fig. 3). In contrast, nanoemulsions always require the input of some external energy to convert the separate components into a colloidal dispersion because they are thermodynamically unstable systems. At the very least an energy input exceeding the positive free energy associated with increasing the contact area between the oil

and water phases must be applied: $\Delta G_1 = \gamma\Delta A$. The way that external energy is applied to form a nanoemulsion varies widely depending on the preparation method utilized. Nanoemulsion fabrication methods can be broadly categorized as either *high-energy* or *low-energy* approaches depending on the underlying physicochemical mechanism of droplet disruption.^{3,32}

High-energy approaches utilize mechanical devices (known as “homogenizers”) capable of generating intense disruptive forces that disrupt and intermingle the oil and water phases so that tiny droplets are formed, *e.g.*, high pressure valve homogenizers, microfluidizers, and sonication methods. Low energy approaches rely on the spontaneous formation of tiny oil droplets within mixed surfactant–oil–water systems when the solution or environmental conditions are altered, *e.g.*, phase inversion and spontaneous emulsification methods. The droplet size that is produced using each approach depends on many different factors, which have recently been discussed elsewhere.^{3,32}

For some surfactant, oil and water systems there are close similarities between the fabrication methods that can be used to produce microemulsions and nanoemulsions. In the spontaneous emulsification method, an optically transparent colloidal dispersion is formed when a mixture of surfactant and oil is added to an aqueous solution with mild stirring. Similarly, in the phase inversion temperature (PIT) method, an optically transparent colloidal dispersion is formed when a mixture of surfactant, oil, and water is heated to around the phase inversion temperature, and then the system is quench-cooled with continuous stirring.³³ The colloidal dispersions formed using these two approaches may be either microemulsions or nanoemulsions depending on the surfactant to oil ratio (SOR): at higher SOR a microemulsion is formed, but at low SOR a nanoemulsion is formed. It is often difficult to distinguish between these two types of colloidal dispersion by simply looking at the system, or by measuring the particle size distribution.

Consequently, it is often difficult to distinguish between nanoemulsions and microemulsions based on the methods used to fabricate them. For example,

mechanical or thermal energy input may be needed to form a microemulsion if there is a sufficiently large kinetic energy barrier (Fig. 3), while a nanoemulsion may be formed a simple mixing process if a low-energy homogenization method is used.

3.5. Long-term stability

A microemulsion is thermodynamically stable under a particular range of conditions (*e.g.*, compositions and storage temperatures), and hence it should remain kinetically stable indefinitely provided that these initial conditions are not changed. In practice, a microemulsion may become unstable if some of the components undergo chemical changes during storage, or if the environmental conditions are altered into a range where the system is no longer thermodynamically stable. For example, a microemulsion may breakdown if it is diluted or if its temperature is changed, which commonly happens during the manufacturing, storage, and utilization of microemulsion-based products. Knowledge of the influence of system composition and temperature on the phase behavior of surfactant–oil–water systems is crucial for the development of successful microemulsion-based delivery systems.

A nanoemulsion is a thermodynamically unstable system that will breakdown over time at a rate that depends on the height of any energy barriers between the nanoemulsion and separated states (Fig. 3). The height of this energy barrier determines the kinetic stability of the emulsion: the higher the energy barrier, the longer the nanoemulsion will persist. Typically, the energy barrier should be above about 20 kT to produce nanoemulsions with long-term stability.¹⁶ The height of the energy barrier is mainly determined by physicochemical phenomena that prevent the droplets from coming into close proximity, such as repulsive hydrodynamic and colloidal (*e.g.*, steric and electrostatic) interactions operating between droplets. The rate at which a nanoemulsion reverts back to the separated phases is also determined by the frequency that the oil droplets come into contact with each other, which depends on the primary mechanism responsible for particle–particle contacts (such as

Brownian motion, applied shear, or gravitational forces).

There are a variety of different physicochemical mechanisms by which a nanoemulsion may breakdown, including gravitational separation (creaming/sedimentation), flocculation, coalescence, and Ostwald ripening.^{16,34,35} The rates at which these degradation processes occur depends on system composition (*e.g.*, oil type, surfactant type, relative concentrations, pH, ionic strength, and solvent type) and environmental conditions (*e.g.*, temperature, and applied forces). A major concern of scientists working with this kind of colloidal dispersion is therefore to create an initial nanoemulsion with sufficiently small particles, and then to ensure that it has a sufficiently long *kinetic* stability for commercial applications. The kinetic stability of nanoemulsions can be improved by controlling their microstructure (*e.g.*, particle size distribution), or by incorporating substances known as *stabilizers*, such as emulsifiers, texture modifiers, weighting agents, or ripening retarders.^{3,32} Nanoemulsions with relatively long kinetic stabilities (months or years) can be prepared by proper selection of particle size distribution, oil type, and emulsifier type. Preparing a nanoemulsion where the vast majority of particles are less than 90 nm in radius should effectively prevent creaming. Using an oil phase with very low water solubility will help prevent droplet growth through Ostwald ripening. Using an emulsifier that generates a strong repulsive force between the droplets will help prevent flocculation and coalescence. Thus, it may be difficult to distinguish a nanoemulsion with high kinetic stability from a microemulsion that is thermodynamically stable on a reasonable timescale.

4. Practical methods of distinguishing nanoemulsions and microemulsions

The discussion so far has highlighted some of the challenges in distinguishing nanoemulsions from microemulsions based on their composition, dimensions, structure, shelf-life, and fabrication methods. In this section, an attempt is made to propose practical methods of

ascertaining the nature of a particular colloidal dispersion. In other words, it attempts to highlight experimental methods that could be used to distinguish thermodynamically stable systems (microemulsions) from thermodynamically unstable systems (nanoemulsions).

- *Long-term storage.* A nanoemulsion is thermodynamically unstable, whereas a microemulsion is thermodynamically stable. Consequently, the structure of a microemulsion should not change during prolonged storage, whereas that of a nanoemulsion should change, *e.g.*, due to Ostwald ripening, flocculation, coalescence and/or gravitational separation. These changes would manifest themselves as alterations in particle size distribution, overall microstructure, creaming, or phase separation during storage. In principle, if the structure and properties of a colloidal dispersion remains constant during storage then it is a microemulsion, but if they change it is a nanoemulsion. In practice, it might not be so clear because the properties of a microemulsion may change due to chemical degradation or microbial contamination, whereas the properties of a nanoemulsion may not change over extended periods because it has a high kinetic stability.

- *Sample history.* Under a particular set of conditions (*e.g.*, composition, temperature, and pressure) the structure of a microemulsion should always be the same, independently of the method used to prepare it, because it is a thermodynamically stable system. Thus, if a microemulsion is mechanically agitated, cooled, or heated and then returned to its original condition, its properties should be the same as the initial system. Conversely, the structure of a nanoemulsion under a particular set of conditions is highly dependent on the method used to prepare it, as well as its subsequent history. Thus, if a nanoemulsion is mechanically agitated, cooled or heated and then returned to its original condition, its properties may be quite different from that of the initial system. In practice it might not always be possible to clearly distinguish the two types of colloid dispersion using this approach. For example, a microemulsion may take some time to reach its equilibrium state due to the presence of energy barriers or slow mass transport processes, or a nanoemulsion

may have a high kinetic stability to the conditions imposed.

- *Particle size distribution.* Microemulsions tend to have a single narrow peak in their particle size distributions, whereas nanoemulsions may have single or multiple peaks that may be narrow or broad. Thus, if a colloidal dispersion contains a single narrow peak then it may be either a microemulsion or nanoemulsion, but if it contains multiple peaks or broad peaks then it is probably a nanoemulsion. It is also possible to have multiple peaks in systems that consist of a mixture of microemulsion and nanoemulsion droplets.

- *Particle shape.* Nanoemulsions tend to contain spherical particles because of the large Laplace pressure acting upon them, whereas microemulsions may form either spherical or non-spherical particles because of the ultralow interfacial tension. It may therefore be possible to distinguish a nanoemulsion from a microemulsion by measuring the shape of the particles, *e.g.*, using scattering (neutron, X-ray, or light) or microscopy (electron) methods. If a system has non-spherical particles, then it is likely to be a microemulsion. On the other hand, if a system contains spherical particles it may be either a microemulsion or a nanoemulsion.

5. Conclusions

This article has highlighted the most important differences and similarities between two types of colloidal dispersions widely used to encapsulate lipophilic components: oil-in-water nanoemulsions and microemulsions. There are many similarities between the composition, dimensions, structures, and fabrication methods for these two systems, which has led to considerable confusion in the literature about the precise nature of the colloidal dispersion being studied. For this reason the following two definitions were proposed to clearly distinguish between microemulsions and nanoemulsions:

- *Microemulsion.* An oil-in-water microemulsion is defined as a thermodynamically stable colloidal dispersion consisting of small spheroid particles (comprised of oil, surfactant, and possibly co-surfactant) dispersed within an aqueous medium.

- *Nanoemulsion.* An oil-in-water nanoemulsion is defined as a thermodynamically unstable colloidal dispersion consisting of two immiscible liquids, with one of the liquids being dispersed as small spherical droplets ($r < 100$ nm) in the other liquid.

It is important to accurately make the distinction between microemulsions and nanoemulsions since this determines the methods used to prepare them, their long term stability, and their functional performances. We also propose a number of practical methods that might be useful for determining whether a given colloidal dispersion is a microemulsion or a nanoemulsion, such as long-term storage studies, altering sample history, particle size distribution measurements, or particle shape measurements.

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