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Review

Design and production of nanoparticles formulated from nano-emulsion templates—A review

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ABSTRACT

A considerable number of nanoparticle formulation methods are based on nano-emulsion templates, which in turn are generated in various ways. It must therefore be taken into account that active principles and drugs encapsulated in nanoparticles can potentially be affected by these nano-emulsion formulation processes. Such potential differences may include drug sensitivity to temperature, high-shear devices, or even contact with organic solvents. Likewise, nano-emulsion formulation processes must be chosen in function of the selected therapeutic goals of the nano-carrier suspension and its administration route. This requires the nanoparticle formulation processes (and thus the nano-emulsion formation methods) to be more adapted to the nature of the encapsulated drugs, as well as to the chosen route of administration. Offering a comprehensive review, this paper proposes a link between nano-emulsion formulation methods and nanoparticle generation, while at the same time bearing in mind the above-mentioned parameters for active molecule encapsulation. The first part will deal with the nano-emulsion template through the different formulation methods, *i.e.* high energy methods on the one hand, and low-energy ones (essentially spontaneous emulsification and the phase inversion temperature (PIT) method) on the other. This will be followed by a review of the different families of nanoparticles (*i.e.* polymeric or lipid nanospheres and nanocapsules) highlighting the links (or potential links) between these nanoparticles and the different nano-emulsion formulation methods upon which they are based.

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1. Introduction

Over the past few decades, extensive research has been done on the study of nanoparticle generating processes. Owing to the variety of the application fields of such colloidal objects (from nanomedicine, drug delivery and cosmetics, to printing ink or petroleum sciences...), and as existing nanoparticles are now innumerable, a thorough knowledge of the formulating processes (and their potentialities) is essential in order to achieve the given purposes and needs for research. Likewise, in that most nanoparticle formulations are effectively based on nanometric-scaled emulsions, so-called *nano-emulsions*, the study of nanoparticle formulation has to include knowledge of nano-emulsion formation governing phenomena. Nano-emulsions are nanometric-sized emulsions, typically exhibiting diameters of up to 500 nm. Nano-emulsions are also frequently known as miniemulsions, fine-dispersed emulsions, submicron emulsions and so forth, but are all characterized by a great stability in suspension due to their very small size, essentially the consequence of significant steric stabilization between droplets, which goes to explain why the Ostwald ripening is the only adapted droplet destabilization process (detailed below). It follows therefore that nano-emulsion systems can be regarded as a template for nanoparticle generation, even if these two steps can often be combined into one. Therefore, the innumerable variants of nanoparticle formulation are mainly based on three different groups of methods for the generation of nano-emulsions, *i.e.* high-energy methods, the low-energy spontaneous emulsification method, and the low-energy phase inversion temperature (PIT) method.

The different kinds, or morphologies, of the nanoparticles generated, can be broken down into polymeric nanospheres, solid lipid nanoparticles (SLNs), or polymeric or lipid nanocapsules. The links between nano-emulsion formulation processes and nanoparticle morphology are neither obvious nor systematic and should be tackled with particular detachment: Such is the purpose of the current review. Indeed, by establishing a link between the formulation of nano-emulsions and nanoparticle generation, our intention has been to highlight the extent to which experimental processes can be adapted to given specifications.

In the first part, the nano-emulsion template is presented by a thorough description of the mechanisms and phenomena governing its formation, including a comprehensive review of the different existing methods. Special attention has been given to the 'low-energy' processes, since they constitute a privileged way to prevent the potential degradation of encapsulated molecules during processing and are also important for, (among others) energy yields in the case of industrial scale-up.

In the second part, nanoparticle formulation processes are reviewed with regard to the place of the nano-emulsion generation methods (amongst others) that they are based on. Furthermore, their potential adaptation to other nano-emulsion forming methods is discussed and their potential significance highlighted. Accordingly, the choice of the energy-type method, the use of organic solvent in the formulation, the choice of the polymer according to its biocompatibility or biodegradability, even the choice of an *in situ* synthesis during nanoparticle generation, as well as the use of preformed polymers and finally the choice of nanoparticle morphology, all of these parameters must be thoroughly considered and closely adapted to the therapeutic objectives.

In the case of polymers *in situ* synthesized with polymeric nanospheres of nanocapsule creation, the potential interactions between drugs (or active molecules to be encapsulated) and the polymers being formed must be systematically considered. Indeed, covalent bonds may be established between drugs and polymers, and thus their potential mutual reactivity must be taken into account in the choice of monomers and nanoparticle-generating systems.

The last remark concerns nano-emulsion and nanoparticle characterization. Given the numerous papers and reviews (*e.g.* [1–3]) where this aspect has been covered in great detail, we have not dealt with it in the present review. The droplet size distribution is essentially disclosed by dynamic light scattering (DLS), but also by transmission electronic microscopy (TEM) coupled with negative staining, or cryo-TEM, freeze-fracturing followed by replication plus TEM, or capillary hydrodynamic fractionation (CHDF), etc. More detailed information on surface particle characterization may be obtained by surface potential characterization (such as [1–3] potential) and an indication of the nanoparticle surface morphology may be highlighted by specific approximations of electrophoretic models (*e.g.* soft particle model [4]). Finally, small-angle neutron scattering (SANS) or small-angle X-ray scattering (SAXS) may be useful for investigating the internal morphology of such colloidal objects.

2. The great stability of nano-emulsions

The main particularity of nano-emulsions, making them prime candidates for nanoparticle engineering, is their great stability of droplet suspension. A kinetic stability that lasts for months, stability against dilution or even against temperature changes, totally unlike the (thermodynamically stable) microemulsions. Emulsions are thermodynamically unstable systems, due to the free energy of emulsion formation (ΔG_f) greater than zero. The large positive interfacial energy term ($\lambda\Delta\mathcal{A}$) outweighs the entropy of droplet formation ($T\Delta S_f$), also positive. The terms λ and $\Delta\mathcal{A}$ respectively represent the surface tension and the surface area gained with emulsification. Emulsion instability is therefore induced by the positive sign of ΔG_f (Eq. (1)).

$$\Delta G_f = \gamma \Delta\mathcal{A} - T\Delta S_f \quad (1)$$

Accordingly, the physical destabilization of emulsions is related to the spontaneous trend towards a minimal interfacial area between the two immiscible phases. Therefore, a minimization of interfacial area is attained by two mechanisms: (i) Flocculation followed mostly by coalescence, and (ii) Ostwald ripening.

In nano-emulsion systems, flocculation is naturally prevented by steric stabilization, essentially due to the sub-micrometric droplet size. In short [5–7], when interfacial droplet layers overlap, steric repulsion occurs,from two main origins. The first one is the *unfavorable mixing* of the stabilizing chain of the adsorbed layer, depending on the interfacial density, interfacial layer thickness δ, and Flory–Huggins parameter $\chi_{1,2}$ (which reflects the interactions between the interfacial layer and solvent). The second one is the *reduction of the configurational entropy*, due to the bending stress of the chains, which occurs when inter-droplet distance h becomes lower than δ.

Generally, the sum of the energies of interaction U_T adopts a typical shape of systems wherein molecules repel and particles attract each other, showing a weak minimum, around $h=2\delta$, and a very rapid increase below this value (see Fig. 1 for illustration). The depth of the