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Formation of nanocapsules by emulsion-diffusion : prediction of the emulsion size

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Nowadays, a considerable range of industrial applications, especially in the pharmaceutical field, relies on the encapsulation of solids or liquids by a polymeric coating. Nanocapsules consist of spherical particles (10 nm to 1000 nm size range), made of a thin polymeric membrane surrounding a liquid core. The objective of this work was to study the formation of nanocapsules by the emulsion diffusion technique. We focused on the emulsion phase and tried to predict the particles and the droplets size distributions. The emulsion diffusion is a two steps process[1], based on the formation of an emulsion, followed by a dilution leading to the deposition of the polymer around the droplets and therefore the formation of nanocapsules. The emulsion involves a partially water-soluble solvent, previously saturated with water, containing a polymer and an oil as the organic phase, and an aqueous phase previously saturated with solvent containing a stabilizer. The subsequent addition of water to the system causes the solvent to diffuse quickly to the external aqueous phase, resulting in polymer aggregation in nanocapsules. The emulsion is made in a two litres reactor equipped with a rotor-stator unit (Ultra Turrax T50®) combined with a classical impeller to promote the formation of micrometric size droplets [2]. The reactor is represented on figure 1, the emulsion composition is the following:

Organic Phase			Aqueous Phase		
Polymer	:	0.3%	Water saturated with solvent:		64.8%
Solvent saturated with water	:	32.4%	Surfactant	:	1.6%
Oil	:	0.8%			

Two polymers were used, PCL (Poly-ε-caprolactone), purchased from Aldrich Chemical Company Inc. and Eudragit® E100, a copolymer of acrylic acid and methacrylate purchased from Röhm GmbH-Chemische Fabrick. The oil used is Miglyol® 812, a mixture of capric and caprylic triglycerides from Condea Chemie GmbH. Pure ethyl acetate (Laurylab) was used as a partially water miscible solvent. The continuous phase of the emulsion was constituted of distilled water saturated with ethyl acetate and PVAL (polyvinyl alcohol, Mowiol® 4-86) as a stabilizer agent supplied by Hoechst.

In a first step, we estimated the droplets Sauter diameters d_{32} using a correlation established with model fluids and a rotor stator mixer[3]: $d_{32}/Di = 0,02(We)^{-0,6}(\mu c/\mu d)^{0,5}$ (equation 1). This equation is referred to the Kolmogoroff theory (average isotropic turbulence) in turbulent regime and it is valid if $L_{macro} \gg l_{micro} \gg d$ (see figure 1 for the definition of L_{macro} and L_{micro}). L_{macro} is often near to $2*10^{-3}$m, $l_{micro} = \left(\dfrac{\mu_c^3}{\rho_c^3 \varepsilon} \right)^{\frac{1}{4}} = 6,78*10^{-6}\,m$, d is $4*10^{-2}$m, so the previous equation can be used. ε is the dissipated power per volume unit, calculated with a power number of 8 for the rotor stator.
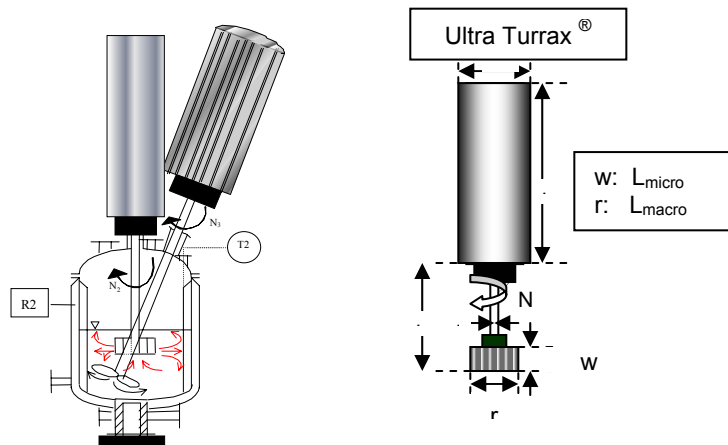
Figure 1: Reactor and rotor-stator used for the emulsion preparation

Then we compared these results with those obtained from the measurement of the particles size distribution by laser diffraction (Coulter LS200®). Assuming that each droplet leads to one particle and that the droplets and the particles are not porous, the droplets size distribution is calculated from the particles size distribution by adding the solvent

volume: $\dfrac{d_{drop}}{d_{part}} = \left[\dfrac{\rho_{part}}{\rho_{drop}} \dfrac{m_{drop}}{m_{part}} \right]^{1/3}$ and $\dfrac{1}{\rho_{drop}} = \dfrac{x_{polymer}}{\rho_{polymer}} + \dfrac{x_{ethylacetate}}{\rho_{ethylacetate}} + \dfrac{x_{oil}}{\rho_{oil}}$ where x_i are mass fractions.

An example of measured particles size distribution and calculated droplets size distribution is given on figure 2. The two curves are similar, the deviation between then representing the solvent volume.

All the results are summarized in table 1, the mean size of particles d_{part} is obtained from laser granulometry. The Sauter diameter of droplets is calculated with equation 1 (d_{32} correlation) and with the droplets size distribution deduced from the particles one (d_{32} distribution). The comparison of the results showed that the d_{32} correlation obtained using the correlation is about 50% to 100% higher than that d32 distribution calculated from the particles size distribution. We believe that this gap is to be associated to the inaccuracy on the measurement of the very low interfacial tension involved in this process. This interfacial tension has been measured with the Wilhemy method (Kruss® K14 tensiometer), it is 6 mN.m^{-1} in our conditions. If this value is decreased by a factor of 2, the d_{32} correlation becomes 0.47µm (N rotor stator = 8800 rpm), so much closer to the value calculated from the experiments. An other assumption was that each droplet could break and lead to several particles, it was rejected due to the small solvent content in the droplets (24%), which represents a size reduction of 25% from the droplets to the particles.

Table 1 : Comparison of d_{32} estimated by the correlation and calculated from the particles size distribution

N rotor stator rpm	ε = P/V kW.m^{-3}	Mean d_{part} (measurement) µm	d_{32} correlation µm	d_{32} calculated from the particle size distribution µm	Correlation /distribution (-)
5200	0.53	0,925	1,30	0.90	1.44
8800	2.56	0,343	0,71	0.4O	1.78
				0.32	2.22
10000	3.75	0,310	0,61	0.38	1.60

(1) QUINTANAR D. et al., PCT Patent n° WO9904766 A, 1999.

(2) COLOMBO APC et al., Drug Development and Industrial Pharmacy, 2001, 27, 10, 1063-1072.

(3) Costaz H., PhD Thesis (N° 041-96 Université Claude Bernard Lyon 1), 1996

Particles and droplets size distribution

N = 10000 rpm

droplets
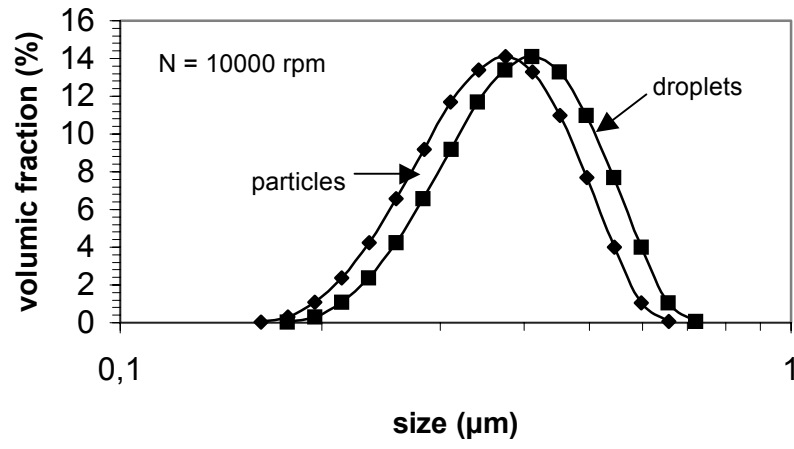
particles

volumic fraction (%)

size (µm)

Figure 2 : Particles and calculated droplets size distributions (N rotor stator = 10 000 rpm)