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Stirring speed influence study on the microencapsulation process and on the drug release from microcapsules

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Summary
Microparticles in the size range of 20-200 µm, loaded with drug model were prepared by complex coacervation method. The influence of the agitation rate of dispersion on the morphology of particles and on the drug release has been studied. Obtained results show that the relationship found between the Sauter mean diameter of particles and the stirring speed of emulsification is in good agreement with the inertial breakup theory. The paper reports the preliminary results of a work intended to link up the process control parameters of the microencapsulation and the factors controlling the drug release.

Introduction

Actually, controlled release formulations are in great development in many sectors (1-5). The drug delivery system must allow the release of the active agent (pharmaceuticals, pesticides, aroma, ...) at the desired rate and site. Several techniques (6) were used to obtain this goal. One of these is the complex coacervation method. In this case, the finished product is a great number of microcapsules, i.e., a great number of hollow polymeric spheres containing the active agent.

The features of the microcapsules and therefore the features of the drug release depend mainly on the operative conditions of the microencapsulation process : nature and concentration of polymers and of active agent, cross-linking agent and surfactant, the volume fraction of the discontinuous phase, coacervation pH,...

But the process control parameter that has the most importance is the stirring speed during the dispersion of the active agent in the continuous aqueous phase, because one can suppose it is responsible of the active agent droplets size and consequently the diameter of the microcapsules (7). This last feature has a great influence on the release rate of the drug.

Many studies, concerning the influence of the operative conditions on the drug release, have been already published (8-11), but most of them are qualitative and there are no quantitative relationships between the process control parameters and the rate of the active agent liberation.

Our ultimate goal is to establish relationships between features of the drug release from microcapsules and the encapsulation process control parameters. In this article, we have tried to quantify the stirring speed influence on the rate of the active agent release.

Because the aim of this work is rather a basic research than an applicated one, we have used a drug model, the ethyl benzoate, that has some physical properties of some pesticides (Henry's law constant, vapor pressure, solubility, octanol-water partition coefficient....) and that is practically non-toxic.
From a theoretical point of view the effect of stirring speed on the particle size has been examined according to the inertial breakup theory (12-13) while the release rate of the drug has been investigated according to the mass transfer laws (14).

Theoretical part

1) Inertial breakup theory and mean diameter of the dispersed phase

The local isotropic theory of turbulence (15) applicated to dispersed phase (12-13) gives a relationship between the mean diameter of Sauter (d_{32}) of the droplets and the agitation speed (N), the stirrer length (L), the volume fraction of discontinuous phase (ϕ_d), the interfacial tension (σ), the density of the continuous phase (ρ_c):

$$d_{32} = k_1(N)^{-6/5}(L)^{-4/5}f(\phi_d)(\sigma/\rho_c)^{3/5} \qquad (I)$$

with $$d_{32} = \Sigma(x_i d_i^3)/\Sigma(x_i d_i^2) \qquad (II)$$

x_i : number of droplets with diameter d_i, $f(\phi_d) = (1 + k_2(\phi_d))$ when $\phi_d \rightarrow 0$, $f(\phi_d) \rightarrow 1$, k_1 and k_2 : dimensionless constants.
The inertial breakup theory and mathematical developments that give relationship like (I) have been recently developed (16-17).
A good agreement between experimental data of d_{32} and the calculated values obtained by the relationship (I) has been found by several authors (18-21). This relation is valid only when the following conditions are satisfied : *i)* the Reynolds number (Re), $Re = (\rho_c N L^2)/\mu_c$ must be greater than 10000 (μ_c is the dynamic viscosity of the continuous phase). *ii)* Kolmogoroff's scale (η), $\eta = \varepsilon^{-1/4}(\mu_c/\rho_c)^{3/4}$ must be smaller than size of the smaller eddies (d) (assimilated to droplet diameter). These latter being very smaller than the bigger eddies (assimilated to stirrer length, L), ε is the power by mass unit ($\varepsilon = (100/\pi)N^3L^2$ (19)). We write these conditions according to :

$$Re >> 10000 \qquad (III)$$
$$d >> \eta \qquad (IV)$$
$$L >> d \qquad (V)$$

If $f(\phi_d)$, L, σ and ρ_c are constant, relationship (I) becomes :

$$d_{32} \propto (N)^{-6/5} \qquad (VI)$$

If one can suppose that the microcapsule size is practically equal to the one of the droplets, relationships (I) and (VI) allow to forecast the microcapsule diameter.

2) Mass transfer and release rate of drug

The release of the active agent in this type of device involves three stages : *i)* penetration of active agent into polymeric membrane of the microcapsules, *ii)* diffusion across the membrane, *iii)* transfer of active agent in solution.
One can suppose that the stage *ii)* is the slowest stage because diffusion in liquid is faster than in solid. Therefore, the release rate of active agent is governed by diffusion into the

shell of the hollow sphere (microcapsules). In this case, the diffusion of active agent can be described by the basic equation for unsteady-state diffusion, called Fick's second law :

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[D\, r^2 \frac{\partial C}{\partial r}\right] \qquad \text{(VII)}$$

with $R_1 < r < R_2$, C is the concentration of substance, D is the diffusion coefficient in the polymer shell and r is the distance. R_1 and R_2 are the diameters of the shell. The solution of this equation depends on initial and boundary conditions and in this case the amount of ethyl benzoate released in the earlier stages of the process is proportional to the square root of time (14).

Experimental part

Wall materials : Gelatin (Aldrich, type B, from bovine skin, 225 bloom) and arabic gum (acacia) (Aldrich, powder). Core material : ethyl benzoate (Fluka, pur 99%, GC) diluted with sunflower oil (50% solution). pH-adjusting : dilute (1M) of acetic acid (Aldrich, pur 99%). Cross-linking agent : glutaraldehyde (50% solution, Aldrich).

Preparation of microparticles

The microparticles were prepared by the complex coacervation method. 80 g of ethyl benzoate solution was dispersed at 40°C in 200 g of arabic gum aqueous solution (2%). Subsequently, an equal amount of a 2% gelatin aqueous solution at 40°C was added and the system was stirred under the same conditions. Coacervation occurred when the pH was lowered to 3.9 with acetic acid solution. When the glutaraldehyde solution was added by drops for cross-linking the gelatin, the temperature of the system was reduced quickly to 5°C. Solid suspension was stirred for approximately 16 hours. The microparticles were studied in preparation medium without other treatment. It has been shown that ethyl benzoate is stable under these operative conditions.

All the experiments were carried out in a cylindrical glass reactor (1000mL, Ø = 90 mm) with a six-blade turbine impeller (blade length = 50 mm, blade width or thickness = 10 mm, mechanic adjusting ± 5rpm, Ika Labortechnik). The suspension was stirred during whole of the encapsulation at speeds of either 500, 750, 1000, 1500 and 1990 rpm.

Physicochemical properties of the liquid dispersion at 40.0 ± 0.5°C

The dynamic viscosities of dispersed and continuous phases are respectively : 4.0 mPa.s and 1.2 mPa.s. They are measured with an Ubbelhode type viscometer (Ø = 0.5 mm). The accuracy was ± 10^{-4} Pa.s. The interfacial tension (10.5 $mN.m^{-1}$) was measured with a pendant drop tensiometer. The accuracy was ± 10^{-4} $N.m^{-1}$. The solubility of ethyl benzoate in water was 770 ± 6 $mg.L^{-1}$.

Particle size measurements

The size distribution and the mean diameter of Sauter were determined with counting of about 800 microcapsules for each experiment. An optical microscope (x100, x400) was used.

Dissolution test method

The released amount of ethyl benzoate from microcapsules in water at a stirring rate of 100 rpm and at 25.0 ± 0.5°C was assayed spectrophotometrically at 231 nm with a Hitachi U-1100 spectrophotometer. 5 mL of suspension (corresponding to 778 ± 37 mg of

dried microparticles) were withdrawn from preparation medium and were put into a filter in vessel with 1000 mL of water at time t_0. Dissolution studies were performed in triplicate during 100 hours (t_{100}).

Results and discussion

Stirring speed influence on the particles morphology

The examination of the final particles with an optical microscope shows that there are two types of particles that appear according to the agitation rate.

The first type of particles appears on Figure (1a). These particles are more dense than the preparation medium. It seems that these are multinuclear microcapsules according to Thies (6), essentially constituted with polymeric material. However, it should be noted that these spheres contain few droplets of organic phase and that their proportion decreases when the agitation rate increases. They do not exist if the agitation rate exceeds 1000 rpm. In addition, the Sauter mean diameter of this type of particles does not vary when stirring speed increases.

Figure (1b) is the photograph of the second type of microparticles, the lighter particles. They float on the surface of the preparation medium. These particles are really microcapsules (labelled mononuclear microcapsules by Kondo (22)) because they are constituted of active agent droplets surrounded by a polymeric wall. The proportion of these microcapsules increases with respect to the agitation rate. When N reaches 1500 rpm there is only this type of particles. Nonetheless, it is interesting to note that the shell of these hollow spheres is much thicker when agitation rate surpasses 1000 rpm. In addition, the shape becomes ovoid and microdroplets of active molecules are entrapped by polymeric wall. Because the thickness of the wall increases, the particles becomes more dense and this type of microcapsules does not float on the surface of the preparation medium. The Sauter mean diameter decreases with respect to the agitation increasing. This result is also obtained by Bachtsi et al. (21).

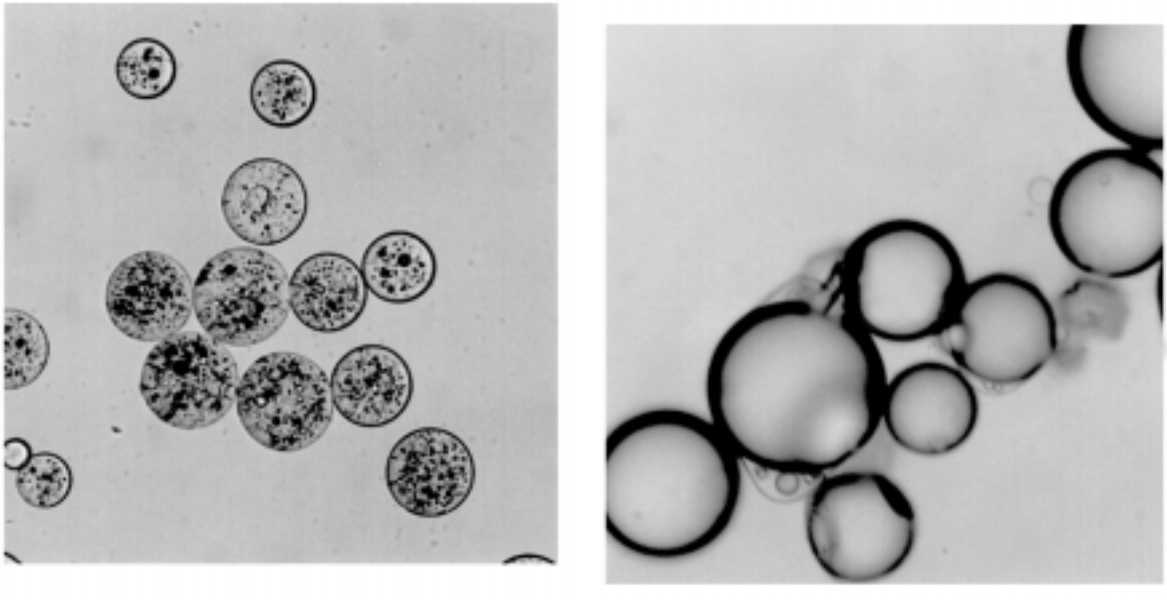

Fig. 1: Photographs (X100) of multinuclear (1a) and mononuclear (1b) microcapsules

Table 1 : Reynolds number (R_e) and Kolmogoroff's scale (η) versus stirring speed

N (rpm)	500	750	1000	1500	1990
R_e	17326	26000	34736	52000	69056
η (μm)	14	10	8	6	5

In order to verify the quantitative correlation (VI), between d_{32} and the agitation rate we have first calculated the values of the Reynolds number (R_e) and Kolmogoroff scale (η) as function of N, the stirring speed. These values, reported in Table (1), show that the conditions III, IV and V are satisfied. Therefore it is possible to test the relationship VI.
From this relation d_{32} is proportional to N to the power of -1.2. But, from the curve (Fig.2) if $Ln(d_{32})$ versus Ln(N) is linear, the slope of the straight line is lower than -1.2 since its value is -1.36, when d_{32} is in μm and N in rpm.

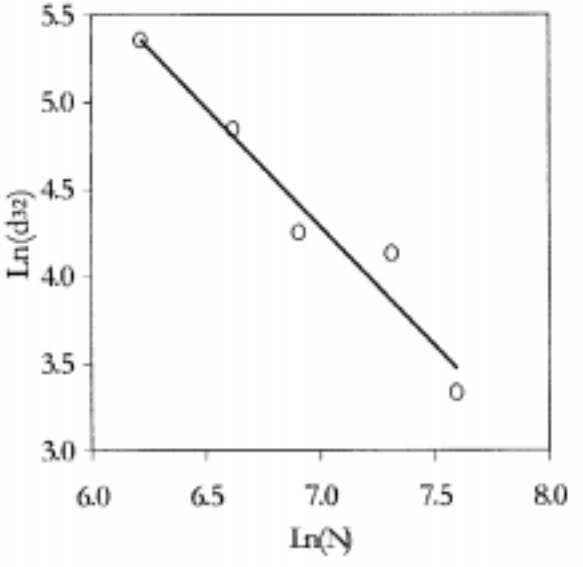

Fig. 2 : Relation between $Ln(d_{32})$ and Ln(N)

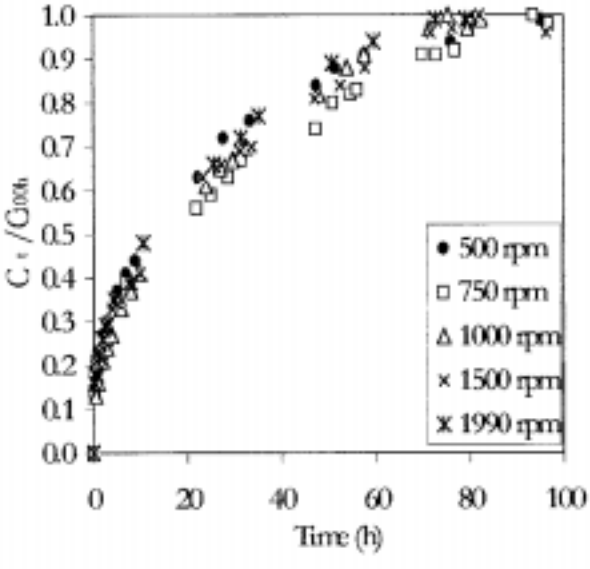

Fig.3 : Fractional release of ethylbenzoate

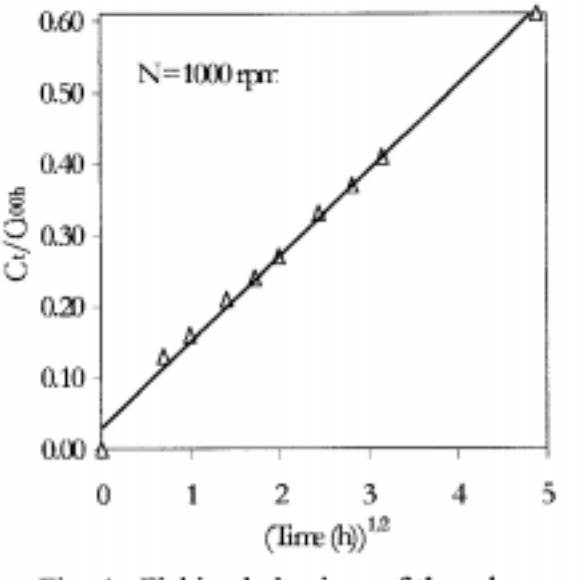

Fig. 4 : Fickian behaviour of the release ethylbenzoate

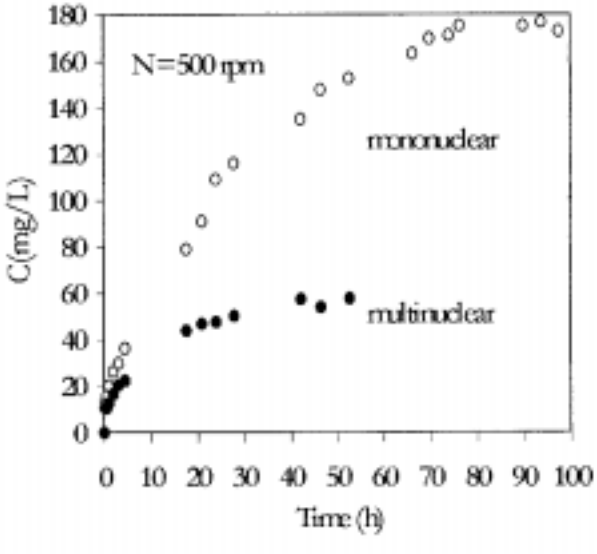

Fig.5 : Release curves of ethylbenzoate

It should be noted that other authors, trying to verify the relation VI, also obtained values different from the theoretical one. For example, Alexandridou et al. (20) found -0.93 instead of -1.2. In our results, the observed deviation may come from multinuclear microcapsules. Indeed, in order to assess the Sauter mean diameter we had not counted the small active agent droplets situated in the multinuclear microcapsules. Now the counting of these microdroplets should decrease the mean diameter and therefore increase the slope of the straight line.

Stirring speed influence on the drug release

The curves (Fig.3) that represent the fractional release of the active agent from microcapsules versus time, at various agitation rates, are very similar. They do not show differences between them as function of stirring speed. In all cases the amount of ethyl benzoate liberated at equilibrium represents about
42% of the total amount initially introduced at the beginning of the manufacturing process.

Nonetheless, Figure (4) shows that the active agent liberation is governed by diffusion. Indeed, the amount of the ethyl benzoate released is proportional to the square root of time (correlation coefficient = 0.99) according to the theoretical part.

In conclusion, these results seem to show that the slowest step of the whole transfer is the diffusion of active agent across the shell of the microcapsule and that the agitation rate during the dispersion of the organic phase in the continuous aqueous phase does not have influence on the active agent release. This last result is rather unexpected because it is evident that increasing agitation rate must decrease particle size and thus increase the release rate of the active agent according to the laws of mass transfer. In fact, thanks to the optical microscope observations depicted in the previous paragraph we can explain this strange result. Indeed we have seen that there are two types of particles which appear or not according to the agitation rate.

Some particles, like true microcapsules (according to Kondo (22)) have their size which decrease as function of the agitation rate but at the same time it seems that firstly, the thickness of their polymer wall increases and secondly one part of microcapsules aggregates at higher stirring speeds. In addition, before agitation rate reaches 1000 rpm, there are multinuclear microcapsules which are essentially constituted by polymeric material. It is very difficult to quantify each of these effects, but it is easy to understand that the increasing of thickness of the wall or aggregates decreases the rate of the drug diffusion.

In order to confirm these assumption we have compared the release rate of ethyl benzoate from mononuclear microcapsules and from multinuclear microcapsules, obtained with the same operative conditions and separated by decantation. The results illustrated by Figure (5), show that the ethyl benzoate release rate is much lower with the multinuclear microcapsules than mononuclear microcapsules. Also, we must change such process parameters as volume fraction of polymeric materials and surfactants concentration to obtain only microcapsules.

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