

## MICROENCAPSULATION BY SOLVENT EVAPORATION

Ming LI<sup>1</sup>, Denis PONCELET<sup>1\*</sup>, Olivier ROUAUD<sup>1\*</sup>

<sup>1</sup> UMR GEPEA, ENITIAA, Rue de la Géraudière,  
F-44322 Nantes cedex 03, France [ming.li@enitiaa-nantes.fr](mailto:ming.li@enitiaa-nantes.fr)



### INTRODUCTION

The solvent evaporation encapsulation technique has widely been used for preparation of microspheres for controlled release of drugs. The preparation method consists basically of four major steps: (i) dissolution or dispersion of the bioactive compound in an organic solvent containing the matrix forming material; (ii) emulsification of this organic phase called dispersed phase(DP) in an aqueous phase called continuous phase(CP) immiscible with the first one; (iii) extraction of the solvent from the dispersed phase by the continuous phase, then accompanied by solvent evaporation at the free surface of liquid to the air, transforming the droplets into solid microspheres (figure 1).

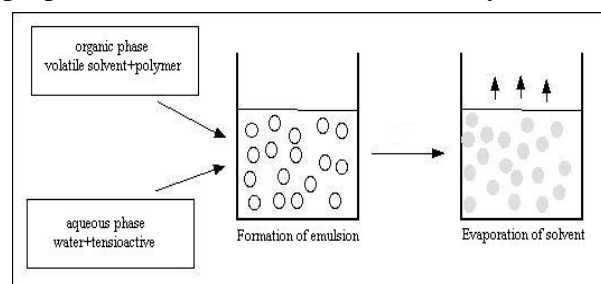


Figure 1: Diagram of process

The microencapsulation process studied in this work is achieved in a closed system. Contrary to the open systems usually used, it has the advantage to permit the recovering and the recycling of the solvent, leading to a reduction of production costs. In a closed system it is necessary to work under vacuum in order to promote the solvent evaporation. The objective of this study is to improve the knowledge on the physical phenomena implied in the process.

The analysis of the literature on microcapsules production by solvent evaporation reveals a surprising large number of publications. However, authors are usually interested only in two aspects: the selection of the polymer as the matrix and the controlled release either in vitro or in vivo. There are few papers that deal with the physico-chemical and engineering process of encapsulation by solvent evaporation. Operating conditions such as ratio of DP to CP, agitation mode, pressure and temperature have a great influence on the solvent evaporation and consequently on the structure of capsules. In order to better understand the influence of each parameter, a first step consists in studying the solvent evaporation at a macroscopic scale. A simple mathematical model is developed. Numerical simulations and experimental data are compared. The results show the influence of the mass transfer coefficient of the water-air interface.

### MATERIALS AND METHODS

The following materials were used to manufacture the microencapsules:

*Organic solvent:* dichloromethane (Sigma Aldrich and Fluka);

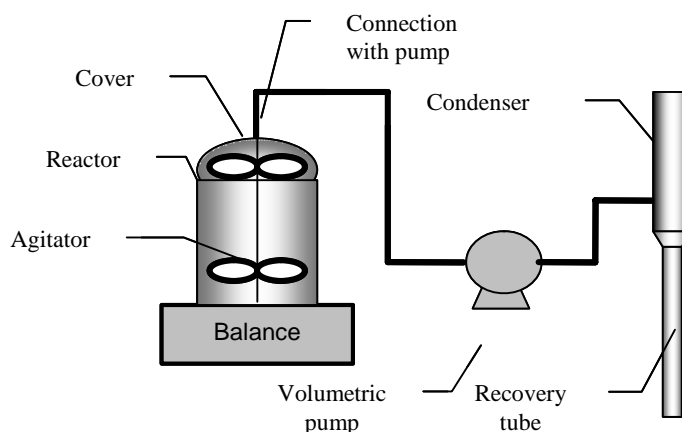
*Polymer:* Ethyl cellulose (100CPS, Sigma Aldrich), polymethyl methacrylate (Mw120 000, Sigma Aldrich);

*Tensioactif:* hydrolyzed polyvinyl alcohol (Sigma Aldrich).

*Reactor:* cylindrical beaker (BATAILLER) with a plat bottom (inner-diameter 10cm, height 10cm) made of of Pyrex glass. The baffles are fixed inside the reactor. A cover with 5 entries can be fixed on the reactor in order to make a closed system for the experiments under vacuum (figure 2).



**Figure 2: Beaker with baffles (left);  
Beaker fixed with the cover (right)**



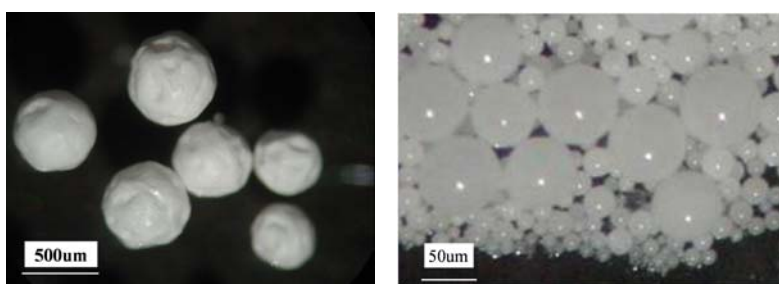
**Figure 3: Diagram of experimental device for  
under vacuum**

The experimental device is shown in figure 3. The reactor with the cover containing the solution is put on the balance. The weight of this assembly is recorded during the time in order to measure the weight loss of solvent. In the 5 entries of cover, we put separately the agitation system, the thermocouple, the pressure detector, the connection with the vacuum pump and the sampling system. The agitation system is composed of two agitators, one in the liquid phase, the other in gas phase above the liquid. In a previous work, the system combined with baffles in the reactor has been proved to be able to enhance the mass transfer between liquid and air. The exit of pump is connected to the condenser. Several liquid samples are taken via sampling system and analyzed by Gas Chromatography (GC). The weight loss of solvent is also measured from concentration measurements (GC), especially at the end of the experiment where the weight loss is too few to be precisely detected by the balance.

## RESULTS AND DISCUSSION

### *Manufacture of microencapsules*

Capsules made with the materials chosen are shown in figure 4. This preliminary trial is carried out under atmospheric pressure. According to the polymer, the surface pattern and the size of capsules are strongly different. The special surface pattern of capsule made of ethyl cellulose is probably due to the surface tension difference on the surface of droplet during its solidification (Marangoni effect). This preliminary study shows the importance of getting a deeper knowledge of mass transfer phenomena in the solvent evaporation process.



**Figure 4: Photos of capsules (Left: ethyl cellulose;  
Right: polymethyl methacrylate (Mw 120 000))**

### *Solvent evaporation under vacuum*

Before studying solvent evaporation in the whole process it is necessary to focus on the pure solvent evaporation without polymer. Based on a mass transfer balance a mathematical model is developed in order to analyze the influence of pressure on pure solvent evaporation. The model is based on the following mass transfer equations (wen-I LI, 1995) (figure 5).

1) The mass transfer between the dispersed phase(DP) and the continuous phase(DP):

$$F_1 = K_{sw} \cdot A_d \cdot (C_s - C_w)$$

$F_1$  : Mass transfer rate of solvent from DP to CP (mol/s)

$A_d$  : Exchange surface between DP and CP (m<sup>2</sup>)

$K_{sw}$  : Mass transfer coefficient (m/s)

$C_s$  : Solubility of solvent in water (mol/m<sup>3</sup>)

$C_w$  : Concentration of solvent in water (mol/m<sup>3</sup>)

2) The mass transfer at the free surface of liquid

$$F_2 = K_{wa} \cdot A \cdot (C_w - C_{wa}) \quad C_{wa} = \frac{P_s}{H}$$

$F_2$  : Mass transfer rate of solvent at liquid surface (mol/s)

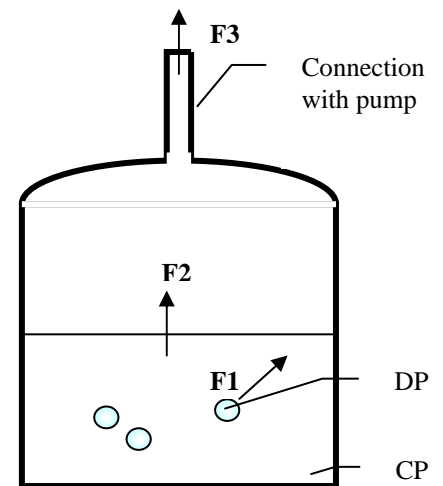
$K_{wa}$  : Mass transfer coefficient at the interface liquid/air (m/s)

$A$  : Surface of liquid in contact with air (m<sup>2</sup>)

$C_{wa}$  : Concentration of solvent in equilibrium with  $P_s$  (mol/m<sup>3</sup>)

$P_s$  : Partial pressure of solvent vapors in the gaz phase (Pa)

$H$  : Henry's constant (Pa/(mol/m<sup>3</sup>))



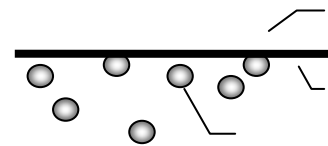
**Figure 5:**  
**Schema of mass transfer**

3) Removal of gas by pump

$F_3$  is determined by the power of the pump. In the flux  $F_3$ , it is a mixture of solvent vapour and air.

Numerical results of pressure and weight loss profiles are compared with experimental data in figure 7. In graph A, the profile of pressure can be divided into 3 stages. (i) The pressure drop in the beginning which is due to the removal of gas by the pump. (ii) Constant stage until the 35<sup>th</sup> minutes where the solvent evaporated into the gas phase ( $F_2$ ) compensates the gas loss due to the pumping ( $F_3$ ). When the values of both flows are equal, the pressure keeps constant. (iii) A second decrease when  $F_2$  decreases and cannot compensate any longer the gas removal by the pump. As observed in graph A, the length of the 2nd stage is overestimated by the numerical model. That means that the evaporation rate is overestimated from the 35<sup>th</sup> minutes. The results are confirmed by the mass loss profile (graph B) where the experimental weight loss profile begins to be non linear from the 45<sup>th</sup> minute.

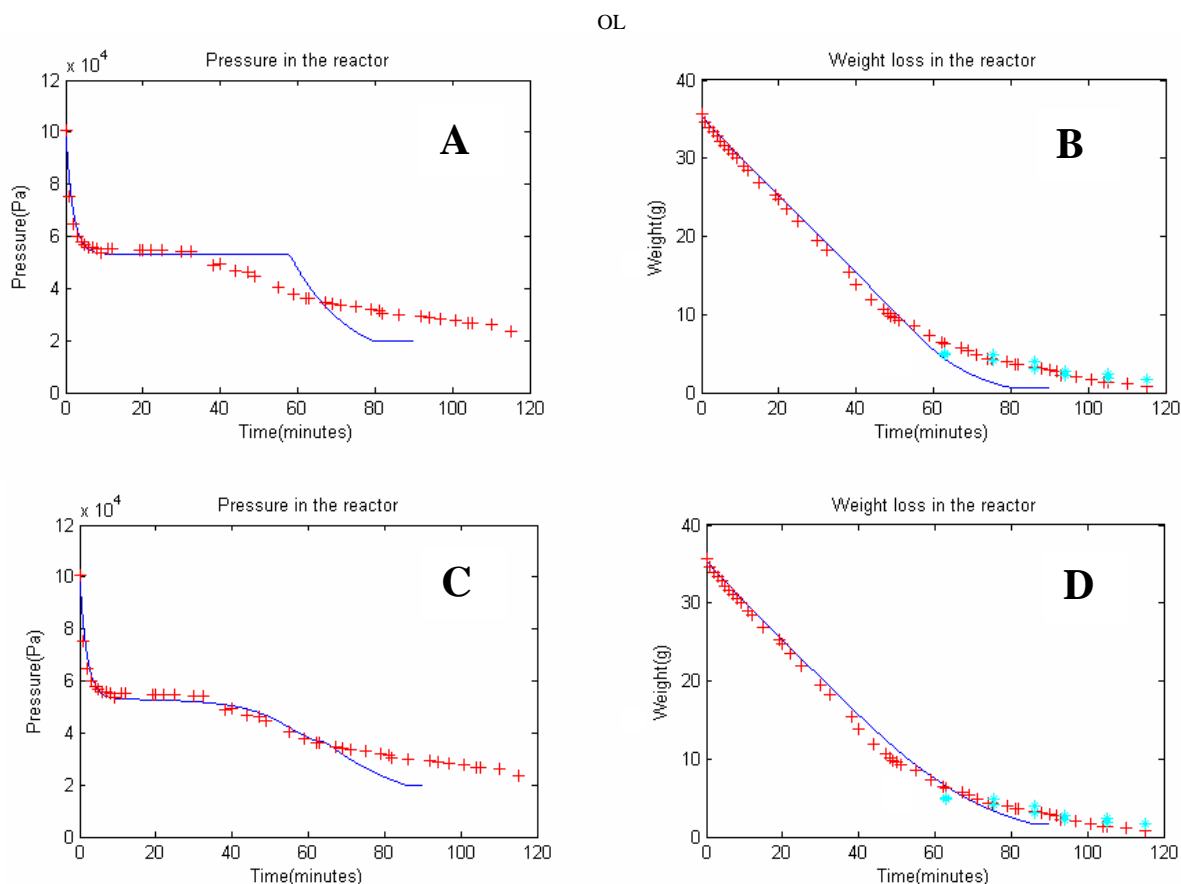
In order to explain this overestimation, a study on the mass transfer at the interface is carried out. We find that because of strong agitation, the drops of solvent can reach to the liquid surface and have a mass exchange directly with air without passing through the continuous phase (figure 6). This mass transfer decreases when the quantity of solvent decreases due to less direct contact of solvent with air. So the  $K_{wa}$  (mass transfer coefficient at liquid/air interface) previously set constant in the model actually varies with the quantity of solvent. Based on this argument, the value of  $K_{wa}$  is the sum of two parts: the mass transfer due to solvent drops at the interface (which decreases when the quantity of solvent decreases) and the mass transfer of solvent into air via water. This relation is represented by



**Figure 6: Mass transfer**  
**at the interface liquid/air**

the following correlation  $K_{wa} = \left( \frac{V_{DP}^t}{V_{CP} + V_{DP}^t} \right)^n \cdot K_1 + K_2$ ,  $n=2$ .  $V_{DP}^t$  is the volume of solvent in dispersed phase at time t,  $V_{CP}$  is the volume of continuous phase.  $K_1$  and  $K_2$  are constant.

After modifying the value of  $K_{wa}$ , the results of modelling are more satisfactory (figure 7, graph C and D).



**Figure 7 : Profiles of pressure and weight loss during solvent evaporation (Blue lines: modelling; Red points: experimental date; Green points: experimental date measured by GC) Graph A and B : when  $K_{wa}$  is constant; Graph C and D : when  $K_{wa}$  is recalculated.**

## CONCLUSIONS AND PERSPECTIVES

A study on the process of solvent evaporation is carried out. A mathematical model is developed for pure solvent evaporation under vacuum and gives promising results. The work in the future is consist of completing the model on solvent evaporation when polymer is present in the dispersed phase and building a model for the mass transfer inside one single droplet of dispersed phase.

## REFERENCES

Wen-I LI (1995), Kimberly W.Anderson, Patrick P.Deluca, 'Kinetic and thermodynamic modelling of the formation of polymeric microspheres using solvent extraction/evaporation methode', Journal of Controlled Release 37(1995) 187-198

Wen-I LI (1995), Kimberly W.Anderson, Patrick P.Deluca, 'Prediction of solvent removal profile and effect on properties for peptide-loaded PLGA microspheres prepared by solvent extraction/evaporation method', Journal of Controlled Release 37(1995) 199-214