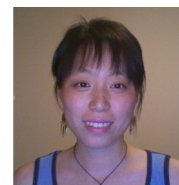


MICROENCAPSULATION BY SOLVENT EVAPORATION



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INTRODUCTION

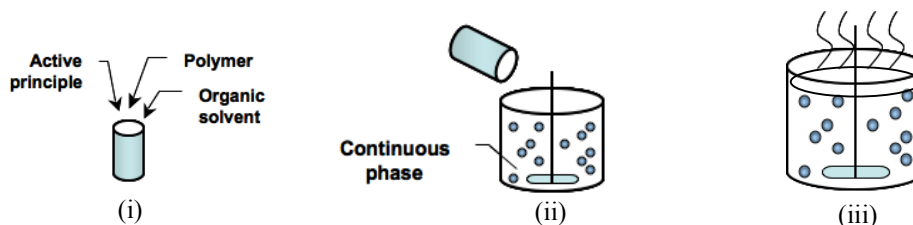


Figure 1: Basic steps of microencapsulation by solvent evaporation

The solvent evaporation encapsulation technique has widely been used for preparation of microspheres for controlled release of drugs. The preparation method consists basically of three major steps (figure 1): (i) dissolution of polymer and active principle in organic solvent; (ii) emulsification of this organic phase called dispersed phase(DP) in an aqueous phase called continuous phase(CP) ; (iii) extraction and evaporation of solvent. Large numbers of publications focus on the choice of polymer and controlled release in vitro and in vivo. Few papers deal with the physico-chemical and engineering aspects. Operating conditions such as ratio of DP to CP, agitation, pressure and temperature have a great influence on the solvent evaporation and consequently on the structure of capsules. For a better understanding of the influence of each parameter, our work consists of studying the solvent evaporation at a macroscopic scale and comparing the quality of capsules obtained.

MATERIALS AND METHODS

The following materials were used to manufacture the microencapsules:

Name of products	Producer	Advantage
Dichloromethane	Sigma Aldrich, Fluka	Solvent which dissolves most of the polymers; almost immiscible in water; high volatility and quite low boiling temperature
Ethyl cellulose	100 CPS Sigma Aldrich	Model polymer with similarity to some agro-pharmaceutics products; low cost
Hydrolyzed polyvinyl alcohol (PVA)	87%-89% hydrolyzed Sigma Aldrich	Surfactant which gives more spherical capsules

Table 1: Choice of materials

The reactor is cylindrical beaker with plane bottom (inner-diameter 10cm, height 10cm) made of Pyrex glass (figure 2). Baffles are fixed inside the reactor to avoid vortex. Double agitators system is put in the middle of reactor to homogenize the gas and liquid. Heating plate is fixed on the bottom of reactor. It is connected with a temperature controller to maintain the temperature of liquid at about 25°C. The experiments were achieved in closed system under vacuum (all entries capped) and in open system under atmospheric pressure (one entry left open) (figure 3). Contrary to open system usually used, closed system has the advantage to permit the recovering and the recycling of solvent, leading to a reduction of production costs. Time of production is also greatly reduced under vacuum. The reactor with cover was put on the balance. The dispersed phase was introduced into reactor when agitation system was switched on. Measurement tools were then fixed on the entries. We measured the weight of reactor containing liquid, pressure inside the reactor, temperatures in

liquid and gas phase, heat flux transmitted between heating plate and reactor. The vacuum pump was finally switched on signifying the start of experiment. The measurement center (AOIP MESURES, SAM20) recorded all measurement data during experiment.

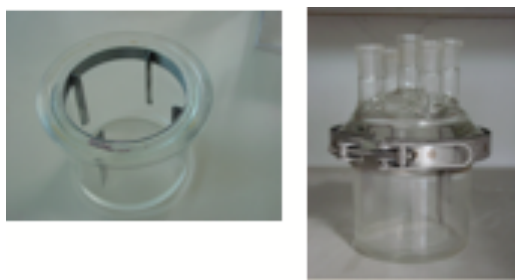


Figure 2: Beaker with baffles (left); Beaker fixed with the cover (right)

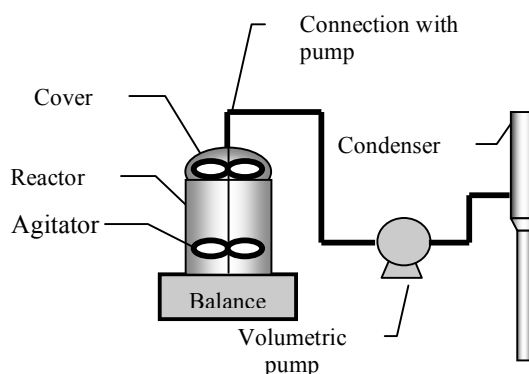


Figure 3: Diagram of experimental device

Validation of model: The experiments were carried out in the following conditions to validate the model. The quantity of solvent and water varied and the temperature varied: 20mL of solvent evaporated in 400mL of water while temperature of water was maintained at about 25°C (A in figure 7); 40mL of solvent evaporated in 200mL of water while temperature of water was maintained at about 25°C (B in figure 7); 40mL of solvent evaporated in 200mL of water while temperature of water decreased from 25°C to 13°C due to lack of heating (C in figure 7);

Characterization: By exporting the measurement data to computer, we can obtain the profile of mass loss in the reactor, pressure revolution, temperature revolution and heat flux. Morphology of capsules was observed by scanning electronic microscope (Joel, JSM-6400F).

RESULTS AND DISCUSSION

Morphology of microcapsules

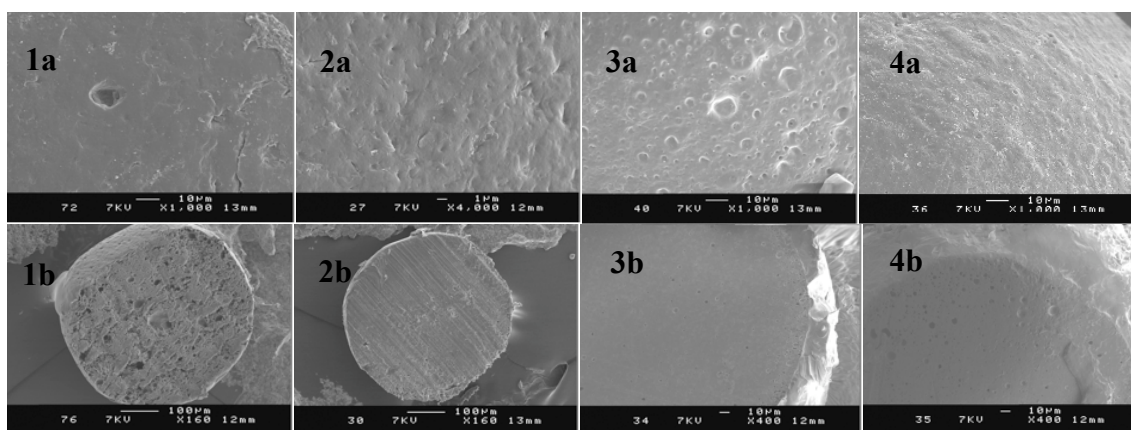


Figure 4: Photos of capsules produced under 4 different conditions:

By very slow evaporation (photo 1); By extraction (photo 2); By evaporation under atmospheric pressure (photo 3); By evaporation under reduced pressure (photo 4). 'a' means the surface of capsule and 'b' the inner structure.

To study the influence of solvent removal rate and pressure on the structure of capsules, solvent was removed under four different conditions. Microcapsules were made (figure 4) by introducing 20mL of dispersed phase (5.2 % (w/w) of ethyl cellulose) in 200mL of 0.2% PVA solution. Solvent was removed by 1) very slow evaporation under atmospheric pressure (6g of solvent /day); 2) extraction of solvent by: it was performed by dropping of emulsion in very large volume of water. Solvent removal is immediate; 3) evaporation under atmospheric pressure; 4) under reduced pressure.

	Very slow evaporation	Extraction	Under atmospheric pressure	Under reduced pressure
Photos	1a, 1b	2a, 2b	3a, 3b	4a, 4b
Surface pattern	Smooth with few pores	Wrinkled surface with numerous pinholes	Concave surface pattern with pores	Concave surface pattern with pores
Size of pores on the surface	10 μm	250nm	1.5 μm	1 μm
Inner structure	Very porous	Very dense without pores	Medium porous	Medium porous
Size of pores inside capsules	10-25 μm	-	Less than 5 μm	Less than 10 μm

Table 2: Observation of morphology of capsules

From table 2, we can conclude that when solvent is removed slowly, capsules have few but big pores on the surface. Their inner structure is quite porous. The pores are big. When solvent is removed quickly, capsules have more pores on the surface but the size of pores is tiny. Their inner structure is very dense. Reduced pressure gives capsules smoother surface, which has also been observed by Izumikawa (1991). Reduced pressure increases the size of pores inside the capsules.

When solvent is removed very fast such as by extraction, a rigid layer rich in polymer is created on outer side of the drop. The diffusion of solvent that is trapped inside the drop thus creates very small pinholes everywhere on the surface of capsules.

When solvent is removed very slowly in case of very slow evaporation, the layer rich in polymer stays very soft since it contains still much solvent. The solvent diffusion can create big holes on the layer. Solvent diffuses through these few big opening without creating new ones on the surface. The porous inner structure of capsules is due to solvent diffusion during slow solidification of capsules.

Reduced pressure increases the solvent evaporation rate, thus leading to a smoother surface compared with capsules made under atmospheric pressure. Reduced pressure improves expansion of gas, making bigger pores inside the capsule. The concave surface pattern of capsules is probably due to marangoni effect. The concentration gradient and temperature gradient among different places on the surface drive heat and mass convection, leaving a moon-surface-like pattern.

Modeling of solvent evaporation under reduced pressure

Before studying solvent evaporation in whole process it is necessary to focus on the pure solvent evaporation without polymer. Based on a mass transfer balance (figure 5) a mathematical model is developed to predict pure solvent evaporation. F_1 is the diffusion mass flux between dispersed phase and continuous phase. It is much bigger than flux of solvent evaporated at air/liquid surface. So we assume that solvent evaporated can always be compensated by diffusion until there is not enough solvent left. F_2 is mass flux of solvent evaporation at liquid/air interface. (Wen-I LI 1995). It can be written as $F_2 = KOL \cdot A \cdot (C_w - P_s / H)$. KOL is mass transfer coefficient at liquid/air surface; A is surface of liquid; P_s is partial pressure of solvent vapour; H is Henry's constant. F_3 is mass flux at the exit of reactor. It is limited by the capacity of pump.

A mathematical model is built by including the mass transfer coefficient KOL. It is capable to predict the pressure evolution and mass loss of solvent. The value of KOL is proved not to be constant by pressure profile from modelling and experimental data. We found a good correlation by assuming that KOL is the sum of two contributions (figure 6): transfer through the water/air interface and transfer through droplet/air interface. The latter one is related to droplets in contact

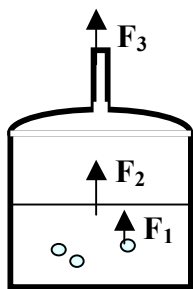


Figure 5: Schema of mass transfer

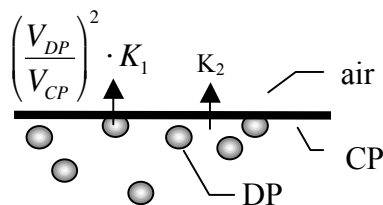


Figure 6: Mass transfer at liquid/air interface

with air and it increases when the quantity of solvent increases. This relation is represented by the following correlation $KOL = \left(\frac{V_{DP}}{V_{CP}}\right)^2 \cdot K_1 + K_2$. V_{DP} is the volume of solvent in dispersed phase; V_{CP} is the volume of continuous phase. K_1 and K_2 are constant.

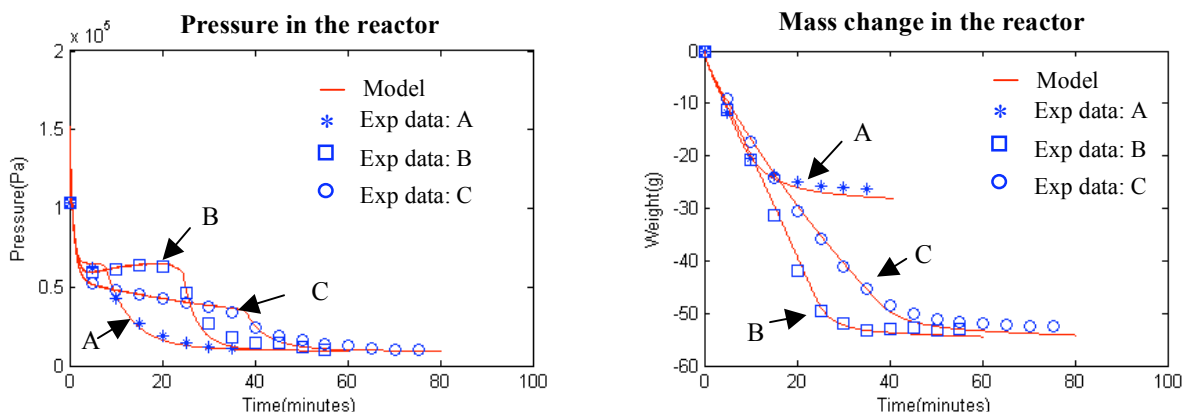


Figure 7: Profiles of pressure and mass change in the reactor

A: 20mL of solvent in 400mL of water at 25°C; B: 40mL of solvent in 200mL of solvent at 25°C; C: 40mL of solvent in 200mL of water from 25°C to 13°C (Experimental data as discrete points and modelling results as continuous line)

Compared with experimental data, model gives satisfying results (figure 7). We can conclude that the quantity of DP does not impact the initial solvent evaporation profile (curve A, B). Influence of quantity of DP on solvent evaporation rate is hidden because capacity of pump is limited and becomes a constraint. Solvent evaporation rate is increased by higher temperature (curve B, C).

CONCLUSIONS

We found that fast solvent removal produces capsules with numerous small pinholes on the surface and a dense inner structure while slow solvent removal produced few but big pores on the surface and a porous structure. Mathematical model has been developed for pure solvent evaporation under reduced pressure and gives satisfying results. Mass transfer coefficient between solvent and air is proved to be the sum of two parts: transfer by water/air interface and droplet/air interface. The work in the future is consisted of building a model on solvent evaporation in one single drop of dispersed phase and integrating this model into the model that predicts the solvent evaporation in the reactor.

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