Novel approach for characterization of microspheres made by solvent evaporation

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Introduction & Objective

➢ In order to shorten the process duration of microencapsulation by solvent evaporation technique. Reducing pressure has been proven to be an efficient way. To evaluate its influence on the physical properties of microspheres, drug free microspheres were prepared under varied pressure and solvent evaporation rate.

➢ The surface and the inner structure of microspheres are examined by different techniques of characterization. The technique of micro-computed tomography (micro CT), capable of detecting the inner structure of a whole microsphere, gives extremely valuable results.

Materials & Methods

Preparation of microspheres

1.45g of ethyl cellulose was dissolved in 20 mL of dichloromethane, forming the dispersed phase. This solution was then introduced under agitation in 200 mL of 0.04% (w/w) of PVA solution at 25 °C (fig.1). The vapors of solvent were removed by the volumetric pump (fig. 2). The solvent evaporation rate was controlled by the flow rate of the pump. The pressure was fixed at atmospheric pressure or at 600 mBar.

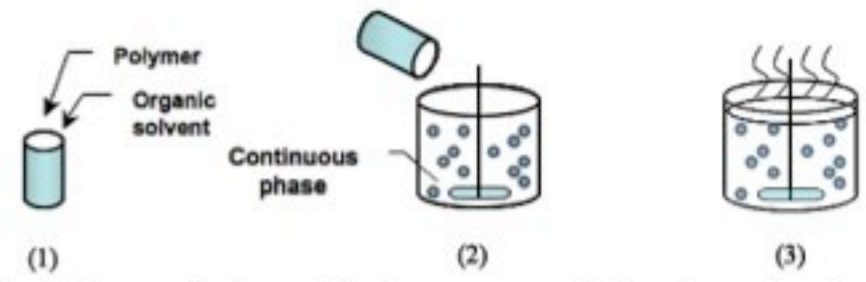


Figure 1: Schema of steps of microencapsulation by solvent evaporation

Materials

- Dichloromethane (SIGMA-Aldrich) as solvent;
- Ethylcellulose (Ref 247499, SIGMA-Aldrich) as polymer;
- Hydrolyzed polyvinyl alcohol (Sigma Aldrich) as tensioactive.

Measurements

- Masse of solvent evaporated versus time (fig.2)
- Surface morphology of microspheres observed by scanning electronic microscopy (SEM)
- Inner porosity of microspheres measured by micro CT and 3-D reconstructed images (carried out in University of Birmingham, UK)
- Size of pores measured by image analysis

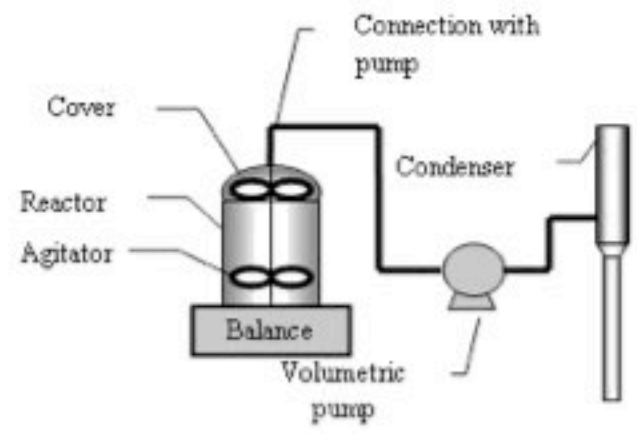


Figure 2: Sketch of experimental device

Experimental results

Influence of solvent evaporation rate

• The fig.3 shows the microspheres prepared under atmospheric pressure at different evaporation rate. It appears that with increasing evaporation rate, the size of pores on the surface decreases and the number of pores per unit area increases.

• The measurement of inner porosity by micro-CT (fig.4a) shows the the inner porosity decreases with increasing evaporation rate. The existence of pores confirms the formation of gas bubble during the solidification of microspheres, even at atmospheric pressure. Moreover, the porosity is very high in the center and decreases gradually in the direction to the center (fig.4b). This observation is valid under all operating condition.

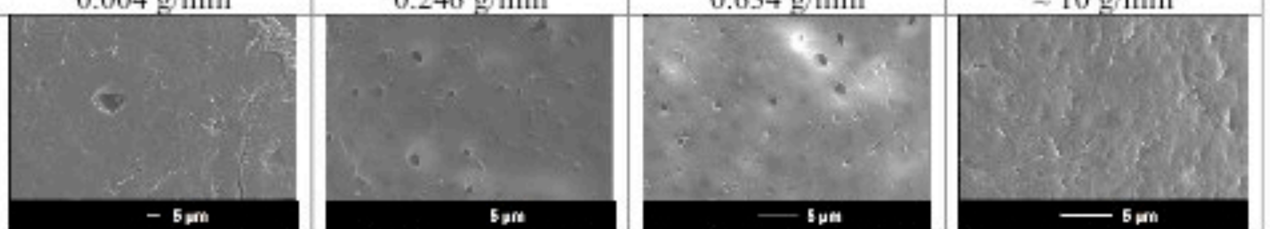
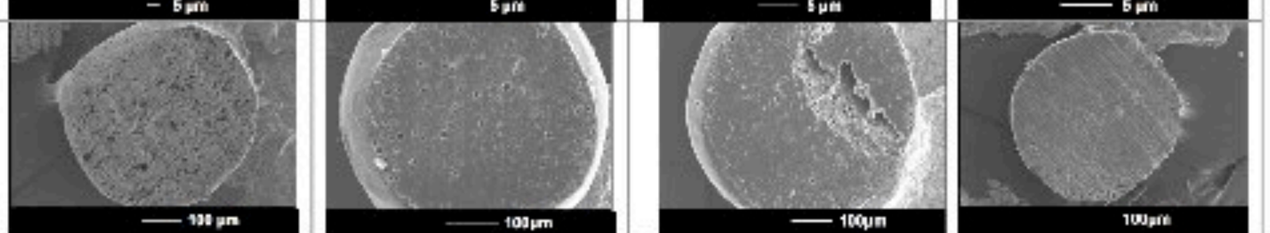
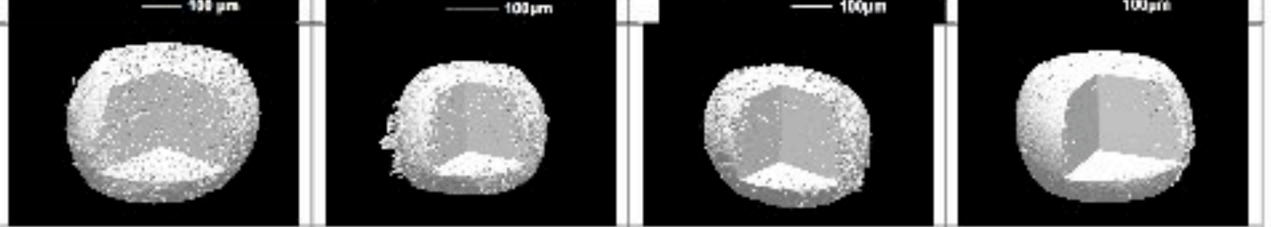
	Very slow evaporation	Slow evaporation	Fast evaporation	Extraction
Evaporation rate	0.004 g/min	0.246 g/min	0.634 g/min	≈ 10 g/min
Surface (SEM)				
Section (SEM)				
3-D images reconstructedwith measurement of micro-CT				
Pore's size on surface	< 14 μ m	< 2 μ m	< 2 μ m	< 150 nm
Inner porosity	24%±2%	13%±1%	10%±1%	4%±0.5%
Pore's size inside	< 20 μ m	< 35 μ m	< 10 μ m	< 3 μ m

Figure 3: Photos of microspheres prepared at different solvent evaporation rate

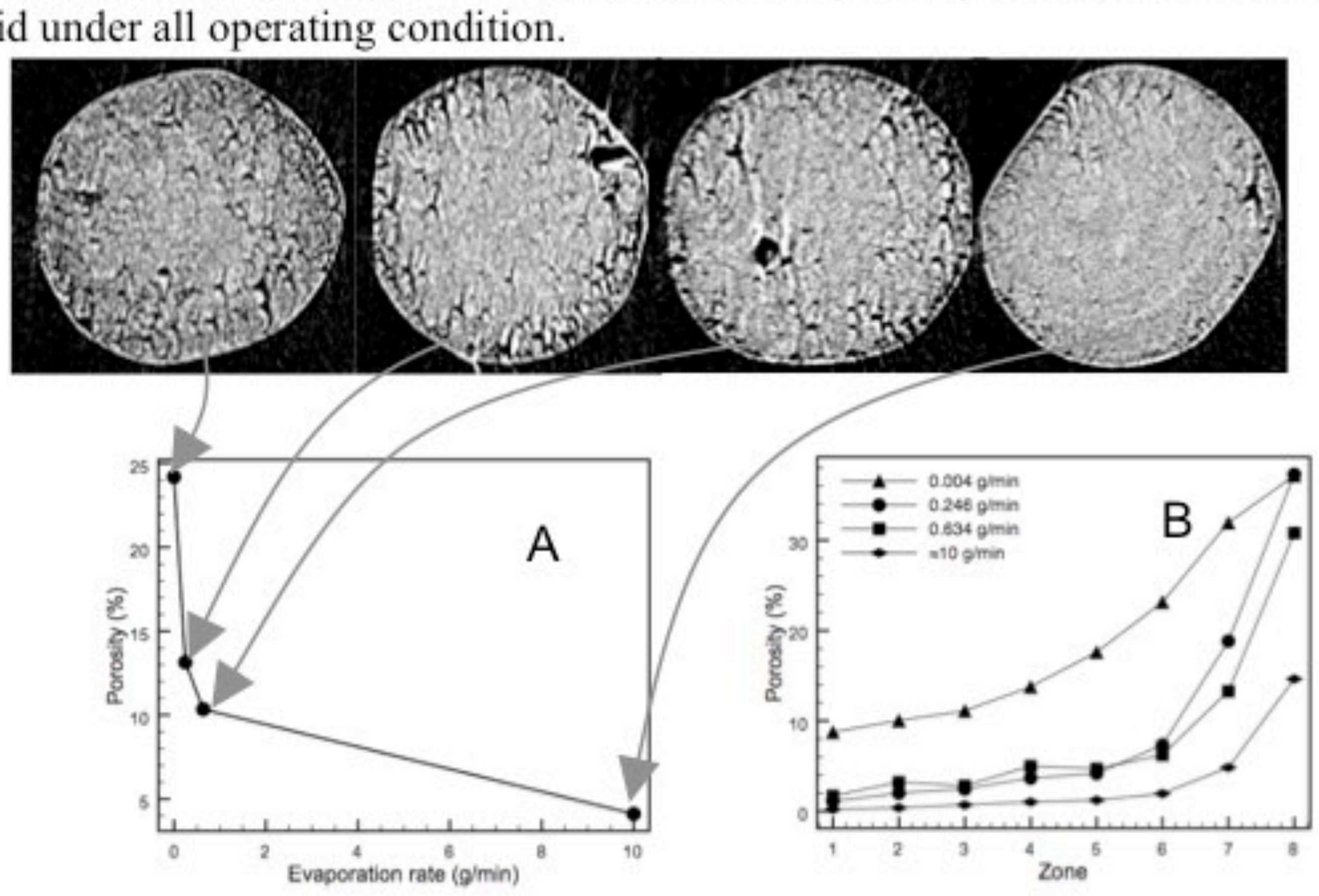


Figure 4: Inner porosity as a function of solvent evaporation rate with images of micro CT (fig. A) and porosity at different zones (fig. B: microspheres were divided into 8 zones according to their distance to the center with constant interval equal to 1/8 of the radius)

Influence of pressure

The fig. 5 shows that the microspheres made under reduced pressure have smaller pores on the surface and inside.This observation is contrary to our initial expectation since pores generated by the gas bubbles should be bigger under reduced pressure. The possible explanation is that slower solidification under atmospheric pressure permits the growth of the gas bubbles and the fusion of bubbles. This means the solvent evaporation rate has more impact on the porosity than the pressure does. The microspheres made under reduced pressure have smaller size. This is apparently not due to the slight difference of porosity.Therefore, the dispersion seems to be more efficient under reduced pressure.

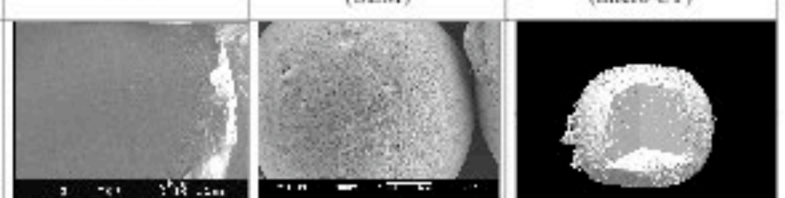
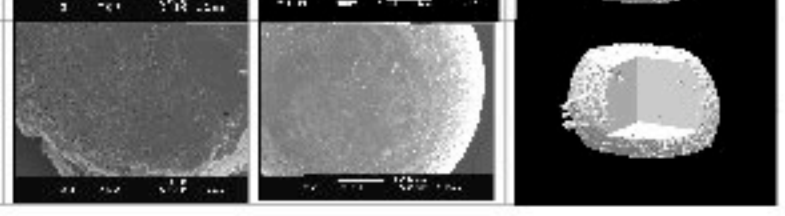
Pressure	Size of microsphere (um)	Inner porosity	Surface	Inner structure (SEM)	Inner structure (micro CT)
Atmospheric pressure	647±50	5%			
600 mBar	460±70	2%			

Figure 5: Comparison of microspheres made under atmospheric pressure and under reduced pressure

Conclusion

➢ The X-ray tomography has been proven to be an efficient and powerful way to carry out a global and quantitative measurement of inner structure of microspheres. Combined with scanning electronic microscopy, most characteristics of microspheres can be obtained.

➢ Even though the pressure influences the formation of the pores, the solvent evaporation rate has more strong impact on the porosity of microspheres, The porosity increases with decreasing evaporation rate. Moreover, it is confirmed that low pressure is not a prerequisite for gas bubble formation which is responsible of the porous structure.

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