

An emulsion preparation for novel micro-porous polymeric hemi-shells

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Abstract

A modified oil-in-water (O/W) emulsion process was developed to produce novel micro-porous hemi-spherical polycaprolactone (PCL) micro-particles called “hemi-shells”. By addition of a porogen such as sodium bicarbonate (NaHCO_3) into the PCL-dichloromethane (DCM) oil phase and emulsification in an acidic polyvinyl alcohol (PVA) aqueous phase, micro-porous hemi-shells formed as solvent evaporated. CO_2 gas evolution from the porogen created particles with an externally micro-porous shell and a large internal cavity. The hemi-shells were characterized by SEM and optical microscopy. The number-average particle yield in the 50–200 μm range was 84%. The number-average hemi-shell yield in the same size range was 41%. These novel micro-particles have potential applications in tissue engineering and drug delivery.

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1. Introduction

Micro-porous polymeric micro-spheres have been fabricated by many methods for a wide range of applications. Typical manufacturing methods include modified emulsion-solvent evaporation systems [1,2], phase separation [3], emulsion polymerisation [4] and spinning disk atomisation [5]. The most widely used route for manufacture still remains the emulsion-solvent evaporation technique [3].

A typical emulsion process involves dissolving a polymer in a volatile organic solvent and emulsifying this phase in an aqueous phase containing a surfactant to form an oil-in-water (O/W) emulsion, followed by solvent evaporation while stirring. By this emulsion process, typically, non-porous micro-particles are obtained. However by controlling the solvent evaporation rate, for example, particles can be modified to be micro-porous [6]. To further increase the particles porosity, porogens such as sodium chloride and ammonium bicarbonate may be added [1,5]. The low density and high degree of porosity of the micro-particles obtained by this technique makes them highly attractive for

tissue engineering applications [1,5] and for pulmonary drug delivery [2]. In this study, we describe the fabrication of novel polycaprolactone micro-porous hemi-spherical micro-particles called “hemi-shells” using a porogen-emulsion-solvent evaporation technique.

2. Experimental

2.1. Materials

Polycaprolactone (CAPA 6500, Mw 50000) was purchased from Solvay Chemicals (USA). Dichloromethane (DCM) and polyvinyl alcohol (PVA, average M_w 18000–23000, 87–89% hydrolyzed) were obtained from Sigma Aldrich (South Africa) and were of reagent grade and used as received. Glacial acetic acid (100%) and sodium bicarbonate (NaHCO_3) obtained from Merck (South Africa) were of analytical grade. NaHCO_3 was ground down and sieved into a narrow size range of 25–38 μm before use.

2.2. Preparation of hemi-shells

Polycaprolactone hemi-shells were prepared by using an O/W technique. PCL (15% w/v) was fully dissolved in 10 ml DCM (oil

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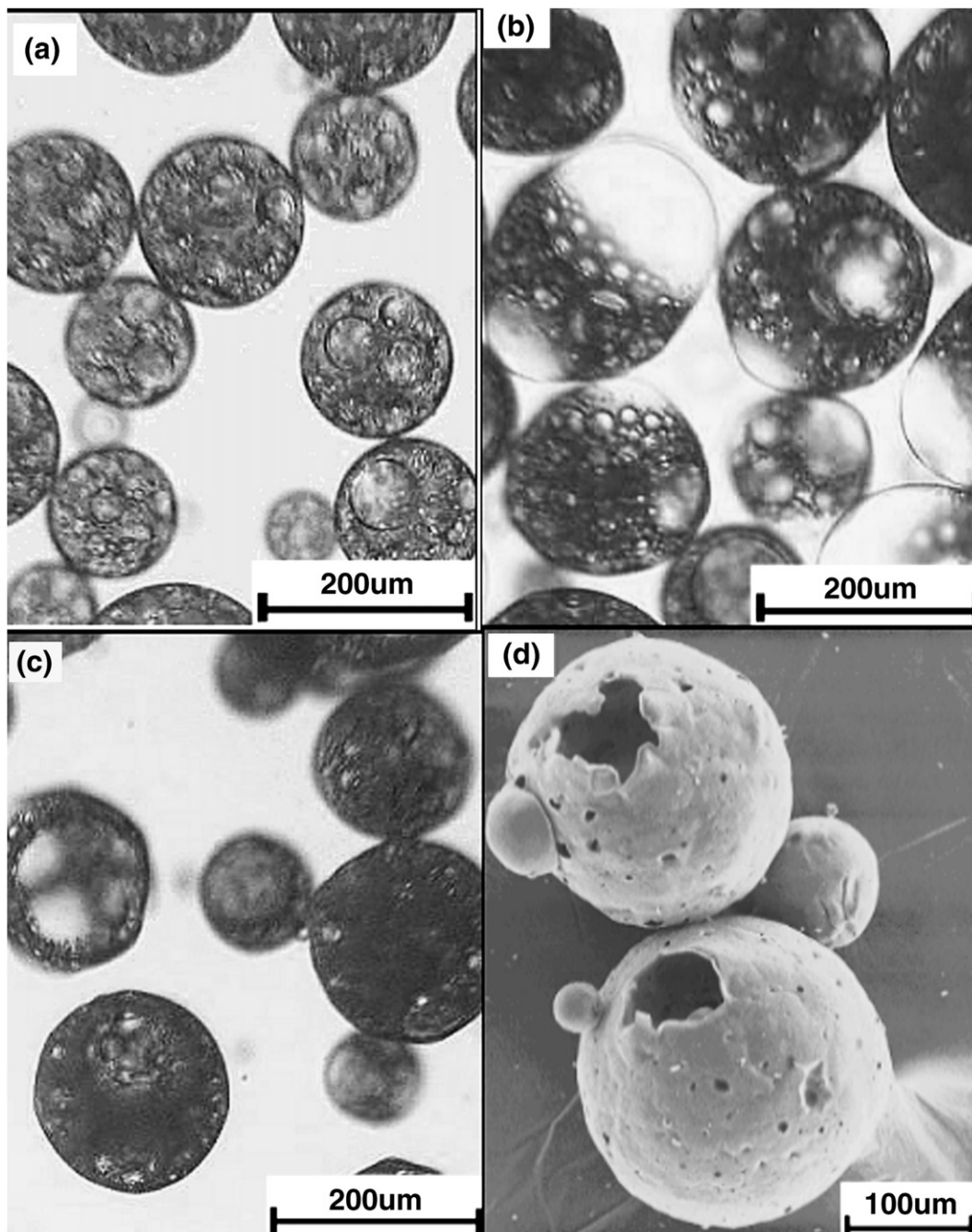


Fig. 1. Optical photomicrographs of the hemi-shell morphological development with time: (a) 10 min, (b) 20 min, (c) 30 min, and (d) SEM micrograph of the final morphology after solvent evaporation was completed.

phase). NaHCO_3 (25–38 μm) was then stirred into the oil phase with a porogen: PCL ratio of 2:1 by weight. PVA (1% w/v) was dissolved in 150 ml deionized water (water phase). The O/W

emulsion was prepared by using a Silverson homogenizer (Model L4RT, Silverson Machines, UK) at 200 rpm for 2 min at 25 °C. The emulsion was solvent evaporated while constantly stirring at

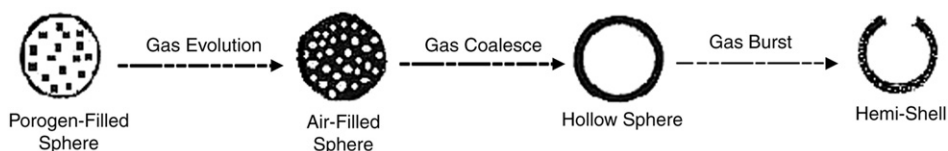


Fig. 2. Schematic of hemi-shell formation.

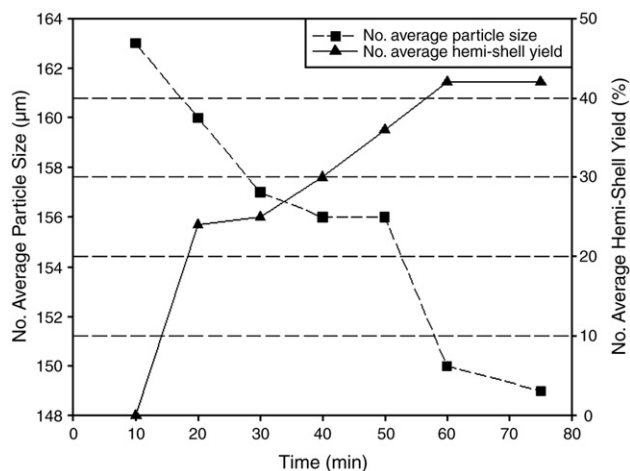


Fig. 3. Plot of change in number-averaged particle size and hemi-shell yield with solvent evaporation time.

the same temperature. Glacial acetic acid (2.4 ml) was added after 30 min to increase CO_2 gas evolution by the reaction (1) as given below:



After solvent evaporation was completed, the hemi-shells were isolated using filtration, washed three times with deionised water and the left to dry at 25 °C.

2.3. Characterisation of hemi-shells

To monitor the morphological changes of the hemi-shells with time, small quantities were removed from the emulsion as solvent evaporation proceeded. These particles were examined using an optical microscope (Leica DME, USA) with a Leica DC 150 digital camera system. By using image analysis software (ImageJ, NIH), the number-average particle size and yield of hemi-shells were obtained with increasing time intervals ($n=200$). Scanning electron microscopy (LEO 1525 field emission SEM with Oxford's INCA system) was used to observe the final hemi-shell morphology.

3. Results and discussion

Fig. 1 shows the morphological changes observed in the stages of hemi-shell development with time as observed using optical microscopy while still wet. After 10 min of solvent-evaporation (Fig. 1a), the porogen dissolved forming small CO_2 gas bubbles which were entrapped within the polymeric micro-spheres. These bubbles gradually coalesced forming larger bubbles as seen at 20 and 30 min (Fig. 1b and c). It is hypothesized that these gas bubbles once fully coalesced (Fig. 2), eventually burst thus creating an internal cavity with an externally micro-porous shell as shown in the SEM micrograph (Fig. 1d).

Acid addition also increased the gas formation thus creating more porosity. Coalescence of smaller bubbles to form larger bubbles can be attributed to the change in Laplace pressure [7]:

$$P_{\text{inside}} - P_{\text{outside}} = \frac{2\sigma}{r} \quad (2)$$

where P_{inside} , P_{outside} is the internal and external pressure, respectively on the bubble, r is the bubble radius and σ is the surface tension. Gas evolution was also noted by Kim et al. [1] in the formation of poly (lactic-co-glycolic acid) (PLGA) interconnected porous particles when using ammonium bicarbonate as a porogen in a water-in-oil-water (W/O/W) emulsion.

Fig. 3 illustrates the change in the number-average particle size and hemi-shell yield with solvent evaporation time. The number-average particle size decreased with time from 163 µm to 149 µm as solvent evaporation progressed from 10 to 75 min. A particle yield of 84% was obtained in the 50–200 µm range after solvent evaporation was completed. Particle size decrease corresponded to an increase in hemi-shell yield where a yield of 41% was achieved after 75 min. The increase in hemi-shell yield as explained above is due to the increase in bubble coalescence as the polymeric micro-spheres shrink during solvent evaporation which is analogous to the coalescence seen in W/O/W emulsions [8]. Other morphologies, such as hollow particles, were also obtained by this emulsion method by changing variables such as the solvent evaporation rate, surfactant type etc. (Results to be published separately).

4. Conclusions

Novel micro-porous polycaprolactone hemi-shells with a number-average particle yield of 84% in the 50–200 µm range have been successfully produced by sodium bicarbonate addition into a modified O/W emulsion. The gas evolution from porogen dissolution leads to a highly porous micro-particle at the onset, which finally develops into a hollow concavity with a micro-porous shell. Hemi-shells displayed central openings of up to 75 µm in diameter with surface micropores of 20 µm in diameter. This unique morphology has potential applications in tissue engineering, and drug delivery amongst others.

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