CHAPTER FIVE

5 CHEMICALLY GRAFTED MICROCAPSULES

5.1 INTRODUCTION

Processes to functionalise polymers and impart some specific property to the polymer are becoming increasingly important in advanced materials technology. The ideal process for polymer functionalisation and grafting to produce microcapsules for medical and animal applications should be mild, done in aqueous media and applicable to important common polymers. The process should be biocompatible and not use toxic materials that cannot be removed.

The previous chapter demonstrated that pH-responsive functional microcapsule could be developed by interfacial polymerisation and plasma-induced grafting. The investigation was a proof of concept on the feasibility of developing a pH-responsive drug delivery system. However, this system has some drawbacks - it needs special equipment, the process is time-consuming, and the biocompatibility of the polyamide has not been studied.

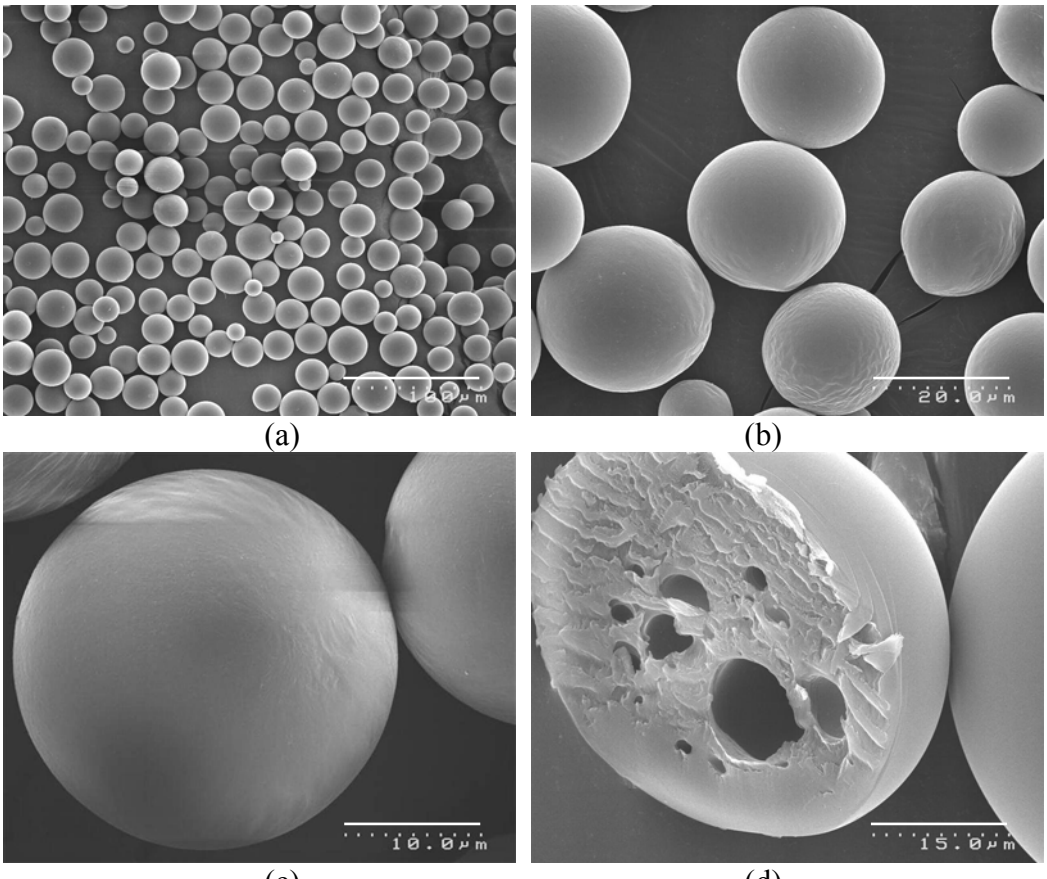
The aim of this chapter is to identify ideal polymers and develop a simple and inexpensive procedure for fabricating and functionalising microcapsules to be used for application in rumen-protection drug delivery systems.

5.2 EXPLORATORY STUDY

Based on the characteristics of polymeric materials for controlled release delivery systems (Chapter Two), polycaprolactone (PCl), polysulfone (PSf) and polystyrene (PSt) were chosen because they are biocompatible and easy to process. Literature shows they have good chemical and mechanical stability (Allcock and Lampe, 1990; Tracy, 1998; Yang *et al.*, 2005). The effect of process conditions on morphology and initial grafting trials were investigated.

5.2.1 Morphology

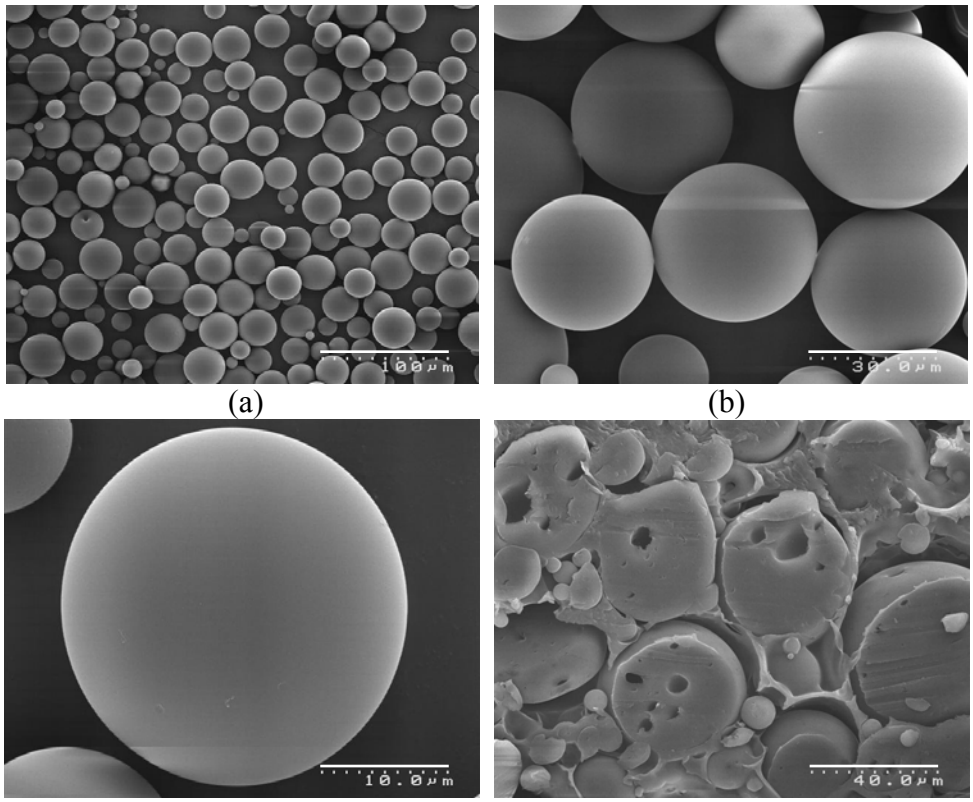
Microcapsules prepared from polycaprolactone, polysulfone and polystyrene by solvent evaporation technique (Section 3.3.2) had similar morphology (Figure 5.1, 5.2, 5.3) with spherical smooth, non-porous surfaces. Cross-sectional images showed the microcapsules had a spongy hollow core matrix or multi-vesicular internal structure. Many investigations of poly(lactide-co-glycolide) microspheres formed by solvent evaporation report a similar structure (Cohen *et al.*, 1991; Crotts *et al.*, 1995; Herrmann *et al.*, 1995).



(a) (b)

(c) (d)

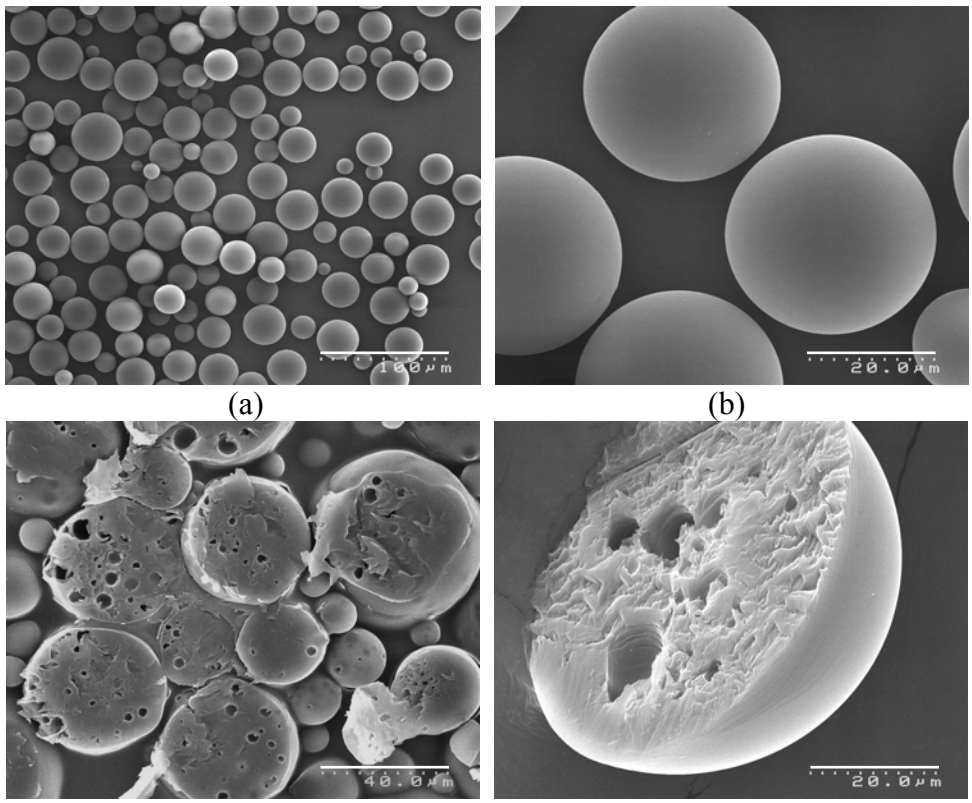
Figure 5.1 SEM images of polycaprolactone microcapsules morphology: (a) and (b) microcapsules, (c) single capsule, (d) cross-section



(a) (b)

(c) (d)

Figure 5.2 SEM images of polysulfone microcapsules morphology: (a) and (b) microcapsules, (c) single capsule, (d) cross-section



(a) (b)

(c) (d)

Figure 5.3 SEM images of polystyrene microcapsules morphology: (a) and (b) microcapsules, (c) and (d) cross-section

Polysulfone microcapsules had a narrow size distribution and polycaprolactone had the broadest size distribution (Figure 5.4).

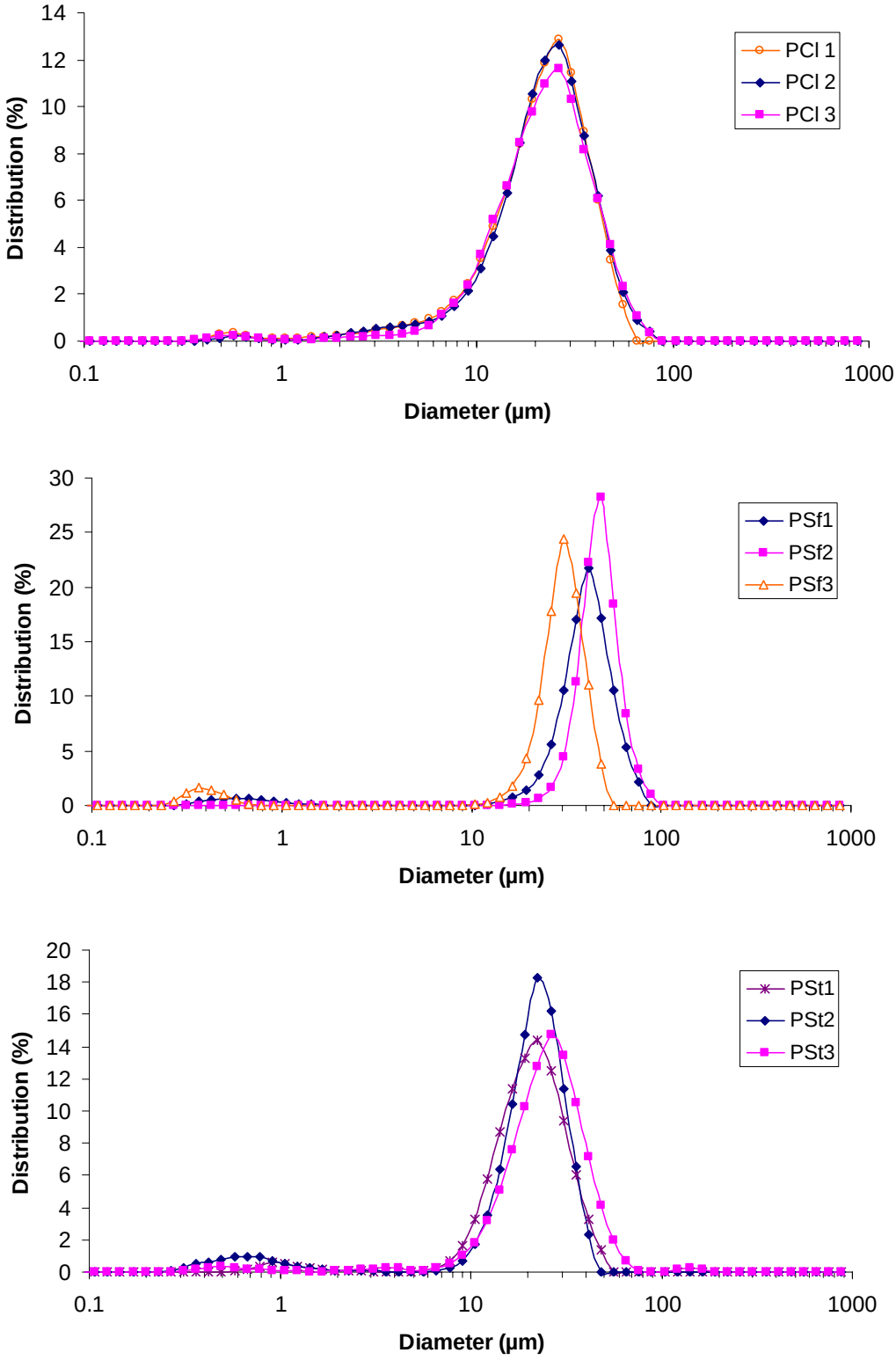


Figure 5.4 Particle size distribution of microcapsules prepared from polycaprolactone (top), polysulfone (middle), and polystyrene (bottom)

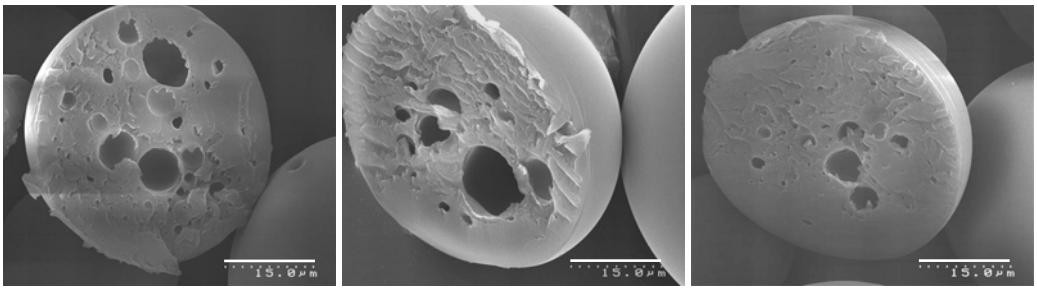
The spreading coefficient theory (Pekarek, 1994) indicates that polymers in a polymer-solvent system will tend to phase separate during the solvent removal stage and configure into the most thermodynamically stable form if given enough time. The three possible configurations of complete engulfing, partial engulfing and no engulfing can theoretically be predicted from the surface and interfacial tensions of the phases. However, microencapsulation by solvent evaporation is a complex process and process parameters such as solvent, surfactant, temperature, and polymer type and concentration influence the final configuration of the polymer microcapsules. These will be discussed later in this chapter.

5.2.2 Effects of process parameters

Many factors can influence morphology of microcapsules produced by solvent evaporation technique. The effects of several major process parameters including polymer concentration, temperature, and surfactant on producing a porous and hollow structure were investigated. Other variables will be discussed in an extended study of preparing microcapsules (Section 5.3).

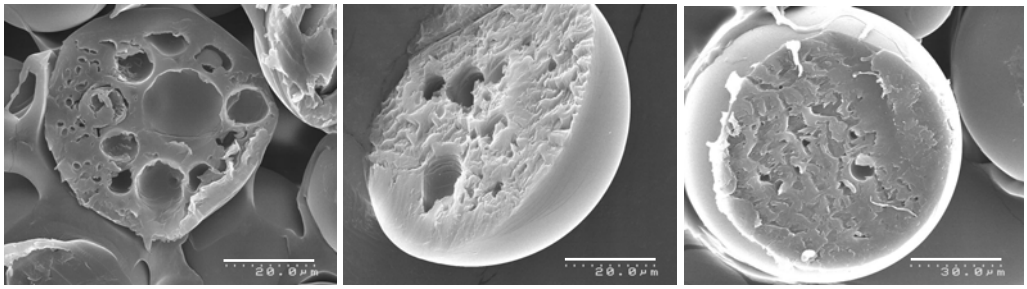
5.2.2.1 Polymer concentration

Polymer concentration is a key factor influencing the characteristics and morphology of microcapsules. The increase in microcapsules size with increasing polymer concentration occurs because viscosity increases. Even though the microcapsules fabricated at various polymer concentrations had similar surface porosity, the cross-section of SEM images show that microcapsules made at lower polymer concentration have a more voids matrix than those fabricated at higher concentrations (Figure 5.5 and Figure 5.6). This may be due to two factors: (1) internal water droplets in low polymer concentrations tend to coalesce more easily, leading to bigger pores and a less tortuous network; and (2) coagulation in the second emulsion is faster at higher polymer concentrations, which produces a tighter structure because of chain entanglement. This occurs because it is more difficult to break the viscous polymer solution into smaller droplets at constant mixing power. Rapid solidification of the microcapsules at a high polymer concentration produces a dense structure throughout the microcapsule.



(a) (b) (c)

Figure 5.5 SEM images of polycaprolactone microcapsules prepared in different concentration: (a) 2%, (b) 5%, (c) 10%



(a) (b) (c)

Figure 5.6 SEM images of polystyrene microcapsules prepared in different concentration: (a) 2%, (b) 5%, (c) 10%

5.2.2.2 Temperature

Two temperatures were studied: room temperature and 37°C to compare their effects on microcapsule structure. All microcapsules were spherical with a porous outer skin. Increasing preparation temperature decreased average microcapsule size from 54.7 to 26.3 μm because viscosity of the W/O/W double emulsion decreases with increasing temperatures (Figure 5.7) and therefore can more easily form smaller droplets at the same mixing power.

Microcapsule skin formation at room temperature is slower so the interior remains soft for longer, allowing the external aqueous phase to diffuse in and create more water pockets. If given sufficient time, the inner water droplets, could move within the soft interior of the matrix and coalesce into bigger droplets. They are still fairly uniformly distributed within the dispersed phase when the polymer solidified, giving even pores throughout the matrix (Figure 5.8 and Figure 5.9).

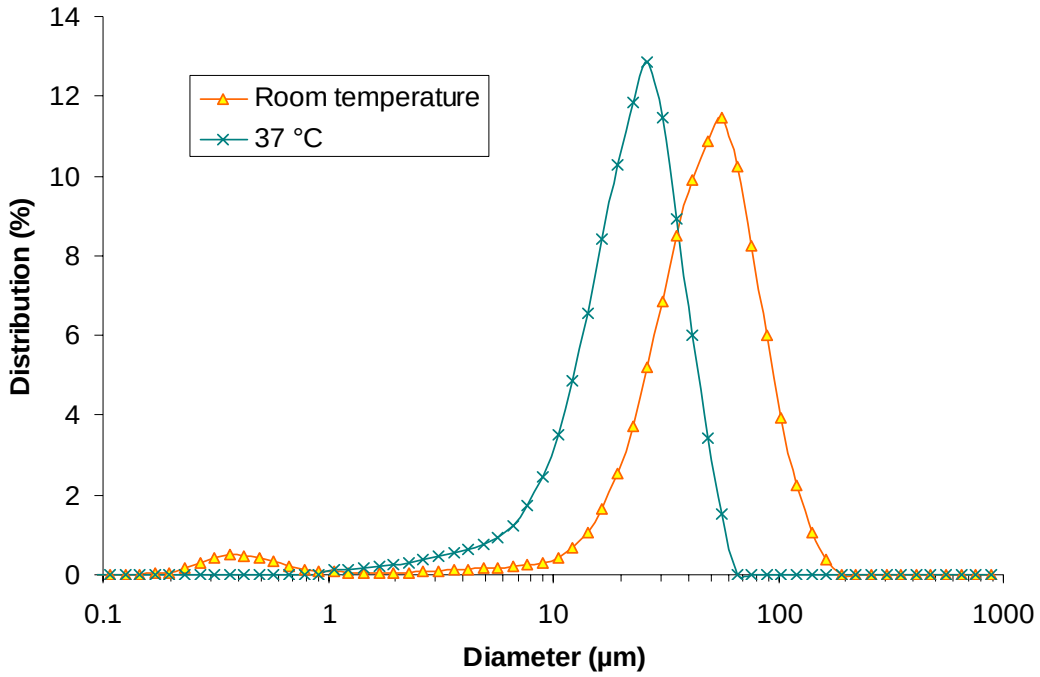
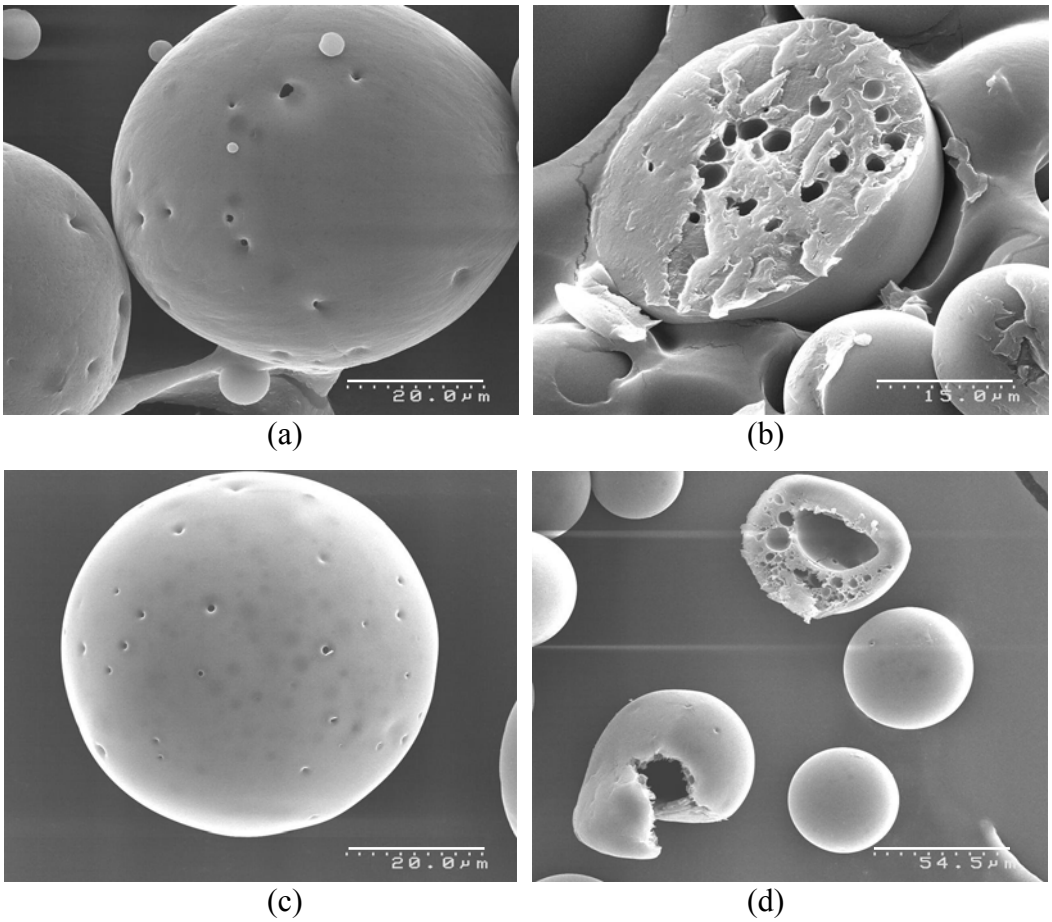


Figure 5.7 Effect of processing temperature on particle size distribution of polystyrene microcapsules (n=3)

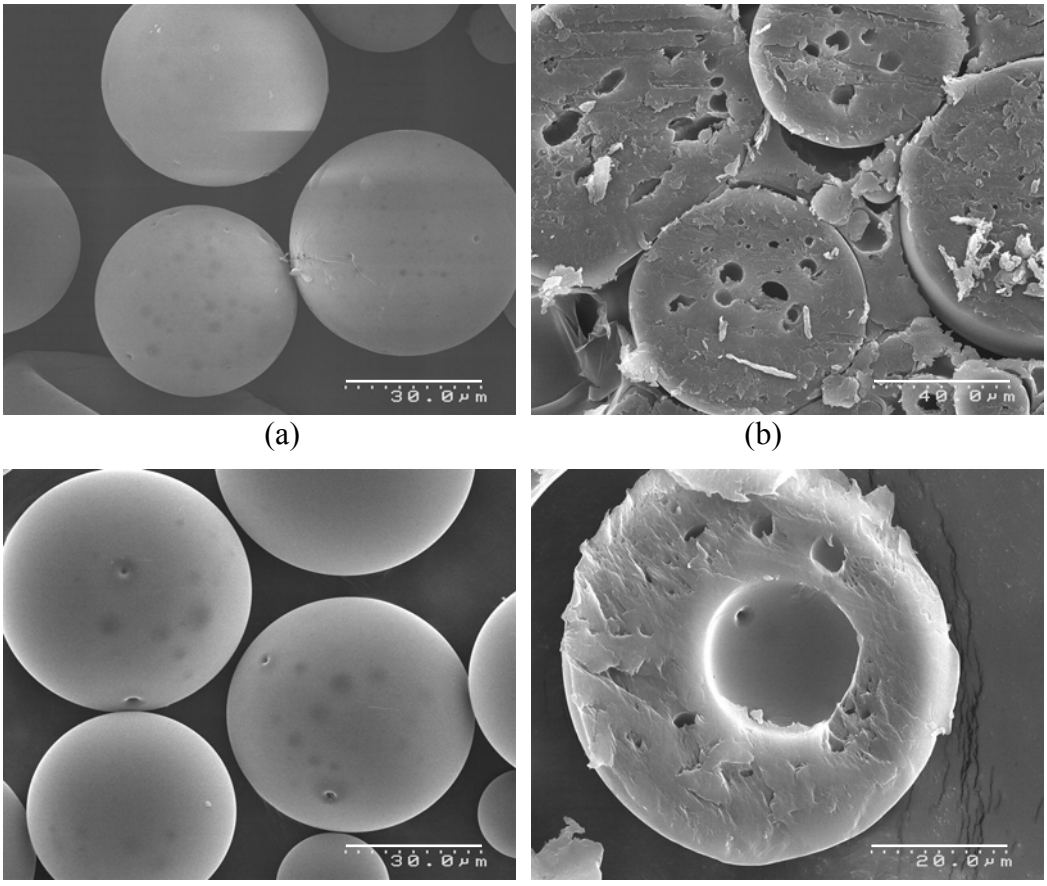


(a) (b)

(c) (d)

Figure 5.8 SEM images of polysulfone microcapsules prepared at room temperature (a, b) and 37°C (c, d)

When microcapsules are made at higher temperatures, solvent removal is rapid and polymer concentration within the dispersed phase increases quickly, allowing a dense, tight skin layer to form, which hinders water influx. Thus, no large water droplets can diffuse into the inner matrix. Rapid solidification allows little time for instability in the water droplets. The polymer solidifies from the edge towards the centre, pushing water droplets gradually towards the centre. These eventually give big holes in the centre of the microcapsules (Figure 5.8 and Figure 5.9).



(a) (b)

(c) (d)

Figure 5.9 SEM images of polystyrene microcapsules prepared at room temperature (a, b) and 37°C (c, d)

5.2.2.3 Surfactant

PVA concentration in the external water phase is a key influence on microspheres size (Jalil and Nixon, 1990). In the present study, polystyrene microcapsules were fabricated with 0.1, 0.5, and 2% PVA in the external water phase to examine the effect of PVA on morphology. Microcapsules had average diameters of 102.6, 56.8, and 23.8 μm, respectively (Figure 5.10). Microcapsule size decreased with

increasing PVA concentration in the external water phase. As PVA is a polymer with a high molecular weight, it will tend to increase the viscosity of the double emulsion, making it more difficult to create smaller droplets and forming bigger microcapsules. However, PVA in the external water phase helps stabilise emulsion droplets and prevents coalescence, resulting in smaller droplets. Similar results of hollow microcapsules have been reported when preparing PLGA microcapsules for use as ultrasound contrast agent (Narayan and Wheatley, 1999; El-Sherif and Wheatley, 2003).

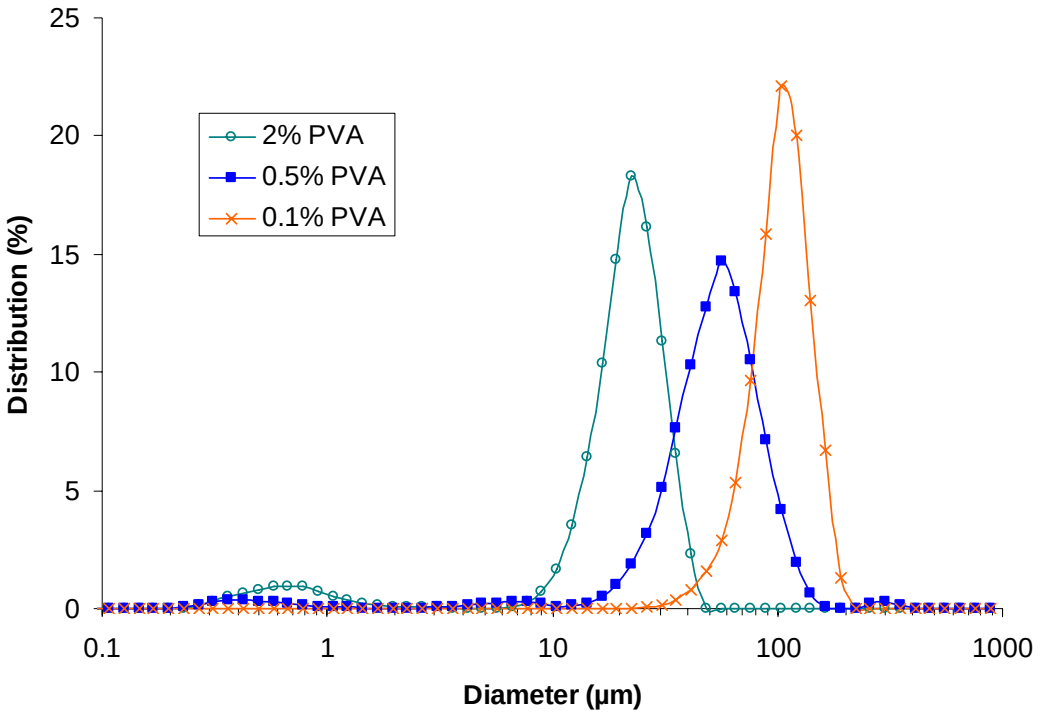


Figure 5.10 Effect of PVA concentrations on particle size distribution of prepared polystyrene microcapsules (n=3)

5.2.2.4 Stirring rate

Microcapsules size is affected by stirring rate, viscosity of the solvent/aqueous emulsion, ratio of oil phase to external water phase, and PVA concentration in the external water phase (Jeffery *et al.*, 1991; Crotts and Park, 1995). Stirring rate is a dominating factor because it provides the energy to disperse the oil phase in the water. The experimental results demonstrated that smaller droplets were produced at the higher stirring rate and hence the mean microcapsules diameter decreased substantially (Figure 5.11).

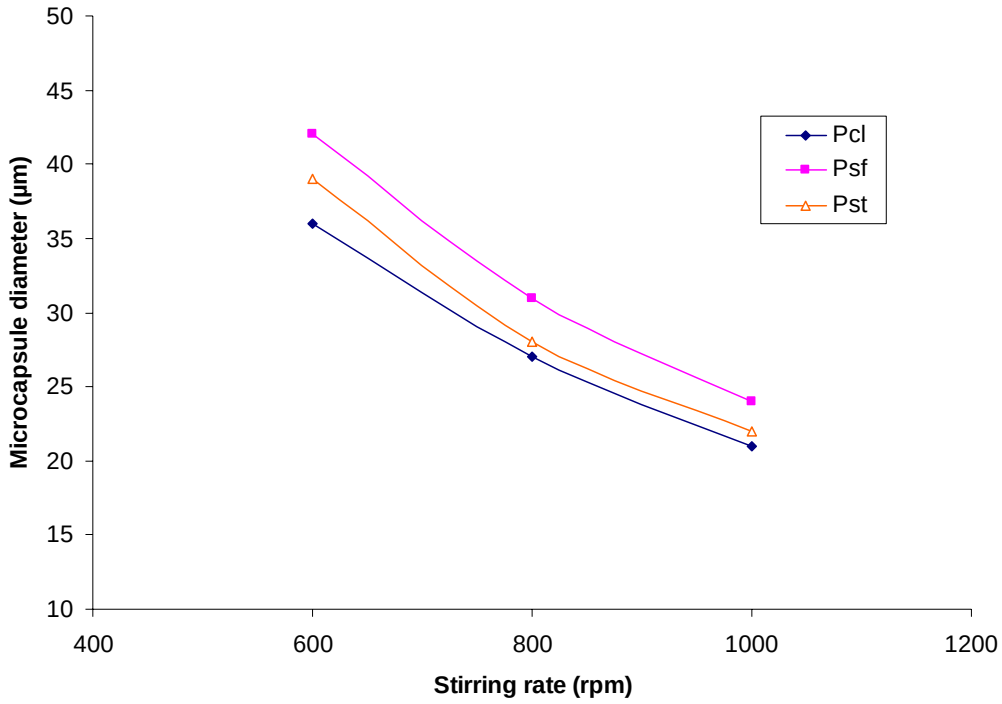


Figure 5.11 Effect of stirring rate on particle sizes of microcapsules prepared from polycaprolactone, polysulfone, and polystyrene (n=3)

5.2.3 Chemical grafting trials

One aim of this study was to develop a simple and inexpensive method to functionalise the prepared microcapsules. Grafting trials were done to identify an ideal polymer and to save time and materials before further developing the microcapsule structure. Chemical methods, with many advantages for surface modifications of polymeric materials, were described in Chapter Two. Chemical grafting by free radical polymerisation was used to functionalise the three types of prepared microcapsules.

5.2.3.1 Ungrafted microcapsules

The chemical grafting process involves ammonium peroxydisulfate (APS) activation and free radical polymerisation (Section 3.5.5). Prepared microcapsules were first activated by APS aqueous thermal decomposition to form hydroperoxides and then carboxylated by free radical polymerisation of acrylic acid in the presence of ferrous ions (Fe^{++}).

It was difficult to detect whether the carboxylic groups had been grafted to the polycaprolactone or polysulfone microcapsules and no increase in mass detected after the grafting reaction was performed. It was assumed that poor grafting could be due to:

1. Unstable free radicals formed on the polymer chain.
2. Lack of electron repulsive functional groups (benzyl ring, methyl, ethyl) that help forming free radicals.

Although other methods can be used to graft polycaprolactone and polysulfone, special equipment is needed. For example, Sodergard (1998) grafted acrylic acid onto polycaprolactone films using electron beam irradiation technique. Yang *et al.* (2002) treated polysulfone membranes with ozone to introduce peroxides and then grafted acrylic acid. However, the aims of this research are to develop a simple and inexpensive method for fabricating and functionalising microcapsules.

5.2.3.2 Grafted microcapsules

Using the knowledge gained in chemical grafting trials, process conditions for free radical graft polymerization were identified. PAA was successfully grafted onto polystyrene microcapsules to produce 0.52 mmol/g of grafting.

Percentage mass increase of grafted microcapsules can be expressed as:

$$\text{Mass gain (\%)} = \frac{\text{mass of grafted (mg)} - \text{mass before grafting (mg)}}{\text{mass before graft (mg)}} \times 100\%$$

$$= (M_g - M_0) / M_0 = (231.1 \text{ mg} - 200 \text{ mg}) / 200 \text{ mg} = 15.5\ \%$$

Grafting acrylic acid onto the surface of polystyrene microcapsule requires new active sites to be initiated on the polystyrene chains. Hydrogen activity on the tertiary carbon of polystyrene chains is high enough to be initiated by an in coming initiator radical.

Ammonium ferrous sulphate is known to cleave hydroperoxide groups in a way that inhibits homopolymerisation during the grafting reaction (Bamford and Al-Lamee, 1994):

$$\text{Polymer–OOH} + Fe^{2+} \longrightarrow \text{Polymer-O}^{\bullet} + OH^{-} + Fe^{3+}$$

Stability may be critical to the existence of free-radicals. Electron repulsive functional groups such as benzyl ring, methyl, and ethyl can be beneficial to generating free-radicals at the tertiary or secondary carbon atoms on the polymer backbone during the hydrogen-abstraction reaction (Figure 5.12).

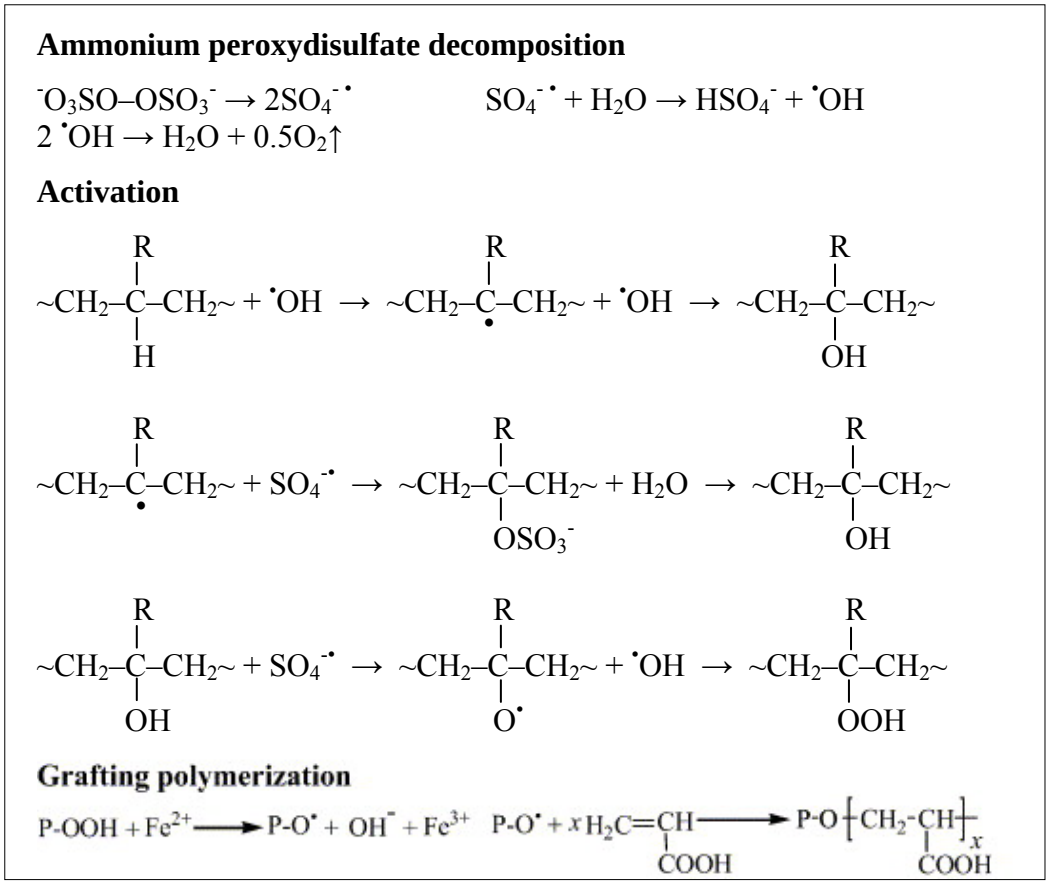


Figure 5.12 Possible chemical grafting reaction (Bamford, 1994)

5.2.4 Summary

To design effective microcapsule for delivery systems, it is essential to understand the relationship between the process parameters influencing microcapsules structure formation and internal morphology. Three types of microcapsules (PCl, PSf, PSt) manufactured in the preliminary trials had similar morphological characteristics (Section 5.2.1) with a porous hollow core-shell structure. However, initial trials indicated that polycaprolactone and polysulfone microcapsules could not successfully be grafted by free radical polymerisation method. Polystyrene microcapsules could be grafted to give 15.5% mass gain representing 0.62 mmol/g grafting. Polystyrene was therefore identified as a promising material for further microcapsule development.

5.3 POLYSTYRENE MICROCAPSULES

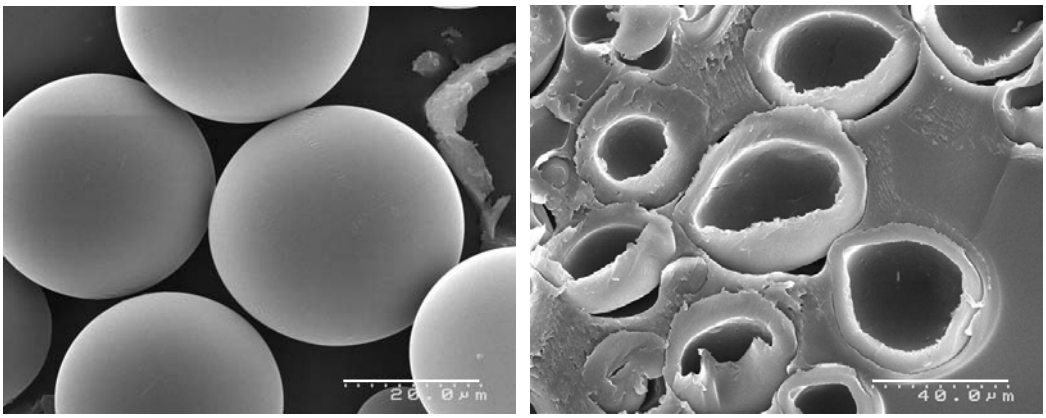
Preliminary research indicated that the morphological characteristics of microcapsules were mainly determined by process conditions. Although solvent evaporation is theoretically a simple process, many process variables can influence the nature of the microcapsule obtained. It is essential to understand the mechanisms of microcapsule formation and the effects of processing parameters on microcapsule characteristics. Further trials were done to improve the porous structure of microcapsules.

5.3.1 Influence of process parameters on morphology

The effects of polymer concentration, process temperature, and surfactant addition on microcapsule morphology were discussed in Section 5.2. The effects of factors such as processing pressure, solvent composition, and additives (including salts, co-polymers, and fatty alcohol) are discussed in this section. Trials were done at room temperature with 5% polystyrene concentration and 0.5% surfactant.

5.3.1.1 Reducing ambient pressure during solvent evaporation

The solvent was removed from the microcapsules under vacuum (produced with a water vacuum device), which increases solvent removal and reduces the time available for a solid matrix to form. The resultant microcapsules had a smooth and dense outer surface with a non-porous wall and large hollow core (Figure 5.13). It indicated that processing pressure did not influence the porosity of microcapsule although it produced a hollow core.

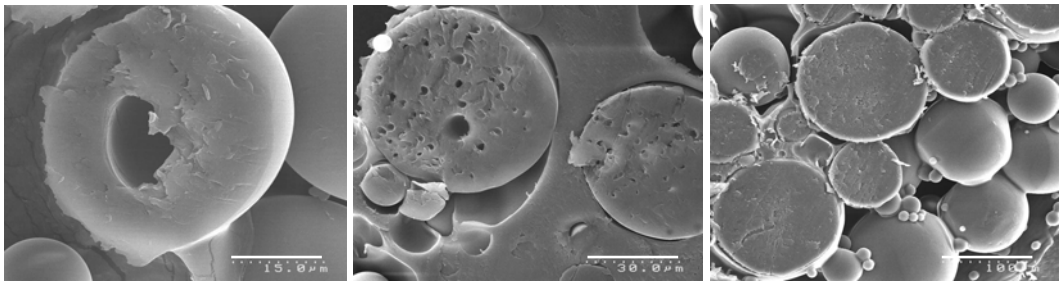


(a) (b)

Figure 5.13 Morphology of polystyrene microcapsules prepared by reducing ambient pressure during solvent evaporation

5.3.1.2 Solvent composition

Ethyl acetate was added into the dichloromethane organic phase to form a solvent mixture. Ethyl acetate is partially miscible with water and affects viscosity and solvent evaporation rate, thus changing the way the polymer precipitates. Various ratio of dichloromethane/ethyl acetate were investigated. The solvent mixture affected polystyrene microcapsules structure (Figure 5.14). The SEM cross-section indicated microcapsules had a small hollow core and a non-porous wall structure when dichloromethane/ethyl acetate in ratio of 2:1; a sponge-like matrix when the ratio was 1:1; and was a non porous microsphere when the ratio was 1:2.



(a) (b) (c)

Figure 5.14 Effect of ethyl acetate/dichloromethane ratio on polystyrene microcapsules structure: (a) 2:1; (b) 1:1; (c) 1:2

5.3.1.3 Salt additives

Ammonium bicarbonate

To develop a porous structure, 5% ammonium bicarbonate was dissolved in the inner aqueous phase as a gas-forming agent. The ammonium bicarbonate in the water droplets spontaneously produced ammonia and carbon dioxide gas bubbles during solvent evaporation at 40°C. All the microcapsules were spherical with porous outer skins. However, cross-sectional SEM images showed the microcapsules had a spongy matrix but no hollow core (Figure 5.15).

Calcium chloride

Salts in the internal aqueous phase promote water influx from the external phase due to osmotic pressure. Adding calcium chloride (2% $CaCl_2$) to the internal aqueous phase produced a sponge-like matrix with some pores on the microcapsules surface (Figure 5.16). Overall, calcium chloride had a similar effect on porosity to ammonium bicarbonate.

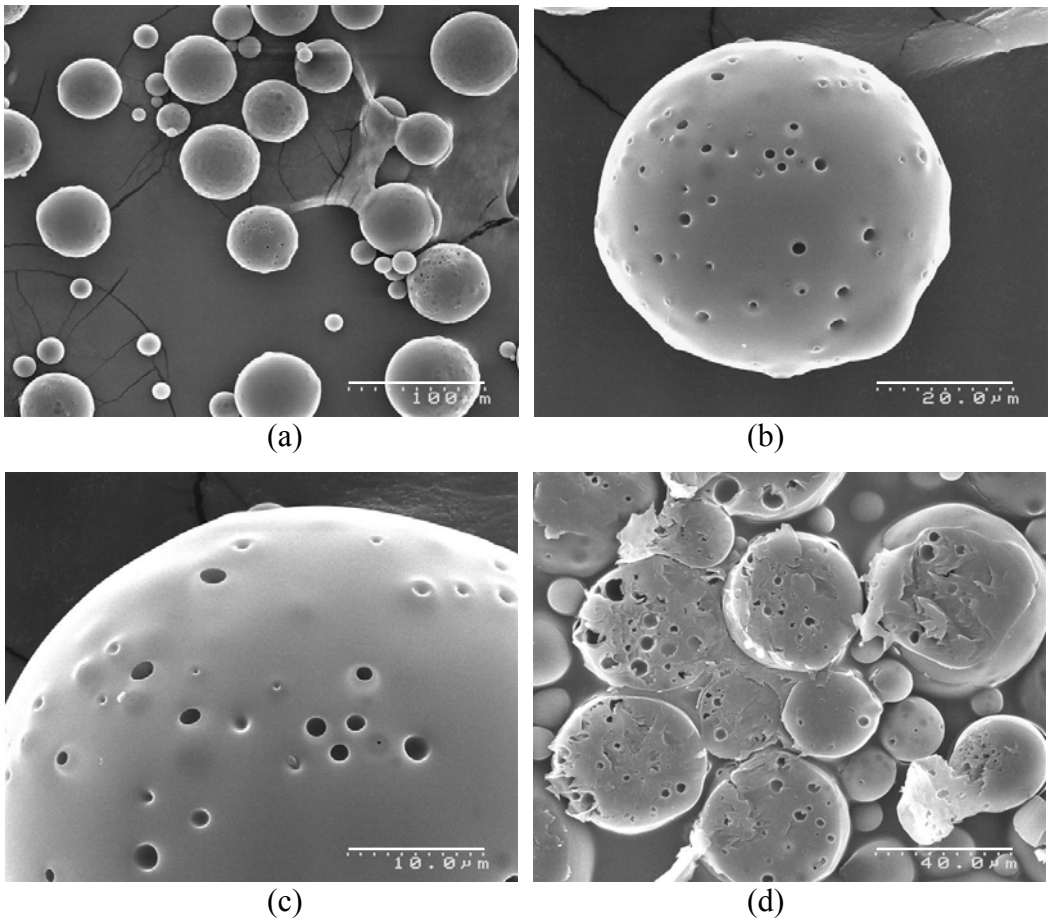
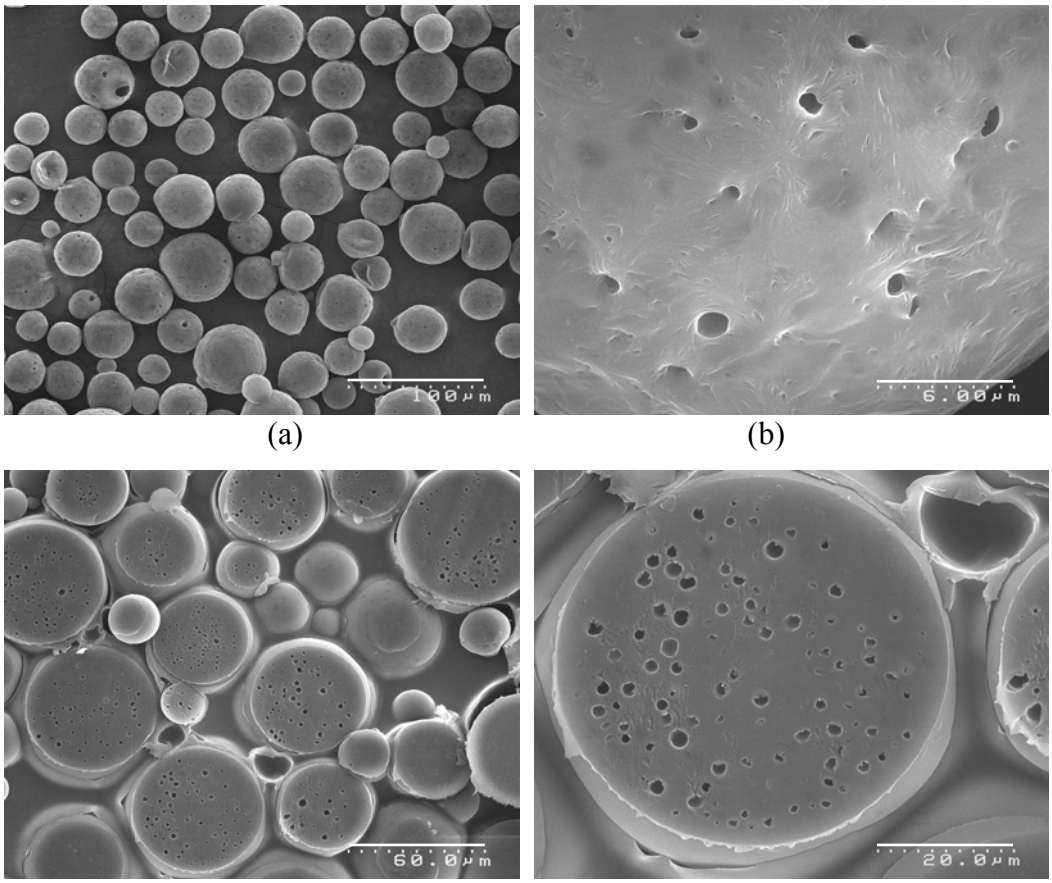


Figure 5.15 Morphology of polystyrene microcapsules prepared when ammonium bicarbonate was added to the internal aqueous phase
(a) microcapsules, (b) and (c) single microcapsule, (d) cross-section

5.3.1.4 Hydrophilic polymer

The water-soluble polymers polyethylene glycol (PEG), polyethylene oxide (PEO), polyvinylpyrrolidone (PVP), and co-polymer (PEG-PPG-PEG) were blended into polymer solution. These polymers are also soluble in the organic solvent, and leach into the aqueous phase. A 1:1 ratio polystyrene and hydrophilic polymer additive was dissolved in the organic phase in this study.

Microcapsules blended with PEG formed a sponge-like matrix with relatively large pores (Figure 5.17). Adding PEO and PVP produced microcapsules with a hollow core and porous wall. Microcapsules produced by adding PVP showed a thinner wall and were more porous compared with the PEO blending ones. It was assumed that the higher molecular weight the more the effect on porosity of internal structure of microcapsule.



(a) (b)

(c) (d)

Figure 5.16 Effect of 2% $CaCl_2$ in the internal aqueous phase on polystyrene microcapsules structure
(a) microcapsule, (b) external surface, (c, d) cross-sectional

Co-polymer PEG-PPG-PEG has a high molecular weight and a high hydrophilic/lipophilic balance value (HLB>24). Blending PEG-PPG-PEG with polystyrene was expected to play a key role in producing surface and internal pore structure. However, the resultant microcapsules showed a sponge-like inner structure with even less porosity and no hollow core.

As polymer solution (PSt dissolved in a solvent) was mixed with the non-solvent (water phase), phase separation into polymer-rich phase and polymer-poor phase took place by liquid–liquid de-mixing by exchange of solvent with non-solvent. Although using a hydrophilic polymer could improve the porous structure of microcapsules, differences in molecular size, solubility, emulsion stability, interactions between blending polymers and the ratio of polymer promote different mechanisms, which inevitably produce different morphological characteristics.

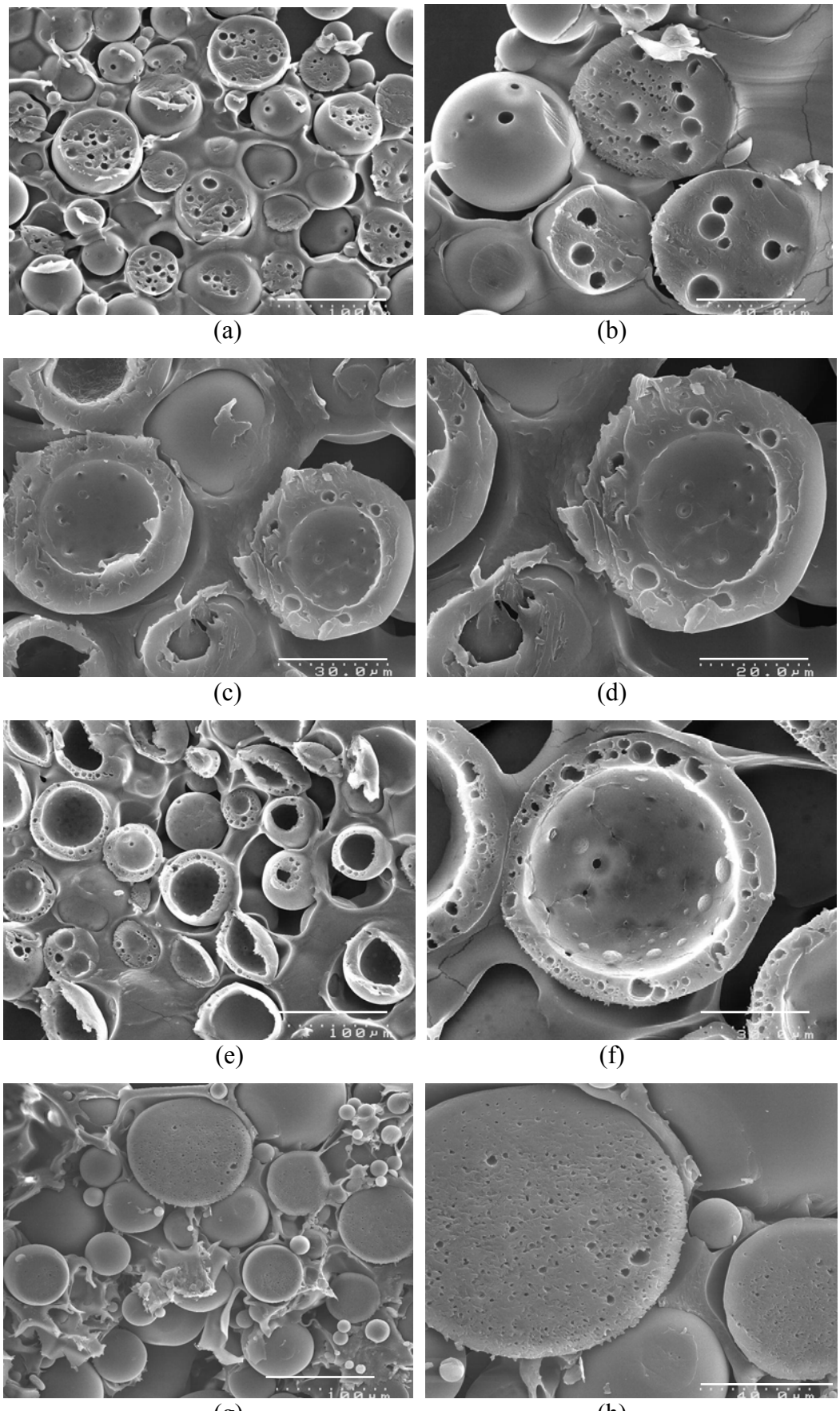
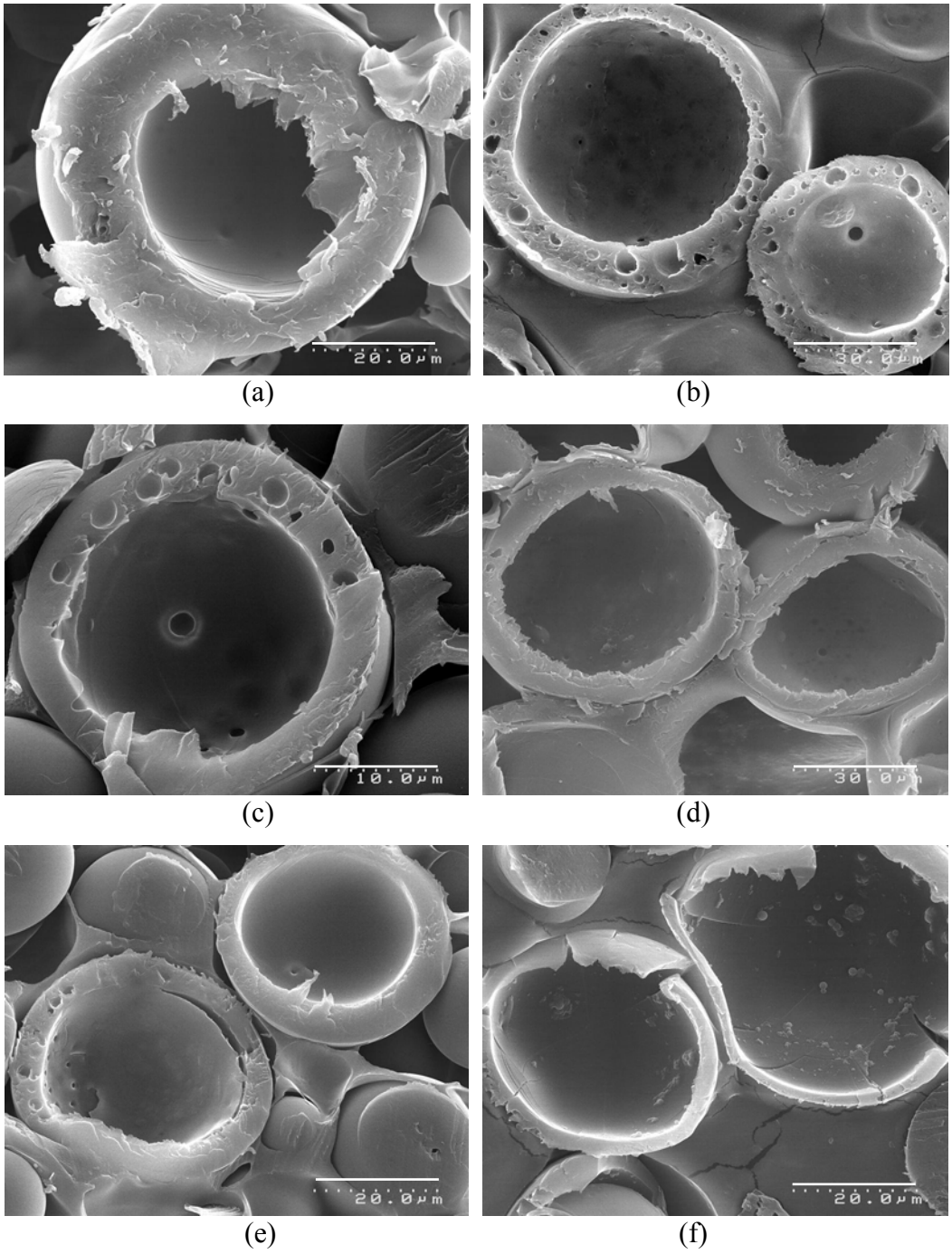


Figure 5.17 SEM images of polystyrene microcapsules prepared by blending with polymers: PEG (a, b); PEO (c, d); PVP (e, f); PEG-PPG-PEG (g, h)

Microcapsules prepared with lower polymer concentrations have a more porous internal structure then those prepared at higher polymer concentration (Section 5.2.2). By adjusting polymer concentration, microcapsule with thinner wall can be obtained. The effect of adding 2%, 5% or 10% PVP to 2% or 5% polystyrene concentration was studied (Figure 5.18).



(a) (b)

(c) (d)

(e) (f)

Figure 5.18 Morphology of PSt microcapsules prepared with different PSt/PVP ratios:
(a) 5%:2%, (b) 5%:5%, (c) 5%:10%; (d) 2%:2% (e) 2%:5%, (f) 2%:10%

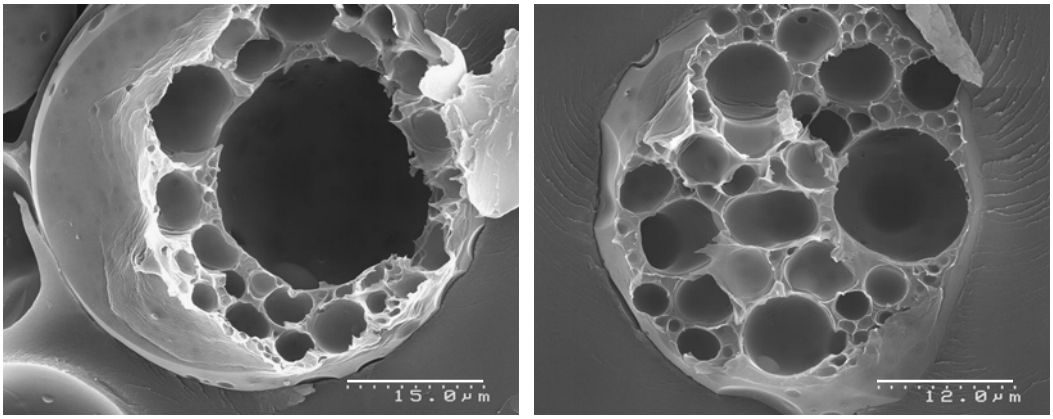
The PVP was very effective in producing hollow microcapsules. The resultant microcapsule when 2% PVP was used had a thin wall, which was not porous. Increasing PVP concentration to 10% did not significantly influence polystyrene microcapsules porosity (Figure 5.18).

When the embryonic polymer droplets contact the aqueous phase, the water influx and concomitant solvent efflux causes phase separation into a polystyrene-rich phase and a water-soluble rich phase. During solvent removal, water diffuses into the organic phase and water-soluble polymer in the organic phase leaches out into the aqueous phase, leaving the polystyrene domains.

5.3.1.5 Fatty alcohol

The fatty alcohol 1-dodecanol is insoluble in water and used to manufacture surfactant, lubricating oils and pharmaceuticals. In present study 1-dodecanol was selected as a porogen to help make the microcapsule wall more porous during solvent evaporation process.

The 1-dodecanol was added at 5% to two different ratios of polystyrene and PVP in the polymer mixture. Microcapsules produced with 5% polystyrene and 10% PVP in polymer solution had a larger core and double-walled porous shell structure (Figure 5.19a), whilst those produced with 5% polystyrene and 5% PVP had multi-vesicular internal structure (Figure 5.19b). However, there was still a dense skin on the external surface of the microcapsules.



(a) (b)

Figure 5.19 SEM images of polystyrene microcapsules prepared with 5% 1-dodecanol in polymer mixture of (a) 5% PSt + 10% PVP; (b) 5% PSt + 5% PVP

5.3.1.6 Summary

Microcapsule formation is a complicated chemical and physical process. It can be divided into three stages: (a) droplet formation, (b) solvent removal and solidification and (c) washing and drying. Solvent removal and solidification probably is the dominant process affecting microcapsule morphology. Jeyanthi *et al*. (1996) used the dilution solvent-removal technique to produce microcapsules with a uniform honeycomb matrix; the pore size depended on the extent of continuous water-phase dilution. Mathiowitz (1990) prepared polyanhydride microspheres and reported that porosity can be varied by changing solvent evaporation rate (via temperature or stirring rate) and polymer concentration. The results of the current study are consistent with those of Mathiowitz's (1990). However, the internal microcapsules structure had limited porosity and did not meet the criteria of proposed structure in the objective of this thesis.

The morphological characteristics of microcapsules were probably formed during the solvent evaporation process. The embryonic dichloromethane droplets containing dissolved polymer hardened from the surface when they contacted to the aqueous phase. Inward progressions of polymer solidification accompanied by influx of water and outflux of solvent, presumably occurred via preferential crystallisation of the polymer in the bulk internal phase. This process forms a porous and reticulated skeletal backbone with leaving pores filled with un-removed residual solvent. Upon further solvent removal, the porous shell structure develops in the wall. The hollow core occurs because of emulsion instability events within the microcapsule during solvent removal.

Porogen additives such as hydrophilic polymers were expected to play a role in surface and internal pore structure. However, the resultant microcapsules either had a sponge-like inner structure with no hollow core, or had a dense skin on the surface of microcapsules with a porous wall and hollow core. This indicated that solvent evaporation method produced microspheres (matrix structure) rather than porous microcapsules (core-shell structure) in the current study.

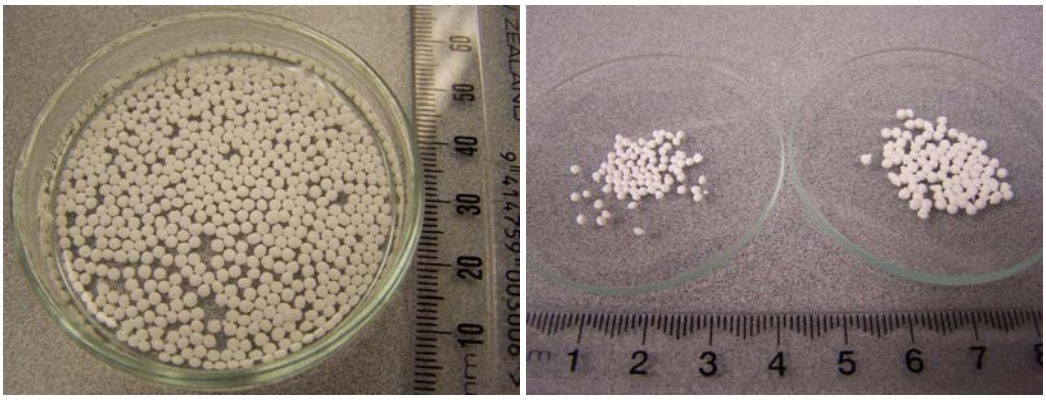
5.3.2 Phase-inversion technique – a novel approach

The purpose of this thesis was to develop a functional microcapsule that could act as a pH-responsive drug delivery system. A porous shell would function as a controlled gate and a hollow core would carry the desired drug. Although the microcapsules developed (Section 5.3.1) had a porous structure and a hollow shell, those prepared using the solvent evaporation method had an undesirable dense outer skin and the wall's honeycomb matrix lacked interconnecting pores across the wall.

To overcome these problems, a novel approach to manufacturing polystyrene microcapsules was attempted using phase-inversion technique. This method has not previously been reported in the literature on fabricating polystyrene microcapsules although it has been used to manufacture membranes from other polymers such as polysulfone and polyethersulfone.

5.3.2.1 Preparing microcapsules

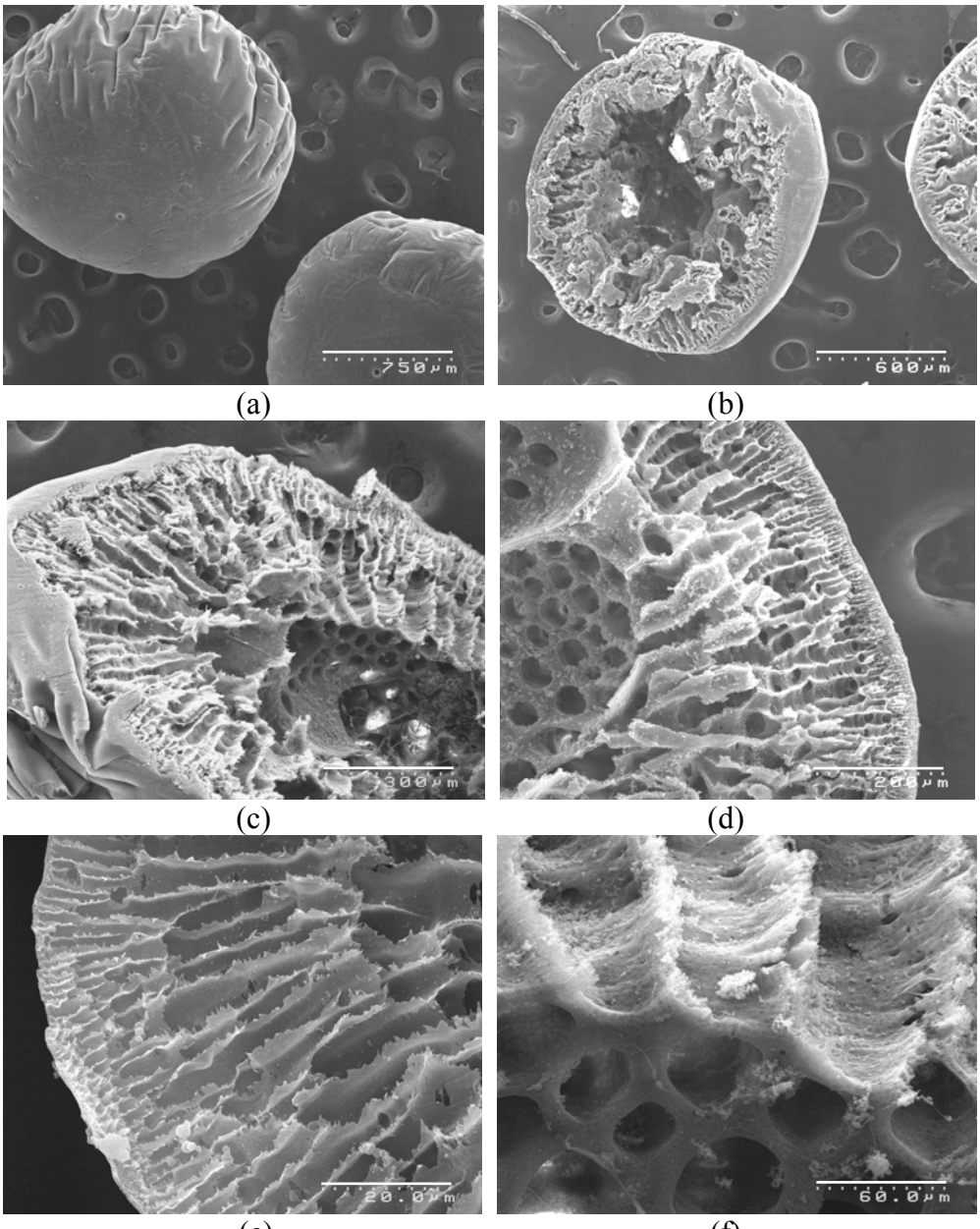
Polystyrene microcapsules prepared using the phase-inversion method (Section 3.3.3) had diameters of 1–1.5 μm (Figure 5.20). The microcapsules were hollow spheres with an external skin layer and a porous rough internal surface (Figure 5.21). Cross-sections showed porous micro-channels across the entire wall. Microcapsule size could be controlled by the needle diameter. Height between the needle and the aqueous ethanol solution was maintained between 25 and 30 cm to prevent irregular shaped microcapsules forming. Microcapsules had similar size produced with ethanol concentrations of 20, 30 and 40% (v/v).



(a) (b)

Figure 5.20 Polystyrene microcapsules prepared by phase inversion: (a) in the coagulating solution, (b) dried

When the polymer solution is added to a non-solvent (water) phase, it undergoes complex reactions to form solvent-rich domains and polymer-rich domains. During the coagulation process, water penetrates the polymer solution and solvent escapes progressively, forming the spongy structure with macrovoids. A polystyrene shell forms on the outside, surrounding the polymer solution. As solvent diffuses out, polystyrene moves from the centre to the wall to form micro-channels (Figure 5.21). The solvent-rich domain becomes interconnected pores and macrovoids after solvent evaporation.



(a) (b)

(c) (d)

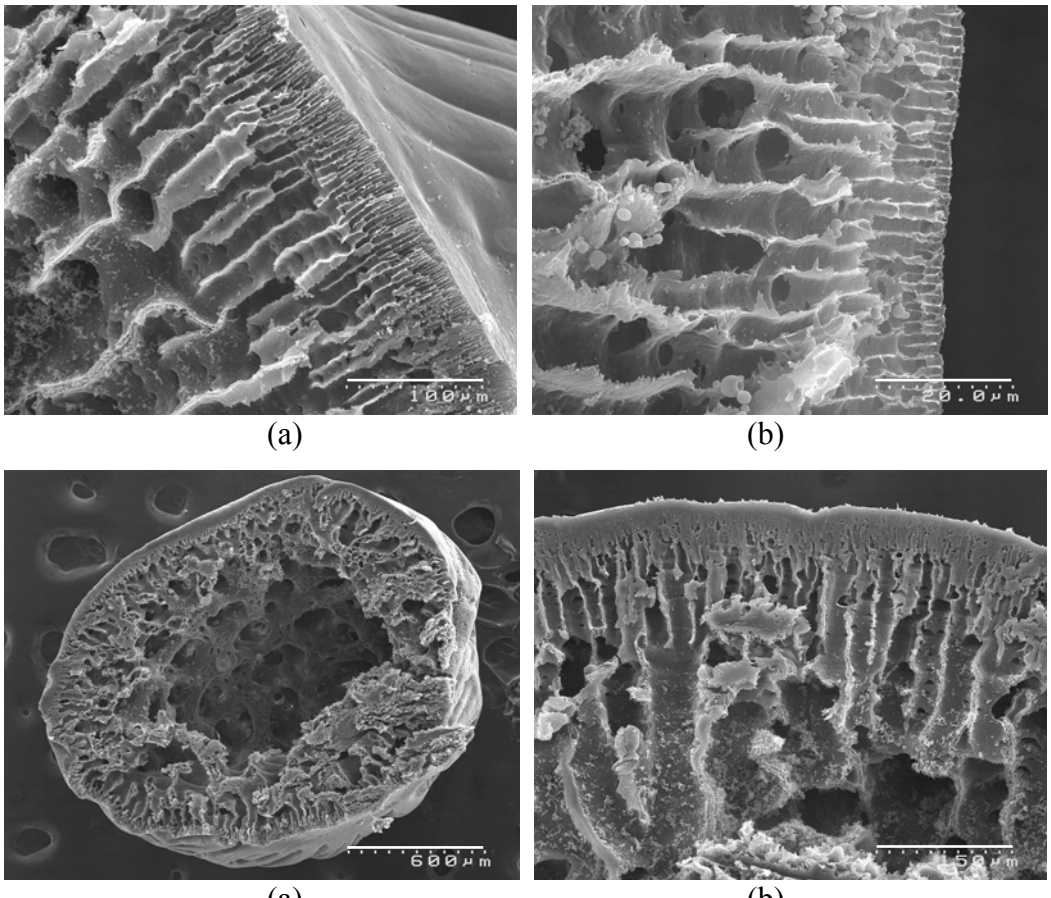
(e) (f)

Figure 5.21 Morphology of polystyrene microcapsules prepared by phase inversion (a) microcapsule, (b) cross-section, (c, d, e, f) enlarged cross-section

Smolders *et al.* (1992) suggested that the macrovoid in the centre of polysulfone membranes was formed by anomalous growth of nuclei. However, the aim of this research is not to explain the mechanism for forming the structure so the influence of process conditions on macrovoid structure will not be discussed.

5.3.2.2 Effect of tetrahydrofuran

Tetrahydrofuran (THF) was used as co-solvent to help develop thinner surface skin layer with well inter-connected micro-channels between the pores. It was assumed that water miscible THF would reduce polymer solution viscosity and, more importantly, delay the solidification process of the phase-separated polystyrene domain. Microcapsule prepared with 2% THF as co-solvent had a thinner outer skin layer than microcapsules prepared without THF (Figure 5.22).



(a) (b)

(a) (b)

Figure 5.22 Morphology of polystyrene microcapsules prepared by phase inversion with (a, b) and without (c, d) THF used as co-solvent

5.3.2.3 Effect of polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) can influence the size of the voids in the microcapsule (Section 5.3.1). Adding PVP into the polystyrene solvent mixture before phase inversion produced microcapsules with bigger voids and thinner walls (Figure 5.23). However, the microcapsule walls had fewer micro-channels than those prepared without PVP (Figure 5.21). Also, the walls may be too thin to maintain the mechanical strength of large capsules.

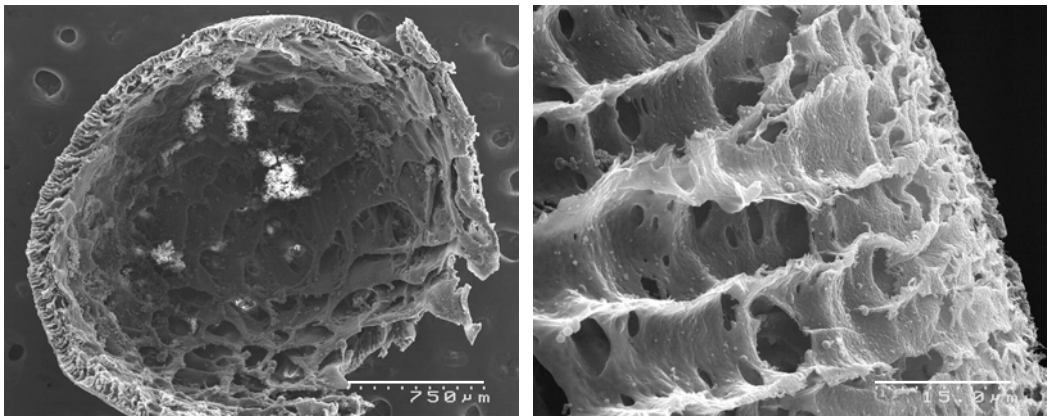


Figure 5.23 Morphology of polystyrene microcapsules prepared by phase inversion with PVP

5.3.2.4 Creating porous surfaces

To prepare porous microcapsules with open pores across the capsule wall, the outer surface skin layer needs to be removed. By mechanically peeling off the surface layer, it may be possible to produce microcapsules with a porous surface (Figure 5.24). Therefore, the resultant microcapsules were immersed in DMAa solvent for various times to remove surface skin layer.

The SEM images showed that immersing the microcapsules in DMAa solvent for various times affected surface porosity (Figure 5.25). A very porous cavity-like structure appeared on the microcapsule surface, indicating the dense outer skin layer had been completely removed by re-dissolving times of up to two minutes. The number of pores increased between 30 seconds and 1 minute but pore size did not change significantly. This means only the outer-most thin layer was dissolved (compared with the cross-sectional view in Figure 5.22), so microcapsule wall thickness did not decrease significantly.

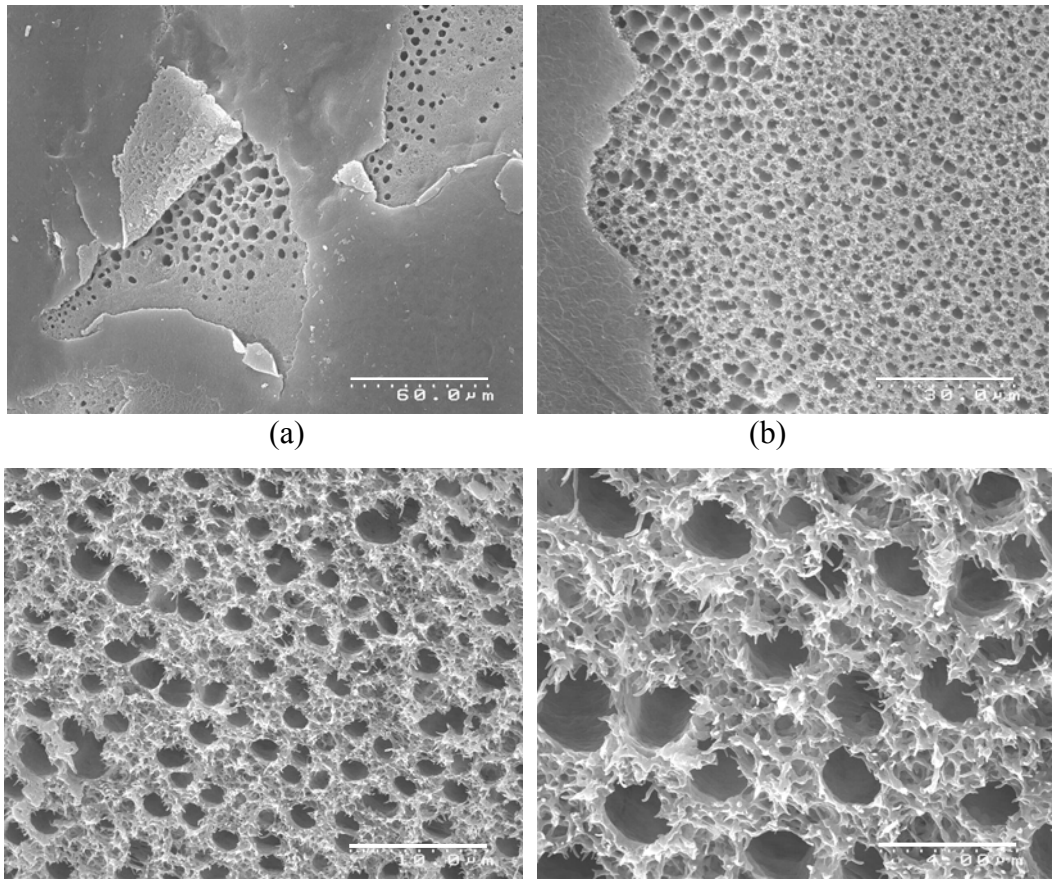


Figure 5.24 Morphology of mechanically removed surface skins of polystyrene microcapsule prepared by phase inversion

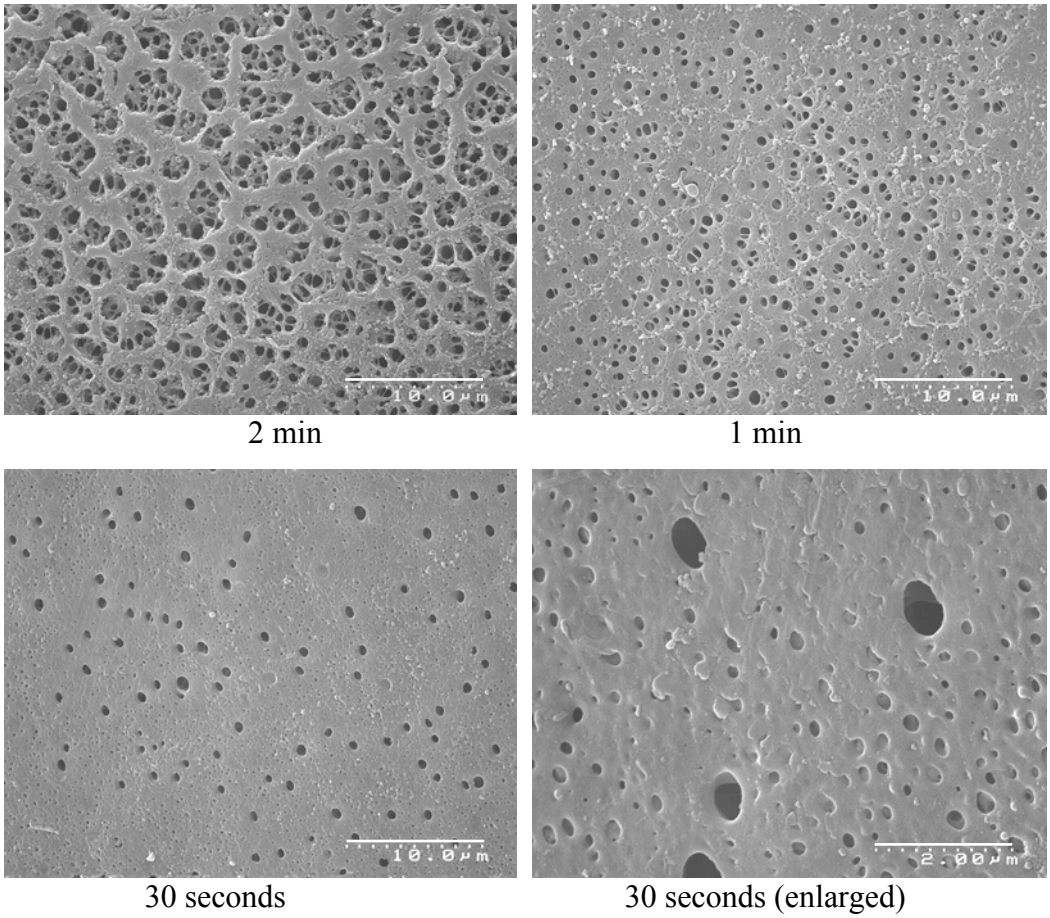
5.3.2.5 Grafting

Prepared skinless microcapsules were chemically grafted by free radical polymerisation (Section 3.5.5) with 5%, 10%, and 20% acrylic acid. After 4 hours of reaction at 50 °C, the extent of grafting on the microcapsules surface was 0.42–0.53 mmol/g (Figure 5.26).

As 10% and 20% acrylic acid produced a similar amount of grafting, 10% acrylic acid was used in the subsequent release study. Higher concentrations of acrylic acid were not used because a gel may form in the solution. Lee *et al*. (1994) found a maximum grafting using 25% monomer and attributed the subsequent sharp decrease to extensive homo-polymerisation.

The present study is a novel approach to functionalise polystyrene microcapsules. There are no previous published reports on chemical grafting of polystyrene

microcapsules although there are some reports on grafting polyethylene hollow fibres and polypropylene film. Bamford and Al-Lamee (1996) studied polymer surface functionalisation of polyethylene hollow fibres and other polymer films by chemical grafting and Zhang *et al.* (2006) studied polypropylene film by free radical grafting and then immobilised collagen on the film.



2 min 1 min

30 seconds 30 seconds (enlarged)

Figure 5.25 Effect of re-dissolving times in DMAa on skin layer morphology of prepared polystyrene microcapsule

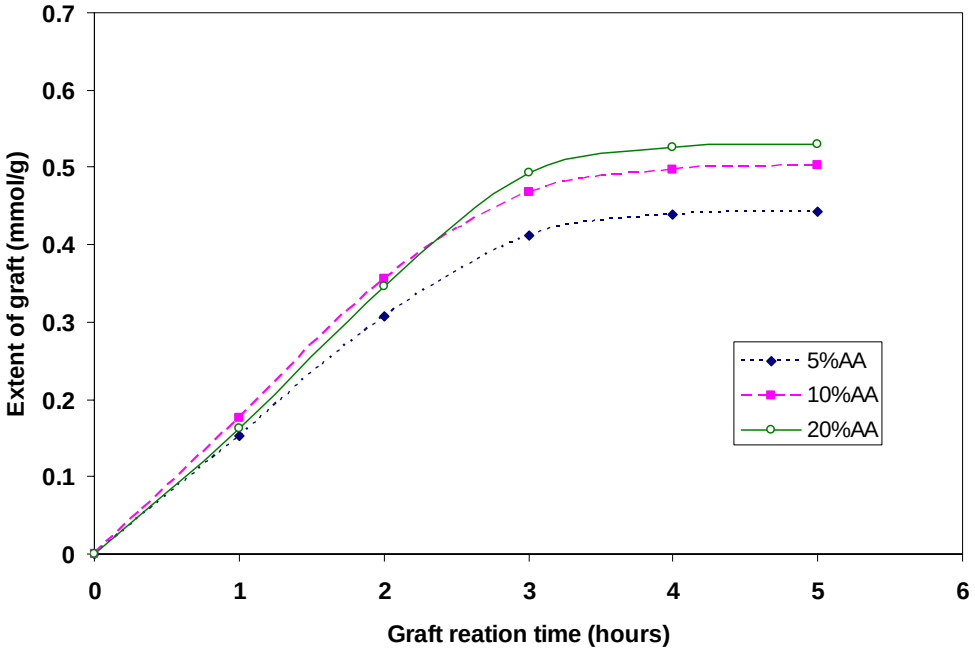


Figure 5.26 Effect of acrylic acid concentration extent of grafting on polystyrene microcapsules (at 50 °C for 4 hours, n=3)

5.3.3 RELEASE STUDY

To evaluate the pH response function in polystyrene microcapsules grafted with PAA, model drug release experiments were carried out using vitamin B_{12} and bovine serum albumin (BSA) using microcapsules with various pore sizes.

Model drug molecules were loaded into the prepared polystyrene microcapsule (Sections 3.6 and 4.4.2). The release profiles of vitamin B_{12} at pH 2 and pH 7 from the polystyrene microcapsules prepared with skin re-dissolving times of 30 seconds, 1 minute, and 2 minutes (Figure 5.27) showed that all microcapsules had a slow release rate, which was assumed to be due to the thick capsule wall making longer diffusion paths.

The contents loaded into all three types of microcapsules were released at both pH 2 and pH 7 and there was no significant effect of pH on release rate. This indicated the grafted PAA did not retain the loading contents at pH 7, which was the pH at which it was expected the pores would be closed. This may have been because there was insufficient grafting on the microcapsule surface, so the pores would not completely close.

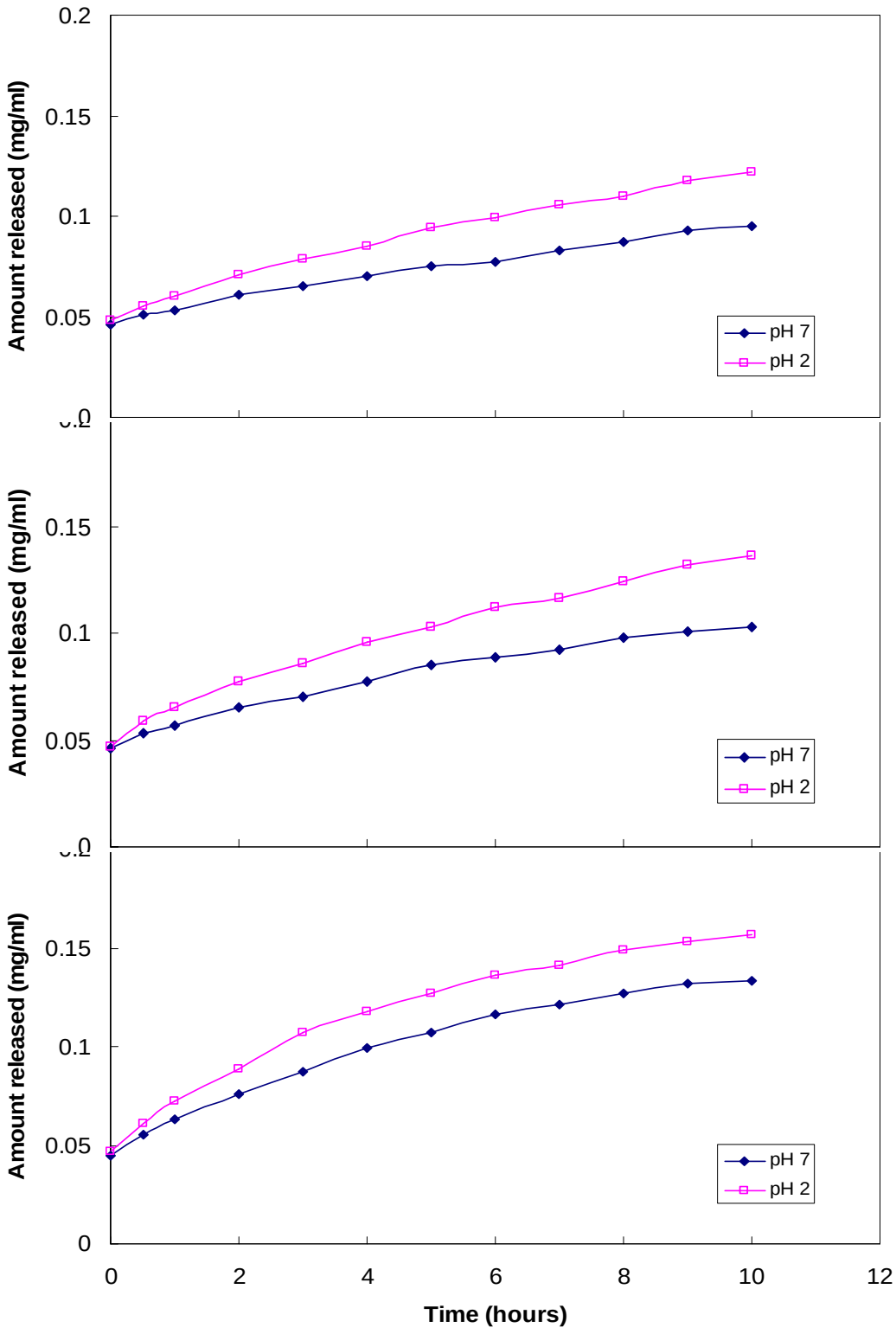


Figure 5.27 Effect of pH on release profile of vitamin B_{12} from polystyrene microcapsule prepared with skin re-dissolving times of 30 sec (top), 1 min (middle), and 2 min (bottom)

This assumption was examined in the vitamin B_{12} release experiment by switching pH between pH2 and pH7 (Figure 5.28). The release profile showed no clear steps changes when the pH was switched.

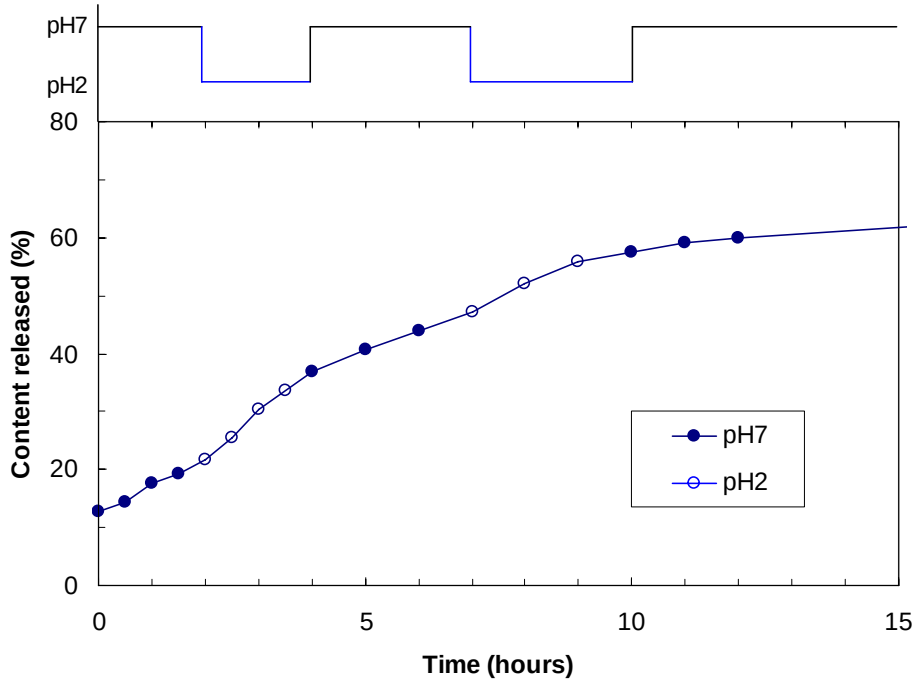


Figure 5.28 Effect of changing pH on vitamin B_{12} released from polystyrene microcapsule

Grafting extent of PAA depends on density of APS activation sites and length of PAA chains. A lower activation density with long PAA chains can result in the same extent of grafting as higher activation site density with short PAA chains. Thus, a better understanding of the relationship between the graft conditions is essential. The activation sites density could be further investigated by determining free radicals using 1,1-diphenyl-2-picrylhydrazyl (DPPH) to quantify the produced peroxides concentration (Shim *et al.*, 1999). PAA graft layers can also be observed using atomic force microscopy (AFM), a technique that many researchers consider very suited to investigating the morphology of polymer surfaces (Chahboun *et al.*, 1992; Bowen *et al.*, 1996). Samples could be examined in their natural state and whether pores are open or closed at different pH can be directly observed (Iwata *et al.*, 1998).

A higher molecular weight model drug (BSA, 66,700 Da) was selected for release experiments to study whether the microcapsules could retain a larger molecule at

pH7 (Figure 5.29). However, a similar release profile was observed, suggesting that the release of contents from microcapsules were not influenced by extent of grafted PAA and therefore not affected by a change in pH.

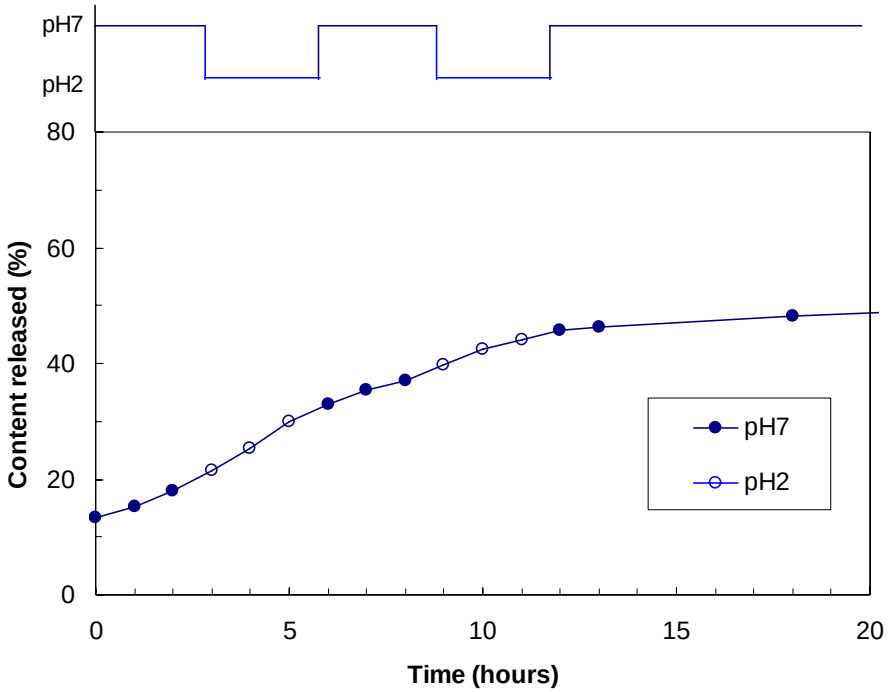


Figure 5.29 Effect of changing pH on BSA released from polystyrene microcapsule

To identify if other factors could affect the release rate, the morphology of the grafted microcapsules was examined. This revealed some splits on the surface of grafted microcapsule (Figure 5.30), which were assumed to be a major reason that the contents leaked from the microcapsules. Further experiments are recommended to investigate and improve the process.

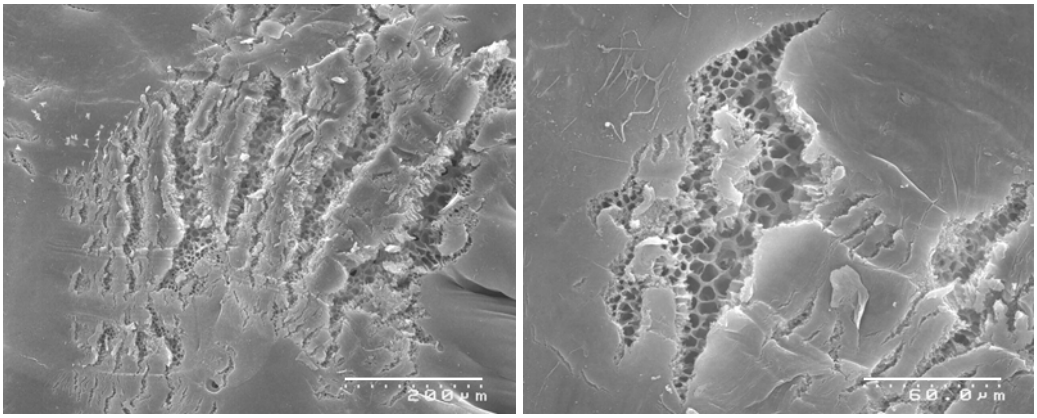


Figure 5.30 SEM images of surface splits on polystyrene microcapsules prepared by phase inversion

5.3.4 Summary

To manufacture microcapsules with open porous shell a novel formulation approach using phase-inversion technique was developed. Factors such as PVP and THF which influence microcapsule porous structure and chemical grafting by free radical polymerisation were investigated. It is important to develop microcapsules with a strong, thin shell and a large hollow centre. This will maximise drug-carrying capacity yet be strong enough to withstand harsh physical conditions.

Polystyrene microcapsules made using a simple and inexpensive phase-inversion technique offer interesting possibilities for loading large quantities of drug as targeted drug delivery device. No special equipment is required. Compared with other type such as polyamide microcapsules, polystyrene microcapsules have the advantage of lower cost, good mechanical strength and are easy to process (Table 5.1). The microcapsules can be re-usable, compared to most other systems that degrade or disintegrate, and may have other applications as a carrier to immobilise desired molecules onto the microcapsules.

Table 5.1 Evaluation of prepared microcapsules

Type	Process	Cost
Polyamide microcapsule	Need special equipment	TDC – A$150/kg Amines – A$48 - 90/kg
Polystyrene microcapsule	Simple equipment	A$46/kg

(Costs in the table were based on materials prices in Sigma-Aldrich catalogue)

5.4 CONCLUSIONS

The research described in this chapter focussed primarily on developing microcapsules with a hollow core and porous shell. Many attempts had been made to achieve this goal. Micron-sized microcapsules with a hollow core and a matrix wall (with an outer dense skin layer) could be made from polysulfone, polycaprolactone or polystyrene using a solvent evaporation technique. Morphological characteristics of microcapsules strongly depend on the way the

coating polymer is precipitated, particularly in the non solvent–solvent–polymer interactions.

The experiments showed that microcapsules porosity could be changed by adjusting the rate of phase separation between the PVP and polystyrene phase, and the rate of solvent removal. Although all water soluble polymer additives could hypothetically improve the porous structure of microcapsules, differences in molecular size, solubility and interaction between polymers and the additives used promote different mechanisms, which inevitably produce different morphological characteristics. If porous channels are present in microcapsule wall, these may prove to be the most important route for manufacturing the proposed microcapsules for drug delivery system. However, the resultant microcapsules either had a sponge-like inner structure with no hollow core or had a dense outer skin on the microcapsules surface with an underlying porous wall and a hollow core. The process used to chemically graft acrylic acid onto the polycaprolactone and polysulfone microcapsules was unsuccessful.

A novel formulation approach using phase-inversion technique successfully manufactured polystyrene microcapsules with a hollow core and open porous micro-channel shell structure. The dense outer skin formed in the process could be removed by immersing the formed microcapsules in DMAa. Open pores with inter-connected micro-channels on the microcapsule surface could be produced by carefully controlling the time the microcapsules were in the solvent. Adding polyvinylpyrrolidone (hydrophilic polymer) and terahydrofuran (co-solvent) played important roles in formation of the microcapsule porous wall. However, the microcapsules formed had a slow release profile and did not completely retain their contents at pH 7. Some recommendations are given on how to improve and optimise the process.