CHAPTER SIX

6 CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

The major objectives of this research were achieved and pH-responsive microcapsules were developed using two different processes – a conventional interfacial polymerisation with plasma-induced grafting and a novel phase-inversion technique with chemical grafting. 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.

The sizes of the pores on the surface of microcapsules produced by interfacial polymerisation were influenced by the attached functional groups (grafted carboxyl groups), which reacted to the pH of the environment. Process parameters and formulation variables such as monomers ratio, polymer concentrations, solvent composition, additives, and grafting conditions, etc influenced morphology, physical characteristics, and configuration of the different types of microcapsules. These then influenced the release profiles of model drugs from the microcapsules manufactured. A novel formulation using phase-inversion technique successfully produced polystyrene microcapsules with a hollow core and open porous micro-channel shell structure, having potential as a targeted drug delivery system.

- **Polyamide microcapsules**

Microcapsules could be prepared from polyamide using an interfacial polymerisation technique. They had a hollow core and a porous shell with a smooth external surface and a rough internal surface. Average diameter (28 μm) decreased if stirring rate during polymerisation was increased. Changing the ratio of the amine monomers, EDA and DETA, from 1:2 to 2:1 changed the degree of crosslinking during polymerisation, which increased shell porosity.

An argon plasma treatment was developed to graft acrylic acid onto the microcapsule surface and produce a functionalised microcapsule with pores that responded to the environmental pH. A plasma treatment of 90 seconds produced 0.56 mmol/g of grafting.

Studies with two different sized molecules (vitamin B_{12} and cytochrome *c*) to simulate model drugs demonstrated that molecular size did not significantly affect release rate from PAA-grafted microcapsules. Microcapsule contents were retained when pH was between 7 and 5.5 and released when pH was between 5 and 3.5. Full release occurred when pH was below 3.

- **Polyester and polysulfone microcapsules**

Micron-sized microcapsules with a hollow core and a matrix wall (with an outer dense skin layer) could be made from polycaprolactone, polysulfone or polystyrene using a solvent evaporation technique. However, it was difficult to manufacture microcapsules that had open pores in the shell. Morphological characteristics of the microcapsules strongly depended on the way the coating polymer is precipitated, particularly between the non-solvent/polymer/solvent interactions. The process used to chemically graft acrylic acid onto the polycaprolactone and polysulfone microcapsules was unsuccessful.

- **Polystyrene microcapsules**

A novel formulation using a phase-inversion technique was developed to produce polystyrene microcapsules with a hollow core and 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 polyvinyl pyrrolidone (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.

6.2 RECOMMENDATIONS

To further develop polystyrene microcapsules as a pH-responsive drug delivery system, it is recommended that the following studies to be done:

- **Scale up of the process**

The processes developed in this research were all carried out on the laboratory scale. To investigate the applicability of the process, it will need to be scaled up. The phase inversion process could be scaled to produce large quantities (kilograms) of hollow microcapsules using a syringe pump with a rotating coagulation bath (with un-stirred solution). This simple and inexpensive process requires basic only equipments.

- **Microcapsule porosity**

Porosity can be defined as total area of pores per unit area of microcapsule cross-section. An alternative and more reliable way is needed to quickly analyse pore sizes of the resultant microcapsules. One possible method is to analyse SEM images using ImageJ software developed at the U.S. National Institutes of Health (http://rsb.info.nih.gov/nih-image/download.html).

- **Release studies**

Further studies need to be done on how microcapsule porosity and extent of grafting affect release rates. Many experimental parameters can influence microcapsule properties using orthogonal tests with multi-variation analysis will help identify that factors that will optimise microcapsule porosity and grafting extent.

Release trials using alternative model drugs such as phlorizin, which has been used as a pharmaceutical and tool for physiology research for over 150 years (Ehrenkranz *et al*., 2005)., would be useful for future applications in rumen-protection animal assessment.

- **Mathematical modelling**

Drug release from the microcapsule could be considered as solely due to diffusion between the high concentration region within the microcapsule and the negligible concentration in the surrounding environment (i.e. the environment is acting as a large sink). Under these conditions, Fick's second law of diffusion could be used to derive a mathematical model for describing release rate. To do this study, the following conditions also need to be considered:

1. Before exposure to the release medium, the drug must be homogeneously distributed throughout the microcapsules.
2. The initial drug concentration must be below the solubility of the drug (molecular dispersion).
3. Diffusional resistance for drug release within the unstirred liquid boundary layers surrounding the microcapsules is negligible compared with diffusional resistance within the polymeric systems under the experimental conditions used.

- **Animal assessment**

The effect of microcapsules on controlled release of a drug in the rumen and the abomasum needs to be investigated. This could be simulated using rumen fluid in fermenters to evaluate the functional microcapsules.