NOVEL POLYMERIC MICROCAPSULES

FOR TARGETED DRUG DELIVERY

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Abstract

Microencapsulation is a technology in which small particles or droplets are entrapped by a coating to give the particles with many useful properties. Microcapsules have been used to protect the encapsulated material from the environmental conditions or to release the active agent in a sustained and controlled manner into the surrounding medium. This thesis investigated how to develop a post-ruminal delivery system based on polymeric microencapsulation. A major criterion was to develop microcapsules with reversible switching in response to changes of pH in the *in vivo* environment so contents could be released. The microcapsules must have a thin shell strong enough to withstand harsh physical conditions and a large hollow centre, which will maximise drug-carrying capacity.

Two processes were developed to manufacture pH-responsive microcapsules - conventional interfacial polymerisation with plasma-induced grafting and a novel phase-inversion technique with chemical grafting. This research demonstrated that microcapsules with a porous shell could be manufactured by interfacial polymerisation. Carboxyl groups introduced onto the pores in the microcapsule by plasma-induced graft polymerisation of acrylic acid allowed pore openings to be controlled by the pH change of the environment.

Polyamide microcapsules made by interfacial polymerisation had a hollow core and a porous shell with smooth external and rough internal surfaces. Their average diameter of 28 μm decreased with increased stirring rate during polymerisation. Shell porosity could be changed by adjusting the ratio of amine monomers used to form the microcapsule shell. An argon plasma treatment was developed to graft acrylic acid onto the microcapsule surface. Plasma treatment with 90 seconds produced 0.56 mmol/g of grafting extent. The effect of pH on releasing contents from poly(acrylic acid)-grafted microcapsules was investigated using two different sized molecules (vitamin B_{12} and cytochrome *c*) to simulate model drugs. Release rate was not significantly affected by molecular size; contents were retained when pH was between 7 and 5.5 and released when pH was between 5 and 3.5. Full release occurred at pH below 3.

Further studies showed that micron-sized microcapsules with a hollow core and a thick matrix wall could be made from polycaprolactone, polysulfone and polystyrene. A modified solvent evaporation process reduced shell thickness but the microcapsules still had a non-porous skin. Process parameters such as polymer concentration, temperature, surfactant, solvent composition, stirring speed, processing pressure, and co-polymer additives influenced structure and internal morphology of the microcapsules. Morphological characteristics of the microcapsules strongly depended on the way the coating polymer is precipitated, particularly the non solvent–polymer–solvent interactions. Chemical grafting was not successful for grafting acrylic acid onto the polycaprolactone and polysulfone microcapsules.

Polystyrene microcapsules with a hollow core and porous micro-channel shell structure were successfully produced using a novel formulation in a phase-inversion process. The outer skin could be removed by re-dissolving the formed microcapsules in a suitable solvent. Open pores with inter-connected micro-channels on the microcapsule surface can be produced by carefully controlling the time the microcapsules are in the solvent. The microcapsule was functionalised using free radical polymerisation to graft acrylic acid onto its surface. However, these microcapsules did not completely retain their contents at pH 7 and had a slow release profile when pH was decreased. Recommendations are given on how to improve and optimise the process.

Polystyrene microcapsules made with a simple and inexpensive phase-inversion technique have potential as a targeted drug delivery system. They could 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. Further investigations to optimise manufacturing polystyrene microcapsules should include: larger scale trials; further investigations, using orthogonal tests with multi-variation analysis to optimise factors affection microcapsule porosity and extent of grafting; identifying an alternative, faster way to analyse pore size; and developing a mathematical model for the release rate.

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Abbreviations

AAc	Acrylic acid
APS	Ammonium peroxydisulfate
ASTM	American Society for Testing and Materials
BSA	Bovine serum albumin
DCM	Dichloromethane
DETA	Diethylene triamine
DMAa	*n*,*n*-Dimethylacetamide
EDA	Ethylene diamine
GRAS	Generally regarded as safe
O/W	Oil-in-water
PAA	Polyacrylic acid
PA	Polyamide
PEG	Poly(ethylene glycol)
PEO	Poly(ethylene oxide)
PCl	Polycaprolactone
PLGA	Poly(lactic-*co*-glycolic acid)
PSf	Polysulfone
PSt	Polystyrene
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
SEM	Scanning electron microscope
TDC	Terephthaloyl dichloride
THF	Tetrahydrofuran
W/O	Water-in-oil
W/O/W	Water-in-oil-in-water emulsion