A polyanhydride sustained release devices for hydrophliic drugs

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INTRODUCTION

Biodegradable polyanhydride polymers are currently widely used for drug delivery, especially as the localized drug delivery carrier. Localized drug delivery is able to reduce systemic toxicity and keep high local drug concentration. Besides, the degradation pattern of polyanhydrides is of the surface erosion type (Fig.1), which enables the release device to maintain stable release rates and mechanical properties.

Figure 1 : Surface and bulk erosion

In our previous studies, polyanhydrideas carriers have been demonstrated to deliver hydrophobic compounds very successfully. But they are not suitable for hydrophilic drugs, where the release is too fast and with severe initial burst. This is because the hydrophilic compounds can accelerate carriers' erosion, and disrupt the structure of the polymeric matrix (Chan 2005). In this study, a new type of release device was designed for extended & stable release of hydrophilic drugs.

A model hydrophilic drug, brilliant blue G (BBG), was used and the desirable releases were obtained by adjusting the polymer components and structure of devices.

MATERIAL AND METHODS

Polymer Synthesis

1, 3-bis (carboxyphenoxy) propane diacid was synthesis by para-hydrinic benezone acid and di-bromopropane (Conix 1966). CPP and SA acids were refluxed with excess acetic anhydride for 20 min under dry nitrogen sweep to form prepolymer. The prepolymer was recovered by evaporating the solution to dryness at 60℃ under vacuum and dissolved in toluene. The prepolymer was re-precipitation in dry petroleum ether and washed 2 times with dry diethyl ether. Homopolymers and copolymers were synthesized via melt condensation at 180℃ under vacuum for 90 min. The molecular weights were determined relative to polystyrene standards and structure was confirmed by ^{1}H NMR recorded in $CDCl_3$. The polymers were preserved in the vacuum at -20℃ before use (Lee 2008).

Preparation of Microspheres

Microspheres were prepared by water-in-oil-in-water double emulsion technique ($W_1/O/W_2$). Poly-anhydrides were dissolved in the dichloromethane and emulsified with aqueous solution of poly-γ-glutamic acid (γ-PGA) and drug by homogenizer to form the initial emulsion (W_1/O). Then the resultant emulsion was added to 3 % poly(vinyl alcohol) (PVA) solution and emulsified by homogenizer to from double emulsion. Finally, the emulsion was diluted to 0.5 % PVA and stirred for 3 hours to remove organic solvent. The resulting microspheres were collected by centrifuge at 4,500 rpm for 8 min and washed 3 times with ddH_2O. The precipitated microspheres were re-suspended in deionized water. The solution was lyophilized overnight and preserved at -20℃ before use.

Particle Characterization

The size and morphology of the microspheres were determined by Scanning electron microscope (SEM).

The Degradation of Polymers and Drug Release

In vitro degradation of polymers and drug release experiments were performed in pH 7.4 phosphate buffer at 37℃. The release of the BBG was quantitated by spectrometer at 610nm.

RESULTS AND DISCUSSIONS

The Characterization of the Polymers

Results for the polymerization of the polymers are summarized in Table 1. The polymers were charactered by ^{1}H-NMR spectrums (data not showed). The composition of PSACPP copolymer was determined by ^{1}H-NMR from the ratio of the peak's integration at 1.3 ppm(8H, SA), and 6.9-8.2 ppm(8H, CPP) and showed at Table 1.

Table 1 : Compositions of copolymer

Polymer	Molar Ratio	
	Feed	Final
PSACPP 9010	90:10	90:10
PSACPP 8020	80:20	79:21
PSACPP 6040	60:40	60:40

The Characterization of the Microspheres

By emulsion technique, homopolymer and copolymers formed microspheres with size ranging

from 2 to 10 μm. According to the SEM image, Fig 2, the microsphere has core-shell structure.

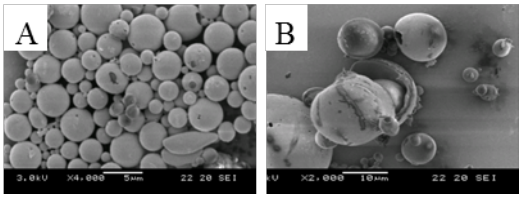

Figure 2 : Size and structure of microspheres
(A) microspheres (B) core-shell structure

The Degradation of the polymers and the drug release

From Table 2, the drug loading efficiency was 40% ~ 60%, and the polymer type was the major factor.

Table 2 : Drug loading of microspheres

polymer	Drug	Loading Efficiency(LE)	Drug Contents (DC)
PSACPP 8020	5%	40%	2%
PSACPP 8020	10%	43%	4%
PSACPP 8020	20%	44%	9%
PolySA	5%	55%	3%
PolySA	10%	59%	6%
PolySA	20%	54%	11%

The morphology and structure change during degradation was observed by SEM. Figs 3 shows the appearance of microspheres after degradation for two weeks. The higher CPP ratio copolymers degradation was slower.

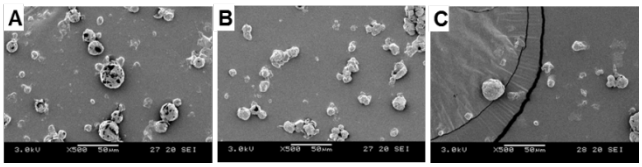

Figure 3 : Degradation of microspheres.
(A) PSA, (B) PSACPP 8020, (C) PSACPP 6040

During degradation, pH value did not change much which can reduce irritation to body when implanted (Fig. 4).

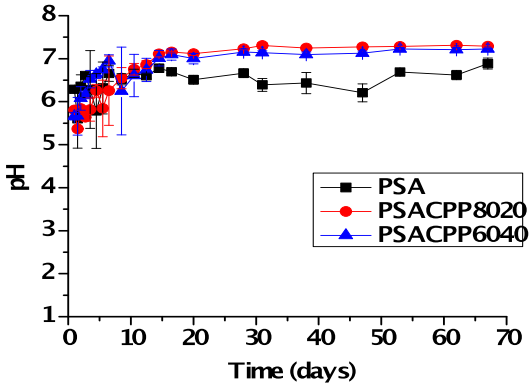

Figure 4 : The pH change of degradation

In this study, there are no initial burst releases from microspheres made by all polymers (Fig. 5). The PSA hydrolyzes faster than CPP, thus the degradation rates are faster with polymers of higher content of SA. BBG release rate was proportional to the polymer degradation rate.

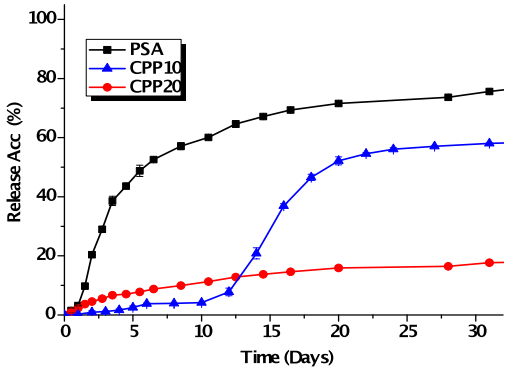

Figure 5 : Accumulation release of BBG

CONCLUSIONS

Polyanhydrides were successfully synthesized through melt-condensation methods and microspheres with core-shell structure were fabricated by W/O/W double emulsion procedures. The hydrophilic drug can be encapsulation in polyanhydride carriers with high loading efficiencies and contents.

The drug release profiles show that the release devices have no initial burst and have stable release rates. The release profile can be adjusted by the components of polymers. The release devices have the potential for long term hydrophilic drug release.

REFERENCE

- Conix A., (1966) *Poly[1,3-bis(p-carboxyphenoxy) propane anhydride]*. Macromolecular Synthesis, 2:95-98.
- Chan C.K., Chu I.M., (2005), *In vitro release of incorporated model compounds in poly(sebacic anhydride-co-ethylene glycol)*. Eur. Polymer J.41(6):1403-1409
- Lee W.C., Chu I.M., (2008) *Preparation and degradation behavior of polyanhydrides nanoparticles.* J Biomed Mater Res B Appl Biomater. 84(1):138-46.