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Preparation of novel polymeric microspheres for controlled release of finasteride

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Abstract

The utility of the novel polycarbonate, poly(propylene carbonate maleate) (PPCM) to encapsulate and control the release of finasteride, *via* microspheres, was investigated. The PPCM microspheres loaded with finasteride were elaborated by a simple oil-in-water (O/W) emulsion-solvent evaporation method. Various manufacturing parameters, including the concentration of polymer in dichloromethane (DCM) and the polymer:finasteride ratios were altered to optimize process variables during the microspheres production. The effects of these changes on the characteristics of the microspheres were examined. The structure and morphology were characterized by wide-angle X-ray diffraction (WXRD) and scanning electron microscopy (SEM). The results showed that the mean diameter of microspheres was approximately 2 μm, and had both smooth and spherical surfaces. Greater encapsulation efficiency was obtained by increasing the ratios of polymer:finasteride and the concentration of PPCM in DCM. *In vitro* drug release of these microcapsules was performed in a pH 7.4 phosphate-buffered solution. The release profiles of finasteride from PPCM microcapsules were found to be biphasic with a burst release followed by a gradual release phase. A prolonged *in vitro* drug release profile was observed. After an initial burst, a continuous drug release was observed for up to 5–6 weeks.

Keywords: Poly(propylene carbonate maleate); Microspheres; Finasteride; Drug delivery systems; Manufacturing parameters

1. Introduction

In recent years, biodegradable polymers have found increasing applications in the pharmaceutical industry as matrices for drug delivery systems (Freiberg and Zhu, 2004). The most active area of contemporary research using synthetic biodegradable polymers such as polyester polymers focuses on controlled drug delivery of pharmaceuticals. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy, reduced toxicity and improved patient compliance and convenience (Uhrich et al., 1999).

Aliphatic polycarbonate represents one family of biodegradable materials used for biomedical applications such as drug carriers and implant materials because of their good biocompatibility, low toxicity, and biodegradability (Zhu et al., 1991; Rokicki, 2000). Aliphatic polycarbonates can be modified by functional groups, such as ester (Hwang et al., 2003; Lu and Huang, 2005; Liu et al., 2007), carboxyl (Talal and Bisht, 2002) to improve their thermal properties and degradability. In recent years, aliphatic polycarbonates have been explored in the search and design of new polyester-related structures for medical applications (Edlund and Albertsson, 2001).

Finasteride is a 5-alpha reductase inhibitors interfere with the effect of certain male hormones (androgens) on the prostate (Brooks et al., 1986), the structure of finasteride is shown in Scheme 1. Finasteride was originally used to treat enlarged prostate glands (benign prostatic hyperplasia) by the U.S. PDF (Roehrborn, 2003). Finasteride can lower the level of androgens, a class of hormone that affects hair loss, it is now also used to treat inherited hair loss in men (androgenetic alopecia) and the most common cause of hair loss (Heinzl, 1999). In addition, finasteride is also used in the prevention of prostate cancer (Coltman et al., 1999). Benign prostatic hyperplasia (BPH) and hair loss are a common occurrence in aging men. Although it is not life-threatening, the condition and its complications have a serious impact on quality of life. Finasteride is recognized as a successful therapy for them. However, possible side effects in men include sexual problems may exist. The use of extended

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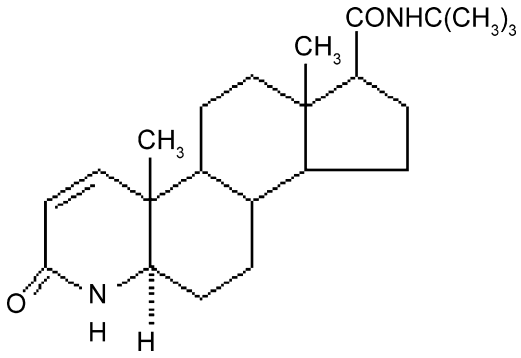

Scheme 1. Chemical structure of finasteride.

release products offers potential advantages like sustained blood levels, attenuation of adverse effects and improved patient compliance. Hence, to develop its formulations in controlled release form is important.

In this research, poly(propylene carbonate maleate) (PPCM) was synthesized by introduction the third monomer, maleic anhydride, into the backbone of poly(propylene carbonate) (PPC), and it was designed as a drug carrier material, finasteride was used as a hydrophobic model drug, the drug-loaded microspheres were prepared by the O/W emulsion-solvent evaporation method. Their *in vitro* drug release profile was performed in a pH 7.4 phosphate-buffered solution. This formulation of controlled delivery of finasteride has not been reported previously.

2. Materials and methods

2.1. Materials

The copolymer PPCM ($[\eta] = 0.772$, $M_w = 67{,}400$, $M_n = 32{,}100$, $M_w/M_n = 2.10$) was prepared in our laboratory (Central South University, China), and their synthesis and characterization were detailed in our earlier work (Liu et al., 2006). Briefly, 1.0 g PBM catalyst, 70 mL toluene, 0.5 mol propylene oxide and 0.3 mol maleic anhydride were added into an FYX-0.3 300 mL stainless steel autoclave equipped with an electromagnetic stirrer in the absence of oxygen. The autoclave was then pressurized to ±4 MPa with a CO_2 cylinder. The reaction mixture was stirred magnetically at 60 °C for 24 h. When the reaction was finished, the resulting viscous mixture was removed, washed and dried. Finally it was purified. The gift sample of finasteride was supplied by Shanghai Asia Pioneer Prarmaceutical Co. Ltd., China, and used as received. Polyvinyl alcohol (PVA-124, Japan) was purchased from Guangzhou Chang Fu Trade Co. Ltd., China. The other reagents and solvents were analytical-grade and were used as received.

2.2. Preparation of microspheres

The O/W emulsion method was applied to the fabrication of hydrophobic drug loaded microspheres. The copolymer PPCM was used as drug carriers, and finasteride was used as a model drug. Various PPCM:finasteride ratios and concentration of PPCM in dichloromethane (DCM) were altered during the microspheres production. Briefly, the amount of finasteride was dispersed in 10 mL DCM containing PPCM by sonication. The organic phase was then emulsified with agitation in an aqueous phase consisting of 200 mL of a 0.2% (w/v) solution of polyvinyl alcohol (PVA). Stirring was continued for 4 h at 800 rpm on a magnetic stirrer at room temperature, until DCM was completely evaporated. The microspheres were collected by centrifugation, washed in distilled water, frozen, and lyophilized with freeze drier. Totally six formulations were prepared, the manufacturing parameters and the assigned formulation codes were shown in Table 1.

Table 1
Formulation codes

Concentration of PPCM in DCM (mg mL^{-1})	Mass ratios of PPCM:finasteride		
	4:1	6:1	9:1
60	F1	F2	F3
100	F4	F5	F6

2.3. Characterization of microspheres

The microspheres were characterized in terms of the morphology, size, the amount of encapsulated and encapsulation efficiency. The morphology of the microspheres was observed by a scanning electron microscope (KYKY2800, China). The particle size and distribution of the microspheres were measured with a laser diffraction particle size analyzer (Malven, Mastersizer 2000, British).

To determine the drug-loading content and the encapsulation efficiency, we dissolved 100 mg of microspheres sample in DCM and extracted finasteride into methanol. The amount of finasteride was determined by HPLC. The chromatograph used was equipped with a Waters 515 solvent delivery pump and a 2487 UV-detector. The separation was achieved by reversed phase column C_{18} (Diamosil 4.6 mm × 200 mm 5 μ). The detection wavelength was 210 nm. The mobile phase used was water–acetonitrile–tetrahydrofuran in the ratio of 8:2.5:1, and the flow rate was 1.0 mL/min. Drug loading and encapsulation efficiency were determined for all batches using Eqs. (1) and (2), respectively.

$$\text{Drug loading} = \frac{\text{weight of finasteride in microspheres}}{\text{microspheres sample weight}} \times 100\% \quad (1)$$

$$\text{Encapsulation efficiency} = \frac{\text{actual weight of finasteride in sample}}{\text{theoretical weight of finasteride}} \times 100\% \quad (2)$$

2.4. Wide-angle X-ray diffraction analysis

To clarify the structure of the microspheres, the wide-angle X-ray diffraction (WXRD) measures of finasteride, placebo microspheres and drug-loaded microspheres were performed at

room temperature using a Rigaku D/max 2550 VB^+ 18 Kw X-ray diffractometer.

2.5. In vitro release studies

Release studies of drug from both batches were determined by adding 15 mg of finasteride equivalent microspheres to 50 mL of phosphate buffered saline pH 7.4 in a shaking water bath at 37 °C. The release profiles were investigated from the measurement of finasteride presented in the release medium at various intervals. The sample (2 mL) was collected at different intervals and replaced with fresh medium, and analysed for drug released by HPLC as described earlier.

3. Results and discussion

3.1. Size and morphological characterization of microspheres

Fig. 1 shows the morphology of microspheres from different concentration of PPCM at a polymer:finasteride ratio of 9:1. The surfaces of microspheres F3 using 60 mg/mL PPCM in DCM was relatively smooth than those of microspheres F6 using 100 mg/mL concentration of PPCM. The diameter of both microspheres was about 2 μm, and the particle size of microspheres F3 was slightly smaller than that of microspheres F6. The microspheres obtained by both batches were spherical, smooth and individually homogeneously distributed without evidence of collapsed spheres. The micrographs do not show any pores on microspheres. Smooth surface reveals complete removal of dichloromethane from microspheres. The particle size and distribution of the microcapsules were measured with a laser diffraction particle size analyzer, all microsphere formulations have particle size smaller than 20 μm diameter with narrow size distribution, and the mean particle size of microspheres ranged from 1 to 3 μm.

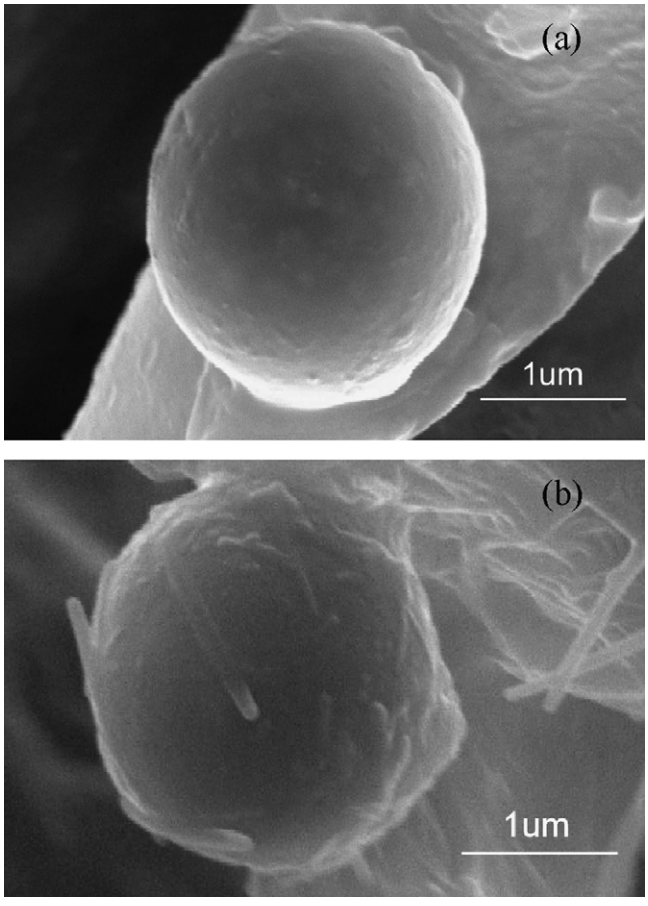

Fig. 1. Scanning electron micrographs of finasteride-loaded microspheres (a) microsphere F3 and (b) microsphere F6.

Table 2
Properties of the PM-loaded microcapsules prepared by various conditions (±S.D., $n = 3$)

Formulation codes	Drug loading, Φ (%)	Encapsulation efficiency, θ (%)	Mean diameter, (μm)
F1	12.03 (±0.69)	60.98 (±1.69)	2.14 (±0.11)
F2	9.65 (±0.43)	69.31 (±2.31)	1.98 (±0.09)
F3	7.78 (±0.38)	82.92 (±1.87)	1.71 (±0.05)
F4	13.42 (±0.60)	62.87 (±1.54)	2.98 (±0.12)
F5	10.76 (±0.54)	73.95 (±2.55)	2.75 (±0.08)
F6	8.45 (±0.32)	85.76 (±2.36)	2.31 (±0.07)

3.2. Effect of manufacturing parameters on particle size and entrapment efficiency of microspheres

The drug loading, encapsulation efficiency and mean diameter of drug-loaded PPCM microspheres elaborated by emulsion-solvent evaporation methods in different conditions were summarized in Table 2. Results indicated that as the concentration of PPCM in DCM increased, the particle size increased ($P < 0.05$), the drug loading and entrapment efficiency increased slightly ($P > 0.05$). It was explained that higher concentration of PPCM in DCM could result in an increased rate of microsphere hardening. An increased hardening rate would also tend to reduce the time available for subdivision of larger globules into smaller ones during stirring, and reduce the loss of drug. As a result the globules of the internal phase were larger in diameter than the other batches with lower concentration of polymer on solidification. Drug loading and entrapment efficiency also enhanced by increased hardening rate. A possible reason for this is that the internal phase of higher concentration of polymer was more viscous and therefore solidified at a faster rate (Bodmeier and McGinity, 1988; Bodmeier and Chen, 1989).

The mean microsphere diameter decreased with increasing polymer:drug ratio, although the differences between ratios were not statistically significant ($P > 0.05$). This could be due to the changes in viscosity resulting from changes in total weight of solids dissolved in the internal phase. An enhancement in viscosity may result in a decreased solidification time and consequently produced smaller microspheres. The drug-loading content and entrapment efficiency were mainly affected by the polymer:drug ratios ($P < 0.05$), encapsulation efficiency increased with increased polymer:drug ratio. This improved encapsulation efficiency may be due to the greater proportion of polymer with respect to the amount of drug, as well as, increased

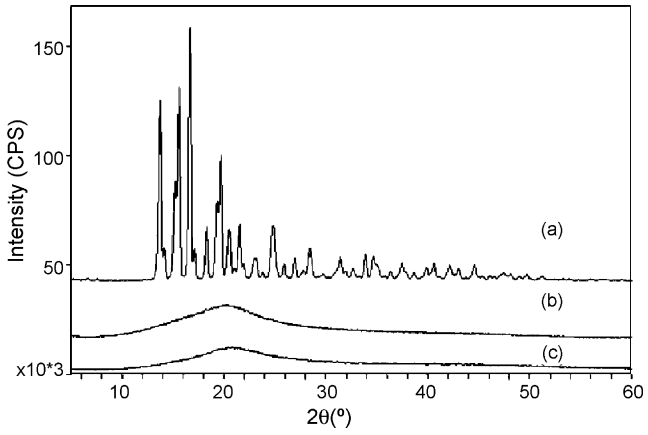

Fig. 2. The wide-angle X-ray diffraction spectra of (a) pure finasteride, (b) finasteride-loaded microspheres, and (c) placebo microspheres.

the PPCM:finasteride ratio, the difference of drug concentration between O/W phases decreased. As a result the loss of drug *via* diffusion into the aqueous phase decreased, and the entrapment efficiency increased.

The results revealed that, as the polymer:finasteride ratio was 9:1, the microspheres prepared showed an optimum entrapment efficiency and smaller particle size among the six formulations of microspheres.

3.3. Wide-angle X-ray diffraction (WXRD) analysis

The WXRD spectra recorded for the pure finasteride, placebo microspheres, and the finasteride-loaded microspheres are presented in Fig. 2. These studies are useful to investigate crystallinity of the drug in the obtained microspheres. The WXRD of the finasteride samples yielded a typical pattern of crystalline substances. X-ray diffraction patterns obtained for placebo PPCM microspheres were also consistent with an amorphous polymer. In our earlier report, the polymer PPCM was amorphous (Liu et al., 2006). The characteristic crystalline peaks of finasteride were not observed in finasteride-loaded microspheres, but instead only peaks observed in the placebo were seen. In view of the WXRD results mentioned above, it is believed that finasteride had been encapsulated inside polymer PPCM. This indicated that drug was dispersed at the molecular level in the polymeric matrix and hence no crystals were found in the drug-loaded matrices (Guyot and Fawaz, 1998).

3.4. In vitro release of finasteride

In vitro release behaviors of finasteride from the PPCM microspheres were studied in pH 7.4 PBS. Many manufacturing parameters determine the drug release behavior from microspheres. The effect of concentration of polymer in DCM and polymer:drug ratios on release profiles were investigated. Fig. 3 shows the percent release of finasteride from microspheres with different concentration of PPCM in DCM (60 mg/mL for F3 and 100 mg/mL for F6) against incubation time in pH 7.4 PBS. The finasteride release profiles from the two microspheres were found to occur in a biphasic manner, with an initial fast release

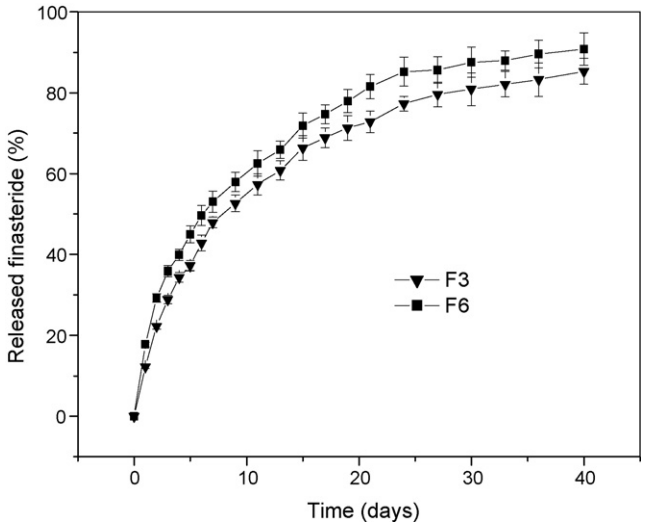

Fig. 3. Release of finasteride from microspheres prepared from different concentration of PPCM in DCM in pH 7.4 PBS, 60 mg mL^{-1} for F3 and 100 mg mL^{-1} for F6 (±S.D., $n = 3$).

phase followed by a slower release phase. However, the burst release and gradual release of finasteride from microspheres F6 were faster than that from microspheres F3. Microspheres F6 released 90.82 ± 4.01% of the loaded finasteride in 40 days compared to 85.32 ± 3.26% released from microspheres F3. This indicated that the release rates increased with increasing concentration of PPCM in organic phase DCM, although the differences were not statistically significant ($P > 0.05$). Fig. 4 shows the release profiles of finasteride from the microspheres with different PPCM:finasteride ratios in PBS (pH 7.4). The ratios of PPCM:finasteride has controlled release profile of finasteride from prepared microspheres. After 27 days, microspheres F1 with the lowest ratio of PPCM:finasteride (4:1) showed 95.16 ± 4.08% drug release which was far higher than 89.35 ± 3.08% release of finasteride from microspheres F2 (PPCM:finasteride = 6:1) and 79.61 ± 3.05% release of finas-

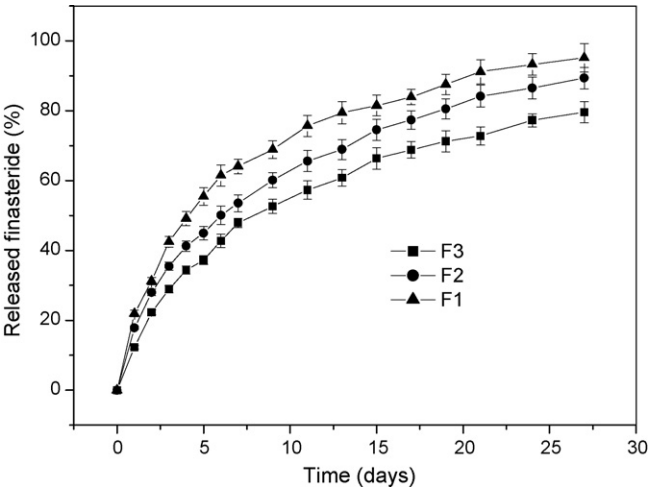

Fig. 4. Release of finasteride from microspheres prepared from different ratios of PPCM: finasteride in pH 7.4 PBS, 4:1 for F1, 6:1 for F2 and 9:1 for F3 (±S.D., $n = 3$).

teride from microspheres F3 (PPCM:finasteride = 9:1). The release rate of finasteride decreased with increasing ratios of PPCM:finasteride ($P < 0.05$). In view of the results mentioned above and the results of drug loading in Table 2, interestingly, it has been found that as the amount of finasteride incorporated increased, drug released from PPCM microspheres was also increased. This suggests that the level of drug loading was a main factor that controlled the rate of drug release, the microspheres with a higher loading released finasteride faster. These results agree with the observations by Spenlehauer et al. (1988) and Sah et al. (1994).

4. Conclusion

The copolymer PPCM was developed as drug carriers for controlled release of finasteride in the present study. The finasteride-loaded PPCM microspheres were elaborated by solvent evaporation method based on an O/W emulsion. The microcapsules had a spherical, smooth morphology and a diameter of approximately 2 μm. More than 80% encapsulation efficiency and a controlled release rate were obtained by varying the process parameters. The finasteride-loaded PPCM microspheres had a long release period of about 5 weeks. The present results suggest that the new polymer PPCM provides an alternative to degradable matrix polymers for controlled drug delivery systems. The obtained microspheres could be useful as a prolonged drug delivery system for BPH and hair loss treatment. Accordingly, the next step of this work will be to study the therapeutic effect of these microspheres *in vivo*.

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