International Journal of Pharmaceutics 386 (2010) 23–29

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Effects of implant diameter, drug loading and end-capping on praziquantel release from PCL implants

Changyan Li[a,1], Liang Cheng[a,1], Yaqiong Zhang[a], Shengrong Guo[a,*], Weiping Wu[b]

[a] School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China
[b] National Institute for Parasitic Diseases, Chinese Center for Control and Prevention, 207 Ruijin 2nd Road, Shanghai 200025, China

ARTICLE INFO

Article history:
Received 10 August 2009
Received in revised form 19 October 2009
Accepted 26 October 2009
Available online 4 November 2009

Keywords:
Praziquantel
Poly(ε-caprolactone)
Cylindrical implant
Drug release
Scanning electron microscope

ABSTRACT

Praziquantel (PZQ)-loaded poly(ε-caprolactone) (PCL) cylindrical implants were fabricated and characterized. Implant diameter (3, 4 and 8 mm), drug loading (25% and 50%), and the end-capping were investigated to evaluate their effects on drug release. The evolution of implants with release time was conducted in terms of implant microstructure, crystallinity, drug content and molecular weight of PCL. The results showed that drug release was fastest for the implant with a diameter of 3 mm and slowest for the implant with a diameter of 8 mm; drug release from the implant with a drug content of 50% was faster than that from the implant with a drug content of 25%; the release of PZQ from the end-capped implants was slightly slower than that from the corresponding end-uncapped implants. The effect of drug loadings on PZQ release was related with diameter of the implants and the effect was weakened as diameter of the implants increased. The drug release data for all the implants were best fitted with Ritger–Peppas model, therefore Fickian diffusion was the predominant release mechanism. The evolution of implants with release time verified that PZQ was gradually released from the exterior to the interior of the implants.

1. Introduction

Biodegradable polymers have been widely used in drug delivery in the past few decades. Within them, aliphatic polyesters, such as poly(ε-caprolactone) (PCL), are of particular interest as they allow for a long sustained and possible modulated drug release rate. PCL has been approved by FDA as pharmaceutical excipient. PCL and its copolymers or blends have been utilized to prepare various drug delivery systems such as implants and micro-/nano-particles (Barbato et al., 2001; Chawla and Amiji, 2002; Cheng et al., 2009; Dong et al., 2008; Fialho et al., 2008; Gou et al., 2009a,b; Hombreiro Peĭrez et al., 2000; Jia et al., 2008; Sinha et al., 2004; Wang and Guo, 2008; Wei et al., 2009; Zhang et al., 2009). The repeating unit of PCL molecule chain consists of five methylenes and one ester group. This structural characteristic endows PCL some specific properties, such as strong hydrophobicity, slow hydrolysis, high permeability to low molecular weight molecules, and good biocompatibility. Thus, PCL is considered ideal for implantable long-term drug delivery. PCL-based drug delivery devices can be easily fabricated by means of some processing techniques, including melt extrusion and injection moulding at mild conditions (e.g. low temperature), due to its low melting temperature of 60 °C and low glass transition temperature of −60 °C.

Injection moulding is widely used in the plastic processing industry, but seldom used in pharmaceutics. Injection moulding is a common technique in preparing complex articles from thermoplastic materials with the aid of heat and pressure. Molten polymer complex is injected into a closed and shape-specific mould cavity, after solidification, the article is recovered by opening the mould to release the product like the cavity of mould in shape. Hot-melt extrusion is often used to prepare the blend of polymer and solid particles. The common hot-melt extrusion instrument is a twin or single screw extruder in industry. Hot-melt extrusion can be combined with injection moulding to fabricate solid dosage forms in an effective way. These techniques can be applied to prepare solid dispersions or solutions for drug controlled release via the homogeneous embedding of drug particles in release-controlling polymers. Many pharmaceutical dosage forms, such as granules (Van Melkebeke et al., 2006), mini-tablets (Verhoeven et al., 2006), matrix tablets (Bruce et al., 2005), implants (Rothen-Weinhold et al., 1999), films (Repka et al., 2005) and transdermal or transmucosal drug delivery systems (Trey et al., 2007) were prepared by hot-melt extrusion (Quinten et al., 2009; Rothen-Weinhold et al., 1999).

Control of drug release is one of the dominant challenges in drug delivery. Drug doses must fit with a specific window whose lower limit is above the therapeutic threshold and whose upper limit is

* Corresponding author. Tel.: +86 21 3420 4793; fax: +86 21 3420 4793.
E-mail address: srguo@sjtu.edu.cn (S. Guo).
[1] Equal contributors.

0378-5173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2009.10.046

below the toxic level. Previous studies show that the rate of drug release from polymeric devices depends on the polymer properties, environmental conditions, and drug characteristics (Koizumi et al., 1975; Rosenberg et al., 2007; Siegel et al., 2006; Siepmann and Göpferich, 2001; Sung et al., 1998). However, it was seldom reported on the influence of the shape, size of polymeric devices and drug loadings on drug release.

Praziquantel (PZQ, 2-cyclohexylcarbonyl [1,2,3,6,7,11b] hexahydro-4H-pyrazin [2,1a] isoquinolin-4-one) is a hydrophobic drug widely used in developing countries for the treatment of schistosomiasis and hydatid. To date, the common dosage form of PZQ is tablet, and its frequent administration is needed in order to decrease morbidity (Dinora et al., 2005; Sotelo et al., 1990). It is necessary to develop a long-term controlled release PZQ implant.

In this paper, we first fabricate the PZQ-loaded PCL cylindrical implants by a combination of hot-melt extrusion and injection moulding, and then investigate the effects of implant diameter, drug loading and end-capping on PZQ release from PCL matrices and the evolution of implant with release time. This will provide a base for developing a new controlled release implant containing PZQ.

2. Materials and methods

2.1. Materials

Poly(ε-caprolactone) was purchased from Daicel Polymer Ltd. (Minatoku, Tokyo, Japan). Praziquantel (PZQ) was obtained from Shanghai Jiachen Chemical Industry Co. Ltd. (Shanghai, China). Methanol (HPLC grade) was purchased from Shanghai Xingke Chemical Co. (Shanghai, China); Ultrafiltrated water was obtained from Milli Q plus (Millipore, USA). All other chemicals were of analytical grade and used without further purification.

2.2. Fabrication of cylindrical implants

The cylindrical implants with a diameter of 3, 4 or 8 mm were prepared by fully blending PZQ particles with melting PCL at different ratios (25:75 and 50:50, w/w) and then molding the blends with a lab-scale injection moulder with a diameter of 3, 4 or 8 mm. Briefly, PCL was fed into the hopper of HAAKE Rheocord System (Rheocord 90, HAAKE Mess-Technic GmbH, Germany) and heated until it was completely melted. Afterward PZQ was added slowly into the melting PCL and mixed at 70 °C for 20 min at a screw speed of 50 rpm. The resultant blend was collected and further molded into implants using a lab-scale injection moulder at 70 °C. The cylindrical implants were end-capped by pressing a PCL sheet on the end surface of the implant.

2.3. Scanning electron microscope (SEM)

The implants were imaged using a JSM-7401F scanning electron microscope (SEM) (JEOL, Tokyo, Japan). The cross-section of implants was obtained by first freezing the implants in liquid nitrogen and then fracturing by means of a scalpel. Samples were placed on metal sample holders and sputter coated (Emitech K-575 Sputter Coater) with a gold–palladium target for 30 s at 20 mA prior to imaging. Images were obtained at 5 kV accelerating voltage and 20 mA current.

2.4. Gel-permeation chromatography

Gel-permeation chromatography (Waters, USA) was used to analyze the molecular weight of PCL in implants. The GPC analyses were performed at 40 °C using a Waters HPLC system equipped with a model 1525 binary HPLC pump, a model 2414 refractive index detector, and a series of Styragel® columns (HR3 and HR4). 200 μl of polymer solutions (3 mg/ml) was injected. THF was used as an eluent at a flow rate of 1.0 ml/min. The GPC system was calibrated with polystyrene standards. Polystyrene standards of known molecular weight were used as reference materials.

PZQ was completely extracted in methanol from implants with a soxhlet apparatus and the residual PCL was dried under vacuum and then used for GPC analysis.

2.5. X-ray diffraction (XRD)

X-ray diffraction (XRD) patterns were obtained using an X-ray diffractometer (D/max 2200, Rigaku, Japan) equipped with Cu-Kα radiation source (40 kV, 20 mA). All the samples were firstly pressed into thin films on a Compression Molding Machine (XLB-D, Shanghai No. 1 Rubber Machine Factory) at ambient temperature. Then the films were placed in a steel holder and scanned over a 2θ range of 5–45° at the rate of 5°/min.

2.6. High-performance liquid chromatography (HPLC)

PZQ was quantitatively analyzed by high-performance liquid chromatography (HPLC) using the method described in the Chinese Pharmacopoeia by a Shimadzu apparatus, equipped with a variable wavelength detector (SPD-10ADvp, Shimadzu, Japan). A pump (model LC-10AD, Shimadzu, Japan) was used at a constant flow rate of 1.0 ml/min. A C-18 reversed-phase column (4.6 mm × 250 mm, 5 μm, Dikma Technologies, Beijing, China) was used for the analysis of the drug. The mobile phase was a mixture of methanol and ultrafiltrated water (100:40, v/v). The ultraviolet detector was used at a wavelength of 263 nm for PZQ. The linear range of PZQ concentration was 0.1–1000 μg/ml ($r^2 = 0.9996$).

2.7. Drug content measurement

Each implant was accurately weighed and dissolved in acetonitrile, subsequently methanol was added to precipitate the PCL. The resulting suspension was centrifuged at 10,000 × g for 10 min and the obtained supernatant was filtered and then analyzed by HPLC. Each experimental datum was generated from ten same implants and expressed as mean value with standard deviation (SD).

2.8. In vitro drug release assay

Each implant sample was weighed and placed in 50 ml vial containing 30 ml phosphate buffer solution (pH = 7.4) with 0.2% SDS to keep sink condition at 37.0 ± 0.5 °C under constant oscillation at 90 rpm. At predetermined time points, the release medium was removed, and replaced by fresh medium and spectrophotometrically assessed for praziquantel at a wavelength of 263 nm. Each experimental datum was generated from five same samples.

3. Results and discussion

3.1. Characterizations of the implants

As listed in Table 1, eight kinds of cylindrical PZQ implants with different diameters and drug loadings, end-capping or end-uncapping were fabricated and investigated in this study. The length of all the implants was 10 mm, the diameter of implants was 3, 4 or 8 mm, and there were two drug loadings of 25% and 50%, which were obtained by adjusting the feed ratio of PZQ to PCL. The drug content for all implants was highly consistent with the feed ratios and the standard deviation (SD) was very low, indicating that PZQ was uniformly distributed in the PCL matrix, and no

Table 1
Characteristics of the PZQ-loaded cylindrical implants.

Implant	Feed ratio (PZQ:PCL, w/w)	Diameter (mm)	Length (mm)	End-capped[a]	Drug content[b] (%±SD)
CI-1	25:75	3	10	N	24.98 ± 0.01
CI-2	25:75	4	10	N	25.01 ± 0.23
CI-3	25:75	8	10	N	24.39 ± 0.50
CI-4	25:75	8	10	Y	25.79 ± 0.34
CI-5	50:50	3	10	N	51.56 ± 0.05
CI-6	50:50	4	10	N	50.23 ± 0.45
CI-7	50:50	8	10	N	49.09 ± 1.24
CI-8	50:50	8	10	Y	48.37 ± 2.32

[a] N, end-uncapped; Y, end-capped.
[b] Determined by HPLC.

significant decomposition of PZQ took place during the fabrication process. There was also no decrease in molecular weights of PCL during the fabrication process (not shown). Thus, the fabrication technology and conditions were acceptable and suitable.

3.2. In vitro drug release

The PZQ cumulative release percents of all the implants at the first sampling time point (0.25 d) were smaller than 5% (see Table 2), showing no obvious burst release, and also illustrating that there was no obvious drug enrichment on the surface of the implants. At a certain sampling time point, the drug release percents were different for the implants with different drug loadings and diameters, end-capping or end-uncapping.

3.2.1. Effect of implant diameter

For the implants with the same drug loading, drug release percent at the first sampling time point or other time points increased as implant diameter decreased (Table 2). Drug release profiles for the implants with diameters of 3, 4 and 8 mm were shown in Fig. 1a (CI-1, CI-2 and CI-3 with 25% PZQ) and Fig. 1b (CI-5, CI-6 and CI-7 with 50% PZQ). It could be seen that, when the drug loading was the same (25% or 50% drug content), the PZQ cumulative release percent quickly rose with time for the implants with smaller diameters. The drug release from CI-3 or CI-7 with a diameter of 8 mm was the slowest, yet the drug release from CI-1 or CI-5 with a diameter of 3 mm was the fastest. This suggested that the larger the diameter of the implants, the slower the drug release. Thus, implant diameters had a significant effect on drug release from the cylindrical PCL implants. If drug diffusion in PCL matrix was the rate-limiting step for drug release, an increase in diameter of implant would result in longer diffusion path for drug diffusion from PCL matrix to the outer release media. As a result, more time was required for drug release from implants with a larger diameter.

3.2.2. Effects of drug loading

Two different drug loadings (25% and 50%) were investigated for the implants with a diameter of 3, 4, or 8 mm, respectively. As shown in Fig. 2, no matter what the diameter of the implant was (3, 4, or 8 mm), drug release from the implants with higher drug loading was always faster. A higher drug loading indicated a lower content of PCL matrix in implants, facilitating drug dissolution from implants. Thus, drug loading had an effect on PZQ release from implant. Nevertheless, compared among these release profiles, it was notable that the difference in PZQ release profiles was the biggest for the implants with a diameter of 3 mm, and the smallest for the implants with a diameter of 8 mm. This was very interesting that the effect of drug loadings on PZQ release was related with implant diameter. It suggested that the effect of drug loading on drug release weakened as diameter of the implant increased.

Table 2
PZQ cumulative release percentages of implants at different sampling time points.

Implant	Cumulative release (%)			
	0.25 d	10 d	50 d	150 d
CI-1	4.2	21.8	42.6	64.3
CI-2	2.8	17.6	34.3	53.4
CI-3	2.3	16.4	32.0	46.8
CI-4	1.3	13.0	27.4	43.0
CI-5	4.9	34.4	64.2	87.7
CI-6	3.5	28.0	52.3	76.4
CI-7	2.5	18.0	37.3	53.0
CI-8	1.2	12.3	28.3	44.6

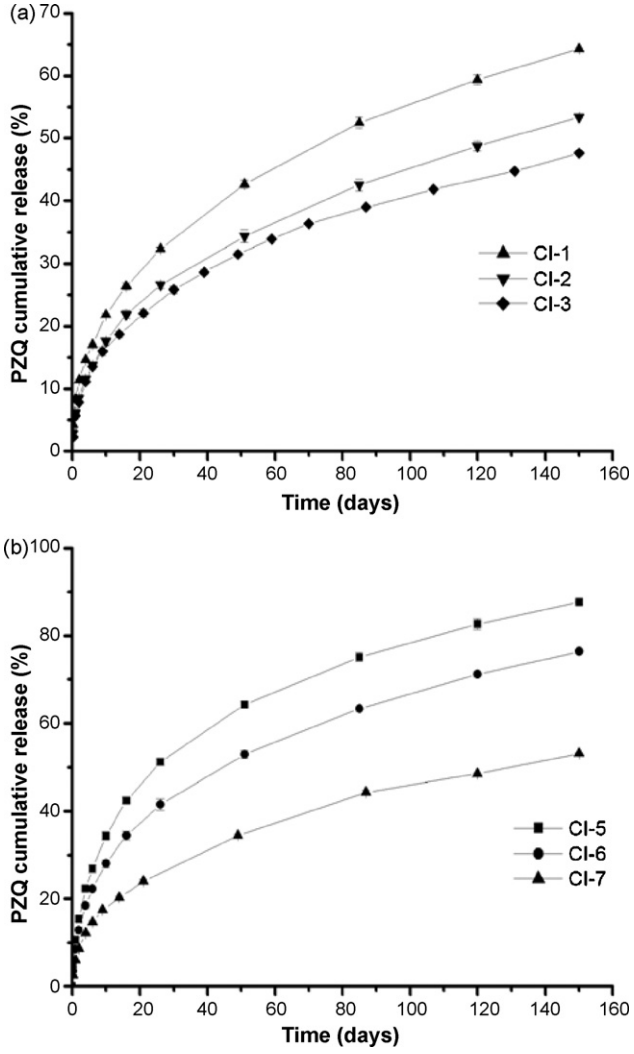

Fig. 1. Effect of implant diameter on drug release from the PZQ-loaded cylindrical implants with the same drug loading.

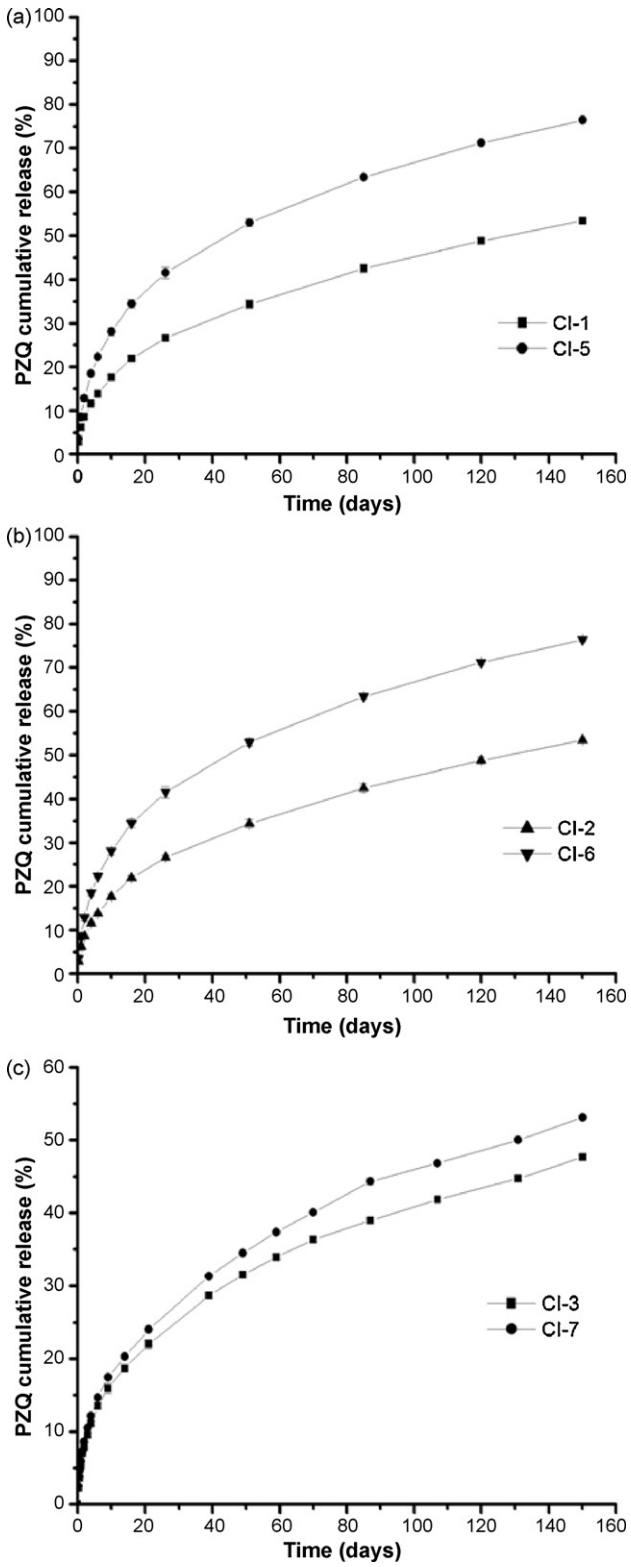

Fig. 2. Effect of drug loading on drug release from the PZQ-loaded cylindrical implants with the same diameter.

3.2.3. Effects of end-capping

On contact with the release medium the cylindrical implant will release the loaded drug via its lateral surface and two end surfaces. In order to prevent drug release from the two end surfaces of the implant, the PZQ-loaded cylindrical implants with a diameter of 8 mm were end-capped with PCL sheets. PCL is poorly permeable

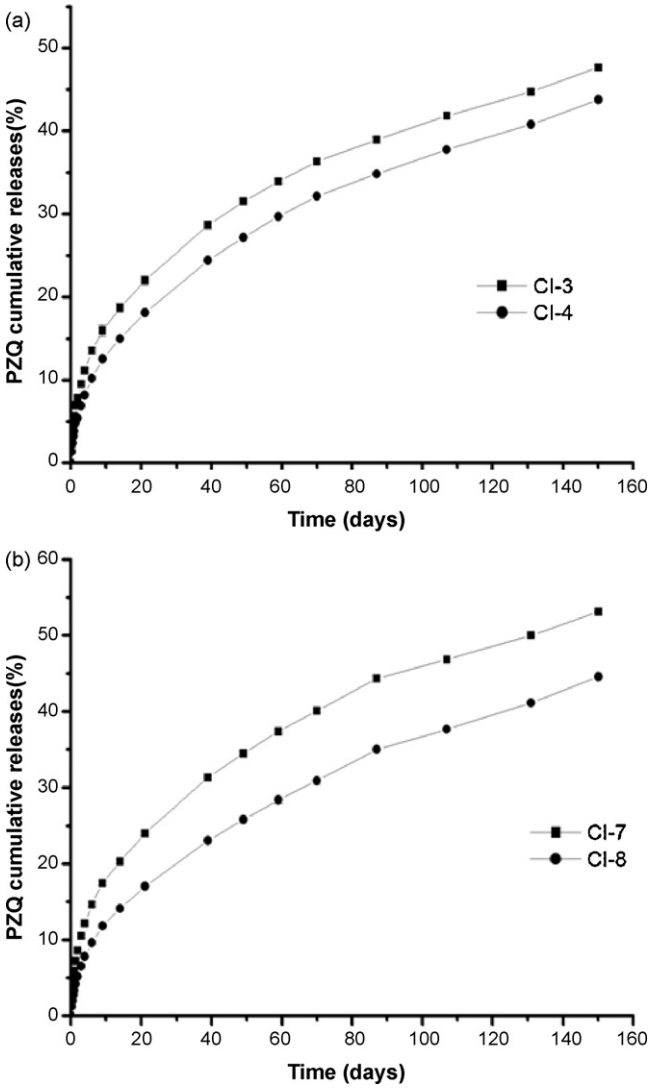

Fig. 3. Effect of end-capping on drug release from the PZQ-loaded cylindrical implants with a diameter of 8 mm.

to PZQ and can effectively prevent PZQ release. The release profiles of drug from the end-uncapped and end-capped implants were compared. It can be seen from Fig. 3a and b that there were similar drug release behaviors for the end-capped and end-uncapped implants with the same drug loading (25% or 50%), and PZQ release was slightly slower from the end-capped implants (CI-4 and CI-8) than that from the corresponding end-uncapped implants (CI-3 and CI-7). It indicated that end-capping was not a significant factor for drug release behaviors of the PZQ-loaded cylindrical implants.

3.2.4. Similarity between the release profiles

In order to explore whether there was statistical difference or similarity between the drug release profiles, f_2 value, called as similarity factor, was introduced for comparison (Moore and Flanner, 1996).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} W_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t is the reference drug release content at time point t, T_t is the test drug release content at time point t, n is the number of the sampling points, and W_t is an optional weight factor. Since all

Table 3
Values of similarity factor (f_2) for the release profiles of implants.

Pairs of the release profiles	Values of similarity factor
Different drug loadings at the same diameter	
$f_{2\,(CI\text{-}1,\,CI\text{-}5)}$	39.95
$f_{2\,(CI\text{-}2,\,CI\text{-}6)}$	42.93
$f_{2\,(CI\text{-}3,\,CI\text{-}7)}$	74.48
Different diameters at the same drug loading	
$f_{2\,(CI\text{-}1,\,CI\text{-}2)}$	60.60
$f_{2\,(CI\text{-}1,\,CI\text{-}3)}$	51.89
$f_{2\,(CI\text{-}5,\,CI\text{-}6)}$	59.97
$f_{2\,(CI\text{-}5,\,CI\text{-}7)}$	32.93
End-capping and uncapping	
$f_{2\,(CI\text{-}3,\,CI\text{-}4)}$	71.10
$f_{2\,(CI\text{-}7,\,CI\text{-}8)}$	57.22

the release time points were treated equally, W_t was taken as 1. According to the guidance recommended by FDA, generally, two drug release profiles may be regarded as equivalence while the f_2 value is greater than 50.

From Table 3, we can find that: (1) $f_{2(CI\text{-}1,\,CI\text{-}5)} < f_{2(CI\text{-}2,\,CI\text{-}6)} < f_{2(CI\text{-}3,\,CI\text{-}7)}$, the degree of similarity between the drug release profiles for the implants with different drug loadings (25% and 50%) increased as the diameter of implant increased from 3 to 8 mm. $f_{2(CI\text{-}1,\,CI\text{-}5)}$ or $f_{2(CI\text{-}2,\,CI\text{-}6)}$ was smaller than 50, indicating the difference between the corresponding two profiles for the implants with a diameter of 3 or 4 mm was significant, and $f_{2(CI\text{-}3,\,CI\text{-}7)}$ was 74.48, greater than 50, indicating the two drug release profiles for the implants with a diameter of 8 mm was equivalent. (2) $f_{2(CI\text{-}1,\,CI\text{-}3)} < f_{2(CI\text{-}1,\,CI\text{-}2)}$ and $f_{2(CI\text{-}5,\,CI\text{-}7)} < f_{2(CI\text{-}5,\,CI\text{-}6)}$ indicated that the degree of similarity between the two drug release profiles for the implants with diameters of 3 and 8 mm was lower than that for the implants with diameters of 3 and 4 mm. (3) $f_{2(CI\text{-}3,\,CI\text{-}4)}$ or $f_{2(CI\text{-}7,\,CI\text{-}8)}$ was greater than 50, indicating that the drug release profiles for the end-capped and end-uncapped implants were highly similar.

3.2.5. Drug release kinetics

All drug release data were fitted by zero-order model, Higuchi model and Ritger–Peppas model. The correlation coefficient (r) and kinetic parameters were listed in Table 4. The best fit was obtained by Ritger–Peppas model ($r > 0.997$). Ritger–Peppas's equation (Ritger and Peppas, 1987) was utilized to illustrate the mechanism of drug release. n was the diffusional exponent indicative of the release mechanism. It was shown that in the case of pure Fickian diffusion the exponent n had the limiting value of 0.45 for drug release from cylinders. All the n values were close to 0.45, indicating that Fickian diffusion was the predominant release mechanism.

3.3. Evolution of implants with release time

3.3.1. Structural evolution

All the investigated implants had similar structural evolution over time. Taking implant CI-7 as an example, both the surface and the cross-section of the implant were dense and devoid of pores before *in vitro* release test. Additionally, prismatic PZQ crystals could be observed in the cross-section and these drug crystals were homogeneously distributed in the PCL matrix (Fig. 4a and b). However, after 150-d drug release it was noteworthy that there existed two layers with different structures in the cross-section of the implant (Fig. 4c). Many discrete pores could be observed in the exterior layer of the implant, and the size and shape of these pores were nearly identical to that of PZQ crystals (Fig. 4d), suggesting that these pores were likely to be the voids left by the released drug crystals. The structure of the interior layer of the implant was almost the same as that before *in vitro* release (Fig. 4e). These results implied that PZQ was released by gradual diffusion from the exterior to the interior of the implant.

Table 5
Drug contents in the exterior and the interior layer of the implants after 150-d drug release.

Implant	Drug content in the exterior layer (%)	Drug content in the interior layer (%)
CI-1	0.17	23.90
CI-2	0.30	22.97
CI-3	0.25	24.09
CI-5	0.32	49.15
CI-6	1.22	50.88
CI-7	0.47	48.91

3.3.2. Evolution of crystallinity

As shown in Fig. 5, the diffraction peaks at 6.22° and 7.92° were attributed to PZQ crystals and the two sharp peaks between 20° and 25° belonged to semi-crystalline PCL (Fig. 5a and b). There were the characteristic diffraction peaks corresponding to PZQ and PCL in Fig. 5c and d, indicating that both PZQ and PCL were crystalline in the implants and the physical mixtures. However, it was interesting that after 150-d drug release the characteristic peaks of both PZQ and PCL were obvious in the interior layer of the implants, while only the characteristic peaks of PCL were detectable in the exterior layer of the implants (as shown in Fig. 5e and f). This result demonstrated that the exterior layer of the implants was mainly the left PCL matrix, while the interior layer of the implants was composed of the unreleased drug and PCL matrix.

3.3.3. Evolution of drug content

Drug contents in the exterior and interior layer of the implants after 150-d PZQ release were determined. The results were listed in Table 5. It could be found that drug contents in the exterior layer of the implants were very low, but the values in the interior layer of the implants were close to the predefined drug loadings. This result suggested that the exterior layer of the implants was the region where the incorporated drug had been completely released, while the interior layer of the implants was the region where drug was still unreleased. This further supported the conclusion that PZQ was gradually released from the exterior to the interior of the implants.

Table 4
Data of drug release profiles fitted by several kinetic models (zero-order, Higuchi and Ritger–Peppas).

Implant	Zero-order, $M_t/M_\infty = Q_0 + k_0 t$		Higuchi model, $M_t/M_\infty = k_H t^{1/2}$		Ritger–Peppas model, $M_t/M_\infty = k_1 t^n$		
	k_0	r	k_H	r	k_1	r	n
CI-1	0.0052	0.7950	0.0565	0.9890	0.0853	0.9998	0.4055
CI-2	0.0043	0.8065	0.0463	0.9912	0.0665	0.9996	0.4169
CI-3	0.0040	0.8012	0.0419	0.9880	0.0638	0.9988	0.4030
CI-5	0.0160	0.7319	0.0983	0.9904	0.1235	0.9974	0.4276
CI-6	0.0094	0.6999	0.0757	0.9852	0.1047	0.9976	0.4109
CI-7	0.0044	0.8164	0.0465	0.9906	0.0680	0.9989	0.4128

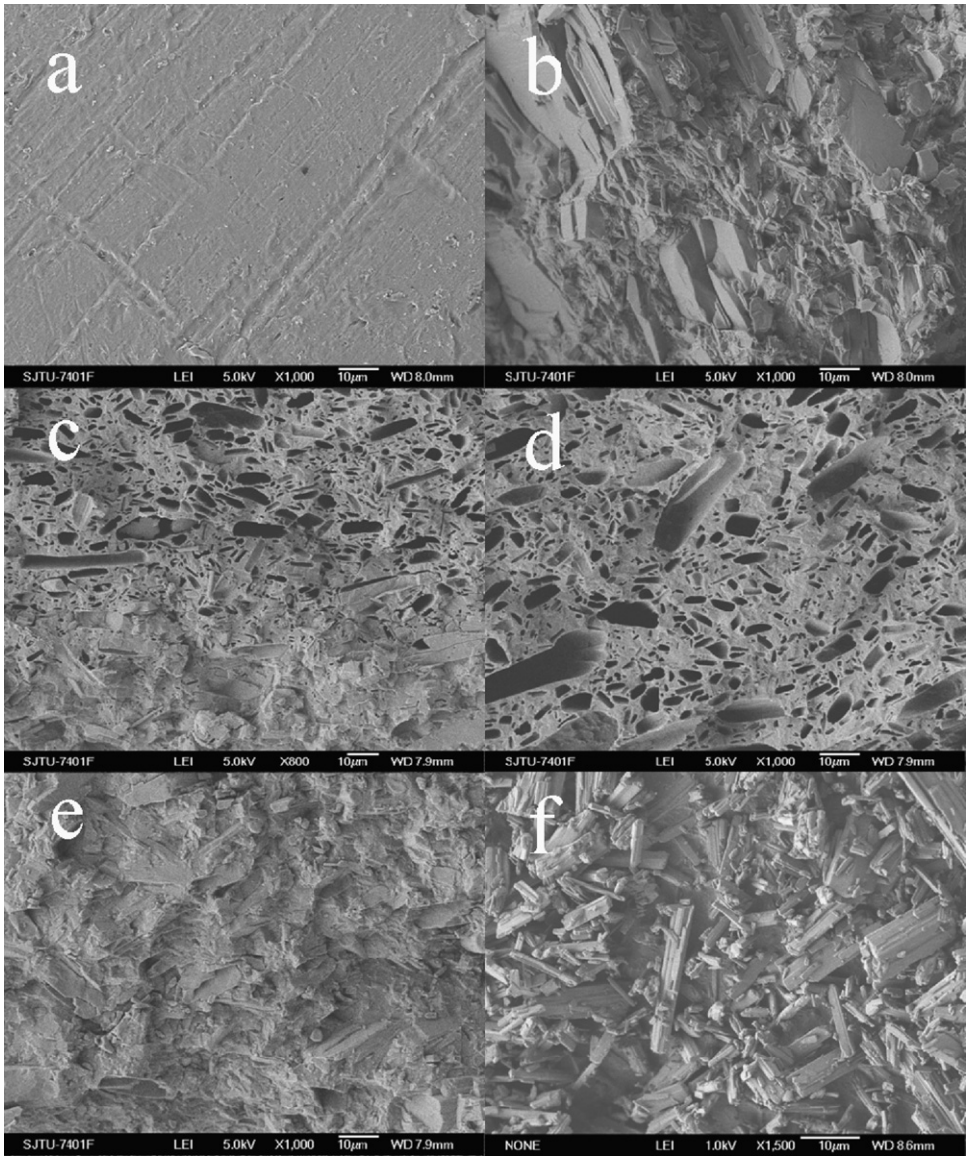

Fig. 4. SEM images of the CI-7 implant and PZQ: (a and b) surface and cross-section morphology of implant CI-7 before drug release, respectively; (c) cross-section morphology of implant CI-7 after 150-d drug release; (d and e) the exterior layer and interior layer in the cross-section of implant CI-7 after 150-d drug release, respectively; (f) PZQ crystals.

3.3.4. Evolution of molecular weight of PCL

All the tested implants preserved an appearance of integrity after 150-d drug release, however, the molecular weights of PCL both in the exterior layer and the interior layer of the implants decreased to some extent (Table 6). The decrease in molecular weights of PCL should be ascribed to the hydrolysis of ester bonds in PCL molecular chain. Even that nearly the whole drug was released in the exterior layer, while little drug was released in the interior layer, the difference in molecular weight between the exterior layer and interior layer of the implant was very small. This indicated that the drug release did not obviously change the degradation rate of PCL and the degradation of PCL followed bulk degradation mechanism. The molecular weights of PCL in the implants with a diameter of 8 mm were slightly lower than those for the implants with diameters of 3 or 4 mm. It might be due to the more acidic hydrolysates of PCL remained in implant with a bigger diameter. The acidic hydrolysates could further accelerate the hydrolysis of ester bonds in PCL molecular chain.

Table 6
Molecular weights of PCL in the exterior and the interior layer of the implants after 150-d drug release.

Sample		M_w	M_n	DPI
PCL material		70,800	51,700	1.37
Implant before release		77,700	50,400	1.54
CI-1	Interior layer	58,500	40,200	1.45
	Exterior layer	58,700	38,200	1.54
CI-2	Interior layer	53,000	48,800	1.50
	Exterior layer	61,700	39,200	1.57
CI-3	Interior layer	43,500	29,100	1.50
	Exterior layer	49,400	31,300	1.58
CI-5	Interior layer	56,800	36,800	1.54
	Exterior layer	66,700	45,300	1.47
CI-6	Interior layer	60,600	41,300	1.48
	Exterior layer	58,000	39,500	1.47
CI-7	Interior layer	44,200	29,500	1.50
	Exterior layer	59,100	37,200	1.59

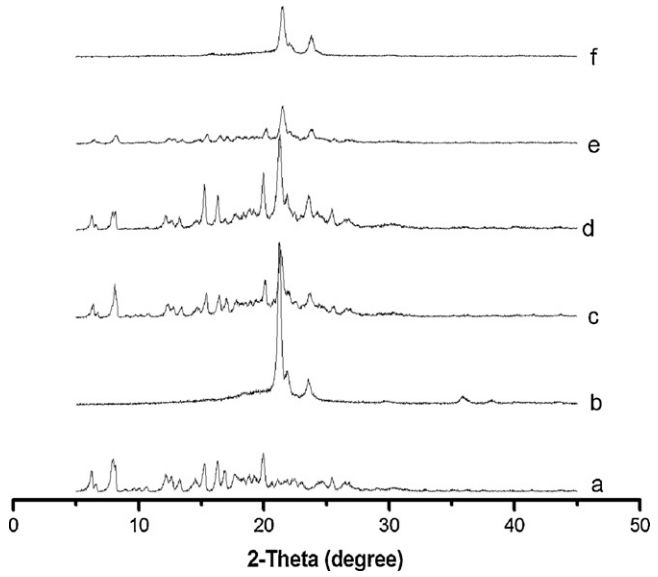

Fig. 5. XRD patterns of (a) PZQ, (b) PCL, (c) CI-7 physical mixture, (d) implant CI-7 before release, (e and f) the interior and the exterior of implant CI-7 after 150-d drug release, respectively.

4. Conclusion

Drug release profiles of PZQ-loaded PCL cylindrical implants are related with the diameter of the implants, drug loading and end-capping. In general, the larger the diameter of the implants, the slower the drug release; faster drug release can be obtained from the implant with higher drug loading; drug release from the end-capped implants is slightly slower than that from the corresponding end-uncapped implants. The effect of drug loading on drug release depends on the diameter of the implant, i.e. the effect is weakened as the increase in diameter of the implants. All release data are well fitted with Ritger–Peppas model and Fickian diffusion is the predominant release mechanism. The evolution of the implants with release time proves that drug is gradually released from the exterior layer to the interior layer of the implants.

Acknowledgements

This work is supported by the National Science and Technology Support Plan of Ministry of Health of China (2006BAI06B06) and the fund of Shanghai Science and Technology Committee (08JC1411500) and the key program of Shanghai Municipal Education Commission (09ZZ24). The authors also thank Shun'ai Che for her assistance in the SEM experiments.

References

Barbato, F., La Rotonda, M.I., Maglio, G., Palumbo, R., Quaglia, F., 2001. Biodegradable microspheres of novel segmented poly(ether–ester–amide)s based on poly(ε-caprolactone) for the delivery of bioactive compounds. Biomaterials 22, 1371–1378.

Bruce, L.D., Shah, N.H., Waseem Malick, A., Infeld, M.H., McGinity, J.W., 2005. Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid. Eur. J. Pharm. Biopharm. 59, 85–97.

Chawla, J.S., Amiji, M.M., 2002. Biodegradable poly(ε-caprolactone) nanoparticles for tumor-targeted delivery of tamoxifen. Int. J. Pharm. 249, 127–138.

Cheng, L., Guo, S., Wu, W., 2009. Characterization and in vitro release of praziquantel from poly(ε-caprolactone) implants. Int. J. Pharm. 377, 112–119.

Dinora, G.E., Julio, R., Nelly, C., Lilian, Y.M., Cook, H.J., 2005. In vitro characterization of some biopharmaceutical properties of praziquantel. Int. J. Pharm. 295, 93–99.

Dong, H., Li, Y., Cai, S., Zhuo, R., Zhang, X., Liu, L., 2008. A facile one-pot construction of supramolecular polymer micelles from α-cyclodextrin and poly(ε-caprolactone). Angew. Chem. Int. Ed. 47, 5573–5576.

Fialho, S.L., Behar-Cohen, F., Silva-Cunha, A., 2008. Dexamethasone-loaded poly(ε-caprolactone) intravitreal implants: a pilot study. Eur. J. Pharm. Biopharm. 68, 637–646.

Gou, M., Zheng, L., Peng, X., Men, K., Zheng, X., Zeng, S., Guo, G., Luo, F., Zhao, X., Chen, L., Wei, Y., Qian, Z., 2009a. Poly(ε-caprolactone)–poly(ethylene glycol)–poly(ε-caprolactone) (PCL–PEG–PCL) nanoparticles for honokiol delivery in vitro. Int. J. Pharm. 375, 170–176.

Gou, M., Zheng, X., Men, K., Zhang, J., Wang, B., Lv, L., Wang, X., Zhao, Y., Luo, F., Chen, L., Zhao, X., Wei, Y., Qian, Z., 2009b. Self-assembled hydrophobic honokiol loaded MPEG-PCL diblock copolymer micelles. Pharm. Res. 26, 2164–2173.

Hombreiro Peĩrez, M., Zinutti, C., Lamprecht, A., Ubrich, N., Astier, A., Hoffman, M., Bodmeier, R., Maincent, P., 2000. The preparation and evaluation of poly(ε-caprolactone) microparticles containing both a lipophilic and a hydrophilic drug. J. Control. Release 65, 429–438.

Jia, W., Gu, Y., Gou, M., Dai, M., Li, X., Kan, B., Yang, J., Song, Q., Wei, Y., Qian, Z., 2008. Preparation of biodegradable polycaprolactone/poly(ethylene glycol)/polycaprolactone (PCEC) nanoparticles. Drug Deliv. 15, 409–416.

Koizumi, T., Ueda, M., Kakemi, M., Kameda, H., 1975. Rate of release of medicaments from ointment bases containing drugs in suspension. Chem. Pharm. Bull. 23, 3288–3292.

Moore, J.W., Flanner, H.H., 1996. Mathematical comparison of dissolution profiles. Pharm. Technol. 20, 64–74.

Quinten, T., Beer, T.D., Vervaet, C., Remon, J.P., 2009. Evaluation of injection moulding as a pharmaceutical technology to produce matrix tablets. Eur. J. Pharm. Biopharm. 71, 145–154.

Repka, M.A., Gutta, K., Prodduturi, S., Munjal, M., Stodghill, S.P., 2005. Characterization of cellulosic hot-melt extruded films containing lidocaine. Eur. J. Pharm. Biopharm. 59, 189–196.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for desciption of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control. Release 5, 23–36.

Rosenberg, R., Devenney, W., Siegel, S., Dan, N., 2007. Anomalous release of hydrophilic drugs from poly(ε-caprolactone) matrices. Mol. Pharm. 4, 943–948.

Rothen-Weinhold, A., Besseghir, K., Vuaridel, E., Sublet, E., Oudry, N., Kubel, F., Gurny, R., 1999. Injection-molding versus extrusion as manufacturing technique for the preparation of biodegradable implants. Eur. J. Pharm. Biopharm. 48, 113–121.

Siegel, S.J., Kahn, J.B., Metzger, K., Winey, K.I., Werner, K., Dan, N., 2006. Effect of drug type on the degradation rate of PLGA matrices. Eur. J. Pharm. Biopharm. 64, 287–293.

Siepmann, J., Göpferich, A., 2001. Mathematical modeling of bioerodible, polymeric drug delivery systems. Adv. Drug Deliv. Rev. 48, 229–247.

Sinha, V.R., Bansal, K., Kaushik, R., Kumria, R., Trehan, A., 2004. Poly-ε-caprolactone microspheres and nanospheres: an overview. Int. J. Pharm. 278, 1–23.

Sotelo, J., Del Brutto, O.H., Penagos, P., Escobedo, F., Torres, B., Rodriguez-Carbajal, J., Rubio-Donnadieu, F., 1990. Comparison of therapeutic regimen of anticysticercal drugs for parenchymal brain cysticercosis. J. Neurol. 237, 69–72.

Sung, K.C., Han, R.Y., Hu, O.Y.P., Hsu, L.R., 1998. Controlled release of nalbuphine prodrugs from biodegradable polymeric matrices: influence of prodrug hydrophilicity and polymer composition. Int. J. Pharm. 172, 17–25.

Trey, S.M., Wicks, D.A., Mididoddi, P.K., Repka, M.A., 2007. Delivery of itraconazole from extruded HPC films. Drug Dev. Ind. Pharm. 33, 727–735.

Van Melkebeke, B., Vermeulen, B., Vervaet, C., Remon, J.P., 2006. Melt granulation using a twin-screw extruder: a case study. Int. J. Pharm. 326, 89–93.

Verhoeven, E., Vervaet, C., Remon, J.P., 2006. Xanthan gum to tailor drug release of sustained-release ethylcellulose mini-matrices prepared via hot-melt extrusion: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 63, 320–330.

Wang, S., Guo, S., 2008. Disodium norcantharidate-loaded poly(ε-caprolactone) microspheres. II. Modification of morphology and release behavior. Int. J. Pharm. 353, 15–20.

Wei, X., Gong, C., Shi, S., Fu, S., Men, K., Zeng, S., Zheng, X., Gou, M., Chen, L., Qiu, L., Qian, Z., 2009. Self-assembled honokiol-loaded micelles based on poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) copolymer. Int. J. Pharm. 369, 170–175.

Zhang, Y., Guo, S., Huang, W., 2009. Tyrosine kinase inhibitor loaded PCL microspheres prepared by S/O/W technique using ethanol as pretreatment agent. Int. J. Pharm. 369, 19–23.