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RESEARCH ARTICLE

Study on hydrophilic 5-fluorouracil release from hydrophobic poly(ε-caprolactone) cylindrical implants

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Abstract

Hydrophilic 5-fluorouracil (5-FU) loaded cylindrical poly(ε-caprolactone) (PCL) implants with different implant diameters (2, 4 and 8 mm), different drug loadings (25% and 50%) and end-capping were fabricated and characterized. The implant structure, drug content and molecular weight of PCL after 120 days drug release were investigated. The *in vitro* release results showed that, when the drug loading was the same, drug release was fastest for the implant with a diameter of 2 mm and slowest for the implant with a diameter of 8 mm; for the implants with the same diameters, the release of drug from the implants with 50% drug loading was faster than that from the implants with 25% drug loading; however, this effect of drug loading decreased with the increase of implant diameter; in addition, 5-FU was released slightly slower from the end-capped implants than from the corresponding uncapped implants; the drug release data for all the uncapped implants were best fit with the Ritger-Peppas model. Drug release from the hydrophobic implants was found to be dominated by diffusion mechanism. Scanning electron microscopy images and drug content measurements revealed that 5-FU release took place gradually from the exterior region to the interior region of the implants.

Keywords: 5-fluorouracil, implants, poly(ε-caprolactone), drug release

Introduction

Poly(ε-caprolactone) (PCL), a biodegradable and biocompatible semi-crystalline polymer, has been studied as a promising candidate for controlled release applications[1]. Up to now, homo- and co-polymers derived from PCL have been utilized to prepare different delivery systems in the form of microspheres, nanospheres and implants[2–5]. Due to its slow degradation rate, PCL is most suitable for implantable long-term drug delivery extending over a period of more than 1 year[6]. PCL-based drug delivery devices can be prepared by means of some processing techniques, including melt extrusion or injection molding[7,8], due to excellent thermal properties of PCL, such as a low melting temperature of 60°C and a low glass transition temperature of –60°C[9].

Controlling drug release is the major challenge in long-term drug delivery. Long-term drug delivery applications require that the drug doses should be within a specific therapeutic window. High release rates can lead to toxic drug levels, whereas low ones may be below the efficacy threshold[10]. Previous studies showed that the rate of drug release from polymer delivery devices varied and depended on factors such as the polymer properties, environmental conditions, and the nature of drugs (hydrophobic/hydrophilic)[11–13]. The effect of polymer properties on the rate of drug release from biodegradable polymer matrices has been widely studied[14–18]. Due to the strong hydrophobic property of PCL and its low degree of swelling in aqueous solutions[19], drug release from PCL matrices has been demonstrated to be dominated by two mechanisms: drug diffusion out of the matrix and/or matrix degradation[20].

Recent studies were concerned with the influence of drug properties on release behavior[21,22]. Different drugs

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released from the same polymer matrix, under identical environmental conditions, displayed large differences in their release behavior[10]. Rosenberg et al.[20,23] showed that the release of hydrophilic drugs from PCL pellet matrices is highly sensitive to the presence of water in the matrix. In addition to diffusion through polymer matrix, a drug can partition and diffuse through the aqueous phase. In our previous study, we prepared praziquantel (PZQ) loaded PCL cylindrical implants by a combination of hot-melt extrusion and injection molding[24]. It was found that the release of PZQ, which is a highly hydrophobic drug, was dominated by gradual diffusion, and PCL did not display significant matrix degradation over our study's time. However, to our knowledge, few works have been reported on release of hydrophilic drugs from PCL cylindrical implants.

In this paper, 5-fluorouracil (5-FU), which has been commonly used in the therapy of different solid tumor types[25,26], was used as a model hydrophilic drug. We prepared 5-FU loaded PCL cylindrical implants and then investigated the effects of drug loading, implant diameter and end-capping on drug release from PCL cylindrical implants. We also investigated that the implant structure, drug content and molecular weight of PCL after 120 days drug release. The major goal of this study was not to necessarily develop a new 5-FU loaded implant but to study it as a model for other hydrophilic drug release processes.

Materials and methods

Materials

PCL was purchased from Daicel Polymer Ltd. (Minatoku, Tokyo, Japan). 5-FU was obtained from Nantong Jinghua Pharmaceutical Co. Ltd. (Nangtong, China). Methanol (chromatographically pure) was purchased from Shanghai Xingke Chemical Co. (Shanghai, China). Ultrafiltered water was obtained from a Milli Q plus system (Millipore, MA). All other chemicals were of analytical grade and used without further purification.

Fabrication of PCL implants containing 5-FU

The implants were prepared by fully blending 5-FU particles with melted PCL at different ratios (25:75, 50:50 w/w) and then molding the blends into cylindrical 2, 4 or 8 mm diameter implants with a lab-scale injection molder. Briefly, PCL was fed into the hopper of the injection molding system (Rheocord 90, HAAKE Mess-Technic GmbH, Germany) and heated until completely melted. The drug, 5-FU, was added slowly into the melted PCL and mixed at 70°C for 20 min at a screw speed of 50 rpm. The resultant blends were collected and further molded into implants using a lab-scale injection molder at 70°C. The cylindrical implants were end-capped by adhering pure PCL lamella to the both end-surfaces of the implants. Dichloromethane, a good solvent of PCL, functioned as the binder solution.

High-performance liquid chromatography

5-FU was quantitatively analyzed by a Shimadzu high-performance liquid chromatography (HPLC) apparatus using the method described in the Chinese pharmacopeia 2005[27]. The HPLC system was equipped with a model LC-10AD pump and a model SPD-10ADvp variable wavelength detector (Shimadzu, Japan). HPLC analysis was carried out under the following conditions: the column was Diamonsil™ C_{18} column (250 mm × 4.6 mm, 5 μm, Dikma Technologies, Beijing, China); the column temperature was at 30°C; the wave length was 266 nm; the mobile phase was composed of methanol and water (80/20, v/v); the flow rate was 1.0 ml/min and the injection volume was 20 μl. The linearity of the response was verified over the concentration range of 0.1–100 μg/ml ($r^2 = 0.999$).

Drug content uniformity

The determination of content uniformity of 5-FU in the PCL implants was performed according to the method stated in the general chapter of the Chinese pharmacopeia 2005[28]. 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 rpm for 10 min, and the obtained supernatant was filtered and then analyzed by HPLC. Each experimental datum was generated from the same 10 implants and expressed as mean value with standard deviation (SD).

X-ray diffraction analysis

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). Before analysis, all samples were pressed into thin films on a Compression Moulding 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.

In vitro release assay

Each implant sample was weighed and placed in a 50 ml vial containing 30 ml phosphate buffered saline (PBS; pH 7.4). The vial was placed in a shaking water bath at 37.0 ± 0.5°C and shaken at a speed of 50 rpm. At the predetermined time points (i.e., 0.02, 0.08, 0.16, 0.33, 0.75, 1.25, 2, 3, 4, 5, 7, 9, 13, 19, 26, 37, 53, 73, 99 and 120 d), the release medium was removed and replaced by fresh medium. The amount of 5-FU released was measured by HPLC. Each experimental datum was generated from the same three samples.

Scanning electron microscopy

The implants were imaged using JSM-7401F scanning electron microscopy (SEM) (JEOL, Tokyo, Japan). To image the interior structure of the implant, sample preparation was conducted according to the method stated in our pervious paper[29]. Briefly, the implant was first

frozen in liquid nitrogen and then fractured 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 1 kV accelerating voltage and 20 mA current.

Gel permeation chromatography

The molecular weight and molecular weight distribution of PCL in implants were determined by gel permeation chromatography (GPC) using a Waters model 1525 pump, a Waters model 2414 refractive index detector, and a series of Styragel® columns (HR3 and HR4) (Waters, MA). Tetrahydrofuran was used as an eluent at a flow rate of 1.0 ml/min. Narrow polystyrene standards were used for calibration. All determinations were performed at 40°C.

5-FU 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.

Results and discussion

Characterization of 5-FU loaded PCL implants

The fabricated 5-FU loaded PCL implants were cylindrical rods with the same length (10 mm) and different diameters (2 mm, 4 mm and 8 mm) (Figure 1A). The end-capped implants with a diameter of 8 mm were obtained by pressing drug-free PCL sheets on the end-surfaces of the implants (Figure 1B).

As listed in Table 1, the 5-FU content for all implants was found to be very close to the predefined value, and the SD values were quite low, indicating that 5-FU was stable during the implant fabrication processes, and 5-FU was homogeneously dispersed in the PCL matrix. The molecular weight of PCL was also determined by GPC right after the fabrication process (see Table 5). There was no significant difference in molecular weight between the raw material and the processed material of PCL, revealing that PCL was also stable during the fabrication. Thus, the implant fabrication technology and conditions were acceptable and suitable.

To examine the physical states of the compositions in the implants, 5-FU, PCL, physical mixtures and implants consisting of PCL and 5-FU were subjected to XRD analysis. As shown in Figure 2, 5-FU is crystalline, as demonstrated by its characteristic intense peaks at 2θ of 16°, 19°, 21°, 29°[30]. PCL displayed two characteristic peaks between 2θ of 20° and 25°, confirming its semi-crystalline structure[31]. For all the implants, there existed obvious crystalline peaks of PCL, indicating that PCL was still in a semi-crystalline state. 5-FU crystalline peaks could be easily observed for the implants or physical mixtures consisting of 5-FU and PCL. The 5-FU peak for

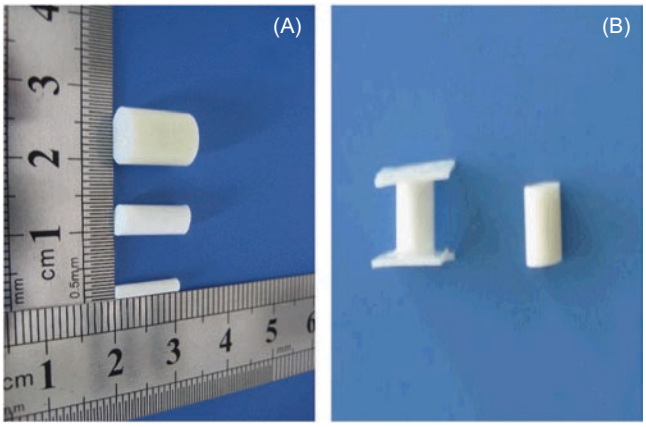

Figure 1. Macroscopical views of (A) the implants with different diameters, (B) end-capped and uncapped implants.

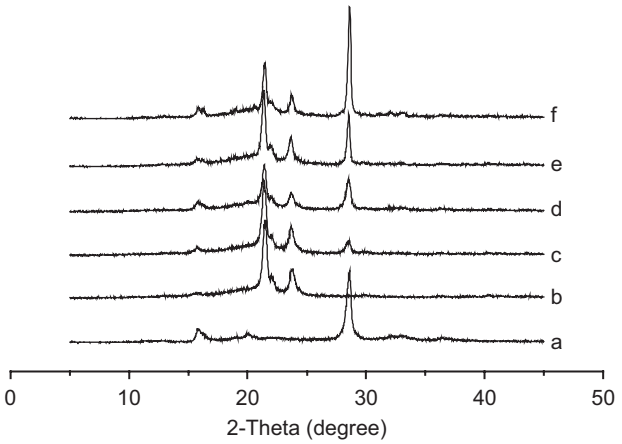

Figure 2. X-ray diffraction patterns of (A) 5-FU, (B) PCL, (C) implant CI-3, (D) implant CI-7, (E) CI-3 physical mixture, (F) CI-7 physical mixture.

Table 1. Characteristics of the 5-FU loaded cylindrical implants.

Implant	Feed ratio (5-FU:PCL, w/w)	Diameter (mm)	Length (mm)	End-capped[a]	Drug content (Mean ± SD, %)
CI-1	25:75	2	10	N	25.01 ± 0.05
CI-2	25:75	4	10	N	
CI-3	25:75	8	10	N	
CI-4	25:75	8	10	Y	
CI-5	50:50	2	10	N	50.43 ± 0.04
CI-6	50:50	4	10	N	
CI-7	50:50	8	10	N	
CI-8	50:50	8	10	Y	

[a]N, uncapped; Y, end-capped.

the implant was higher than that for the corresponding physical mixture. This suggested that there existed a certain fraction of amorphous 5-FU in implant.

In vitro drug release

Effect of implant diameter

The amount of 5-FU released *in vitro* from PCL implants in PBS was studied for up to 120 days. Figure 3 depicts the release profiles of 5-FU from PCL implants with the same drug loading (25% or 50%) but different diameter of 2 mm, 4 mm and 8 mm. It was observed that, when the drug loading was the same, the drug release rate decreased with the increase of implant diameter. As shown in Figure 3A, for the implants with 25% drug loading, the cumulative drug release from CI-1 was higher (54.5% drug release after 120 d), than those of CI-2 and CI-3 (34.2% and 21.9% drug release after 120 d, respectively). For the implants with a higher drug loading (50%), the effect of diameter on drug release was bigger (Figure 3B). Almost 74.4% drug was released from CI-5 after 120 d; in contrast, those of CI-6 and CI-7 implants showed only 22.0% and 17.2% drug release. The remarkable effect of implant diameter on drug release implied that drug diffusion from PCL may be the dominant behavior of drug release, because an increase in diameter of implant resulted in longer diffusion path of drug to the release medium.

Effect of drug loading

The effect of the initial 5-FU loading on drug release from PCL implants are shown in Figure 4. To the implants with 2 mm diameter (Figure 4A), release data show

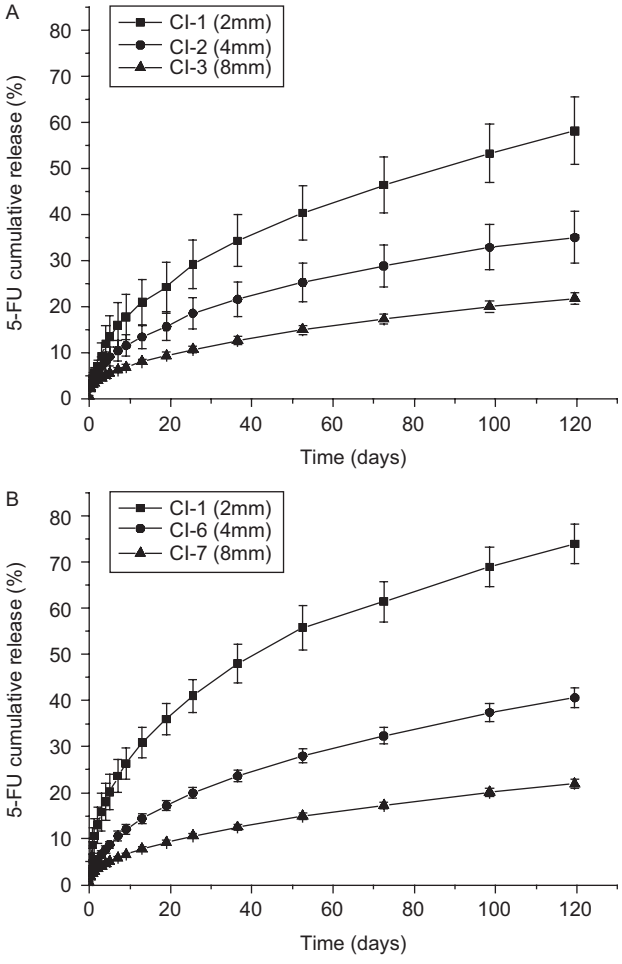

Figure 3. Effect of implant diameter on drug release from the 5-FU loaded cylindrical implants with the same drug loading: (A) 25% drug loading, (B) 50% drug loading.

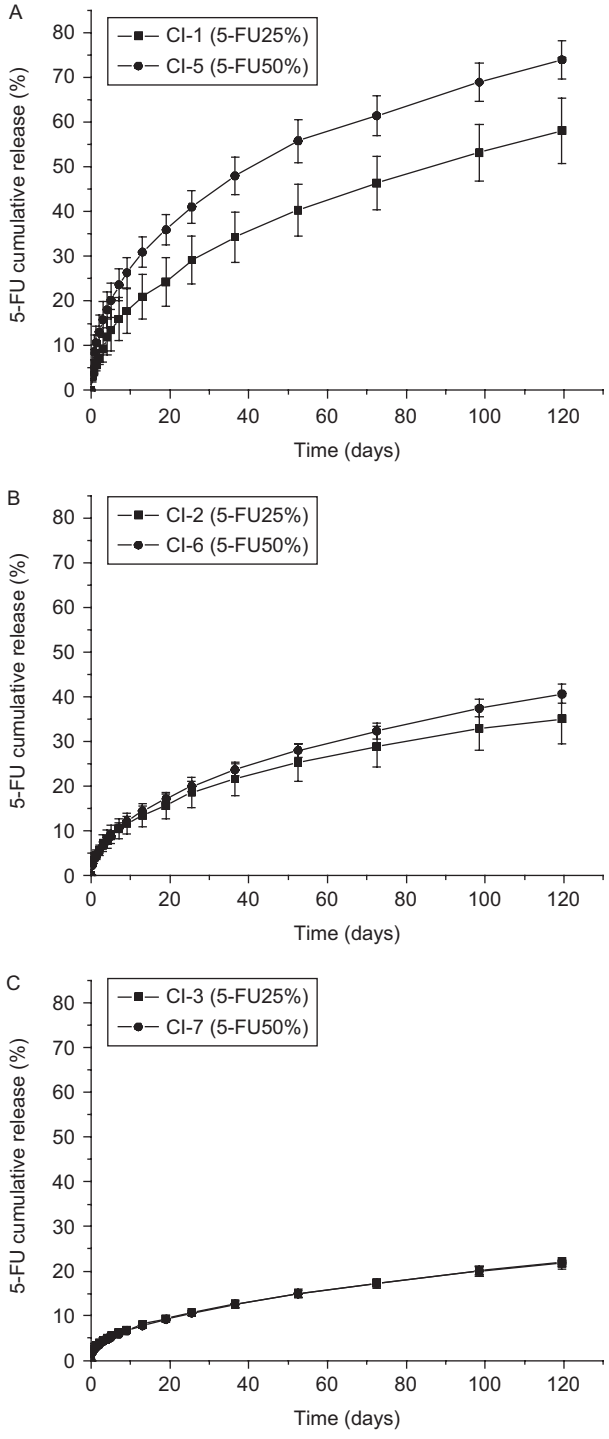

Figure 4. Effect of drug loading on drug release from the 5-FU loaded cylindrical implants with the same diameter: (A) 2 mm, (B) 4 mm, (C) 8 mm.

that implants containing higher amount of drug (50%) displayed the faster and higher release rates than those implants containing the lower amount of 5-FU (25%). During 120-day releasing period, 54.5% 5-FU was released from the implant with an initial drug loading of 25% (CI-1), whereas almost 74.4% 5-FU was released from the implant with 50% drug loading (CI-5). For the implants with a larger diameter of 4 mm (Figure 4B), the difference between the two release profiles of CI-2 and CI-6 was smaller. With further increase of implant diameter to 8 mm (Figure 4C), cumulative drug release percents of CI-3 and CI-7 were both less than 30% up to 120 days, and their release curves were almost identical. The data suggested that the effect of drug loading on drug release decreased as implant diameter increased.

Effect of end-capping

The influence of end-capping on drug release profiles was also investigated. As shown in Figure 5, the drug release profiles from end-capped and uncapped implants with the same drug loading (25% or 50%) could be considered similar. End-capping of the implant showed only a slightly decline in the slope of the release curve that resulted in lower cumulative drug release during all the sampling times, as compared to the uncapped systems. It indicated that implant end-capping was not a significant factor for 5-FU release behaviors from the implants.

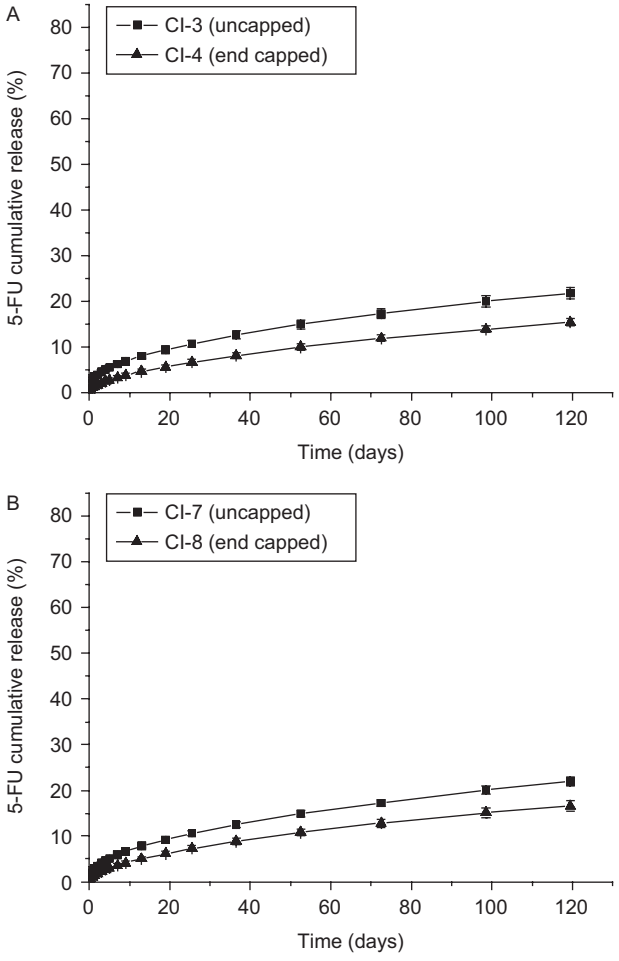

Figure 5. Effect of end-capping on drug release from the 5-FU loaded cylindrical implants with a diameter of 8 mm: (A) 25% drug loading, (B) 50% drug loading.

Similarity between the release profiles

Similarity factor (f_2) was introduced to compare the release profiles[32,33]:

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

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 the investigated release time points were treated equally, W_t was taken as 1 in the current study. Two release profiles may be regarded as equivalent when the f_2 value is greater than 50[32].

The values of f_2 between different release profiles are summarized in Table 2. The values of $f_{2\,(\text{CI-1, CI-3})}$, $f_{2\,(\text{CI-5, CI-6})}$ and $f_{2\,(\text{CI-5, CI-7})}$ were 39.46, 35.12 and 26.71, respectively, which indicated that the drug release profiles were not similar for CI-1 and CI-3, CI-5 and CI-6, or CI-5 and CI-7. The values of $f_{2\,(\text{CI-1, CI-5})}$, $f_{2\,(\text{CI-2, CI-6})}$ and $f_{2\,(\text{CI-3, CI-7})}$ were 43.43, 74.96 and 99.40, respectively, which suggested that the larger the diameter, the higher similarity between two release profiles from implants with different initial drug loadings. The uncapped and end-capped implants exhibited highly similar drug release profiles (f_2 value = 71.16 for 25% drug loading, 75.25 for 50% drug loading, respectively), indicating that the end-capping did not significantly influence their release behaviors.

Drug release kinetics

The kinetics of 5-FU release from PCL implants was clarified by plotting the cumulative release data versus time and by fitting these data to three widely used drug release kinetics models, the zero-order model, the Higuchi model and the Ritger-Peppas model (Table 3). The best fit was

Table 2. Values of similarity factor (f_2) for the release profiles of implants.

Pairs of the release profiles	Values of similarity factor
Different diameters at the same drug loading	
$f_{2\,(\text{CI-1, CI-2})}$	50.56
$f_{2\,(\text{CI-1, CI-3})}$	39.46
$f_{2\,(\text{CI-2, CI-3})}$	58.97
$f_{2\,(\text{CI-5, CI-6})}$	35.12
$f_{2\,(\text{CI-5, CI-7})}$	26.71
$f_{2\,(\text{CI-6, CI-7})}$	55.68
Different drug loadings at the same diameter	
$f_{2\,(\text{CI-1, CI-5})}$	43.32
$f_{2\,(\text{CI-2, CI-6})}$	74.96
$f_{2\,(\text{CI-3, CI-7})}$	99.40
End-capping and uncapping	
$f_{2\,(\text{CI-3, CI-4})}$	71.16
$f_{2\,(\text{CI-7, CI-8})}$	75.25

obtained with the Ritger-Peppas equation ($r > 0.999$). The n value of the Ritger-Peppas model is an empirical parameter characterizing the release mechanism[34]. It is known that in cases of pure Fickian release the exponent n has the limiting value of 0.45 for a cylindrical shape. In the present study, all the obtained n values of the uncapped implants were less or a little more than the critical value 0.45, supporting that the dominating release mechanism of 5-FU from these implants was diffusion controlled. However, two n values of end-capped implants were both positively deviated from 0.45, denoting a non-Fickian mechanism.

Evolution of implants

Morphological evolution

The cross-section morphologies of the CI-2 implant after 120-day release were characterized by SEM. As shown in Figure 6A, peripheral contours of the cylindrical implant were clearly visible. It was noteworthy that two distinct zones existed (exterior zone and interior zone) with different cross-section structures, and the boundary was sketched by the dashed line in the image. At a higher magnification (500×), it could be more obviously observed that the exterior zone was porous and the interior zone compact (Figure 6B). Many discrete pores appeared in the exterior cross-section zone of the implant (Figure 6C), and the size and shape of these pores were nearly identical to that of 5-FU particles (Figure 6E). These observed pores could be attributed to the voids left behind by the release of the drug crystals. In contrast, a compact structure was observed in the interior zone at the same magnification (Figure 6D) and voids after drug release were hardly observed. Similar results were also obtained for other implants investigated (images not shown).

Drug content of exterior and interior zones

To further investigate the above-mentioned phenomenon, drug content in the exterior and interior zones were

Table 3. Data of drug release profiles fitted by several kinetic models (zero-order, Higuchi and Ritger-Peppas).

	Zero-order model $M_t/M_\infty = Q_0 + k_0 t$	Higuchi model $M_t/M_\infty = k_H t^{1/2}$	Ritger-Peppas model $M_t/M_\infty = kt^n$	
Implant	r	r	R	n
CI-1	0.8720	0.993	0.9994	0.5121
CI-2	0.8163	0.9982	0.9997	0.4654
CI-3	0.7781	0.9943	0.9991	0.4398
CI-4	0.8965	0.9986	0.9998	0.5363
CI-5	0.6823	0.9901	0.9991	0.4238
CI-6	0.8226	0.9987	0.9998	0.4693
CI-7	0.8084	0.9974	0.9997	0.4573
CI-8	0.9034	0.9034	0.9999	0.5466

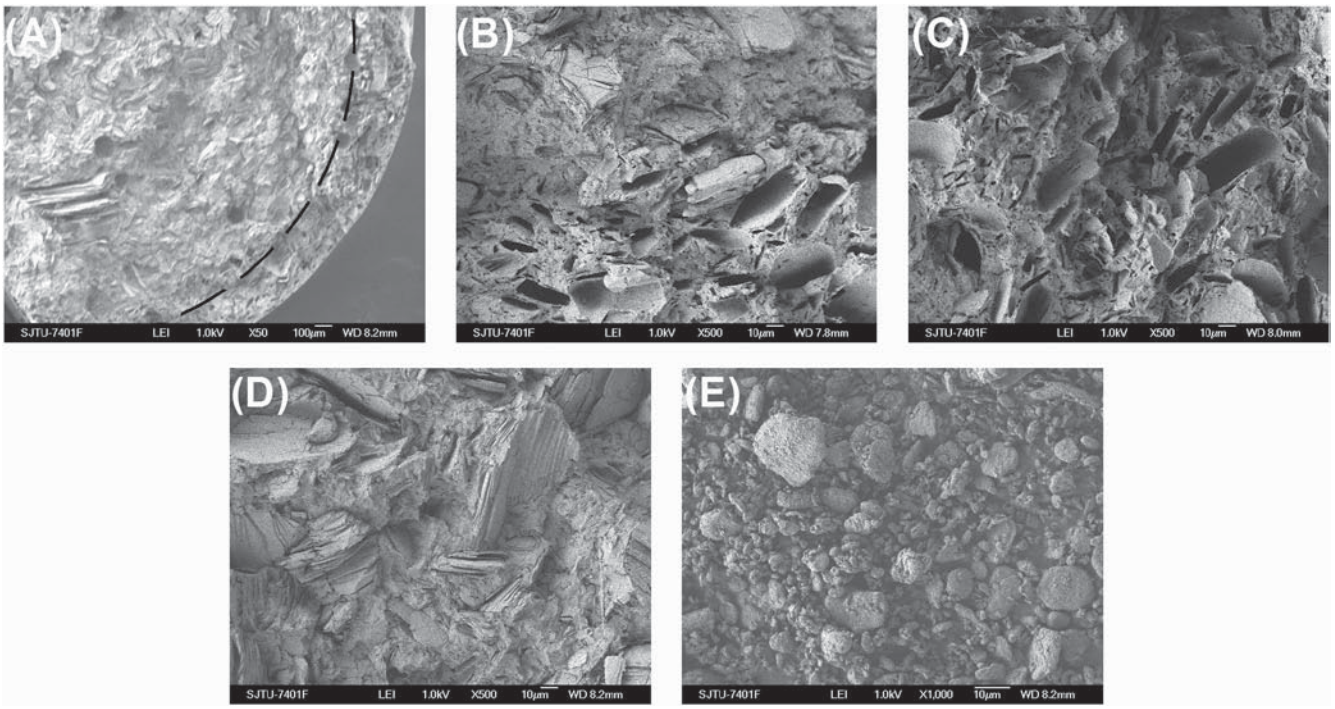

Figure 6. SEM images of implant CI-2 after 120-day release: (A and B) cross-sectional morphologies of the implant at magnification 50× and 500×, respectively, (C and D) cross-sectional morphologies of the exterior zone and the interior zone of the implant at magnification 500×, respectively, (E) 5-FU crystals.

determined for the implants at the same release time. As listed in Table 4, 5-FU content in the exterior zone was very low (less than 1.5%) in comparison with that in the interior zone, which was almost the same as the predefined drug loading. This result suggested that the exterior porous zone shown in Figure 6C should be the remaining PCL matrix and functioned as a diffusion barrier after the initial drug was almost depleted; whereas, the interior compact zone (Figure 6D) was the section where drug was basically unreleased and functioned as a drug depot. It indicated that 5-FU release took place gradually from the exterior region to the interior region of the implants.

Evolution of molecular weight of PCL

GPC was applied to determine changes in molecular weight of PCL implants during the *in vitro* release assay. As shown in Table 5, compared with the molecular weights of raw material and implants before release, molecular weights of PCL in the exterior and interior zones of CI-1 and CI-5 slightly decreased (less than 10%), thus no significant PCL degradation and resultant erosion of matrix occurred over 120 days, which also indicated that the drug release was dominated by a diffusional mechanism.

According to all the obtained results, the 5-FU release region shifted from the exterior to the interior of the implants. As the drug was diffusing out of PCL matrix, water was counter-diffusing into the matrix, particularly diffusing into the voids left by the drug, as found in the SEM images. Similar reports can be found in many literatures[23,35]. In the present study, as 5-FU is a hydrophilic drug with a small molecular weight, its diffusion in the PCL implant is both matrix and pore controlled. Moreover, since 5-FU has a very low PCL/water partition coefficient of 0.09 (experimental data), the drug would prefer to partition and diffuse through the water-filled pores rather than diffuse via PCL domains. The existence of water-filled pores in the diffusion layer could enhance the rate of drug diffusion, and therefore drug release. At the early stage, 'matrix diffusion' dominated the release process; however, at the later stage, as the number of pores increased with the increasing amounts of drug released, 'pore diffusion' began to contribute.

For the implants with the same drug loading, both 'matrix diffusion' and 'pore diffusion' dominated the drug release process, and the drug release rate should be mainly determined by the diffusion distance, suggesting that the larger the diameter of the PCL implants, the slower the drug released. The differences in release profiles between implants with different diameter were significant. Whereas, for the implants with the same diameter, after an early stage present the similar release profile, 'pore diffusion' became the major rate-limiting step. Therefore, the implants with higher drug loading released more drug than those with lower drug loading, thus generating more pores and leading to faster drug release. However, as the diameter increased to some extent, the release rate was relatively slow because of the longer diffusion pathway, thus there could not form enough pores to influence the release process and 'pore diffusion' was negligible. This may be why the effect of drug loading on drug release decreased as implant diameter increased.

Table 4. Drug content in the exterior and interior zones of the implants after 120-day drug release.

Implant	Drug loading (%)	Drug content (Mean ± SD, %)	
		Exterior zone	Interior zone
CI-2	25	0.24 ± 0.03	24.37 ± 0.84
CI-3	25	0.72 ± 0.18	23.95 ± 0.87
CI-6	50	0.43 ± 0.16	49.38 ± 1.41
CI-7	50	1.39 ± 0.31	48.12 ± 1.26

Table 5. Molecular weights of PCL material, and PCL in the implants before and after 120-day release.

Sample		M_n	M_w	PDI
PCL material		53,700	77,800	1.45
Implant before release		53,400	77,700	1.44
CI-1 after release	Exterior zone	48,800	75,400	1.54
	Interior zone	47,300	71,200	1.50
CI-5 after release	Exterior zone	48,300	73,700	1.52
	Interior zone	48,800	72,500	1.54

Conclusion

Cylindrical 5-FU loaded PCL implants with uniform drug distribution were fabricated by a combination of hot-melt extrusion and injection molding. The drug release profiles of 5-FU from PCL implants were related to the diameter of the implants, drug loading and end-capping. Generally, the larger the diameter of the PCL implants, the slower the drug released; more rapid drug release could be obtained from the implants with higher drug loading; the release profiles of end-capped and uncapped implants showed no obvious differences. The effect of drug loading on 5-FU release decreased as the diameter of implant increased. The drug release data were best fit with the Ritger-Peppas model, and Fickian diffusion was the predominant release mechanism for all the uncapped implants. The SEM results showed that the 5-FU release region shifted from the exterior to the interior of the implants. The GPC results suggested that PCL matrix degradation was very slow during the period of the study.

Declaration of interest

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