Materials Research Express

**PAPER**

**Mechanical properties and drug loading rate of a polycaprolactone 5-fluorouracil controlled drug delivery system**

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**Keywords:** PCL/5-Fu controlled drug delivery system, mechanical properties, drug loading rate, *in-vitro* experiments

**Abstract**

In the context of precision medicine, controlled drug delivery systems (CDDSs) have become a research focus. The structural integrity of CDDSs is critical for ensuring an acceptable drug release rule; hence, a CDDS must possess appropriate mechanical properties. In this study, a polycaprolactone/5-fluorouracil (PCL/5-Fu) CDDS was fabricated via solvent evaporation, and the effects of the PCL molecular weight and 5-Fu loading rate on the mechanical properties of the CDDS were evaluated. The results of tensile testing, scanning electron microscopy, and substance analysis indicated that when the content of 5-Fu was less than 9.09% in the developed CDDS, 5-Fu was completely compatible with PCL, and no crystal aggregation was induced. In addition, the maximum 5-Fu loading rate required to retain acceptable mechanical properties was 23.08%, and the corresponding tensile strength of the sample was 12.9 MPa. This strength is sufficient to prevent structural failure and instantaneous drug release due to strength reduction during application of the drug delivery system. *In-vitro* experimental results demonstrated that the PCL/5-Fu CDDS can achieve controlled drug release over 1000 h. These findings provide a basis for establishing a drug release model for the proposed CDDS.

1. **Introduction**

Precision medicine is a novel medical concept developed on the basis of personalised medicine. It utilises the rapid progress in genome sequencing technology and the integration of expertise from diverse biological fields [1–3]. Both accurate diagnosis and disease treatment are required to facilitate the implementation of precision medicine. In this context, controlled drug delivery systems (CDDSs) offer efficient and targeted drug release along with fewer side effects compared with conventional drug delivery modes; therefore, such systems have become a primary research focus [4–6].

Implanting a CDDS near a lesion is an important method of controlling drug release [7–9]. Drugs are often carried within a polymer matrix with high biocompatibility and are subsequently released via diffusion, degradation, and several other mechanisms. The drug release cycle varies significantly, from days to months or even years. The drug load modes for implantable CDDSs can be divided into two categories—storage and matrix. With regard to the storage mode, polymer materials with various structures are fabricated into cavities to transport drugs and release them. These structures include nanospheres [10], multi-layer capsules [11], shell-core tablets [12], and honeycomb [13]. Storage-type CDDSs have a large drug-loading capacity and a long release cycle. However, the technology behind such CDDSs is complex, which translates into a correspondingly high preparation cost; moreover, the release law is difficult to control owing to the complexity of the structure. In matrix-type CDDSs, polymer materials are mixed with the required drugs for preparation and moulding. This provides a facile and low-cost preparation method and is more feasible for the commercialization of controlled drug release over short and moderate periods of time.
Commonly used materials for matrix-type drug delivery systems include polyglycolide (PGA), polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL) [14]. The glass-transition temperature of PCL is relatively low (–60 °C); PCL also has good thermoplastic forming conditions. In addition, PCL exhibits acceptable biodegradability and biocompatibility and is cost-effective. Owing to its high initial strength and stable mechanical properties, PCL is currently the most widely used fixation material for the treatment of bone diseases. It is also an important material for three-dimensional (3D) printing of biological bones [15, 16]. Moreover, PCL has been studied with regard to its application in CDDSs [17, 18]; in this regard, most related studies have focused on the release rules [19] and CDDS structure design [20], whereas few reports have been published regarding the safety of PCL CDDSs from the perspective of their mechanical properties. The mechanical properties of the CDDS structure represent a critical component in the realisation of drug release. Unfavourable mechanical properties can cause damage to the CDDS during storage, transportation, and use, resulting in instantaneous drug release and subsequent harm to the human body. Moreover, the rate of drug loading in the CDDS is critical during the preparation process. If the volume added during drug loading falls below a critical value, the drug release cycle will be shortened, whereas excessive drug loading will reduce the strength of the drug delivery system and even inhibit the formation of the drug delivery system.

In this study, a PCL/5-Fu CDDS was fabricated via solvent evaporation, and the effects of both the PCL molecular weight and 5-Fu loading rate on the mechanical properties were analysed. The mechanical properties of the CDDS and the maximum loading rate of 5-Fu in the CDDS were evaluated via tensile testing, scanning electron microscopy, and substance analysis. The results of this study can provide a basis for establishing a drug release model for the proposed PCL/5-Fu drug delivery system.

2. Materials and methods

2.1. Materials

PCL materials with average molecular weights of 30, 50, and 80 kDa were used as the polymer matrix. The loaded drug 5-Fu (>98% pure), which has been used extensively in clinical applications related to cancer chemotherapy, was acquired from Shandong Qilu Pharmaceutical Co., Ltd (Shandong, China).

2.2. Fabrication of PCL/5-Fu CDDS

The moulding process for the PCL/5-Fu CDDS is illustrated in figure 1. Firstly, the PCL particles were placed in an oven at 30 °C for drying. After drying until a constant weight was recorded, the PCL particles were removed and sealed for preservation. Secondly, PCL/5-Fu mixed solutions were prepared. PCL and 5-Fu were placed in a beaker containing tetrahydrofuran (THF) solvent, and the solution was stirred uniformly using a magnetic stirrer at 25 °C. Subsequently, the mixture was moved to a fume cupboard until the THF in the solution had
completely evaporated. The residue was then vacuum-dried at 30 °C to obtain the PCL/5-Fu mixture. Thirdly, the obtained mixture was placed in a beaker at 70 °C, where it melted and was subsequently defoamed in vacuum. The mixed solution was poured into a template; thereafter, pressure was applied, and the resultant mixture was then dried in an oven at 30 °C. Finally, the mixture was demoulded to obtain the PCL/5-Fu matrix drug delivery system, which was placed in a sealed bag until further use.

2.3. Characterization methods
Tensile tests were carried out using the standard dumbbell-shaped testing samples with the length of 150 mm and thickness of 4 mm, respectively. The tests were conducted using an electronic universal servo testing machine (MTS 370), in which the nominal accuracy of the load sensor was 0.1 N. The tension was applied uniformly along the axial direction at a rate of 2 mm min⁻¹.

Scanning electron microscopy (SEM) images of the fractured surface of the impact specimens were captured. The samples were previously fractured in liquid nitrogen, afterwards the gold-coated process for all the specimens were completed in the coating machine. A scanning electron microscope (Hitachi S-3000N) was used with a voltage of 10 kV under high vacuum.

Differential scanning calorimetry (DSC) analysis was performed in a calorimeter (DSC1, Mettler Toledo). The scans were computed from 25 to 300 °C at a heating rate of 10 °C min⁻¹ and under a nitrogen atmosphere; samples weighing approximately 5 mg were tested.

X-ray diffraction (XRD) analysis was conducted using a Bruker Advanced D8 diffractometer. The analysis was performed under an applied current of 40 mA and an accelerating voltage of 40 kV. The diffraction data were recorded from 5° to 50° at a scan rate of 2° min⁻¹.

In-vitro drug release tests were conducted using a high-performance liquid chromatograph (HPLC, SPD10A, Shimadzu) at a wavelength of 270 nm. Regular saline (37 °C) was used to simulate the fluids found in the human body.

3. Results and discussion
3.1. Influence of PCL molecular weight on mechanical properties
To evaluate the influence of the molecular weight of PCL on the mechanical properties of the samples without drug addition, PCL with molecular weights of 30, 50, and 80 kDa was fabricated to stretch the standard specimens using the moulding method described in section 2. The stress–strain curves of the specimens are shown in figure 2, and the corresponding elastic moduli, yield strengths, and tensile strengths were calculated according to the method shown in figure 3; the values of these properties are listed in table 1.

As shown in figure 2 and table 1, an increase in the PCL molecular weight results in a corresponding increase in the parameters used to measure mechanical properties. However, the increase in the extension strength and yield strength were not significant. As shown in table 1, the average extension strength of the standard PCL specimens with different molecular weights was approximately 16.5 MPa. As PCL is commonly used for scaffold matrices in artificial bone [21] and tissue engineering [22], its mechanical strength is sufficient to prevent structural failure and instantaneous drug release due to strength reduction during the functioning of CDDSs.
addition, a higher molecular weight leads to an increased glass transition temperature, along with a corresponding reduction in machinability; hence, the PCL with the molecular weight of 30 kDa was selected as the carrier material for the drug delivery system in this study.

3.2. Influence of 5-Fu loading rate on PCL/5-Fu mechanical properties

In the PCL/5-Fu CDDS, the PCL acts as a binder, and the 5-Fu is dispersed throughout the PCL. To quantify the influence of the 5-Fu loading rate on the mechanical properties of the PCL/5-Fu specimens, various quantities of 5-Fu were dispersed throughout a fixed quantity of PCL. The specific parameters of the as-prepared specimens are listed in table 2.

Initially, several PCL/5-Fu CDDSs with various drug loading rates were fabricated; these CDDSs had a pie structure with a diameter of 10 mm and a thickness of 5 mm. The microstructure of each sample was evaluated using SEM, the results of which are shown in figure 4. Figure 4(a) shows an SEM image obtained from the pure PCL sample, the material texture is uniform; As shown in figure 4(b), there is no significant change in the material texture and the aggregated 5-Fu particles were barely observed, the 5-Fu exhibited a homogeneous distribution within the PCL; As the loading rate of the 5-Fu increased (figures 4(c)–(f)), 5-Fu aggregates were observed within the PCL materials. When the 5-Fu content reached 1.6 g (figure 4(e)), the drug accumulation at the interface became severe, with the development of cracks and holes; this, in turn, affected the mechanical properties of the CDDS and resulted in failure. To ensure adequate fabrication quality, the content of the 5-Fu within the PCL was set to not exceed 23.08% (1.2 g).

Then, to evaluate the mechanical properties of the PCL/5-Fu CDDS containing various quantities of 5-Fu, standard testing samples were fabricated using the moulding method described in section 2. The stress–strain curves obtained from each sample are shown in figure 5.

| Serial number | PCL weight (g) | 5-Fu weight (g) | 5-Fu mass proportion (%) |
|---------------|---------------|-----------------|--------------------------|
| 1#            | 4.0           | 0               | 0.00                     |
| 2#            | 4.0           | 0.4             | 9.09                     |
| 3#            | 4.0           | 0.8             | 16.67                    |
| 4#            | 4.0           | 1.2             | 23.08                    |
| 5#            | 4.0           | 1.6             | 28.57                    |
| 6#            | 4.0           | 2.0             | 33.30                    |
As shown in figure 5, the tensile and yield strengths of the PCL/5-Fu specimens both decreased with an increase in drug loading. Based on the stress–strain curves in figure 5, the influence of the 5-Fu loading rate on the tensile and yield strengths of the sample was determined. These relationships between these parameters are presented graphically in figure 6.

As shown in figure 5, when the 5-Fu content was less than 9.09% (0.4 g), the values of the mechanical properties of the PCL/5-Fu specimens did not decrease significantly in comparison with those of the pure PCL specimens. Therefore, it can be concluded that when the 5-Fu content is less than 9.09%, the 5-Fu can dissolve or disperse throughout the PCL in molecular form. Moreover, strong intersolubility was observed between 5-Fu and PCL, and no 5-Fu crystal structures were present in the CDDS; therefore, the mechanical properties of the PCL/5-Fu specimens have little effect. To verify this, DSC analysis was performed on the PCL/5-Fu CDDS specimens with drug loadings of 0.40 g, 0.35 g, and 0.30 g; the results are presented in figure 7.
As shown in figure 7, when the drug loadings were 0.30 g and 0.35 g, no 5-Fu crystallisation peak was detected in the drug-loaded specimen. XRD analysis was also conducted on the PCL/5-Fu specimens with drug loadings of 0.30 g and 0.35 g. The results (figure 8) show that the curves of the PCL/5-Fu with drug loadings of 0.30 g and 0.35 g are similar to those of the pure PCL, without the characteristic peaks associated with 5-Fu. This suggests that the drug and PCL material exhibited a strong state of mutual solubility. Moreover, no 5-Fu crystal precipitates were observed. However, when the drug loading was increased to 0.40 g, the corresponding DSC characteristic curve (figure 7) exhibited a 5-Fu crystallisation peak, indicating that 5-Fu and PCL were microphase-separated in the material. In addition, the 5-Fu began to appear in an aggregated state, and therefore, 5-Fu crystals were detected. When the 5-Fu content was below 9.09% in the PCL/5-Fu specimens, the 5-Fu exhibited strong compatibility with the PCL. When the drug loading exceeded 9.09% (0.4 g), the yield and tensile strengths of the PCL specimens exhibited a continual decrease, and the values were significantly lower than those for the pure PCL specimens (figure 6). This trend can be attributed to the fact that in the PCL/5-Fu specimens, PCL acted as a connector. As the proportion of 5-Fu increased, 5-Fu was increasingly dispersed throughout the specimens in the form of crystal particles. These crystal particles acted as stress concentrators, and their presence induced weak spots within the material. Initially, molecular chain fracture and relative slip occurred in the vicinity of the defects. Subsequently, the stress was transferred to other regions in the material, inducing further molecular chain fracture, which eventually resulted in specimen failure. This directly affected the modulus and strength during

![Figure 6. Influence of 5-Fu ratio on tensile and yield strengths.](image6)

![Figure 7. DSC curves for pure PCL, pure 5-Fu, and PCL/5-Fu with different 5-Fu proportions.](image7)
While the static mechanical property test, while the tensile and yield strengths of the specimen were reduced under tensile loading.

Considering the aforementioned findings in combination with the conclusions drawn from the mechanical properties, it was determined that when the drug loading was below 23.08% (1.2 g), the PCL/5-Fu CDDS adopted an integrated structure, and its tensile strength exceeded 12.9 MPa. Moreover, the PCL/5-Fu CDDS exhibited sufficient structural intensity to ensure high-quality fabrication. Thus, structural failure of the PCL/5-Fu CDDS during use and the subsequent instantaneous drug release can be prevented.

3.3. In-vitro experiments for evaluating drug release

To verify the drug release characteristics of the PCL/5-Fu CDDS, in-vitro drug release experiments were performed with the following parameters: 4.0 g PCL, 0.6 g 5-Fu, and 13.1% 5-Fu loading.

The results are shown in figure 9. The curves indicate that the PCL/5-Fu CDDS can achieve controlled drug release over 1000 h. However, compared with the theoretical linear drug release curve, minor fluctuations were observed. These fluctuations can be mitigated by optimising the structure of the drug delivery system and the drug loading volume; this will be addressed in a subsequent study.
4. Conclusions

In this study, the influence of the drug loading rate on the mechanical properties of a PCL/5-Fu CDDS was analysed. The maximum loading capacity of the 5-Fu in the PCL was determined on the basis of the mechanical properties and moulding quality of the CDDS. When the 5-Fu loading rate was less than 9.09%, the 5-Fu was completely compatible with the PCL, and no crystal aggregation was observed. In the developed CDDS, the maximum 5-Fu content was 23.08%; the corresponding tensile strength of the drug delivery system was 12.9 MPa. This strength is sufficient to prevent structural failure and the instantaneous drug release induced by strength reductions occurring during the application of the drug delivery system. According to the results of in-vitro experiments, the PCL/5-Fu CDDS can achieve controlled drug release over 1000 h.

The findings of this study serve as a foundation for establishing a mathematical model for PCL/5-Fu CDDSs and for simulating the drug release process to optimise the structure of such CDDSs. Such a model can provide a basis for ensuring safe and effective drug release from PCL/5-Fu systems in precision medicine.

Acknowledgments

The authors gratefully acknowledge the support of the National Natural Science Foundation of China (No. 51605379), Basic Research Plan of Natural Science of Shaanxi Province (2019JQ-804), and the State Key Laboratory for Manufacturing Systems Engineering (Xi’an Jiaotong University).

Data availability statement

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

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