International Journal of Pharmaceutics 434 (2012) 161–168

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

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

Treatments of paclitaxel with poly(vinyl pyrrolidone) to improve drug release from poly(ε-caprolactone) matrix for film-based stent

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ARTICLE INFO

Article history:
Received 16 February 2012
Received in revised form 28 April 2012
Accepted 19 May 2012
Available online 27 May 2012

Keywords:
Solid dispersion
Paclitaxel (PTX)
Poly(vinyl pyrrolidone) (PVP)
Film
Drug delivery systems

ABSTRACT

Drug-loaded biodegradable films as a principal part of film-based stent were investigated for controlled drug delivery systems. In this study, solid dispersion technique, a pretreatment method of paclitaxel (PTX), was applied to prepare the PTX-loaded poly(ε-caprolactone) (PCL) films. Drug dissolution rates and characteristics of the poly(vinyl pyrrolidone) (PVP)/PTX solid dispersions (SDs) and physical mixtures (PMs) were investigated to show that the PVP/PTX SDs were successfully prepared before being incorporated in biodegradable films. Afterwards, the effect of the application of SDs on improving drug release behavior, weightlessness, crystalline states, and surface and internal morphologies of the films were studied. It was found that, the films with SDs showed a higher drug release rate than the films with PMs or pure PTX. In addition, the content of PVP in the SDs also had impact on drug release behavior: the more PVP in SDs, the faster the drug was released. According to the drug release test and weightlessness study, the possible drug release mechanism was put forward for the films with SDs. The application of solid dispersion technique showed a remarkable effect on improving drug release behavior for film-based biodegradable stent drug delivery systems.

1. Introduction

Stents have been widely used in interventional therapy and act not only as scaffolds to support the occluded tubular organs or structures, but also as drug delivery systems for therapeutic management of benign/malignant tumor (Guo et al., 2007; Ramcharitar et al., 2007; Sterioff, 1997). Biodegradable stents are made from biodegradable materials containing different antitumor drugs. With regards to the biodegradable materials, biodegradable polyesters or polyanhydrides (PLGA, EVA, PCL, PLA and so on), have been studied by many researchers as a major part of drug delivery system (Lei et al., 2010; Sarisozen et al., 2009).

Poly(ε-caprolactone) (PCL), a biodegradable aliphatic polyester with its good biocompatibility and permeability for drug, was used as the matrix material of the films (Li et al., 2010). Paclitaxel (PTX), a nature compound originally isolated from taxus brevifolia, is now widely used in the treatment of a variety of cancers (Jiang et al., 2011), such as oophoroma (Wang et al., 2002), mammary (Kars et al., 2011), and colon (Mitra et al., 2011) cancers. PTX can block cell cycling at the G_2/M stage, inhibit mitosis and DNA synthesis, thus result in the death of apoptotic cell (Mugabe et al., 2011; Wang et al., 2011; Yao et al., 2011). Meanwhile, it has been reported that PTX-loaded drug-eluting stents show obvious effect on restenosis of tubular organs (Grube et al., 2003), and here PTX would be tried to load in the biodegradable films. Because of PTX's antineoplastic mechanism and activities, we elected PTX as model drug in our study. However, PTX was a poorly water-soluble drug and had a low drug release rate in some biodegradable films reported in previous papers (Tang et al., 2010), how to improve poorly water-soluble antitumor drug release behavior in drug delivery system of biodegradable stents become an important puzzle for medical workers.

Solid dispersion (SD), a kind of intermediate, shows remarkable effects on improving the dissolution rate, solubility, and bioavailability of poorly water-soluble drug (Ozeki et al., 2000; Srinarong et al., 2011). The method of solid dispersion, compared to physical mix, enhance the dissolution rate of poorly water-soluble drug by changing crystalline drugs into amorphous forms (Bikiaris, 2011; Krasnyuk et al., 2011). Drug dissolution rate mainly depends on

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http://dx.doi.org/10.1016/j.ijpharm.2012.05.043

properties (non-toxic, non-cancerigenic, stability, law cost) of the carrier material (Nakanishi et al., 2011), thus common materials used in research are poly(vinyl pyrrolidone) (PVP), polyethylene glycol (PEG) (Unga et al., 2009), poloxamer and so on (Li et al., 2011). PVP, an amorphous polymer materials with high melting point, has a crystallization-inhibited impact on many drugs (Dhirendra et al., 2009; Sinha et al., 2010).

Many methods were used to improve the drug release behavior in biodegraded films, such as adding hydrophilic additives and mixing a second matrix (Lei et al., 2010; Liu et al., 2011). Solid dispersion technique is rarely used to raise drug release rate for film-based stent. With this motivation, we tried to prepare PVP/PTX solid dispersions (SDs) and PVP/PTX physical mixtures (PMs) to enhance the dissolution rate of PTX, and incorporate the SDs and PMs into the PCL films to improve the drug release behavior. The characterization of SDs and PMs were studied. The influences of addition of SDs and PMs in films on drug release rate, crystalline states, weightlessness, surface and internal morphologies were also discussed.

2. Materials and methods

2.1. Materials

PCL 80k (Mw = 80,000) was obtained from Shenzhen Bright China Industrial Co., Ltd. (Shenzhen, China). Poly(vinyl pyrrolidone) (PVP, K90) was obtained from ISP Technologies Inc. (NJ, USA). Paclitaxel was obtained from Xi'an Haoxuan Biological Technology Co., Ltd. (Xi'an, China). The size of paclitaxel powder was about 10 μm. All other chemicals were of analytical grade and used without further purification.

2.2. Preparation of paclitaxel solid dispersions and physical mixtures

The PVP/PTX solid dispersions were prepared with a solvent evaporation method reported in previous papers (Wu et al., 2011). In brief, accurately weighed amounts of PTX and PVP were both dissolved in dehydrated ethanol. After complete dissolution, they were dried in a rotary evaporator under reduced pressure at 50 °C to evaporate the solvents. Then, the obtained solid dispersions were left in a vacuum oven at 35 °C for 24 h to completely remove the residual solvents. Then the solid dispersions were milled in a mortar, sieved through 80 mesh and stored in a desiccator before further analysis.

Physical mixtures with a drug carrier ratio of 1:1 were prepared by intensive mixing. Then processed in the same way before further analysis.

2.3. HPLC analysis method

A HPLC system (Waters, USA), equipped with a photodiode array detector (2998), a binary HPLC pump (1525), an Autosampler (2707) and a Venusil C18 reversed phase column (particle size 5 μm, 4.6 mm × 250 mm), was used to determine the PTX concentration in our study. The mobile phase consisted of water/methanol (25/75, v/v) with a flow rate of 1 ml/min. The injection volume was 50 μl and the UV detection was performed at 227 nm with the column oven temperature at 30 °C. The retention time of PTX was 7.1 min. For PTX peaks, the parameters (i.e., retention time and peak area) maintained a %RSD of <1. The intra and inter-day precision and accuracy were found to be well within acceptable limits (i.e., 5%). The calibration curves exhibited linear concentration ranges of 1–100 μg/ml for PTX (R^2 = 0.9997).

2.4. Dissolution studies

The dissolution tests of PTX from SDs, PMs and pure PTX were conducted in 15 ml polyethylene tubes containing 15 ml phosphate buffer solution (PBS, pH 7.4) with 1% (w/v) sodium dodecyl sulfate (SDS). The tubes were placed in a shaking water bath at 37 °C and shaken at a speed of 65 rpm. At predetermined time points, 1 ml dissolution medium was withdraw and replace with 1 ml fresh PBS with 1% (w/v) SDS. The PTX in dissolution medium was filtered through a 0.45 μm nylon filter and then analyzed by HPLC with the method described above.

2.5. Film preparation

The films with SDs, PMs and pure PTX were prepared as following: PCL 80k was first fed into the chamber of a HAAKE MiniLab II Rheomex System (Thermo Fischer Scientific, Waltham, MA) and heated, then SDs or PMs or pure PTX were added into the chamber. The mixtures were fully blended at 70–85 °C for about 20 min. The obtained mixtures were next pressed into films with a predetermined thickness on a compression molding machine (XLB-D, Shanghai No. 1 Rubber Machine Factory) at 100 °C for 5 min. At last, the films were cooled at room temperature.

2.6. In vitro release study

For in vitro drug release tests, the films were cut into 1 cm × 1 cm squares. Each film was placed in a 15 ml polyethylene tube containing 15 ml PBS with 1% (w/v) SDS. Then the experiments were performed in a shaking water bath at 60 rpm and 37 °C. Afterwards, at predetermined time intervals, the release medium in the tubes was completely withdraw and 15 ml fresh PBS with 1% (w/v) SDS would be poured into the tubes. The PTX in release medium was filtered through a 0.45 μm nylon filter and then analyzed by HPLC described in Section 2.3.

2.7. In vitro weightlessness study

The films (4 cm^2 squares; thickness: 1 mm) were weighted (recorded as W_0) and then immersed in a 50 ml polyethylene tube containing 50 ml phosphate buffer solution (PBS, pH 7.4) with 1% (w/v) SDS placed in a shaking incubator (37 °C 60 rpm). At predetermined time points, the films were took out and subsequently placed in a vacuum oven at 35 °C for 2 days to remove the residual water. Then, the films would be weighted again (recorded as W_t). The weight loss was calculated by Eq. (1)

$$\text{Weight loss } (\%) = \frac{W_0 - W_t}{W_0} \times 100. \quad (1)$$

2.8. Characterizations

2.8.1. X-ray diffraction (XRD) analysis

An X-ray diffractometer (D/max-2200/PC, Rigaku Corporation, Japan), at 40 kV and 20 mA with a scanning speed of 10°/min, was adopted to analyses the crystallinity of SDs, PMs, pure PTX and films. The particles were pressed onto the sample holder by a glass sheet, while films were directly placed on the sample holder.

2.8.2. Scanning electron microscopy (SEM)

The surface and internal morphology of SDs, PMs, pure PTX and films were examined using a JSM-7401F scanning electron microscopy (SEM) (JEOL, Tokyo, Japan). The particles and the surface of films were directly put on the conductive adhesive and the cross-section of the films were obtained by freeze-fracturing the films in liquid nitrogen. The samples were coated with gold on an

Table 1
Classification of PVP–PTX particles.

Sample	Classification	PVP/drug (w/w)
SD_1	PVP–PTX solid	1/1
SD_2	dispersion	3/1
PM	PVP–PTX physical mixture	1/1

Emitech K-575 Sputter Coater. The accelerating voltage for SEM images was 1 kV and the current was 20 mA.

3. Results and discussion

3.1. Preparation and characterization of the paclitaxel solid dispersions and physical mixtures

3.1.1. The ratio of the paclitaxel solid dispersions and physical mixtures

The PVP/PTX solid dispersions with different ratios of PVP and PTX were prepared as listed in Table 1. In order to raise the drug loading in the films in the following studies, the percentage of the drug was higher than the best ratio reported in some previous papers (Narang and Srivastava, 2002; Sammour et al., 2006). The PVP/PTX physical mixtures were prepared with the only ratio of 1:1 as control.

3.1.2. In vitro dissolution studies

PVP was a hydrophilic polymer used in drug delivery systems (Gaucher et al., 2005; Lian and Ho, 2001). Fig. 1 shows the dissolution profiles of the PVP/PTX (1:1) solid dispersion (SD_1), PVP/PTX (3:1) solid dispersion (SD_2), PVP/PTX (1:1) physical mixture (PM) and pure PTX. The dissolution rate of SD_1 and SD_2 were obviously higher than PM and pure PTX. At 180 min, the dissolution of PTX in the solid dispersions were about 90%, while that in the physical mixture with the same ratio was nearly 45% and the pure PTX was only 5%. It could also be observed that the dissolution profiles of the solid dispersions with the same drug content varied depending on the content of PVP, the higher content of PVP in the solid dispersions, the faster the drug was released.

The ratio of the PVP and PTX used in this study was not the best, but the results showed that the solid dispersions prepared indeed had a significantly effect on drug release behavior in the dissolution study.

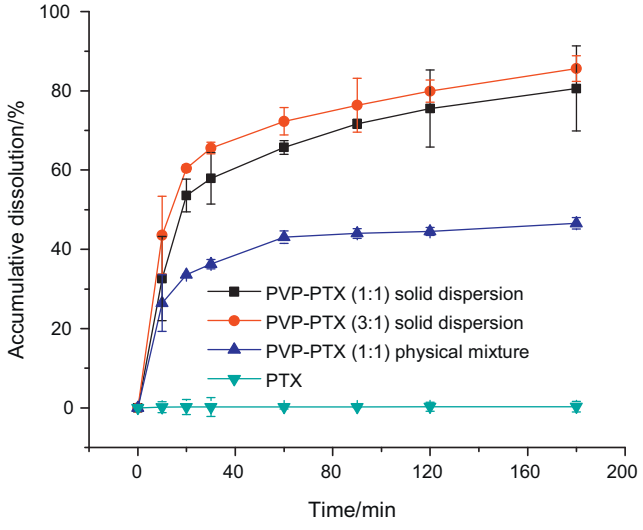

Fig. 1. Dissolution profiles of SD_1, SD_2, PM and pure PTX.

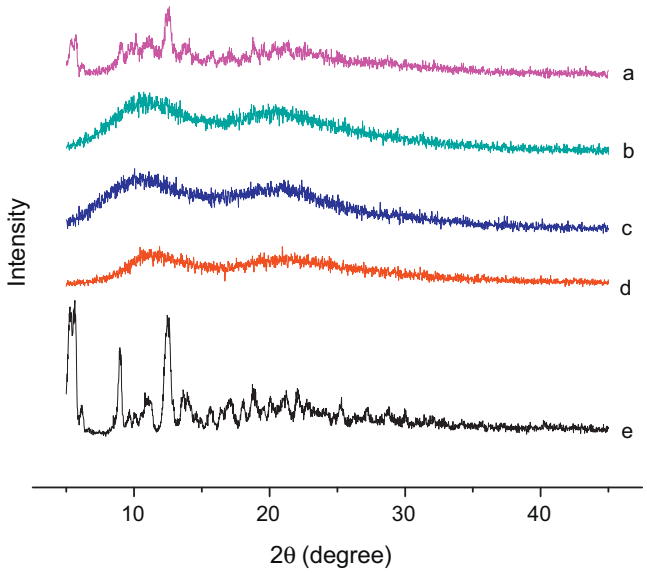

Fig. 2. The XRD patterns for (a) PM, (b) SD_2, (c) SD_1, (e) pure PTX and (d) pure PVP particles.

3.1.3. XRD patterns of the granules

XRD was used to characterize the crystalline state of the composition in the mixtures. The XRD patterns for pure PTX (e), pure PVP particles (d), physical mixture (a) and solid dispersions (b and c) are shown in Fig. 2. PTX granules presented its crystallinity by three sharp peaks at 5°, 9°, 13° and a series of weak peaks between 10° and 30° (Fig. 2e). However, PVP particles were in an amorphous state with no crystallinity peak presented in Fig. 2d. Some PTX peaks were observed in the X-ray diffraction spectrum of the physical mixture, but were hardly observed in that of two solid dispersions, indicating that PTX granule existed in an amorphous state in the PVP/PTX solid dispersions. The results of the XRD study were highly consistent with the results of the release behavior of the drug in Section 3.1.2.

3.1.4. Microstructures of the prepared particles

The micrographics of the pure PTX, pure PVP, solid dispersion and physical mixture of PTX with PVP are displayed in Fig. 3. The pure PTX granules were prismatic with a size about 10 μm (Fig. 3A), and the pure PVP particles were irregular with the size ranging from 50 μm to 200 μm (Fig. 3B). The surface micrographic of the PVP/PTX solid dispersion in Fig. 3C was rather smooth without any PTX granules, while in physical mixture, both PVP particles and PTX granules could be found in the image (Fig. 3D), indicating that PTX was dispersed in the internal part of PVP particles in SDs. What's more, the image of the solid dispersion with no obvious PTX granule better explained the amorphous state of PTX studied in Section 3.1.3.

Table 2
Compositions of the films.

Sample	PCL 80k (%)	Additives content (%)	Thickness (μm)
Film 1	90	SD_1 10	1000
Film 2	80	SD_1 20	1000
Film 3	70	SD_1 30	1000
Film 4	80	SD_2 20	1000
Film 5	80	PM 20	1000
Film 6	90	PTX 10	1000

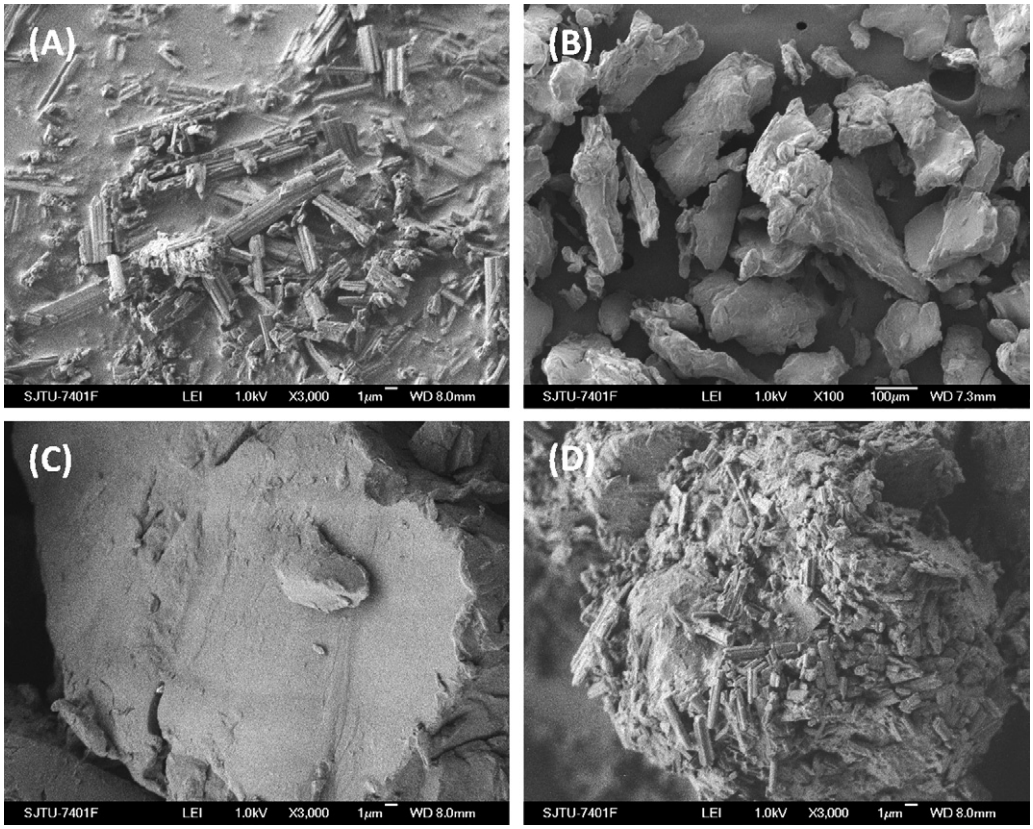

Fig. 3. SEM images of pure PTX (A) pure PVP (B) solid dispersions (C) and physical mixtures (D) of PTX with PVP. The ratio of PVP/PTX was 1:1 (w/w).

3.2. Film components analysis

The compositions of the PCL films are listed in Table 2. Three percents (10%, 20% and 30%) of SD_1 were mixed with PCL and compressed into Film 1, Film 2 and Film 3, respectively. Also, two types of solid dispersions (SD_1, SD_2) were added in the films with same content of drug. Correspondingly, 20% PM and 10% PTX were mixed with PCL and compressed into Film 5 and Film 6 as controls.

3.3. Crystalline evaluation of the films

XRD analysis was an important method to investigate the crystalline states of the compositions in the films in many previous papers (Ho et al., 2008; Xu and Czemuszka, 2008). The crystalline states of PTX granules and PVP particles (Fig. 4A) were the same with that in Fig. 2. The PCL film exhibited two sharp peaks at 21° and 24°. The XRD patterns of the PCL films with SD_1 (Film 1, Film 2, Film 3) still showed the two characteristic peaks at 21° and 24° (Fig. 4A) and the intensity, respectively increased, indicating that PCL was still in a semi-crystalline state but the peaks' intensity was increased with the content of PCL after the incorporation of SD_1. In Fig. 4B, Film 5 presented obvious peaks at 5°, 9° and 13°, suggesting that PTX granules in Film 5 still had crystallinity compared to Film 2.

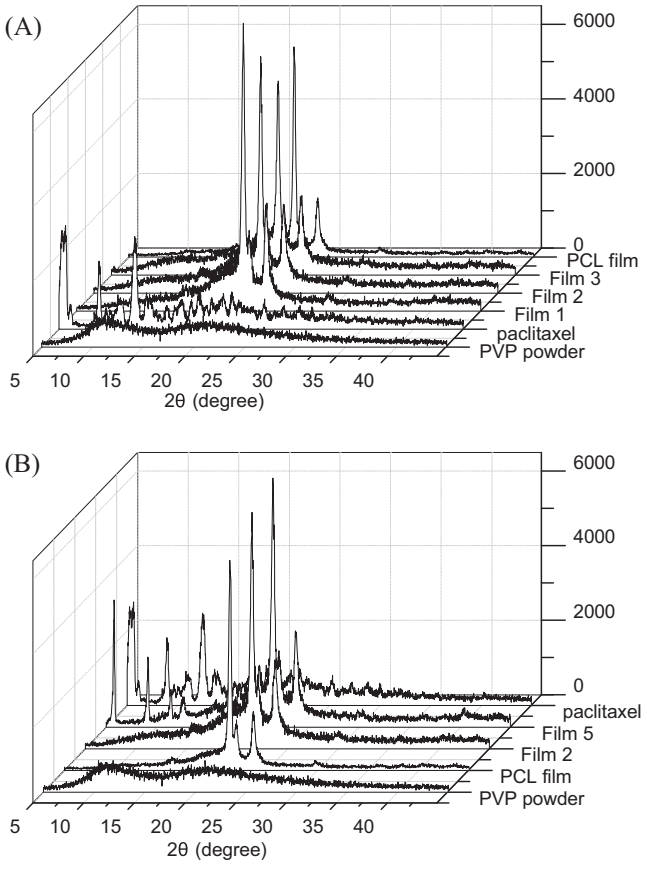

Fig. 4. XRD patterns of films.

3.4. Drug release study

3.4.1. Effect of the different additives in the films

Many methods were used to improve the drug release behavior in biodegradable films, such as adding hydrophilic additives and mixing a second matrix (Lei et al., 2010; Liu et al., 2011). In our study, PTX and PVP particles were prepared into solid dispersions before adding to the PCL films while another part of the particles

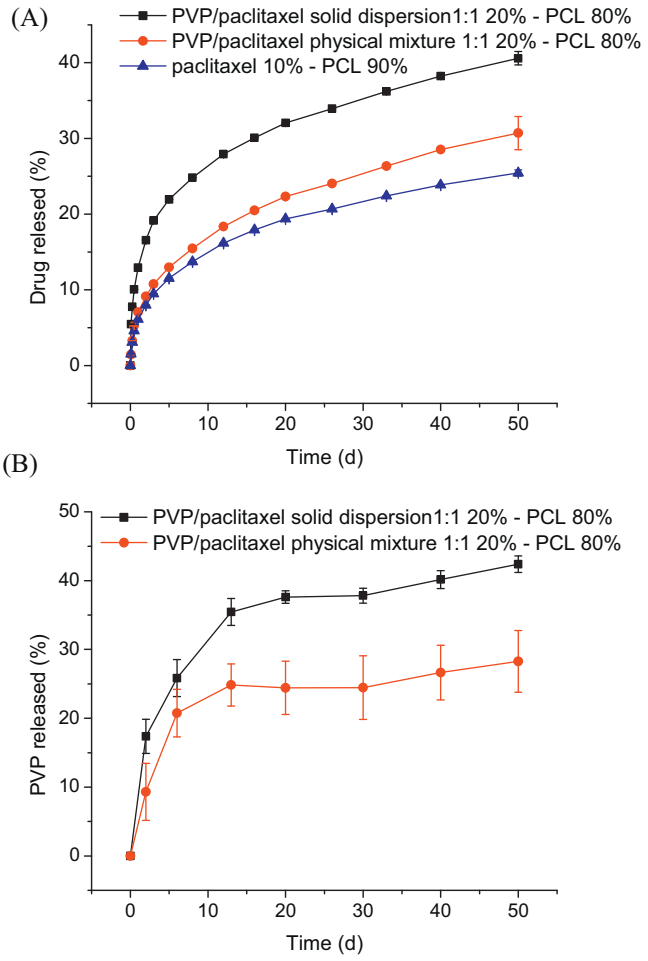

Fig. 5. (A) Drug release profiles of the films with the content of SD_1 and PM. (B) Cumulative PVP release curves for the films with the corresponding solid dispersions and physical mixtures (mean ± SD, $n = 3$).

were just physical mixed. Fig. 5A displays three drug release profiles of Film 2, Film 5 and Film 6, respectively. The absolute content of PTX and PVP in Film 2, Film 5 and Film 6 was the same. During the same period time, the drug release rate of Film 2 was much faster than Film 5 and Film 6, indicating that the preprocessing of PTX and PVP particles into solid dispersions showed a significant effect on drug release behavior. In the other hand, we investigated the release behavior of PVP from the films. As shown in Fig. 5B, nearly 50% of PVP in Film 2 and 25% of PVP in Film 5 released within 50 days. What's interesting, both PTX and PVP released faster in Film 2 than that in Film 5. An explanation to the release behavior of drug and carrier may be that the existence of amorphous state PTX in solid dispersions incremented the distance of PVP polymer chains and weakened the function between PVP polymer chains, so that the PVP release rate of Film 2 was also faster than that of Film 5.

3.4.2. *Impact of PVP addition on the drug release*

In order to explore the effects of added PVP on drug release behavior, the films (Film 1 and Film 4) with different kinds of solid dispersions were used to do the drug release test. Fig. 6 shows the drug release profiles of Film 1 and Film 4, the absolute percentage of PVP in Film 1 is 5%, while that in Film 4 is 15%. For a fixed drug content (5%), the drug release rate of Film 4 with 20% SD_2 was higher than that of Film 1 with 10% SD_1, that is to say PVP as a hydrophilic polymer could improve the drug release behavior: the higher content of PVP in the film, the faster the drug was released.

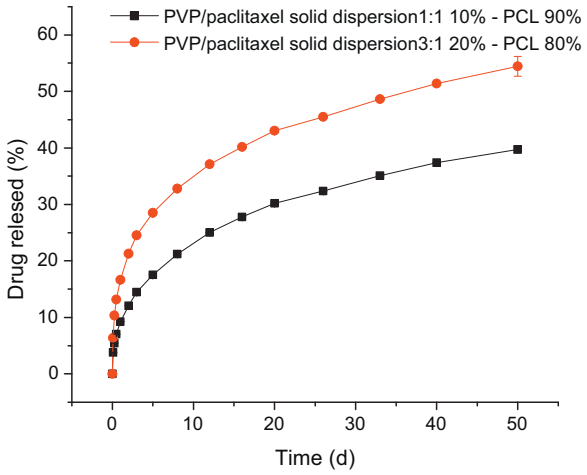

Fig. 6. Drug release profiles of the films incorporated with the same content of PTX but different contents of PVP (mean ± SD, $n = 3$).

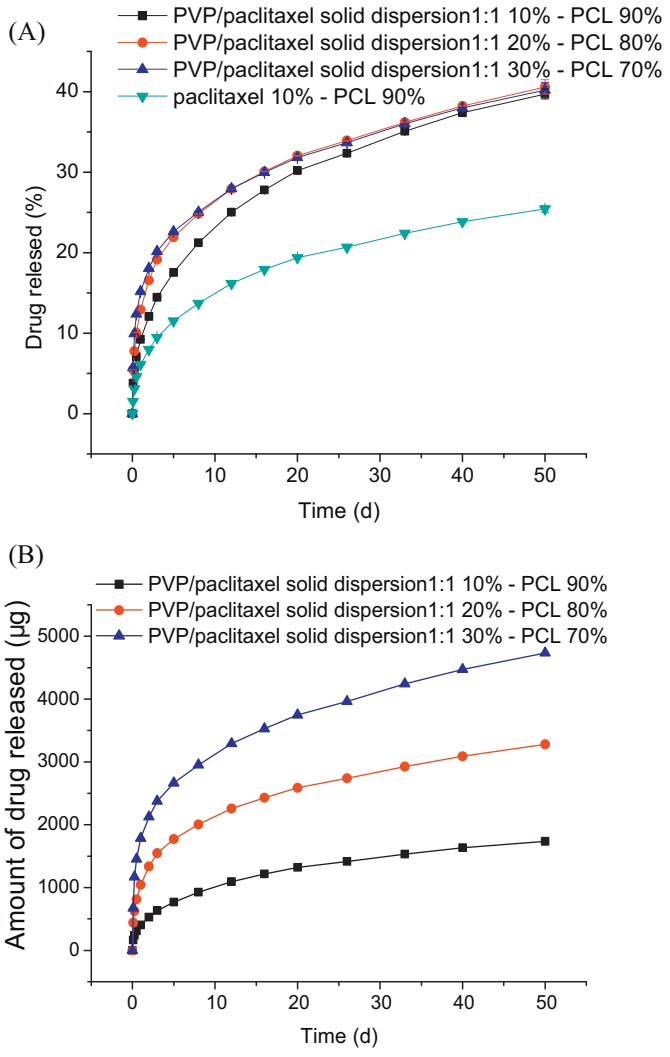

Fig. 7. (A) Drug release profiles of films with different content of SD_1. (B) PTX release curves of the absolute amounts of drug released with different content of SD_1 (mean ± SD, $n = 3$).

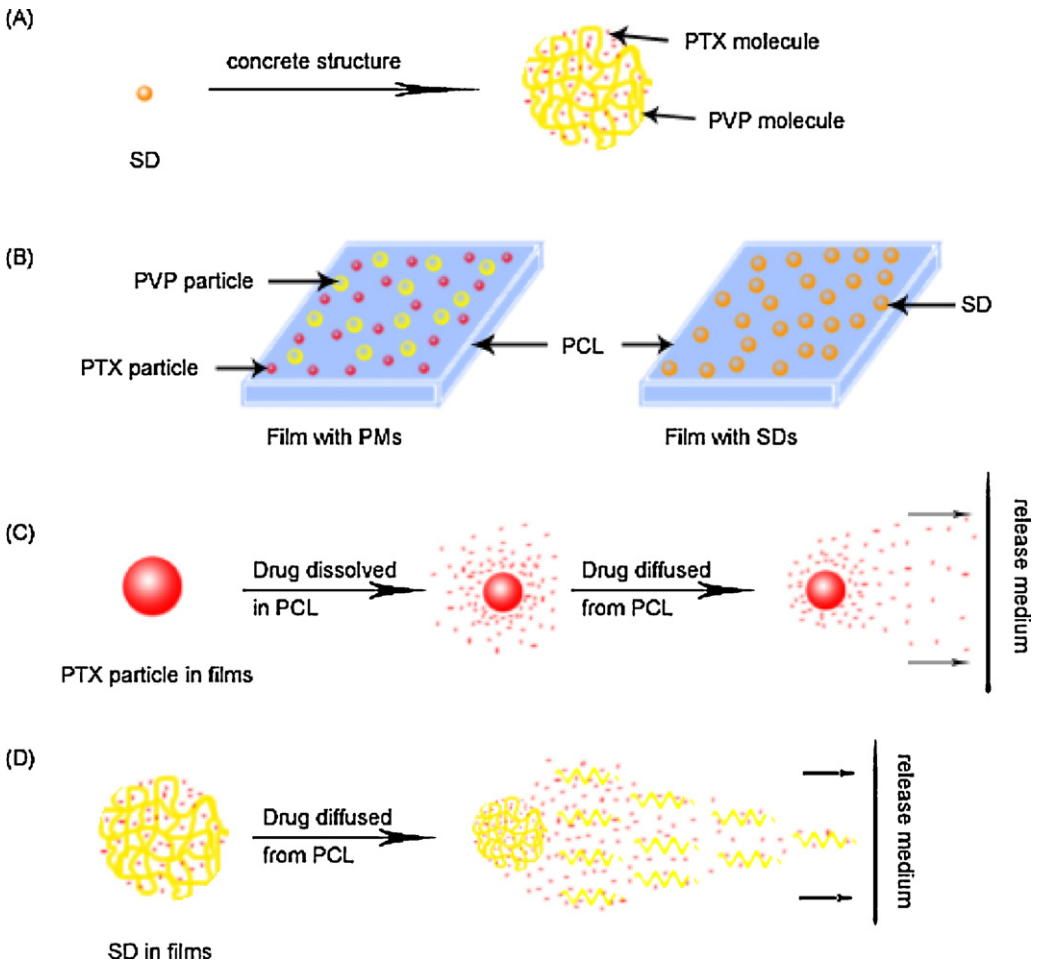

Fig. 8. (A) The structure of SD. (B) The model of PCL films. Schematic illustrations of (C) the mechanism of crystalline PTX release from the PCL matrix and (D) the mechanism of the SD with amorphous state PTX release from the PCL matrix.

3.4.3. Effect of the content of the paclitaxel solid dispersions on drug release

Drug dissolution test showed that solid dispersing technique used in this study remarkably raised the drug release behavior of PTX from the PVP/PTX solid dispersions. In order to investigate the effect on drug release rates after adding the SDs to the films, three contents (10%, 20% and 30%) of SD_1 were added into the PCL films. Fig. 7A shows the drug release curves for Film 1, Film 2, Film 3 and Film 6. The drug release rate of the film without SD_1 was obviously lower than other three films with SD_1, suggesting that the addition of SD_1 could improve the drug release rate, but there were almost no difference between the drug release profiles of Film 1, Film 2 and Film 3, which indicated that the content of PTX and PVP both had effects on drug release behavior. According to the results of Figs. 6 and 7A, it could be found that the drug release rate was inversely proportional to the content of PTX. However, the cumulative absolute amount of drug released increased with the increasing content of PTX in the films (Fig. 7B), indicating that raising the content of SD_1 in the films could enhance the drug dosage in the same period time but not the drug release rate.

3.4.4. The schematic illustrations of the existence and release mechanism of drug in PCL films

The schematic illustrations of the existence and release mechanism of drug in PCL were shown in Fig. 8. As shown in Fig. 8A, PTX is distributed molecularly in PVP molecule random coils for the PTX/PVP solid dispersions (SDs). PVP is an amorphous and flexible linear polymer and becomes soft at 150–180 °C (Nair et al., 2001). The PVP and PTX particles are separately distributed in the PCL film with PTX/PVP physical mixtures (PMs), while the PTX/PVP solid dispersions distributed as a whole in the PCL film with SDs (Fig. 8B). This is because that the SD particles did not dissolve in PCL and could not melt at 90 °C during the preparation of the PCL film with SDs at 90 °C. The PTX/PVP physical mixtures consisted of PTX and PVP particles actually, thus, the PTX and PVP particles were separately dispersed in melting PCL during the preparation of the PCL film with PMs at 90 °C. For the PCL film with PMs, the drug release mechanism is schematically illustrated in Fig. 8C, the PTX particles are firstly dissolved in PCL and then diffused within PCL towards release medium, PTX is very poor PCL soluble and dissolved very slowly in PCL, thus slowing down it release from PCL matrix very much. Water penetrated in PCL might play a certain but not main role for drug release, as we know, PCL is a hydrophobic polymer with good penetrability and poor water swelling capacity (Li et al., 2010). For the PCL film with SDs, PTX is molecularly distributed in PVP molecule coils, as water soluble PVP is released from PCL to release medium, PTX molecules are diffused within PCL to release medium simultaneously (Fig. 8D). In comparison with the PCL film with PMs, drug release from the PCL film with SDs lacks the process of dissolving PTX particles in PCL. Thus, PTX should be faster released from the PCL film with SDs than that with PMs, which was confirmed by the drug release results in Fig. 5.

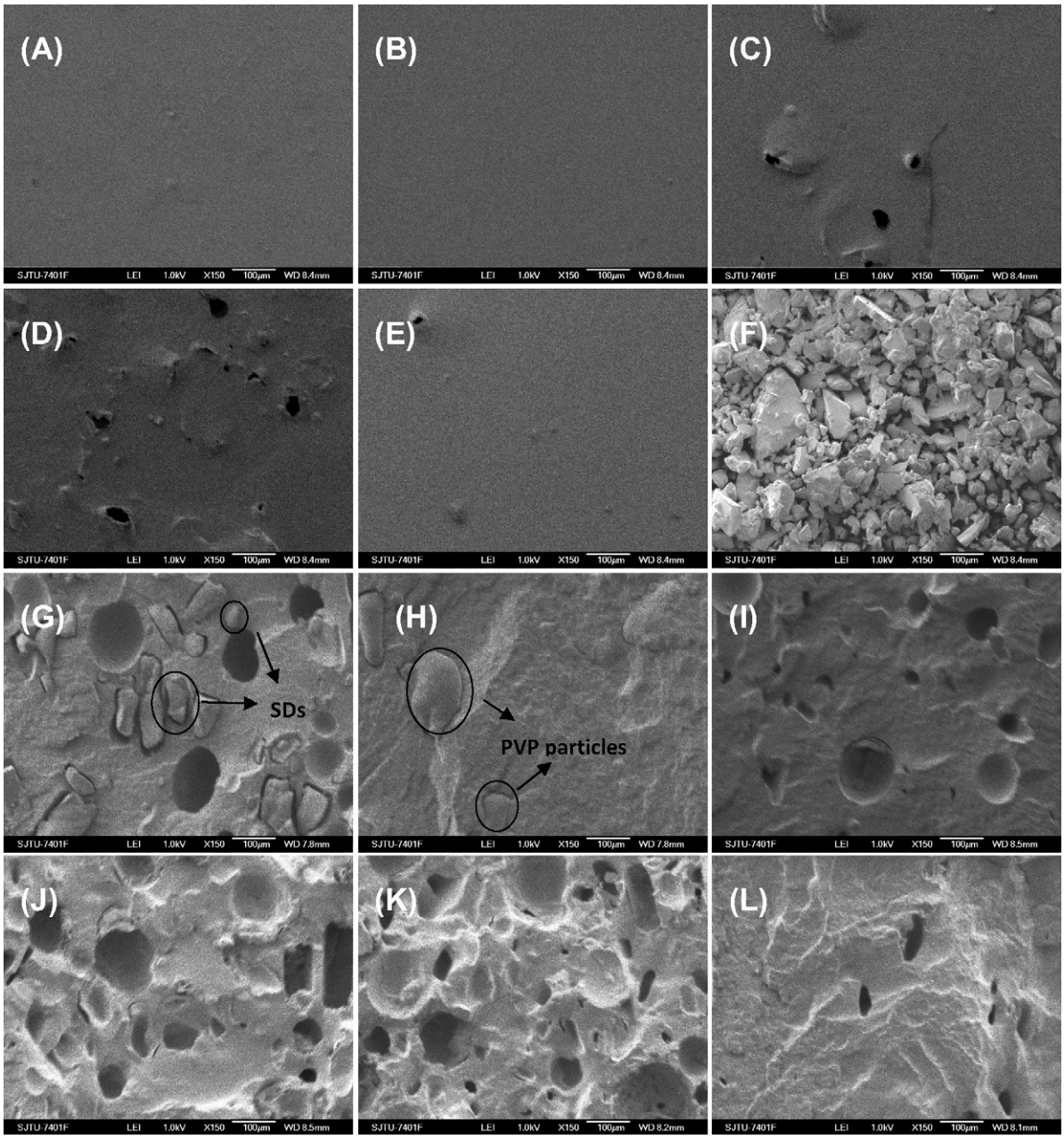

Fig. 9. Surface images of films before and after drug release: (A and D) Film 2 and (B and E) Film 5 at 0 day and 50 days, respectively; (C) Film 1 at 50 days. (F) SEM images of SD_1. Cross-section views of films before and after drug release: (G and J) Film 2 and (H and L) Film 5 at 0 day and 50 days, respectively; (I and K) Film 1 and Film 3 at 50 days, respectively.

3.5. Evolution of the surface morphologies and internal structures of films

SEM images in Fig. 9 show the microstructures of the PVP/PTX (1:1) SDs and the surface/cross-section morphologies of the films before or after drug release test. From SEM images of Fig. 9A and B, the surfaces of the prepared films were relatively smooth before drug release test. After drug release, various numbers of pores and protuberances emerged on the surfaces of the films with SDs (Fig. 9C and D), indicating that the release of SDs located on or near the surface of the PCL films might present pores. However, the surface of Film 5 (film with PM) had less pores or protuberances (Fig. 9E) than Films 1 and 2 (films with SDs), which could be attributed to the relatively slower release rate of PTX and PVP in the films (Fig. 6).

PVP/PTX (1:1) SDs were irregular with a size of 50–150 μm (Fig. 9F). The size of PVP particles mentioned in Section 3.1.4 were about 50–200 μm (Fig. 3B). As shown in Fig. 9G and H, obvious particles, whose sizes and shapes were similar to SDs and PVP particles, could be observed in the cross-section views of Films 2 and 5 before drug release study. Also, several circular bubbles could be observed in cross-section images before drug release test which was caused by the preparation method in our study. However, after drug release, many new pores were observed except the bubbles (Fig. 9I, J, K and L). The sizes and irregular shapes of the pores were also similar to the SDs and PVP particles, suggesting that the pores were left by the release of the two particles. What's more, the number of the pores was influenced by the release of different compositions of films: Film 3 with higher SD_1 content (Fig. 9K) had more pores than Film 1 with lower SD_1 content; Film 2 with SD

presented more pores than Film 5 with PM. These results correspond highly to the different drug release rate investigated in drug release test (Figs. 5 and 7B).

4. Conclusion

Treatments of paclitaxel with poly(vinyl pyrrolidone) on improving the drug release rate for film-based biodegradable stent drug delivery systems was proved to have a significant efficiency. The SDs were successfully prepared with a higher dissolution rate and no drug crystallinity. Compared to films with traditional PMs or pure PTX, the drug in films with SDs had a relatively higher drug release rate during the drug release test. The mechanisms of the drug release behavior of SDs and PMs were different from each other which were related to the existence of PTX in the films. Also, with a same PTX content, the higher content of PVP in films with SDs, the faster the drug was released. With these advantages, the solid dispersion technique provided a novel way to improve drug release behavior in biodegradable stent drug delivery systems.

Acknowledgements

This work was supported by National Natural Science Foundation of China (NSFC) (grant nos. 81171439 and 30901882), Key Program of Shanghai Science and Technology Committee (grant no. 10441902000) and Science and Technology Commission of Shanghai Municipality (grant no. 10441902002). The authors also gratefully acknowledge Instrumental Analysis Center of Shanghai Jiao Tong University for their technical support.

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