NAPROXEN-LOADED POLY(LACTIC ACID) MICROSPHERES: ELECTROSPRAY PREPARATION AND PROPERTIES

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Naproxen (NPX) is widely used to treat pain and inflammation but also causes gastrointestinal upset and ulcers. It is believed that further improvements in extended-release technology can mitigate these issues. Toward this end, we used electrospray to prepare NPX-loaded poly(lactic acid) (PLA) microspheres. The effects of NPX content on PLA/NPX composites were evaluated by characterization methods: scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Drug-releasing behaviors of pure NPX and NPX-loaded PLA microspheres were explored by ultraviolet–visible spectroscopy. The microspheres were smooth and well dispersed based on SEM analysis. NPX was molecularly dispersed and incorporated into the PLA matrix, as evidenced by the XRD, FTIR DSC, and TGA results. An in vitro study suggested that compared to pure NPX, the initial burst of NPX release was reduced in the first 8 h, followed by a sustained release. For PLA/NPX microspheres, as the content of NPX increased, the release amount of NPX from PLA/NPX composites increased. The release behavior of PLA/NPX microspheres with 10% NPX content reached 29.1% at the end of 24h. PLA/NPX electrospray microspheres have potential utility for drug delivery.

Keywords: Poly(lactic acid); Naproxen; Electrospray; Properties

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1. Introduction

Naproxen (NPX), a non-steroidal anti-inflammatory drug, has inflammatory, anti-thermic, and analgesic action [1]. However, many challenges exist with the use of NPX, including its burst release and poor water solubility [2]. With prolonged use of NPX, gastrointestinal irritation, ulcerogenicity, and renal injury may occur [3]. Therefore, it is of vital importance to develop drug delivery products to control drug release, give prolonged action, and decrease adverse effects. An approach that has been used previously is to form microspheres from the combination of NPX with a polymer matrix.

Many approaches have been attempted to design and fabricate NPX-loaded microspheres. Enhanced oral bioavailability was achieved with NPX-loaded polymer hybrid enteric microspheres prepared with the aid of molecular modeling and a modified solvent evaporation technique [4]. The excessive use of solvents may be a disadvantage of the method. Another approach has been the NPX-polymer precipitation using a supercritical antisolvent [5, 6], but the experimental setup and processes have complexities. Several studies have shown that the NPX delivery systems prepared by spray drying exhibited increased dissolution rates when compared to pure NPX [7]. The reported process uses a spray-drying temperature near 120 °C, which may affect the bioactivity of the substance.

Recently, the electrospray method has attracted much attention and provides an attractive means of fabricating particles for drug delivery. Advantages of the electrospray process include operational simplicity and ease of particle size control [8]. Poly(lactic acid) (PLA) is considered a renewable, biocompatible, and biodegradable polymer. The polymer is approved by the Food and Drug Administration (FDA) and has been widely used for the preparation of various controlled-release composites in drug delivery systems [9]. More importantly, the electrospray of PLA/NPX composites for drug delivery systems and release profiles from these composites have not yet been investigated. Therefore, we prepared PLA/NPX microspheres using the electrospray method and investigated the effects of the NPX content on the morphology, structure, thermal properties, and release behavior.

2. Experimental details

Materials

PLA (4032D) was bought from NatureWorks. NPX (98% purity), was produced by Macklin, China. Dichloromethane (DCM) was purchased from Sinopharm Chemical Reagent Co., Ltd, China. Phosphate buffer solution, PBS, BL601A, pH = 7.2–7.4, was purchased from Beijing Labgic Technology Co., Ltd.

Sample preparations

0.5 g PLA was dissolved in 10 mL DCM using magnetic stirring, followed by the addition of NPX (0.025, 0.0375, or 0.05 g). Homogeneous solutions formed and were named PLA/NPX 5%, PLA/NPX 7.5%, and PLA/NPX 10%, respectively. A 10-mL plastic syringe with a G20 stainless steel nozzle with an inner diameter of 0.6 mm was loaded with the prepared solutions and placed in a syringe pump. A high-voltage power source (DW-P303-1, TianJin Dongwen High Voltage Power supply Corp) was utilized to provide the electric field between the nozzle and the collector. A piece of aluminum foil was used to collect the deposited samples. Compositions of resulting PLA/NPX microspheres and electrospray parameters are listed in Table 1.

Table 1

Composition of prepared PLA/NPX solutions and electrospray parameters

Formulation	Ratio of NPX and PLA (w/w)	Flow rate(ml/h)	Voltage (kV)	Collection distance (cm)
F1	5:100	0.5	17.5	15
F2	7.5:100	0.5	17.5	15
F3	10:100	0.5	17.5	15

Drug release

Standard curve determination

Pure NPX was weighed and fully dissolved in a PBS solution, and a series of concentrations (0.01, 0.02, 0.04, 0.06, 0.08, and 0.1 mg/mL) were prepared and used to generate a standard curve using a UV–Vis spectrophotometer (U3900 Hitachi, Japan) at 331 nm. The equation of the standard curve was obtained by fitting the NPX concentration in the PBS solution against the absorbance data (Fig. 1). Fig. 1 shows the linear dependence and consistency with the Beer–Lambert law.

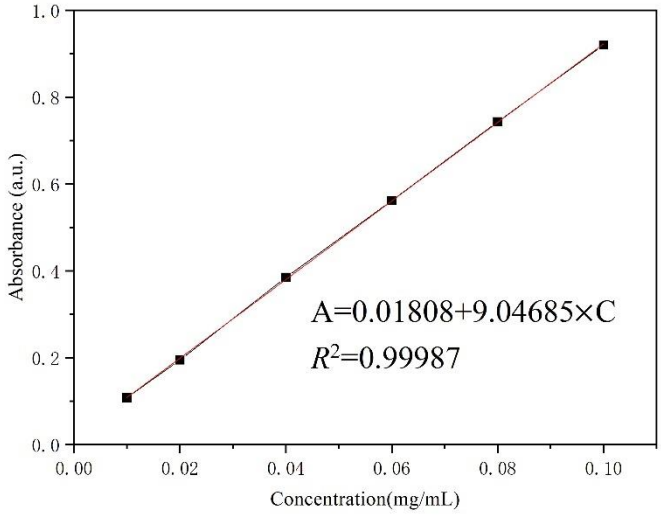


Fig. 1. Standard calibration curve of NPX at 331 nm

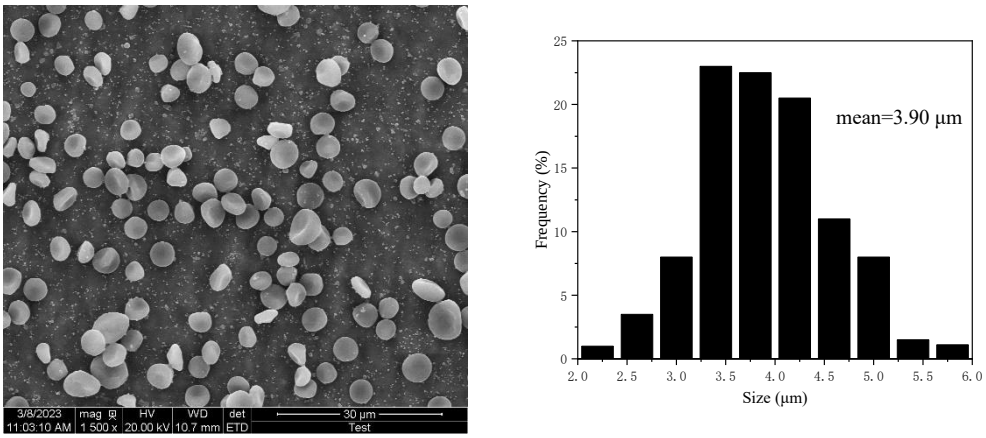
In vitro drug release profile

In vitro drug release of pure NPX and NPX from the PLA matrix was conducted in 100 mL of PBS buffer solution at 37 °C and a constant oscillation rate of 100 rpm using a thermostatic oscillator (TH2-312, Shanghai Jinghong Experimental Equipment Co., Ltd, China). 4 mL fluid samples were removed after 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 24 h. At each of these time points, 4.0 mL of fresh PBS medium was added. The NPX content was computed based on the NPX standard curve. Three replicate samples were analyzed for each group, and the results were averaged.

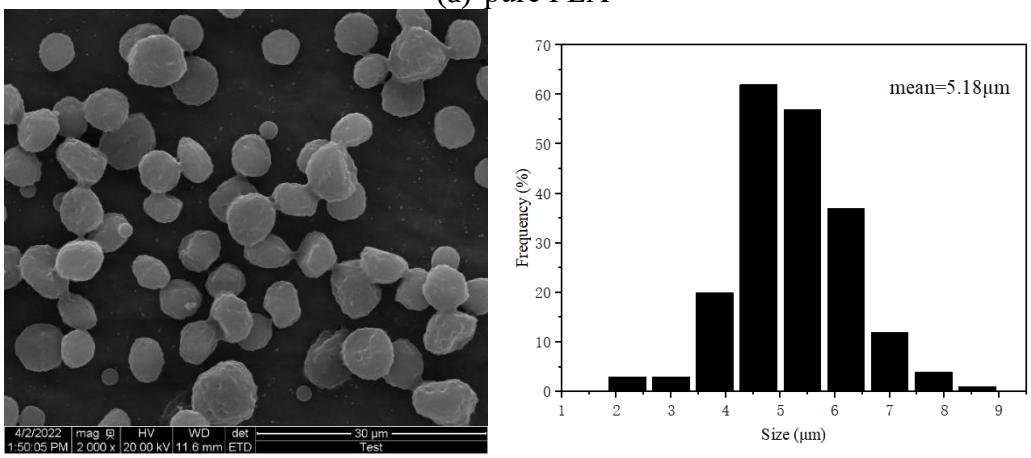
3. Result and discussion

Morphology

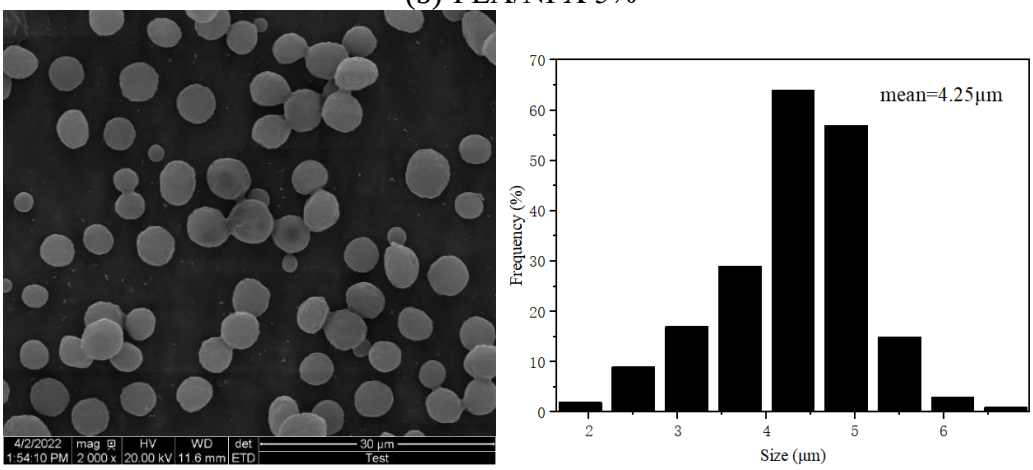
Fig. 2 shows representative SEM (FEI Quanta FEG 250) images of pure PLA and PLA/NPX microspheres with different contents of NPX prepared under electrospray conditions. The particle size distribution (Fig. 2) was determined using Nano Measurer 1.2 software by randomly selecting 200 microspheres from the SEM micrographs. As shown in Fig. 2, the resulting pure PLA and PLA/NPX particles were well dispersed, and most of the particles had a smooth surface and few structural defects. As shown in Fig. 2, mean particle sizes of 3.90, 5.18, 4.25, and 4.75 μm were obtained for pure PLA, PLA/NPX 5%, PLA/NPX 7.5%, and PLA/NPX 10%, respectively. The results indicated that the average particle sizes of PLA/NPX composites became larger than pure PLA but did not change significantly as a function of NPX content.



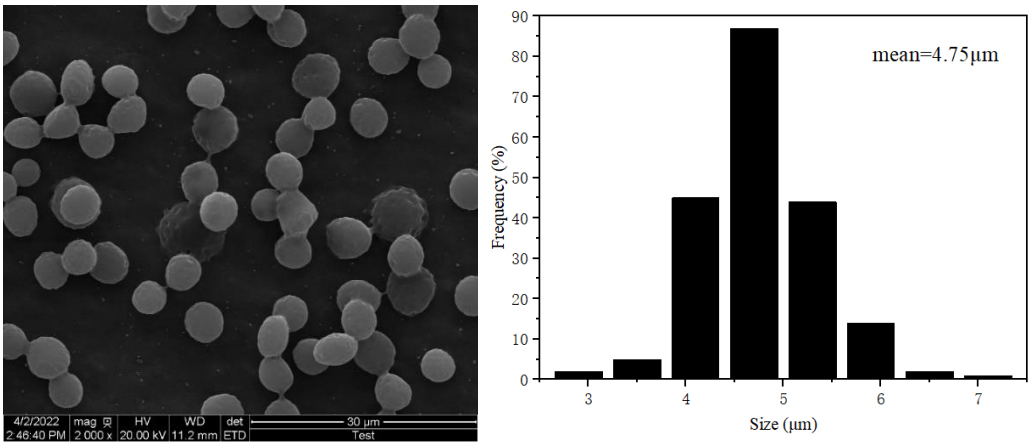
(a) pure PLA



(b) PLA/NPX 5%



(c) PLA/NPX 7.5%



(d) PLA/NPX 10%

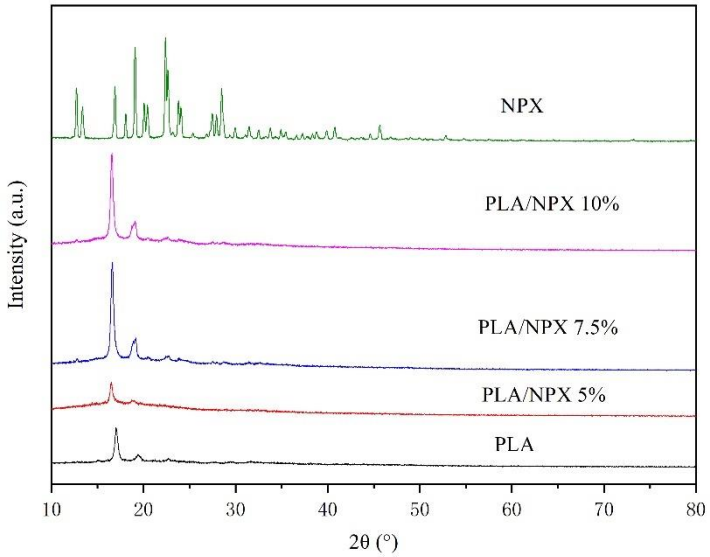
Fig. 2 SEM images and size distribution of prepared PLA/NPX composites with different NPX content: a) pure PLA, b) PLA/NPX 5%, c) PLA/NPX 7.5%, d) PLA/NPX 10%

Structure analysis

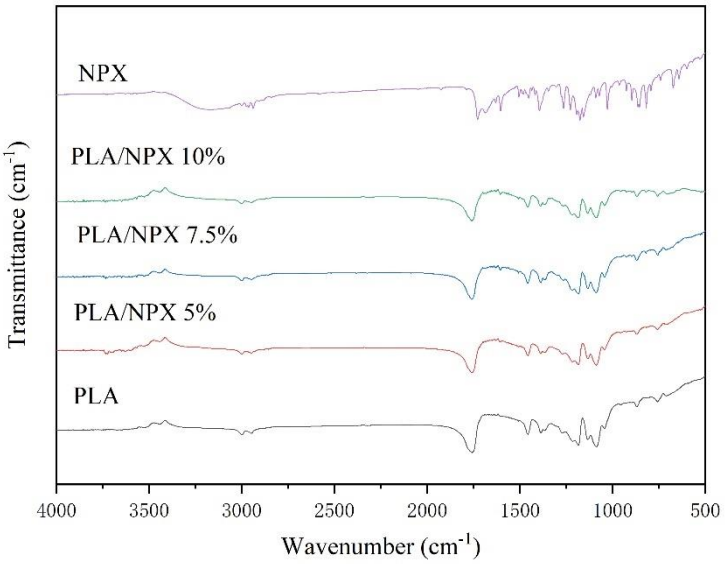
Fig. 3 shows the XRD (Rigaku Corporation SmartLab SE) and FTIR (Thermo Scientific Nicolet IS-10) measurements of NPX, PLA, and PLA/NPX composites. The main diffraction peaks of NPX were at 2θ = 2°, 9°, and 22°, indicating a polycrystalline structure of NPX. Pure PLA is a semi-crystalline polymer with a prominent peak at 2θ = 16°. As for NPX-loaded PLA composites prepared by electrospray method, similar XRD data were obtained with a weak and broad peak at 2θ = 16°, which indicated that these materials had an undefined structure. These results can be explained as follows. During the electrospray process, the receiving distance is relatively short, and the evaporation rate of the DCM solvent is fast, so there is not enough time for the PLA chains to crystallize before solidification, which gives rise to an amorphous structure [10]. There was no crystalline peak attributed to the NPX molecule on the XRD pattern for the PLA/NPX composites, indicating that NPX was predominantly incorporated into PLA in an amorphous form [11].

From the FTIR results of Fig. 3b, a strong absorption peak at 1750 cm^{-1} was observed for PLA, which was due to the C=O stretching vibration of the ester on PLA chains [12]. The peaks at 1181, 1084, and 1043 cm^{-1} were characteristic of the C-O-C absorption of PLA [13]. In pure NPX, carbonyl and carboxylic acid OH stretch absorptions at 1728 cm^{-1} and 3195 cm^{-1} were observed [14]. For the NPX-loaded PLA composites, the main peaks of PLA remained unchanged after adding NPX into the system. The main peaks of NPX were observed to decrease and even overlapped by that of PLA in the FTIR spectra of the PLA/NPX composites, which supported the conclusion that NPX was incorporated into the PLA matrix. As

shown in Fig. 3, no new characteristic peak was found, indicating no covalent changes during the electrospray process.



(a) XRD record



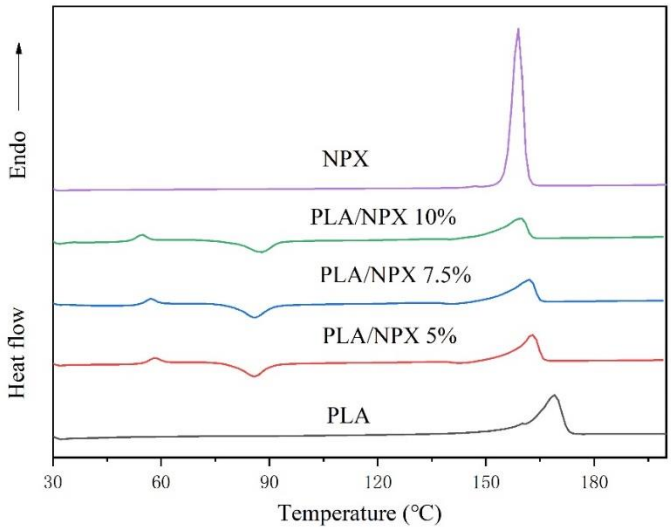
(b) FTIR results

Fig. 3 XRD and FTIR profiles of pure NPX, PLA, and PLA/NPX composites

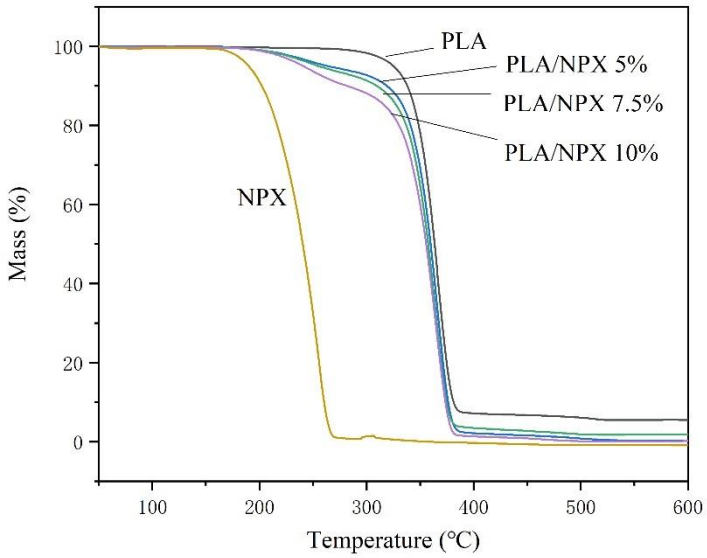
Thermal properties

Fig. 4 shows the thermal properties of pure PLA, NPX, and PLA/NPX composites measured by DSC (Mettler-Toledo DSC823e) and TGA (Mettler-Toledo TGA/SDTA851e) with a heating rate of 10℃/min. As shown in Fig. 4a, there is one main melting process for NPX. The peak melting temperature and melting enthalpy values (ΔH_m) were 159.0 °C and 144.8 J/g, respectively. Pure PLA showed a melting peak temperature of 169.0 °C with a ΔH_m of 90.7 J/g. The DSC curves of NPX-loaded PLA composites showed prominent melting processes, and the peak temperatures were 162.7, 161.9, and 159.8 °C corresponding to the PLA/NPX 5%, PLA/NPX 7.5%, and PLA/NPX 10% composites, respectively. The related ΔH_m values were 50.4, 49.0, and 42.6 J/g for the PLA/NPX 5%, PLA/NPX 7.5%, and PLA/NPX 10%, respectively. The peak temperatures and ΔH_m decreased slightly as the NPX content of the PLA/NPX composites rose. The DSC profiles of the PLA/NPX composites were similar to that of pure PLA, and the melting process of NPX was absent. The results showed that NPX changes from a crystalline state to an amorphous state in the PLA matrix during the electrospray process [15].

As seen in Fig. 4b, both neat NPX and PLA had one step of weight loss as the temperature rose in the ranges of 160~300 °C and 240~400 °C, respectively. For PLA/NPX composites, two steps of weight loss were observed, which could be attributed to the thermal degradation of NPX and the PLA matrix. In addition, the first thermal degradation of the PLA/NPX composites became more apparent when the content of NPX increased from 5% to 10%. The thermal degradation rate of PLA/NPX composites corresponding to that of NPX became much lower than those of neat NPX and PLA. These results suggested that the presence and dispersion of NPX within the PLA matrix resulted in improved thermal stability of NPX. The DSC and TGA profiles of the NPX-loaded PLA composites suggested that NPX was well dispersed in PLA.



(a) DSC



(b) TGA

Fig. 4 DSC and TGA thermograms of pure PLA, NPX, and PLA/NPX composites

Release behavior

As shown in Fig. 5, the pure NPX had a burst release or approximately 75% during the first 8 h, whereas the PLA/NPX formulations had significantly less release during the first 8 h and a relatively constant release from 8 h to 24 h.

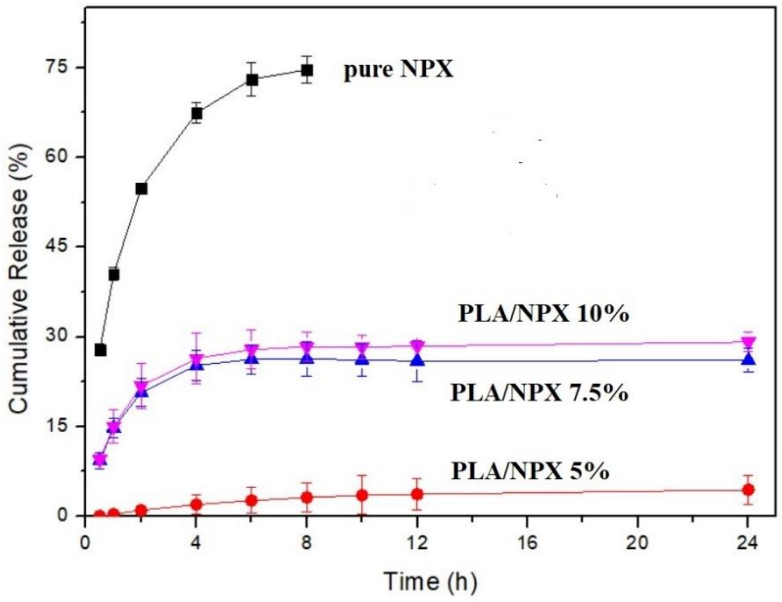


Fig. 5 The cumulative drug release of pure NPX and PLA/NPX composites

In PLA/NPX 5%, only 4.4% of NPX was released over 24 h. This value is close to what was observed for an electrospun PLA nanofiber loaded with 5% of ceftriaxone or cefpodoxime [16]. The low release of NPX could be attributed to the fact that most of the NPX was encapsulated inside of PLA and the interaction between PLA and NPX delayed the release of NPX. As the NPX content increased, the release rate during the first hours and cumulative release of NPX from the PLA/NPX matrix increased. The cumulative release amounts of NPX from the PLA/NPX composites were 26.1% and 29.1% at 24 h for PLA/NPX 7.5% and PLA/NPX 10%, respectively. As the NPX content increased, more NPX may be found on the outer surface of the PLA/NPX composites. This can quickly diffuse in the PBS medium, and a large concentration gradient could be generated [17]. This resulted in an improved release rate and cumulative release.

4. Conclusions

In the present study, NPX-loaded PLA microspheres were prepared using an electrospray method. The effects of NPX content on the morphology, structure, thermal properties, and release behavior of the PLA/NPX composites were explored. The prepared microspheres were smooth, well dispersed, and had few structural defects by SEM. NPX was molecularly dispersed into the PLA matrix, as evidenced by XRD, FTIR, DSC, and TGA measurements. *In vitro* drug release profiles showed that the PLA/NPX matrix gave a decreased release rate during the first 8h and prolonged drug release over 24 h. With an increase in NPX content, the

drug release rate of PLA/NPX composites increased. Approximately 29.1% of the drug was delivered over 24 h for PLA/NPX 10%. Further studies are planned regarding the formulations design and optimization of different polymers for sustained release of NPX.

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