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Preparation of PLLA/PLGA microparticles using solution enhanced dispersion by supercritical fluids (SEDS)

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Abstract

In this work, poly(L-lactic acid)/poly(lactide-*co*-glycolide) (PLLA/PLGA) microparticles were prepared using the technique of solution-enhanced dispersion by supercritical fluids (SEDS). For comparison, separate PLLA and PLGA microparticles were also produced by the same SEDS process. The produced microparticles were characterized by scanning electron microscopy, laser particle size analyzer, X-ray diffraction, differential scanning calorimetry, Fourier transform infrared spectroscopy, and gas chromatography. Results indicate that PLLA/PLGA microparticles possess sphere-like shapes with smooth surfaces. The mean particle size of PLLA/PLGA microparticles ranges from 1.76 to 2.15 μm, depending on the feeding ratio of PLLA to PLGA used in the SEDS process. The crystallinity of PLLA/PLGA microparticles decreases after the SEDS processing, so that the produced microparticles are in an amorphous state. Pure PLGA was hard to precipitate in small, fine microparticle form without the presence of PLLA. A model drug, paclitaxel, was encapsulated into PLLA/PLGA microparticles by the same SEDS process, and the in vitro release rate of paclitaxel from these PLLA/PLGA composites could be modulated by variation of the mixing ratio PLLA:PLGA. The prepared microparticles have negligible residual organic solvent. Drug-loaded PLLA/PLGA microparticles produced by SEDS have potential as an advanced colloidal suspension for pharmaceutical applications.

Keywords: Supercritical CO_2; Poly(L-lactic acid) (PLLA); Poly(lactide-*co*-glycolide) (PLGA); Microparticles; Drug carrier

1. Introduction

In the past decade, supercritical fluid (SF) techniques have gained significant attention in many fields, such as extraction, chromatography, chemical reaction engineering, organic and inorganic synthesis, waste management, material processing (nanomaterials, nanostructured materials, thin films, coating, particles), porous materials, and pharmaceutical applications materials [1–8]. SFs possess low viscosity (matrix penetration as gas-like), relatively high density (solute solubilization as liquid-like), high diffusion, and near-zero surface tension. At the critical point, the density of the gas phase becomes equal to that of the liquid phase, and the interface between gas and liquid disappears. Supercritical CO_2 ($scCO_2$) is the most widely used SF because of its relatively low critical conditions ($T_c = 31.1\,°C$, $P_c = 7.38$ MPa), nontoxicity, nonflammability, and low price [9,10]. Today, particle processing is one of the major developments of supercritical fluid applications in industrial fields such as the chemistry, pharmaceutical, cosmetic, and agriculture and food industries, especially in pharmaceutical research. It not only shows promise in pharmaceutical regard but also accommodates the principles of green chemistry. Various modified supercritical techniques based on different nucleation and growth mechanisms of precipitating particles have been developed [11]. The well-known techniques for particle formation using $scCO_2$ include the rapid expansion of supercritical solutions (RESS) [12,13] and a variety of antisolvent processes such as gas antisolvent (GAS) [14], aerosol solvent extraction systems (ASES) [15], particles from gas-saturated solutions (PGSS) [16], supercritical antisolvent (SAS) processes [17–19], and solution-enhanced dispersion by supercritical fluids (SEDS) [20].

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The SEDS process is a modified SAS process, in which the $scCO_2$ and liquid solution are simultaneously introduced into the high-pressure vessel using a specially designed coaxial nozzle. When the droplets contact the $scCO_2$, a rapid mutual diffusion at the interface of the droplets and the $scCO_2$ takes place instantaneously, inducing phase separation and supersaturation of the polymer solute, thus leading to nucleation and precipitation of the polymer particles [11]. It was developed by the Bradford University in order to achieve small droplet size and intense mixing of SF and solution for increasing mass transfer rate at the interface [21,22]. The SF is used both as an antisolvent for its chemical properties and as a 'spray enhancer' by mechanical effects. The temperature and pressure, together with accurate metering of flow rates of solution and SF, provide uniform conditions for particle formation. The morphology and particle size of the product can be controlled by employing optimum process parameters [9,23].

Poly(L-lactide) (PLLA) and poly(lactide-*co*-glycolide) (PLGA) have been widely studied in drug delivery systems because of their excellent biocompatibility and biodegradability [24–26]. There have been many reports on the preparation of PLLA microparticles by $scCO_2$ [27–30]. In our previous work [31], PLLA microparticles were also successfully prepared by the SEDS process, and the effect of various processing parameters (pressure, temperature, concentration and flow rate of PLLA solution, and molecular weight of PLLA) on the mean particle size and morphology of PLLA microparticles was systematically investigated. However, there are few reports about the formation of PLGA microparticles using the SEDS technique. Ghaderi et al. reported that DL-PLG microparticles were produced by the SEDS process [32,33], but the mean volumetric diameter was beyond 130 μm, and a strong tendency to agglomerate was also observed. Therefore, it is more difficult to precipitate and form small microparticles from amorphous polymers than from semicrystalline polymers by SEDS. For a semicrystalline polymer, PLLA may easily and quickly form particles in the SEDS process. But another problem might be encountered: a higher crystallinity of PLLA results in a lower degradation rate in vivo, compared to PLGA [34].

The respective limitations of PLLA and PLGA motivated us to prepare a new biodegradable matrix polymer, which can potentially be applied in drug carriers for controlled drug delivery. Therefore, in this work, it is interesting to study the co-precipitation of PLGA with the addition of PLLA for obtaining PLLA/PLGA microparticles by the SEDS process. PLLA and PLGA have different structural properties and degradation rates [35]. By mixing PLLA and PLGA, the degradation rates of microparticles might be modulated, thus further changing the release property of drugs from these microparticles. To investigate this effect of different PLLA:PLGA ratios in the microparticles on the drug release properties, a model drug, paclitaxel (an anticancer drug), was encapsulated into the PLLA/PLGA, and an in vitro release study was also performed. The drug-loaded microparticles would potentially be made into advanced colloidal suspensions for pharmaceutical applications.

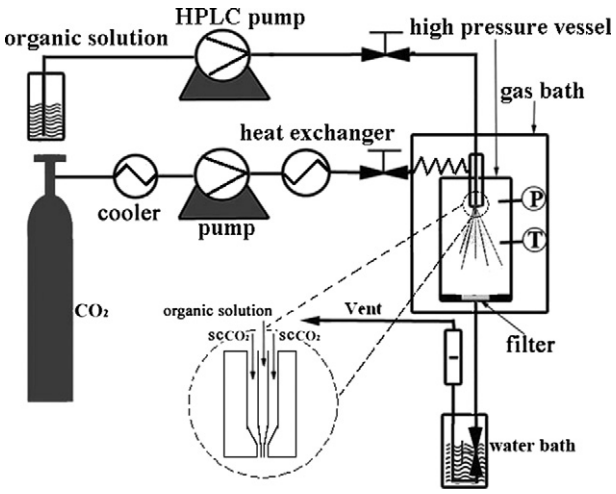


Fig. 1. The schematic diagram of the apparatus for the SEDS process.

2. Materials and methods

2.1. Materials

PLLA ($M_w = 100$ KDa) and PLGA (LA:GA 50:50; $M_w = 100$ KDa) were purchased from the Institute of Medical Polymers of Shandong (Jinan, China). CO_2 with 99.9% purity was supplied by Chengdu Tuozhan Gas Co. Ltd. (Chengdu, China). Dichloromethane (DCM) and all other compounds were of analytical purity. Paclitaxel was purchased from Meilian Pharmaceutical Co. Ltd. (Chongqing, China).

2.2. Apparatus and SEDS process

The experimental apparatus of the SEDS process used for the formation of microparticles consists of three major components: a CO_2 supply system, an organic solution delivery system, and a high-pressure vessel. The $scCO_2$ and the polymer organic solution were separately fed to the high-pressure vessel through different inlets located on top of the high-pressure vessel and continuously discharged from the bottom. The high-pressure vessel for microparticle precipitation was a cylindrical vessel of 500 ml. The schematic graph of the SEDS procedure is shown in Fig. 1. First, CO_2 fed from a CO_2 cylinder was cooled down to about 0 °C by a cooler (Maneurop, France) to ensure the liquefaction of the gas and also to prevent cavitation. Then, liquefied CO_2 was delivered by a high-pressure metering pump to the high-pressure vessel. The feed rate of $scCO_2$ was controlled by this metering pump by regulating the frequency of the piston. Before entering the high-pressure vessel, the liquefied CO_2 was preheated to the desired operating temperature using a heat exchanger. The high-pressure vessel was simultaneously incubated in a gas bath to keep the temperature constant during the experiment. The pressure in the high-pressure precipitation vessel was monitored by a manometer. It was regulated by a downstream valve located at the exit of the high-pressure vessel. A rotameter located downstream of the valve was used to measure the flow rate of $scCO_2$. When the desired pressure in

the high-pressure vessel was reached, a steady flow of $scCO_2$ was kept by adjusting the downstream valve. After the desired pressure and temperature were both stabilized, the polymer solution was delivered into the high-pressure vessel through a stainless steel coaxial nozzle (ID 800 μm, and the nozzle of polymer solution with ID 330 μm was used in this study) using a HPLC pump (P3000, Knauer, Germany) at a flow rate of 0.5 ml/min. On entering the high-pressure precipitation vessel full of $scCO_2$, a rapid mutual diffusion at the interface between the $scCO_2$ and the polymer solution occurred instantaneously; the organic solvent was extracted into the $scCO_2$, resulting in supersaturation of the polymer solute and the formation of solid microparticles in the vessel. After the delivery of polymer solution was finished, the pure organic solvent was delivered for 20 min at a flow rate of 2 ml/min to avoid blockage of the nonreturn valve of the HPLC pump. Simultaneously, fresh CO_2 continued to flow for 30 min to remove the residual organic solvent in the products. This step is necessary and important because the DCM arising from phase separation between the organic solvent and $scCO_2$ would redissolve the polymer on the surface of particles during later depressurization. During the process of washing, the system operating conditions were maintained as described before. After the washing process was completed, the CO_2 flow was stopped and the high-pressure vessel was slowly depressurized to atmospheric pressure. Then the products were collected.

In this work, all the experiments were performed with the following process parameters: $scCO_2$ flow rate 300 ml/min, flow rate and concentration of polymer solution 0.5 ml/min and 5 mg/ml respectively, pressure of the high-pressure vessel fixed at 12 MPa and temperature at 33 °C. These process parameters were obtained according to our previous studies [31,36]. In this work, PLLA/PLGA microparticles and drug-loaded microparticles were prepared by the SEDS process according to these parameters. For comparison, separate PLLA and PLGA microparticles were also prepared by the same process.

2.3. Preparation of microparticles

A total of 200 mg of PLLA and PLGA (three ratios of PLLA to PLGA, i.e., 1:1, 1:2, and 1:4 w/w) polymer was dissolved in 40 ml DCM to obtain 5 mg/ml PLLA/PLGA solution under continuous magnetic stirring. Similarly, pure PLLA or PLGA polymer solution at a concentration of 5 mg/ml was also prepared by dissolving 200 mg PLLA or PLGA polymer in 40 ml DCM solvent. Then the polymer solution was delivered into the high-pressure vessel by a HPLC pump, and microparticles were immediately precipitated from the solution in the SEDS process. Microparticles were collected after the SEDS process, and their related properties were also measured.

Paclitaxel with 4 times the total mass of PLLA and PLGA (i.e., the ratio of drug to polymer was 1:4; the mass ratio of PLLA to PLGA was 1:1, 1:2, and 1:4) was dissolved in DCM solvent, and the mixture solution experienced the same SEDS process.

2.4. Characterization of microparticles

Surface morphologies of samples were observed by scanning electron microscopy (SEM) (JSM-5900LV, Japan). Samples were coated with gold and palladium using a vacuum evaporator and observed at accelerating voltage 20 kV.

The mean particle size (PS) and particle size distribution (PSD) of each sample was determined using a laser particle size analyzer (Rise-2008, Shandong, China). Approximately 5-mg microparticles were suspended in the sample cell filled with distilled water. Before measurement, the suspension was dispersed by ultrasonic waves with power 100 W for 1 min. Next, the rotative pump started at 1250 rpm to circulate the sample's suspension. Analytic software was automatically used to assay the mean particle size and PSD. PSD is expressed by span, which can be calculated by the following equation: $(D_{90} - D_{10})/D_{50}$ (according to *the Pharmacopeias of the People's Republic of China* (2000) and Ref. [37]). The smaller the span is, the narrower the PSD is.

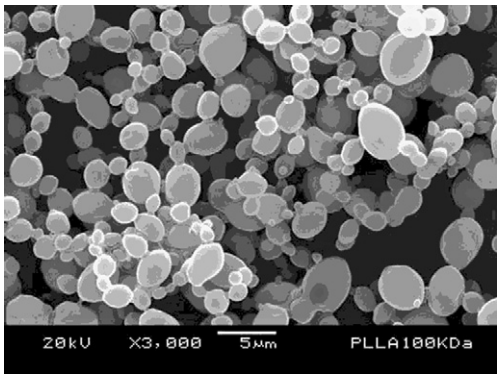
Differential scanning calorimetry (DSC) (STA449C, Netzsch, Germany) was used to analyze the effect of the SEDS process on the thermal properties of polymer samples. Approximately 10-mg samples were heated in a sealed aluminum pan under nitrogen (investigated temperature range 0 to 300 °C, heating rate 5 °C/min).

X-ray diffraction (XRD) of the samples was carried using a Philips X'Pert MDP diffractometer. The measurement was performed in the range of 10°–40° with a step size of 0.02°. Fourier transform infrared (FTIR) spectra were measured using a NEXUS 670 spectrometer. Approximate 1 mg of fine microparticles was ground with KBr and pressed into a pellet for IR characterization.

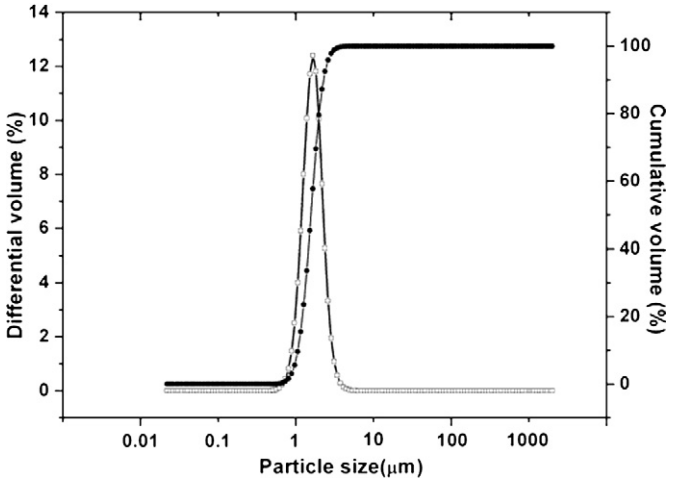
The residual DCM in the PLLA/PLGA microparticles was analyzed using gas chromatography (GC) (Agilent 6850A, USA). A sample of 200 mg of the products without any further treatment was accurately weighed, and the analysis was performed by the static head-space method. The method of external standardization was used to calculate the residual solvent content.

2.5. Drug loading and in vitro drug release studies

An accurately weighed 3.0 mg of paclitaxel–PLLA/PLGA microparticles was first dissolved in 1 ml of DCM, and then 3 ml of acetonitrile:water (50:50, v:v) mixture was added to extract the paclitaxel. Subsequently a nitrogen stream was introduced to volatilize DCM till a clear solution was obtained. The clear solution was put into a vial for high-performance liquid chromatography (HPLC) (Agilent 1100 series) assay following the methodology and procedures reported at length in the literature [38]. To investigate the effect of different ratios of PLLA to PLGA on drug release properties, in vitro drug release studies were performed in triplicate. A quantity of 20 mg paclitaxel-PLLA/PLGA microparticles was replaced in the pretreated dialysis bag (Stone container corporation, North Chicago, USA) that was hung in 100 ml phosphate buffered saline (PBS, pH 6.8, containing 0.1% (w/v) Tween 80 and

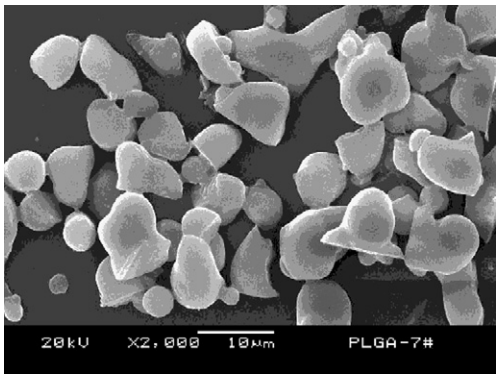


(a)

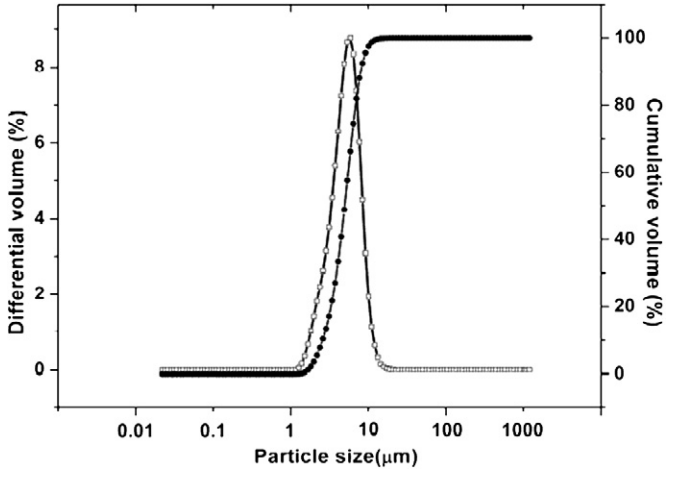


(b)

Fig. 2. The SEM morphology of PLLA microparticles (a) and the PS and PSD (b). The cumulative and differential PSDs are presented on the logarithmic scale.



(a)



(b)

Fig. 3. The SEM morphology of PLGA microparticles (a) and the PS and PSD (b). The cumulative and differential PSDs are presented on the logarithmic scale.

0.02% Na_3N). The glass vial containing PBS was incubated in a shaking water bath at 37 °C at 60 rpm. At predetermined time intervals, 10 ml of solution was periodically removed. To maintain the original PBS volume of 100 ml, 10 ml of fresh PBS was periodically supplied. The release concentration of paclitaxel in the release medium was determined by HPLC, which is described elsewhere [38]. The release curve was plotted according to the cumulative release percentage of paclitaxel (%, w/w). Each experiment was carried out in triplicate.

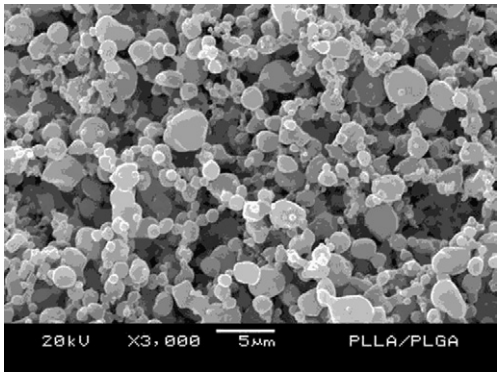
3. Results and discussion

3.1. Morphology and PS of PLLA, PLGA, and PLLA/PLGA microparticles

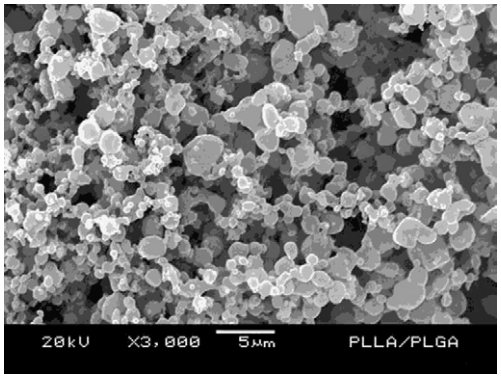
SEM photomicrograph of PLLA microparticles is shown in Fig. 2a. It is clearly seen that discrete PLLA microparticles are sphere-like in shape with smooth surfaces. The PS and PSD of the PLLA microparticles are shown in Fig. 2b. PLLA microparticles present a small PS of 1.63 μm and a narrow PSD of 0.777. Fig. 3a shows the SEM of PLGA microparticles. Though the surface is smooth, the shape of PLGA microparticles demonstrates irregularity. Fig. 3b shows that the PS and PSD of PLGA microparticles are about 8.55 μm and 1.36, respectively.

Therefore, it can be seen from Figs. 3a and 3b that irregular PLGA microparticles were formed and the PS of PLGA was larger than that of PLLA microparticles. The PS is a fundamental parameter of microparticles used for drug carriers, relating to the method of administration of drugs. For PLGA, the amorphous property is the essential factor in forming large particles in the SEDS process [32]. Therefore, it is more difficult to form fine microparticles by SEDS from amorphous polymers than from semicrystalline polymers. One of the major difficulties is the interaction between the $scCO_2$ and the amorphous polymers, due to the slight solubility of the CO_2 in amorphous materials. The CO_2 acts as a plasticizer in this process [33]. Co-solvent interaction effects might also happen. These effects can make it difficult for the solution droplet to achieve immediate supersaturation, and thus make it hard for small microparticles to be formed [31].

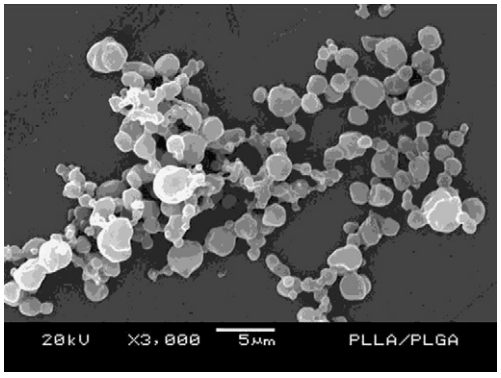
In this work, co-precipitation of PLGA with the addition of PLLA was mainly investigated. SEM of microparticles shows that PLLA/PLGA microparticles have a sphere-like shape with a smooth surface (Fig. 4), but a tendency to agglomerate is also observed with the decrease of PLLA feeding ratio in the PLLA/PLGA. When the feeding ratio of PLLA to PLGA was 1:1, the microparticles possessed a sphere-like shape with a smooth surface and less agglomeration (Fig. 4a). However, the



(a)



(b)



(c)

Fig. 4. SEM morphology of PLLA/PLGA microparticles prepared at different ratios of PLLA to PLGA: (a) 1:1; (b) 1:2; (c) 1:4.

PLLA/PLGA microparticles became agglomerated and irregular (Fig. 4c) when the ratio of PLLA to PLGA was 1:4. The PS and PSD of three PLLA/PLGA groups are shown in Fig. 5, indicating that the PS of PLLA/PLGA (1:1) is 1.76 μm with a PSD of 0.918, and the PS of 1:2 group is 1.91 μm with a PSD of 0.927. With the decrease of PLLA fraction, the PS increases and the PSD becomes wide. For the PLLA/PLGA = 1:4 group, the PS increases to 2.15 μm with a PSD of 1.056. After the t-test, there is a significant difference between the PS of these three groups ($p < 0.05$).

3.2. Characterizations of PLLA/PLGA microparticles

To investigate the crystalline changes of microparticles after SEDS processing, XRD analysis was performed. Figs. 6a and 6b show typical diffraction patterns of semicrystalline PLLA and amorphous PLGA, respectively. The main peak at about 15.41° in Fig. 6a shows the presence of semicrystalline domains of PLLA specimens, and Fig. 6b shows the broad peak between 15° and 25° of PLGA, indicating the amorphous property of PLGA. But significant disappearance of these peaks is observed in PLLA/PLGA (1:1) (Fig. 6d) as compared to the PLLA + PLGA (1:1 w/w) in the physical mixture (Fig. 6c). These results clearly show a notable decrease in crystallinity of the PLLA/PLGA microparticles after processing in $scCO_2$ (Fig. 6d), suggesting that the resulting products are in an amorphous state.

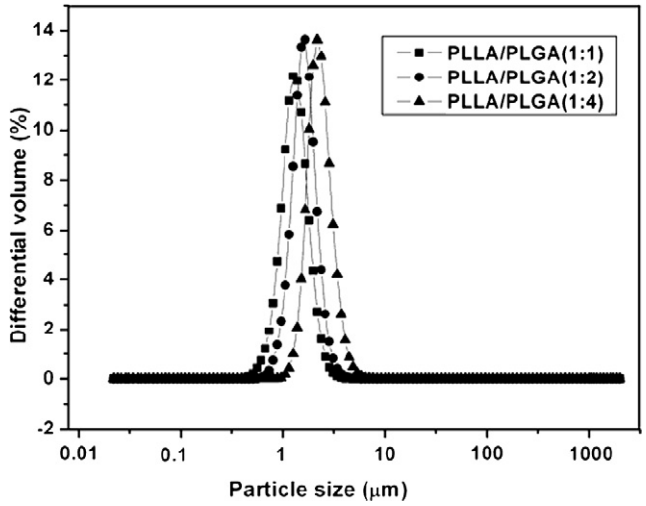


Fig. 5. The PS and PSD of PLLA/PLGA microparticles prepared at different ratios of PLLA to PLGA. The differential PSD is presented on the logarithmic scale.

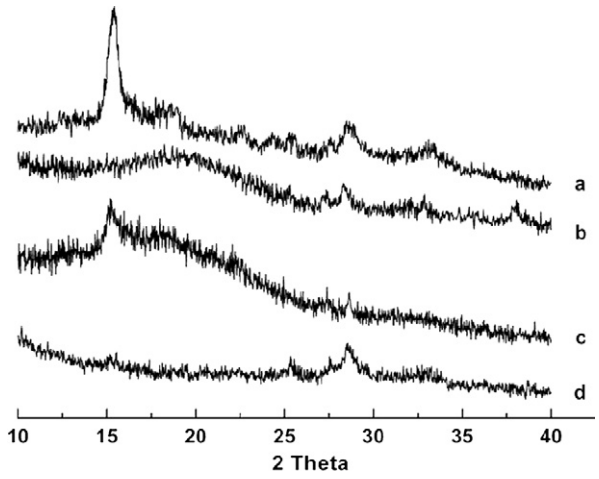


Fig. 6. X-ray diffraction pattern: (a) PLLA microparticles, (b) PLGA microparticles, (c) PLLA + PLGA (1:1, w/w) in physical mixtures, and (d) PLLA/PLGA microparticles (1:1, w/w) by the SEDS process.

FTIR was used to study the chemical composition of the microparticles prepared by the SEDS process. Figs. 7c and 7d show the FTIR spectra in the region 400–4000 cm^{-1} of PLLA + PLGA (1:1 w/w) in the physical mixture and the microparticles (1:1 w/w) prepared by the SEDS process, respectively. After the SEDS process (Fig. 7d), the main bands hardly change, com-

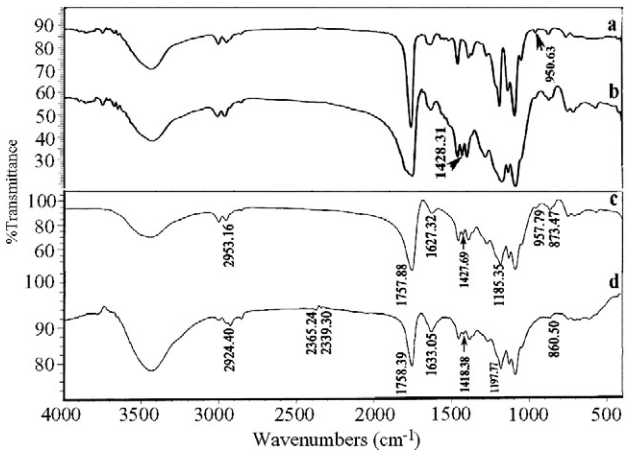


Fig. 7. FTIR of pure PLLA (a), pure PLGA (b), PLLA + PLGA (1:1 w/w) in physical mixture (c), and PLLA/PLGA (1:1 w/w) prepared by the SEDS process (d).

pared with the physical mixture of PLLA + PLGA (Fig. 7c), which indicates that PLGA and PLLA exist in the resulting products. This could be supported by the following results: One difference between PLLA and PLGA is the existence of the 1428.31 cm^{-1} peak presented in PLGA, which is absent in PLLA (Fig. 7a) [39]. This peak corresponds to the C–H deformation in the –O–CH_2– structure, which is present only in the glycolic acid structure of PLGA. In Fig. 7d, the existence of the peak at 1418.30 cm^{-1} can be observed, indicating that the PLGA is present in the resultant products. PLLA also exhibits a peak at 950.63 cm^{-1} (Fig. 7a), which is absent in the amorphous PLGA (Fig. 7b) [39]. There is a little difference at this position between PLLA + PLGA prepared in the physical mixture (Fig. 7c) and PLLA/PLGA microparticles prepared by the SEDS process (Fig. 7d).

Fig. 8 shows the DSC curves of PLLA, PLGA, and PLLA/PLGA microparticles (1:1 w/w) prepared by the SEDS process. Original PLLA is observed as a semicrystalline polymer with a melting temperature (T_m) of about 179.0 °C, and a glass transition temperature (T_g) is also observed at 79.0 °C (Fig. 8a). After the SEDS process, the T_m is shifted to 142.9 °C, and the T_g also to 61.3 °C, implying that the crystallinity had slightly decreased through the SEDS process. This result is consistent with the XRD results. Fig. 8b shows clearly that the original PLGA (50:50) is an amorphous copolymer with a glass transition temperature (T_g) at 55.2 °C. After the SEDS process, the T_g is shifted to 51.1 °C, implying that the amorphous state of PLGA (50:50) was slightly changed. The curve of PLLA/PLGA microparticles shows two glass transition temperatures at 62.5 and 40.9 °C, representing the T_g's of PLLA and PLGA, respectively, but the T_g is found to shift to lower temperature than that of original polymers. There is an endothermic peak at 156.9 °C that represents the melting point of PLLA (Fig. 8c), but the peak height is lower than that of pure PLLA. These results show that in the co-precipitated PLLA/PLGA microparticles, PLLA and PLGA are both present in the final products. This also shows that PLGA was able to precipitate in fine particle form in the presence of PLLA. The state of products is more amorphous form than crystalline. Further, the SEDS process slightly decreased the T_m of PLLA and the T_g of two polymers.

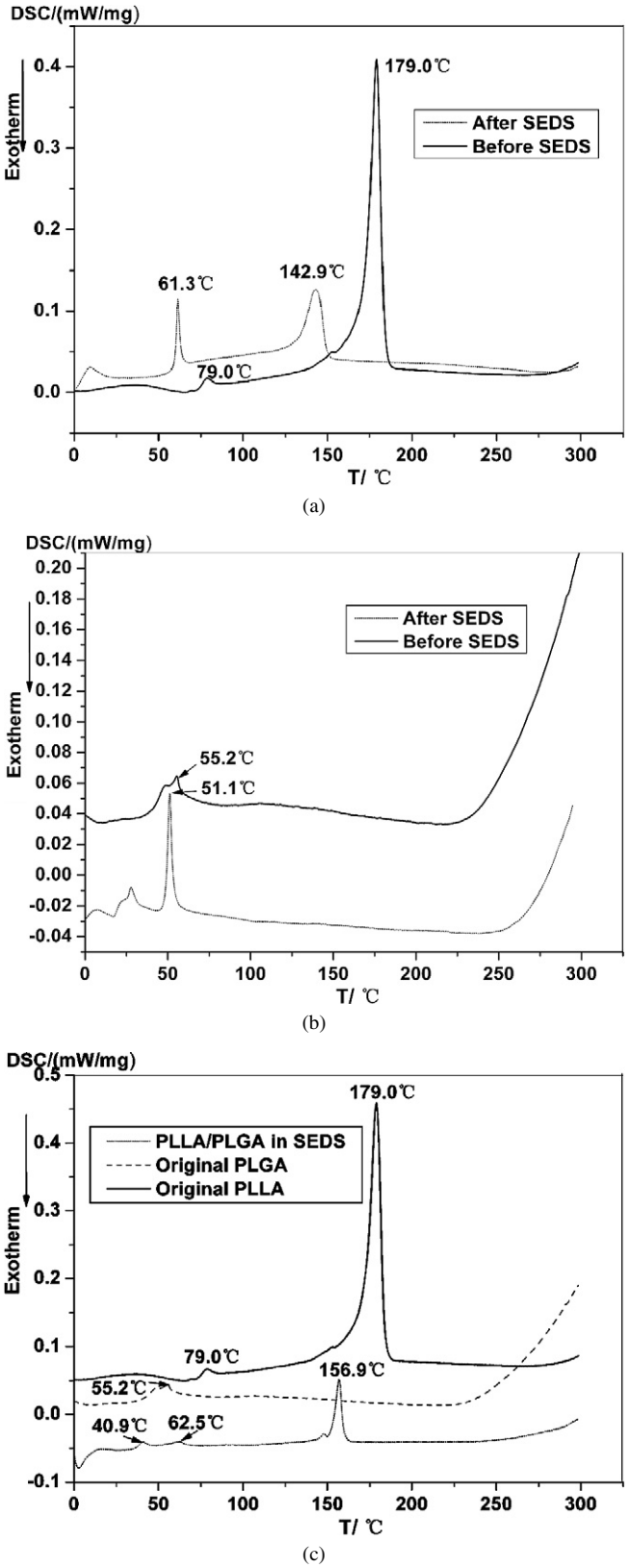


Fig. 8. DSC curves for (a) PLLA, (b) PLGA, and (c) PLLA/PLGA (1:1, w/w) microparticles produced by the SEDS process.

Table 1
The composition of blend microparticles calculated by ^{1}H NMR spectrum and drug loading of drug-loaded microparticles investigated by HPLC

Microparticles	The ratio of PLLA to PLGA	Drug loading (%)
PLLA/PLGA (1:1)	1:0.90	–
PLLA/PLGA (1:2)	1:1.81	–
PLLA/PLGA (1:4)	1:3.21	–
Paclitaxel–PLLA/PLGA (1:1)	–	16.33
Paclitaxel–PLLA/PLGA (1:2)	–	16.11
Paclitaxel–PLLA/PLGA (1:4)	–	14.71

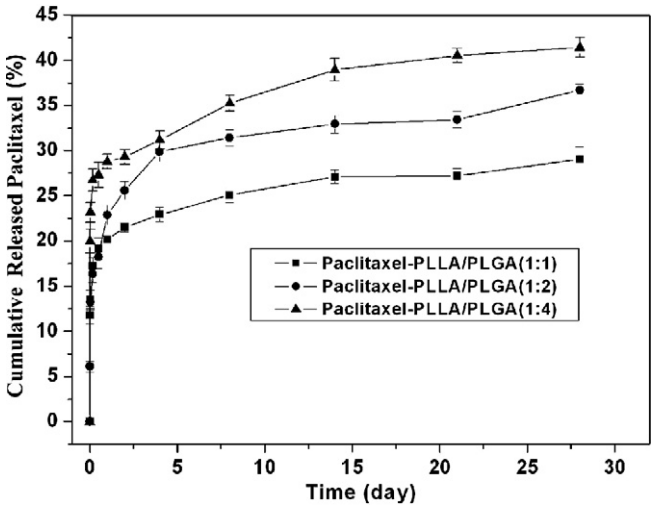


Fig. 9. In vitro cumulative release profiles of paclitaxel from different PLLA/PLGA microparticles.

To further quantify PLLA and PLGA in PLLA/PLGA microparticles after the SEDS process, ^{1}H NMR analysis (Bruker 400, Germany) was performed on a 400-MHz Bruker in $CDCl_3$. Results indicate that the mass ratio of PLLA to PLGA after the SEDS process is not quite the same as the original feeding ratio, as shown in Table 1 (the ^{1}H NMR spectra are shown in the supplementary material). This indicates that PLLA and PLGA from DCM in the SEDS process were not precipitated according to the original feeding ratio. The precipitation properties of these microparticles may be related to the physicochemical properties and the thermodynamic interaction of the polymers. The thermodynamic description of this four-component system (DCM, $scCO_2$, PLLA, and PLGA) is rather complicated. Different mass transfer rate and interface diffusion ability of the $scCO_2$ into the liquid phase usually make the diluted polymer solution split into a polymer-rich phase and a solvent-rich phase [40]. A qualitative thermodynamic interpretation of these phenomena can be based on the competition of enthalpy and entropy contributions to the Helmholtz energy of mixing [41].

3.3. In vitro release study

The successful preparation of PLLA/PLGA microparticles has promising applications in preparing the microparticles encapsulating active ingredients (drug) that can be used as an advanced colloidal suspension for controlled drug release application (the drug loading was shown in Table 1). Fig. 9 indicates the in vitro release profiles of the model drug (paclitaxel) from the different blends matrix. It is observed that the drug release from the PLLA/PLGA microparticles composite displays an initial burst, followed by a relatively slow release. The release of paclitaxel from PLLA/PLGA microparticles may depend on the drug diffusion and the swelling or erosion of the microparticle matrix. It is worth noting that the release rate of paclitaxel from three groups' composite microparticles is different, depending on the different ratios of PLLA to PLGA. A greater fraction of PLGA in the PLLA/PLGA matrix can accelerate the degradation rate of the matrix and thus the drug release rate. This implies that different amounts of PLGA can affect the degradation rate of PLLA/PLGA microparticles and the drug release property. Through modulating the ratio of PLLA to PLGA in the PLLA/PLGA, different degradation rates can be obtained for ideal drug release properties.

3.4. Residual DCM in the PLLA/PLGA microparticles

In this work, the DCM residue in the microparticles without any further treatment is 39 ppm, which meets the requirements of the *Pharmacopeias of the People's Republic of China* (2005) (max. 600 ppm) and is lower than the one required by the *United States Pharmacopoeia* and the *European Pharmacopoeia* (400 and 600 ppm, respectively) [42]. Removal of residual solvents to very low concentrations is important to ensure a safe and stable microparticle product [43]. In the second stage of the spray-drying process, the residual solvent of the microparticles was approximately 40,000 ppm [43,44]. Koushik and Kompel [45] reported that methylene chloride content in the untreated deslorelin–PLGA microparticles prepared using an emulsion–solvent evaporation method was approximately 4500 ppm. Thus the SEDS process can produce polymer microparticles with little DCM residue, which will be preponderant especially in drug delivery systems.

4. Summary

In this work, SEDS was successfully used for the preparation of biodegradable PLLA/PLGA microparticles. The prepared PLLA/PLGA microparticles have a sphere-like shape with a smooth surface. The morphology and the mean particle size of PLLA/PLGA microparticles are different, depending on the addition fraction of PLLA. The mean particle size becomes small with increased of PLLA. The ratio of PLLA to PLGA in the PLLA/PLGA microparticles after the SEDS process is close to the feeding ratio. PLLA/PLGA microparticles are in an amorphous state. The pure PLGA microparticles have a large mean particle size and minor agglomeration due to the amorphous property of PLGA. The in vitro cumulative release rate of paclitaxel from different PLLA/PLGA blends microparticles is different, depending on the different ratios of PLLA to PLGA. These results are useful and feasible in directing the research for the exploitation of the proper PLLA/PLGA carrier to encapsulate drugs as advanced colloidal suspension for controlled drug delivery system.

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Supplementary material

Supplementary material for this article may be found on ScienceDirect, in the online version.

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