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The development and scale-up of biodegradable polymeric nanoparticles loaded with ibuprofen

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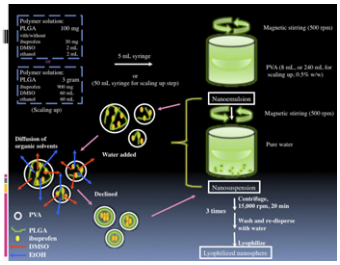
HIGHLIGHTS

- Blank NP and IbNP were prepared by modified SESD.
- IbNP has small size, high encapsulation efficiency and high drug-loading ratio.
- A 30-fold scaled-up batch of IbNP was prepared without the change in key characteristics.
- Variables on nanoparticle production by modified SESD were systematically analyzed.

GRAPHICAL ABSTRACT



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ABSTRACT

This study aims to ascertain the influence of variables in the production of blank and ibuprofen-loaded polymeric nanoparticles (IbNPs), as well as to scale up nanoparticle (NP) preparation 30-fold. Blank NP and IbNP with a matrix of poly (lactide-co-glycolide) (PLGA) were prepared by modified spontaneous emulsion solvent diffusion (SESD). The variables, organic solvent type, surfactant type and concentration, polymer concentration, aqueous phase volume, mixing speed, and manufacturing temperature, were investigated. Particle size, encapsulation efficiency (EE), drug loading and drug release were characterized. The smallest blank NP (175 nm) was obtained using a dimethy sulfoxide (DMSO):ethanol (50:50) organic solvent system with poly (vinyl alcohol) (PVA, 0.5% (w/w)) under magnetic stirring. The smallest IbNP obtained was 152 nm. The EE was highest at 30:100, drug:polymer ratio with a drug loading of 17.2%. Key NP characteristics, particle size, EE, drug loading and total drug release time of 30-fold scaled-up batch were not significantly different from lab-scale batch; however, 50% drug release for the scaled-up batch was significantly sooner ($p < 0.05$) than the lab-scale batch.

1. Introduction

Nanoparticles (NPs), because of their size, can penetrate capillary walls and can deposit their payload at target sites [1]. Entrapped drugs and imaging agents in NPs enjoy prolonged circulation, retarded degradation, and efficient allocation at the necessary site [2]. However, few nanoparticle (NP) systems have tenable clinical applications because of the barriers to large scale production under the current good manufacturing practice (cGMP) to fulfill industrial demands [3]. Therefore, studying the alterations in key nanoparticle characteristics before and after scaling up is imperative to industrial applications.

Of the many methods of nanoparticle preparation, modified spontaneous emulsion solvent diffusion (SESD), for its narrow size distribution, high encapsulation efficiency (EE) and high batch-to-batch reproducibility [4], is adopted for nanoparticle preparation and scaling up. Despite the general understanding of the influence of production variables in modified SESD as evidenced in literature [5,6], a systematic analysis of the variables with theoretical support is lacking. In this study, the effects of production variables on

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particle size, EE and *in vitro* drug release kinetics were investigated systematically. Production parameters that reduced nanoparticle size and increased encapsulation efficiency were used for scaling up.

Ibuprofen (Ib), a non-steroidal anti-inflammatory (NSAID), the biopharmaceutics classification system (BCS) class II drug, was chosen as a model drug in this study because of its low water solubility, relatively high permeability and low price. Also, its side effects, gastric irritation, and a short, 2 h, plasma half-life [7] call for modified dosage options such as polymeric nanoparticles.

One of the most used polymers for nanoparticles is poly (lactide-*co*-glycolide) (PLGA). PLGA is widely used in the medical field due to its established clinical safety [8], favorable degradation characteristics and the ability to release the drug in a sustained manner [2]. Drugs of interest can be adsorbed, attached or encapsulated into nano-sized PLGA matrices and then released *in vivo* as desired [1].

In this study, the properties of ibuprofen-loaded polymeric nanoparticles (IbNPs), such as particle size, encapsulation efficiency drug loading and *in vitro* drug release kinetics, were investigated. The formulation with small particle size and the highest encapsulation efficiency at laboratory scale was scaled up 30-fold, with 20-fold being the former largest scale up in modified SESD nanoparticle production [9].

2. Materials and methods

2.1. Materials

Ibuprofen was obtained from GAK engineering (Middletown, PA, USA). Kolliphor® EL (Polyoxyl 35 castor oil) was obtained from BASF corporation (Ludwigshafen, Germany). Poly (vinyl alcohol) (PVA, MW 11,000–31,000) was obtained from B.J, Baker corporation (Phillipsburg, NJ, USA). Poly (lactide-*co*-glycolide) (PLGA, 50:50, MW 7,000–17,000) was bought from Sigma–Aldrich (St. Louis, MO, USA). Other chemicals: acetone, acetonitrile (ACN), ethanol (EtOH), dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were purchased from Sigma–Aldrich (St. Louis, MO, USA) and were of analytical grade.

2.2. Analytical method

HPLC (Waters 717 plus Autosampler series) was used for the analytical assay of ibuprofen. The column used was Waters Symmetry C18 Column (5 μm, 3.9 × 150 mm). The mobile phase was a mixture of acetonitrile:water at 70:30 (v/v) with a flow rate of 1 mL/min. The pH was adjusted to 2.4 with phosphoric acid. Ibuprofen was detected by UV detector (Waters 486 Tunable Absorbance Detector) at a wavelength of 264 nm.

2.3. Preparation of nanoparticles

Modified SESD was used to prepare PLGA NP. At lab scale, PLGA (100 mg) was dissolved in a DMSO:EtOH (4 mL, 50:50, v/v) binary organic solvent. Then, the organic solution was added drop wise to a PVA water solution (8 mL, 0.5% w/w) under magnetic stirring (No. 1278, Lab-Line multimagnestir/Lab-Line Instruments, Inc., Melrose Park, IL, USA). The formed nanoemulsion was then poured into distilled water (160 mL) under magnetic stirring to form nanosuspension, followed by centrifugation using Sorvall RC-5C (Sorvall, Logan, UT, USA) at 26,260 × *g* for 20 min. The nanoparticle pellet was washed, resuspended in distilled water, and centrifuged again. The washing step was repeated twice, and the final pellet was lyophilized for 8 h using Labconco Shell Freeze Dry Equipment (Labconco Corporation, Kansas City, MO, USA).

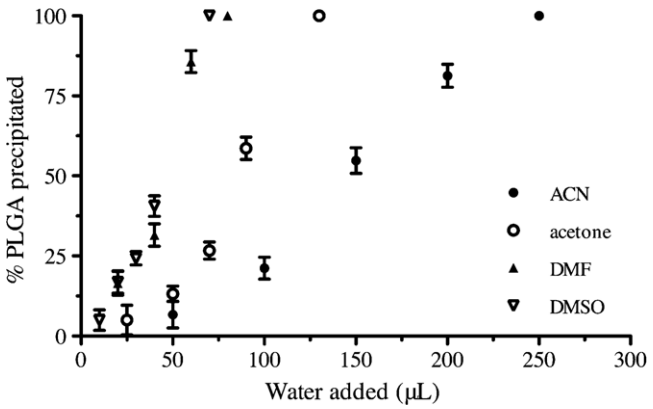

Fig. 1. PLGA precipitation tendency with water added into different organic solvents.

The production of IbNPs at lab scale was the same except that 30 mg ibuprofen was dissolved with 100 mg PLGA in the binary organic solvent initially. IbNPs scaled-up batch was 30 times that of IbNPs lab-scale batch *ceteris paribus*.

2.4. Particle characterization

Particle size, *i.e.*, mean diameter was detected by photon correlation spectroscopy (PCS) using Delsa TM Nano Series Zeta Potential and Submicron Particle Size Analyzer (Brea, CA, USA). We systematically studied the effects of processing variables on particle size.

2.4.1. Effect of organic solvent used

To learn the effect of organic solvent on blank nanoparticle size, a PLGA precipitation tendency experiment was conducted to study the diffusion process of organic solvent to water and how this may influence nanoparticle size. An organic solution (2 mL) was formed by dissolving PLGA (100 mg) into one of four water-miscible organic solvents, acetone, ACN, DMF and DMSO. Measured quantities of water were added into the organic solution to precipitate PLGA due to the loss of organic solvent to PLGA. The precipitated PLGA were centrifuged, weighted and recorded until all the PLGA were precipitated. The PLGA precipitation experiment was repeated three times for each organic solvent. The relation between the volume of the added water and the amount of PLGA precipitated was explored (Fig. 1).

Then, blank NP was produced with the four organic solvents respectively. To do that, an organic solution (4 mL) was formed by dissolving PLGA (100 mg) into one of the four organic solvents. The formed organic solution was added drop wise into PVA solution (8 mL, 0.5% w/w) under magnetic stirring to form a nanoemulsion, which was then added to purified water (160 mL) under magnetic stirring to form a nanosuspension. The particle sizes were detected by PCS and listed in Table 1.

Table 1
Calculated solubility parameters of four organic solvents and the practical particle sizes they made (without ethanol).

Solvent	Solubility parameter (δ)	Solvent–polymer parameter (χ)	Particle size (nm ± S.D.)
ACN	11.9	0.11	377 ± 25
Acetone	9.8	0.13	312 ± 23
DMF	12.0	0.19	271 ± 21[a]
DMSO	14.5	1.68	260 ± 17[a]

Average solubility parameter of PLGA 50:50 = 10.8 $(cal/cc)^{1/2}$, of water = 23.0 $(cal/cc)^{1/2}$, $R = 1.986\ cal\ K^{-1}\ mol^{-1}$, $V_{solvent}$ is calculated when 100 mg PLGA was added into 4 ml organic solvent.

[a] The two values do not have significant difference.

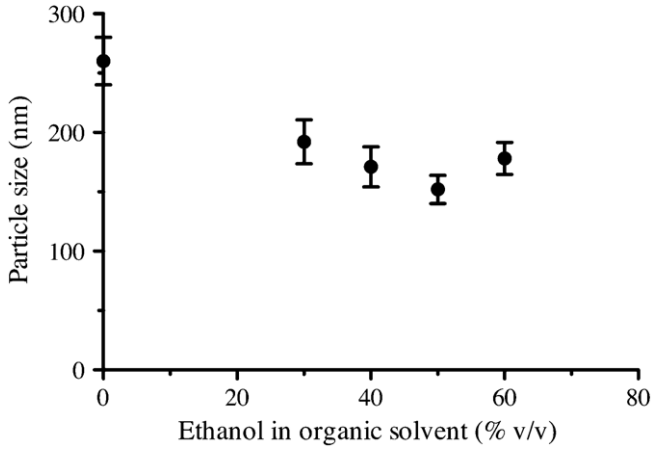

Fig. 2. Effect of ethanol proportion in organic solvent on blank NP size.

2.4.2. Effect of ethanol proportion in organic solvent

The proportions of ethanol in organic solvent system (4 mL, DMSO + EtOH) were prepared at 0%, 30%, 40%, 50%, and 60% (v/v) while the other variables were kept the same as in Section 2.4.1 to produce NPs. The relation between particle size and ethanol proportion in organic solvent is shown in Fig. 2.

2.4.3. Effect of surfactant type and concentration

Three surfactants, Kolliphor® EL, PVA, and SDS, were used in varying concentrations (8 mL, 0.5–3% w/w) in water while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH). The relation between particle size and surfactant concentration for each surfactant is shown in Fig. 3.

2.4.4. Effect of polymer concentration

The polymer concentration in organic solution was increased (1, 1.5, 2.5, 5 and 10% w/v) while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH). The relation between particle size and polymer concentration is discussed in Section 3.1.4.

2.4.5. Effects of the volume of surfactant solution and successively added water

The effects of the volume of surfactant solution (8–32 mL, 0.5% w/w) and the successively added water (80–1280 mL) on particle size were determined while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH). The relation between particle size and the volume of aqueous phase is shown in Fig. 4.

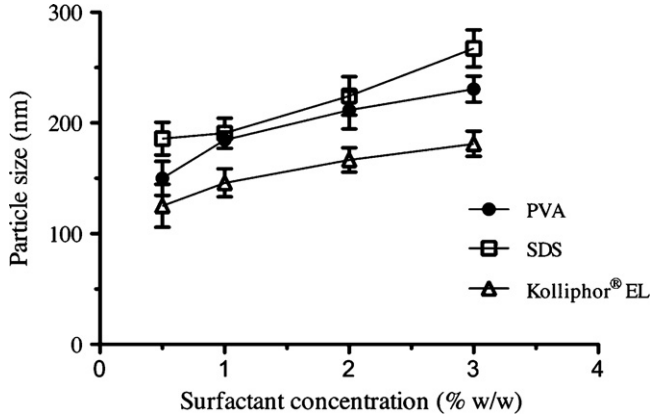

Fig. 3. Effect of surfactant type and concentrations on blank NP size.

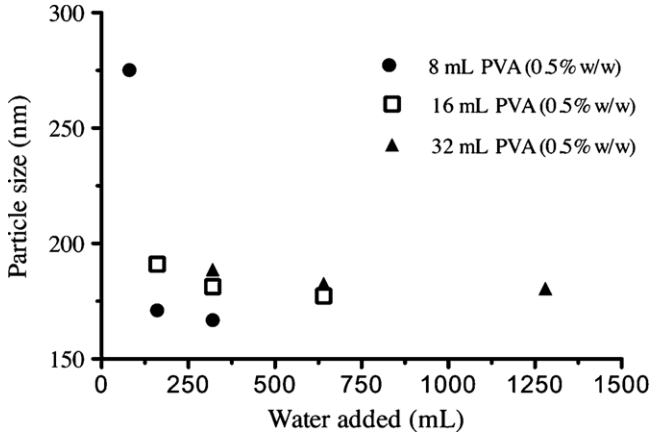

Fig. 4. Effect of the amount of surfactant solution and successively added water on blank NP size.

2.4.6. Effect of mixing speed

Three different mixing speeds (500 rpm, 5000 rpm and 10000 rpm) were studied while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH). The effect of mixing speed on blank NP size is shown in Table 2.

2.4.7. Effect of manufacturing temperature

The manufacturing temperature was increased from 20 °C to 70 °C while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH). The effect of manufacturing temperature on blank NP size is demonstrated in Table 2.

2.5. Determination of drug encapsulation efficiency and drug loading

About 10 mg of lyophilized nanoparticles was dissolved in ACN (5 ml) and diluted to 25 ml with mobile phase and analyzed using HPLC. The drug encapsulation efficiency (EE) was calculated as the ratio of total drug in the prepared nanoparticles to initial amount of drug used for the preparation of nanoparticles and expressed as percentage.

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Amount of drug in nanoparticles (mg)}}{\text{Total amount of drug initially added (mg)}} \times 100\%$$

The dependence of EE on amount of drug input and manufacturing temperature was determined.

Table 2
Effect of mixing speed and manufacturing temperatures on NP size and encapsulation efficiency.

Mixing speed (rpm)	Temperature (°C)	Particle size (nm ± S.D.)	Encapsulation efficiency (% ± S.D.)
500	20[a]	175 ± 13	N/A
5000	20[a]	175 ± 15	N/A
10000	20[a]	183 ± 19	N/A
500	40[a]	161 ± 12	N/A
500	60[a]	157 ± 15	N/A
500	70[a]	177 ± 16	N/A
500	20	160 ± 11	66.5 ± 2.0
500	40	143 ± 13	53.1 ± 2.3
500	60	133 ± 12	46.2 ± 3.5
500	70	176 ± 16	34.0 ± 3.7

[a] blank nanoparticles.

2.5.1. Effect of drug input

Ibuprofen input was varied from an Ib:PLGA ratio of 20:100–50:100 while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH). The relation between EE and drug input is discussed in Section 3.2.1.

2.5.2. Effect of manufacturing temperature

The manufacturing temperature was varied from 20 °C to 70 °C while the other variables were kept the same as in Section 2.4.1 to produce NPs with a binary organic solvent (4 mL, 50:50 DMSO:EtOH) containing PLGA (100 mg) with Ib (30 mg). The relation between EE and manufacturing temperature is shown in Table 2.

2.5.3. Drug loading

The drug loading was determined from the ratio of the encapsulated ibuprofen amount to the total nanoparticle mass. The detection of ibuprofen content in lyophilized nanoparticles was as the same as in Section 2.5 described.

2.6. In vitro drug release

The *in vitro* drug release was tested on a heated stir plate (Thermolyne Nuova II) at 37.0 °C ± 0.2 °C with constant stirring, using dialysis. Lyophilized IbNPs (10 mg) was suspended in 1 mL phosphate buffered saline (PBS) in a sealed filter membrane (MWCO 10000, Spectra/ Porr, Spectrum laboratories, NJ, USA). The sealed membrane was immersed into PBS (50 ml, pH 7.4). At preset time points, samples (2 mL) were withdrawn and analyzed by HPLC. Fresh PBS solution was used to replace the withdrawn samples to maintain the volume at 50 mL. Ib powder release kinetics was used as control.

3. Results and discussion

3.1. Preparation and characterization of blank NP

3.1.1. Effect of organic solvent used

The sizes of blank NPs prepared with four organic solvents (without ethanol), ACN, acetone, DMF, and DMSO, ranged from 260 nm to 377 nm. (Table 1)

It was proposed that the more miscible an organic solvent was with water, *i.e.* the smaller the difference in solubility parameters ($\Delta\delta$) between the organic solvent and water, the smaller the NP would be produced [10].

Hence, in this case, we wanted to understand the diffusion process of organic solvent to water because the ease of the diffusion increases with the miscibility of the solvent with water. PLGA precipitation tendency is used as an indicator of the ease of solvent diffusion. Fig. 1 and Table 1 showed that particle size decreased with higher precipitation tendency for PLGA.

The relation between the ease of organic solvent diffusion and NP size has also been studied in other NP productions with solvent evaporation. When water-immiscible organic solvents (*e.g.* chloroform) diffused slowly into aqueous phase, polymer precipitation was retarded and that led to larger particles [11]. Similarly, in this case, the difficulty of organic solvent diffusion into water disfavored small nanoparticle size produced by SESD and vice versa.

Also, the Flory–Huggins "chi (χ) " parameter, χ, or called as the solvent–polymer interaction parameter, was also introduced to explain the effect of organic solvent on NP size it forms. The calculation of χ can be expressed as:

$$\chi = \frac{V^{\text{solvent}}}{RT} \times (\delta_{\text{solvent}} - \delta_{\text{polymer}})^2$$

where V_{solvent} is the molar volume of the solvent and R is the gas constant, T (K) is the absolute temperature.

The χ values of the four organic solvent/ polymer systems were calculated and the size of practically made NP listed in Table 1. The particle size decreased with increasing χ (decreased cohesion between polymer and solvent), in accordance with the results of Choi's [12].

DMSO was chosen for nanoparticle preparation because it produced the smallest nanoparticles and is less toxic than DMF.

3.1.2. Effect of ethanol proportion in organic solvent

Fig. 2 showed that from 30% to 50% (v/v), ethanol proportion in organic solvent, particle size decreased (minimum 175 nm). After that, increasing in EtOH proportion increased particle size. Ethanol, because of its high affinity to water, was used to promote the diffusion of the organic solvent to the aqueous phase. However, PLGA has low solubility in EtOH. When EtOH exceeded 50% of the solvent system, PLGA did not dissolve well at the beginning (cloudy solution) and led to a large particle size. Ethanol was also used in SESD to prevent particle aggregation [13]. Ethanol proportion was fixed at 50% (v/v) as it produced the smallest particles.

3.1.3. Effect of surfactant type and concentration

Fig. 3 showed that the sizes of the particles prepared with Kolliphor® EL, PVA, and SDS (0.5% w/w) were 125 nm, 160 nm and 186 nm respectively. SDS (0.5% w/w) produced the largest NP mainly due to its ionic property. Compared to non-ionic surfactants, SDS micelles are relatively difficult to form because of the electrostatic repulsion between the ionic head groups. While the critical micelle concentration (CMC) for ionic surfactants is in the order of 1 mM, the typical CMC for most non-ionic surfactants is in the order of 0.01 mM [14]. Hence, an ionic surfactant, below CMC, would experience electrostatic repulsion, which would hinder the formation of emulsion droplets and lead to a large size. The NP size for the different surfactants increased with the increase in CMC from 0.08 mM (Kolliphor® EL) to 0.25 mM (PVA) to 8.00 mM (SDS).

NP size increased from 186 nm to 267 nm for SDS-prepared NP, from 160 nm to 231 nm for PVA-prepared NP, and from 125 nm to 181 nm for Kolliphor® EL-prepared NP, when the concentration of the three surfactants increased from 0.5% to 3% (w/w) respectively (Fig. 3). The increase of NP size with the increase of surfactant concentration is in accordance with former articles [16,17]. Enhanced surfactant concentration increases the viscosity of aqueous phase, which disfavors the dispersion of organic solvent into it and results in large particle size.

However, the small variations in viscosity from 0.5% to 3% for surfactant solutions may not be a convincing account for the increase of particle size. In order to explain the effect of surfactant on nanoparticle size, ouzo effect is worth mentioning. Ouzo effect was first introduced for auto-formed emulsification and was considered to make spontaneously the emulsification during SESD [18]. For the emulsification forced by ouzo effect, surfactant solution is only needed at low concentration (0.5% w/v) [19]. Consequently, when surfactant concentration exceeds 0.5% (w/w) in this case, the excess amount of surfactant would be adsorbed on particle surface [19] and increase particle size. Surfactant concentration was fixed at 0.5% (w/w) due to the obtained small particle size.

3.1.4. Effect of polymer concentration

Particle size increased (148–258 nm) with the increase of PLGA concentration in organic solution (1–10%, w/v).

This result agreed with former articles [20,21]. When PLGA concentration in organic solution increased, the viscosity of organic solution also increased, resulting in a poor dispensability of the

organic solvent into the aqueous phase and leading to large particle size. At the three PLGA concentrations (1%, 1.5% and 2.5%, w/v), the obtained particle sizes do not have significant difference ($p = 0.3$). Therefore, 2.5% (w/v) of PLGA concentration was chosen because of drug-loading consideration.

3.1.5. Effect of the volume of surfactant solution and successively added water

Fig. 4 showed that the size of nanoparticles decreased with the increased volume of the successively added water when the volume of surfactant solution is kept the same. 166 nm, the lowest particle size was obtained with 8 mL PVA (0.5%, w/w) solution and 320 mL successively added water. The increase of aqueous phase volume enhanced polymer concentration gradient from organic phase to aqueous phase; therefore, the diffusion of organic solvent to aqueous phase increased, leading to a decreased particle size.

The second lowest particle size, 171 nm was produced with 8 mL PVA (0.5%, w/w) solution and 160 mL successively added water. As the two particle sizes, 167 nm and 171 nm, do not have significant difference ($p = 0.6$), the amount of aqueous phase for 171 nm NPs production were chosen because less amount of water was needed.

3.1.6. Effect of mixing speed

Table 2 demonstrated that the particles were 175 nm, 175 nm and 183 nm when mixing speed was at 500, 5,000 and 10,000 rpm respectively. Therefore, shear stress does not have significant influence on nanoparticle size when mixing speed is above 500 rpm. As mentioned in Section 3.1.3, the emulsification by modified SESD is spontaneous and rapid, forced by ouzo effect, high-speed homogenization cannot help to reduce the particle size.

3.1.7. Effect of manufacturing temperature

The effect of manufacturing temperature on particle size was tabulated in Table 2. The increase of temperature (20–60 °C) decreased the particle size (174–157 nm). However, further increased temperature (60–70 °C) increased particle size (157–177 nm). As the diffusion of organic solvent to aqueous phase can be promoted by high temperature, particle size decreased with the increase of temperature at first. Then, it may due to the cloud point of PVA (50 °C for 0.5% PVA [22], the temperature when surfactant starts to separate from its aqueous phase), the amount of PVA in its aqueous phase decreased due to phase separation and led to increased particle size when temperature reached 70 °C.

3.2. Preparation and characterization of IbNP

The formulation parameters, *i.e.* 100 mg PLGA, 4 mL binary organic solvent (DMSO:ethanol, 50:50 v/v), 8 mL PVA solution (0.5%, w/w) and 160 mL water, were chosen for the preparation of IbNP. For IbNP, our studies mainly focused on the effects of variables on encapsulation efficiency. Organic solvent type and ethanol proportion in organic solvent do not have significant influence on EE (data is not shown). The effects of other variables on EE will be discussed below.

3.2.1. Effect of drug input on encapsulation efficiency

With the increase of ibuprofen input (20–30 mg) in 100 mg PLGA, the encapsulation efficiency increased from 45.4% to 67.8%; nevertheless, further increase of drug input (40 mg and 50 mg) led to decreased encapsulation efficiency (35.1% and 20.2%).

This result is similar with former research, where the highest EE was achieved at the ratio of 30:100 (Ib:PLGA) [23], when Ib can get the strongest bond with PLGA molecules [23]. While, further lower or higher ratio of Ib:PLGA weakened the bond, leading to decreased EE.

Table 3
Comparison of key parameters between lab-scale and scale-up batches.

Parameters	Lab scale batch (100 mg PLGA + 30 mg Ib)	Scaled-up batch (3 g PLGA + 900 mg Ib)
Particle size (nm ± S.D.)	152 ± 16	178 ± 23
EE (% ± S.D.)	67.2 ± 1.9	62.3 ± 2.6
Yield (% ± S.D.)	90.1 ± 2.3	88.3 ± 3.1
Drug loading (% ± S.D.)	17.2 ± 1.4	16.3 ± 1.8
50% Ib released time (Min ± S.D.)	190 ± 23	90 ± 12
100% Ib released time (Min ± S.D.)	600 ± 25	660 ± 28

The ratio of 30:100 (Ib:PLGA) was chosen for further IbNP production due to the obtained high EE and drug loading accordingly.

3.2.2. Effect of surfactant type on encapsulation efficiency

The EE obtained with 3 surfactants, Kolliphor® EL, PVA and SDS (0.5%, w/w), were 36.6%, 66.3% and 55.7% respectively.

PVA achieved the highest EE, not only because of its high viscosity, but also due to its polymeric property, which can help to reduce the leaking of drug to external aqueous phase [24].

Kolliphor® EL got lower EE than SDS, which may due to the higher solubility of Ib in Kolliphor® EL than in SDS (data is not shown). Surfactant, in which drug has high solubility, can help to promote the leaking of drug into external aqueous phase [25].

Therefore, PVA was chosen as the surfactant for the high EE it achieved.

3.2.3. Effect of manufacturing temperature

Table 2 showed that with the increase of temperature (20–70 °C), EE decreased (66.5–34.0%). The decreased EE in this case is due to the increased leaking of drug promoted by high temperature, which is also presented in other articles [26,27]. Consequently, manufacturing temperature was fixed at 20 °C for the obtained high EE.

3.3. In vitro drug release kinetics

Fig. 5 showed that for Ib bulk powder, 240 min was needed to get its equilibrium solubility; while, for lab-scale batch and scaled-up batch, it needed 600 and 660 min to get the release equilibrium respectively.

Lab-scale batch and scaled-up batch all demonstrated burst release within the first 45 min, which is owing to the amount of Ib adsorbed on particle surface. Moreover, the scaled-up batch demonstrated a higher initial release than the lab-scale batch . It

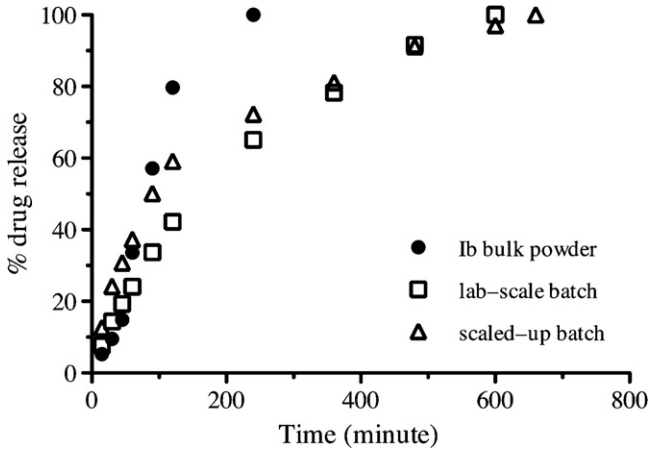

Fig. 5. Drug release kinetics.

only needed 90 min for the scaled-up batch to release 50% Ib while 190 min was used for the lab-scale batch ($p = 0.03$). On the other hand, for 100% drug release, the scaled-up batch consumed 660 min while the lab-scale batch needed 600 min ($p = 0.05$).

The reason for the difference in drug release kinetics needs us to recall the effects of the amount of surfactant solution and successively added water (see Section 3.1.5). For scaling up, the volume of surfactant solution and successively added water was enhanced 30-fold, which largely promoted the diffusion of organic solvent containing Ib to aqueous phase. Therefore, more Ib leaked into aqueous phase or got adsorbed on particle surface at scaling up step [28], leading to a decreased EE or higher initial release when compared with the NP prepared at lab-scale batch.

3.4. Characteristic comparisons between the lab-scale batch and scaled-up batch

Table 3 demonstrated that nanoparticle size increased (152–178 nm, $p = 0.2$) after scaling up. For a given magnetic stirring rate (500 rpm), the largely increased volume of aqueous phase at scaling up step decreased the power input per unit mass, which disfavored the droplet break-up process, leading to a larger particle size [29]. The difference in particle size was not significant ($p = 0.2$).

Table 3 also showed that EE decreased (67.2–62.3%, $p = 0.06$)) after scaling up. This is ascribed to the increased leaking of Ib promoted by the 30-fold enlarged aqueous phase volume, as discussed in Section 3.3.

The difference in EE between lab-scale batch and scaled-up batch may account for the difference in the yield and drug loading for the two batches. Besides, the increased particle aggregation during the production of the scaled-up batch may contribute to its decreased yield, as tabulated in Table 3.

In Fig. 5, the scaled-up batch showed a more retarded release than the lab-scale batch after 500 min. As the average nanoparticle size of the scaled-up batch was larger than the lab-scale batch, the drug entrapped in the "core" of NP needed a longer time to release outside for the scaled-up batch.

4. Conclusion

This study successfully developed a modified spontaneous emulsion solvent diffusion for nanoparticles' preparation and 30-fold scaling up. It enables nanoparticles, with or without ibuprofen, obtained under mild conditions without high temperature and high-speed homogenization.

Firstly, blank nanoparticle size was minimized to 175 nm by adopting a binary organic solvent (DMSO:ethanol, 50:50) and using PVA water solution (0.5% w/w). Increasing manufacturing temperature decreased the particle size. Mixing speed over 500 rpm did not have significant influence on particle size. Ibuprofen-loaded NPs followed similar trends to blank NPs with the lowest particle size of 152 nm. The encapsulation efficiency peaked at 30:100 (drug:polymer) with a 17.2% drug loading. Higher manufacturing temperature reduced the encapsulation efficiency.

Besides, the scaled-up batch had the same process variables as the lab-scale batch of IbNPs but was 30 folds as large. No significant differences were observed in key nanoparticle characteristics in particle size, encapsulation efficiency, drug loading and the time taken for 100% drug release. The scaled-up batch released 50% of the encapsulated drug sooner than the lab-scale batch ($p = 0.03$).

For further optimization of NP preparation with SESD, stability related issues should be taken into account. Further considerations could be put on nanoparticles' surface charge, the ability to re-suspend after freeze-drying and drug degradation problems *etc.*

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