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

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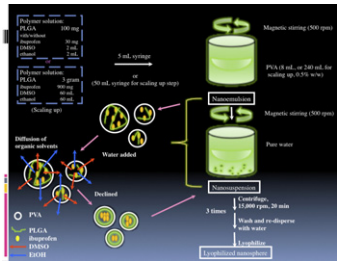
HIGHLIGHTS

- 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).

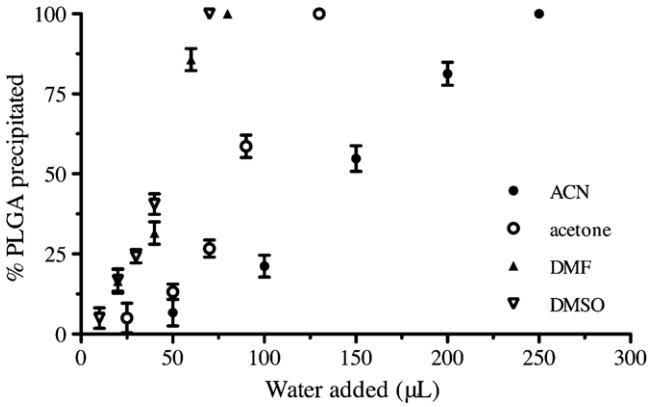

Fig. 1. PLGA precipitation tendency with water added into different organic solvents.

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.