

# Formulating food protein-stabilized indomethacin nanosuspensions into pellets by fluid-bed coating technology: physical characterization, redispersibility, and dissolution

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**Background:** Drug nanosuspensions are very promising for enhancing the dissolution and bioavailability of drugs that are poorly soluble in water. However, the poor stability of nanosuspensions, reflected in particle growth, aggregation/agglomeration, and change in crystallinity state greatly limits their applications. Solidification of nanosuspensions is an ideal strategy for addressing this problem. Hence, the present work aimed to convert drug nanosuspensions into pellets using fluid-bed coating technology.

**Methods:** Indomethacin nanosuspensions were prepared by the precipitation-ultrasonication method using food proteins (soybean protein isolate, whey protein isolate,  $\beta$ -lactoglobulin) as stabilizers. Dried nanosuspensions were prepared by coating the nanosuspensions onto pellets. The redispersibility, drug dissolution, solid-state forms, and morphology of the dried nanosuspensions were evaluated.

**Results:** The mean particle size for the nanosuspensions stabilized using soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin was 588 nm, 320 nm, and 243 nm, respectively. The nanosuspensions could be successfully layered onto pellets with high coating efficiency. Both the dried nanosuspensions and nanosuspensions in their original amorphous state and not influenced by the fluid-bed coating drying process could be redispersed in water, maintaining their original particle size and size distribution. Both the dried nanosuspensions and the original drug nanosuspensions showed similar dissolution profiles, which were both much faster than that of the raw crystals.

**Conclusion:** Fluid-bed coating technology has potential for use in the solidification of drug nanosuspensions.

**Keywords:** nanocrystals, nanosuspensions, food proteins, poorly water-soluble drugs, indomethacin, fluid-bed coating

## Introduction

A large number of poorly water-soluble drugs and drug candidates have significant bioavailability problems which limit their therapeutic efficiency or development beyond an early stage. For Biopharmaceutics Classification System II drugs, which are characterized by low solubility and high permeability, dissolution is the limiting step with regard to their oral absorption and bioavailability.<sup>1,2</sup> The dissolution rate can be improved by reducing the particle size because of their increased surface area.

Nanosuspensions containing drugs (amorphous or crystalline) are nanoscale colloidal dispersions of pure drug particles stabilized by surfactants.<sup>3</sup> Compared with

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other nanoscale drug delivery systems, nanosuspensions show promise for enhancing dissolution and hence the bioavailability of poorly water-soluble drugs, by eliminating the effects of food, allowing for dose escalation, and improving efficacy and safety.<sup>4–6</sup> Since the 1990s, many commercial products, including Rapamune®, Emend®, Tricor®, Megace ES®, Avinza®, Focalin XR®, Ritalin®, and Zanaflex Capsules™ have been marketed successfully.<sup>7</sup> However, in spite of the advantages of nanosuspensions, there are many drawbacks associated with nanosuspension technology. A critical aspect concerns the poor stability of nanosuspensions in aqueous medium. Common processes, such as hydrolytic/oxidative degradation, particle growth, aggregation/agglomeration, change in crystallinity state, and sedimentation or creaming, may occur.<sup>8–10</sup> Moreover, nanosuspensions are always diluted, and have to be administered in large volumes to achieve therapeutic levels in the circulation.<sup>11</sup> To overcome these problems, it is desirable to formulate nanosuspensions into solid dose forms.<sup>3,12</sup> Freeze-drying and spray-drying are the two most commonly used solidification methods.<sup>10,13</sup> However, the freeze-drying process is very costly and time-consuming, and spray-drying, although quite a robust process, requires manipulation at relatively high temperatures and is difficult to scale up. Other strategies, such as granulation, fluid-bed coating, and tableting, have not been widely investigated to date.<sup>13</sup>

Fluid-bed coating is a “one-step” technique that is commonly used to add a film coating onto a substrate, and has widespread applications in the pharmaceutical industry. This technique involves solvent removal and simultaneous deposition of coating materials onto nonpareil pellets. In comparison with conventional spray-drying, fluid-bed coating is a much more efficient method of preparing solid formulations from bulk aqueous or organic solutions or suspensions. Moreover, fluid-bed coating is more scalable. Because of the advantages of improved drug dissolution, modified drug release, taste masking, and enhanced drug absorption,<sup>14–16</sup> solidification of nanosuspensions by fluid-bed coating appears attractive and promising. However, the process of solidification of drug nanosuspensions by fluid-bed coating is challenging because solidified formulations need to have the ability to reconstitute into their original nanosuspensions. Möschwitzer and Müller<sup>17</sup> formulated drug nanosuspensions into pellets using a fluid-bed process, but did not report any data on the redispersibility of the nanocrystals upon reconstitution with water. Recently, Kayaert et al<sup>18</sup> also reported on the feasibility of fluid-bed coating of nanosuspensions, but did not identify the solid state of the drug nanocrystals used. To date,

there have been few reports on the art of solidification of nanosuspensions by fluid-bed coating.

Our previous findings<sup>19</sup> indicated that amorphous indomethacin nanosuspensions could be prepared using a precipitation-ultrasonication method involving stabilization by biocompatible food proteins, eg, soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin. To improve the stability of such suspensions further for long-term storage, in this study we coated drug nanosuspensions onto pellets using fluid-bed coating technology. Specific attention was paid to the ability of the solidified nanosuspension to reconstitute by studying changes in particle size and distribution, drug particles in the solid state, and drug dissolution.

## Materials and methods

### Materials

Indomethacin was purchased from Sine Pharmaceuticals (Shanghai, People's Republic of China), whey protein isolate from Davisco Foods International Inc (Le Sueur, MN, USA), soybean protein isolate from Hufeng Chemical Industry Co, Ltd (Shanghai, People's Republic of China), and  $\beta$ -lactoglobulin (from bovine milk, L3908, >90% purity grade) from Sigma Chemical Co (St Louis, MO, USA). Polyvinylpyrrolidone (PVP) K30 was kindly supplied by International Specialty Products (Shanghai, People's Republic of China). Nonpareil pellets (sugar spheres 0.5–0.7 mm in diameter) were provided by Gaocheng Biotech and Health Co, Ltd (Hangzhou, People's Republic of China). Deionized water was prepared using a Milli-Q purification system (Millipore, Billerica, MA, USA). Other reagents were of analytical grade and used as received.

### Preparation of nanosuspensions

An aqueous suspension of protein was obtained by dispersing 300 mg of protein (soybean protein isolate, whey protein isolate, or  $\beta$ -lactoglobulin) powder into 25 mL of water under magnetic stirring for one hour at 25°C, then adjusting the samples to pH 7 using 1 M NaOH. To denature the proteins and expose the nonpolar and disulfide bonds buried in the protein interior and thus increase the stabilizing capacity of the proteins, the soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin solutions were heated to 105°C, 85°C, and 85°C, respectively, in closed centrifuge tubes (50 mL, Corning Incorporated, Tewksbury, MA, USA) for 30 minutes.<sup>19–22</sup> The denatured protein solution was then cooled to 25°C for two hours.

The nanosuspensions were prepared according to the precipitation-ultrasonication method described previously

by Mateucci et al and Xia et al, with some modifications.<sup>2,23</sup> The aqueous dispersion of denatured protein functioned as the aqueous phase (30 mL), in which the concentrations of soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin were 8.5 mg/mL, 8.5 mg/mL, and 3.3 mg/mL, respectively. The drug-containing organic phase was prepared by dissolving indomethacin in 2 mL of acetone. The amount of indomethacin in the nanosuspensions stabilized by soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin was 150 mg, 150 mg, and 200 mg, respectively. The organic and aqueous phases were precooled to below 3°C in an ice-water bath. The organic phase was then added to the aqueous phase under mechanical stirring at 1,200 rpm. After the antisolvent precipitation process, the samples were immediately treated with an ultrasonic probe (20–25 kHz, Scientz Biotechnology Co, Ltd, Ningbo, People's Republic of China) at 500 w for 15 minutes. The probe, which had a tip diameter of 8 mm, was immersed 1 cm into the liquid, resulting in the wave traveling downwards and reflecting upwards. The period of ultrasound burst was set to 3 seconds, with a pause of 3 seconds between each burst of ultrasound. Temperature was controlled throughout using an ice-water bath.

## Coating nanosuspensions onto pellets

The layered pellets were produced by coating the indomethacin nanosuspensions onto nonpareil pellets using a fluid-bed coater (DPL1/3 Multi-processor, Jingong Pharmaceutical Machinery Co, Ltd, Chongqing, People's Republic of China, Figure 1). Briefly, trehalose was first dissolved in the protein-stabilized nanosuspension, and PVP K30 was mixed with the aqueous dispersion of denatured soybean protein isolate under gentle stirring. Dispersion of the coating formulations was done by introducing the aqueous soybean protein isolate dispersion containing PVP into the nanosuspension slowly under gentle stirring. The dispersion was sprayed through a

nozzle into the surface of the nonpareil cores in the fluid-bed coater. The operating conditions were as follows: inlet air temperature, 40°C–45°C; product temperature, 35°C; blower frequency, 12–26 Hz; rotational speed of peristaltic pump, 4–12 rpm; atomizing air pressure, 0.15–0.25 MPa; and spray nozzle diameter, 0.5 mm. After coating, the pellets were dried in the coating chamber at 35°C for a further 15 minutes.

The yield (%) was expressed as the theoretical percentage of the weight gained (TWG, %) to the weight of the layered pellets, and was calculated using the following formula:

$$\text{TWG \%} = \left( \frac{W_1}{W_0} - 1 \right) \times 100 \quad (1)$$

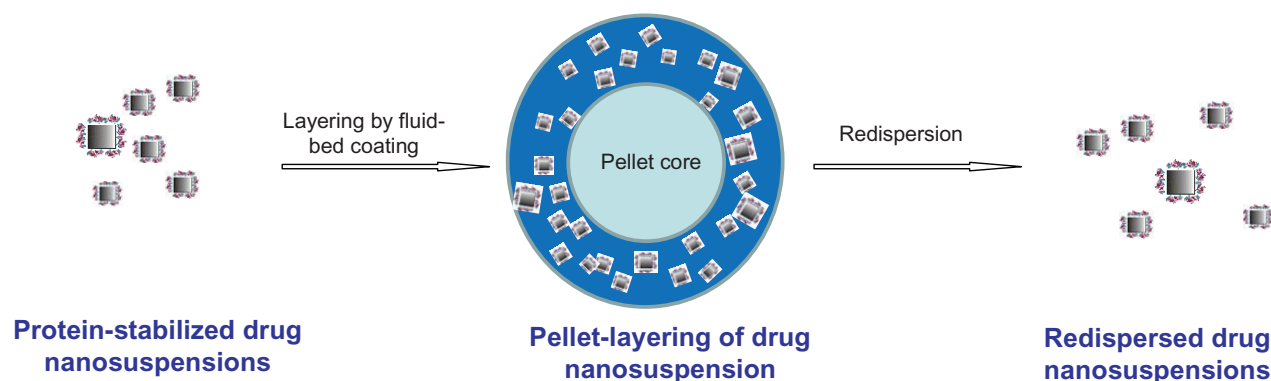
where  $W_0$  and  $W_1$  are the weights of the nonpareil pellets and layered pellets, respectively.

## Redispersibility study

The pellets (100 mg) layered by the nanosuspensions were dispersed in 10 mL of deionized water by shaking for about 1 minute. One milliliter of the resulting redispersed aqueous suspension was placed in a test tube and allowed to stand for a few minutes. The supernatant was withdrawn and characterized for mean particle (intensity weight) size and distribution by dynamic laser scattering.

## Determination of particle size and zeta potential

The particle size and size distribution of the nanosuspensions were measured using a dynamic laser scattering instrument (380 ZLS, Nicomp Instruments, Santa Barbara, CA, USA). Raw data were collected over 5 minutes at 25°C and at an angle of 90 degrees, and processed further using the ZPW388 software program. The mean intensity-weight particle size was expressed as a volume-weighted Gaussian distribution (with a chi-squared value <3). The surface



**Figure 1** Schematic representation of the formation of pellets coated by nanosuspensions containing indomethacin.

charge of the nanosuspensions was determined by measuring electrophoretic mobility at 25°C with the Nicomp 380 ZLS. Nanosuspensions were diluted 50-fold in water before measurement.

## Scanning electron microscopy

The surfaces of the nanosuspensions and pellets were studied using a scanning electron microscope (XL30, Philips, Eindhoven, the Netherlands). Prior to examination, the samples were fixed on a brass stub using double-sided tape and gold-coated in a vacuum by a sputter coater. The photographs were taken at an excitation voltage of 10 kV.

## Transmission electron microscopy

A transmission electron microscope (JEM-1230, JEOL Ltd, Tokyo, Japan) was used to determine the morphology of the nanosuspensions. The nanosuspensions and redispersed nanosuspensions were placed on copper grids and negatively stained with 1% (w/v) uranyl acetate for 5 minutes at room temperature.

## In vitro dissolution

The drug dissolution profiles for the raw crystals, nanosuspensions stabilized using soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin, and the layered pellets were determined using US Pharmacopeia II apparatus (ZRS-8G release tester, Tianjin, People's Republic of China) at 100 rpm and a temperature of 37°C  $\pm$  0.5°C. Nanosuspensions, layered pellets, or raw crystals (25 mg) were added to 900 mL of fluid (phosphate buffer pH 6.8). Five milliliters of the samples were withdrawn at specific time intervals, filtered through a 0.2  $\mu$ m filter, and the drug concentration was determined by ultraviolet spectrophotometry.

## Differential scanning calorimetry

Dried nanosuspension powder samples carefully peeled off from the outer layer of the glass pellets were used for physical characterization by differential scanning calorimetry (DSC) and subsequent powder x-ray diffraction analysis. Briefly, the indomethacin nanosuspension formulation was layered onto glass pellets (0.8–1 mm) using a fluid-bed coater under the conditions described above. The layered glass pellets were placed in a porcelain mortar (180 mm) and then gently ground to peel off the coating layer. About 5 mg of the samples (pure indomethacin, freeze-dried nanosuspension powder, and dried powder) were weighed into a nonhermetically sealed aluminum pan, and DSC analysis was performed using a 204A/G Phoenix 1 instrument (Netzsch, Selb, Bavaria, Germany).

The samples were heated from 20°C to 250°C at a heating rate of 10 K per minute. The instrument was calibrated using indium. All DSC measurements were carried out in a nitrogen atmosphere at a flow rate of 100 mL per minute.

## Powder x-ray diffraction

Powder x-ray diffraction analysis of the samples (pure indomethacin, freeze-dried nanosuspension powder, and dried powder) was done using an X'Pert PRO diffractometer (Panalytical, Almelo, the Netherlands) over a  $2\theta$  range of 2.5–50 degrees at a scan rate of 3 degrees per minute, where the tube anode was Cu with  $K\alpha=0.154$  nm monochromatized with a graphite crystal. The pattern was collected at 40 kV of tube voltage and 60 mA of tube current in step scan mode (step size 0.02 degrees, counting time 1 second per step).

## Statistical analysis

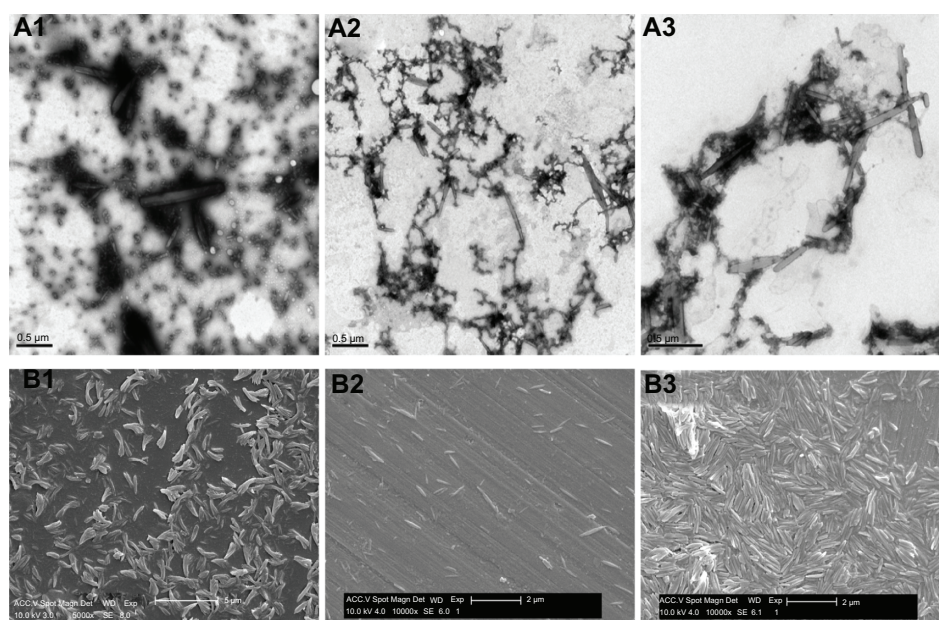
The results are expressed as the mean  $\pm$  standard deviation. One-way analysis of variance was used to assess the statistical significance of differences between samples. Results with  $P<0.05$  were considered to be statistically significant.

## Results and discussion

### Preparation and characterization of nanosuspensions

The food protein-stabilized nanosuspensions were successfully prepared using a precipitation-ultrasonication method. The particle size and size distribution were unchanged after the nanosuspensions were stored at 4°C for more than 30 days, indicating excellent stability. The particle sizes/zeta potentials of the nanosuspensions stabilized with soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin were 588 nm/–23.7 mV, 320 nm/–30.8 mV, and 243 nm/–25.9 mV, respectively. The polydispersity index is a measure of the homogeneity of dispersion, with values ranging from 0 to 1, where  $<0.3$  suggests a homogeneous dispersion.<sup>24</sup> The polydispersity index for nanosuspensions based on soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin was 0.17, 0.17, and 0.21, respectively, indicating a narrow particle size distribution. Further, transmission and scanning electron micrographs of the nanosuspensions revealed a needle-like morphology with particle diameters of about 200–600 nm (Figure 2), corresponding closely to the results obtained by dynamic light scattering. The stabilization effects on the nanosuspensions were attributed to two factors. Firstly, adsorption of protein onto the drug particles produced effective steric stabilization,<sup>3,25</sup> and secondly, the surface charge from





**Figure 2** Transmission (A1–3) and scanning (B1–3) electron micrographs of nanosuspensions stabilized by soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin (from left to right).

the  $-\text{COOH}$  groups on the proteins generated electrostatic repulsion, with an absolute zeta potential value of 20 mV being sufficient to maintain a stable nanosuspension.<sup>26</sup>

## Coating nanosuspensions onto pellets

Given that an increase in surface area results in an increase in free energy, the stability of drug nanosuspensions is a very challenging issue during pharmaceutical product development.<sup>3,8</sup> An ideal way of addressing this problem is to convert the nanosuspension into a solid form.<sup>10,13</sup> Therefore, in this study, we solidified the drug nanosuspensions using an easily scalable fluid-bed coating technology (Figure 1). The nanosuspensions coated into pellets were stabilized by soybean protein isolate-150 (containing 150 mg of indomethacin in acetone), whey protein isolate-150 (containing 150 mg of indomethacin in acetone), and  $\beta$ -lactoglobulin-200 (containing 200 mg of indomethacin in acetone). The coating formulations and their efficiency are shown in Table 1. The yield

of soybean protein isolate-150, whey protein isolate-150, and  $\beta$ -lactoglobulin-200 was 85.7%, 92.9%, and 88.3%, respectively, indicating excellent coating efficiency, mainly attributable to the excellent film-forming properties of PVP.<sup>27</sup> Similar yields were obtained from these three formulations, likely because the three proteins used have similar structures and physicochemical properties.<sup>28–30</sup> The surfaces of pellets layered with nanosuspensions stabilized by soybean protein isolate, whey protein isolate, or  $\beta$ -lactoglobulin were smooth (Figure 3A1–C1) and each layer of solidified nanosuspension was tightly packed and could be distinguished easily from the pellet cores (Figure 3A2–C2, 3A3–C3).

## Redispersibility study

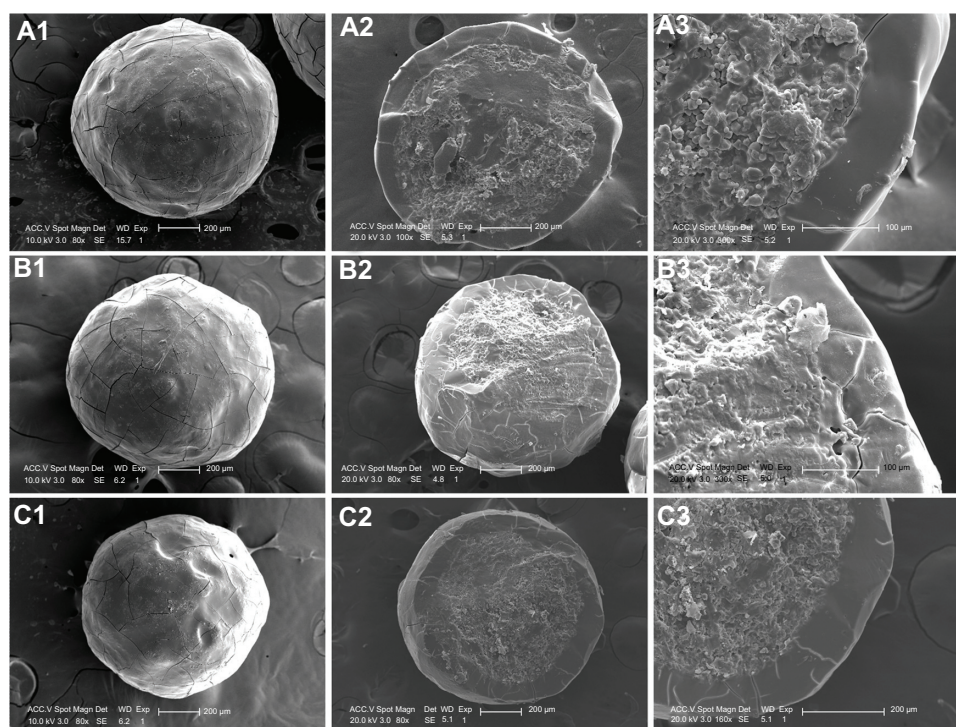
The redispersibility of solidified nanosuspensions is the most important factor and the main challenge in product development.<sup>31</sup> Therefore, we did a redispersibility study for the solidified nanosuspension pellets. The particle size and

**Table 1** Coating formulations and coating efficiency

Formulation (F)	Composition for coating							Yield (%)
	PVP K30 (g)	Aqueous of denatured SPI (mL)	Trehalose (g)	Water (mL)	Protein-stabilized nanosuspension (mL)			
					SPI	WPI	β-LG	
F1	3	10	1	20	50	–	–	85.7
F2	3	10	1	20	–	50	–	92.9
F3	3	10	1	20	–	–	50	88.3

**Note:** Concentration of denatured SPI in aqueous dispersion was 67 mg/mL.

**Abbreviations:** SPI, soybean protein isolate; WPI, whey protein isolate;  $\beta$ -LG,  $\beta$ -lactoglobulin; PVP, polyvinylpyrrolidone.



**Figure 3** Scanning electron micrographs of the surface and cross-section of pellets layered by nanosuspensions stabilized by soybean protein isolate (**A1–3**), whey protein isolate (**B1–3**), and  $\beta$ -lactoglobulin (**C1–3**).

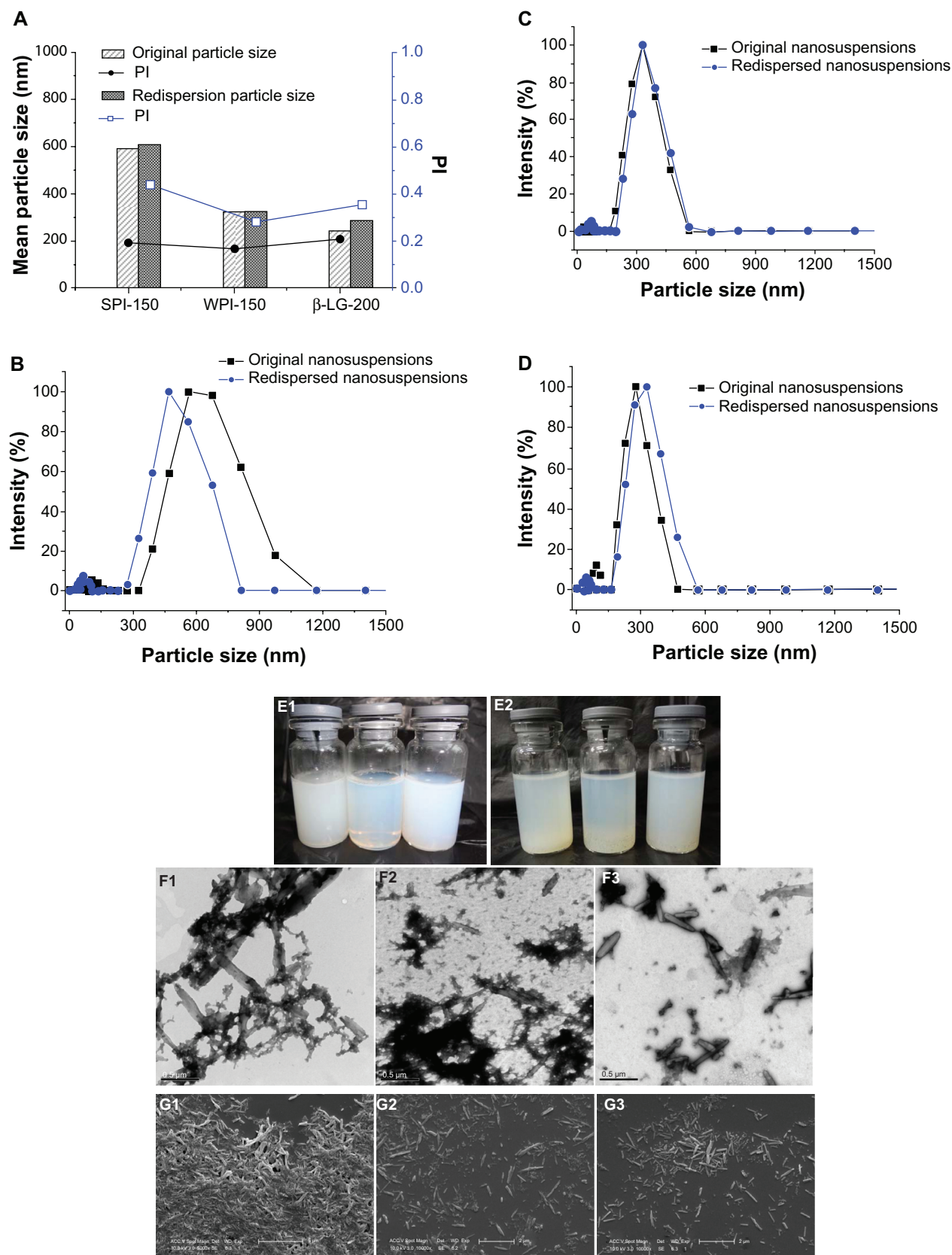
size distribution (intensity-weight Nicomp distribution) for the redispersed nanosuspensions are shown in Figure 4A–D. The particle size of redispersed nanosuspensions stabilized by soybean protein isolate was similar to that of the original nanosuspensions, but its size distribution showed a bimodal pattern and a slight shift into the smaller range. This may be because the denatured soybean protein isolate could not be rehydrated completely after the redispersion process. A similar phenomenon was observed with dried nanocapsules based on a soybean protein isolate in another report (He and Wu, unpublished data, 2013). The particle size and size distribution for the redispersed nanosuspension stabilized by whey protein isolate were almost identical to that of the original nanosuspension. The particle size of the redispersed nanosuspension stabilized by  $\beta$ -lactoglobulin was slightly increased to 289 nm from the original particle size of 243 nm, and the size distribution also shifted slightly towards the larger particle size range, which could be attributed to the smaller amount of protein used in formulation of the  $\beta$ -lactoglobulin-200 nanosuspension in comparison with that of the nanosuspensions containing soybean protein isolate or whey protein isolate. Our previous report suggested that, to some extent, food proteins with a globular structure could act as cryoprotectants, protecting the product from the stresses of freezing and drying.<sup>29</sup> The increased polydispersity index was ascribed to the fact that not

only the redispersed nanosuspensions but also the polymer PVP contribute to the intensity versus size distribution determined by dynamic light scattering.<sup>32</sup> Preservation of the nanoparticle diameter size after the drying process indicates that nanosuspensions stabilized by soybean protein isolate, whey protein isolate, and  $\beta$ -lactoglobulin can be converted successfully into a solid dosage form by fluid-bed coating technology.<sup>10</sup>

To confirm the results of dynamic light scattering, transmission and scanning electron microscopy were carried out to determine the morphology and particle size of the redispersed nanosuspensions. As shown in Figure 4E–G, redispersed nanosuspensions stabilized by soybean protein isolate, whey protein isolate, or  $\beta$ -lactoglobulin had a morphology and particle size similar to that of the original nanocrystals, consistent with the results obtained by dynamic light scattering.

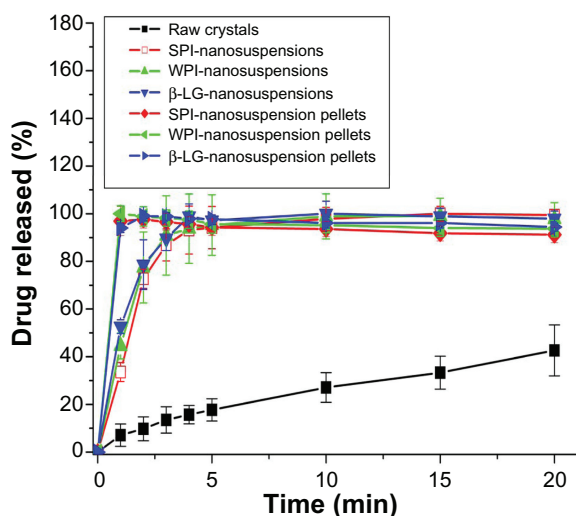
The synergistic protection afforded by soybean protein isolate and trehalose ensured redispersibility of the dried nanosuspensions in water. Firstly, nanocapsules stabilized by soybean protein isolate can be freeze-dried and coated onto the pellets directly, maintaining their original particle size and size distribution.<sup>29</sup> Secondly, it was shown that the soybean protein isolate-60, whey protein isolate-60, and  $\beta$ -lactoglobulin-30 nanosuspension formulations could be freeze-dried directly without addition of any other





**Figure 4** Particle size and polydispersity index data for original and redispersed nanosuspensions (A). Particle size distribution of original and redispersed nanosuspensions from pellets [stabilized by soybean protein isolate (B), whey protein isolate (C), or β-lactoglobulin (D)]. Optical photographs of the original (E1) and redispersed nanosuspensions (E2). Transmission (F1–3) and scanning (G1–3) electron micrographs of nanosuspensions redispersed from pellets. From left to right: soybean protein isolate, whey protein isolate, and β-lactoglobulin.

**Abbreviations:** PI, polydispersity index; SPI, soybean protein isolate; WPI, whey protein isolate; β-LG, β-lactoglobulin.



**Figure 5** In vitro dissolution profiles for indomethacin from the raw crystals, original nanosuspensions, and pellets layered by nanosuspensions in pH 6.8 phosphate-buffered solution at 37°C (n=3).

**Abbreviations:** SPI, soybean protein isolate; WPI, whey protein isolate; β-LG, β-lactoglobulin

cryoprotectants, with the ability to reconstitute to their original particle size and size distribution (data not shown). Trehalose clearly acts as a common protectant, and can also protect nanosuspensions against aggregation during the drying process.<sup>10</sup> However, the concentration of trehalose in our suspensions was too low to ensure redispersibility, and too high a concentration (>2%, w/w) would have greatly hindered the process of film coating. Another feature of the soybean protein isolate was its behavior as an antisticking agent in the coating formulation.

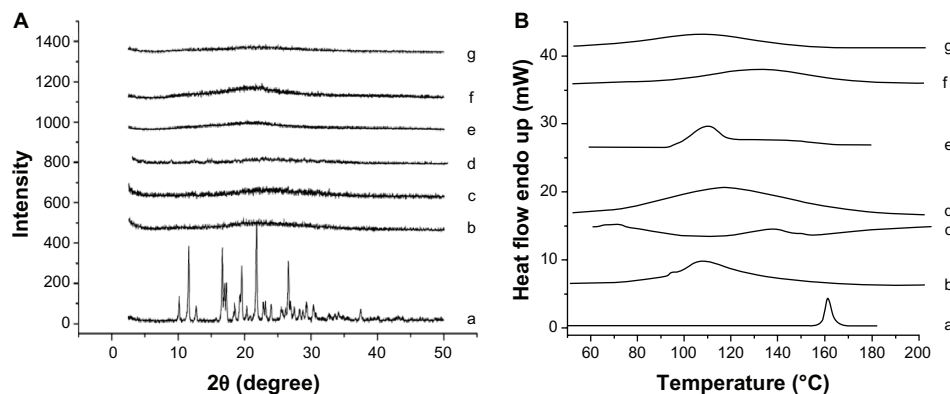
## In vitro dissolution

Preservation of rapid dissolution is another important property of solidified nanosuspensions.<sup>13</sup> The dissolution profiles for the raw drug powder, original drug nanosuspensions, and pellets layered by the nanosuspensions are shown in Figure 5.

Compared with dissolution of the raw drug powder, both the original drug nanosuspensions and pellets layered with the nanosuspensions showed much faster dissolution, with near complete dissolution within 5 minutes. The nanosuspension pellets showed dissolution profiles similar to those of the original drug nanosuspensions, but with a delay of 3 minutes, which could be explained by the fact that reconstitution of the compactly coated pellets took longer.<sup>33,34</sup> It is concluded that the dissolution capacity of the original nanosuspensions was preserved in the solidified nanosuspensions.

## Powder x-ray diffraction and DSC

Drug dissolution, absorption/bioavailability, and stability are influenced greatly by the form of the drug particle in the solid state. Herein we assessed the solid-state form of the drug particles by powder x-ray diffraction and DSC, by comparing the dried nanosuspensions prepared using fluid-bed coating and the original nanosuspensions obtained from freeze-drying. As shown in Figure 6A, the raw crystal powder showed diffraction peaks at 11.6, 17.3, 19.6, 21.8, and 26.6, ranging from 2.5°–50° (2θ), suggesting that the drug was highly crystalline in nature.<sup>35,36</sup> The same diffraction peaks were also observed in samples of the physical mixture. The diffraction peaks for the drug taken from samples of the original nanosuspensions disappeared, indicating that the drug particles were present in an amorphous state. Importantly, the powder x-ray diffraction patterns for the dried nanosuspensions prepared by fluid-bed coating did not show any diffraction peaks, suggesting that the drug particles were also present in an amorphous state. The DSC pattern (Figure 6B) confirmed the results obtained by powder x-ray diffraction. At about 160°C, the endothermic peaks of the active compound and its physical mixture were observed, whereas the melting peak was absent from the dried nanosuspensions prepared by fluid-bed coating



**Figure 6** Powder x-ray diffractograms (A) and differential scanning calorimetry thermograms (B) from bottom to top: raw crystals, freeze-dried powder from nanosuspensions stabilized by soybean protein isolate, whey protein isolate, or β-lactoglobulin, and pellet powder from nanosuspensions stabilized by soybean protein isolate, whey protein isolate, or β-lactoglobulin.



and from the original nanocrystals. Based on the results of DSC and powder x-ray diffraction, the dried drug particles in nanosuspensions prepared by fluid-bed coating are present in an amorphous state, and are not changed by the drying process.

## Conclusion

Nanosuspensions of indomethacin stabilized by food proteins were converted into a solid dosage form by fluid-bed coating. The solidified nanosuspension pellets preserved the redispersibility, solid state, particle size, and size distribution of the original nanosuspensions. Drug dissolution from the dried nanosuspensions was much faster than that from the raw crystals. The dissolution profile for the dried nanosuspensions was similar to that of the original nanosuspensions, save a delay of a few minutes. In summary, fluid-bed coating technology shows potential for the solidification of drug nanosuspensions. It is expected that a variety of fluidic nanoparticle dispersions could be converted into solid dosage forms using this strategy.

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## Disclosure

The authors report no conflicts of interest in this work.

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