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Simultaneous micronization and surface modification for improvement of flow and dissolution of drug particles

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ABSTRACT

Simultaneous micronization and surface modification of drug particles is considered in order to mitigate disadvantages of micronization, e.g., agglomeration, poor flowability, marginal increase in surface area and low bulk density. Particles of ibuprofen (102 μm), a model drug, pre-blended with hydrophilic nano-silica, are micronized down to 10 and 5 μm in a continuous fluid energy mill (FEM) to obtain fine surface modified particles. The solid feeding rate and the grinding pressure are shown as critical parameters for achieving the desired particle size and size distribution. The powder properties were characterized via SEM, laser scattering, powder rheometer with shear-cell, and dissolution test. Significant improvement in flow properties and dissolution rate was observed when micronization accompanied surface modification. Additionally, co-grinding with water-soluble polymer during micronization led to further increase in bulk density and more enhanced dissolution rate improvement, which is attributed to improved wettability. XRD, DSC and Raman were used to examine crystallinity, indicating minimal detectable physical transformation with FEM processed ibuprofen. The surface modified, micronized powders also showed improved dispersion, higher bulk densities (>0.4 g/ml), reduced electrostatic, and higher flowability (FFC ≥ 6) compared to just micronized powder (0.19 g/ml, FFC = 1.0), indicating they may be used in high drug loaded formulations amenable to direct compression.

1. Introduction

The Biopharmaceutics Classification System (BCS) has classified class II drugs as both poorly water-soluble and high intestinal permeability, indicating that their bioavailability is strongly controlled by their dissolution rate (Amidon et al., 1995). Since nearly 40% of all drugs being developed in the pharmaceutical industry are poorly water-soluble (Hu et al., 2004; Merisko-Liversidge et al., 2003), improving the dissolution rate of poorly water-soluble drugs is an important research area. It is well recognized that micronization that can increase the specific surface area, is a promising method to improve the dissolution rate (Liversidge and Cundy, 1995; Vogt et al., 2008; Hargrove et al., 1989; Merisko-Liversidge et al., 2003), as suggested by the Noyes–Whitney equation (Noyes and Whitney, 1897). Micronization alone, however, can lead to downstream processing problems related to their poor flow and dispersion properties. It is therefore important to develop a method that can simultaneously overcome these processing issues and micronize the drug particles. Although there are several top-down approaches, such as slurry mill (Liversidge and Cundy, 1995), or ball mill (Choi et al., 2001), in this paper, micronization of poorly soluble drugs utilizing jet mill (Midoux et al., 1999; Vogt et al., 2008) is considered. Jet milling uses the energy of the fluid (high pressure air) to achieve the required grinding, thus it is a dry process with no moving parts, and does not require any solvent and potentially can have minimal contamination. The process is also suitable for heat sensitive drugs and it is capable of manufacturing large quantities of powder in continuous fashion.

Simple micronization, however, will not always result in an increase in surface area and the expected improvement in dissolution rate. The high cohesion of micronized powders (Kendall and Stainton, 2001) results in the tendency for these particles to agglomerate (Perrut et al., 2005; Liversidge and Cundy, 1995; de Villiers, 1996). This subsequently gives rise to poor flowability, low bulk density and may lead to an increased tendency for electrostatic charging and thus adversely affecting downstream processing and handling. It can also lead to a significant loss of revenue due to non-uniformity of drug content in the final product (Räsänen et al., 2003). Subsequently, extra processing steps such as granulation may be required. Thus there is a significant motivation for developing approaches that improve the flow of fine powders obtained from micronization.

The importance of the flowability of pharmaceutical powders is well-documented (Staniforth, 2002; Liu et al., 2008). Many methods to improve the flowability of cohesive powders are

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based on controlled agglomeration or by coating of polymer films (Nokhodchi et al., 2007; Bajdik et al., 2004). A recent method that is effective and simple for improving the flowability of powders (Ramlakhan et al., 2000; Yang et al., 2005) is based on surface modification via dry coating, where the surface of the cohesive drug particles (host) is coated with small amount of nano-sized particles (guest). It has been also shown that cohesion is reduced due to the creation of nano-scale surface roughness (Chen et al., 2009, 2010; Yang et al., 2005), making this approach useful for present topic. Accordingly, simultaneous micronization and surface modification of drug particles is considered in order to improve the dissolution rate of poorly water-soluble drugs, while eliminating typical disadvantages of the simple micronization process such as, agglomeration, poor flowability, loss of expected large surface area and low bulk density. In the proposed process, a continuous fluid energy mill (FEM) is used where larger drug particles pre-blended with nano-silica are micronized to achieve fine surface modified drug particles via dry-coating of nano-silica. This was first suggested in (Yang et al., 2006), where non-pharmaceutical powders were shown to have improved flow due to surface coating with nano-silica. While it is expected that improved dispersion or reduced agglomeration after surface modification during micronization, may lead to improved dissolution, it could be further enhanced by co-grinding with water-soluble polymers in the FEM with a hope of imparting improved surface wettability. Generally large quantities (e.g. 75–90 wt%) of water-soluble excipients such as polymers and sugars are employed as solid dispersion excipients (Barzegar-Jalali et al., 2010; Otsuka et al., 1998; Mura et al., 2002), where drugs may typically attain amorphous content due to high mechanical energy co-grinding using ball-mills. In contrast, our study employs small amount of Polyvinylpyrrolidone (PVP) as co-grinding excipient, while nano-silica is added to enhance flow. It is hoped that PVP will impart improved wettability to drug powders, at the same time, using FEM that has significantly lower mechanical stresses and orders of magnitude shorter processing/residence time will not affect the crystalline form of the drug considered, and thus would be favorable in terms of physical stability of the drug (Vogt et al., 2008).

Ibuprofen, one of the widely used analgesic or anti-inflammatory drugs, is selected as a model poorly water-soluble BCS class II drug. Aqueous solubility of ibuprofen (molecular weight 206.28 g/mol) is very low (0.056 ± 0.004 mg/ml (Kocbek et al., 2006), 0.09 mg/ml (Milhem et al., 2000) and 0.081 mg/ml (Wikarsa et al., 2008)). In this paper, micronization of ibuprofen in the FEM along with dry coating using nano-silica with or without co-grinding with PVP was carried out in order to investigate if it leads to improved dissolution along with increase in flowability and bulk density, as compared to uncoated micronized ibuprofen powder.

2. Experimental

2.1. Materials

Ibuprofen 110 was purchased from Alfa Chem, (NY, USA), having volume median particle size (d_{50}) of 102 μm, and volume mean particle size ($d_{[4,3]}$) of 123 μm, and is found to be cohesive and difficult to feed through a volumetric feeder. Pharmaceutical grade amorphous hydrophilic silica (M-5P type, primary particle size of 15 nm) was received from Cabot Corporation (MA, USA). PVP 40 (average mol wt 40,000, median particle size 95 μm), monosodium phosphate, sodium dodecyl sulfate and disodium phosphate were purchased from Sigma-Aldrich Inc., USA. All other chemicals used were analytical grade.

2.2. Preparation of FEM processed samples

2.2.1. Pre-mixing of powders in V-blender

Pre-mixing of powders was performed in a 6-quart V-shaped blender (BlendMaster, Patterson-Kelley, PA, USA) operated at 25 rpm with intensifier bar rotated at 3600 rpm. Three types of pre-mixed powders were prepared: (1) ibuprofen (500 g) pre-mixed with silica (varied from 0.5 wt% to 5.0 wt%), was processed for 10 min with intensifier bar followed by 20 min without intensifier bar; (2) ibuprofen pre-mixed with silica (400 g) and PVP (100 g) was processed for 5 min; and (3) ibuprofen (400 g) and PVP (100 g) was processed for 5 min.

2.2.2. Processing in fluid energy mill

Pre-mixed powders were processed in a qualification FEM unit (Sturtevant Inc., MA, USA). Solid feeding rate (SFR) was controlled by a volumetric feeder (Schenck Accurate, WI, USA) and was calibrated using the pre-mixed powder before each experiment. Fig. 1 illustrates the experimental setup and methodology. Processed powder was stored in vacuum desiccators for subsequent flow characterization and dissolution test. Based on the preliminary experiments and literature (Yang et al., 2006; Teng et al., 2009), a constant feeding pressure (FP) of 30 psi, grinding pressure (GP) in range 10–30 psi, and SFR in range 1.0–10.0 g/min were used; see Table 1. From these experiments, two typical samples with different sizes (d_{50} are 5 and 10 μm) were selected for further study (Table 2). Co-grinding with PVP was carried out only for 10 μm particles using the processing condition similar for 10 μm particles. For uncoated samples (for nomenclature, see Table 2), UC-IBU-5, UC-IBU-10 and UC-IBU-PVP-10, due to their cohesivity, it was difficult to control the solid feed rate and hence multiple experimental runs were required to collect required size samples.

2.3. Powder characterization

2.3.1. Particle size measurement

Particle size distribution was measured via the laser diffraction technique (Rodos/Helos system, Sympatec, NJ, USA) where the d_{10}, d_{50}, d_{90} and $d_{[4,3]}$ size statistics are reported. In addition, pressure titration tests were performed by a series of repeat measurements at different dispersion pressures (0.2–2.0 bar). All FEM processed powders were tested twice using the Rodos/Helos system to characterize their dispersibility.

2.3.2. Scanning Electron Microscope (SEM)

The morphology of particles was examined using a Field Emission Scanning Electron Microscope (FESEM) (LEO 1530 170, Carl Zeiss SMT Inc., MA, USA). All powder samples were pre-coated with carbon using a sputter coater to enhance conductivity.

2.3.3. Angle of repose test

Angle of repose is the internal angle between the surface of a pile of powders and the horizontal surface, one of four conventional methods for characterizing powder flow according to the United Stated of Pharmacopeia (USP) (Geldart et al., 2009; Thalberg et al., 2004; Lavoie et al., 2002). AOR measurements were done using the Hosokawa powder tester (Model PT-N, Hosokawa Micron Powder System Co., NJ, USA) according to the standard ASTM D6393-08, "Bulk solids Characterization by Carr Indices". AOR in the range of 25–35° indicates excellent flowability, AOR less than 40° is considered to be acceptable and AOR greater than 45° is considered to be cohesive or poorly flowing (Carr, 1965). Each measurement was repeated at least 4 times and average values are reported.

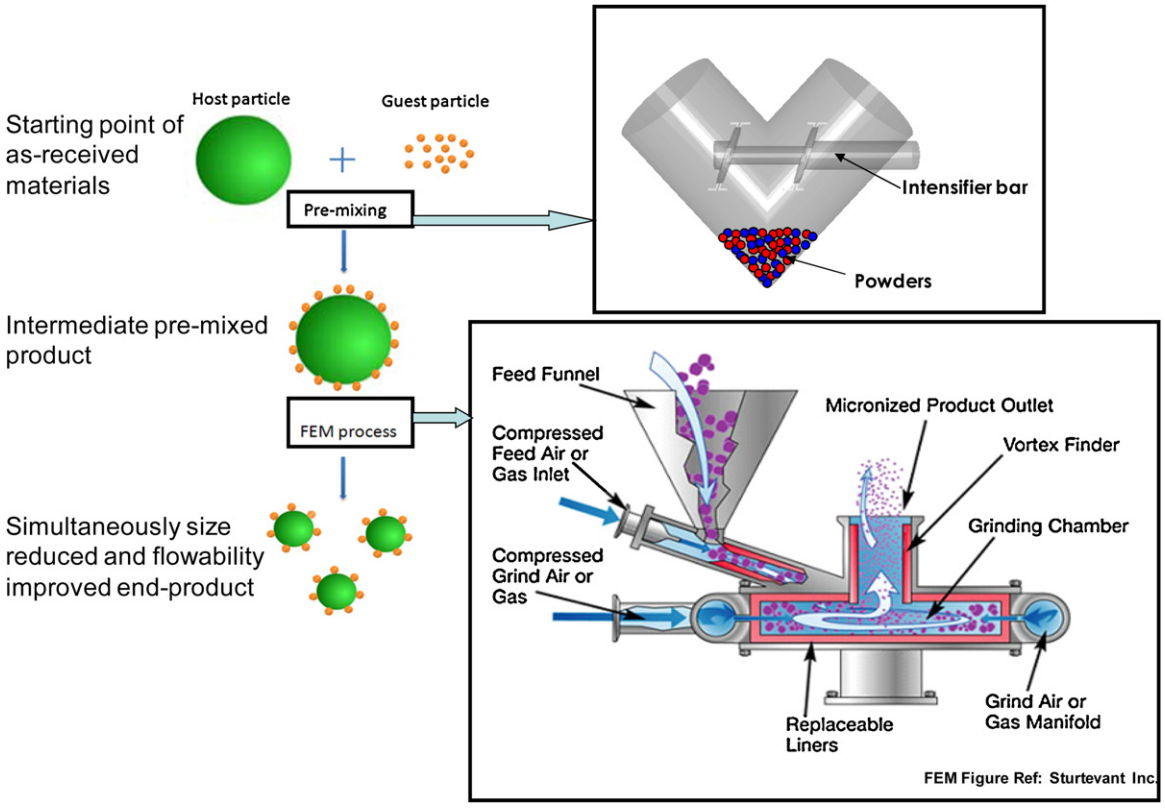


Fig. 1. Schematic illustration of the experimental setup and methodology.

Table 1
List of experiment for studying the effect of FEM operating conditions on particle size.

Serial #	Experiment code	Material	FP (psi)	GP (psi)	SFR (g/min)	d_{50} (μm)	span
1	FEM-GP10-SFR1	Ibuprofen pre-mixed with 1.0 wt% of nano-silica	30	10	1.0	3.6	1.4
2	FEM-GP10-SFR5		30	10	5.0	9.1	2.0
3	FEM-GP10-SFR10		30	10	10.0	16.8	2.1
4	FEM-GP20-SFR1		30	20	1.0	2.3	1.3
5	FEM-GP20-SFR5		30	20	5.0	5.4	1.7
6	FEM-GP20-SFR10		30	20	10.0	8.3	1.9
7	FEM-GP30-SFR1		30	30	1.0	1.7	1.3
8	FEM-GP30-SFR5		30	30	5.0	3.4	1.5
9	FEM-GP30-SFR10		30	30	10.0	5.1	1.7

span = $[(d_{90} - d_{10})/d_{50}]$.

2.3.4. Powder characterization using FT4 powder rheometer

Powder properties were also characterized using a powder rheometer (Lindberg et al., 2004; Zhou et al., 2010) using a Freeman FT4 powder rheometer with a shear cell module (Freeman Technology Ltd., Worcestershire, UK) utilized for the following three tests: (1) conditioned bulk density test, (2) compressibility test and (3) shear cell test. Detailed experimental procedure is described elsewhere (Freeman, 2007). All

Table 2
Sample list.

Sample code	Sample description	$d_{[4,3]}$ (μm)	d_{10} (μm)	d_{50} (μm)	d_{90} (μm)	span
As-received-IBU	Original as received ibuprofen	122.5	22.1	102.8	245.5	2.1
DC-IBU-5	Dry coated and micronized ibuprofen with median particle size about 5 μm	6.2	1.7	5.5	11.3	1.7
UC-IBU-5	Uncoated and pure micronized ibuprofen with median particle size about 5 μm	5.6	1.1	5.2	9.9	1.7
DC-IBU-10	Dry coated and micronized ibuprofen with median particle size about 10 μm	11.2	3.5	10.9	21.5	1.7
UC-IBU-10	Uncoated and pure micronized ibuprofen with median particle size about 10 μm	15.0	3.0	11.8	30.9	2.4
DC-IBU-PVP-10	Dry coated ibuprofen co-ground with PVP, median particle size about 10 μm	11.2	2.4	11.4	19.1	1.5
UC-IBU-PVP-10	Uncoated ibuprofen co-ground with PVP, median particle size about 10 μm	10.4	2.2	9.9	19.2	1.7

DC: dry coated, UC: uncoated, IBU: ibuprofen, 5: median particle size of 5 μm, PVP: co-ground with PVP, 10: median particle size of 10 μm.

the powder samples were tested twice and average values are reported.

Before each measurement, sample was conditioned to ensure reproducibility of the powder testing. During conditioning, the energy required to move the blade was measured as specific energy (SE). Typically, for SE < 5, powder has low cohesion; for 5 < SE < 10, powder has moderate cohesion; for SE > 10, powder has high cohesion.[2]

Compressibility of powder sample was determined by measuring the volume (or density) change of the powder sample as a function of applied normal stress. Conditioning blade was replaced by a vented porous piston which was programmed to apply 1, 2, 4, 6, 8, 10, 12 and 15 kPa normal stresses across the whole cross section of the vessel.

The shear cell module of FT4 was used to measure the shear stress at different normal stresses applied on the powder, which was pre-consolidated at 3 kPa based on the recommendation of ASTM standard for powders having low density (Emery et al., 2009) and the range normally used for pharmaceutical powders. A Mohr's diagram was constructed from which several parameters were obtained, namely, maximum principle stress (σ_1), the unconfined yield stress (σ_c), the flow function coefficient (FFC) and cohesion. FFC, the ratio of maximum principle stress to the unconfined yield stress, is the most commonly used parameter for powder flow characterization (Schulze, 2008; Schulze). Powder flow behavior similar to that by Jenike (Jenike, 1964) has been defined by Schulze: i.e., FFC < 1, not flowing; 1 < FFC < 2, very cohesive; 2 < FFC < 4, cohesive; 4 < FFC < 10, easy flowing, and FFC > 10, free-flowing (Schulze, 2008).

2.3.5. X-ray powder analysis (XRD)

For examining crystallinity of processed drug powders, X-ray powder diffraction (XRD) was performed using Siemens Philips PW3040 X-ray diffractometer (MA, USA) using Cu as a target at a voltage of 45 kV and current of 40 mA. Samples were scanned for a 2θ range of 5–45° at 1° (2θ)/min by a Cu_K radiation source of wavelength 1.542 Å.

2.3.6. Raman spectroscopy

Raman spectroscopy as an additional technique was applied to test the crystallinity of the samples. EZRaman LE Raman Analyzer System (Enwave Optronics, Inc., CA, USA) coupled to MicroView adapter with a 4× objectives, 15 μm spot size, 250 mW 785 nm excitation laser was used to scan the samples. Each sample measurement corresponded to an average of 2 scans, each 10 s long, totaling 20 s in scanning time.

2.3.7. Differential scanning calorimeter (DSC)

Differential scanning calorimetry was performed using DSC Q100 analyzer (TA Universal Instruments, DE, USA) equipped with a refrigerated cooling system. The chamber was flushed with N_2 at a flow rate of 40 ml/min during the test. About 3 mg of sample was heated in an aluminum pan from 35 °C to 90 °C at a constant heating rate of 10 °C/min. The DSC data were analyzed by using Universal Analysis 2000 software. The heat of fusion was calculated (Niwa et al., 2010) from the peak area of thermogram corresponds to melting point of ibuprofen. The crystallinity (X_{cr}) was calculated according to Eq. (1). Silica content was ignored because of small amount used (1.0 wt%).

$$X_{cr} = \frac{H}{H_0} \times 100\% \quad (1)$$

where H_0 and H are the heat of fusion of the original crystals and the micronized crystals respectively. Samples were tested twice and average values are reported.

2.3.8. Surface area measurement

The Brunauer–Emmett–Teller surface areas of the samples were measured using a nitrogen adsorption instrument, NOVA 3200 (Quantachrome instruments, FL, USA), using a standard protocol. Before testing, each sample with known weight was degassed overnight at room temperature under vacuum to remove adsorbed gases and nitrogen was used as adsorbent gas. Samples were tested twice and average values are reported.

2.3.9. Electrostatic measurement

The electrostatic charge accumulated by the powders during the FEM processing was measured by utilizing a Nanocoulombmeter equipped with a Faraday Cup (Model 230, Electro-Tech Systems, Inc., PA, USA) in a temperature and humidity controlled environment. For each measurement, certain amount of powder, collected fresh after FEM processing, was gently placed into the faraday cup. The charge was transferred to the cup and measured by the Nanocoulombmeter. For each powder, at least three measurements of each sample were performed and average value was reported.

2.4. Powder dissolution test

Dissolution studies were performed according to the USP 30 dissolution procedure for apparatus 1 (Rasenack and Müller, 2002) using a Distek 2100A dissolution apparatus (Distek Inc., NJ, USA) with a temperature control system (TCS 0200). The dissolution medium (900 ml) was phosphate buffer solution (pH 7.2) with 50 mg sodium dodecyl sulfate (SDS). The basket rotating speed was 50 rpm, and the temperature was maintained at 37 ± 0.2 °C. Powder samples equivalent to 200 mg of ibuprofen were added to the dissolution apparatus for dissolution test. Liquid medium was collected at pre-determined time intervals, and filtered through a 0.45 μm filter for further quantitative test. Quantitative test of dissolved amount of drugs was carried out using an Agilent 8543 UV–visible spectrophotometer (Agilent Technologies, CA, USA) at 221 nm. All the experiments were performed in triplicate and average values are reported.

3. Results and discussion

3.1. Effect of FEM operating conditions on the particle size

The effects of experimental conditions on particle size of ibuprofen (pre-mixed with 1.0% of silica) were investigated, as listed in Table 1, with the constant feeding pressure at 30 psi. The effect of grinding pressure and feeding rate on particle size is depicted in Fig. 2. At a constant feeding rate, an increase in grinding air pressure leads to a decrease in resulting median particle size due to more energy input to the feed powders, leading to faster particle movement in the grinding chamber and more intense particle–particle and particle–wall collisions. The effect of feeding rate on milling behavior is also shown in Fig. 2, indicating that under the same grinding pressure, a higher feeding rate results in larger ground particles. This may be attributed to the shorter residence time of particle in the grinding chamber and lower kinetic energy available for grinding, resulting in some large particles leaving the milling chamber sooner (Yang et al., 2006; Teng et al., 2009). In addition, span $[(d_{90} - d_{10})/d_{50}]$ calculated from the particle size distribution is also shown in Table 2. It is observed that at fixed grinding pressure, an increase in feeding rate increases the span, implying wider particle size distributions.

[2] From FT4 manual.

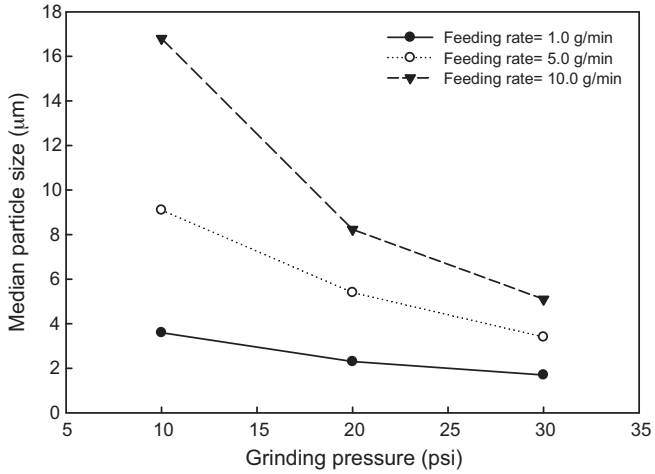


Fig. 2. Effect of experimental conditions on particle size.

These results show that it is possible to control the particle size in the FEM by altering the experimental conditions; thus as received ibuprofen (102.8 μm) was successfully micronized into particles smaller than 20 μm. As shown in Table 2, samples DC-IBU-5 and DC-IBU-10 have median particle size of 5.5 and 10.9 μm, respectively. The shapes of particle size distribution for both powders are almost same with a relatively narrow size distribution as shown in Fig. 3.

3.2. Morphology from SEM

SEM images of as received and processed ibuprofen are shown in Fig. 4. As depicted by Fig. 4a, b, the rod shaped original ibuprofen particles have rough surfaces and high aspect ratio (length over width (Liu et al., 2008)) of approximately 5. This highly non-spherical shape is expected to affect the flow properties and bulk density (Nokhodchi et al., 2007). When pure ibuprofen was micronized in the FEM, micronized particles are found to adhere to each other due to strong inter-particle force and form irregular shape agglomerates (as shown in Fig. 4c, d). This greatly affects the flowability of ibuprofen. This phenomenon will be discussed further in Section 3.6. In contrast, after FEM processing of ibuprofen with silica coating, ibuprofen was found to be micronized into fine and more spherical particles (as shown in Fig. 4e, f). In addition, silica coating reduces the cohesion force among particles; as a result tendency to form agglomerates decreased greatly (Fig. 4e).

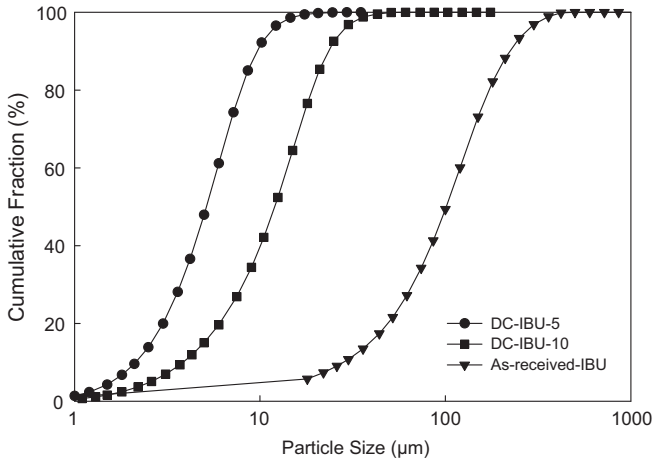


Fig. 3. Particle size distribution of as received ibuprofen and micronized samples: DCIBU-5 and DC-IBU-10.

This is expected to improve the flowability of ibuprofen powder (Nokhodchi et al., 2007).

3.3. Effect of amount of silica

The effect of amount of silica on the flowability of powder was studied. All DC-IBU-10 samples were processed with different amount of silica under the same experimental conditions (grinding pressure = 10 psi, feeding pressure = 30 psi and feeding rate = 5.7 g/min). For sample UC-IBU-10, as mentioned before, different experimental conditions were applied to produce powders with comparable size. The median size of all the samples is about 10 μm. The angle of repose results after the FEM process with different weight percentage of silica coating are shown in Fig. 5. The results indicate that 1.0 wt% of silica is the optimum coating amount, because further increase of nano-silica (up to 5.0 wt%) does not affect the AOR much (about 38°). Similar experimental procedures were followed with DC-IBU-5 samples (grinding pressure = 30 psi, feeding pressure = 30 psi and feeding rate = 10 g/min), and it was found that the optimum amount of silica for 5 μm powders is 4.0 wt%, which makes sense because of the increase in specific surface area for finer powder. Thus in the following section, all the flowability results of 5 and 10 μm powders are based on 4.0 wt% and 1.0 wt% silica coating, respectively.

3.4. Effect of FEM process on flowability and bulk density

The angle of repose results for all 5 and 10 μm ibuprofen samples are summarized in Table 3. From the table, it can be observed that the as-received-IBU is cohesive and does not flow well and the corresponding angle of repose is 53.0°. For the 10 μm uncoated sample UC-IBU-10, the AOR is also 53°, which is considered in "poor" flow range. While for the dry coated DC-IBU-10 sample, the AOR is reduced to less than 40°, 15° lower than the uncoated and also the as-received-IBU. This indicates that after dry coating the flowability is significantly improved and silica coating played an important role in improving the flowability. For the uncoated sample UC-IBU-10, it seems that it flows just as poorly as as-received ibuprofen and not much worse, which is likely due to the agglomeration among the pure micronized particles, as confirmed by actual photographs of these powder samples (actual images of DC-IBU-10 and UC-IBU-10 are shown in Fig. 6). The angle of repose for corresponding co-ground sample (DC-IBU-PVP-10) is 36°, which is slightly less than DC-IBU-10, indicating improved flowability similar to DC-IBU-10. Thus, the AOR results indicate that simultaneous micronization and dry coating in FEM can produce micro-sized particles with improved flowability ascribed to the nano-sized silica coating on the surface. The ibuprofen samples, when milled to 5 μm (DC-IBU-5 and UC-IBU-5), had comparable AOR values to their 10 μm counterparts (DC-IBU-10 and UC-IBU-10), respectively, as listed in Table 3.

Flow properties of different ibuprofen samples were also characterized with the FT4 powder rheometer (Table 3). The results from the shear test are very reproducible. It is shown that the as-received-IBU is cohesive with a FFC of 3.9. The FEM processed uncoated sample, UC-IBU-10 is found to be very cohesive (FFC = 1.0) and has very low bulk density of 0.19 g/ml. For FEM processing with silica (dry coated), DC-IBU-10, not only the FFC increased by 6 times to 6.1 but also the density increased by 1.7 times to 0.33 g/ml. These results confirm that dry coated sample (DC-IBU-10) has much better flowability and can be classified as easy flowing powder. In fact, the FFC for sample DC-IBU-10 (~10 μm) is even higher than the original as-received-IBU (~100 μm). Similar improvement in flowability and bulk density for 5 μm samples was observed and results are summarized in Table 3.

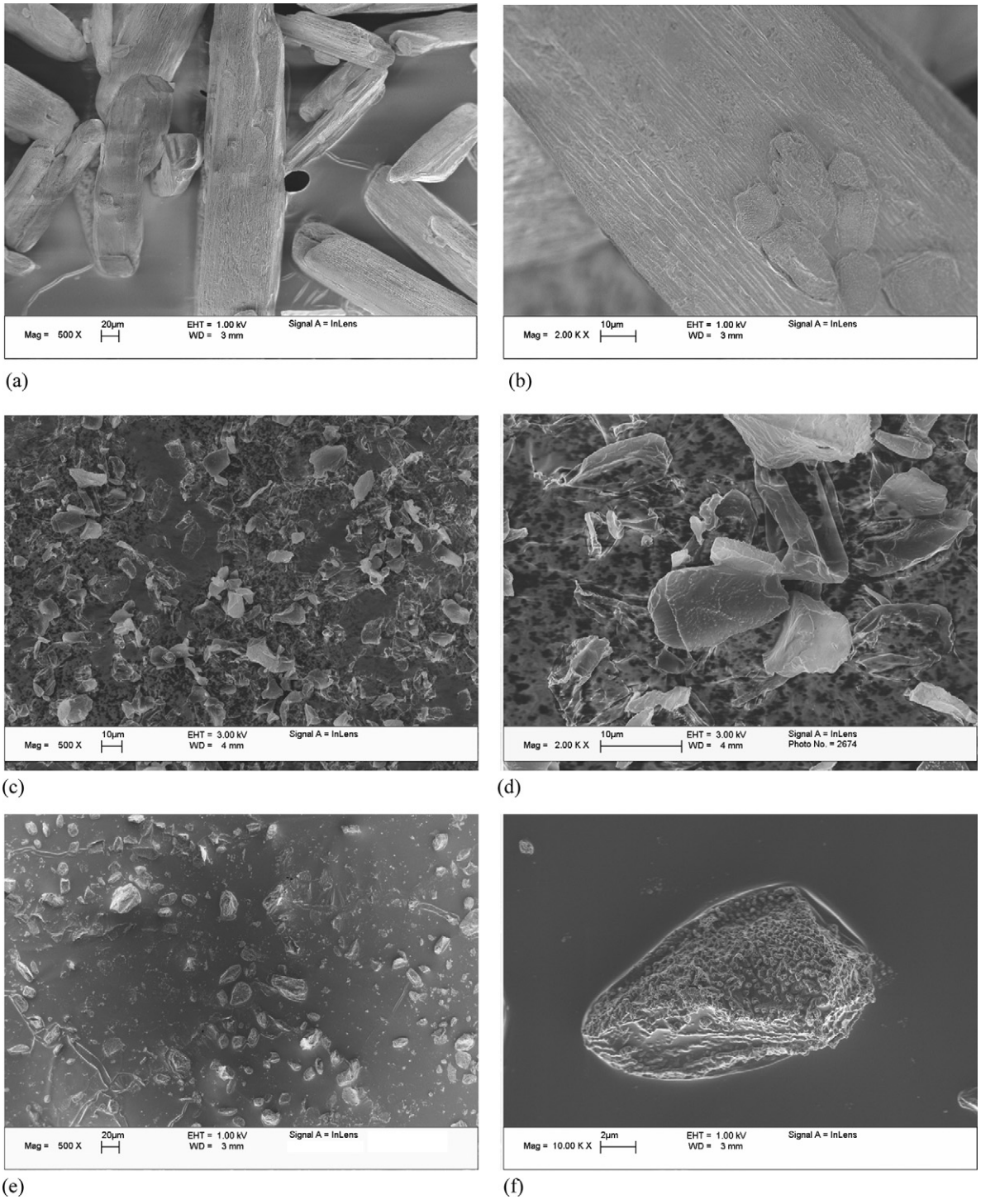


Fig. 4. SEM images of ibuprofen powders: (a, b) As-received-IBU, (c, d) UC-IBU-10 and (e, f) DC-IBU-10.

Table 3
FT4 results summary.

	As-received-IBU	As-received-PVP	UC-IBU-10	DC-IBU-10	UC-IBU-PVP-10	DC-IBU-PVP-10	UC-IBU-5	DC-IBU-5
AoR (°)	53.0 (0)	36.3 (0.6)	53 .0 (2.2)	38 .0 (0.5)	54.8 (2.1)	36.0 (0.7)	55.1 (1.8)	38.0 (0.7)
Bulk density (g/ml)	0.45	0.45	0.19	0.33	0.24	0.48	0.20	0.23
FFC	3.9 (0.17)	8.1 (1.39)	1.0 (0.08)	6.1 (0.86)	1.1 (0.20)	5.9 (0.41)	1.1 (0.10)	4.7 (0.10)
Cohesion (kPa)	0.40 (0.03)	0.18 (0.02)	1.37 (0.15)	0.24 (0.03)	1.38 (0.83)	0.23 (0.02)	1.36 (1.73)	0.28 (0.02)
Specific energy (mJ/g)	7.0 (0.32)	3.4 (0.11)	7.4 (0.10)	2.5 (0.21)	8.0 (0.25)	4.2 (0.12)	11.1 (0.92)	3.0 (0.18)

Standard deviations are shown in the parentheses. For bulk density, standard deviation is not shown because of the very low values.

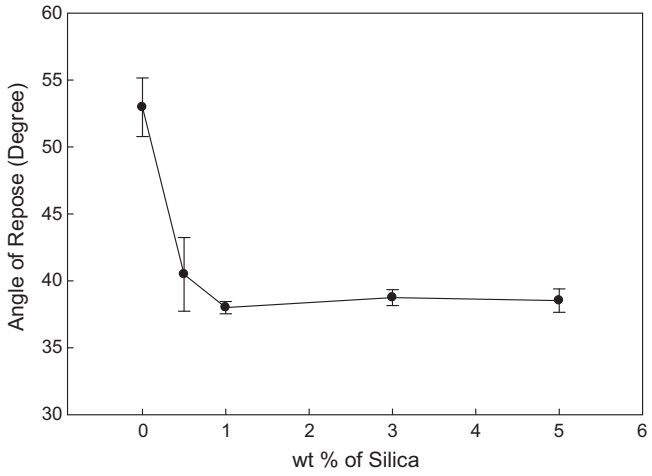


Fig. 5. Angle of repose of ibuprofen after FEM process with different weight percentage of silica (median particle size for all the powders are 10 μm).

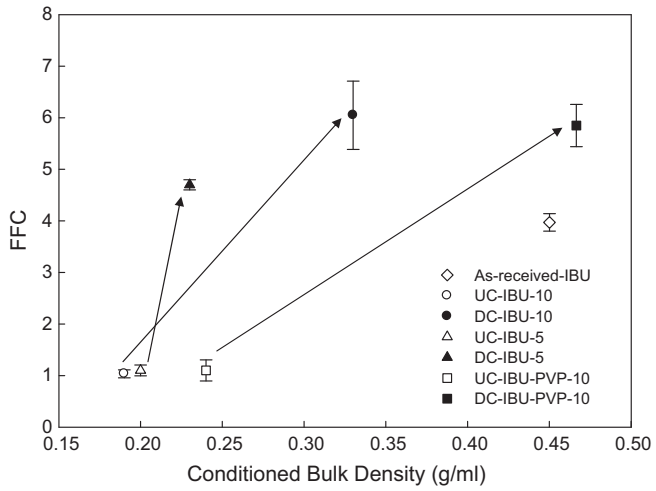


Fig. 7. Phase map: FFC vs. bulk density.

The results for co-grinding with PVP are also shown in Table 3. Comparing the FFC and bulk density of samples (DC-IBU-PVP-10, UC-IBU-PVP-10 and DC-IBU-10), it is clear that the surface modification helps improve the flowability of the powders, and co-grinding with PVP helps to further increase the bulk density of the powder, without having any adverse effect on powder flow. Specific Energy, SE values and cohesion also confirm that powder flow is improved for dry coated samples indicated by significantly lower SE values below 5 and low cohesion (Table 3). All the results from FT4 rheometer also correlate well with the AOR results from Hosokawa powder tester. These results indicate that the disadvantages of simple micronization, such as poor flow and low bulk density, can be eliminated by simultaneous micronization and surface modification using silica due to the reduced inter-particle cohesion force between the surface modified ibuprofen particles (Yang et al., 2005; Chen et al., 2009).

As mentioned in the introduction, both the flowability and bulk density are important parameters for powder processing as they may be used together as useful indicators of rank ordering of powder flow properties and assessment of various modes of property enhancements. The ability to discern flow improvement through these two parameters is illustrated in a simple but informative phase map of FFC against bulk density in Fig. 7. From this figure, three arrows indicate the extent of the improvement in both flow and bulk density after surface modification and/or co-grinding. For both the sizes (5 and 10 μm samples), dry coating and co-grinding in the FEM changed the powder from very cohesive to easy flowing powder and the bulk density improvements are significant.

3.5. Effect of FEM process on compressibility

Compressibility is a characteristic measurement of powders indicating the ease of storage, handling and transport (Carr, 1965). Lower compressibility indicates there is efficient packing among the particles and a minimal amount of excess air in the bulk, which is a desirable property for pharmaceutical powders intended for solid dosage forms (Carr, 1965). This typically occurs when the inter-particle cohesive forces are low in comparison to particles own inertial forces. Compressibility results for all the samples are presented in Fig. 8. As seen, compressibility of all processed samples with silica coating and co-grinding (DC-IBU-5, DC-IBU-10 and DC-IBU-PVP-10) is lower than as-received-IBU. In contrast, compressibility for pure micronized powders (UC-IBU-5, UC-IBU-10 and UC-IBU-PVP-10) is higher than as-received-IBU. It can be concluded that over the range of normal stress (1–15 kPa), dry coated micronized ibuprofen shows an improved compressibility property compared to both the pure micronized (without silica coating) and as received powders. Similar observation is also reported for mechanically dry coated samples (Zhou et al., 2010).

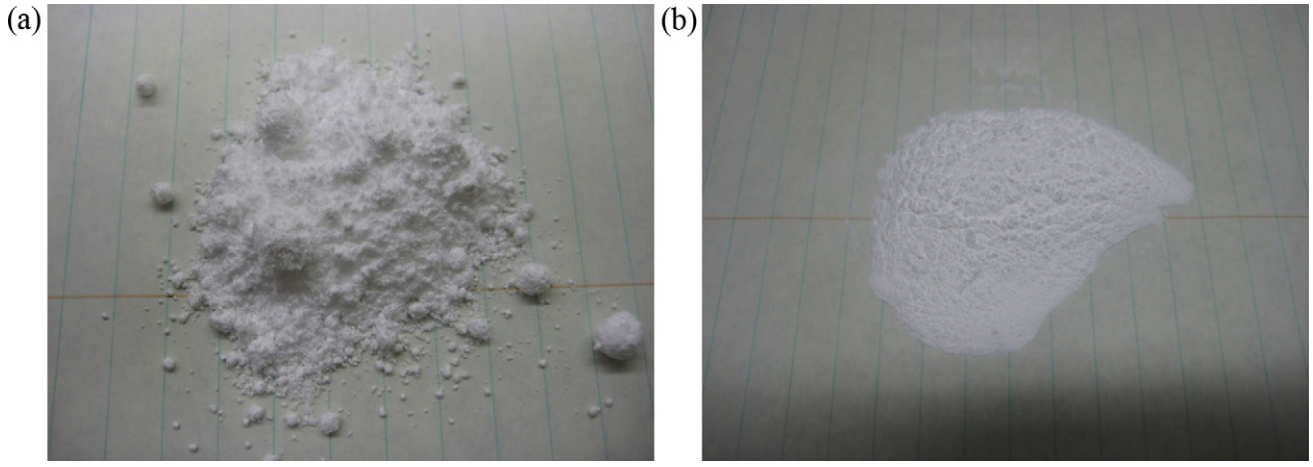


Fig. 6. Images of FEM processed samples: (a) UC-IBU-10 and (b) DC-IBU-10.

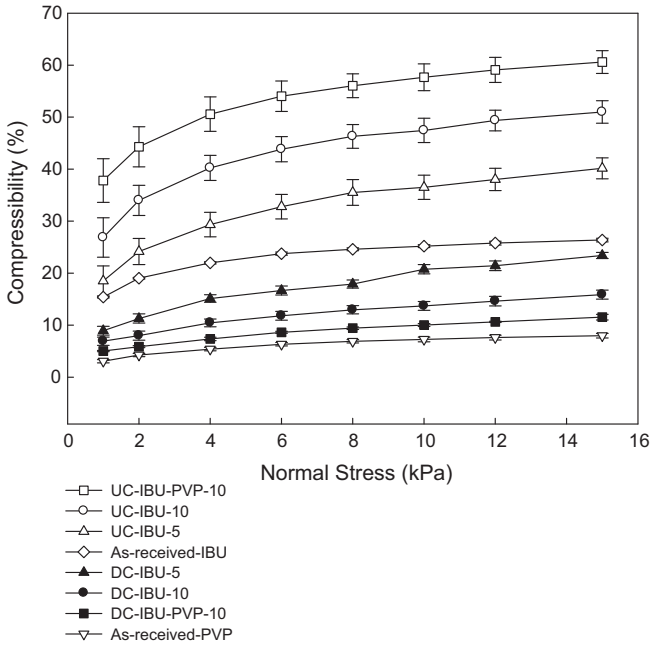


Fig. 8. FT4 compressibility results.

3.6. Effect of FEM process on dispersibility

Generally dispersibility of particles is significantly impacted by particle size and size distribution given that other particle or material properties are similar. As described by Kaye et al. (2009), the gradient in d_{90} over the dispersion pressure range can be used as an indication of the dispersibility for the powders. A smaller gradient indicates better dispersibility. Pressure titration curves of samples UC-IBU-10 and DC-IBU-10 along with co-ground sample DC-IBU-PVP-10 are shown in Fig. 9. It can be observed that for pure micronized powders without surface modification, there is a sharp drop in the d_{90} and d_{50} with increasing the dispersion pressure. This is believed to be an indication of deagglomeration of severely agglomerated original powders, which is confirmed by SEM imaging (Fig. 4c, d). It can also be observed that the dry coated micronized powders (DC-IBU-10) and the co-ground/coated powders (DC-IBU-PVP-10) have fairly flat pressure titration curves, indicating little deagglomeration due to increased pressure, implying no agglomeration in the original dry coated powders as indicated by SEM imaging (Fig. 4e, f). It is evident from these plots that there is a clear difference in dispersibility between the micronized ibuprofen powders with and without silica coating.

3.7. Effect of FEM process on electrostatic charge tendency

The tendency of fine powders to electrostatically charge, especially during dry micronization is a major problem in pharmaceutical manufacturing (Matsusaka et al., 2010). Fig. 10 shows preliminary experiments, performed at a temperature of 17.8 °C and relative humidity of 15%, to measure the electrostatic charge of the pure and silica coated ibuprofen after FEM processing. It can be seen that the electrostatic charge for the pure micronized sample is very high, which may affect downstream processing. Such material processing may also require certain idle time to allow dissipation of charge before powder recovery, which adversely impacts the processing time and efficiency. It was observed that discharging and transferring these powders between processing equipment was indeed difficult and a significant amount of powders stick to the equipment. In contrast, for the micronized dry coated sample the electrostatic charge is significantly reduced as compared to the uncoated micronized powders, indicating that simultaneous coating and micronization can produce fine powders with reduced electrostatic charge. In a future study, a more comprehensive investigation will be carried out to determine the influence of processing parameters and material properties (drug particles as well as coating material) on the electrostatic charging tendency.

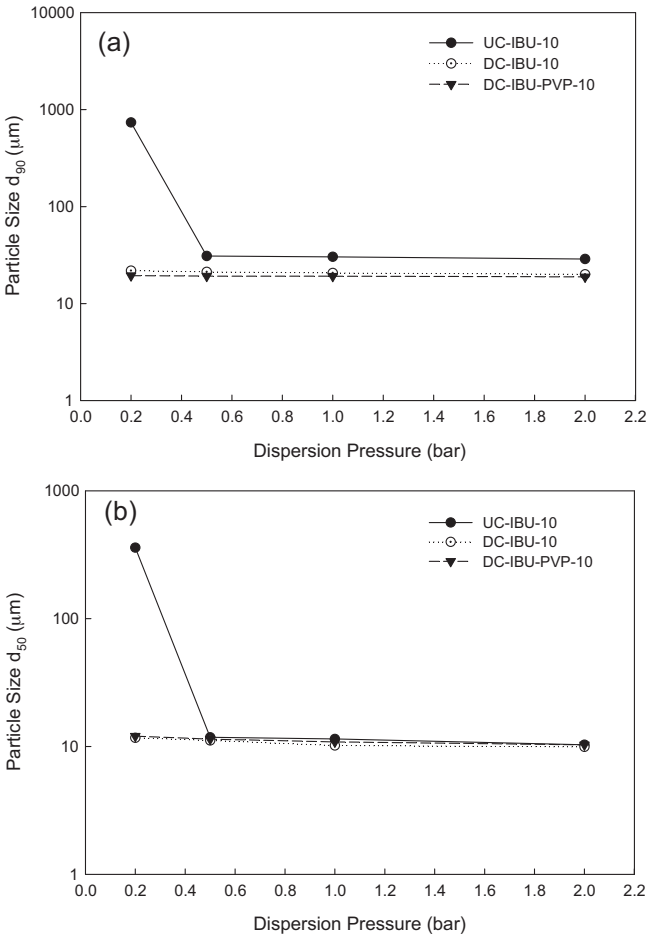


Fig. 9. Pressure titration curves: d_{90} (a) and d_{50} (b) for sample UC-IBU-10, DCIBU-10 and DC-IBU-PVP-10 d_{50} and d_{90} are the volumetric diameters at which 50% and 90% of the particles are smaller.

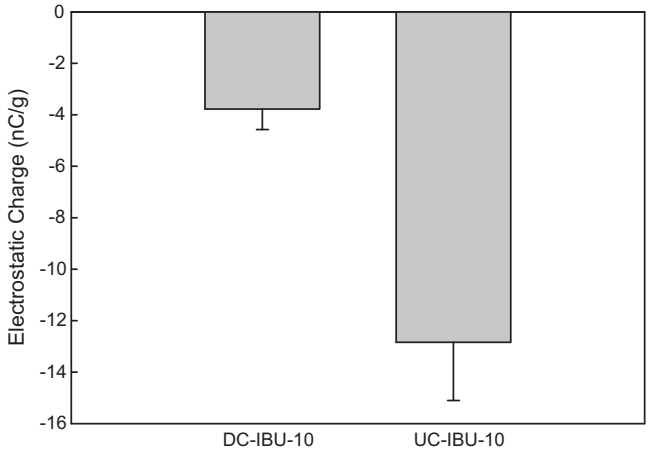


Fig. 10. Electrostatic charge test results for sample UC-IBU-10 and DC-IBU-10.

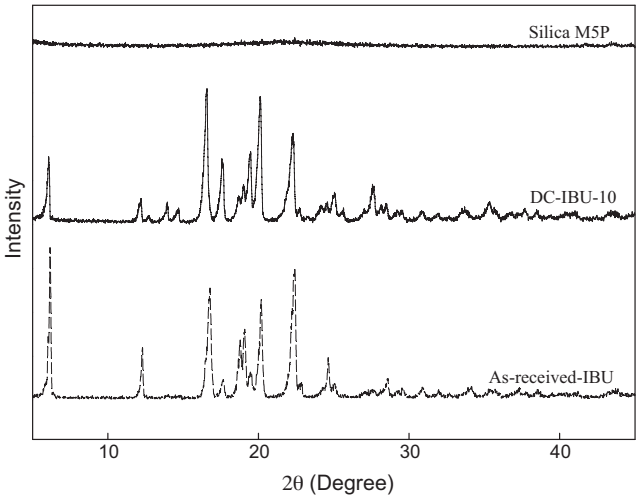


Fig. 11. XRD spectrum results for sample: as-received-IBU, DC-IBU-10 and Silica M5P.

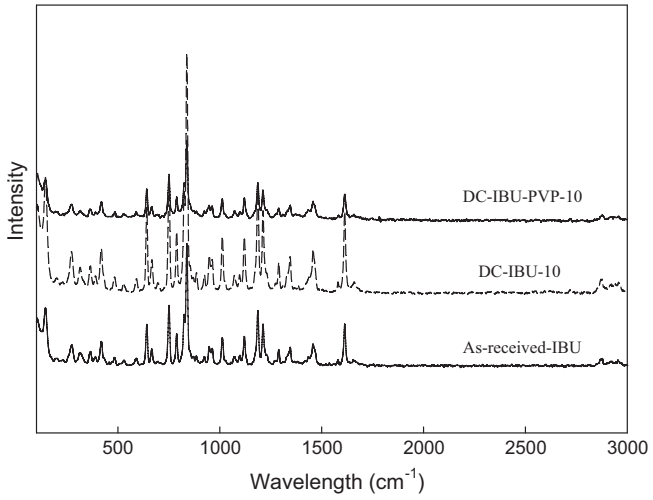


Fig. 12. Raman spectrum for sample: as-received-IBU, DC-IBU-10 and DC-IBU-PVP-10.

3.8. Effect of FEM process on crystallinity

The crystallinity of a pharmaceutical substance has an effect on its dissolution and bioavailability, and on its physical and chemical stability. Most of the pharmaceutical products are formulated to contain drug in the stable crystalline form due to the long-term stability concerns with respect to amorphous and unstable crystal forms. Therefore it is necessary to evaluate the effect of FEM process on crystallinity. XRD studies show that unprocessed ibuprofen (as-received-IBU) and processed ibuprofen (DC-IBU-10) powders have nearly the same patterns and peak positions (2θ values, Fig. 11). Although not shown, the DC-IBU-PVP-10 sample also did not exhibit any loss of crystallinity. This suggests that the milling process for ibuprofen does not induce a polymorphic transition or amorphization of the model drug, Ibuprofen, used in this study. However, the slight difference in the relative intensities of their peaks may be due to differences in the particle sizes (Chingunpitak et al., 2008).

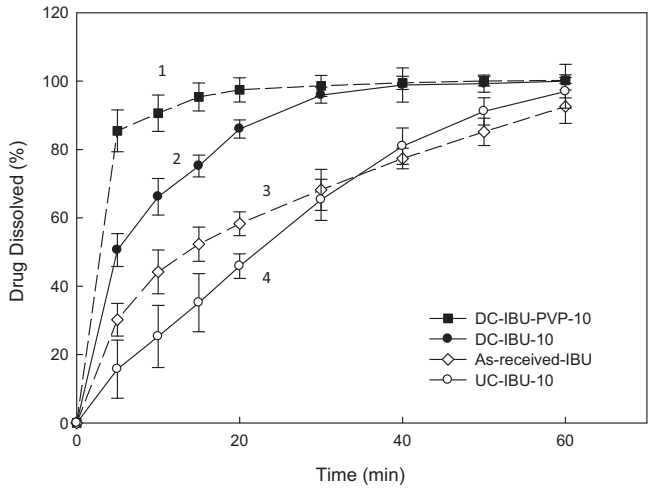
A DSC study was also performed and it was found that the as-received-IBU has a single endothermic peak at 76.4 °C, due to the melting of the drug. This result is similar to the one reported by Charoenchaitrakool et al. (2000). DSC curves of processed ibuprofen with or without silica show similar single endothermic peak at about 76 °C. Moreover, the degree of crystallinity for the dry coated sample is 98.6% calculated by Eq. (1).

In addition, Raman spectra were performed (Fig. 12). Similar to XRD results, Raman studies show that unprocessed ibuprofen (as-received-IBU) and processed ibuprofen (DC-IBU-10 and DC-IBU-PVP-10) powders have nearly the same patterns and peak positions. Raman results along with DSC and XRD results confirm that after FEM process, ibuprofen retains its crystal form, indicating there is minimal detectable physical transformation with FEM processed ibuprofen.

It should to be pointed out that although the XRD, DSC and Raman tests were performed as soon as the samples were prepared, indeed recrystallization of the disordered fraction during the course of the measurement was not considered in this paper. Also, the limit of quantification of amorphous content for XRD is about 5%, and DSC is about 1%.

3.9. Effect of FEM process on dissolution

The dissolution profiles of as-received-IBU and the processed ibuprofen are shown in Fig. 13. From the figure, it can be seen that the increase in the dissolution rate occurs in the following order: DC-IBU-PVP-10 > DC-IBU-10 > As-received-IBU > UC-IBU-10. The enhanced dissolution rate for sample DC-IBU-10 as compared to the original, as well as FEM processed without silica, is attributed to the highly dispersible non-agglomerated micronized powders resulting from the simultaneous surface modification and micronization. It is also believed that the hydrophilic nano-silica on the surface enhances the surface wettability and will further improve the dissolution rate. The co-ground powder DC-IBU-PVP-10 exhibited the fastest dissolution rate, which is likely due to the enhanced dispersibility imparted by the nano-silica as well as the hydrophilic and highly water-soluble nature of PVP. The slower rate of dissolution of pure micronized ibuprofen without surface modification (UC-IBU-10) than as-received-IBU is most likely due to larger hydrophobic drug surface area and heavy agglomeration of micronized powder, which leads to trapped air. Perrut et al. (2005) discussed similar dissolution trends for both bulk and micronized powders, in which the micronized powders (4 μm) had a slower dissolution rate compared to the bulk powders (29 μm). In (de Villiers, 1996), dissolution rate was compared for micronized powders before and after dispersion; agglomerated powders had slower dissolution rate compared to those



t_1= 4.8 min, t_2= 16.9 min, t_3= 41.6 min, t_4= 40.0 min

Fig. 13. Powder dissolution profile.

Table 4
BET results.

	As-received-IBU	DC-IBU-10	UC-IBU-10
Specific surface area (m^2/g)	0.1477 (0.003)	3.7588 (0.11)	0.3347 (0.05)
Ratio of specific area for processed and as received IBU	–	25.4	2.3

Standard deviations are shown in the parentheses.

after dispersion. In addition, the dissolution profile characteristics also corroborate the particle sizes from Rodos/Helos system at low dispersion pressure (0.2 bar): the d_{50} for sample UC-IBU-10 is 359.4 μm showing significant agglomeration, 134.3 μm for as-received-IBU and 11.7 μm for DC-IBU-10. The dissolution profile time constants, t (Charoenchaitrakool et al., 2000) (defined as the time required to dissolve 80% of the original material) are also shown in Fig. 13. The constants for as-received-IBU and UC-IBU-10 (t_3 and t_4, respectively) are almost the same, indicating that the agglomeration and poor wetting of pure micronized powder leads to lack of improvement in the dissolution rate. On the other hand, the time constant for sample DC-IBU-10, t_2, is much smaller than that of both as-received-IBU, t_3, and the pure micronized (uncoated) sample, t_4, indicating that micronization with surface modification results in faster dissolution rate which is what one would expect from micronization. When simultaneous micronization and surface modification also included co-grinding with PVP, the time constant, t_1, further decreased indicating further improvement in dissolution rate due to improved wettability from PVP.

Corresponding BET results are shown in Table 4 where the specific surface area for sample DC-IBU-10 is about 25 times higher than the as received ibuprofen. Assuming powders are nearly spherical, if particle size decreases 10 times, then specific surface area should increase 10 times accordingly (from 0.15 m^2/g to 1.5 m^2/g). Since the specific surface area of nano-silica M5P is about 200 m^2/g, 1 wt% would correspond to about 2 m^2/g of additional increase in specific surface area. Thus the observed value of 3.8 m^2/g from the BET results for DC-IBU-10 seems reasonable. This increase in the specific surface area is partially explained by the presence of the nano silica but much of it comes from micronization, indicating enhanced dispersibility and diminished agglomeration. It also suggests that nano-sized silica is coated/distributed on the surface and is not just present as agglomerates as would be in case of a physical mixture. In contrast, specific area for sample UC-IBU-10 is only 2.3 times greater than the as received sample, which is lower than expected based on the size reduction. This corroborates the evidence from the pressure titration and dissolution experiments, all further proving that there is significant agglomeration in the pure milled ibuprofen. These results indicate that micronization without surface modification may not improve the dissolution rate as expected; while higher specific surface area, better dispersibility, and better wettability may be the reasons for the improved dissolution rate for both dry coated and co-ground samples, in particular since the FEM process did not result in any amorphous ibuprofen.

4. Summary and conclusions

In this paper, simultaneous micronization and surface modification of drug particles was considered. The main objective of the work was to perform micronization in order to achieve dissolution rate improvement while eliminating typical disadvantages of micronization such as, agglomeration, poor flowability, loss of expected large surface area, low bulk density, and insignificant or no dissolution improvement. The process utilized was a continuous fluid energy mill where larger particles of ibuprofen, pre-blended with nano-silica were micronized to achieve fine surface modified drug particles via nano-silica dry-coating. Process optimization confirmed that the feeding rate and the grinding pressure are critical parameters for achieving the desired particle size with relatively narrow size distribution. Through this process, ibuprofen was micronized from 102 μm (as received) down to 10 and 5 μm, and was simultaneously dry-coated with hydrophilic nano-silica. The results for various critical properties of the surface modified micronized (dry-coated) powders were evaluated and compared with as received ibuprofen powder and micronized ibuprofen without surface modification. The results showed significant improvement in flow properties and dissolution rate when micronization was performed in conjunction with surface modification. As per the Noyes–Whitney equation, the increase in the dissolution rate may be attributed to the reduction of the particle size, which leads to increased surface area. However, the increase in the dissolution rate for micronized silica coated drug powder does not appear to be 10-fold as one would expect based on the corresponding increase in the surface area. This is attributed to insufficient wetting of the dry coated micronized powder.

In addition to size reduction along with dry coating, co-grinding with small amount of water-soluble polymer during the micronization process was carried out and found to significantly improve dissolution rate along with increased bulk density, without any detectable phase transformation of ibuprofen. It is believed that since the amount of PVP used was very low as compared to what is commonly used, and processing in FEM is relatively low energy (as compared to ball-milling, for example), there was no amorphous content in co-grinding for ibuprofen. As validated by XRD, Raman and DSC, there is no appreciable formation of amorphous content so the effect of PVP in increasing dissolution in this case is not due to amorphous phase formation. When we combine the fact that there was a very large improvement in the dissolution rate due to the addition of PVP, but not without it, it is apparent that particle size reduction along with improved dry dispersion (or lack of agglomeration as indicated by Rodos pressure titration curves) alone may not lead to significant dissolution rate improvement. In other words, wettability of hydrophobic drug powder, which has very large surface area due to micronization, is also critical. Thus when PVP was used, better dissolution rate was achieved as poor wettability of micronized powder even in presence of hydrophilic silica is mitigated by presence of PVP. Thus the improved dissolution due to PVP was most likely due to the improved wettability imparted by PVP.

Preliminary experiments also indicated that micronized powders that were surface modified collected significantly less charge during processing as compared to those that were not surface modified. Overall, the surface modified, micronized powders showed improved dispersion, significantly higher bulk densities, and higher flowability, i.e., the flow function coefficient (FFC $\geq$ 6, from shear tests). Along with high bulk densities (>0.4 g/cm^3) these fine drug particles may be used in formulations amenable for direct compression with high drug loading (assuming good compressibility of the drug) and would achieve expected increase in dissolution rates due to micronization, particularly when surface wettability is increased by addition of material like PVP.

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