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Improving flow properties of ibuprofen by fluidized bed particle thin-coating

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ABSTRACT

The surfaces of ibuprofen particles (d_{50} 42 μm) were modified by coating the particles with diluted aqueous hydroxypropyl methylcellulose (HPMC) solution in an instrumentated top-spray fluid bed granulator. The objective was to evaluate whether an extremely thin polymer coating could be an alternative to granulation in enhancing powder flow and processing properties. The studied variables were inlet air temperature and spray rate. The treated powders showed a clear improvement in flow rate as measured with a flow meter designed for powders with poor flow properties. The particle size was determined using optical microscopy and image analysis. The particle size, size distribution and circularity of the treated and untreated ibuprofen batches showed no difference from each other. Consequently, the improvement in flow properties can be attributed to the trace amounts of hydroxypropyl methylcellulose applied onto the particle surfaces. In conclusion, fluidized bed particle thin-coating (PTC) alters the surface of ibuprofen powder particles and improves the flow properties of ibuprofen powder with changes in neither particle size, size distribution nor morphology.

1. Introduction

Fluidized bed coating is widely used in the pharmaceutical and food industry to physically modify powders in order to enhance their processibility, to mask unpleasant tastes or appearances and to enhance or create functional features such as delayed release or increased stability of active ingredients (Tenou and Poncelet, 2003; Werner et al., 2007; Turton, 2008). The process of fluidized bed particle coating is based on fluidizing particulate material with turbulent air and depositing droplets of coating liquid onto the surface of the particles. High inlet air temperatures promote drying, and high spray rates promote wetting (Ichikawa and Fukumori, 1999; Donida and Rocha, 2002; Tenou and Poncelet, 2003; Jiménez et al., 2006). These two factors in combination with the air flow rate (de Oliveira et al., 1997) determine whether the particles become coated or agglomerated, what the degree of agglomeration is and, on the contrary, if the binder liquid is spray-dried and transported to the upper filter. The wetting properties of both the coating material and the surface of the particles clearly affect the growth rate of the coating (Maronga and Wnukowski, 2001; Donida and Rocha, 2002; Tenou and Poncelet, 2003; Donida et al., 2005; Saleh and Guigon, 2007). Other properties affecting the application of coating onto particles include particle size, density, surface properties, drying temperature and spray rate (Guignon et al., 2003; Hemati et al., 2003).

Granulation is not always suitable as a preprocessing method for powders. For instance in tableting, the compression properties of powders vary according to particle size (Alderborn and Nyström, 1982). Though, as the particle size decreases gravitational forces become less significant while adhesive forces, such as electrostatic and van der Waals' forces gain significance, resulting in reduced flow properties (Heim et al., 1999). Being able to keep the particle size small without loss of flow properties can be of essence in direct compression of tablets, and could be achieved by fluidized bed coating. Though, in cases when the particle size of the starting material is small, interparticle cohesion can prevent successful film coating of particles (Maa et al., 1996; Yuasa et al., 1997, 1999; Dewettinck et al., 1998; Nakano et al., 1999; Jono et al., 2000; Nakano and Yuasa, 2001; Guignon et al., 2003; Hede et al., 2007). In such cases, fluidized bed particle thin-coating (PTC) can be used as a method in powder preprocessing.

In the present study, fluidized bed coating and diluted aqueous polymeric solution were used to improve the flow properties of ibuprofen with fluidized bed PTC. Ibuprofen is known for its poor flow and compaction properties, which are most often avoided by, for example, granulation (Rasenack and Müller, 2002). The aim of this study was to alter the surface of ibuprofen powder particles by applying an extremely thin-coating onto the particles with a dilute hydroxypropyl methylcellulose (HPMC)-solution (0.15%, m/V) in a top-spray fluidized bed granulator. The objective was to investigate whether fluidized bed PTC could be an option to granulation in enhancing powder flow and processing properties.

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Table 1
The range of the variables in the central composite design.

Variable	$-\alpha$	−1	0	+1	$+\alpha$
Temperature (°C)	20.86	25	35	45	49.14
Spray rate (g/min)	0.42	0.5	0.7	0.9	0.98

2. Materials and methods

2.1. Materials

The materials used in the experiments included ibuprofen 50 (Boots Pharmaceuticals, UK), 2910-substituted HPMC (Methocel E5 Premium LV EP, Dow Chemical Company, USA) and purified water.

2.2. Experimental design

The studied variables were inlet air temperature and spray rate (Table 1). The range of the process variables was determined in preliminary experiments. The experimental design used was a partially randomized central composite design with a triplicate centre point (first, middle and last) in order to verify the reproducibility of the process (Table 2). The experimental design was created using MODDE for Windows (MODDE 7, Umetrics AB, Sweden).

2.3. Equipment

The coating was applied in an instrumentated Aeromatic STREA-1 laboratory-scale fluidized bed granulator (Aeromatic AG, Switzerland) with a top-spray arrangement. The coating was applied using a Schlick model 970/7-1 two-substance nozzle (Düsen-Schlick GmbH, Germany). The nozzle was mounted on an aluminium/brass tripod and mounted between the chamber and the oscillating upper sieve. The relative humidity of the process facilities was monitored, and all batches were processed in ambient conditions of 28 ± 5 RH%.

2.4. Preparations

The 0.15% (m/V) HPMC solution was prepared according to instructions readily available in the literature (Harwood, 2000). The obtained product was a clear and slightly viscous solution. The ibuprofen was sieved with a 1-mm sieve and a batch size of 300 g was weighed for each batch. The atomizing pressure was empirically set to be 0.5 bar. The air flow rate of 3.5 l/s was determined in the preliminary experiments.

Table 2
Temperature (*T*), spray rate (Spray), spray time (Time), flow rates and standard deviations (Flow) of the flow rates of all batches.

Batch	*T* (°C)	Spray (g/min)	Time (min)	Flow (mg/s)
ibu	–	–	–	6.1 ± 0.7
N1	−1	−1	100	10.5 ± 1.3
N2	1	−1	100	8.9 ± 1.2
N3	−1	1	56	14.7 ± 1.4
N4	1	1	56	6.6 ± 0.9
N5	$-\alpha$	0	71	13.9 ± 1.5
N6	$+\alpha$	0	71	8.4 ± 1.1
N7	0	$-\alpha$	119	9.3 ± 1.3
N8	0	$+\alpha$	51	11.9 ± 1.5
N9	0	0	71	11.3 ± 1.1
N10	0	0	71	10.2 ± 1.3
N11	0	0	71	10.6 ± 1.5

2.5. Thin-coating

The chamber was dried for 5 min at an inlet air temperature of 35 °C and air flow rate of 5 l/s before filling. The ibuprofen was mixed for 6 min before beginning the spraying-phase. During the mixing-phase, the air flow rate was increased every second minute by 0.5 l/s from 2 l/s to 3.5 l/s. The inlet air temperature was increased stepwise to avoid temperature peaks. The endpoint of the spraying phase was determined as the point in time when a 0.025% theoretical mass addition was achieved based on preliminary experiments. The drying-phase was continued until the difference between inlet and outlet air humidity was constant. The moisture content of the powders was determined using a Sartorius MA 100 moisture analyzer (Sartorius AG, Germany).

2.6. Flow properties

The flow rate of the powders was determined using an in-house-developed flow meter especially designed for powders with poor flow properties (Seppälä et al., 2007). The measurement is based on powder flow through an orifice assisted by vertical oscillations with a frequency of 1 Hz and an amplitude of 10 mm. The sample chamber remains in the "down-position" for 80% of the cycle, and remained in the "up-position" for 20% of the cycle. The changes between movement and rest in the up- and down-positions are abrupt. The method is based on powder arching and breakage of the arches formed. The powder is transported through an orifice onto a scale, which records the powder's mass as a function of time, thus, providing the flow rate (mg/s). Further details regarding the flow meter have been published elsewhere. The measurements were performed in controlled humidity (52 ± 5 RH%) after a minimum of 24 h of acclimatization.

2.7. Scanning electron microscopy (SEM)

SEM micrographs were taken of untreated ibuprofen and two batches selected for further studies at magnifications of 200× and 2000×.

2.8. Determination of particle size and morphology

The particle size was determined with optical microscopy and image analysis using Matlab (Matlab 7.5.0 (R2007b), MathWorks Inc., USA). The equivalent diameter (d_e) was calculated according to the following equation:

$$d_e = 2\sqrt{\frac{(A \cdot (pix^2))}{\pi}}, \quad (1)$$

in which A is the projection area of particles in square pixels and *pix* is the coefficient that converts pixels to microns. The value for *pix* (2.994 μm/pixel) was obtained by measuring a known distance from an image taken with the magnification used in the image analysis (2.5×), and dividing the length with the number of pixels covering the distance. The circularity (M) of the particles was calculated using the following equation:

$$M = \frac{4\pi A}{P^2} \quad (2)$$

in which A is the area of the particle and P is the perimeter. X-ray powder diffractometry served to identify possible process-induced polymorphic changes.

Table 3
The particle size of coated ibuprofen (N3 and N4) in comparison with untreated ibuprofen (ibu).

	ibu	N3	N4
n	1092	1159	1052
d_{10}	25	21	21
d_{50}	42	39	37
d_{90}	72	65	72

2.9. Data analysis and modelling

A model of the obtained data was created with MODDE software (MODDE 7.0, Umetrics AB, Sweden) using multilinear stepwise regression. The flow rate data was treated using one-way ANOVA followed by Tukey's Multiple Comparisons test (Bolton, 1990). All batches combined and the triplicate centre point runs were treated separately.

3. Results and discussion

3.1. General observations

The fluidizability of the ibuprofen was, as expected, poor due to the cohesive nature of the powder. Even if the fluidization of the powder was good, however, at any given time only a small fraction of the powder is located in the spray region of the chamber where the coating is applied. Poorly fluidizable powders can reach the spray region through bursting and imperfect fluidization, resulting in slow, but progressive, coating. In the present study, the fluidizability changed distinctively at 20–30 min spray time in all batches, indicating a reduction in internal cohesion and, hence, flowability. All batches showed a similar moisture content of roughly 0.1% directly after the process.

3.2. Particle size and morphology

In the present study, the particle size, shape and size distribution of the treated ibuprofen batches showed no difference from the untreated powder (Table 3, Fig. 1, Fig. 2). The d_{50} of 42 μm is considerably lower than those reported in previous publications in the same field. No differences in size and morphology could be detected from the obtained SEM micrographs with 200× magnification (Fig. 3). However, SEM micrographs with 2000× magnification reveal systematic differences in surface structure, which indicates that the application of a homogenous HPMC-coat onto the particle surface was successful. To the authors' knowledge, no reports of successful fluidized bed top-spray coating of particles

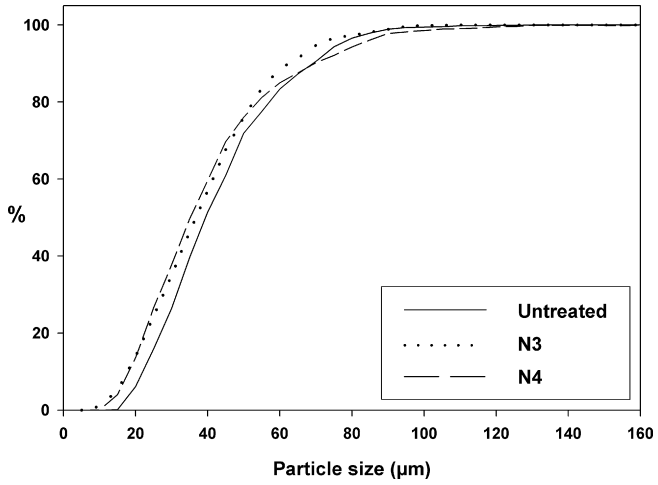

Fig. 1. Particle size distribution of coated ibuprofen (N3 and N4) and untreated ibuprofen (Untreated).

with a particle size less than 100 μm appear in previous experiments by other authors and in the literature in general. Ronsse (2006) has also reported this same conclusion.

The results of the particle size measurements in the present study show that no agglomeration occurred as a result of the coating. Agglomeration is widely considered a serious problem to overcome in fluidized bed coating, as is the increasingly strong tendency of particles to agglomerate as particle size decreases (Maa et al., 1996; Yuasa et al., 1997, 1999; Dewettinck et al., 1998; Nakano et al., 1999; Jono et al., 2000; Nakano and Yuasa, 2001; Guignon et al., 2003; Hede et al., 2007). The particle size range used in the present experiment is usually associated with Wurster-processes; processing particulates in this size range with a top-spray system is uncommon (Ichikawa and Fukumori, 1999; Cheng and Turton, 2000; Maa et al., 2004; Iida et al., 2005; Ronsse, 2006; Werner et al., 2007).

3.3. Polymorphism

To rule out polymorphic transformations as a cause of the improved flowability, X-ray powder diffractometry was performed. No process-induced polymorphic changes were observed (Fig. 4).

3.4. Flow properties

3.4.1. Intermediate relative humidity

In the present study, the flow rate of the treated powders ($n = 15$) improved statistically ($P < 0.001$) in all but one of the batches (N4;

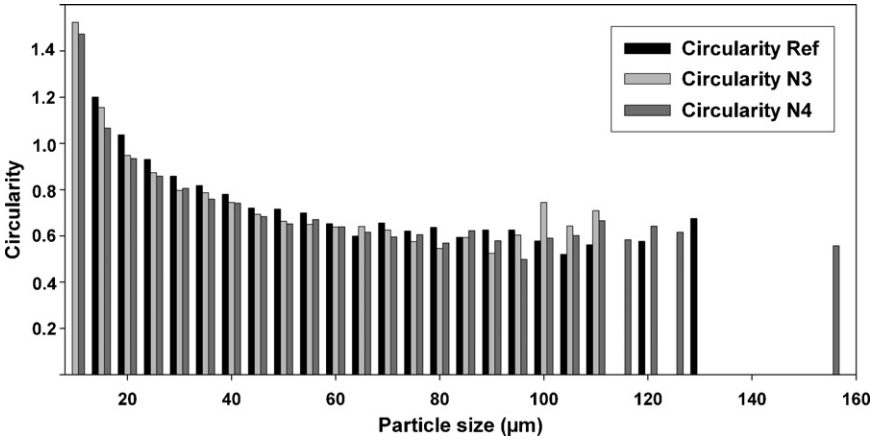

Fig. 2. Circularity of coated ibuprofen (N3 and N4) and uncoated ibuprofen (Ref).

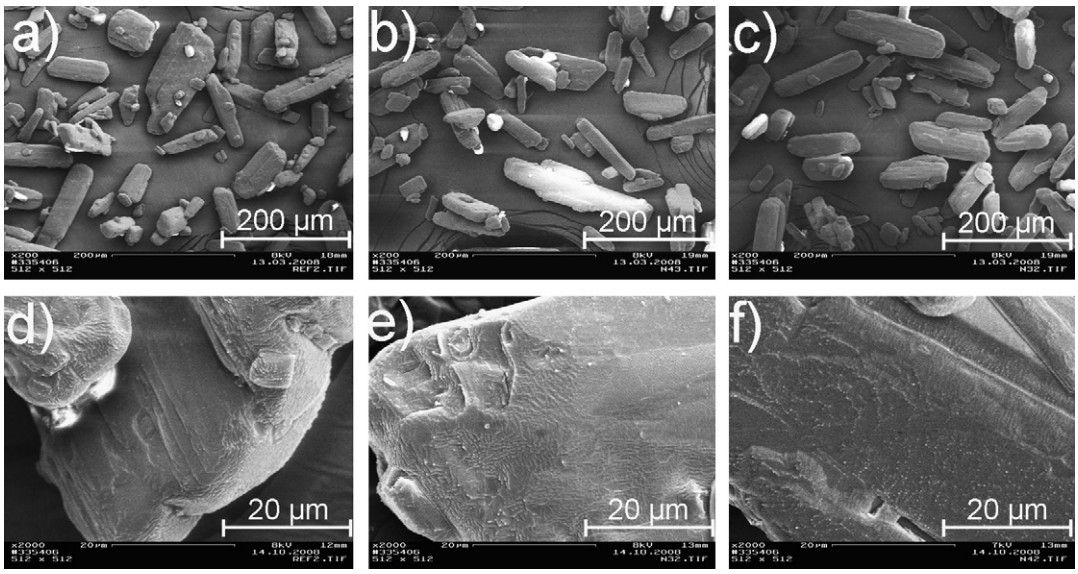

Fig. 3. SEM micrographs with magnifications 200× (a–c) and 2000× (d–f). (a and d) ibu; (b and e) N3; (c and f) N4.

$P = 0.08$) in comparison to the untreated ibuprofen in intermediate humidity (52 ± 5 RH%) (Table 2). Batch N3 showed the greatest improvement: a 2.5-fold increase in flow rate. The results of the batch in question, however, showed no statistical difference from batch N5 ($p > 0.05$). The reproducibility of the process was found to be good, as the triplicate centre point runs showed no statistical difference from each other (one-way ANOVA; Tukey's Multiple Comparisons test, $p > 0.05$ in all pairwise comparisons). Based on these findings, the data was fitted into a second-order polynomial expression, and the predictive power of the model was enhanced by reducing the least significant factors in the expression, resulting in the following equation:

$$z = z(S, T) = 0.35 \cdot T + 31.92 \cdot S - 0.812 \cdot T \cdot S - 4.126 \quad (3)$$

in which z stands for the flow rate of the powder (mg/s), T for inlet air temperature (°C) and S for spray rate (g/min). The R^2 and Q^2 values were 0.949 and 0.826, respectively.

The results indicate that low temperatures and high spray rates improve the quality of the coating, as verified by the model (Fig. 5). Evaporation of the droplets of coating liquid seems to be the factor that determines the quality of coating; in short, lower evaporation rates improve the quality of coating. The range of the variables is, according to the results obtained, unlikely to reveal the maximum flow rate value; no peaks occurred. No agglomeration occurred either. The coating thickness would presumably be at its largest when the wetting is as extensive as possible, but without the formation of liquid bridges. This indicates that a further reduction in temperature and an increase in the spray rate could yield powders with even higher flow properties.

However, as the temperature decreases and the spray rate increases the risk of agglomeration grows; the quality of the coat is probable to improve until agglomeration occurs. After the initiation of agglomeration the improvement in flow properties can no longer be attributed solely to the coating, as increased particle size is likely to enhance the significance of gravitational forces and diminish the effect of cohesive forces (Heim et al., 1999) resulting in improved flow properties. No peaks in flow rate are thus, to be expected in the model. As there was no agglomeration the experiment was successful in revealing the flow enhancing effects of the described method.

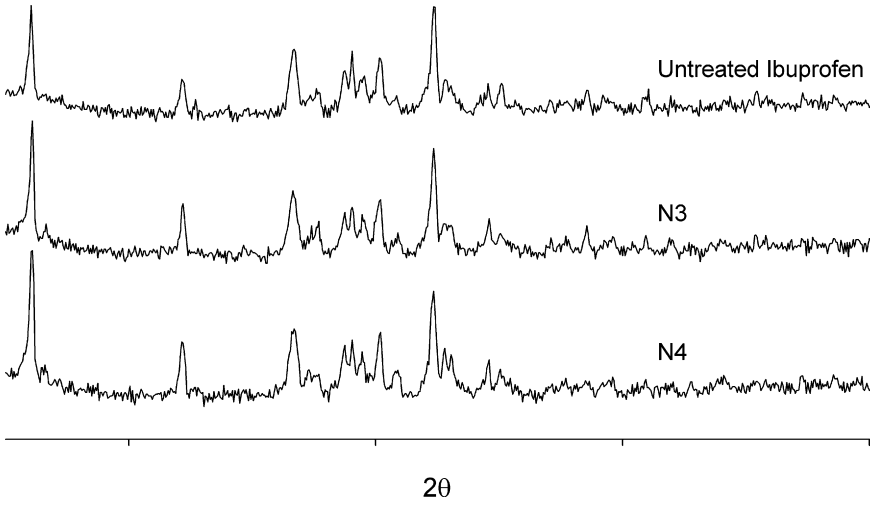

Fig. 4. X-ray powder diffractograms of batches N3 and N4 in comparison with untreated ibuprofen.

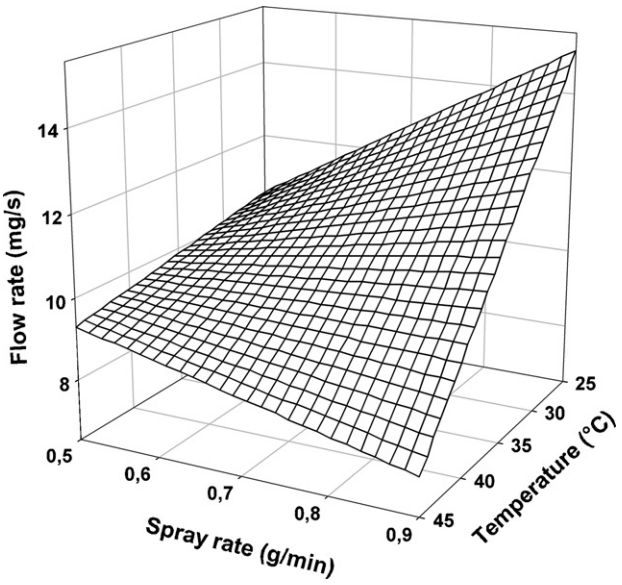

Fig. 5. 3-D model of the effect of process spray rate and temperature on the flow rate of ibuprofen.

Powder coating has been cited as an alternative to granulation in preprocessing powders before compaction (Bolhuis and Armstrong, 2006). Holgado et al. (1995) reported an improvement in lactose powder flow rates after coating with different Eudragit® acrylic polymers, although the statistically significant improvement was only roughly 15–20%. Holgado et al. (1996) coated paracetamol with different Eudragit® acrylic polymers using solvent evaporation and comminution of the dried final product. The obtained powder showed improved rheological properties, but no statistically significant improvement of flow properties was obtained. An explanation to this can be found in the method used. The surfaces have probably been uniformly coated after the solvent evaporation and drying, but the comminution might have exposed uncoated surfaces, resulting in insufficient improvement of flow properties. Aqueous solutions of HPMC have previously served as a coating material for particulate material (Yuasa et al., 1997, 1999; Maronga and Wnukowski, 2001; Nakano and Yuasa, 2001; Elversson and Millqvist-Fureby, 2006; Heng et al., 2006; Yu et al., 2006; Tang et al., 2008). The viscosity grade of the HPMC is of importance, as lower viscosity of the coating liquid results in smaller droplets, and reduced risk of particle growth (Parikh et al., 1997). Achieving significant improvements in flow properties as well as using HPMC as a powder flow enhancer, as in the present study, is uncommon.

Consequently, the findings presented in the present study confirm the results of several other authors with regard to the effect of inlet air temperature and spray rate on coating efficiency (e.g. de Oliveira et al., 1997; Ichikawa and Fukumori, 1999; Donida and Rocha, 2002; Tenou and Poncelet, 2003; Jiménez et al., 2006). As comparison, lactose 80 M is suitable for direct compression (Ishino et al., 1990) and has a flow rate of 93.8 ± 11.6 mg/s. The suitability for direct compression, however, cannot be compared based on powder flow properties only as other material and equipment properties also have an influence. Even though PTC statistically significantly improved the flow rate of ibuprofen powder the improvement cannot, however, be regarded as sufficient for process relevance, as direct compression of neither untreated nor treated ibuprofen was possible. Furthermore, conclusions regarding the potential of other polymer solutions as flow enhancers cannot be drawn based on the obtained results, as liquid–solid interfacial behavior shows material-dependent variation (Parker et al., 1990).

Consequently, additional research is needed to improve the process further in order to achieve processibility enhancements of industrial relevance. The batches treated with the most (N3, N5) and least (N4) improved flow rate and untreated ibuprofen (ibu) were selected for further flowability studies.

3.4.2. *Low, intermediate and high relative humidity*

An increase in the moisture content in a particulate system often leads to changes in flow properties, depending on the ability of the powder to absorb water (Nomura et al., 2003; Rowley and Mackin, 2003; Faqih et al., 2007). High relative humidity leads to water condensation on the surface of poorly absorbing powders and consequently results in poorer flow properties (Forsyth et al., 2002; Faqih et al., 2007). On the other hand, powders that absorb moisture nicely show improved flow properties in high relative humidity (Faqih et al., 2007). HPMC is hydrophilic and ibuprofen hydrophobic, which indicates that the powders coated in the present study react differently to changes in relative humidity depending on the extent of the thin-coating.

Batches of ibu, N3, N4 and N5 were acclimatized in low (25 ± 1 RH%), intermediate (52 ± 5 RH%) and high (70 ± 10 RH%) relative humidity for 70 h and the flow properties were subsequently determined ($n = 5$). The flow rates in intermediate relative humidity showed no substantial differences from those in low relative

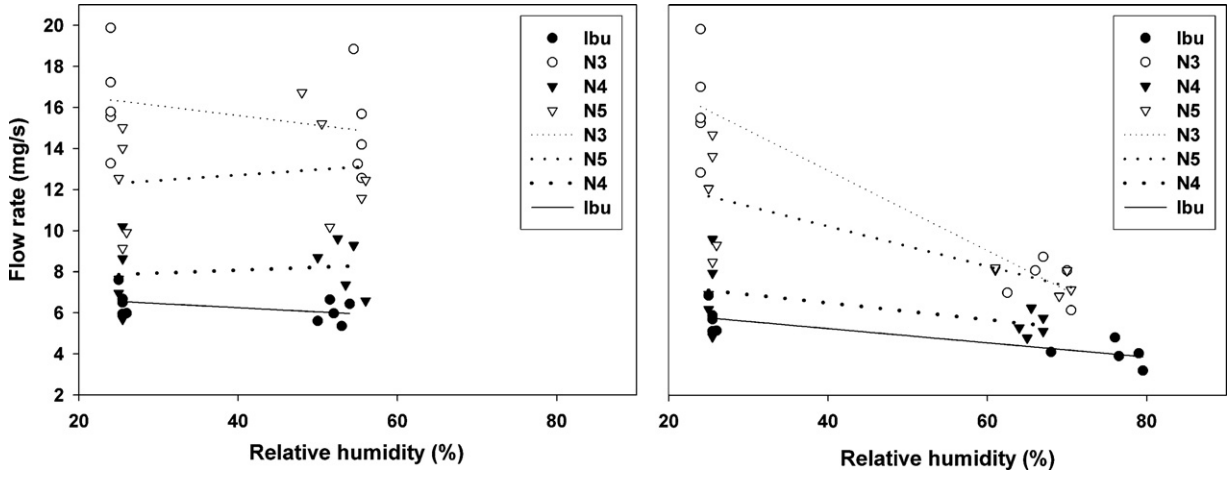

Fig. 6. The differences in flow properties of coated ibuprofen (N3, N4 and N5) and uncoated ibuprofen (Ibu) between low and intermediate relative humidity compared to the differences between low- and high-relative humidity.

humidity (Fig. 6). However, all batches showed reduced flow properties in high humidity (Fig. 6). The lines combining the results in different humidities in Fig. 6 are merely aids to alleviate visual inspection, and should by no means be interpreted as curves. The phenomenon observed can be attributed to changes in affinity to atmospheric water, which is an expression of the amount of hydrophilic HPMC present on the hydrophobic ibuprofen particle surfaces. The differences in the reduction of flow rate between low and high relative humidity seem to correlate with the flow rates measured in intermediate relative humidity.

4. Conclusions

The present study presents method to enhance physical properties of powders, fluidized bed PTC. Ibuprofen powder particles with a median d_e of 42 μm can be thin coated in a top spray fluidized bed granulator without agglomeration. The results of the present study confirm that PTC with trace amounts of HPMC does alter the surface of particles and improves the flow properties of cohesive powders such as ibuprofen.

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