International Journal of Pharmaceutics 387 (2010) 65–70

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Thin-coating as an alternative approach to improve flow properties of ibuprofen powder

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ARTICLE INFO

Article history:
Received 30 March 2009
Accepted 3 December 2009
Available online 25 December 2009

Keywords:
Ibuprofen
HPMC
Ultrasound
Particle thin-coating
Powder flow
Surface properties

ABSTRACT

In the present study, thin-coating as a potential method for improving flow properties of cohesive ibuprofen powder was introduced. Briefly, the technique was based on the successive deposition of ultrasound-assisted fine polymer mist onto the surface of the powdered active pharmaceutical ingredient (API), producing individual particles with a hydrophilic thin-coat. A 0.15% m/V aqueous solution of hydroxypropyl methylcellulose (HPMC) was used. Particle size and surface analysis revealed a decrease in the cohesiveness of ibuprofen powder and an increase in the homogeneity of particle surfaces as a result of polymer treatment. Superficial changes caused a substantial improvement on the flowing characteristics of coated substance over uncoated. The enhancement in flow rate proceeded as the uniformity of the HPMC layer increased. In conclusion, the proposed technique is a simple and effective method that can be used as a continuous process to modify API particle surface properties, which in turn improve the handling of poorly flowable powder.

1. Introduction

The particle morphology of powder plays a critical role in the performance of active pharmaceutical ingredients (APIs) during the manufacturing of dosage forms. The coating can be an option to improve powder behaviour for further application. The created interparticulate barrier can reduce attraction forces such as electrostatic and molecular interactions and result in better flow and packing properties of powder. As well, the coating of the particulate system can be beneficial for the reasons of taste masking, environmental protection and controlled release properties.

Numerous approaches have been done for a liquid coating of solid powdered particles. Recently, particle thin-coating in a fluidized bed system has been performed to improve the flow properties of ibuprofen powder (Ehlers et al., 2009). However, this technique is a complex system that requires comprehensive knowledge about the properties of materials used to predict an influence of process variables on the potency of coating (Dewettinck et al., 1999; Tang et al., 2008). Spray-drying has been also applied to modify particle properties and enhance their manufacturing performance (Elversson and Millqvist-Fureby, 2006). The resulting spray-dried product is free-flowing powder, but the technique is very bulky and energy consuming. The drawbacks of the above-mentioned liquid coatings such as air pollution and long processing time were overcome by environmentally friendly and safe dry powder coating technique (Pfeffer et al., 2001; Luo et al., 2008). The disadvantage of this method is the heat applied or generated during mechanical interactions that can cause the degradation of temperature sensitive materials.

Reduction in particle size of spraying solution in a particle coating is possible to achieve by atomization it using ultrasound. The acoustic waves create cavitation and compression regions that collapse giving rise to a cold fountain of fine droplets. Ultrasound-assisted atomizers were applied to obtain surface modified microparticles through spray-congealing technology (Rodriguez et al., 1999; Albertini et al., 2005). Besides sonication of binder liquids, acoustic energy based techniques were used for the initiation of crystallization to control the physical properties of solid materials (Kaerger and Price, 2004; Ruecroft et al., 2005).

The objective of this study was to introduce a new ultrasound-assisted technique for thin-coating of poorly flowable ibuprofen with hydroxypropyl methylcellulose (HPMC) in order to improve the flowing of the API powder. The system produces the fine mist of the polymer solution (0.15%, m/V) that deposits on the surface of powdered particles and no additional drying step is needed.

2. Materials and methods

2.1. Materials

Ibuprofen (IBUPROFEN 50, Boots Pharmaceuticals, the U.K.) presieved with a 1-mm sieve was used as a poorly flowable model drug.

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doi:10.1016/j.ijpharm.2009.12.005

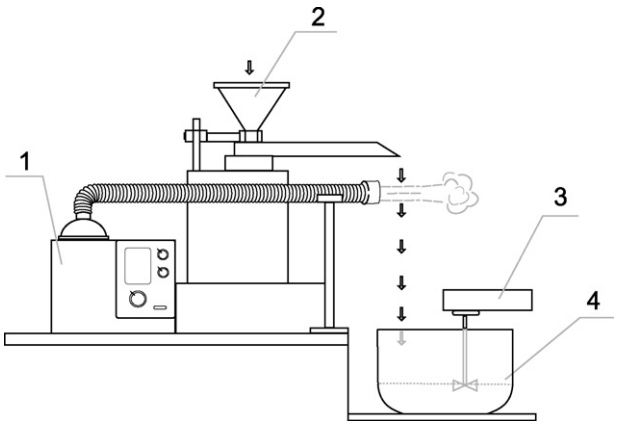

Fig. 1. Schematic diagram of the system employed to thin-coated ibuprofen particles: (1) ultrasound nebulizer, (2) vibrating feeder, (3) stirrer and (4) collector.

Coating solution consisted of 0.15% (m/V) hydroxypropyl methylcellulose (HPMC) (Methocel E5 Premium LV EP, Dow Chemical Company, USA) and purified water.

2.2. The coating process

The experimental setup has been previously presented by Genina et al. (2009) and the schematic diagram is illustrated in Fig. 1. A clear solution of the 0.15% (m/V) hydroxypropyl methylcellulose (HPMC) was atomized by means of the ultrasound nebulizer (Ultrasonic Nebulizer NE-U17, Ultra Air, Omron, Netherlands). The stream of generated HPMC containing mist was applied onto the powdered particles of ibuprofen supplied by a vibratory feeder (Laborette 24, Germany). The batch size of powder was 120.0 g. The mist procedure was repeated 30 times with the same solid substance. The sampling of 20 g was taken every fifth cycle. After the last treatment, the processed mass was left for 1 h to equilibrate in ambient conditions. During the entire procedure, the ibuprofen powder was periodically mixed by a stirrer (IKA®-WERKE, RW 11 basic, Staufen, Germany) to prevent the formation of liquid bridges between individual particles. The difference in the moisture content of the untreated and treated materials was obtained by measuring the water activity of the samples using AquaLab water activity meter (AquaLab 3 TE, Decagon Devices, Inc., Washington, USA). All process parameters are presented in Table 1.

2.3. Analysis of particle size

At-line spatial filtering technique (SFT) was applied to measure the particle size and size distribution of ibuprofen powder (Petrak, 2002). The samples were fed to the SFT apparatus (Parsum® IPP 70; Gesellschaft für Partikel-, Strömungs und Umweltmesstechnik GmbH, Chemnitz, Germany) through the orifice (diameter 4 mm) using a funnel and dispersed by pressurized air. The chord length of each particle passed trough the laser light beam was transformed to volume particle size for subsequent data analysis. Each sample was measured in triplicate.

Table 1
Applied process parameters.

Number of cycles	0–30
Air flow (l/min)	17
Flow rate of mist (g/min)	3.0
Droplet size of water mist (μm)	4.4
Feeding rate of powder (g/min)	2.2
Supplement rate of HPMC (mg/min)	4.5
Rotation rate of stirrer (rpm)	240
Time between cycles (min)	10
Yield (%)	95.2

2.4. Scanning electron microscopy (SEM)

A SEM (Zeiss DSM 962, Carl Zeiss, Oberkochen, Germany) was used in order to investigate particle shape and surface roughness. Before scanning, samples were coated with platinum using a vacuum evaporator. SEM images were obtained at the magnification of 200× and 2000× using an accelerated voltage of 8 kV.

2.5. Atomic force microscopy (AFM)

An AFM (Autoprobe CP, Thermomicroscopes, USA) was applied to study the detailed surface topography of ibuprofen particles over 5 μm × 5 μm area. The AFM mapping was performed in a contact mode with a cantilever of 0.35 N/m spring constant (Silicon cantilever CSCH11A, NT-MDT Ltd., Russia) at a scan rate of 0.5 Hz. The measurements were carried out in ambient conditions using a large area scanner (100 μm lateral scan size). The AFM height data ($n = 6$) was used to calculate the average roughness parameter (Ra) (Seitavuopio, 2006) for the treated and untreated samples.

2.6. Flow properties

The flowing characteristics of powder were measured by using an in-house designed flowability testing method (Seppälä et al., 2007). The discriminating feature of the developed system is its ability to induce the up and down movements of the sample holder that are sufficient to discharge poorly flowable cohesive powders through the orifice onto the analytical scale. Connection of balances with a PC gives possibility to determine a change in powder's mass as a function of time (mg/s). The treated and untreated samples were equilibrated for 72 h at different levels of controlled relative humidity to evaluate the effect of it on the rheological properties of ibuprofen powders. At least five parallel measurements were performed in each level of low (0.26 ± 0.04), intermediate (0.50 ± 0.02) and high (0.70 ± 0.03) water activities of the samples. The water activity of modified and unmodified powders corresponded to the values of relative humidity in the acclimatization environment.

2.7. X-ray powder diffractometry (XRPD)

The X-ray powder diffraction (XRPD) analysis of treated and untreated samples was conducted with a theta–theta X-ray diffractometer (D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany). Measurements were performed in a symmetrical reflection mode with Cu Kα radiation ($\lambda = 1.54$ Å) using Göbel mirror. The range measured was 5–40° (2θ) with steps of 0.05° (time per step 1 s).

3. Results and discussion

3.1. The polymer thin-coating procedure

The treatment by successive steps of ultrasound's assisted spraying of polymer mist and a short time equilibration of the powder bed did not give any increase in the water content of modified samples. The values of water activity were in agreement with processing environment. The same finding of unchanged water content directly after treatment has been previously reported by Genina et al. (2009). Obviously, the open setup of the introduced technique facilitates the evaporation of excessive liquid during processing, making the additional drying step unnecessary. It in turn prevents the attrition and breakage of the treated powder, minimizing the coating defects. The application of the fine mist instead of the spray

Table 2
Particle size and surface roughness of untreated and treated ibuprofen powders (data are presented as mean ± SD, $n = 3–6$).

Sample	Particle size (μm)			Surface roughness (nm)
	d_{10}	d_{50}	d_{90}	Ra
Ibuprofen, untreated	65.4 ± 1.4	109 ± 7	781 ± 380	41.6 ± 18.9
Ibuprofen, treated (30 cycles)	63.1 ± 0.4	95.8 ± 0.4	215 ± 5	20.0 ± 6.1[a]

[a] $p < 0.05$, significant difference compared to untreated substance by Student's unpaired t-test.

droplets of polymer solution reduces the risk of undesired granule formation. In addition, the process can operate in a continuous mode that makes the technique industrially beneficial. However, the duration of treatment has to be considered when the coating procedure is done several tens of times. Furthermore, the method is not fully optimized to date, and consequently, the loss of polymer mist to the environment has to be taken into account as well.

3.2. Morphological analysis

The analysis of particle size distribution of treated and untreated ibuprofen powder revealed no significant differences (Table 2). It means that granulation of primary particles due to the binding nature of HPMC solution was avoided. Progressive size enlargement was not aimed and it could negatively affect the interpretation of the results. The values of d_{10}, d_{50}, d_{90} descriptors decreased, where the largest reduction can be seen in the later case. A thin HPMC coat on the surface of individual substances provided a barrier that decreased the cohesiveness of ibuprofen powder. This phenomenon can be observed in Fig. 2, where the cumulative particle size distribution curve shifted left as the progressive powder treatment proceeded. It can be attributed to the diminution in the electrostatic interactions and van der Waals forces as polymeric film became more uniform. The obtained d_{50} values of 109 μm for raw powder were higher than recently showed results by image analysis (Ehlers et al., 2009). It can be due to the fact that the SFT does not disperse completely highly charged powder, providing the size values of agglomerated particles.

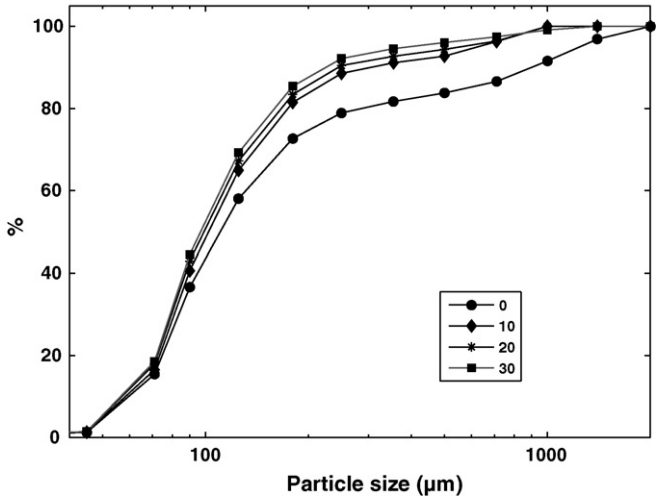

Fig. 2. Cumulative particle size distribution for original and polymer processed ibuprofen samples ($n = 3$).

From the SEM micrographs, the absence of granule formation can be seen after HPMC treatment procedure (Fig. 3a and c). This

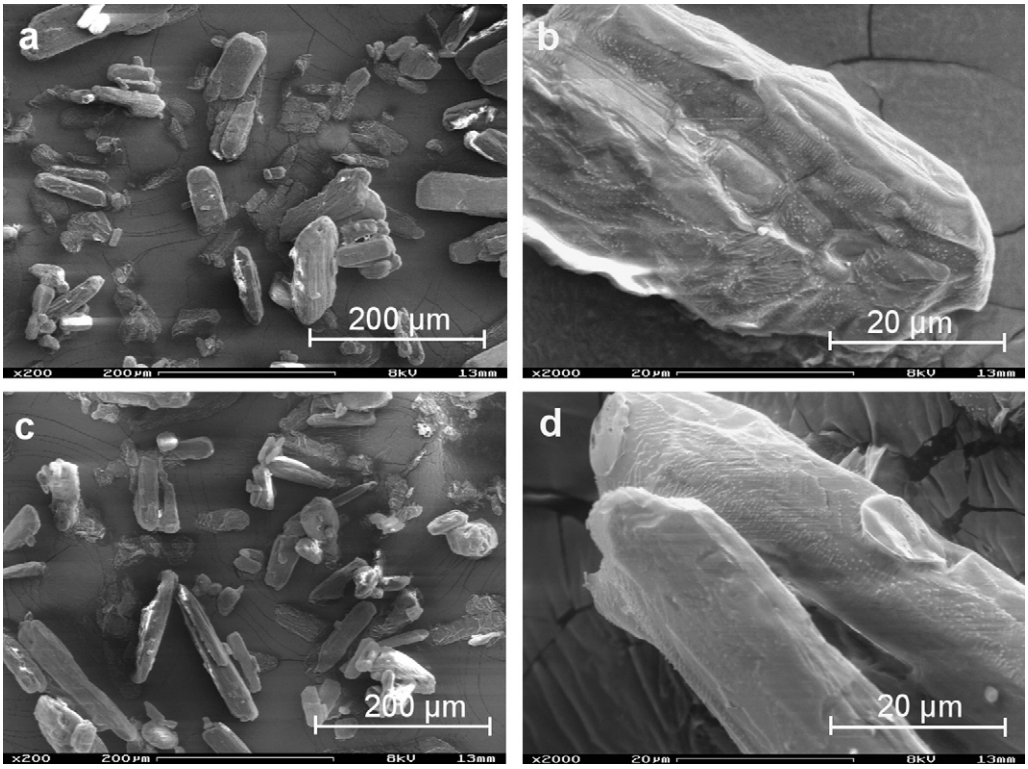

Fig. 3. Scanning electron micrographs of untreated (a and b) and HPMC coated (c and d) ibuprofen samples. Magnification is 200× for (a and c) and 2000× for (b and d).

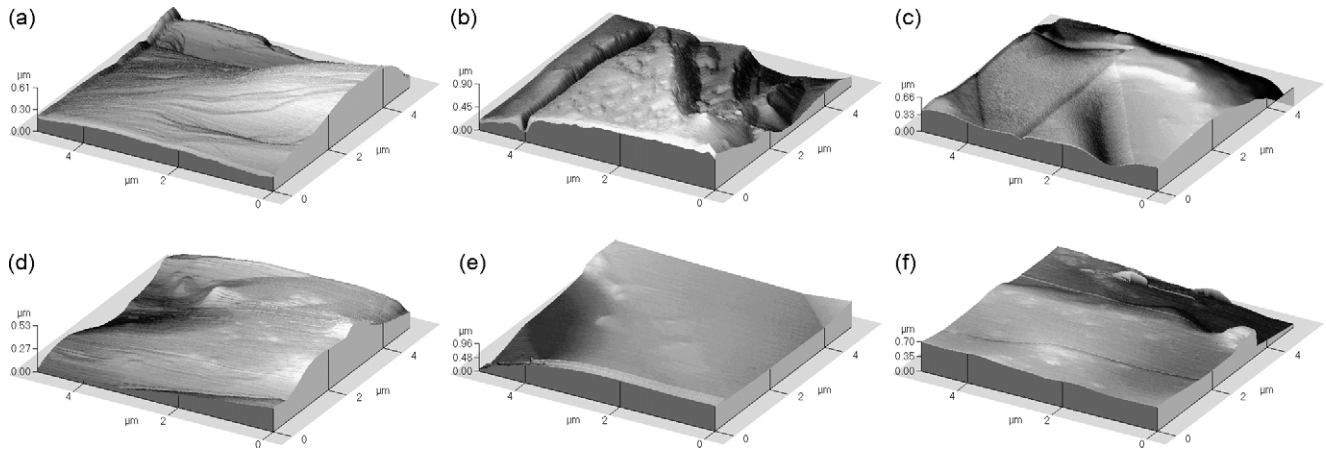

Fig. 4. Representative AFM height images of particle surface of untreated (a, b, and c) and treated (d, e, and f) ibuprofen samples.

observation is in agreement with the results obtained from particle size analysis. The closer look at ibuprofen species showed that the surface of treated substance became more flat in comparison with the superficial structure of raw substance. It can be explained with the formation of more or less smooth polymer thin-coat on the surface of rough particles.

The finding of SEM micrographs was confirmed by the detailed observation of particle surface topography using the AFM technique (Fig. 4). The numeric values were obtained by performing the qualitative analysis of acquired AFM images. The average roughness parameter (Ra) of HPMC treated areas of particle surfaces decreased significantly, indicating the reduction in the height differences of the probes (Table 2). The smaller value of standard deviation underlined the fact that HPMC thin-coating made the surface of ibuprofen particles more homogeneous.

3.3. Analysis of flow properties

3.3.1. Flow properties of the processed ibuprofen powder

It was expected that decreasing the interlocking of the polymer coated particles and increasing the smoothness of treated particle surfaces would have impact on the flow properties of ibuprofen. The improvement in the flow rate of HPMC thin-coated powder could already be observed after 10 cycles of the mist treatment procedure (Fig. 5). The particle size analysis and flowability measurements indicate that the higher amount of cycles gave the more uniform coating of particle surfaces as it can be seen from gradual growth in the flow rate. It increased greatly after 25 cycles of treatment, whereas the further processing did not give any significant improvement. Obviously, the raw surface of ibuprofen particles has already been completely hidden by polymer thin-coat after

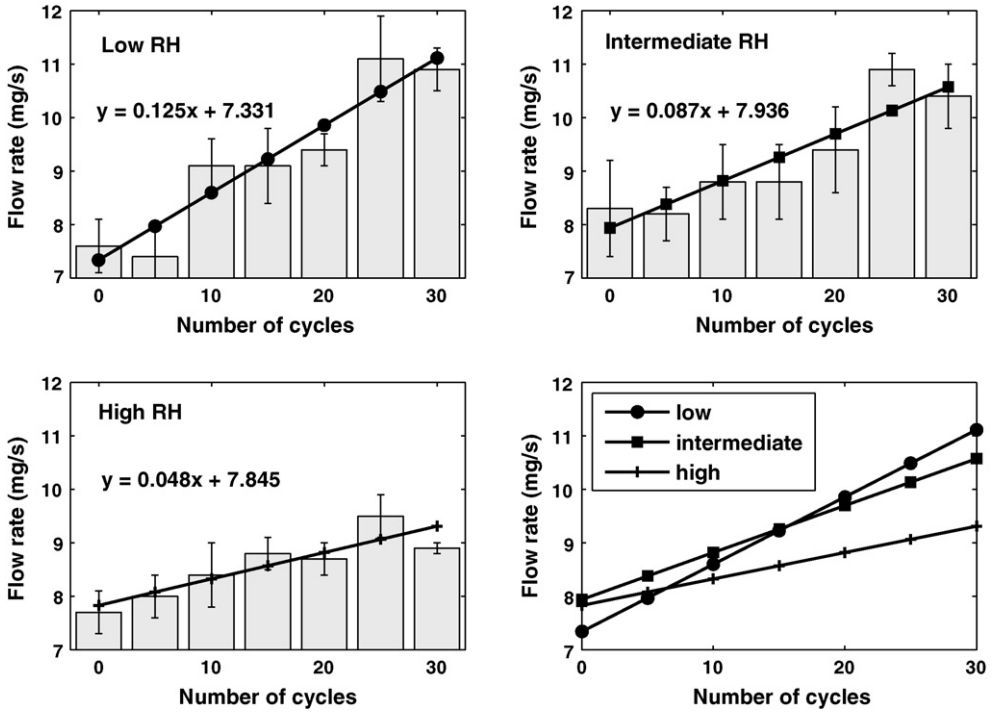

Fig. 5. The influence of the uniformity of HPMC coating layer and the relative humidity on the flow properties of ibuprofen powders ($n = 5$).

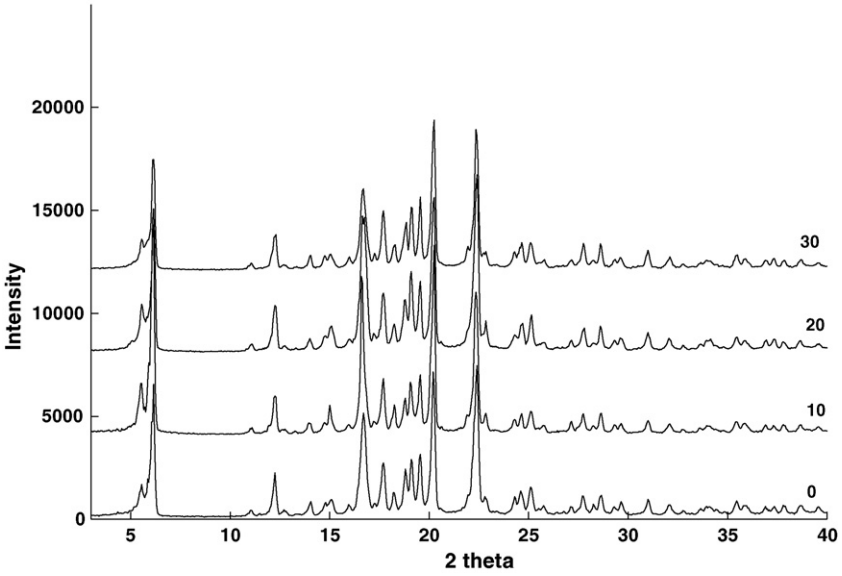

Fig. 6. X-ray powder diffraction patterns for uncoated and progressively HPMC coated materials.

20 times of treatment. The effect of the coating layer on the technical properties of powder could be explained by the increase in the hydrophilicity of particle surfaces that reduced the electrostatic interactions and thus decreased the cohesion forces of hydrophobic ibuprofen particles. The influence of hydrophilic species onto the flow properties of hydrophobic substances was previously reported by Kawashima et al. (1998).

3.3.2. The effect of the relative humidity on the flow properties

It is a well-known fact that moisture has a significant influence on the flow properties of cohesive powders (Forsyth et al., 2002; Faqih et al., 2007). The effect of relative humidity on the flow characteristics of treated and untreated ibuprofen was studied in the conditions of low (0.26 ± 0.04), intermediate (0.50 ± 0.02) and high (0.70 ± 0.03) water activities of the samples. Fig. 5 shows that moisture content affected the rheological properties of the processed powder. The slope of the plots decreased from 0.125 to 0.048 when the conditions changed from low to high. In other words, the flowability impaired as the water content of the powders increased. It is obvious that at high relative humidity the water vapours condensed onto particle surfaces, creating a water sorption layer (Führer, 1996; Nyström and Karehill, 1996). Further increase in relative humidity caused the separation of water phase, which gave rise to capillary forces (Iida et al., 2004). These liquid interactions held particles together, preventing their flow. The effect of humidity on the flow properties of the modified powder became more noticeable when the uniformity of the HPMC layer enhanced. The thin-polymer coating made the surface of ibuprofen particles more hydrophilic as it was mentioned above. The hydrophilic surface had more affinity to water molecules and as a consequence more subject to pronounced capillary effect. As well, the more planar surface of HPMC coated particles could enhance the hydrostatic forces (Rodczeck et al., 1997). At the low water activity of the samples, less adsorbed water acted probably as a lubricant, facilitating powder flow (Kaerger et al., 2004). The changes in the water activity did not have a significant effect on the flowing characteristics of the raw material. The obtained results are in agreement with the recent discovery done by Ehlers et al. (2009), where the flow properties of ibuprofen particles coated with HPMC in the fluidized bed showed the identical trend in the conditions of low, intermediate and high relative humidity.

3.4. Solid state properties

XRPD analysis was performed to find out any solid state modifications on the particle surface. No crystal lattice changes or the appearance of the hollow pattern were observed. The X-ray powder diffractograms were rather identical even after 30 cycles of treatment with HPMC coating solution (Fig. 6). The minor changes in the intensities of peaks are related to the preferred orientation of crystal plans in the probes or it can be as a result of the superficial changes of coated ibuprofen particles.

4. Conclusions

The alternative robust technique for thin-coating of ibuprofen particles was presented. The proposed method provided API powder with the improved physico-technical properties. The relative humidity had a significant impact on to the flow properties of coated samples. The obtained data did confirm early findings, where the fluidized bed was used as a coating tool for the cohesive powder. In conclusion, the introduced method is insensitive to batch size and environment conditions technique that can be used as a continuous process to improve the flow properties of heat, moisture and shear/stress sensitive powders. In addition, it can be applied for freshly crystallized highly charged material to make further unit operations such as granulation, functional coating, weighing, packing easier and more cost effective.

Acknowledgements

The Estonian National Scholarship Fund is acknowledged for financial support. Ms. Anna Halenius is thanked for helping with AFM measurements.

References

Albertini, B., Passerini, N., Rodriguez, L., 2005. Evaluation of ultrasonic atomization as a new approach to prepare ionically cross-linked chitosan microparticles. J. Pharm. Pharmacol. 57, 821–829.

Dewettinck, K., Messens, W., Deroo, L., Huyghebaert, A., 1999. Agglomeration tendency during top-spray fluidized bed coating with gelatin and starch hydrolysate. Lebensm. Wiss. Technol. 32, 102–106.

Ehlers, H., Räikkönen, H., Antikainen, O., Heinämäki, J., Yliruusi, J., 2009. Improving flow properties of ibuprofen by fluidized bed particle thin-coating. Int. J. Pharm. 368, 165–170.

Elversson, J., Millqvist-Fureby, A., 2006. *In situ* coating—an approach for particle modification and encapsulation of proteins during spray-drying. Int. J. Pharm. 323, 52–63.

Faqih, A.M.N., Mehrotra, A., Hammond, S.V., Muzzio, F.J., 2007. Effect of moisture and magnesium stearate concentration on flow properties of cohesive granular materials. Int. J. Pharm. 336, 338–345.

Forsyth, A.J., Hutton, S., Rhodes, M.J., 2002. Effect of cohesive interparticle force on the flow characteristics of granular material. Powder Technol. 126, 150–154.

Führer, C., 1996. Interparticulate attraction mechanisms. In: Alderborn, G., Nysröm, C. (Eds.), Pharmaceutical Powder Compaction Technology. Marcel Dekker, New York, pp. 1–15.

Genina, N., Räikkönen, H., Heinämäki, J., Antikainen, O., Siiriä, S., Veski, P., Yliruusi, J., 2009. Effective modification of particle surface properties using ultrasonic water mist. AAPS PharmSciTech 10, 282–288.

Iida, K., Hayakawa, Y., Okamoto, H., Danjo, K., Luenberger, H., 2004. Influence of storage humidity on the *in vitro* inhalation properties of salbutamol sulfate dry powder with surface covered lactose carrier. Chem. Pharm. Bull. 52, 444–446.

Kaerger, J.S., Edge, S., Price, R., 2004. Influence of particle size and shape on flowability and compactibility of binary mixtures of paracetamol and microcrystalline cellulose. Eur. J. Pharm. Sci. 22, 173–179.

Kaerger, J.S., Price, R., 2004. Processing of spherical crystalline particles via a novel solution atomization and crystallization by sonication (SAXS) technique. Pharm. Res. 21, 372–381.

Kawashima, Y., Serigano, T., Hino, T., Yamamoto, H., Takeuchi, H., 1998. Design of inhalation dry powder of pranlukast hydrate to improve dispersibility by the surface modification with light anhydrous silicic acid (AEROSIL 200). Int. J. Pharm. 173, 243–251.

Luo, Y., Zhu, J., Ma, Y., Zhang, H., 2008. Dry coating, a novel coating technology for solid pharmaceutical dosage forms. Int. J. Pharm. 358, 16–22.

Nyström, C., Karehill, P.-G., 1996. The importance of intermolecular bonding forces and the concept of bonding surface area. In: Alderborn, G., Nysröm, C. (Eds.), Pharmaceutical Powder Compaction Technology. Marcel Dekker, New York, pp. 17–53.

Petrak, D., 2002. Simultaneous measurement of particle size and particle velocity by the spatial filtering technique. Part. Part. Syst. Charact. 19, 391–400.

Pfeffer, R., Dave, R.N., Wei, D., Ramlakhan, M., 2001. Synthesis of engineered particulates with tailored properties using dry particle coating. Powder Technol. 117, 40–67.

Rodczeck, F., Newton, J.M., James, M.B., 1997. Variations in the adhesion force between a drug and carrier particles as a result of changes in the relative humidity of the air. Int. J. Pharm. 149, 151–160.

Rodriguez, L., Passerini, N., Cavallari, C., Cini, M., Sancin, P., Fini, A., 1999. Description and preliminary evaluation of a new ultrasonic atomizer for spray-congealing processes. Int. J. Pharm. 183, 133–143.

Ruecroft, G., Hipkiss, D., Ly, T., Maxted, N., Cains, P.W., 2005. Sonocrystallization: the use of ultrasound for improved industrial crystallization. Org. Process Res. Dev. 9, 923–932.

Seitavuopio, P., 2006. The Roughness and Imaging Characterization of Different Pharmaceutical Surfaces. Ph.D. Thesis. University of Helsinki, Finland.

Seppälä, K., Yliruusi, J., Heinämäki, J., 2007. Development of a new method to get a reliable powder flow characteristics using only one to two grams of powder. Oral presentation. In: AIChE, Annual Meeting, Salt Lake City, Utah, USA, November 4–9.

Tang, E.S.K., Wang, L., Liew, C.V., Chan, L.W., Heng, P.W.S., 2008. Drying efficiency and particle movement in coating—impact on particle agglomeration and yield. Int. J. Pharm. 350, 172–180.