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Research Article

Effective Modification of Particle Surface Properties Using Ultrasonic Water Mist

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Abstract. The goal of the present study was to design a new technique to modify particle surface properties and, through that, to improve flowability of poorly flowing drug thiamine hydrochloride and pharmaceutical sugar lactose monohydrate of two different grades. The powdered particles were supplied by a vibratory feeder and exposed to an instantaneous effect of water mist generated from an ultrasound nebulizer. The processed and original powders were evaluated with respect to morphology (scanning electron microscopy, atomic force microscopy, and spatial filtering technique), flow, and solid state properties. It was found that rapid exposition of pharmaceutical materials by water mist resulted in the improvement of powder technical properties. The evident changes in flowability of coarser lactose were obviously due to smoothing of particle surface and decreasing in the level of fines with very slight increment in particle size. The changes in thiamine powder flow were mainly due to narrowing in particle size distribution where the tendency for better flow of finer lactose was related to surface and size modifications. The aqueous mist application did not cause any alteration of the crystal structures of the studied materials. The proposed water mist treatment technique appears to be a robust, rapid, and promising tool for the improvement of the technological properties of pharmaceutical powders.

KEY WORDS: flow properties; lactose monohydrate; surface properties; thiamine hydrochloride; ultrasonic water mist.

INTRODUCTION

For the successful production of oral solid dosage forms, it is essential to provide suitable particle properties of pharmaceutical materials. Effective modification of particle surfaces may be one possibility to improve powder behavior during the industrial process. Preparation of particles with smooth surface gives decrease in attractive forces between them, reducing a tendency to interlock. It results in better flow and packing properties that is of great importance in the technology of tablets and capsules of uniform mass and content. In addition, efficient processing of particle surfaces could avoid time-, energy-, and cost-consuming granulation step and allow the direct compression of formulation. As well, smoothed surface has better detachment properties that are extremely important in the preparation of ordered mixture for dry powder inhalers (DPI).

Many approaches have been done in the field of particle surface engineering (1), especially in the processing of lactose carrier surfaces for DPI. Controlled crystallization of lactose from different solvents was carried out to produce regular crystals with smooth surface (2,3). Iida *et al.* used several methods for effective surface treatment of excipient by dissolving surface asperities in aqueous ethanol solution (4), covering lactose particles with antistatic properties owning sucrose tristearate (J-1803F) (5) and magnesium stearate (6), applying shear stress in a high-speed powder mixer (7), and covering with hydroxypropyl methylcellulose in a Wurster fluidized bed (8). Kumon *et al.* applied a novel mechanofusion approach in the presence of additives to modify the shape and the surface texture of lactose (9). The smoothing procedure, based on the wetting in water–ethanol mixture with or without ternary component (magnesium stearate) and drying of lactose powder in high-shear mixer, was successfully carried out by other workers (10,11). Recently, studies at elevated temperature with alcoholic solution were conducted to control surface dissolution of lactose particulate (12,13).

The promising attempts were made to improve flow and/or detachment properties of active pharmaceutical ingredient (API) through modification of its surface characteristics. A surface treatment approach, based on interplay at the solid–liquid interface in a drug suspension, was successfully applied on APIs with poor flowability (14,15). The recrystallization of sulfadiazine, methyldopa, and salbutamol sulfate from preselected solvents in the absence or presence of additive has been carried out to change crystal habit with altering surface topography (14,16).

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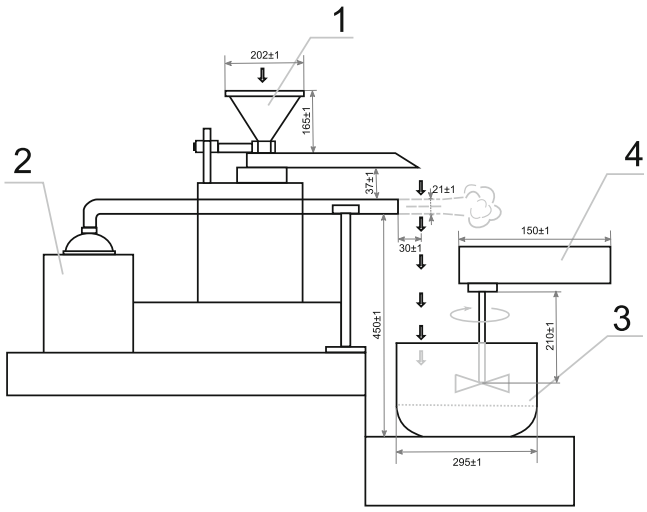

Fig. 1. Processing setup: *1* vibrating feeder, *2* ultrasound nebulizer, *3* collecting vessel, and *4* stirrer (the parameters of the technique are given in millimeters)

The goal of the present study was to design a new technique to modify particle surface properties and, through that, to improve flowability of poorly flowing drug thiamine hydrochloride and pharmaceutical sugar lactose monohydrate. Briefly, the technique was based on the application of ultrasonic water mist on to the powder mass. The aqueous mist influence was very rapid due to extremely small size of water droplets that avoided drying step at elevated temperature or long-lasting moisture evaporation in ambient conditions.

MATERIALS AND METHODS

Materials

Lactose α-monohydrate of different grades (Pharmatose® 80M, Pharmatose® 200M, Division of Campina BV, The Netherlands) was used as test material in an ultrasonic water mist processing. Thiamine hydrochloride (USP; Hawkins, Minneapolis, MN, USA) was chosen as a water-soluble model drug. Both thiamine hydrochloride and lactose were used in all experiments as solid substances (powders).

Ultrasonic Water Mist Treatment Procedure

The powdered particles as solid substances were supplied by a vibratory feeder (Laborette 24, Germany) and exposed to an instantaneous effect of stream of water mist generated from an ultrasound nebulizer (Ultrasonic Nebulizer NE-U17, Ultra Air, Omron, The Netherlands) (Fig. 1). When all powder was processed, slightly wetted solid material was equilibrated for 10 min. The ultrasonic water mist procedure was repeated five times with the same solid substance. After the last treatment, wetted powder was left for 1 h to give collected moisture to evaporate in ambient conditions (19.3±0.5°C and 21.5±0.3% relative humidity). During the entire procedure, the powder mass was periodically mixed by a stirrer (IKA®-WERKE, RW 11 basic, Staufen, Germany) to prevent the formation of water bridges between individual particles. All process parameters are presented in Table I.

The treated and untreated materials were stored in sealed glass bottles. Powders were equilibrated for 1 day in climate control room at 21.4±2.6°C and 46.5±6.3% relative humidity prior to testing.

Analysis of Particle Size

Particle size and size distribution measurements were performed by the spatial filtering technique (SFT) (17). The powdered materials were supplied 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 was transformed to volume particle size for data analysis. At least three measurements were done per sample.

Analysis of Particle Shape and Surface

Particle shape and surface roughness was investigated by scanning electron microscopy (SEM) (Zeiss DSM 962, Carl Zeiss, Oberkochen, Germany). Before scanning, samples were coated with platinum using a vacuum evaporator. SEM images were obtained at an accelerated voltage of 10 kV.

The detailed surface texture of the particles was studied by atomic force microscopy (AFM) (Autoprobe CP, Thermomicroscopes, USA) over 5×5 and 10×10 μm areas. AFM imaging was performed in noncontact mode with a cantilever of 0.9 N/m spring constant (Silicon cantilever NSCH21A, NT-MDT Ltd., Russia) at a scan rate of 0.35 Hz. The slow scan rate was set mainly due to a high roughness of some probes. AFM imaging was carried out in normal conditions using a large area scanner (100 μm lateral scan size). The average

Table I. Applied Process Parameters

	Pharmatose® 80M	Pharmatose® 200M	Thiamine•HCl
Batch size (g)	250.0	250.0	200.0
Number of cycles	5	5	5
Air flow (L/min)	17	17	17
Flow rate of water mist (g/min)	3.0	3.0	3.0
Droplet size of water mist (μm)	4.4	4.4	4.4
Feeding rate of powder (g/min)	42.3	21.2	7.3
Rotation rate of stirrer (rpm)	240	240	240
Time between cycles (min)	10	10	10
Yield (%)	99.5	99.2	98.1

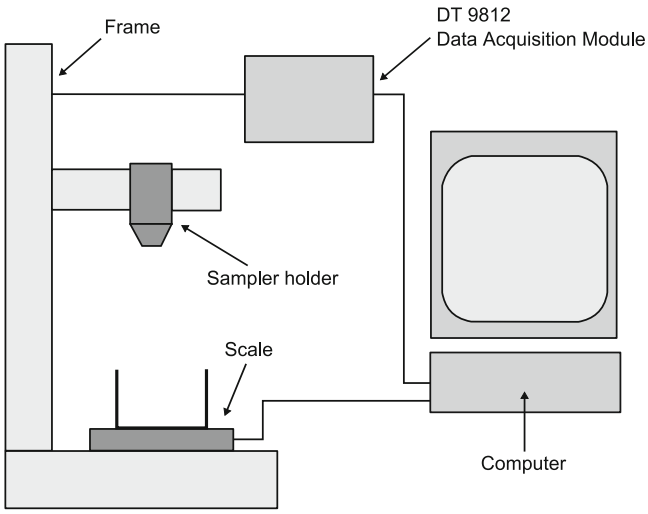

Fig. 2. Block diagram of the powder flow measuring arrangement (19)

roughness parameter (Ra) for each sample was calculated from the AFM height data according to equation:

$$Ra = \sum_{n=1}^{N} \frac{|Z_n - \overline{Z}|}{N}$$

where Z_n is the individual height value of one measurement point, $\overline{Z}$ is the mean value of all the height data points, and N is the number of measurement points (18). Five parallel measurements were performed per sample.

Moisture Content

Moisture content of the samples was determined as a loss of weight at 105°C using infrared apparatus (Sartorius MA 100, Sartorius AG, Germany). Before analysis, the device was preheated to avoid an unreliable result of the first measurement. The tests were conducted in triplicate.

Particle Packing and Flow Properties

The flow rate as a practical property described as flowability was determined as the time for a fixed amount of powder (50.0 g) to flow trough a glass tunnel with standard orifice diameter according to the method described in the European Pharmacopeia 5. Three measurements were done per sample.

Flow properties of powders were determined using a new flowability testing method (FlowPro) (19). The in-house developed system consists of a frame, motor, sample holder, funnel (5.96 mL) with orifice (3 mm), and analytical scale (Fig. 2). The motor induces up and down movements of the funnel that make the powder flow through the orifice onto the analytical scale. Connection of balances with a PC gives possibility to calculate the flow rate (in milligrams per second and microliters per second) of powdered particles. Three parallel measurements were performed.

Angle of repose was measured according to the modified method presented by Zeng *et al.* (2). Powdered particles were poured into a copper tube (2.8×3.15 cm), which had been introduced over a flat metal base with a diameter of 3.0 cm. After the powder filled the tube completely, it was slowly raised vertically, leaving a cone of powder. The cones were recorded by a digital camera (Olympus Stylus 820 *I* μ 820, Hamburg, Germany) using super macro mode. Analy-

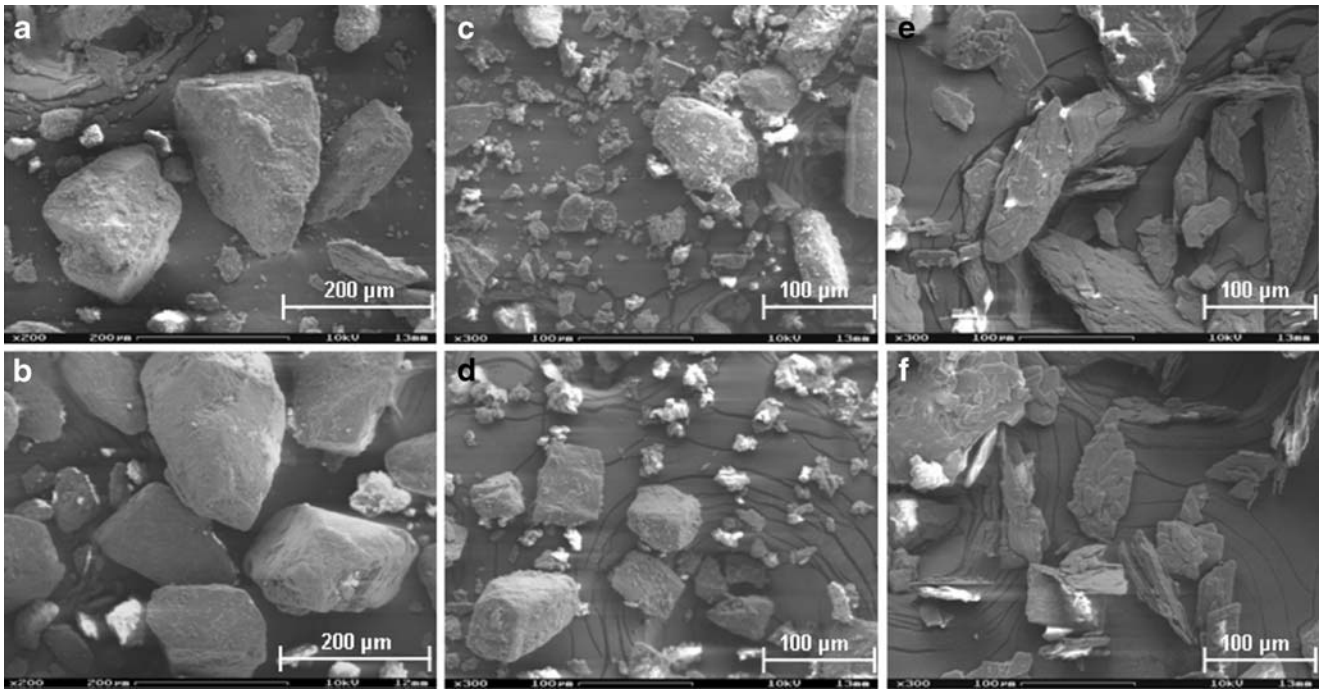

Fig. 3. Scanning electron micrographs of untreated (**a**) and treated (**b**) Pharmatose® 80M; untreated (**c**) and treated (**d**) Pharmatose® 200M; untreated (**e**) and treated (**f**) thiamine hydrochloride powders

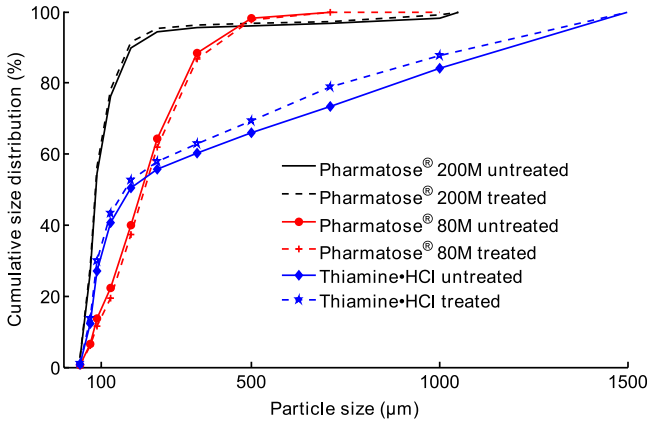

Fig. 4. Particle size distribution for original and processed samples

sis of pictures was done by Matlab software (version 7). The angle of repose (θ) was calculated from the tangent (cone height/cone base radius). Each sample was measured in triplicate.

To evaluate packing properties of powders, the bulk density was determined from the mass of the analyzing material occupying 150 mL volume. Each sample was measured three times.

Solid State Properties

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

Differential scanning calorimetry (DSC) was done with Mettler DSC823. Samples of 4.5±0.5 mg for drug and 9±1 mg for excipient were analyzed using closed 40 μL aluminum pan with two pinholes in the cover. The heating rate of the samples was 10 K min^{-1}. The DSC system was calibrated using indium (429.85 K). The raw data were edited and graphically visualized using Matlab software (version 7).

RESULTS

Morphological Analysis

Representative scanning electron micrographs of untreated and water mist-treated lactose and thiamine samples are shown in Fig. 3. The unmodified materials owned particles with rough surface. The perfunctory morphology of treated lactic sugar of both grades appeared to be flatter. At the magnification used, the visual changes of the surface of processed thiamine particles were not so obvious. A slight excess of fines attached to the surface of the original substance in comparison with the amount of dust on the surfaces of treated material could be observed.

Cumulative particle size distributions for original and aqueous mist-processed lactose of different grades and thiamine hydrochloride, done by SFT, are shown in Fig. 4. The 10% (d_{10}), 50% (d_{50}), and 90% (d_{90}) fractiles are illustrated in Table II.

Water mist-processed coarser lactose (Pharmatose® 80M) showed statistically significant reduction in the level of fines, which was confirmed by SEM observations (Fig. 3b). The size parameters of treated finer lactose (Pharmatose® 200M) and thiamine hydrochloride were slightly decreased, but the particle size distribution of processed powders became more narrow in comparison with untreated materials.

The detailed surface topography of lactose monohydrate and thiamine hydrochloride samples through AFM mapping, before and after water mist treatment, is presented in Fig. 5. The average roughness parameters for each pattern, calculated over 5×5 and 10×10 μm areas are reported in Table II.

Flow and Packing Properties

Flow and packing properties together with water content are presented in Table III. Moisture content remained almost unchanged after water mist processing. The technological characteristics for lactose and thiamine powders were improved by the treatment. The measurements of flowability according to the European Pharmacopoeia were successfully performed only with coarser lactose. The flow rate of processed powder was significantly increased from 18.0±1.7 to 28.3±0.32 g/s (mean±SD, n=3, Student's unpaired t test, p<0.01). Tests with other substances were impossible to

Table II. Particle Size and Surface Roughness of Untreated and Treated Powders (Data are Presented as Mean±SD, n=3–5)

Sample	Particle size (μm)			Surface roughness (nm)	
	d_{10}	d_{50}	d_{90}	Ra[a]	Ra[b]
Pharmatose® 80M, untreated	80.7±0.59	209±2.1	369±5.2	262±180	227±81
Pharmatose® 80M, treated	85.0±1.4*	216±4.8	379±4.4	168±74	220±130
Pharmatose® 200M, untreated	58.1±0.31	87.5±1.5	183±10	333±240	251±160
Pharmatose® 200M, treated	57.2±0.46	85.9±1.1	172±15	251±290	170±88
Thiamine•HCl, untreated	68.6±0.71	179±17	1160±98	166±140	225±79
Thiamine•HCl, treated	67.0±1.2	163±18	1080±50	66.5±38	317±96

*p<0.05, significant difference compared to untreated substance by Student's unpaired t test
[a] Ra over 5×5 μm area
[b] Ra over 10×10 μm area

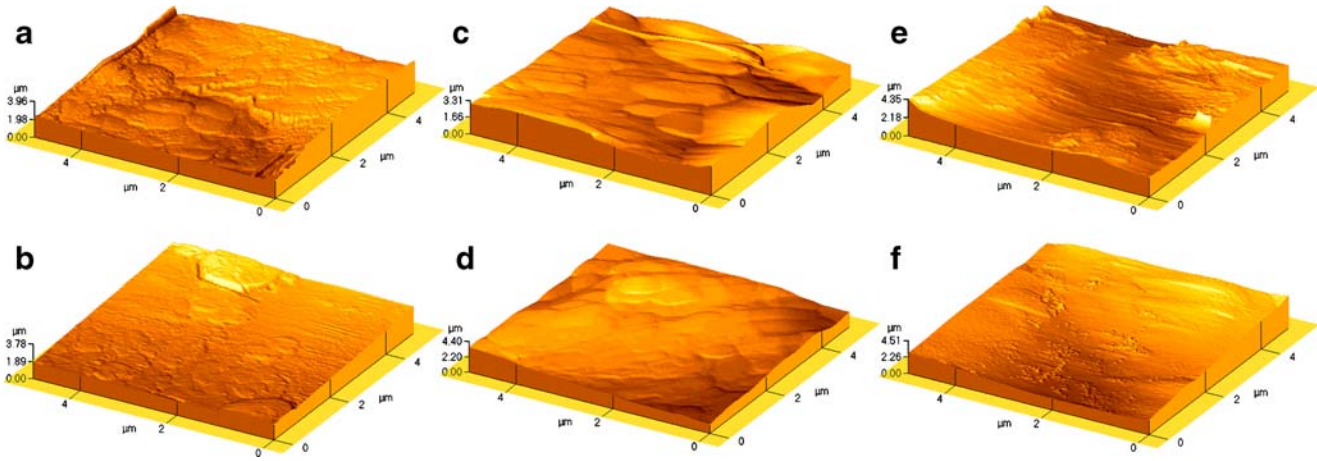

Fig. 5. Representative AFM height images of particle surface of untreated (**a**) and treated (**b**) Pharmatose® 80M; untreated (**c**) and treated (**d**) Pharmatose® 200M; untreated (**e**) and treated (**f**) thiamine hydrochloride powders

carry out due to disability of these powders to pass through the orifice even after knocking.

Solid State Properties

X-ray and DSC analysis (Figs. 6 and 7, respectively) were conducted for both original and processed lactose monohydrate and vitamin B_1 samples in order to investigate possible changes of crystallinity. No significant modifications of crystal structure before and after water mist treatment were found.

DISCUSSION

Morphological Analysis

SEM micrographs showed that the surface of treated lactose particles of both grades became plainer where the shape of the species remained almost unchanged (Fig. 3). The aqueous mist, applied directly to the powder, brought about dissolution of superficial prominences and fine particulate. Dissolved material more probably deposited in the pits of bigger particles according to Ostwald ripening phenomenon (11), making particle surface smoother. It was difficult to make defined conclusions about the changes of the surface of layered flake-like particles of thiamine.

The water mist treatment reduced significantly the number of fine particulate in the bulk of coarser lactose (Pharmatose® 80M): the value of d_{10} increased from 80.7 to 85.0 μm. The disappearance of fines caused a slight increment in the particle size (d_{50} and d_{90} values) due to recrystallization most likely on the surface of larger species. The aqueous mist procedure did not, in the main, influence on the particle size of finer lactose (Pharmatose® 200M) and thiamine powders. The insignificant reduction of d_{10}, d_{50}, and d_{90} values might be related to surface smoothing effect (three to five parallel measurements were done per sample). The visual observation and spatial data analysis of size distribution suggested the absence of granule formation that was highly desirable.

The AFM technique of imaging of particle surface permitted a visual (3D images) and a quantitative evaluation (Ra parameter) of the detailed topography of particle surface at the nanoscale level. Representative images obtained over the 5×5-μm area (Fig. 5) showed a decrease of surface roughness of powdered particles after water mist processing. Directly measured Ra parameter corroborated this observation: the decreased values of Ra over the 5×5-μm area were obtained for all aqueous mist-treated samples (Table II). The Ra values, calculated over the 10×10-μm area showed as well a reduction of surface irregularities of processed lactose powders of both grades. Ra parameters of thiamine particles suggested an increase of surface roughness of aqueous mist-treated material. Five parallel measurements were performed per sample. Rather high values of standard deviation in average roughness parameters, mainly due to a small

Table III. Flowability, Angle of Repose, Bulk Density and Moisture Content Values for Water Mist-Treated and Untreated Materials (Data are Presented as Mean±SD, $n=3$)

Sample	FlowPro		Angle of repose (°)	Bulk density (g/cm^3)	Moisture content (%)
	mg/s	μL/s			
Pharmatose® 80M, untreated	86.5±7.6	146±11	49.6±0.66	0.766±0.009	0.191±0.036
Pharmatose® 80M, treated	174±10*	278±21*	46.5±0.79*	0.787±0.005*	0.163±0.041
Pharmatose® 200M, untreated	9.30±1.7	23.8±3.7	56.5±2.1	0.505±0.007	0.277±0.13
Pharmatose® 200M, treated	11.4±1.7	29.3±5.5	54.8±1.9	0.501±0.008	0.193±0.025
Thiamine•HCl, untreated	6.39±0.61	24.1±2.1	64.9±0.11	0.326±0.004	4.06±0.011
Thiamine•HCl, treated	12.1±0.66*	41.5±2.3*	62.6±1.8	0.361±0.004*	4.05±0.061

*$p<0.01$, significant difference compared to untreated substance by Student's unpaired t test

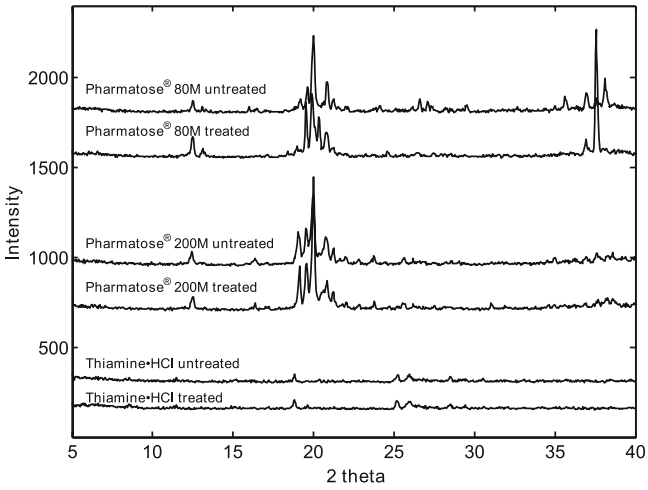

Fig. 6. The X-ray powder diffraction patterns for water mist-treated and untreated materials

scanning area of AFM mapping and a high roughness of the probes, make quantitative analysis less reliable. Large standard deviation of the average heights due to the heterogeneous height distribution on the surfaces has been reported in the literature as well (20). However, the results of surface properties of original and processed material from AFM mapping do support the data observed on SEM micrographs, as AFM as SEM techniques could not exactly show certain differences in surface roughness between treated and untreated vitamin B_1 samples.

Flow and Packing Properties

It was supposed that the treatment by aqueous mist at the solid–liquid–air interface and in the bulk of powder provided an improvement of the powder flow and packing properties as a result of decreases in the particle surface roughness and changes in the particle size range. The smoothing procedure was expected to cause the diminution of the internal friction between particles and the more compact packing of the powder bed. Preparation of more equidimensional particles was thought to be also related to better technical properties of processed material. The results from the new flowability measurement tool revealed that the flow rate of coarser lactose and thiamine powders increased approximately two times. The flowability of finer lactose appeared to improve, but this was not statistically significant ($p>0.01$). Three parallel measurements were performed per sample. Similar increase in the flow rate of Pharmatose® 80M powder was obtained from flowability tests according to the European Pharmacopeia. The impossibility of the last method to be applied for powders with poor flow properties highlights the usefulness of the new flowability measurement tool. The smaller values of angle of repose of processed powders underlined the fact that treated substances exhibited superior flowability in comparison to that observed with original materials ($n=3$). But the angle of repose was less sensitive to the changes in flow properties of modified powders than FlowPro tool: statistically significant reductions in the value of θ showed only coarser lactose. It can be due to the fact that the angle of repose as an indirect flowability measurement method is determined by least stable particle (2), whereas the results from FlowPro depend extensively on the bulk properties of the powder bed. Also, the more dense packing was observed for processed Pharmatose® 80M and thiamine samples ($n=3$). Their poured densities were increased significantly. It was supposed that improvement in flow properties for coarser lactose was due to smoothing of surface and decreasing in the level of fines with very slight increment in particle size. The changes in technological characteristics of thiamine powder were assumed to be mainly due to narrowing in particle size distribution, whereas the tendency for better flow properties of finer lactose was related to surface and size modifications.

Solid State Properties

Analysis of the XRPD and DSC thermograms for both untreated and water mist-treated powders showed no modification of crystal structure and were typical for α-lactose monohydrate and thiamine hydrochloride anhydrate. The minor differences in the intensity and position of protuberant peaks of XRPD spectra, especially in the case of coarser lactose, is related to the "preferred orientation" of the crystals and lattice planes in the probes and as result of the subtle changes in the particle morphology. The DSC traces of processed and original materials were rather identical. Thermograms of treated and untreated lactose powders showed two endothermic events: the first starting at about 143°C, corresponding to dehydration of water of crystalliza-

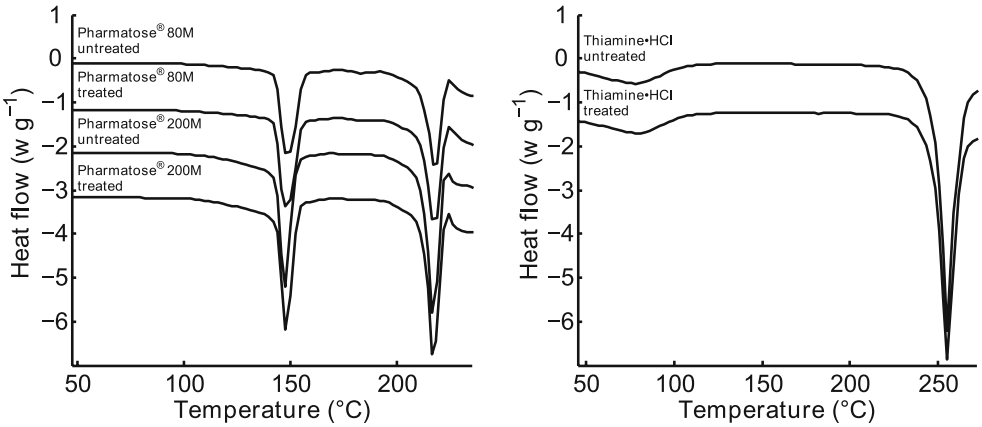

Fig. 7. DSC thermograms of water mist-treated and untreated powders

tion and the second around 217°C, which is the melting point of α-lactose (2). DSC thermograms of processed and original vitamin B_1 powders included two endothermic peaks: the first beginning at about 40°C was attributed to moisture elimination and the second above 248°C, corresponding to melting of thiamine hydrochloride. No hydrate formation during powder processing was observed due to the nonappearance of the peak, corresponding to the elimination of water of crystallization in the region between 140°C and 185°C (21). Minor dissimilarities in the molar enthalpy of fusion confirmed the absence of significant changes in crystallinity after aqueous mist treatment.

CONCLUSIONS

The ultrasonic water mist treatment technique introduced in the present work evinces promises as a robust, rapid, and repeatable tool for the improvement of technological properties of pharmaceutical powders. It can be employed to alter particle surface of water-soluble excipients and drug substances, giving rise to powders with desired properties. Improvement of flow and packing properties may have practical application for the effective processing of powders for direct compression of tablet formulation. Furthermore, the proposed technique can be directly utilized during milling of crystallized material before final packaging without any significant loss of powder, making the new tool economically beneficial.

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