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The Surface Roughness of Lactose Particles Can Be Modulated by Wet-Smoothing Using a High-Shear Mixer

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ABSTRACT

The surface morphology of α-lactose monohydrate particles was modified by a new wet-smoothing process performed in a high-shear mixer using solvents. Successive steps of wetting and drying of lactose powders during rolling in the mixer's cylindrical bowl were performed. Smoothed particles were tested for size distribution, flow, and packing. The wet-smoothing process flattened the surface and rounded the edges of lactose particles. In comparison with original lactose, an improvement of powder packing and flow properties was evidenced. When the process was performed in the presence of a ternary agent such as magnesium stearate, the smoothing was improved. The evolution of rugosity during the smoothing process was assessed through a fractal descriptor of SEM picture. Atomic force microscopy and surface area measurements quantified the surface rugosity. A very significant reduction of the rugosity, more remarkable in the presence of magnesium stearate, was measured. This new process of powder wet-smoothing allows the preparation of lactose particles with different degrees of smoothed surface for the control of flow and packing properties and particle-particle interactions.

KEYWORDS: lactose, smoothing, roughness, high-shear mixer

INTRODUCTION

A range of lactose powders with different physico-chemical characteristics is available for pharmaceutical applications. Appropriate size, shape, packing, and flow characteristics of lactose powders are required by a specific solid dosage form. For example, the surface properties of lactose used in inhalation products are known to affect their aerosolization performance.[1-3] Numerous investigations[4-14] have indicated that the use of engineered lactose particles exhibiting modified surface could lead to more predictable aerosolization performance. However, the availability of lactose powders having improved flow and packing properties is stringent also in capsule and tablet technology.

There are numerous examples in the literature that describe techniques to affect the surface rugosity of lactose particles.[9,15,16] These techniques are based on controlled crystallization procedures or processes in which the edges or asperities of the particles have been eliminated by a controlled mild milling.[17] As part of ongoing research,[18-20] the aim of this work was to focus on an innovative procedure of the surface modification of lactose particles based on a smoothing process that involves the processing of powder in a high-shear mixer in the presence of wetting solvents. Briefly, successive steps of wetting and drying of the powder under fast particle rolling is the core of the process.

Using α-lactose monohydrate, several wet-smoothing procedures with or without ternary components, such as magnesium stearate having antistatic and lubricant properties,[21] were investigated. The smoothing level obtained was assessed and the powder properties affected by particle rugosity modification were identified. Collected samples of smoothed powders were tested for particle size distribution, flow and packing, and surface rugosity by scanning electron microscopy (SEM), atomic force microscopy (AFM), and surface area determination. Finally, residual water content was determined, since it is reported that humidity can affect particulate interactions in lactose-based dry powder inhaler formulations.[22] Lactose for inhalation 90 to 150 μm was used for the wet-smoothing study, since it is very common in the field.

MATERIALS AND METHODS

Materials

The following materials were used in the study:

Lactose for inhalation 90 to 150 μm; solubility at 50°C: 1 in 2.04 parts of water; practically insoluble in ethanol (Spherolac 100, Meggle, D, sieved by Chiesi Farmaceutici, Parma, Italy. Batch 9900170).

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Magnesium stearate, European Pharmacopoeia 4, particle size 5 μm (Chiesi Farmaceutici, Batch 95/0974/0).

Ethanol EP4.

High-shear mixer (Rotogranulator Roto Junior, Zanchetta, Lucca, Italy) having a cylindrical bowl with a capacity of 10 L in which there is a 3-arm impeller at the bottom and a chopper and a nebulizer at the top. The bowl can be heated and the internal pressure reduced.

Methods

Lactose Smoothing Procedure

The wet-smoothing process was performed in a Roto Junior high-shear mixer. After several assays for process variable optimization, ~750 g of lactose was introduced into the bowl heated at 50°C. The bowl was tightly closed and 400 mL of a purified water:ethanol mixture (5:3) was sprayed in successive steps by means of the internal nebulizer. Each step consisted of spraying 40 mL of hydroalcoholic solution for 30 seconds during kneading of the powder with the impeller rotating at 50 rpm. During the successive drying step, lasting 15 minutes under vacuum at 0.2 to 0.3 bar, the impeller rotation was increased to 450 rpm. This operation was repeated 10 times. For samples modified with ternary agent, the amount of magnesium stearate (0.25% wt/wt of the lactose) was dispersed in a smoothing solution made of water:ethanol (1:1). At the end of the 10 smoothing steps, the lactose powder was dried until constant weight in an air-circulating oven at 50°C. The lactose dried powders were equilibrated for 1 day at 20°C, 65% relative humidity, prior to testing. Six smoothed lactose batches were prepared.

Lactose Characterization

Scanning electron microscopy was performed on lactose samples sputtered with carbon (layer deposition of 200 to 400 Å) using a Jeol 6400 (Jeol, Tokyo, Japan). The SEM resolution was 10 nm. Analysis was conducted at 15 KeV and the magnification was between ×130 and ×250.

Particle size distributions of the lactose samples were measured by laser diffraction (Malvern Series 2600, Malvern Instruments, Malvern, UK). Each sample was dispersed in a cyclohexane solution containing lecithin 0.1% wt/wt.

Carr's Index (CI) of lactose samples was calculated from the apparent volumes (apparent V_0 and tapped volume V_{500}), using the method described in European Pharmacopoeia 4. Carr's index was determined using the following formula: $CI = 100\ (V_0 - V_{500})/V_0$. Flowability was determined with the apparatus Flodex Tester (Copley Instruments, Nottingham, UK) loading 100 g of powder and measuring the time to flow through an orifice of 4 mm. Three measurements were performed per sample.

Contact angle determination was performed on 200 mg of lactose cylindrical compacts compressed at 300 MPa in a hydraulic press (porosity <5%). Three samples were tested per determination. The deposition of a drop (14 μL) of distilled water at 20°C on the compact surface was recorded by a digital camera (Nikon Coolpix900, Tokyo, Japan) taking 40 images in 2 seconds. Analysis of the pictures taken during the drop deposition allowed the angle of contact between the drop and the solid to be calculated.

Residual water was determined according to the European Pharmacopoeia 4 "Water:semi-micro determination, Method A."

Rugosity factors were calculated using 3 different approaches:

1. A fractal descriptor of the texture of SEM images was calculated by means of gray level distribution analysis measured over the lactose particle images. In simple terms, the analysis was performed with the IMAGE 1.4 program (Wayne Rasband, National Institutes of Health, Bethesda, MD) using the algorithm called the "box counting" method.[23] Image analysis of the SEM pictures was conducted on a fixed area selected on the particle flat base in order to avoid tilting angle shadow effect. By scanning on the selected area of the image, an up and down, line showing the variability of gray level as a function of the position was obtained. The fractal dimension of this line, illustrating the gray color variability measured with the "box counting" method, was elected as a descriptor of the texture of the surface.[24]

2. Atomic force microscopy surface topography was performed in a Tapping Mode operation by means of a Digital Nanoscope III AFM (Digital Instruments, Buffalo, NY) on a particle surface of 10 × 10 μm and scanning frequency of 0.7 Hz. The Mean Roughness (Ra) was calculated from the measurements of the average height deviations of surface asperities,

3. Specific surface area was measured (3 replicates for each sample) by gas adsorption according to multiple point BET (Brunauer, Emmett and Teller) procedure[25] using 2 different experimental approaches. The first was the dynamic gas flow measurements: 4 g of each sample were degassed at 70°C for 2 hours under a pressure of 760 Torr in a Flowsorb II 2300 apparatus (Micromeritics Italy, Peschiera Borromeo, Milan, Italy), using a gas flow composed of a nitrogen/helium mixture 70:30 (vol/vol). Mixtures of nitrogen/helium 30:70, 20:80, and 10:90 were then used with partial nitrogen pressure of 0.2943, 0.1962,

Figure 1. SEM pictures of the lactose for inhalation 90 to 150 µm before and after the wet-smoothing procedure. A) original lactose; B) smoothed lactose; and C) lactose smoothed in the presence of magnesium stearate.

Table 1. Mean Geometric Diameter (d_g), Geometric Standard Deviation (σ_g), Carr's Index, Flowability, Contact Angle, and Water Content Values for Smoothed and Unsmoothed Lactose for Inhalation 90 to 150 µm (Mean Values and SD, n = 6)

	d_g µm	σ_g	Carr's Index %	Flow g/s	Contact Angle (Degrees)	Water (%)
Untreated	110.1 (1.5)	1.005	10.9 (0.5)	0.95 (0.003)	--	6.1 (0.3)
Smoothed	98.1 (2.1)	1.006	8.8 (0.3)	1.24 (0.001)	56.2 (0.3)	6.1 (0.2)
Mg stearate smoothed	94.5 (1.2)	1.006	8.4 (0.2)	1.37 (0.02)	68.0 (4.2)	6.2 (0.3)

and 0.0981; the changes in concentration of the adsorbate (N_2) in the gas mixture due to the adsorption were measured.

The second method was the volumetric gas adsorption measurements effected by means of a static gas adsorption apparatus: 10-g samples were degassed for 15 hours at 25°C under a pressure of $7.x10^{-4}$ Torr; afterwards, surface area was determined by means of a static gas adsorption apparatus (Sorptomatic 1990, Thermoquest, CE Instruments, Rodano, MI, Italy), in a pressure range between 7 and 292 Torr using nitrogen as adsorbate. The amount of gas adsorbed was determined on a volumetric basis by measuring the reduction in gas pressure due to adsorption.

The rugosity factor of the powder was calculated as the ratio between the mean specific surface areas determined experimentally by gas adsorption and the mean specific surface area calculated from the volume-surface mean diameter, obtained from the laser diffraction particle size distribution.

Differential scanning calorimetry (DSC) was performed using an Indium calibrated DSC 821e STARe (Mettler Toledo, Columbus, OH). Samples of 3 to 6 mg were placed in a 40-µL Al pan and heated to between 35°C and 260°C at a scanning rate of 10°C/min, under a purging nitrogen atmosphere (200 mL/min).

X-ray determination was performed with a Philips PW 1050 diffractometer using Cu-K_{alfa} radiation, 2θ range 5° to 35°, and scanning rate 0.5°/min.

Results

The lactose for inhalation 90- to 150-µm powder exhibited particles with rough surface. Representative SEMs of the 90- to 150-µm lactose prior to and postsmoothing are shown in Figure 1A and B, respectively. At the magnification used, the surface of the treated lactose particles appears to be significantly flattened. Lactose 90 to 150 µm has been smoothed also with a dispersion of magnesium stearate in water/ethanol solvent. In this case, the ethanol fraction in the mixture was increased to 1:1 in order to allow the wetting of magnesium stearate. The particles smoothed with the dispersion of magnesium stearate are reproduced in Figure 1C. The magnesium stearate–smoothed particle surface appears flatter.

The particle size distribution of the original and smoothed 90- to 150-µm lactose powders (Table 1) showed that there was a small reduction of mean particle size due to smoothing. The CI, the flowability, and the contact angle of the rough and smoothed powders are reported in Table 1, together with water content. Flow and packing properties for the lactose powders have been improved by smoothing.

The particle surfaces of lactose for inhalation 90 to 150 µm seen through AFM, before and after the smoothing, are illustrated in Figure 2.

The specific surface area of lactose for inhalation 90 to 150 µm has been determined by gas adsorption using both the dynamic flow and the static volumetric methods. Rugosity

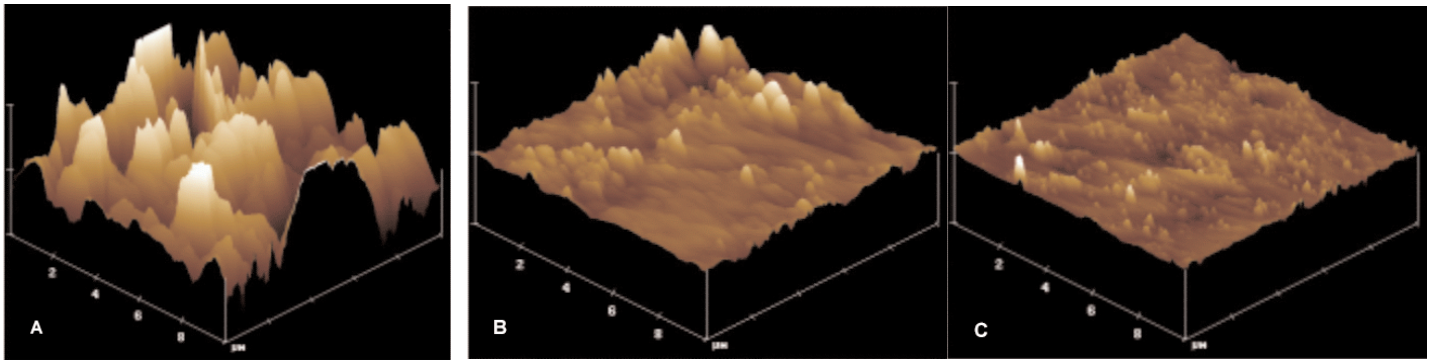

Figure 2. AFM mapping of surface of the lactose for inhalation 90 to 150 μm before and after the wet-smoothing procedure. A) original lactose; B) smoothed lactose; and C) lactose smoothed in the presence of magnesium stearate.

Table 2. Rugosity Factor Values for Original and Smoothed Lactose 90 to 150 μm, Determined Through Surface Area Measurements, Using 2 Gas Adsorption Methods

	Dynamic Flow	Static Volumetric
Untreated lactose	6.99	14.17
Smoothed lactose	3.64	7.24
Smoothed lactose with Mg stearate	4.33	7.04

Table 3. Fractal Descriptor of the Texture of the Image of Lactose 90 to 150 μm Particle Surface, Collected at Different Steps of the Smoothing Process (Mean Values and SD, n = 6)

	Fractal Descriptor
Untreated lactose	1.23 (0.05)
After step 1	1.08 (0.02)
After step 7	1.06 (0.02)
After step 10	1.00 (0.01)

factors, calculated as the ratio between the experimentally measured value of surface area and the value estimated by calculation from the volume-surface mean diameter (laser diffraction particle size distribution), are reported in Table 2. Fractal descriptor of the texture of the image of the lactose 90 to 150 μm particle surface, collected at different steps of the smoothing process, is reported in Table 3.

X-ray and DSC analysis were performed on the smoothed lactose in order to assess possible relevant modifications of crystallinity. No significant differences were found comparing the sample DSC traces and x-ray spectra before and after the smoothing.

DISCUSSION

The wet-smoothing process consisted of successive steps of superficial wetting and drying of lactose particles during their rolling on the wall of the cylindrical bowl of the mixer. The high-shear lab scale mixer is normally used for 1-step powder granulation; in this new application it was used for sliding powder particles over each other and against the bowl wall in the presence of a solvent, while avoiding the development of excessive binding effects. The wetting of lactose powder induced a superficial dissolution of particles, particularly effective on the more sharp asperities, like protuberances or edges. The lactose dissolution was controlled by the composition of the solvent that was a mixture of water and ethanol. The dissolution action was performed during a slow kneading of the powder. Then, during a fast rolling on the wall of the bowl, the drying phase took place, determining the deposition of dissolved lactose in the fractures or "valleys" of the particles. The Otswald ripening phenomenon[26] could be evoked in this situation, ie, the higher solubility at a smaller radius of curvature determined the dissolution of small particles and asperities and deposition on relatively flat surfaces. However, the surface frictions due to powder rolling provoked the nonuniform deposition of dissolved substance on the particles. In any case, the result was the elimination of the asperities and the sealing of the fractures, giving rise to smoothed particles. In the case of the 90- to 150-μm lactose for inhalation, 10 steps of wetting/rolling/drying actions were performed assessing by SEM the smoothing of particles. The reproducibility of the wet-smoothed product obtained after a process in 10 steps was quantified by the variability of fundamental and derived properties of powders and rugosity factors.

SEM pictures of lactose for inhalation 90 to 150 μm showed the typical particle morphology characterized by the tomahawk shape with evident surface roughness (Figure 1A). The wet-smoothing process substantially modified the surface of these lactose particles without affecting the tomahawk shape (Figure 1B). The particles were efficiently smoothed showing rounded edges and plain surface in comparison with the untreated lactose. In addition, water content remained almost unchanged after the smoothing process (see Table 1).

The smoothing did not substantially reduce the particle size of the lactose for inhalation and, more importantly, did not agglomerate the particles in granules, as the microscopic examination and dimensional analysis showed. The dissolution effect of the hydro-alcoholic solvent used for the wet-

kneading slightly decreased the size of large particles. For example, a shifting of the geometric mean diameter values from 110 μm to 94 μm was obtained, likely attributable to the elimination of the particle roughness. Comparing the pictures before and after the smoothing procedure, the disappearance of fines present in the original lactose was noticed, likely due to the complete dissolution of the small size lactose particles. However, the size distribution remained practically unaffected.

It was expected that the elimination of the particle surface asperities provided an improvement of the powder-packing and flow properties, due to the reduction of the friction between particles and to more dense packing of the powder bed. The CI values revealed that the smoothing process led to a significant improvement in the packing of the lactose powder. Also, the flowability was significantly improved by the treatment. When the smoothing process was performed in the presence of magnesium stearate, a further improvement of packing and flow properties was measured. Often in inhalation particle technology, adjuvants such as magnesium stearate were used for modifying the surface conditions of the carrier particles. Some concerns have arisen about the possibility of inhaling these adjuvants. No magnesium stearate particles were observed on the lactose particle smoothed surface, but the use of magnesium stearate affected the particle surface hydrophilicity. In fact, the values of contact angle reported in Table 1 showed that magnesium stearate–smoothed lactose possessed a more hydrophobic surface compared with the lactose smoothed without adjuvants. Therefore, it was deduced that magnesium stearate remained embedded on the lactose surface, so reducing the risk of inhalation. The interaction with drug particles of this surface-smoothened lactose has been described in a previous paper.[20]

The quantification of the smoothing level of the lactose particle surface (rugosity) was done with different techniques in order to have appropriate levels of analysis; in particular, SEM, AFM, and surface area measurements were performed. From the SEM pictures, a micro-size scale rugosity could be quantified as a variation of gray level of particle image, a quick and useful technique for comparative evaluation of the modifications induced by the successive steps of the smoothing. Samples representative of successive smoothing steps were withdrawn during the process and SEM pictures were taken at the same magnification. The evolution of smoothing was assessed through a fractal descriptor calculation. The results reported in Table 3 indicated that a large reduction of roughness was performed already during the first step; then, the smoothing proceeded slowly ending in a highly smooth surface for the SEM level of magnification after the tenth step (fractal descriptor = 1).

The AFM technique of mapping the surface of lactose particles allowed for the estimation of the roughness of the lactose surface at the nano-size level. Three-dimensional images of the treated lactose surface could be obtained, together with a quantitative evaluation of the surface conditions through the Ra parameter, directly measured from the AFM procedure. Pictures obtained (Figure 2) show an impressive reduction of the surface roughness of lactose powder due to the smoothing process. The calculated Ra confirms this observation: fewer and lower peaks, compared with the untreated lactose (Ra = 110 nm), are exhibited by smoothed lactose (Ra = 25 nm). The effect of the smoothing was improved by the addition of magnesium stearate to solvent used during smoothing. The measured roughness value in this case indicated a significant decrease in the surface roughness of lactose particles, confirming the benefit of magnesium stearate addition (Ra = 10 nm).

An additional roughness factor based on the specific surface area of the powder was calculated for quantifying the effect of the smoothing process. The factor is the ratio between the experimentally measured specific surface area and the geometric surface area calculated from particle size distribution. This roughness factor has been previously proposed using air permeability for surface area determination. Since the air permeability method[27] could be not sufficiently accurate for the surface area measurement of a powder bed having large particles, gas adsorption methods were employed. In particular, we used 2 BET methods having different sensitivity. The results (Table 2) show that the multiple-point BET gives rise to rugosity values coherent with the differences seen with the other techniques. In particular, the difference among the smoothing levels is more evident using the more sensitive static volumetric method.

Finally, analysis done by DSC and x-ray diffraction demonstrated that the smoothing process did not modify the crystal structure of lactose. In fact, the comparison between the x-ray spectra before and after the smoothing revealed that the position and intensity of the peaks were not significantly changed. In addition, the DSC traces of lactose are characterized by the presence of 2 endothermic peaks, the first at 150°C corresponding to the water elimination, and the second around 210°C corresponding to the fusion of lactose. The smoothed and unsmoothed lactose samples showed negligible differences in terms of molar heat of fusion and peak temperature. We considered that no modification of crystallinity took place after the smoothing process. However, storage at 20°C, 65% RH, would quickly make the smoothed material completely crystalline, even in the case of small crystallinity modifications not detected by DSC.

CONCLUSION

This new process of powder wet-smoothing, performed by means of an automated high-shear mixer designed for granulation, allows for the preparation of lactose particles with a significantly smoothed surface. Samples of the same product

with differing roughness levels could be prepared. The particles showed an evident smoothed surface with improvement of flow and packing. The smoothing was easy to reproduce. Furthermore, the scale of production is accessible for large amounts of lactose due to the availability of high-capacity mixers.

Smoothed lactose powders can have various applications in pharmacy, the most prominent of them is in inhalation for the preparation of a drug/carrier ordered mixture in dry powder inhalers. However, powder, tablet, or capsule technologies could benefit from the substantial flow and packing improvement of the smoothed powder. Other excipients, for which the process of smoothing by dissolution/deposition could be applied, are candidates for the process.

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