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Effect of process variables on the Small and Wide Angle X-ray Scattering (SWAXS) patterns of powders, granules and pharmaceutical tablets

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ABSTRACT

This paper reports that the small-angle X-ray scattering (SAXS) pattern of pharmaceutical granules and tablets is affected by the number of granulation steps and the compaction force and that SAXS-based parameters for powder, granules and tablets correlate with tablet hardness. The fact that changes in the value of SAXS parameters for powder and granules are reflected on the value of the same parameters for tablets suggests that these SAXS parameters could be used as a predictor of powder and granule tabletability. A powder blend was used to make tablets at three compaction forces. Subsequently, tablets were milled and the granules were used to make new tablets under the same compaction forces. The milling of the tablets and the tableting of the granulation was repeated one more time. The powder, granules and tablets were all analyzed with SAXS. The X-ray scattering curves for the powders and granules show the effect of the number of granulation steps. The X-ray scattering curves for tablets show the effect of the different compaction forces. Wide-angle X-ray scattering (WAXS) spectra of powders, granules and tablets show that process variables do not affect the crystalline state of components in these samples.

1. Introduction

Granulation and compaction (tableting) are common process steps in the manufacturing of pharmaceutical tablets, which are still by far the largest fraction of drug products [1]. Typically, granulated particles, called granules, are used for tableting because they posses good flow properties and ensure tablet content uniformity. Granule properties depend on the granulation process used (i.e., wet or dry granulation by high-shear wet granulation or dry roller compaction, respectively) and they have a strong effect on tablet structure (and the associated quality attributes). Moreover, the compaction process itself is affected by granule geometric factors (e.g., particle shape and size distribution, surface roughness), mechanical properties (e.g., elastic modulus and strain behavior, elastic or plastic deformation, brittle fracture) and particle–particle and particle–wall friction. In fact, particle reorientation, deformation and fracture during compaction depend on all these granule (or particle) properties [2–11]. During compaction, particle reorientation occurs first, followed by elastic and plastic deformation, and possibly fracture, at higher compaction loadings [11–15]. Numerous techniques such as Raman spectroscopy [16,17], scanning electron microscopy (SEM) [18], thermal analysis [19], X-ray powder diffraction (XRPD) [20] are available to characterize granule properties that are critical to pharmaceutical manufacturing.

In this paper we report the novel use of small angle X-ray scattering (SAXS) to characterize powders, granules and their compacts [21]. Although SAXS has already been used to characterize dry powders and their compacts [21–25], in the current work we extend the use of SAXS parameters traditionally used to characterize polymers, liquid crystals, solids [26] to tablet hardness prediction by the analyses of the powders and granulates used to manufacture them [27]. The SAXS parameters are M0, Q, k and k/Q and they are evaluated using X-ray scattering curves and the well established Porod law [28], as it is described at length in Materials and methods. The parameter M0 represents the intensity of scattering and it is defined as the integral of the zero-th moment of the SAXS scattered curve from angle 0 to infinity. The parameter Q is the second moment of the SAXS scattering curve from angle 0 to infinity. Finally, there is the parameter k, also called the tail-end constant, which is proportional to the interfacial area between two phases (i.e., air/solid or solid A/solid B) and it is used to calculate the parameter k/Q. We show that the values of these SAXS parameters correlate with tablet hardness and that the values of these SAXS parameters for powder and granules correlate with those of tablets. The latter finding suggests that the SAXS characterization of powder and granules could be used as a predictor of their tabletability.

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Tablets are first manufactured with a lubricated powder blend of common pharmaceutical excipients using three different compaction pressures. Subsequently, each batch of tablets is milled (as in a dry granulation process), and the coarse granules used to make tablets under the same compaction pressure. The procedure is repeated once more: tablets from the different batches are milled and the granules used to make tablets.

Small-angle X-ray scattering (SAXS) is considered to take place approximately in the range 0.06°–8° 2θ and to be caused by electron density differences at the scale of about 1 to 100 nm [29–34]. The structural origins of X-ray scattering for compacted powders is still not clear. However, electron density differences associated with the molecular architecture of mixtures and with intra-granular pores are likely to be the source of X-ray scattering [21]. Electron density differences are found, for example, at the interface between solid-air. Pharmaceutical granules have several components and show chemical and density differences that are also associated to electron density differences. Due to the ability of X-ray to penetrate matter, internal surfaces (and interfaces) that are otherwise not reached by other analytical methods contribute to the X-ray scattering. The main finding is that the scattering of the X-ray signal is affected by the compaction force used to manufacture tablets (and hence their hardness) and by the number of dry granulation steps for the granules. Then, when these powder and granules are used to make tablets, the X-ray scattering of tablets is a function of the material used (powder or granules) as well as the tableting compaction force. These X-ray scattering curves are used to assess the SAXS parameters mentioned before (M0, Q, k and k/Q).

The wide-angle X-ray scattering (WAXS) spectra of powders, granules and tablets, which provides information about the polymorphic state of the components through the identification of Bragg peaks [34], was simultaneously collected. The crystalline structure of pharmaceutical components is important as it affects product stability, solubility, and ultimately bioavailability [35].

2. Materials and methods

2.1. Materials and tablet preparation

A 100-kg blend with 49% (mass basis) lactose monohydrate (Tablettose 80; Meggle, GmbH, Germany), 49% microcrystalline cellulose (Comprecel M102D; Mingtai Chemical Co. Ltd., Taiwan), 1% silicone dioxide (Aerosil 200 Pharma; Evonik Degussa GmbH, Germany) and 1% magnesium stearate (Eur. Phar. Pflanzlich; FACI SpA, Italy) was prepared in a 200-lt stainless-steel Müller container using a Rhönrad blender. The blending time was 30 min. Silicone dioxide and magnesium stearate were previously and independently delumped using a Frewitt TC 200 mill (1.5 mm sieve, and a rotor speed of 32 Hz). Two-kilogram portions of this blend were tableted in a single-punch tablet press (EK 0-DMS, Korsch AG, Germany) at three different nominal compaction forces (5 kN, 10 kN, and 20 kN) and a compaction speed of 30 strokes/min. The tablets are made using oval (12 mm × 5 mm) flat-faced punches (area $= a \cdot b \cdot \pi = 188.5$ mm^2). Subsequently, each batch of tablets was milled in a mill (Frewitt TC 200, Switzerland) with a rotor speed of 16 Hz and a sieve of 0.8 mm and the granules were tableted again using the same compaction pressure. These new tablet batches were milled and the tableting of granules was performed once more. The tablets were planar to avoid undesired X-ray scattering effects and their thickness was less than 2 mm to avoid the full absorption of X-rays.

2.2. Tablet hardness, weight, thickness and density

Fig. 4 shows the crushing strength of groups of ten tablets made with powder or granules using different compaction pressures. The standard deviation of these ten measurements is presented by the error bars of each condition. Crushing strength was measured immediately after compression using a Schleuniger strength tester (Dr. Schleuniger Pharmatron AG, Solothurn, Switzerland). In addition, the weight, the thickness and the density of these same tablets was measured (Table 1).

2.3. Small- and Wide-Angle X-ray Scattering Instrument

The first commercially available SWAXS camera was developed many years ago [36], however, the camera used in our experiments (Hecus S3-Micropix, Austria) uses shorter acquisition times and has a higher resolution provided by point-focus optics (FOX3D) and a high-brilliance micro-beam delivery system that is operated at 50 kV and 1 mA. The powder sample (85 mg) was placed in a glass capillary (2 mm internal diameter), which was sealed with wax and rotated while exposed to the X-ray beam to allow for angular averaging of the powder scattering patterns. The tablets were simply positioned in a sample holder and the beam was directed at the center of the oval tablets. The samples were exposed to X-ray beam with a diameter of 200 μm and a wavelength λ of 1.54 A. Triplicate measurements were performed at room temperature with the exposure time of 700 s. The data were normalized by the sample with the highest value.

2.3.1. SAXS parameters

Four parameters are derived from the entire X-ray scattering curves. These curves present the intensity of scattered X-ray, which is measured by the sensors located behind the sample, versus the scattering angle. The angle 0° in this curve corresponds to the line of the X-ray beam. The detector is never positioned at 0° because it would measure X-ray transmission, that is to say, the portion of the X-ray beam that simply goes through the sample without suffering scattering. The scattering at an angle of infinity is obviously not measured. The SAXS curves are in fact recorded with a 1D-detector (PSD-50, Hecus X-ray Systems, Graz, Austria) in the angular range of $0.06° < 2\theta < 8°$. However, the scattering intensity at angles of 0° and infinity are necessary to estimate the values of the following

Table 1
Average weight, average thickness and average density of groups of ten tablets made with powder and granules. The standard deviation of the tablet density and the average compaction pressures of the upper and lower punches are also reported.

Material	Compaction force. upper punch (kN)	Compaction force. lower punch (kN)	Average tablet weight (mg)	Average tablet thickness (mm)	Average tablet density (mg/mm^3)
Powder	5.10	4.50	85.90	1.78	0.2558 ± 0.00
Powder	9.90	8.80	85.91	1.62	0.2809 ± 0.00
Powder	19.30	17.70	85.56	1.57	0.2894 ± 0.00
Granules S1	5.20	4.70	93.28	1.88	0.2640 ± 0.00
Granules S1	11.20	10.10	92.99	1.74	0.2836 ± 0.00
Granules S1	19.70	18.00	91.13	1.66	0.2905 ± 0.01
Granules S2	5.10	4.60	95.16	1.90	0.2646 ± 0.00
Granules S2	9.90	8.90	94.98	1.80	0.2787 ± 0.00
Granules S2	19.80	18.10	90.98	1.67	0.2886 ± 0.00