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Quantitative surface topography assessment of directly compressed and roller compacted tablet cores using photometric stereo image analysis

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ABSTRACT

Surface topography, in the context of surface smoothness/roughness, was investigated by the use of an image analysis technique, MultiRay™, related to photometric stereo, on different tablet batches manufactured either by direct compression or roller compaction. In the present study, oblique illumination of the tablet (darkfield) was considered and the area of cracks and pores in the surface was used as a measure of tablet surface topography; the higher a value, the rougher the surface. The investigations demonstrated a high precision of the proposed technique, which was able to rapidly (within milliseconds) and quantitatively measure the obtained surface topography of the produced tablets. Compaction history, in the form of applied roll force and tablet punch pressure, was also reflected in the measured smoothness of the tablet surfaces. Generally it was found that a higher degree of plastic deformation of the microcrystalline cellulose resulted in a smoother tablet surface. This altogether demonstrated that the technique provides the pharmaceutical developer with a reliable, quantitative response parameter for visual appearance of solid dosage forms, which may be used for process and ultimately product optimization.

1. Introduction

Since a tablet is made from particulate materials the properties of starting materials may influence the compaction behavior and attributes of the final compact itself such as hardness, disintegration and dissolution. Optimizing these properties is a natural part of any pharmaceutical tablet formulation development. Appearance of a tablet product may also be important to the consumer's perception of the product quality, and as such it is an important cosmetic parameter to consider during drug product development. Furthermore, as companies often aim to launch new products globally, the developers should recognize that there may be regional differences between regulatory authorities and their criticality assessment of a product's visual appearance. Many elements are important to the appearance of tablet dosage forms, including size, shape and color, but also elements as gloss and surface topography (also termed roughness in some literature) could be important parameters to consider. Further, the surface roughness of uncoated tablets may have an influence on important pharmaceutical properties as dissolution (Healy et al., 1995), friability, disintegration (Riippi et al., 1998), and adhesion of film coatings (Rowe, 1978; Ohmori et al., 2004; Felton and McGinity, 1999; Missaghi and Fassihi, 2004).

Surface roughness of pharmaceutical products have been determined by both qualitative and quantitative methods as scanning microscopy (SEM), atomic force microscopy (AFM), non-contact optical profilometry (NOP) (Narayan and Hancock, 2003) and recently by terahertz (Bawuah et al., 2014). SEM provides information about the variation on the surface within a 2-D image. It is a widely used technique (e.g. Riippi et al., 1998; Seitavuopio et al., 2003, 2005; Narayan and Hancock, 2003), however, time-consuming sample preparation and long analysis time makes it less suitable for quality control. AFM allows data acquisition at a very high resolution, however, direct contact with the surface is required and only a small area can be scanned (Poon and Bhushan, 1995; Seitavuopio et al., 2003; Masterson and Cao, 2008). NOP operates via principles of interference from reflected light allowing 3-D resolution. Sample preparation is minimal and the method has been used in several different setups (Narayan and Hancock, 2003, 2005; Halenius et al., 2014; Seitavuopio et al., 2006; Podczek, 1998; Inman et al., 2007; Bashaiwoldu et al., 2004a,b). A variation of the photometric stereo technique (Woodham, 1980) is used in the equipment MultiRay.[2] In the simplest form it

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[2] MultiRay™ is a trademark of Videometer A/S, www.videometer.com

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combines reflected light from two illumination sources in the visible range, that is, a blue LED illumination at 465 nm for coaxial brightfield illumination and a red LED illumination at 650 nm for oblique darkfield illumination. The brightfield illumination has an incidence angle of approximately 0°, and the darkfield illumination has an incidence angle of close to 90°. Both are independent of the rotation of the sample as the oblique darkfield light spans 360° around the sample. The image is acquired by a normal RGB color camera providing the brightfield image in the blue channel and the darkfield image in the red channel. The green channel could be used for an additional illumination e.g. another incidence angle or a backlight, but this is not done here. The measurement principle is illustrated in Fig. 1. The more perpendicular the surface is to the brightfield light and the more gloss the surface has, the higher the response in the brightfield band. In contrast to this the darkfield band will have higher values the more topographic structure the surface has. Hence, the darkfield is responding to surface topography. Combined, brightfield and darkfield provide a two-dimensional response over the surface and through ratios or linear combinations of the two components we can make a map of the finish properties of the tablet. An example of darkfield and brightfield images is shown in Fig. 2. The area covered by the dark spots appearing in darkfield can be quantified by classical morphological image analysis (Vincent, 1993). The method provides a mathematical quantification of the surface topography and can therefore be used as a rapid, quality measurement, alongside traditional tablet technical measurements such as hardness and friability. The method, however, has to our knowledge never been applied to pharmaceutical products.

A recent proposal on a Manufacturability Classification System (Leane et al., 2014), has suggested three preferred production methods for tablets, being direct compression (DC), dry granulation (roller compaction; RC) and wet granulation (WG). From the number of process step and the associated complexity increased from DC to RC and WG, this ranking seems well agreed between industry experts. DC requires a stringent control of both API and excipient particle size to minimize the risk of segregation and deblending. As it is not always possible to implement a strict control strategy on API particle size, dry granulation, also referred to as roller compaction has gained significant industrial interest despite the introduction of an extra compaction step in addition to tablet compression. The process stages of a roller compactor may roughly be split into: (1) powder feeding to the compaction zone (2) powder densification into ribbons (or flakes) and (3) milling/downsizing of ribbons into the final granule product (Kleinebudde, 2004), which can finally be compressed into a tablet. It is common practice to consider ribbon porosity and the link to tablet hardness as a critical attribute describing the extent of work hardening of the initial powder blend as a consequence of the two compaction steps. This is in particular relevant to plastic deforming materials, such as microcrystalline cellulose, for which the formation of inter-particle bonds is irreversible, i.e. the bonds participating in plastic deformation of the ribbon cannot contribute to the tablet compact. Besides tablet hardness, one would expect the negative effect of compaction history on particle interlocking to also manifest as a less smooth tablet surface.

There is a general agreement in the scientific literature that a higher compression force usually produces smoother tablets (Riippi et al., 1998; Seitavuopio et al., 2003; Sindel and Zimmermann, 2001; Muster and Prestige, 2002), i.e. leading to a product that appears more complete and with a higher perceived quality. Bashaiwoldu et al. (2004b) investigated the surface roughness of compacts made at a defined pressure from pellets containing microcrystalline cellulose dried by different methods. Porous freeze-dried pellets produced the smoothest tablet surface, however, no previous studies have to our knowledge looked into this important quality element of roller compaction and what influence the process history may have on the appearance of the final product. The purpose of the present study was therefore to evaluate the use of a new surface topography measurement method applied to an MCC-based placebo tablet formulation with different process history, either directly compressed or roller compacted at two different roll forces.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH102) and croscarmellose sodium (Ac-Di-Sol) were sourced from FMC Health and Nutrition (Philadelphia, PA, USA) and used as diluent and disintegrant, respectively. Magnesium stearate (Peter Greven GmbH & Co.KG, Bad Münstereifel, Germany) was added as lubricant and colloidal silica, Aeroperl 300 (Evonik Industries AG, Essen, Germany) as glidant to improve flow of the powder blend.

2.2. Experimental design

Placebo formulations were prepared consisting of microcrystalline cellulose (diluent), 3.0% croscarmellose sodium, 1.50% magnesium stearate and 0.25% colloidal silica. To investigate the impact of compaction history on the surface topography of the tablet product, the primary placebo blend was divided into sub-batches and treated at various combinations of roller pressure in a roller compactor and compression pressure on the tablet press in comparison with a DC based batch. The experimental scheme is outlined in Fig. 3.

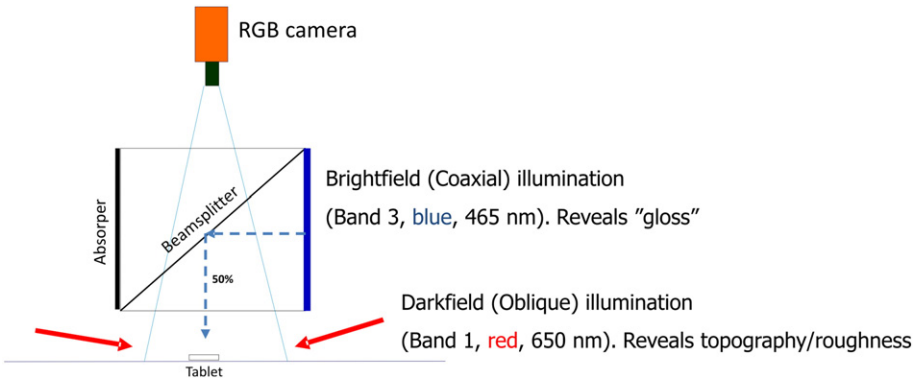

Fig. 1. Illustration of the MultiRay™ measurement principle. The MultiRay™ image is a combination of reflected light from two illumination sources in the visible range, namely blue (band 3 also termed brightfield and red (band 1) termed darkfield. Green (band 2) is not used.