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Texture analysis as a tool to study the kinetics of wet agglomeration processes

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ABSTRACT

In this work wet granulation experiments were carried out in a planetary mixer with the aim to develop a novel analytical tool based on surface texture analysis. The evolution of a simple formulation (300 g of microcrystalline cellulose with a solid binders pre-dispersed in water) was monitored from the very beginning up to the end point and information on the kinetics of granulation as well as on the effect of liquid binder amount were collected. Agreement between texture analysis and granules particle size distribution obtained by sieving analysis was always found. The method proved to be robust enough to easily monitor the process and its use for more refined analyses on the different rate processes occurring during granulation is also suggested.

1. Introduction

Wet granulation is a common pharmaceutical operation aiming at eliminating unfavorable properties of fine powders, improving flow properties, compaction characteristics and composition homogeneity of the granulated products. It is usually performed in four phases: (1) homogenization of dry powders; (2) liquid addition; (3) wet massing with liquid feeding system switched off; (4) granules drying. All these phases (excepted drying) are often carried out in mechanically agitated vessels which can promote efficient mixing also of cohesive materials. Such mixers exert an intense local shear on the powder which breaks down the small cohesive aggregates (Harnby, 1997), promotes a good liquid dispersion and a proper product consolidation (Cavinato et al., 2010). They are generally constituted by a vessel and an impeller rotating about an horizontal or a vertical axis. When rotating about a vertical axis, the impeller can also revolve following circular trajectories so that these mixer-granulators are called planetary or orbital mixers (Laurent, 2005; Hiseman et al., 2002). In some cases the rotating axis does not revolve but it is the vessel that rotates (Boerefijn et al., 2009). Despite the large use of this type of granulators in many industrial processes, the agglomeration mechanisms caused by liquid binder addition are currently not totally understood (Laurent, 2005; Knight et al., 2001). Granulation can be indeed affected by a large number of variables, including process parameters, material properties and formulation variables (Faure et al., 2001). Monitoring the behavior of a wet bed of powders and following its evolution during time is of paramount importance to design, analyze and control the pharmaceutical manufacturing process in a process analytical technology (PAT) perspective. Different techniques have been used in the past to monitor and carry out a description of the powder agglomeration process within the mixer-granulator. A comprehensive review of such techniques can be found in Watano (2001). Most of the measurement methods can give an indirect information on the status of the granulation process since they do not observe the particles directly but they measure physical variables supposed to be related to particle size. Acoustic emission, for example, has shown possibilities for granulation end-point detection (Briens et al., 2007). Also amperage or motor power consumption and impeller torque are frequently monitored as indirect measures of the agglomeration process. Particularly, power consumption and impeller torque have been used to identify how the system evolve during the agglomeration as a function of mixer geometric configuration (impeller and bowl shape) and impeller speed (Paul et al., 2003). Leuenberger et al. (2009) have investigated the relationship between granule growth and power

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consumption curves and have demonstrated the possibility of end-point determination by power consumption monitoring. Bier et al. (1979) also reported that records of power consumption and torque were in good agreement. In alternative to the end point determination Leuenberger et al. (2009), torque has been used also to predict the starting point of granulation (Cavinato et al., 2010, 2011, 2013) as a function of liquid binder amount. All this methods however, even if effective in collecting information about the process, are indirect; other techniques can give a more direct information on the status of the granules in the mixer-granulator. Techniques such as the focused beam reflectance measurement (FBRM), which allows to follow the granule chord length evolution in real time (Huang et al., 2010), are starting to be used in wet granulation studies. Also the simultaneous combination of different techniques such as FBRM, acoustic emission measurement and near infrared spectroscopy have been used to asses granulation rates in fluidized beds (Tok et al., 2008). A direct measurement and control of granule growth can be also achieved through the use of sensors capturing digital images of the powder bed and analyzing them with image analysis techniques. Image processing systems have been used for direct and continuous monitoring of the granule growth in fluidized bed granulation (Watano, 2001) and in high shear granulators (Watano et al., 2001). Since all the above techniques try to identify each particle individually, issues related to particles overlapping and contacts, and to the minimum number of particles to be analyzed exist. For process control purposes it would be advisable to develop PAT analyzers able to process thousand of particles simultaneously and extract averaged information on the status of the granular mixture during time, possibly providing real-time process information. Texture analysis (TA) of digital images of the powder bed surface (also known as surface imaging (Lakio et al., 2012)) can be potentially used in this sense. TA is already used in a variety of applications spanning from remote sensing to automated inspection and medical image processing (Russ, 1999; Gonzales et al., 2004). The basic idea behind the use of TA is that smooth surfaces will have small variation in gray scale values and the rougher the surface the larger are the variations. In the pharmaceutical context it has been used to determine the particle size distribution (PSD) (Laitinen et al., 2002) and the segregation tendency of granulated products (Lakio et al., 2012) in static conditions. In this work the wet granulation process was studied with TA by taking time series of digital images of the moving powder bed inside the granulator during the whole granulation process. The subsequent analysis was therefore carried out on the bulk powder (not on single granules) and its evolution from being a dry mixture up to a wet mass of distinct aggregates was monitored and studied. The aim of the work was to assess if TA can be

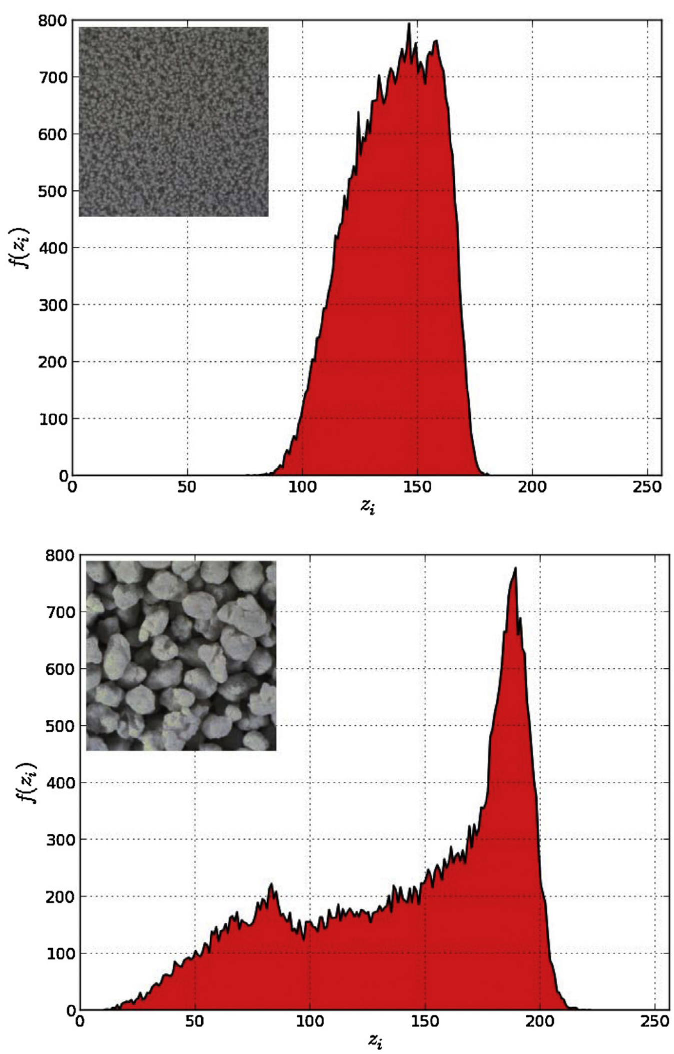

Fig. 1. Example of histograms of intensity levels for two different particle sizes.