PHARMACEUTICAL TECHNOLOGY

Real-Time Assessment of Granule and Tablet Properties Using In-line Data From a High-shear Granulation Process

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ABSTRACT: A method for real-time assessment of granule and tablet properties was investigated. A mixture of microcrystalline cellulose:mannitol:povidone (78.5:18.5:3) was used in the study and granulated with five different water amounts and two impeller speeds. This represents a full-factorial design with two factors, thus giving a causal structure to the variation between the experiments. Process data (power consumption, temperature and in-line near-infrared spectra) were collected during the granulations. In addition to the in-line process data, critical granule and tablet quality properties (such as particle size, porosity and tablet hardness) were measured in order to achieve in-depth process understanding. Neither power consumption nor temperature gave information that could be directly attributable to tablet properties, and these techniques were also heavily dependent on the speed of the impeller. In contrast, when using the first NIR overtone band for water (1460 nm), in-line real-time assessment of dry granule and tablet properties could be achieved. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:950–959, 2008
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INTRODUCTION

Wet granulation in high-shear mixers is an important process step often used in the development and manufacturing of pharmaceutical oral solid dosage forms. It is a complex process that consists of a dry high-shear mixing step and a wet high-shear mixing step with agglomeration. In recent years, the pharmaceutical industry has increased its efforts in the area of real-time process understanding and characterization. This effort has been supported by FDA's PAT initiative. There is however no easy way to control and adjust the granulation process in high-shear mixers. The best possible industrial tools today are based on using the granulator power consumption as an indicator of the status of the process. Another technique that has been presented recently to control the high-shear granulation process is *in situ* image processing.[1]

Leuenberger et al.[2] divided a typical power consumption profile into five different phases using the tangent technique. Phase I reflects the uptake by the components of the added amount of

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granulating liquid until moisture saturation. In Phase II, liquid bridges are formed between primary particles. Stronger resistance between particles causes an increase in power consumption. In Phase III, liquid fills up the interparticulate void space. This phase is also called the plateau state. According to Leuenberger et al.[3] and Imanidis,[4] the best granules for tableting can be produced in the plateau state. Phase IV is the state where uncontrollable ball growth occurs.

The relationship between power consumption, process variables and resulting properties of granules has been extensively studied by the granulation group in Copenhagen.[5–9] However, the theory behind which physical and chemical phenomena are reflected by power consumption is far from complete. Leuenberger et al.[2] and Holm et al.[7,10] demonstrated a correlation between power consumption and granule growth. In addition, power consumption has been related to the cohesive forces arising from capillary pressure,[2] to the liquid saturation,[6] to intragranular porosity,[8] to the strength of the agglomerates,[2,6,8,11] to interparticle friction forces[12] and to the stickiness of the surface of the granules.[13]

Bardin et al.[14] made a critical review of the use of mixer torque and mixer work for process control and suggested a method where the work done by the mixer, i.e. the integrated power over time, is used as an indicator of when to stop the process. Holm et al.[6] showed that the consumed energy is primarily converted into heat during granulation and that there is a relationship between heat generation and granule growth. Furthermore, Betz et al.[15] used a ratio of temperature to power consumption as a signature of formulation design, where the ratio is said to be dependent on particle size, particle surface, water absorption capacity and solubility. However, keep in mind that none of these methods give direct information about the state of the wet mass or granules.

Near-infrared (NIR) spectroscopy has been used in characterization of wet granules by the group of Rantanen.[16–19] Luukkonen et al.[20] were able to show good correlation between (baseline corrected) at-line NIR water bands measured on wet granules and tablet hardness. In the paper of Niklasson Björn et al.,[21] at-line NIR, bulk density and particle size distribution were measured during the granulation where the amount of microcrystalline cellulose (MCC) and impeller speed were varied. The moisture content, mean particle size and bulk density showed good correlation to NIR spectra. Rantanen et al.[22] were among the first to report on the use of in-line NIR spectroscopy as a process analytical tool for high-shear granulation. They used NIR spectroscopy together with multivariate data analysis to determine the particle size based endpoint for the wet massing phase.

During product development work of immediate release tablet formulations, the compaction properties are considered to be among the most important properties of the dry granules. There are several time-consuming steps, like drying, milling and final mixing between the granulation process and tableting (Fig. 1). Thus, there is a desire and an obvious benefit to be able to assess tablet properties from the properties of the granules or directly from the granulation process performance. When the relevant process data are

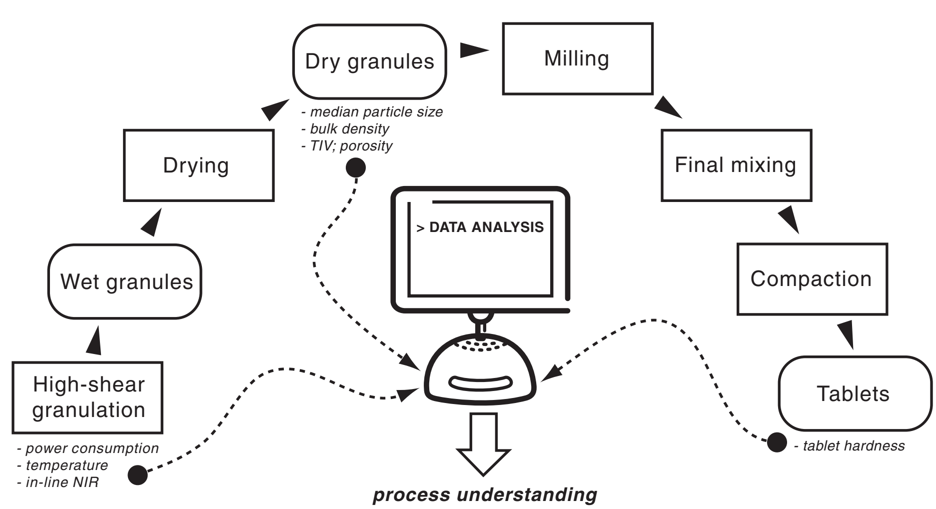

Figure 1. An overview of the data flow for developing a model used for prediction of tablet hardness.