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Detection of component segregation in granules manufactured by high shear granulation with over-granulation conditions using near-infrared chemical imaging

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ABSTRACT

The objective of this study was to evaluate the high shear granulation process using near-infrared (NIR) chemical imaging technique and to make the findings available for pharmaceutical development. We prepared granules and tablets made under appropriate- and over-granulation conditions with high shear granulation and observed these granules and tablets using NIR chemical imaging system. We found an interesting phenomenon: lactose agglomeration and segregation of ingredients occurred in experimental tablets when over-granulation conditions, including greater impeller rotation speeds and longer granulation times, were employed. Granules prepared using over-granulation conditions were larger and had progressed to the consolidation stage; segregation between ethenzamide and lactose occurred within larger granules. The segregation observed here is not detectable using conventional analytical technologies such as high pressure liquid chromatography (HPLC) because the content of the granules remained uniform despite the segregation. Therefore, granule visualization using NIR chemical imaging is an effective method for investigating and evaluating the granulation process.

1. Introduction

In the pharmaceutical manufacturing of solid dosage forms, the major aim of the granulation process is to produce granules with attributes that are beneficial for manufacturing, such as flowability, and contribute to high quality, such as homogeneity. Flowability and homogeneity depend on the conditions used during granulation. Despite the best efforts of manufacturers, the granulation process is sometimes poorly controlled and is characterized by quality control problems such as delay in dissolution. Granulation is one of the most critical processes in the manufacture of pharmaceutical solid dosage forms. Establishment of reliable manufacturing processes requires an understanding of the granulation process and identification and application of the critical factors that determine granulation quality. The ICH Q8 guidelines emphasize the adoption of quality by design (QbD) in the development of pharmaceutical products; this is a systematic approach based on scientific principles. Information gained from pharmaceutical development studies provides scientific knowledge to support the optimization of manufacturing processes, which in turn promotes quality in pharmaceutical products. In order to sufficiently understand the granulation process and produce higher quality products, highly accurate evaluation methods are necessary. Near-infrared (NIR) chemical imaging is one of the best methods for analyzing granulation because it can characterize heterogeneous solid dosage forms at a micron scale along with spatial and chemical information. In addition, this technique is rapid and nondestructive and requires a simpler sample preparation than that required for other chemical mapping methods. NIR chemical imaging has revealed more chemical information about solid dosage forms, such as tablets, capsules, powders, and freeze-dried product than that revealed by HPLC or other conventional analytical technologies (El-hagrasy et al., 2001; Jovanovic et al., 2006; Lewis et al., 2004; Linda et al., 2007; Lyon et al., 2002; Shah et al., 2007). This imaging method has been used to identify the causes of problems that occur during blending, granulating, and tableting (Clarke et al., 2001; Clarke, 2004; Hammond and Clarke, 2002). In addition, NIR has been successfully used to assess the quality of pharmaceutical products purchased on the Internet and to screen for counterfeit drugs in the US (Dubois et al., 2007;

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Veronin and Youran, 2004; Westenberger et al., 2005). Thus, previous research has shown that NIR chemical imaging is useful for various types of pharmaceutical analysis. Therefore, the method has attracted much attention for potential uses in process analysis, quality control, and product evaluation in pharmaceutical manufacturing.

Several granulation methods are presently used in pharmaceutical manufacturing. Wet granulation methods are now more widely used in the manufacturing process than dry granulation and direct compression methods. In the Japanese pharmaceutical industry, wet granulation methods are used in more than 70% of all manufacturing runs (Sunada et al., 2003). The mechanism of high shear granulation, which is one of the commonly used wet granulation methods, has been the subject of several investigations with respect to its mechanisms (Iveson et al., 2001; Saleh et al., 2005; Vonk et al., 1997). These studies have determined that the process of high shear granulation involves 3 key stages: wetting and nucleation, consolidation and growth, and breakage and attrition. Granules made under different formulation and granulation conditions have different properties (Benali et al., 2009; Vemavarapu et al., 2009). The process of high shear granulation is not well-understood due to its high complexity. A better understanding of this mechanism could lead to applications that would enhance the manufacture of pharmaceuticals.

In this study, we systematically investigated high shear granulation. The granulation conditions were selected based on previously reported data (Tanino et al., 2006) to produce both appropriate-granulation and over-granulation. We used NIR chemical imaging to observe differences between good and poor quality granules and tablets made under differing granulation conditions. Additionally, the feasibility of using NIR chemical imaging to describe granule properties and to evaluate the pharmaceutical development process is discussed.

2. Materials and methods

2.1. Materials

Ethenzamide, which was the active ingredient, was provided by Shionogi & Co., Ltd. (Osaka, Japan). Cornstarch, 200 mesh lactose monohydrate, and methylcellulose were purchased from Nihon Shokuhin Kako Co., Ltd. (Tokyo, Japan), DMV International (Veghel, The Netherlands) and Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan), respectively. The other reagents used in this experiment were of laboratory grade.

2.2. Methods

2.2.1. High shear granulation process

The granules were manufactured on a scale of 5 kg. Four compounds (ethenzamide, 70% (w/w); cornstarch, 7.9%; lactose, 18.6%; and methyl cellulose, 3.5%) were mixed with an impeller rotation speed of 240 rpm for 2 min, then supplemented with water (1100 g) and granulated using a VG-25 high shear granulator (Powrex Corporation, Itami, Japan). The chopper rotation speed was 3000 rpm and the water addition rate was about 27.5 g/s. The granules were made using different granulation times (3, 5, and 10 min) and impeller speeds (40, 120, and 200 rpm). The coarse milling of the wet granules was performed using a Comill QC-197S screening mill (Powrex Corporation) with an open mesh screen of 4.75 mm diameter and an impeller speed of 2400 rpm. The granulated wet mass was dried with a compartment dryer (Yamato Scientific Co., Ltd., Tokyo, Japan) at 60 °C for 12 h. The final water content of the granules was less than 1.0% (loss on drying test).

2.2.2. Particle size analysis

The particle size of the material components was measured using a particle-viewer laser diffraction particle size analyzer (Powrex Corporation) with a 632.8 nm He–Ne laser beam. From these results, a particle size distribution curve was drawn and the diameters (D_{10}, D_{50}, and D_{90}) were calculated.

The size of granules produced by high shear granulation was measured by the sieve analysis method using an Iida testing sieve (Iida Manufacturing Co., Ltd., Tokyo, Japan). The particle size of the granules was evaluated using an 8.6, 16, 22, 30, 50, 83, 140, or 200 mesh sieve. The granule size distributions were calculated by determining the ratios of the residual weight of the granules on each sieve to the granule weight before sieving. On the basis of these results, a particle size distribution curve was drawn and the median diameter (D_{50}) was calculated.

2.2.3. Preparation of samples for measurement

The granule samples were obtained from various areas in the ball of the granulator. The granules were compressed by hand into experimental tablets using 300 mg of granules and 2 kN pressure and then analyzed using an NIR imaging system. For producing a spectral library of the components, pure reference wafers were prepared in the same manner as the samples.

The sieved granules were classified into 3 categories: large-size granules that were left on the 8.6 and 16 mesh sieves (>1000 μm), medium-size granules left on the 22 and 30 mesh sieves (500–1000 μm), and small-size granules passed though the 30 mesh sieves (<500 μm). Size-classified granules were then compressed by hand into experimental tablets using 300 mg of granules and 2 kN pressure and measured using an NIR imaging system to investigate the relationship between granule size and chemical image. Size-classified granules were also analyzed using a UV quantitative assay.

The granules for single granule measurement by NIR chemical imaging were embedded in wafers of anhydrous caffeine. The embedded granules were then trimmed by EM trim (Leica Microsystems, Wetzlar, Germany) and sectioned to observe the interior of each granule. The distinct NIR spectrum of anhydrous caffeine allowed for easy removal of this substance from the NIR chemical images using chemometrics.

2.2.4. NIR chemical imaging

The Spotlight 350 (Perkin Elmer, Waltham, MA), a chemical imaging system equipped with a liquid nitrogen-cooled 16 × 1 mercury cadmium telluride (MCT) linear array detector, and Spotlight data acquisition software (Version 1.0), were used to collect NIR spectra of the samples. Each spectrum came from a square pixel of 25 μm × 25 μm. The background scan was recorded at 16 cm^{-1} spectral resolution with 90 scans using a gold mirror as the reflectance standard, and the sample scan was recorded at 16 cm^{-1} spectral resolution with 4 scans across the wavelength 7600–3800 cm^{-1}.

An area of approximately 4.5 mm × 4.5 mm (approximately 30,000 pixels) on the surface of each experimental tablet was measured using the NIR chemical imaging system. Approximately 30 min were required to obtain the measurements for each tablet. Reference wafers of pure components were scanned in the same manner as the samples to create a reflectance spectral library of the components.

Analysis of the data was conducted using Isys chemical imaging software (version 4.0; Malvern Instruments, Ltd., Worcestershire, UK). The reflectance spectra were converted to absorbance spectra using the inverse common logarithm to convert to $\log(1/R)$; spectral data were normalized using the standard normal variate (SNV) method (Barnes et al., 1989) to remove any offsets due to physical variations such as path length. The normalized spectral data for