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Clarifying the mechanism of aggregation of particles in high-shear granulation based on their surface properties by using micro-spectroscopy

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ABSTRACT

The present study aimed to clarify, by means of micro-spectroscopy, the mechanism of aggregation of particles into granules during high-shear granulation. We used two types of pharmaceutical granules prepared by high-shear granulator, one containing mefenamic acid and the other containing flavoxate hydrochloride as poorly soluble active pharmaceutical ingredients (APIs). Lactose, cornstarch, and microcrystalline cellulose were used as excipients; and hydroxypropyl cellulose (HPC) was used as the binding agent. The distributions of components in granules were visualized by mapping cross-sections of individual granules with techniques utilizing mid-infrared spectroscopy at the SPring-8 synchrotron radiation facility and micro-Raman spectroscopy. In the distribution maps of mefenamic acid granules, distributions of mefenamic acid, cornstarch, and microcrystalline cellulose overlapped; in flavoxate hydrochloride granules, on the other hand, distributions of flavoxate hydrochloride and lactose overlapped. Assessment of the surface free energy of each component found that ingredients with overlapping distribution had similar surface properties. Therefore, it was revealed that in high-shear granulation, in addition to the granulator operating conditions and general properties of the formulation itself (such as the solubility and particle size of each ingredient), the surface properties of the ingredients and their interrelationships were also factors that determined the aggregation behavior of the particles.

1. Introduction

In the pharmaceutical industry, granulation is a generally used process in the manufacture of tablets and capsules. Among the variety of granulation methods, high-shear granulation is one of the most widely used. In high-shear granulation, powders are agitated by an impeller in a vessel and sprayed with a binder solution from the top, while, simultaneously, coarse particles are crushed by a chopper. As droplets of the binder solution are dispersed into the powder, liquid bridges form between primary particles that become nuclei around which granule size subsequently increases (Faure et al., 2001). Granulation is carried out in order to control dust of the active pharmaceutical ingredients (APIs) and to prepare granules of high flowability, which facilitates subsequent steps in the manufacturing process (e.g., tableting). Also, producing homogeneous granules is an important objective in ensuring uniformity of content. Therefore, granulation is considered one of the most important processes in the manufacturing process of pharmaceutical products, and a lot of research has been directed at understanding the complex mechanisms of granule formation. Studies of granulation have been conducted under various manufacturing conditions to examine the effects that process parameters and formulation variables (such as the rotational speeds of the impeller and chopper, granulation time, proportion of water, proportions of feed ingredients, and viscosity of the binder solution) have on physical properties of the granules (e.g., particle size, particle size distribution, structure, and strength) (Belohlav et al., 2007; Bouwman et al., 2005; Cavinato et al., 2011; Nguyen et al., 2010; Rahmanian et al., 2011; Smirani-Khayati et al., 2009; Tu et al., 2009). Previous research has shown that the formation of granules is controlled by a combination of 3 major mechanisms:

(1) *Wetting and nucleation*: droplets of binder solution are dispersed into powder and liquid bridges are formed between primary particles; these form the nuclei of granules.
(2) *Consolidation and aggregation*: nuclear particles coalesce with each other, and particles enlarge and become stronger.

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(3) *Breakage and growth*: particles are crushed by impeller blades and chopper.

Many researchers have tried to explain these mechanisms in detail (Benali et al., 2009; Iveson et al., 2001a; Van den Dries and Vromans, 2004, 2009; Van den Dries et al., 2003; Vonk et al., 1997). Nucleation occurs at the beginning of granulation, and aggregation and fragmentation is repeated as particles continue to grow. Eventually, granules reach maximum strength and equilibrium is reached and further growth and breakage does not occur, at which point granulation is complete. Other studies have evaluated the relationships between the physical properties of the granules (e.g., particle size, particle size distribution, flowability, compressibility, and uniformity) and the properties of the APIs and excipients (e.g., particle size, specific surface area, solubility, and wettability). For example, it has been found that highly soluble materials tend to grow into granules rapidly (Iveson et al., 2001b; Saleh et al., 2005; Van den Dries and Vromans, 2002; Vemavarapu et al., 2009).

The many studies mentioned above were carried out at the macroscopic level. However, it is also important to evaluate granules from a more microscopic perspective to more clearly understand the mechanisms of granulation (Le et al., 2011). Microscopic imaging techniques are used in many studies, and it is amply demonstrated that they are suitable for assessing extremely microscopic regions in formulations of various types (Gendrin et al., 2007; Li et al., 2008; Maurer and Leuenberger, 2009; Yonemochi et al., 2008). For example, the distribution of the API and additives at the surface of tablets has been assessed by microscopic imaging using NIR (near-infrared) spectroscopy (Amigo and Ravn, 2009; Franch-Lage et al., 2011), and the distribution of API and additives in ointments produced by different methods has been evaluated by using attenuated total reflection infrared (ATR-IR) spectroscopy (Yamamoto et al., 2012). An investigation using techniques combining micro-Raman mapping, scanning electron microscopy (SEM), and transmission electron microscopy (TEM) has been conducted to differentiate between the amorphous molecular level dispersion and nano dispersions of API in a solid dispersion (Karavas et al., 2007).

By using micro-spectroscopy, it is possible to assess the dispersion state of each component in individual granules, and this information could be very useful for explaining the mechanism of granulation. In this study to describe the mechanism of granulation, the dispersion states of each component in granules prepared using different granulation times were examined using micro-spectroscopy. We confirmed that the dispersions of each component in the granules changed with the progress of granulation. In addition, all ingredients except the binder were considered to be almost insoluble under the granulation conditions in this study. In such cases, it is considered that it is the surface properties of the powdered ingredients that most affects the distribution of each component in the granules during granulation. By using micro-spectroscopic mapping techniques and assessment of the surface properties of ingredients, we attempted to clarify the mechanism of aggregation of components that occurs in high-shear granulation.

2. Materials and methods

2.1. Materials

Mefenamic acid (Sanchemipha Co., Ltd, Miyagi, Japan) and flavoxate hydrochloride (Sanchemipha) were used as models of poorly water soluble APIs: solubility of mefenamic acid (0.00174 mg/mL at 20 °C) (PMRJ, 2002a) was lower than that of flavoxate hydrochloride (17.2 mg/mL at 20 °C) (PMRJ, 2002b). Lactose (DMV-Fonterra Excipients GmbH & Co, Goch, Germany), cornstarch (Nihon Shokuhin Kako Co., Ltd., Inc., Tokyo, Japan), and microcrystalline cellulose (Asahi Kasei Chemicals Corporation, Tokyo, Japan) were used as excipients, and hydroxypropyl cellulose (HPC; Nippon Soda Co., Ltd., Tokyo, Japan) was used as the binding agent.

Table 1
Formulations of the two types of granules experiments.

Materials	Percentage (%)	
	Mefenamic acid granules	Flavoxate hydrochloride granules
Mefenamic acid	9.80	–
Flavoxate hydrochloride	–	9.80
Lactose	52.90	52.90
Cornstarch	26.40	26.40
Microcrystalline cellulose	8.80	8.80
Hydroxypropyl cellulose	2.10	2.10
Total	100.00	100.00

2.2. Granulation conditions

Two types of granules were prepared, each with a different type of API. The percentage of API in each type of granule was 9.8%, and the percentages of excipients were the same (Table 1). Granules were prepared in a high-shear granulator (VG-25; Powrex Inc., Hyogo, Japan) with impeller speed of 180 rpm and chopper speed of 3000 rpm. The volume of the granulator was 25 L and the charge amount was set at approximately 7.5 kg. After 2 min of premixing, a 7% (w/v) aqueous solution of HPC was added all at once. Granules were sampled from three fixed points positioned equally around the circumference of the powder bed, with the samples taken at specified times from the time that the HPC was added (10 s, 30 s, 1 min, 1.5 min, 2 min, 3 min, 4 min, 5 min, 7 min, 10 min, 15 min), and then dried on a shelf dryer at 80 °C.

2.3. Measurement of mean particle size

The average particle size of the granules was measured by sieve analysis. Samples of about 100 g were sieved through 12-, 32-, and 48-mesh (1.40, 0.50, and 0.30 mm) sieves. The proportion of sample retained on each sieve was used to obtain the mean particle size, and granules of the greatest weight fraction remaining on the sieve at each granulation time were analyzed by micro-spectrophotometer.

2.4. Mid-infrared spectroscopy (MIR)

2.4.1. Determination of standard spectra by MIR

The spectrum of each ingredient was determined with the BL43 IR beamline of the SPring-8 synchrotron radiation facility (Hyogo, Japan) and a mercury cadmium tellurium (MCT) detector. The spectra were collected in transmission mode and measured at a wavenumber resolution of 4 cm^{-1} with 32 scans in the mid-infrared range (4000–400 cm^{-1}).

2.4.2. Sample preparation for MIR

In order to map cross-sections of the granules in transmission mode, granules were embedded in acrylic resin (LR white resin; Okenshoji Co., Ltd, Tokyo, Japan) and then sliced to a thickness of 5 μm using a microtome. At least three granules were evaluated for each of the specified sampling times.