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Measuring granule phase volume distributions using X-ray microtomography

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ABSTRACT

Although granule microstructure has been shown to have a significant influence on granule performance, e.g., impact attrition resistance, dissolution rate, and granule strength, there has been a lack of research on methods to identify granule components in 3D space to describe granule microstructural properties. This paper presents techniques to non-destructively identify and describe spatial distributions of particle, binder, and air volumes within wet-granulated granules using X-ray microtomography (XRμT).

Ten granules were produced from glass ballotini particles and aqueous PVP binder and were imaged using XRμT. Particle and binder volumes were identified from the output images by using a combination of gray intensity value thresholds and image processing techniques. A new technique, utilizing the intersection of convex hulls defined along the granule's three principal planes, was developed to distinguish between the intra-granular and extra-granular air space.

Segmented glass ballotini masses were accurate and insensitive to the gray value thresholds. Segmented PVP mass was sensitive to both the lower gray value threshold and the elimination of particle partial voxels. Therefore, the effect that the segmentation method had on image measurements was investigated. Identified internal air volumes gave good agreement when compared to the powder bed porosity and to the predicted average particle coordination number.

The spatial distributions of the phases are described both radially from the granule's center of mass and with planes starting from the top of each granule. While phase volume fractions are uniformly distributed in the radial direction, axial distributions show that the binder volume fractions at the top of the granules are approximately 3% larger than at the bottom of the granules. This localization of binder was found to be consistent regardless of the binder identification method and is the first quantitative proof of intra-granular binder segregation for granules formed with a binder solution.

1. Introduction

Wet granulation is a particle engineering process in which binder is added to a powder bed in order to transform primary particles into agglomerates with improved properties. Improved properties can include reduced segregation potential, increased flowability, decreased dustiness, and increased bulk density. Improvement of fine powder properties makes wet granulation an important process in the pharmaceutical, food, detergent, enzyme, chemical, and fertilizer industries [1]. In some applications, granules are the final product whereas in other applications granules may be milled, coated, or compressed in order to create the final product. In all applications it is important to understand how material and process parameters affect granule properties and how granule properties relate to end use quality. Therefore, both process and product models need to be developed for wet granulation and downstream processes.

In order to link the process and product models, the process model must pass relevant granule properties to the product model. Granule properties that determine performance, for example granule strength and dissolution rate, include size, composition, structure, and morphology distributions [2]. There are standard methods for the measurement of granule size and composition; however, structure and morphology remain a characterization area to be investigated. The structure of granules has, until recently, been measured by the average porosity of several granules. However, in order for granule structure to be predictive of granule performance, the structure of granules must be defined on a sub-granule length scale.

The granulation literature has shown the importance of microstructure in determining the performance of granules. Ansari and Stepanek [3–5] have shown that granule dissolution profiles depend on the size

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and radial locations of granule components as well as the overall granule porosity. Granule deformation behavior has been shown to depend on the orientation of the applied force and the presence of large central pores throughout the granule [6,7]. Granular impact attrition behavior has also shown sensitivity to the number and size of large pores [8,9]. While these studies indicate the importance of granule microstructure, quantitative description of the spatial distribution of components was not conducted. Without quantitative structure descriptors, it is difficult to understand the role of structure in determining granule performance.

In order to obtain information about the granule microstructure, imaging methods that can distinguish between phases in 3D space must be implemented. Phase is used not only to represent differences in gas, liquid, and solid, but also to distinguish between components within those physical states. With recent advances in the resolution and the ability to make phase contrast measurements, X-ray microtomography (XRμT) is becoming a key technique in identifying the microstructure of materials [10].

XRμT measurements return an X-ray absorption coefficient for a specified volume (voxel) in space throughout the sample. The absorption coefficient is a function of the material's density and atomic number and the initial X-ray intensity for the measurement [11]. If absorption coefficients differ substantially between phases, image analysis can be used to isolate the different phases in space. This technique has been used by several authors in order to obtain the spatial locations of different phases in various materials [11–14].

One limitation of this technique is that materials can have overlapping absorption coefficients. To avoid this limitation, it is possible to use correlative microscopy. Crean et al. [15] and Van Dalen et al. [16] have shown that using 2-D imaging methods, such as SEM–EDX, Raman microscopy, and infrared microscopy, in combination with XRμT results can improve the phase resolution. Another limitation in using XRμT is that quantitative image analysis is limited by the resolution of the instrument and the resulting quality of the obtained images. For example, the output of the XRμT in the setup used in the current study has a cubic voxel edge length of 6 μm. To accurately quantify volumes of any phase, the phase must have volume that is several voxels in each dimension. Therefore, it is necessary to optimize the XRμT imaging parameters and to validate the segmentation technique. These limitations are addressed in Results and discussion section of this paper.

The reader is referred to the reviews by Stock [10] and Landis and Keane [17] for a more extensive review of XRμT and the applications of measurements made from the resulting images. The following overview will focus on applications of XRμT to particulate systems. Once the spatial locations of all phases are known, one must have a method for describing the spatial distribution of the phases. Berrera-Medrano [18] made radial distribution measurements of the average gray scale intensity on granules assuming that gray scale intensity was only a function of material density. The radial distribution was used to describe how the density changed as a function of the distance from the granule's center of mass. However, the granule components were not clearly segmented so density changes due to varying amounts of binder, particle, and air could not be differentiated.

Several authors have used stereology methods to analyze XRμT images of granules [14,19,20]. Using different probes, such as lines and points, information can be obtained about the phase volume fractions, the average size of the phases, and the distance between phases. These techniques are useful when measuring phase sizes, such as pore size, which are difficult to define in 3D space. However, XRμT gives volumetric data of whole granules; therefore, volume distributions can be explored without the need for the statistical assumptions needed in stereology.

Volumetric data has been used in defining the size, shape, coordination number, and fractal dimension of particles along with various aspects of the pore size distribution [21–23]. The distribution of binder in granules, however, has not been previously examined, despite its likely strong impact on granule strength, attrition resistance, and disintegration/dissolution.

It is the goal of this paper to segment particle, binder, and air phases within granules using XRμT imaging. In order to accomplish this task, a new image processing algorithm for differentiating intra-granular and extra-granular air volume is introduced. Using a controlled granulation technique along with model materials, segmented volumes are compared to expected values. Description of the phase distributions is conducted both along one of the granule's axes and as a function of radius from the granule's center of mass. Ten granules made using the same technique are analyzed in order to infer consistency in the granule structure and the analysis methods.

2. Materials and methods

2.1. Materials

Glass ballotini impact beads (Potters Industries) and Plasdone® K90 polyvinylpyrrolidone (PVP) (ISP Technologies Inc.) were selected as model materials due to the expected X-ray absorption coefficient contrast between the materials. Glass ballotini are expected to absorb significantly more energy than PVP due to having both a larger true density and a larger average atomic number. Glass ballotini, sieved to a size fraction of 250–355 μm, were used to form all granules. This size fraction is larger than primary particles used in typical pharmaceutical granules, but was chosen to limit the error in measurement of the particle volume while using an XRμT voxel size of 6 μm in each dimension. The true density of glass ballotini was 2.49 g/cm^3 as measured by helium pycnometry (Micromeritics AccuPyc II 1340). Binder was introduced as an aqueous solution of 0.15 g PVP per gram of distilled water. The density of dry binder bridges was measured by drying binder solution on glass slides, removing and fracturing the film formed, and placing the resulting binder film pieces in a helium pycnometer. Dry binder had a true density of 1.24 g/cm^3.

2.2. Granule formation

Glass ballotini bed preparation was automated with the use of an FT4 powder rheometer (Freeman Technology). The FT4 standard 48 mm twisted blade traversed through a 50 mm diameter cylinder containing the glass ballotini five times prior to splitting the powder bed to create a level surface. The average powder bed porosity after five conditioning cycles was 38.8 ± 0.4%. PVP solution drops were created with the aid of a syringe pump by pumping the solution through silicone tubing to a 22 gauge needle that was located 1 cm above the powder bed. The powder bed was moved in between drops to ensure that an individual nucleus was created with each drop. Drops were allowed to dry within the static bed for at least 24 h before they were excavated with a spatula and placed on a 1.4 mm sieve to remove glass ballotini that were not bound to the granule.

2.3. Imaging

After the binder was solidified, granules were imaged with a Scanco Medical μCT 40 XRμT instrument. X-rays were produced using a voltage of 55 kVp and a current of 145 μA. Two thousand intensity projections were taken per 180° rotation of a cylindrical acrylic holder, which contained the granules. An average of two measurements was used to calculate the average absorption coefficient of each voxel. An aluminum filter of 0.5 mm was used to reduce low energy X-rays, which can be preferentially absorbed and cause beam hardening artifacts [24]. A calibrated beam hardening correction was also used during the calculation of the absorption coefficients. Results from the absorption coefficient calculations were output as a stack of 2D images from corresponding volume slices throughout the granules. The original intensity range of 0–32,767 was normalized by 32,767 to assign gray intensity integer values between 0 and 255, with larger values corresponding to larger