The Granule Porosity Controls the Loss of Compactibility for Both Dry- and Wet-Processed Cellulose Granules but at Different Rate

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ABSTRACT: The aim of this study was to investigate the role of porosity on the compression behavior and tablet tensile strength for granules produced by a dry granulation procedure. Microcrystalline cellulose was used as a typical pharmaceutical excipient and a comparison was made with the effect of granule porosity on the compression behavior and tablet tensile strength of wet-processed granules of the same composition. Both the wet and dry granulation process caused a loss in compactibility of the material that was controlled by the granule porosity up to a critical point of porosity and friability. Above this threshold value of porosity, the granules nearly collapsed completely into primary particles during compression. In these cases, the micro-structure and tensile strength of the formed tablets resembled that of tablets formed from the original ungranulated powder. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2029–2039, 2015

Keywords: compaction; compression; granulation; granules; cellulose; porosity; powder technology; tablets; tableting; tensile strength

INTRODUCTION

Granulation of pharmaceutical powders is usually required to increase the manufacturability of the particles and is hence one common and important operation in the production of solid dosage forms. Granules are often created by adding a liquid binder into the powder bed, that is, by a wet granulation procedure, for example, in a high-shear granulator or in a fluidized bed in a batch-wise manner.[1] A dry granulation procedure represents an interesting option, not only because heat- and moisture-sensitive formulations can be processed but also because that the logistics of the process enables a continuous manufacturing of granules.[2] In dry granulation, the powder can be precompacted by briquetting (in a similar way as tablet production) or by passing through two counter-rotating rolls (roller compaction), which produces briquettes or in the latter case ribbons that is then milled to produce granules.[3,4] One of the problems identified with roller compaction is the variation in structure of prepared ribbons and consequently variation in functionality related characteristics of the produced tablets.[5,6]

Another issue that has been addressed in the context of dry granulation is the loss in compactibility compared with the raw material, that is, tablets formed from granules formed by dry granulation have been shown to have a lower tensile strength than tablets formed from direct compression of the corresponding ungranulated powder.[7–9] This phenomenon has been suggested to be a result of size enlargement during the granulation or that the resistance of the granules toward plastic deformation is increased.[10] When wet and dry granulation formulations are compared, contradictory results are reported, such as reduced[9,11] and improved compactibility[12] because of dry granulation. In one study where the wet granulation process generated granules of higher compressibility and of higher compactibility compared with the dry granulated formulation, the observation was partly explained by the higher initial porosity of the wet processed granules.[13] This is consistent with other findings that an increased porosity increases the degree of deformation of wet-processed granules expressed during the compression that corresponds to an increased tensile strength of the produced tablets.[14–17] Other factors can also influence the compression behavior such as the shape and the surface roughness of the granules.[18–20]

The question whether the structure of granules prepared by dry granulation is critical for the evolution of tablet structure and the tensile strength of the formed tablet needs to be further explored. The aim of this study was to investigate the phenomenon of loss of compactibility of dry granulated powders and if this loss depends on the microstructure of the granules. This was carried out by preparing granules by dry granulation (compaction and grinding) with varying structure in terms of porosity and study the effect of porosity on the compression behavior and one critical product attribute, that is, tablet tensile strength. Microcrystalline cellulose (MCC) was used for this purpose as a typical pharmaceutical excipient that can form binder-free granules. Briquetting was chosen as dry granulation technique in order to generate granules of a wide range of porosity in such a controlled matter as possible. A comparison was made with the effect of granule porosity on the compression behavior and tablet tensile strength of wet-processed granules formed from the same powder.

MATERIALS AND METHODS

Materials

The starting powder material used was MCC (Avicel PH101; FMC, Wellingstown, Ireland; with a particle size of ~50 μm). The powder was conditioned by storage in desiccators over a saturated K_2CO_3 solution (~40% RH) at room temperature (~20°C) for at least 5 days before further characterization and compression analysis were performed. Ethanol (95%,

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w/w; Solveco Chemicals AB, Rosersberg, Sweden; hereafter referred to as E) and deionized water (hereafter referred to as W) were used as granulation liquid. Magnesium stearate (Ph. Eur., Kebo, Sweden) was used as a lubricant in the compression experiments.

Preparation of Granules by Wet Granulation

A total powder weight of 400 g was agitated in a high shear mixer (QMM-II; Donsmark Process Technology, København K, Denmark) at 500 rpm for 1 min before the granulation liquid (400–440 g) was added into the powder at a flow rate of 100 mL/min. Wet mixing was then continued for 1 min at 500 rpm. Different proportions of water and ethanol were used in the granulation liquid (see Table 1) in order to produce granules of different porosities.

The wet granules were spread out in a thin layer on plates to dry in ambient conditions for at least 3 days before different size fractions of the granules were prepared by dry sieving 100 g granules with a set of standard sieves with square openings mechanically shaken for 10 min at a relative agitation intensity of 50 (Retsch, Type RV, Germany). The size fraction 500–710 μm of each granule type was selected for further analysis. The granules were then conditioned by storage in desiccators over a saturated K_2CO_3 solution (~40% RH) at room temperature (~20°C) for at least 5 days before further characterization and compression analysis were performed.

Preparation of Granules by Dry Granulation

The first step in the dry granulation procedure was to produce briquettes. This was carried out by compressing approximately 1.8 g MCC powder (corresponding to the maximum fill volume of the die with the tooling used) in an instrumented single-punch press (Korsch EK0, Berlin, Germany), equipped with flat-faced punches (with a diameter of 20 or 11.3 mm), at eight different pressures (see Table 2). No lubricant was used in the production of the briquettes. A feeder was used to feed the powder into the die. The pressure was increased by moving the lower punch and/or the upper punch. After testing [see section Characterization of Compressed Powder (Briquettes and Tablets)], the briquettes were grinded by hand in a mortar and the size fraction of 500–710 μm of each granule type was prepared and conditioned as described in section *Preparation of Granules by Wet Granulation* before further characterization and compression analysis were performed.

Table 1. Composition of the Different Types of Granules Prepared by Wet Granulation

Granule Nomination	Water/Ethanol (%, w/w)
WG_1	100/0
WG_2	75/25
WG_3	50/50
WG_4	25/75
WG_5	0/100

Table 2. The Pressures Used when Preparing Different Types of Granules by the Dry Granulation Process and Characteristics of the Briquettes

Granule Nomination	Pressure (MPa)	Briquette Porosity (%)	Briquette Tensile Strength (MPa)
DG_1	150	24	4.2
DG_2	125	26	3.8
DG_3	100	34	2.2
DG_4	75	38	1.7
DG_5	50	43	1.2
DG_6	25	52	0.5
DG_7	15	62	0.1
DG_8	5	65	0.1

Particle and Granule Characterization

Particle Densities

The apparent primary particle density (ρ_{app}) of the ungranulated MCC powder was determined using helium pycnometry (AccuPyc 1330; Micromeritics, Norcross, Georgia) ($n = 2$ and each sample was measured with an automatic procedure 10 times).

The intragranular porosity of the granules (produced from the wet and dry granulation procedures described above) was calculated as one minus the ratio between the effective and the apparent particle densities. The effective particle density (ρ_{eff}) for each type of granulated powder was determined by using a mercury pycnometer (Autopore III 9420; Micromeritics) according to a procedure described in detail elsewhere.[21]

The poured bulk density of the ungranulated MCC powder (ρ_{bulk}) was measured by gentle pouring of powder sample (~16 g) into a graduated 50 mL cylinder with a diameter of approximately 23 mm. The height or volume of the powder bed was measured visually ($n = 3$).

From the weight and height of the bed of granules and the dimensions of the glass cylinder described below in section *External Surface Area*, the granule bed bulk density (ρ_{bulk}) was also calculated for the granulated powders (poured bulk density, $n = 3$).

External Surface Area

The volume-specific surface area (S_0) of the MCC powder was determined using a transient (Blaine) air permeability apparatus.[22] S_0 was calculated using a slip flow-corrected Kozeny–Carman equation[23] ($n = 5$ with three recordings of flow time for each experiment).

The external surface areas of the granules were assessed by steady-state air permeametry ($n = 3$). The granules were poured into a glass cylinder of 11.47 mm diameter. The weight (3.7–9.4 g) and height (~10 cm) of the granule bed were then measured and the container was connected to a pump. Air was pumped through the sample bed at a series of controlled flow rates (Brook flow meter; Brook Instruments B.V., WX Ede, The Netherlands) and the corresponding pressure drop was recorded by a digital differential manometer (P200 S; Digitron Instrumentation Ltd., Torquay, Devon, UK). The permeametry surface area was calculated with the Kozeny–Carman equation as described in a previous work.[24]

Particle Morphology

Some of the particles were inspected visually with a stereomicroscope (Stereomicroscope, Discovery.V8; Carl Zeiss, Göttingen, Germany) to get a visual estimate of the shape and surface roughness of the granules.