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Research paper

Studies on the reduction of tensile strength of tablets after roll compaction/dry granulation

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Abstract

Roll compaction/dry granulation is a widely used technique for granulation. A major drawback is the reduction of tablet tensile strength compared to other granulation methods. The purpose of this study was to determine the reasons for the partial loss in compactibility.

Microcrystalline cellulose of different particle sizes was roll-compacted/dry-granulated. The granules were sieved to obtain two sieve cuts and then compressed into tablets. The particle-size distribution within the sieve cut was determined using image analysis. The specific surface area of sieve cut was obtained by nitrogen adsorption. Heckel equation was used to determine the change in compressibility.

The work-hardening phenomenon was found to be caused by a combination of particle-size enlargement and hardening of material. Although particle size of granules was equal, the use of smaller particles as raw material resulted in tablets with higher tensile strength due to higher specific surface area.

Both work-hardening and particle-size enlargement cause the partial loss in compactibility. The reduction in tensile strength could be compensated by producing smaller granules or using raw materials with small particle sizes.

Keywords: Roll compaction/dry granulation; Tablets; Dry binder; Tensile strength; Particle size; Microcrystalline cellulose; Work Hardening; Compression; Compactibility

1. Introduction

Granulation is often a necessary step to improve the powder properties in pharmaceutical industry. Roll compaction/dry granulation and slugging are widely used techniques for granulation without water. Major advantages of roll compaction are the continuous production of granules and the lack of a drying stage leading to a reduction of costs [1]. However, dry granulation results in tablets with inferior tensile strength compared to direct compression.

In the literature this phenomenon was first described as work-hardening by Malkowska and Khan in 1983 [2]. It was explained with a limited binding potential which is partially consumed in the first compression step [3]. Materials with plastic deformation properties are particularly sensitive to this phenomenon. However, no evidence of direct hardening of powders was stated for this hypothesis. In a more recent paper by Sun and Himmelspach [4], the effect of reduced tensile strength was related solely to a particle-size increase during granulation. This resulted in a smaller binding area available for bonding. The authors used two sieve cuts (44–106 μm and 250–500 μm) with different types of microcrystalline cellulose (MCC) to avoid different particle-size distributions within the same sieve cut. Non-compacted and compacted materials were compared. The authors showed that there was a negative correlation between particle size of granules and tensile strength of tablets. The roll compaction was only performed at one compaction force level. In addition, according to Fig. 3 in their publication the same sieve cuts of granules made from different particle sizes of raw MCC resulted in different

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tensile strengths. The same amount of magnesium stearate (0.5%) was added independently of the particle size. This might explain partly the lower tensile strength of larger granules with a smaller surface area [5].

Recently, a significant correlation between particle size and tensile strength could not be observed by Herting and Kleinebudde [6]. In their study larger granules resulted in higher tensile strength values. Furthermore, in the study of Sun and Himmelspach [4] the values for tensile strength of tablets were not consistent with the values already reported in the literature [7]. Sun and Himmelspach did not provide detailed compression data and, therefore, statements about further changes of the material during roll compaction could not be stated.

Thus, the statement by Sun and Himmelspach explaining the reduction of tensile strength after roll compaction needs to be reconsidered. Therefore the purpose of this study was to examine if the reduction of tensile strength can solely be related to particle-size enlargement or, additionally, to a loss in binding potential due to double mechanical treatment. To investigate that, different types of MCC varying in particle size were roll-compacted/dry-granulated at various specific compaction forces. Two sieve cuts were obtained. Image analysis was performed to check the particle-size distribution within a certain sieve cut. The sieve cuts were then compressed into tablets using an instrumented tabletting press. The compression was performed using external lubrication and tensile strength of tablets was measured. The Heckel equation was used to determine the change and dimension of change in tabletting behaviour. The specific surface area of granules was measured using nitrogen adsorption.

2. Materials and methods

2.1. Materials

MCC was used in three different particle sizes. Vivapur 105 (MCC105) and Vivapur 101 (MCC101) were supplied by Rettenmaier, Rosenberg, Germany. MCC102G (MCC102) was supplied by Pharmatrans Sanaq, Basel, Switzerland. The investigated MCCs possessed the same degree of polymerisation (228 ± 3). The degree of polymerisation affects the compactibility of MCC [8].

Magnesium stearate was used as a lubricant (Caelo, Germany).

Prior to investigations, the materials were stored at least for 2 weeks at 21 °C and 45% relative humidity (rh).

2.2. Methods

2.2.1. Sampling

Prior to further analysis the powders and granules were divided using a rotary sample divider (PT, Retsch, Haan, Germany) in order to obtain representative samples with adequate amount.

2.2.2. Particle density and particle-size measurement

The apparent particle density of all excipients was determined with an AccuPyc 1330 Helium Pycnometer (Micromeritics, Norcross, USA). For each excipient the determination was repeated 10 times and the mean value was reported.

The particle-size distributions of non-compacted MCCs were determined by laser diffraction analysis (Helos H1402/KF-Magic, Sympatec, Clausthal-Zellerfeld, Germany) using lenses of 50, 200 and 500 mm focal length. The powders were dispersed with a Rhodos dry disperser (Sympatec, Germany). For characterisation of each powder the average median particle size (d_{50}) of three measurements was used.

For granules, the particle-size distribution was determined by combined vibrating sieve analysis and air jet sieve analysis (Alpine 200LS-N, Hosokawa, Osaka, Japan). The applied sieves for vibrating sieve analysis (180, 315, 500, 800, 1000, 1250 and 1400 μm) were shaken on the sieve tower (Vibrio, Retsch, Haan, Germany) for 5 min at an amplitude of 1 mm. The used air jet sieves were 32, 63, 90 and 125 μm. The median particle size and the amount of fines, which were defined as the fraction of particles smaller than 90 μm [9], were used as descriptive factors for sieve analysis.

2.2.3. Roll compaction/dry granulation

All experiments were performed using an instrumented roll compactor (Mini-Pactor, Gerteis, Jona, Switzerland) equipped with smooth rim rolls. The diameter and the width of the rolls are 25 and 2.5 cm, respectively. The gap between the rolls was kept constant at 3 mm. Speed of the rolls was set to 1 rpm. The roll compactor was set at the automatic mode [10], whereas the speed of the temping auger was adjusted by a control circuit keeping the gap constant.

Ribbons were roll-compacted to four (MCC102, MCC105) or five (MCC101) predefined specific compaction forces. The specific compaction force is applied force per width of rolls. Granules were retained after reaching constant gap and force (steady state section) [7].

The ribbons were directly granulated with a pocket mould-grooved granulator using a 1.25 mm sieve. The oscillating (150°/160°) granulator was operated at a rotor speed of 30 rpm clockwise and 40 rpm counter-clockwise. Distance between sieve and rotor was set to 1 mm.

2.2.4. Image analysis

Each batch of granules was sieved into fractions 180–200 μm and 630–800 μm. Image analysis of these fractions was conducted using a system consisting of a stereomicroscope (MZ 75, Leica, Cambridge, UK), a ringlight with cold light source (KL 1500, Leica, Cambridge, UK), and a digital camera (CS 300F, Cambridge, UK). Software Leica Qwin (Cambridge, UK) was used to control and display data acquisition. Images of 500 particles of each sample at an adequate magnification [11] were translated into