Critical Evaluation of Root Causes of the Reduced Compactability after Roll Compaction/Dry Granulation

JOHANNA MOSIG, PETER KLEINEBUDDE

Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf 40225, Germany

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ABSTRACT: The influence of lubrication and particle size on the reduced compactability after dry granulation was investigated. Powder cellulose, lactose, magnesium carbonate, and two types of microcrystalline cellulose were roll compacted, granulated, and sieved into particle fractions. Particle fractions were compressed into tablets using internal and external lubrication. Internal lubrication resulted in an overlubrication of the granule material compared with the powder material. This resulted in extraordinary high reduction of compactability after dry granulation for lubricant-sensitive materials. The granule size can cause differences in strength, whereby the degree of this effect was material dependent. The loss in strength with increasing compaction force was comparable for different particles sizes of one material, suggesting a change in material properties independently of the size. Granule hardening could be one reason as for higher compaction forces the integrity of the granule structure survived the compression step. The results demonstrated that granule lubrication mainly influence the degree of the reduced compactability after dry granulation and must be considered for the evaluation of mechanism for this phenomenon. Hardening of the material as well as size enlargement will cause the loss in strength after recompression, but the influence of both depends strongly on the material. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:1108–1118, 2015

Keywords: compression; granulation; tableting; compaction; powder technology; roll compaction; lubrication; work-hardening; reduced compactability; particle size

INTRODUCTION

Tableting is a central process during drug formulation. As many materials are not suitable for direct compression (DC), most times the materials are granulated prior to tableting. Roll compaction or slugging and subsequently dry granulation are common processes for the granulation without liquids. Because of the absence of water and solvents, granulation of moisture- and heat-sensitive materials is possible.[1]

The major drawback of dry granulation is the loss of strength after a re-compression step. Malkowska and Khan[2] showed that tablets made from dry granules exhibited a lower strength as those from DC and explained it by a work hardening of the material. They defined this as the resistance to permanent deformation, which is increasing with the amount of deformation. This is caused by increasing the level of difficulty to introduce new dislocations in the crystal structure. They observed the phenomenon for the plastically deforming microcrystalline cellulose (MCC) and starch as well as for the brittle behaving dicalcium phosphate. Reduced compactability is often related to this phenomenon in the literature. However, there is no direct evidence for a work hardening of the material as the direct verification is difficult. In more recent papers, the mean yield pressure calculated by the Heckel equation was used as surrogate parameter for the work hardening.[3,4]

Sun and Himmelspach[5] hypothesized that granule size enlargement is the primary mechanism for the reduction of strength after re-compression. In this study, two granule sieve fractions of different MCC types were tableted with same amounts of lubricant as for the powder material. It was stated that the reduction in strength with multiple roll compaction was just an effect of the increase in granule size but independent of the total number of compaction steps. Herting and Kleinebudde[3] stated that a combination of hardening and particle-size enlargement caused the loss in compactability. Here, external lubrication was performed to ensure a comparable lubrication between the powder material and different granule fractions of MCC. The impact of the particle size on the compaction of dry granules of brittle materials was investigated by Wu and Sun.[6] It was suggested that the compactability of brittle granules was insensitive to size enlargement effects as extensive fracture minimized differences in the initial granule size. In the study, the roll compaction force was low and no comparison with uncompacted material was performed. Therefore, investigations on the reduced compactability could not be made here. Patel et al.[7] related the loss of compactability of dry granulated MCC to the nominal single fracture strength of granules. Higher slugging pressure led to harder granules, which caused a higher reduction in compactability after a second compression step. The impact of the particle size was also studied and it was suggested that granule hardening affected the tensile strength more than the granule size enlargement.

The consequences of feedstock lubrication on the mechanical strength of tablets were investigated by He et al.[4] A modest increase in dynamic hardness and mean yield pressure was found for unlubricated MCC after roll compaction, which was related to a work hardening of the material. The lubrication prior to the roll compaction step led to an overlubrication especially in the milling step, which overshadowed the effect of the work hardening. It is stated in literature that magnesium stearate adhered on the surface area and formed a film around the particles during mixing.[8] This resulted in interferences in particle bonding

Correspondence to: Peter Kleinebudde (Telephone: +49-211-81-14220; Fax: +49-211-81-14251; E-mail: kleinebudde@hhu.de)

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Table 1. 10%, 50%, and 90% Quantiles of the Particle Size Distribution of the Starting Materials (μm) (Mean ± SD; $n = 3$)

	MCC	MCC (High Density)	Magnesium Carbonate	Powder Cellulose	Lactose
x_{10}	29.36 ± 0.18	24.67 ± 0.32	5.76 ± 0.25	26.55 ± 0.08	3.77 ± 0.03
x_{50}	103.37 ± 0.27	102.37 ± 0.98	31.18 ± 0.36	66.59 ± 0.54	26.93 ± 0.15
x_{90}	219.57 ± 0.06	207.95 ± 0.58	69.83 ± 0.30	134.53 ± 2.56	91.82 ± 0.28

during the compression leading to lower tensile strength. The sensitivity for the reduction in strength with increasing lubricant amounts depends on the compression behavior of the material. De Boer et al.[9] showed that materials undergoing a complete plastic deformation were most influenced. Brittle materials were less sensitive.[10] Moreover, the lubricant sensitivity could be related to the particle size of the excipient by Almaya and Aburub.[11] According to this, smaller particles will be less affected by magnesium stearate. Therefore, the lubrication of the fine powder material and coarser granule particles will result in different lubricant preconditions, which can offer a large impact on the results of the comparison between granule and powdered material.

Aim of this study was the critical evaluation of stated reasons for the reduced compactability after dry granulation with respect to the lubrication method. Internal and external lubrication were performed to investigate the influence of the lubrication on the phenomenon of the loss of reworkability for different plastically deforming as well as for brittle behaving materials. The impact of the particle size was examined in detail taking the impact of lubrication into account.

MATERIALS AND METHODS

Materials

Granulation and compression experiments were performed for five different excipients. Powder cellulose (Arbocel P290; JRS Pharma GmbH & Company, Holzmühle, Germany); two qualities of MCC, normal (Vivapur 102; JRS Pharma GmbH & Company) and high density (Vivapur 302; JRS Pharma GmbH & Company); α-lactose monohydrate (Granulac 200; Meggle Excipients and Technology, Wasserburg, Germany) and magnesium carbonate (Magnesia 18; Magnesia GmbH, Lüneburg, Germany) were used as received. Magnesium stearate (Parteck LUB; Merck Millipore, Darmstadt, Germany) was served as lubricant. Particle sizes of the starting materials are listed in Table 1. All materials were stored at least for one week at 21°C and 45% relative humidity (rH) for equilibration.

Methods

Roll Compaction/Dry Granulation

Roll compaction/dry granulation was performed with an instrumented roll compactor (Minipactor 250/25; Gerteis Maschinen + Prozessengineering AG, Jona, Switzerland). A gap width of 2 mm and a roll speed of 3 rpm were used. Ribbons were compacted with five different specific compaction forces (2, 4, 8, 10, and 12 kN/cm) and directly dry granulated through a 1 mm sieve. Therefore, a star granulator (Gerteis Maschinen + Prozessengenineering AG), rotating 120° clockwise and 180° counterclockwise, was used and the rotor speed was set to 40 rpm clockwise and 60 rpm counterclockwise. Approximately 2 kg of granules was produced and fractionated in different size classes. Portions of nearly 100 g were sieved (Retsch Vibrio AS 200 control; Retsch GmbH, Haan, Germany) for 5 min with an amplitude of 1.5 mm using meshes of 800, 630, 315, and 125 μm.

Particle Size Distribution

The particle size of the starting materials was determined by laser diffraction (Helos H1402+; Sympatec, Clausthal-Zellerfeld, Germany) using the dry dispersing unit (Rodos; Sympatec) and a dispersing pressure of 1 bar. Starting materials were measured three times and the particle size distributions were evaluated by the instrument software. The particle size distributions of granules from each specific compaction force were determined in triplicate by digital image analysis (Camsizer XT; Retsch GmbH). The X-Jet modul was used and a dispersing pressure of 0.3 bar applied to avoid agglomeration of the particles as well as a destruction. Quantiles of the particle size distribution within the fractions were calculated using the instrument software.

External Surface Area

External surface area of the granule fractions between 315 and 630 μm for each material was determined by air permeatry measurements in a Friedrich manometer[12] (self-construction of Evonik Industries, Darmstadt, Germany) equipped with a sample holder according to Gupte.[13] For external surface area determination, approximately 100 g of material was filled in the graduated powder container. The material was tapped 1250 times within the powder container (volumetric analyzer; J. Engelsmann AG Apparatebau, Ludwigshafen, Germany) to keep the granule bed porosities comparable. Flow time was determined in triplicate for each sample preparation and each material was measured three times. The detected flow times were corrected by the blank value of the instrument (3.92 s, $n = 100$).

External surface area was calculated according to Eqs(1). and (2) using an experimentally determined instrument constant $\left[\left(\int -\frac{dv}{h}\right) = 2.27\right]$, the corrected flow time and listed values for the air viscosity and water density at the measuring temperature.[14]

$$S_V^2 = \frac{1}{k}\frac{\rho_m g A}{L\int -\frac{dv}{h}}\frac{\varepsilon^3}{(1-\varepsilon)^2}\frac{t}{\eta}\ (cm^{-2}) \tag{1}$$

$$S_m = \frac{S_v}{\rho}\ \left(cm^2/g\right) \tag{2}$$

S_V, volume-specific surface area; k, particle shape factor; ρ_m, density of manometer fluid; g, gravitational constant; A, cross-sectional area of the powder bed; L, length of the powder bed; V, volume of manometer fluid in one arm from starting to end position; h, height difference of fluid level in the manometer arms; ε, porosity of the powder bed; t, permeation time; η, air viscosity; S_m, mass-specific surface area; ρ, powder density.