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Roll Compaction/Dry Granulation of Dibasic Calcium Phosphate Anhydrous—Does the Morphology of the Raw Material Influence the Tabletability of Dry Granules?

Simon Grote, Peter Kleinebudde*

Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Universitaetsstrasse 1, Duesseldorf, Germany

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ABSTRACT

The influence of raw material particle morphology on the tabletabilty of dry granules was investigated. Therefore, dibasic calcium phosphate anhydrous was used as a model material. One milled grade, 2 agglomerated grades with different porosities, and a functionalized structure, that is, an agglomerate formed by very small primary particles, were included. Particle size, density, and specific surface area of raw materials were measured. The starting materials and 2 fractions of dry granules were compressed to tablets. The tabletability of granules was compared to that of the powders and the influence of specific compaction force, granule size, and lubrication on tablet tensile strength was evaluated. All materials showed a loss in tabletability induced by a previous compaction step but to a varying extent. Only in case of the functionalized calcium phosphate morphology, this effect depended on the specific compaction force. In contrast to the other materials, the tabletability of functionalized calcium phosphate was influenced by the granule size. This effect was not related to an overlubrication as internal and external lubrication resulted in similar tensile strengths. A clear influence of the particle morphology on tablet strength was demonstrated by the study. The functionalized structure showed aspects of a more plastic deformation behavior. The functionalized dibasic calcium phosphate and the more porous agglomerate performed as potential filler/binder in the field of roll compaction/dry granulation.

Introduction

Roll compaction/dry granulation (RCDG) is a frequently used technique for the enlargement of particle size.[1] The main advantage of the process is the absence of liquids, this enables the granulation of hydrolysis sensitive substances and likewise reduces the costs by the absence of a drying step. In times with increasing interest in continuous manufacturing, the possibility to implement the process in such a production line is another benefit.[2] Nonetheless, this work dealt with one of the main disadvantages of RCDG. Often, the strength of tablets produced from dry granules is reduced compared with tablets of the equivalent powder mixture.[3] In the past, different authors focused on this problem and identified various reasons and influences.

One of the first proposed concepts refers to “work hardening”. Malkowska and Khan[4] claimed the entanglement of dislocations on particle level as reason for an increased resistance toward recompression. Other authors focused their investigations on granule level. Sun and Himmelspach[5] identified the reduced surface area of granules and the therefore decreased potential bonding area as negative influence on the granule tablet strength. Furthermore, they found out that this effect was mainly related to materials with a plastic deformation behavior.[6] Granules produced from a brittle raw material broke during the tableting process, and the rearrangement of surfaces made the effect of the granule size negligible. The reduced tablet strength caused by size enlargement can be connected to a potential overlubrication of granules, more pronounced in case of plastic materials as well. By using the same amount of lubricant for granules and powders, the amount of lubricant per area increased for granules caused by the reduced surface area. As a result, the bonding strength in the tablet was reduced, and the tensile strength decreased.[7]

Beside the bonding area of a material, the deformation behavior strongly influences the strength of produced tablets. Deformation behavior is often related to the porosity of particles. Therefore, granule porosity was identified as an important influence factor. Nordström and Alderborn[8] described that the ability of granules to

* *Correspondence to:* Peter Kleinebudde (Telephone: +49-211-8114220; Fax: +49-211-8114251).
E-mail address: Kleinebudde@hhu.de (P. Kleinebudde).

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form tablets with a sufficient mechanical strength increased with higher porosity. Above a critical level of compression pressure, the agglomerates collapsed into the primary particles, and the strength of the corresponding tablet was similar to the directly compressed tablet. With increasing granule porosity, the critical compression pressure was lower. Other authors described the influence of the applied specific compaction force during RCDG. An increased specific compaction force induced a loss of granule porosity and thereby increased the resistance toward recompression during tableting. The result was a loss of tabletability of dry granules according to the applied specific compaction force.[9]

The influence of raw material particle size on the granule and tablet properties was demonstrated for microcrystalline cellulose (MCC).[10] Smaller particles led to coarser granules and tablets with a higher tensile strength. The authors explained these findings with increased cohesion properties due to the higher surface area of smaller particles. Nevertheless, the choice of smaller starting particles can compensate the loss of tabletability compared with larger particles of the same material but cannot prevent the loss in tabletability induced by increasing specific compaction forces. Mosig and Kleinebudde[11] showed that in comparison to materials like MCC or magnesium carbonate, the tablet strength of a milled alpha-lactose monohydrate was not affected by previous RCDG even at higher specific compaction forces. This cannot be explained only by the fragmentation tendency of lactose, as magnesium carbonate was also described to have a brittle deformation behavior.[12] The authors assumed that the raw material morphology may influence the loss in tabletability. The used magnesium carbonate consisted of highly porous agglomerates, in contrast to the denser primary particles of lactose. A previous compression may have induced a loss in porosity of an agglomerated raw material and therefore increased the resistance toward recompression. As a result, the tablet tensile strength decreased.[11] Based on the findings of Mosig and Kleinebudde[11] it was hypothesized that the tensile strength of granule tablets from dense particles of a brittle material was unaffected by a previous RCDG, whereas with an increasing porosity of the starting material, the loss in tabletability increased. Based on this consideration, the present study dealt with the influence of the morphology and particulate architecture of the raw material of the brittle[13,14] dibasic calcium phosphate anhydrous (DCPA) on the tablet properties of granules with a special focus on different porosities of the particles.

Material and Methods

Material

Four different grades of DCPA were included in this study. A milled grade, DI-CAFOS A12 (Milled DCPA) and 3 grades containing agglomerated particles of different porosities: DI-CAFOS A60 (Agglomerate A) a dense agglomerate, DI-CAFOS A150 (Agglomerate B) with an increased porosity and Fujicalin, with a functionalized structure (Functionalized DCPA). The functionalized particles consisted of very fine particles,[15] agglomerated by spray drying of the aqueous dispersion. Chemische Fabrik Budenheim KG (Budenheim, Germany) donated all DI-CAFOS, whereas Fuji Chemical Industry (Toyama, Japan) donated the Fujicalin. All materials were stored under climatic controlled conditions (21°C, 45% rH) for 2 weeks before processing.

Production Methods

Roll Compaction/Dry Granulation

All raw materials were roll compacted on a Mini-Pactor 250/50 (Gerteis, Jona, Switzerland). Different specific compaction forces (3, 6, 9, and 12 kN/cm) were applied, and the gap size of 2 mm was maintained by automatic gap control. Smooth rolls with a diameter of 25 cm and a width of 2.5 cm were used combined with a rim roll sealing system and a roll speed of 3 rpm. The ribbons were milled with an oscillating star granulator through a 1000 μm sieve using a granulator speed of 40 rpm and an angle of 120° clockwise and 60 rpm and 180° counterclockwise.

Tablet Manufacturing Process

Prior to tableting, all granules were fractionated on a sieve tower (Retsch, Solingen, Germany) using sieve sizes of 160, 355, 630, and 800 μm. The sieving time was 5 min, and the amplitude was set to 1.5 mm. All powders and granules were blended for 2 min (Turbula blender; Willy A. Bachofen AG Maschinenfabrik, Muttenz, Switzerland) with 0.5% magnesium stearate (Parteck LUB MST; Merck, Darmstadt, Germany) as lubricant. Compression was performed on an instrumented rotary die press (PressIMA; IMA Kilian, Cologne, Germany). Flat-faced punches with a diameter of 8 mm were used to produce tablets with a weight of 200 ± 2 mg. A speed of 10 rpm was adjusted, and pressures of 60, 99, 139, 199, 239, and 298 MPa were applied.

For evaluation of potential overlubrication, some tablets made from granules were lubricated externally by using an eye-shadow applicator. In case of the milled starting material, the die was filled manually due to poor flow properties.

Analytical Methods

Scanning Electron Microscopy

Samples were sputtered (MSC 1T; Ingenieurbüro Peter Liebscher, Wetzlar, Germany) with 12 nm of gold to avoid charging effects and to increase the resolution. A scanning electron microscope (Phenom G2 pro; Phenom World, Eindhoven, the Netherlands) was used to analyze particle shape and morphology. Pictures were taken using vacuum and an operating voltage of 5-10 kV.

Determination of Particle Size Distribution

Particle size distribution of the different types of DCPA was measured by laser light diffraction (Mastersizer 3000; Malvern Instruments, Malvern, UK). The dry dispersion unit Aero S was used to disperse the samples. Dispersion pressure was set to 2 mm bar, and the powder feed rate was adjusted during the process for an optimal detector obscuration of approximately 6%. The volume size distributions were calculated using the Mie theory. All materials were measured in triplicate.

X-Ray Powder Diffraction

X-ray powder diffraction was performed using an X'Pert PANalytical PRO X-ray diffractometer (PANalytical, Almelo, the Netherlands) using Cu Kα radiation (λ = 1.54 Å), and acceleration voltage and current of 45 kV and 40 mA, respectively. The samples were scanned in reflectance mode between 5° 2θ and 35° 2θ with a scan speed of 0.067° 2θ/s and a step size of 0.026° 2θ. Data were collected and analyzed using the software X'Pert Data Collector (PANalytical).

Particle Density

Particle density of the powders was measured using helium pycnometry (AccuPyc 1330; Micromeritics, Norcross, GA). Measurements were performed at 25 ± 0.1°C to exclude the influence of changes in temperature. Measurements were performed in triplicate.

Nitrogen Adsorption

The specific surface area of all raw materials was determined in triplicate using the surface area and porosity analyzer Tristar