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Roll compaction/dry granulation: Suitability of different binders

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ABSTRACT

As dry granulation as a continuous process becomes steadily more important, the interest of different materials and their processing is growing. Binders are of high importance as they have to compensate granule hardening, reduce the fines, and ensure adequate tablet tensile strengths.

A simple formulation was used for roll compaction/dry granulation with subsequent tableting to produce granules and tablets, containing paracetamol (70% w/w), a filler and a binder (10%). With this formulation other influences were negligible and the influence of the binder was almost isolated. Eight different binders were compared with special attention to raw material properties. Six of them were cellulose based and two of them were based on povidone.

Granule size distributions were typically bimodal. With the same method of preparation, large differences between the formulations occurred. The median particle size of granules differed from 200 μm, up to barely 700 μm. The larger the resulted particles, the higher was the tensile strength after tableting. Tablets with fine grades of HPC and copovidone achieved highest tensile strength exceeding 2.5 MPa at a compaction pressure of 350 MPa. Formulations with other binders were inferior, but mostly adequate. MCC performed insufficient and led to capping.

1. Introduction

The agglomeration of powders to granules is often a necessary procedure in manufacturing tablets, especially for the improvement of flowability. This is in particular important as many active pharmaceutical ingredients are micronized and show a poor flowability. There are multiple techniques to proceed, widely used is wet granulation (Parikh, 2005), in which a liquid or a binder solution is sprayed on or fed to a powder bed. Another possibility is to work without any liquids and produce granules via roll compaction/dry granulation (RCDG). RCDG is a well-established technique, which is recently shifting more into the focus of attention (Vervaet and Remon, 2005). A rethinking of manufacturing processes is ongoing, traditional batch processes are questioned, heading towards continuous manufacturing. As roll compaction/dry granulation is a continuous process, the interest in different materials for dry granulation and their processing is growing. Interest is mounting too, as in the currently developing manufacturing classification system (MCS) for oral solid dosage forms (Leane et al., 2015), RCDG is considered first, when direct compression is not recommended. The MCS should help to rank the feasibility of different processing routes based on selected API properties and give an advice to select the best process for a product. If more information about the APIs and excipients are available and can be included into the selection process, the assessed risk for the selected manufacturing route can be more accurate.

During roll compaction, a ribbon is being produced out of different materials by densification between two counter-rotating rolls. Subsequently, the ribbons are milled to granules. Not only granules are resulting in RCDG, fines appear anyway during the milling process and by leaking material which bypasses the compaction zone without being processed (Inghelbrecht and Remon, 1998).

The ribbon, granules and later on the tablet hold together, mainly due to intermolecular forces (especially Van der Waals forces) and other material specific properties (e.g. mechanical interlocking connections). The specific surface area and deformation behavior of the materials can influence these effects (Nyström et al., 1993). Depending on what kind of materials are used and the applied compaction force, the cohesion can be strong, barely or insufficient.

A less adequate binding, brought in by the properties of materials, can increase the residual fines, which has a negative impact on the flowability (Gamble et al., 2010). This is one reason why a binder can be important in this application. Furthermore, these granules often show a reduced tabletability compared to direct compression. This effect is described in literature as work

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hardening (Malkowska and Khan, 1983). To improve the mechanical properties in the tablet and compensate work hardening, a binder is often added to the formulation. Different binders are available, most of them are based on cellulose, starch and povidone. Joneja et al. (1999) compared starch, povidone, hydroxypropyl cellulose (HPC) and methyl cellulose in a wet granulation process and evaluated, that HPC provided the best characteristics of tablets in their comparison, referring to lowering the ejection force during tableting and suppressing capping issues. Skinner et al. (1999) tested the same HPC, a fine particle HPC (Klucel EXF), in RCDG using different proportions and compaction pressures and focused on physical properties of the tablets and the drug release. They could show that with higher amounts of binder and higher compaction pressures during dry granulation capping could be eliminated. Inghelbrecht and Remon (1998) compared different HPMC grades to reduce the dust during compaction. They used micronized and non-micronized qualities of their materials but they did not observe a difference in granule quality or fines reduction. Turkoglu et al. (1999) optimized a process for the production of acetaminophen tablets from roll compacted granules. They concluded that 20% of HPMC K4 M resulted in mechanically acceptable tablets. Moroni (2001) compared copovidone, hydroxypropylmethylcellulose and microcrystalline cellulose and came to the conclusion that copovidone (Plasdone S-630) is a suitable binder in roll compaction. Herting et al. (2007) focused mainly on povidone based binders and demonstrated, that again copovidone (Kollidon VA 64 fine) and crospovidone (Kollidon CL-M) are suitable binders in dry granulation. They compared different grades and showed that fine grades performed better. Herting and Kleinebudde (2007) focused on the effect of raw material particle size on granule and tablet properties and demonstrated that this correlation is not only valid for binders. They used microcrystalline cellulose and theophylline in different grades and showed the fine grades performed better regarding tablet tensile strength and granule flowability.

Suppliers are steadily developing new dry binders. Nisso introduced a new hydroxypropylcellulose with very fine particles, which was already tested in direct compression (Nisso HPC, 2012), but there is no data available for dry granulation. This study picks up the results of previous studies, mentioned above and continues the binder comparison by adding several types of hydroxypropylcellulose in order to check if comparable results could be outlined for HPC and if other characteristics can be identified which makes a binder suitable for dry granulation. This information could help to gain knowledge about different binders and build a database, which could be used as information platform e.g. for simplifying the formulation development.

2. Materials and methods

2.1. Materials

2.1.1. Raw materials

Mainly two different types of binders were used, cellulose based and povidone based. The cellulose based binders were the following: MCC (Avicel pH 101, FMC Biopolymer, USA) a microcrystalline cellulose, which is a typical excipient in dry granulation, HPMC (Pharmacoat 603, Shin-Etsu, Japan), which is a hydroxypropylmethylcellulose often used as water soluble polymer in coatings, and various types of hydroxypropylcellulose, which differed in particle size or molecular weight: HPC L FP, HPC SSL, HPC SSL SFP (Nisso, Japan) and HPC EXF (Klucel EXF, Ashland, USA). Povidone based binders were PVP CL SF (Kollidon CL-SF, BASF, Germany), which is a crosslinked povidone grade with fine particles, typically used as disintegrant and PVP PVAc 64 F (Kollidon VA 64 fine, BASF, Germany) which is a povidone polyvinylacetate copolymer. Molecular weights of used binders are illustrated in Table 1.

Table 1
Molecular weight of used binders, based on literature research, determined with different methods.

Material	Average molecular weight
HPC L FP	140000 (Nisso HPC, 2012)
HPC SSL	40000 (Nisso HPC, 2012)
HPC SSL SFP	40000 (Nisso HPC, 2012)
HPC EXF	80000 (Klucel, 2012)
HPMC	16000 (Shin-Etsu, 2006)
PVP PVAc 64 F	45000–70000 (BASF, 2011)
PVP CL SF	non-determinable
MCC	36000 (Mallipeddi, 2009)

Active pharmaceutical ingredient was paracetamol (Atabay, Turkey) and dibasic calcium phosphate anhydrate (DI-CAFOS A150, Budenheim, Germany) was employed as filler. Magnesium stearate (Parteck LUB MST, Merck, USA) was used as lubricant. All materials were stored and processed in a climate-controlled room with 21 °C and 45% relative humidity.

2.1.2. Formulation

A high drug load was chosen, which was kept constant in all formulations (Table 2). As reference a binder free formulation was used in which the binder was replaced by filler material. The formulation was kept as simple as possible to minimize other influences and to isolate the influence of the binder.

2.2. Methods

2.2.1. Blending

The powders were weighed and blended for 20 min with a Turbula mixer type T2C (Willy Bachofen AG, Switzerland). The batch size was 500 g for each formulation.

2.2.2. Roll compaction/dry granulation

A roll compactor (Mini-Pactor, Gerteis, Switzerland) was used for dry granulation. In preliminary investigations different specific compaction forces were tested. In the following, all experiments were conducted at 5 kN/cm, a roll speed of 2 rpm and a gap width of 1.5 mm. The gap was automatically controlled by adjusting feeding and tamper auger speeds. A star shaped granulator was used with a changing direction of rotation (clockwise, counterclockwise) every two rounds and a rotor speed of 50 rpm. Furthermore, a sieve with 1 mm mesh width was installed.

2.2.3. Tableting

Granules were compressed to tablets using compaction pressures of 50–350 MPa on an instrumented rotary press (Pressima, IMA Kilian, Germany). The punches were flat-faced and had a diameter of 8 mm. The rotation speed was set to 10 rpm. External lubrication was performed by using an eyeshadow applicator in order to avoid lubrication effects. The applicator was slightly dipped into magnesium stearate, powdered off to lose excessive material and upper and lower punch, as well the die were lubricated. This process was repeated every three densification

Table 2
Formulation.

Material	Fraction [%]
Paracetamol, micronized	70
Dibasic calcium phosphate anhydrate	20 (30)[a]
Binder	10 (0)[a]

[a] Fraction in formulation without binder.