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Research paper

Increased compactibility of acetames after roll compaction

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ABSTRACT

A common technique for manufacturing granules in a continuous way is the combination of roll compaction and subsequent milling. Roll compaction can considerably impact tableting performance of a material. The purpose of this study was to investigate the influence of roll compaction/dry granulation on the compaction behavior of acetames, a class of active pharmaceutical substances, which are mainly used for the treatment of central nervous diseases. Some representatives of acetames were roll compacted and then compressed into tablets. Compactibility of granules was compared with the compaction behavior of the directly compressed drug powders. In contrast to many other materials, the roll compaction step induced an increase in compactibility for all investigated acetames. Specific surface areas of the untreated and the roll compacted drugs were determined by nitrogen adsorption. The raise in compactibility observed was accompanied by an increase in specific surface area during roll compaction.

1. Introduction

Roll compaction/dry granulation is a frequently used agglomeration technique in the pharmaceutical field and other industries for many different materials [1,2]. The compaction between two rolls is a continuous process. Primarily, the powder is transformed into a ribbon by passing two counter-rotating rolls. Then, the ribbon is deaggregated into granules in a subsequent grinding step. Advantages of roll compaction are lack of moisture, high throughput and easy scale-up. Therefore, the operational costs are reduced compared to wet granulation [3]. Besides a high amount of fines due to powder leakage and irregular dimensions of the produced granules [4], one main drawback of roll compaction is the decrease in compactibility of the obtained tablets compared to direct compression [5,6].

In literature, the phenomenon of loss in compactibility by roll compaction was discussed by several authors: Malkowska and Khan [7] defined the reduced compactibility as work hardening. They explained this phenomenon as a result of consumption of binding sites in the first compaction step. Other authors associated the reduced crushing force after roll compaction to an enlargement in particle size, leading to less available binding areas between the particles [8]. The loss on compactibility is described for plastically deforming as well as for fragmenting materials irrespective of the individual compaction behavior [9,10]. However, brittle fragmenting materials are less prone to decrease compactibility after roll compaction [11]. An increase in tablet crushing force after roll compaction has rarely been reported. For crystalline lactose, Riepma et al. [12] found that dry granulation had only a small effect on compactibility. Tablets made of α-lactose monohydrate and β-lactose exhibited comparable crushing force values when compressed directly or with previous dry granulation at the same pressure.

Origin of the present study was an observation in industrial practice. Compared to the directly compressed blend, tablets containing a high amount of levetiracetam exhibited enhanced crushing forces after roll compaction/dry granulation. Levetiracetam is an anticonvulsive drug, belonging to the group of acetames. In general, acetames are used in the treatment of central nervous diseases. Aim of the present study was to evaluate the influence of roll compaction on the compression behavior of some representatives of acetames and to investigate the mechanism causing the increase in crushing force after roll compaction. Since an influence of added materials should be excluded by design, the trials were conducted using the pure acetames only.

2. Materials and methods

2.1. Materials

The powdered drugs levetiracetam (Keppra®), seletracetam (in development), piracetam (Nootropil®) and brivaracetam (in development) were used as received from UCB Pharma SA (Brussels,

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Belgium). The particle size distribution was determined by laser diffraction, and the following results were obtained: levetiracetam x_{10} = 28 μm, x_{50} = 102 μm, x_{90} = 251 μm; seletracetam x_{10} = 6 μm, x_{50} = 320 μm, x_{90} = 615 μm; piracetam x_{10} = 139 μm, x_{50} = 281 μm, x_{90} = 451 μm; brivaracetam x_{10} = 29 μm, x_{50} = 226 μm, x_{90} = 571 μm.

Additionally, the particle size of levetiracetam was reduced by milling in a centrifugal mill (Ultra Centrifugal Mill ZM 200, Retsch, Haan, Germany) with a ring sieve size of 1 mm and a rotating speed of 18,000 rpm. Laser diffraction analysis resulted in the following values: x_{10} = 6 μm, x_{50} = 35 μm, x_{90} = 120 μm.

2.2. Roll compaction/dry granulation

The powdered drug substances and the milled levetiracetam were compacted in a roller compactor (Mini-Pactor, Gerteis, Jona, Switzerland) equipped with one smooth and one knurled roll. Diameter and width of the rolls were 25 and 2.5 cm, respectively. The gap between the rolls was kept constant at 3 mm. For levetiracetam, specific compaction forces of 9 kN/cm, 12 kN/cm, 15 kN/cm and 18 kN/cm were selected. For the trials, roll speed was adjusted to 3 rpm. At the specific compaction force of 15 kN/cm, levetiracetam was additionally processed at roll speeds of 1 rpm, 5 rpm and 7 rpm. A specific compaction force of 7 kN/cm was applied for seletracetam, piracetam and brivaracetam at a roll speed of 3 rpm. The obtained ribbons were directly granulated with a star granulator using a 1 mm sieve.

Additionally, levetiracetam was roll compacted/dry granulated in triplicate at 15 kN/cm to investigate the influence of multiple compaction on compactibility. Roll speed was adjusted to 3 rpm.

2.3. Compression

All powdered drugs and roll compacted granules were subsequently compressed on a rotary die tablet press (IMA Pressima, Kilian, Cologne, Germany) at a tableting speed of 10 rpm. Tablets of 1100 mg were produced using 19.0 mm × 10.2 mm oblong punches. Different pressures were applied depending on the individual compression behavior. Levetiracetam, brivaracetam and piracetam were compressed at 118 MPa, 205 MPa and 293 MPa, respectively, seletracetam at 90 MPa, 118 MPa and 205 MPa. The powdered drug substances brivaracetam and seletracetam and their granules were manually filled into the die. All powdered drugs and granules were compressed without lubrication due to their low sticking tendency.

2.4. Characterization of the samples

2.4.1. Particle size distribution

For the determination of the particle size distribution, the powdered drugs and the granules were investigated by laser light diffraction (Helos H1402/KF-Magic, Sympatec GmbH, Clausthal-Zellerfeld, Germany). The powder samples were dry dispersed with a pressure of 2.5 bar and a feed rate of 80% (Vibri, Rhodos T4.1, Sympatec GmbH, Clausthal-Zellerfeld, Germany). The granules made of levetiracetam were dry dispersed with a pressure of 0.5 bar. Particle size distribution of powdered levetiracetam was additionally measured with a dispersion pressure of 0.5 bar to allow a comparison with the granules. The measurements were performed in triplicate.

2.4.2. Resistance to crushing

The crushing force of the obtained tablets was measured using a hardness tester (HT1, Sotax, Basel, Switzerland) at a constant speed of 1 mm/s. Ten tablets of each formulation were analyzed, and their mean value was determined. The tablets were stored for 48 h at defined conditions (21 °C/45%RH) prior to testing.

2.4.3. X-ray powder diffraction

To evaluate the crystallinity of the powdered drugs and the granules, respectively, a XPERT-PRO diffractometer system (PANalytical B.V., Almelo, Netherlands) was used in reflection mode. Diffraction patterns were obtained at a voltage of 45 kV and a current of 40 mA. The samples were examined within a 2Θ scan range from 5° to 50° with a step size of 0.013°. The data were collected and analyzed with the associated software (XPert Data Collector, ver 2.2 h APPLAB, Austin, USA).

2.4.4. Nitrogen adsorption

The specific surface area of the drug substances and of the granules was measured by nitrogen adsorption. About 2 g of each sample was weighted in a sample tube and was then degassed on a SmartPrep (Micromeritrics, Norcross, GA, USA) for 1 h at a temperature of 60 °C using nitrogen as purge gas and further 24 h under vacuum at room temperature. The degassed sample was transferred to a Tristar 3000 (Micromeritrics, Norcross, GA, USA), where a mixture of nitrogen and helium flowed over the powder. Eight adsorption steps in the region of p/p_0 from 0.1 to 0.3 were measured. By calculating the adsorbed amount of nitrogen, the specific surface of the sample was determined using the equation according to Brunauer, Emmet and Teller. The measurements were conducted in triplicate.

2.4.5. Differential scanning calorimetry

Differential scanning calorimetry was performed using a DSC 1 calorimeter (Mettler-Toledo, Gießen, Germany). The temperature ranged between 25 °C and 150 °C with a scan speed of 10 K/min. An empty pan served as reference during the measurements. Each measurement was performed in duplicate.

3. Results and discussion

3.1. Compaction behavior of levetiracetam

The compactibility is one physicotechnical attribute of a material and is considered as the ability to be densified into a compact of a specific strength [13]. It directly impacts the tableting performance of a solid [14] and can be influenced by the granulation process and the composition of the starting material. The influence of roll compaction force and roll compaction speed on the compactibility of levetiracetam is shown in Fig. 1. As expected, the results depict increasing crushing forces with increasing tableting pressures, for the directly compressed system and the granules, respectively. Surprisingly, an increase in compactibility for levetiracetam was observed after roll compaction (Fig. 1a): the higher the applied roll compaction force, the higher the crushing force of the obtained tablets. Variation of the roll speed did not influence the crushing force of the produced tablets (Fig. 1b). As outlined above, roll compaction/dry granulation typically reduces the compactibility of a material compared to the uncompacted powder. In contrast to the well-known loss in compactibility, roll compaction enhanced the capability of levetiracetam to form strong compacts. In this context, the question arose whether multiple compaction affects the tableting behavior of levetiracetam. Bultmann [15] performed multiple compaction trials with microcrystalline cellulose and observed a decreased crushing force of the prepared tablets. For levetiracetam, the contrary observation could be made (Fig. 1a, multiple). By increasing the number of roll compaction cycles, a further increase in compactibility occurred. Resistance to crushing of the tablets made of multiple compacted granules was found to