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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

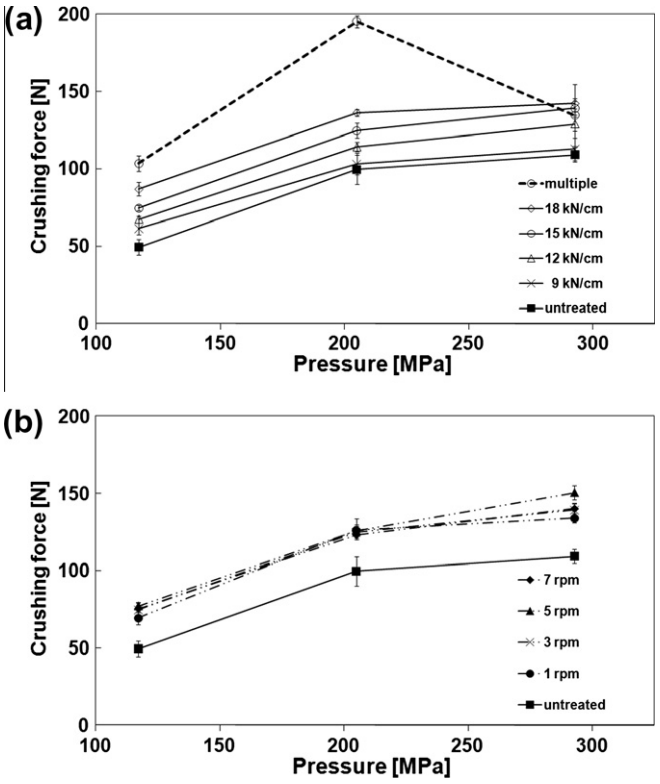

Fig. 1. Compactibility of levetiracetam. (a) Influence of compaction force. (b) Influence of roll speed on granules made at 15 kN/cm. Mean and standard deviation, $n = 10$.

be increased compared to the single compacted granules. Multiple roll compaction further increased the dry binding potential of levetiracetam being in contrast to Bultmann's findings for microcrystalline cellulose. By raising the tableting pressure up to 293 MPa, the resistance to crushing of tablets made of multiple compacted granules dropped due to capping and cracking phenomena. This may be due to the formation of intensive shear bands within the tablets at high compression loads [16,17].

3.2. Hypothesis – amorphization

In a study of a roll compacted macrolide antibiotic formulation, an increased compactibility and a reduced capping tendency were reported at tableting pressures above 100 MPa [18]. This was associated with a partly amorphization of the drug. Furthermore, milling of crystals can also induce an alteration in the solid state behavior of a material. Complete or partial changes into an amorphous form during mechanical treatment are known for other substances, e.g. piroxicam or budesonide [19], and might affect the deformability or the surface energy, i.e. the capability of the material to create interparticulate attractions [20].

The crystal structure of levetiracetam was investigated by X-ray diffraction analysis. From the diffraction pattern (Fig. 2), it is evident that the crystal structure was not significantly changed during the roll compaction step. The diffraction peaks before and after roll compaction were sharp and well defined, demonstrating a high degree of crystallinity. DSC measurements supported the interpretation of the results obtained by X-ray diffraction: each thermogram depicted only one sharp melting endotherm at approximately 116 °C (onset).

Hence, amorphization was not considered as the underlying cause for the increased compactibility observed.

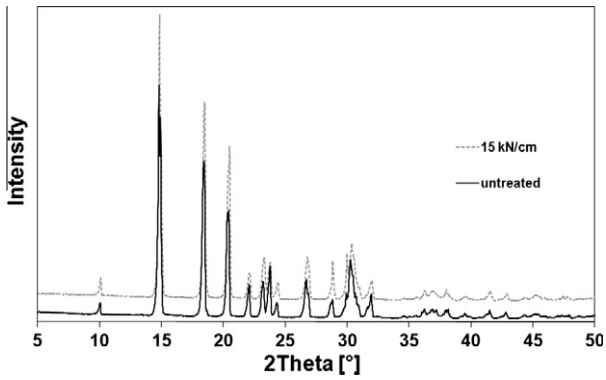

Fig. 2. X-ray diffraction pattern of levetiracetam before and after roll compaction (15 kN/cm).

3.3. Hypothesis – alteration in particle size

As shown in Fig. 3, increasing specific compaction force led to granules of higher sizes. Crushing forces of the tablets made of granules raised by increasing specific compaction force in the roll compaction step (Fig. 1a). Therefore, it might be assumed that a larger granule size is related to higher crushing force.

The influence of original particle size on tablet strength was discussed by several authors. In general, decrease in particle size of starting material results in stronger tablets by increasing the total amount of possible binding sites. However, conflictive results might be found in literature. Relationship between particle size and crushing force is rather complex and depends strongly on material properties. McKenna and McCafferty [21] studied the impact of changes in particle size on tensile strength for some directly compressible materials. They found higher mechanical resistance of lactose and starch compacts with decreasing particle size of the starting materials and suggested increased cohesive and frictional forces. Almost no influence of particle size on compact strength was observed for different sieve fractions of Avicel PH-101. Tablets of L-lysine monohydrate were found to crush at higher values with decreasing particle size of the starting material [22]. For particles larger than 710 μm, fragmentation of L-lysine reduced influence of initial particle size. Alderborn and Nyström [23] reported decreased tablet strength with increased particle size for acetylsalicylic acid, sodium citrate and lactose. No influence of particle size on compactibility could be determined for dicalcium phosphate and saccharose, which mainly fragment under pressure. In contrast to this, an increased tensile strength was obtained for coarse sodium chloride when starting material with increased

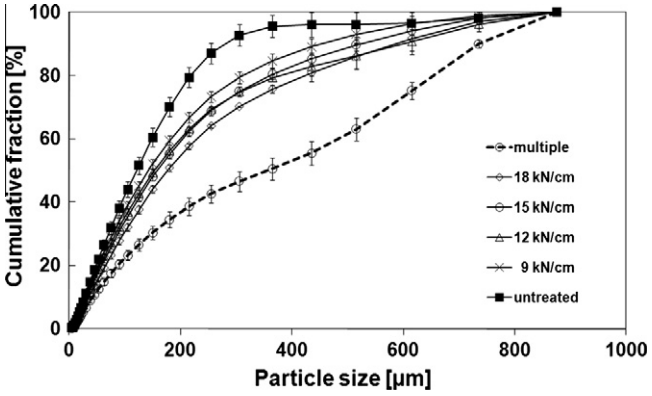

Fig. 3. Particle size distribution of untreated levetiracetam and of levetiracetam granules. Mean and standard deviation, $n = 3$.

particle size was used. Additionally, tableting speed and tableting pressure have been found to impact relationship between particle size and compact strength [24,25].

For roll compacted binary mixtures of microcrystalline cellulose and theophylline, a decrease in particle size of the staring materials could compensate insufficient crushing force after roll compaction [26].

As an agglomeration process, roll compaction/dry granulation typically induces an increase in particle size and thus a better flowability of a material [1]. A correlation can be found between the increase in compaction force and the size enlargement of the resulting granules [6]. As mentioned above, granule size enlargement is discussed as underlying cause for the observed reduced compactibility by roll compaction/dry granulation [8]. Thus, the contrary relation might be expected for levetiracetam. The increase in crushing force of levetiracetam tablets might be due to a decrease in particle size of levetiracetam induced by roll compaction/dry granulation. However, by increasing the applied compaction force, the median particle size increased from about 102 μm for the untreated levetiracetam up to 177 μm for the granules made at 18 kN/cm (Fig. 3). It should be noted that almost equal particle size distributions were obtained for the granules made at 12 kN/cm and 15 kN/cm. The highest increase in particle size was observed for the multiple compacted levetiracetam. Tablets compressed with this material displayed the highest resistance to crushing. Thus, a decrease in particle size can be excluded to explain the increase in compactibility after roll compaction/dry granulation.

3.4. Hypothesis – alteration in surface area

3.4.1. Milling trials

Particle size enlargement by roll compaction/dry granulation was associated with a decrease in surface area available for bonding [8]. Due to the unexpected enhanced compactibility, the contrary conclusion might be drawn for levetiracetam granules. It could be suggested that roll compaction/dry granulation induced a raise in surface area of levetiracetam irrespective of the observed enlargement in granule particle size. To follow-up on this hypothesis, milling of the levetiracetam was performed to increase its specific surface area. In this context, the milling step was supposed to lower the effect of roll compaction on the compactibility of levetiracetam during tableting as this would limit the possible increase in specific surface area during roll compaction. Milled levetiracetam was compacted at 15 kN/cm and compressed to tablets. The resistance to crushing was compared (i) with the milled levetiracetam directly compressed, (ii) with the unmilled levetiracetam directly compressed and (iii) with the unmilled compacted levetiracetam (Fig. 4).

Compared to the unmilled systems, both the milled uncompacted and the milled compacted levetiracetam exhibited increased crushing forces due to an increase in available surface area for binding sites between the particles. It should be noted that almost equivalent resistance to crushing values were obtained for tablets compressed at the same pressure from milled levetiracetam powder and roll compacted granules, respectively. Thus, for the milled levetiracetam, the prior compaction step had almost no effect on the resistance to crushing. Therefore, the hypothesis of an increased specific surface area could be supported.

3.4.2. Determination of surface area

Vromans et al. [27] detected a relationship between the crushing force of tablets and the internal surface area, i.e. the surface area within a tablet for different types of lactose. They postulated a correlation between the amount of binding sites and the specific surface area of a tablet measured by nitrogen adsorption.

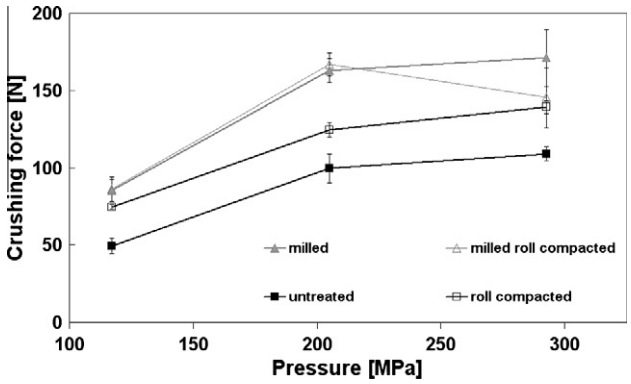

Fig. 4. Compactibility of milled levetiracetam in comparison with the compactibility of the unmilled material. Mean and standard deviation, $n = 10$.

To gain information about a possible change in surface area during roll compaction, the specific surface areas of powdered levetiracetam and granules were determined by BET analysis. Fig. 5 depicts the crushing force as a function of the specific BET surface area. It could be shown that roll compaction/dry granulation increased the specific surface area of unmilled levetiracetam. The general tendency was an increase in crushing force with increase surface area. In accordance with the presented data of compactibility (Fig. 4), the specific surface areas of the milled and the milled and subsequently compacted levetiracetam were almost equal, 0.48 m^2/g and 0.46 m^2/g, respectively. Generally, a roll compaction step is associated with a decreased surface area available for bonding for a plastically deformable material. Different grades of microcrystalline cellulose exhibited decreased surface area after roll compaction/dry granulation and thus a reduced compactibility [8]. Herting and Kleinebudde [6] described a decreased surface area of microcrystalline cellulose granules with increased roll compaction pressure. Comparable results were achieved by Patel et al. [28] for ibuprofen. In contrast, an increase in surface area after roll compaction was reported by Freitag et al. [9] for different types of magnesium carbonate and could be correlated with the strongly fragmented behavior of these substances. At the same time, a loss in compactibility after roll compaction/dry granulation was reported for brittle materials despite of their increase in surface area.

For levetiracetam, the results suggested a complex relationship between surface area and specific surface area (Fig. 5). Especially for granules made at increased specific compaction forces, raise in tablet crushing force may not be only explained by the alterations in specific surface area.

Another independent influence factor on the final crushing force of the tablets might be a change in surface energy of the

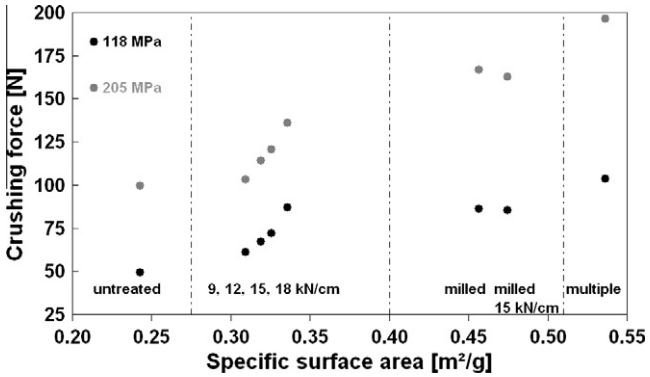

Fig. 5. Relationship between specific surface area and crushing force of levetiracetam.

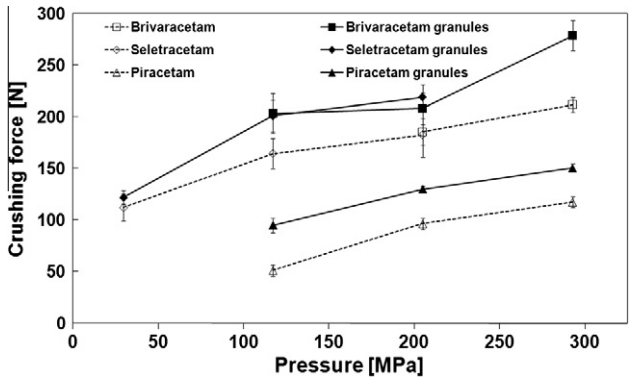

Fig. 6. Compactibility of different acetames. Mean and standard deviation, $n = 10$.

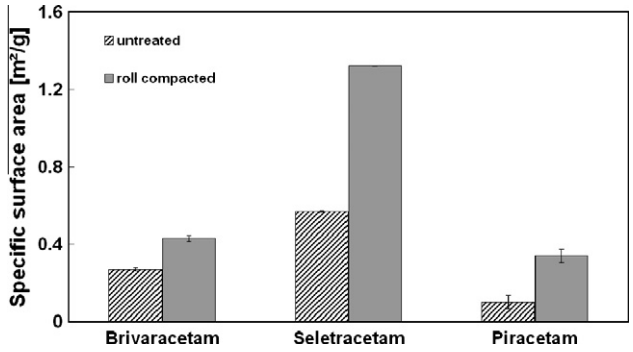

Fig. 7. Specific surface area values of different acetames. Mean and standard deviation, $n = 3$.

starting materials induced by roll compaction/dry granulation. Since highly energetic particles tend to agglomerate to reduce their surface energy, elevated compactibility of roll compacted granules might be explained by an increase in surface energy after roll compaction/dry granulation. Charmathy et al. [29] reported differences in compactibility of two batches starches, which were virtually identical in common physical test procedures. Different compaction behavior was correlated with alterations in surface energy by an additional washing step in the manufacturing of one batch. For sprayed dried lactose with varying amounts polysorbate, it was found that surface energy influenced compactibility, however, microstructure and compressibility were almost unaffected [30].

3.5. Investigations on further acetames

The influence of roll compaction/dry granulation on further representatives of acetames was examined: seletracetam, piracetam and brivaracetam. All investigated acetames exhibited an enhanced compactibility after roll compaction/dry granulation (Fig. 6). In accordance with the results of levetiracetam, the increase in crushing force was accompanied by an increase in specific surface area measured by nitrogen adsorption (Fig. 7). No direct correlation could be found between the relative increase in compactibility and the relative increase in surface area for each acetame. However, both observed effects seem to be characteristic behaviors of the group of acetames.

4. Conclusions

The process of roll compaction had a significant influence on the compactibility of the investigated acetames. In contrast to common literature findings, a higher compactibility was found for the dry granulated systems compared to the directly compressed systems for all investigated acetames. The increase in crushing force of the roll compacted materials was associated with an increase in the specific surface area. For levetiracetam as a representative of the class of acetames, crushing force tends to increase with increase in surface area of the processed starting materials. Surface activation by roll compaction might be taken into account as additional impact factor on compaction performance of acetames.

Supplementary investigations are required to gain deeper understanding of the different variables influencing compaction behavior and processability of acetames.

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