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Crystal habit and tableting behavior

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Abstract

The tableting behavior of drugs can be affected by changes in the crystal habit. Different crystal habits of the common analgesic drugs ibuprofen and acetaminophen were prepared. Their tableting behavior was characterized. In the case of ibuprofen, a plate-shaped crystal was compared with the common needle-shaped form. In the case of acetaminophen, plate-shaped and prismatic crystals of two different particle sizes were prepared. The aim was to find a crystal form that is suitable for direct compression with only a low amount of excipients. This requires a substance that forms stable compacts at low punch forces, having a good flowability and only a low tendency to stick to the punches. In order to compare the tableting behavior of different substances, a comparative factor (*T*-factor) was calculated, based on typical parts of the punch force/displacement-profile and properties of the resulting compact. This method works with low amounts of substance and allows a rapid reproducible determination of the tableting behavior. The method was evaluated by characterizing different typical excipients normally used for the production of tablets.

Keywords: Tableting behavior; Preformulation studies; Crystal habit; Heckel-plot; Ibuprofen; Acetaminophen

1. Introduction

Tablets are the most common dosage form. Production should be as economical as possible. Especially in the case of drugs that have to be administered in high doses, the excipient amount should be kept down. The production should only comprise a few working steps. For example, a granulation step is time- and energy-intensive and exposes the formulation to water or solvent and heat. That is why a directly compressible powder is preferred which has free flowing properties, is able to form stable compacts at low punch forces and does not stick to the punches.

By changing the crystal structure, the compression and tableting-behavior can be affected. For example, acetaminophen can exist in two polymorphic forms: The common crystal form is the thermodynamically stable form I (monoclinic) which leads to unstable tablets with high capping tendency due to a stiff construction of the molecules inside the crystal. Form II (orthorhombic) shows better compression behavior (Martino

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et al., 1996). Its physical structure contains sliding planes. The disadvantage of the orthorhombic form is the possible transition to form I.

But not only changes of the crystal lattice can influence the physicochemical properties of a substance. Isomorphic crystals can also show different properties due to changes in the crystal habit. Habit is the description of the outer appearance of a crystal. If only the external shape of a growing crystal is affected without changing the internal structure, a different habit results. In the case of tableting behavior, a free flowing powder can be filled homogeneously into the die. Depending on the alignment of the crystals in the die, the contact area between the particles can vary. Therefore, an exclusive variation only of the external crystal structure (the crystal habit) can optimize substance properties. The effect of crystal habit on tablet properties was demonstrated by Shell (1963). He described crystal habits by measurement of preferred particle orientation that is related to the compression characteristics of the powder. Optimization of tableting behavior of excipients was carried out by Staniforth et al. (1981). They examined alternative crystallization conditions in order to design a directly compressible mannitol and obtained a highly porous surfaced mannitol by using a special crystallization medium. Garekani et al. (1999) compares the compressibility (using the Heckel-plot) of different crystal forms (polyhedral and thin plate-like crystals) of acetaminophen. The plate-like crystals prepared in this study had a particle size of ≈ 200 μm, polyhedral crystals had a mean particle size of 100 μm. Differences in compressibility were found as the polyhedral crystals showed the higher slope in the Heckel-plot. Jbilou et al. (1999) examined the properties of ibuprofen. A directly compressible ibuprofen was developed, not by crystal engineering but by spherical agglomeration.

Especially for drugs that have to be administered in high doses (which means that there is a high drug load in the tablet), tableting behavior of the pure drug plays an important role. It is known that most drugs can exist in different (pseudo-) polymorphic forms. But even isomorphic forms can exhibit different crystal habits. The choice of the suitable crystal form can affect the physicochemical properties of the drug. It is important to have the drug substance in the final form fairly early in the development scheme (Carstensen et al., 1993). Accordingly, in early-phase-development the appropriate crystal has to be found by analyzing powder flow characteristics, dissolution and tableting properties, so that the biopharmaceutical and manufacturing properties can be affected and consequently optimized. At this stage of development, in most cases there is only a small amount of drug available in high quality. Therefore, especially for characterizing the tableting properties of different crystal forms, a method has to be used which needs only low quantities of materials, but which allows the development of reliable data. For this reason, the T-factor used in this study for comparing the tableting behavior can be used.

For characterizing the processability of a substance on a tableting machine, different terms characterizing the forming of a tablet have to be distinguished (Joiris et al., 1998). The compressibility describes the reduction of the volume in the die at applied punch force. It is characterized by the relation powder density versus force. Compactability describes the formation of stable compacts under the effect of compression. It is characterized by the relation stability versus density of the resulting compact. The properties of the resulting compact depending on the applied punch force are described by the term tabletability. It is characterized by the relation stability versus force. When calculating the T-factor, the compressibility (represented by the factor $s_{F\max}/F_{\max}$) and the tabletability (crushing strength/$F_{\max}$) are considered. Another important aspect in the tableting process is the relationship between elastic and plastic energy. Elastic deformation is a reversible phenomenon hindering the formation of stable tablets. Plastic deformation and brittle fracture are irreversible and promote tableting.

In the literature, several methods for characterizing the compressibility are given (Panelli and Filho, 1998). The most common is the Heckel-plot (Heckel et al., 1961). The density of the powder at different applied punch forces is calculated. A high slope in the plot (density versus

pressure) shows high compressibility. However, the measurement by the static Heckel-plot (calculation is based on the force-maximum) requires measurements at different maximal punch forces. Therefore, this method is not suitable for substances that are only available in very small amounts. Many other equations (Table 1) have been proposed to support a relation between porosity and applied pressure.

To compare different crystal habits of ibuprofen and acetaminophen, a punch force/displacement-profile of the pure drug and powder mixtures was recorded using an instrumented single punch tablet machine press. By mathematical calculation based on characteristic data of the compression process and the resulting compact, a factor (T-factor) for comparing the tableting properties was obtained. In a first step, the method was evaluated by measuring different excipients.

2. Materials

Avicel® PH 102 (FMC Corp. PA), AcDiSol® (FMC Corp.), Elcema® G250 (Degussa, Frankfurt, Germany), Emcompress® (Mendell, Patterson, NY), Granulatum simplex (Ph. Eur. quality), maize starch, mannitol, PharmDC® 93000 (all Cerestar, Krefeld, Germany), sieved lactose (SpheroLac®100, Meggle, Wasserburg, Germany) and preagglomerated lactose (Tablettose®, Meggle) were of Ph. Eur. quality. Ibuprofen and acetaminophen were supplied by BASF AG (Ludwigshafen, Germany). Methanol and isopropyl alcohol were obtained from Merck KG (Darmstadt, Germany). Water was used in double-distilled quality.

3. Methods

3.1. Crystallization procedures

Crystals that are available on the market are called habit I (Acetaminophen crystal resp. Ibuprofen 50, BASF). The other crystal forms were prepared by the following method: all crystallizations were carried out using the solvent change method. A double-walled glass vessel with thermostat was used. First, the drug was dissolved in the solvent. The concentration was below the saturation concentration to avoid remaining crystals that would affect the crystallization process. After precipitation by the addition of water, the crystals were collected by filtration under vacuum. They were dried in a desiccator under vacuum.

3.1.1. Ibuprofen

A total of 45 g ibuprofen was dissolved in 100 ml of isopropyl alcohol at room temperature. Precipitation was carried out by solvent change method as described by Rasenack et al. (2001).

3.1.2. Acetaminophen

3.1.2.1. Large prismatic crystals (= habit II). Acetaminophen (30 g) was dissolved in 100 ml

Table 1
Most common equations for characterizing the compressibility

Author	$y = mx + b$		
Heckel	$\ln\left(\frac{1}{1-D}\right) = k*P + A$	Density versus pressure	D = rel. density at pressure p
Konopicky	$\ln\left(\frac{1}{1-D}\right) = k*P + \ln\left(\frac{1}{1-D_0}\right)$	Density versus pressure	D = rel. density at pressure p; D_0 = rel. density without pressure
Balshin	$\ln p = -L*V_r + c$	Pressure versus volume	p = pressure; V_r = spec. volume
Ge	$\log\left[\ln\left(\frac{1}{1-D}\right)\right] = k*\log P + c$	Density versus pressure	D = rel. density at pressure p

methanol at 40 °C. Precipitation was carried out by adding 300 ml of water (5 °C) continuously over 120 min under stirring conditions. During this process, the temperature was lowered continuously to 10 °C. The crystals were collected immediately.

3.1.2.2. Small prismatic crystals (= habit III). A total of 30 g acetaminophen was dissolved in 100 ml methanol at 40 °C. Precipitation was carried out by adding 300 ml of water (5 °C) continuously over 30 min under stirring conditions. During this process temperature was lowered continuously to 20 °C. The crystals were collected immediately.

3.1.2.3. Large plate-like crystals (= habit IV). Acetaminophen (30 g) was dissolved in 100 ml methanol at 40 °C. Precipitation was carried out by adding 300 ml of water (5 °C) over 30 s under stirring conditions. The resulting suspension was cooled down to 2 °C under stirring over 2 h to induce further crystallization and crystal growth.

3.1.2.4. Small plate-like crystals (= habit V). Acetaminophen (30 g) was dissolved in 100 ml methanol at 40 °C. Precipitation was carried out by adding 300 ml of water (5 °C) over 30 s under stirring conditions. The crystals were collected immediately.

3.2. Characterizing techniques

3.2.1. Method for tableting

The compressions were carried out using a Fette Exacta 11 (Wilhelm Fette Inc., Schwarzenbek, Germany) single punch press, equipped with flat punches of 12 mm diameter. Data (punch force, displacement, time) were recorded (piezoelectric, resp. inductive).

For measuring the mechanical properties (crushing strength) of the compacts a Pharma Test PTB300 (Frankfurt, Germany) was used.

To obtain comparable data, constant true volumes were poured manually into the previously cleaned die. The amount of powder required was calculated from the true density. Every powder was tableted ten times. The R.S.D. of the calculated T-factors was $< 5\%$.

3.2.2. True density

True density of excipients and drug substances were determined using the helium gaspycnometer AccuPyc 1330 (Micromeritics Instrument Corp., Norcross).

3.2.3. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (DSC7, Perkin Elmer, CT) was used. The equipment was calibrated using indium and zinc. Samples were heated at 10 °C/min in sealed aluminium pans under nitrogen atmosphere. The onsets of the melting points and enthalpies of fusion were calculated by the software (Pyris, Perkin Elmer).

3.2.4. X-ray diffractometry

Powder X-ray diffraction (PXRD) patterns were collected in transmission using an X-ray diffractometer (Stoe, PSD supply unit, Darmstadt, Germany) with Cu Kα1 radiation (monochromator: Germanium) generated at 30 mA and 40 kV. Powder was packed into the rotating sample holder between two films (PETP).

3.2.5. Flowability

Flowability was quantified using avalanche analysis to quantify powder flowability (AeroFlow—TSI Modell 3250, TSI, Aachen, Germany). The powder sample was put in a cylindrical drum that slowly rotated about its horizontal axis at a constant rate. When the incline angle of the powder's surface became too great for its molecular structure to support, the powder collapsed down toward the bottom. This event is referred to as an 'avalanche'. The time interval between avalanches and the amplitude of the avalanche is recorded. Before measurement, the powder was disagglomerated through a sieve (710). Some 60 ml of each powder were used and measurement was carried out over 300 s with 1 UpM. Factors characterizing the flowability are the mean time between avalanches, the scatter and the maximum time. A high mean and high max show cohesivity; irregular flow characteristics result in a high scatter.

Table 2
Readings used for the calculation

Factor	Unit	
Plastic deformation	%	Percentage of the plastic energy
Total energy	Nm	Plastic and elastic energy
Crushing strength F_c	N	Stability of the compact
F_{max}	kN	Upper punch force (maximum)
s_{Fmax} (up)	mm	Displacement of upper punch in F_{max}
e	cm^3	Volume (true) tableted

3.2.6. Scanning electron microscopy (SEM) and microscopy

Electron-micrographs of crystals were obtained using a scanning electron microscope (Philips XL 20, Philips, Eindhoven, Netherlands). Samples were fixed on an aluminium stub with conductive double-sided adhesive tape (Leit-Tabs, Plannet GmbH, Wetzlar, Germany) and coated with gold in an argon atmosphere (50 Pa) at 50 mA for 50 s (Sputter Coater, Bal-Tec AG, Liechtenstein). Photographs of the big acetaminophen crystals (habit II and IV) were obtained using a microscope (Zeiss, Heidenheim, Germany).

3.2.7. Method for comparing the tableting properties

Due to the fact that most of the common ways only analyze the compressibility and do not look at the resulting compacts (= tabletability), here another way for comparing the tableting properties was evaluated. For determination of the tableting properties (especially in view of suitability for direct compression) of a drug, this is an important aspect. For these reasons, a method was developed which includes the quality of the resulting compacts (inserted in the equation as crushing strength). Together with other properties, such as flowability or sticking to the punches, a complete evaluation of a drug/powder mixture can be achieved.

The T-factor [$J \times cm^4$] is calculated from characteristic data (Table 2) using Eq. (1). A high value shows good tableting behavior. The equation is suitable for comparing different powders at the same machine parameters: the values of the most important parameters do not seem to be transferable when using different adjustments. So for comparability, the same experimental set-ups (same adjustment of upper and lower punch, same true volume of each substance compressed) are required.

$$T = \text{plastic def} \times \text{energy}_{\text{total}} \times \frac{F_c}{F_{\max}} \times s_{F\max(\text{up})} \times e \quad (1)$$

The relation between elastic and plastic deformation is important for the compaction behavior of any substance. Beside this, the absolute value for the plastic energy (in relation to the maximum of punch force) is important. The factor (plastic deformation [%] × total energy [Nm]) characterizes the effectiveness of the compression process. The factor ($s_{F\max\ (up)}$ [mm]/F_{max} [kN]) characterizes the compressibility (analogous to the Heckel-plot): a high displacement of the upper punch at a low maximal force shows good compressibility (corresponding to a high slope in Heckel-plot). The factor ($F_c[N]/F_{max}$ [kN]) represents the properties of the resulting compact (characterizing the tabletability). The adjustment of the tableting machine and the compressed powder-volume (true volume) must be the same in one run—small deviations in weight are corrected by the factor e. If the die is overfilled, the maximum punch force increases and thus the plastic deformation decreases. This would effect a wrongly lowered T-factor. Therefore, the volume e is inserted in the equation for correction of small deviations in compressed volume.

4. Results and discussion

4.1. Comparison of different excipients

The excipients were chosen to represent a variety of deformation characteristics—microcrystalline cellulose (Avicel®) and pregelatinized starch (PharmDC® 93000) exhibit high plastic deformation. Even at low punch forces, they are able to form stable tablets. Dicalciumphosphate (Emcompress®), sieved lactose (SpheroLac® 100)

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