

Crystal habit and tableting behavior

Norbert Rasenack, Bernd W. Müller *

*Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University Kiel, Gutenbergstrasse 76,
D-24118 Kiel, Germany*

Received 14 December 2001; received in revised form 7 May 2002; accepted 29 May 2002

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. © 2002 Elsevier Science B.V. All rights reserved.

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

* Corresponding author. Tel.: +49-431-880-1333; fax: +49-431-880-1352

E-mail address: bwmueller@pharmazie.uni-kiel.de (B.W. Müller).

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 $s_{F_{\text{max}}}/F_{\text{max}}$) 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 gas pycnometer 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 K α 1 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)
$s_{F_{\max}}$ (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 (= tableability), 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 [$J \times \text{cm}^4$] 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 [%] \times total energy [Nm]) characterizes the effectiveness of the compression process. The factor ($s_{F_{\max}(\text{up})}$ [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 tableability). 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.

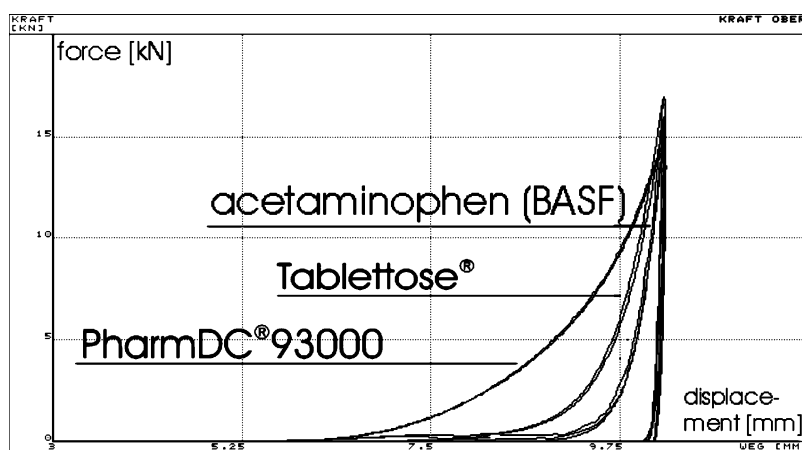
4. Results and discussion

4.1. Comparison of different excipients

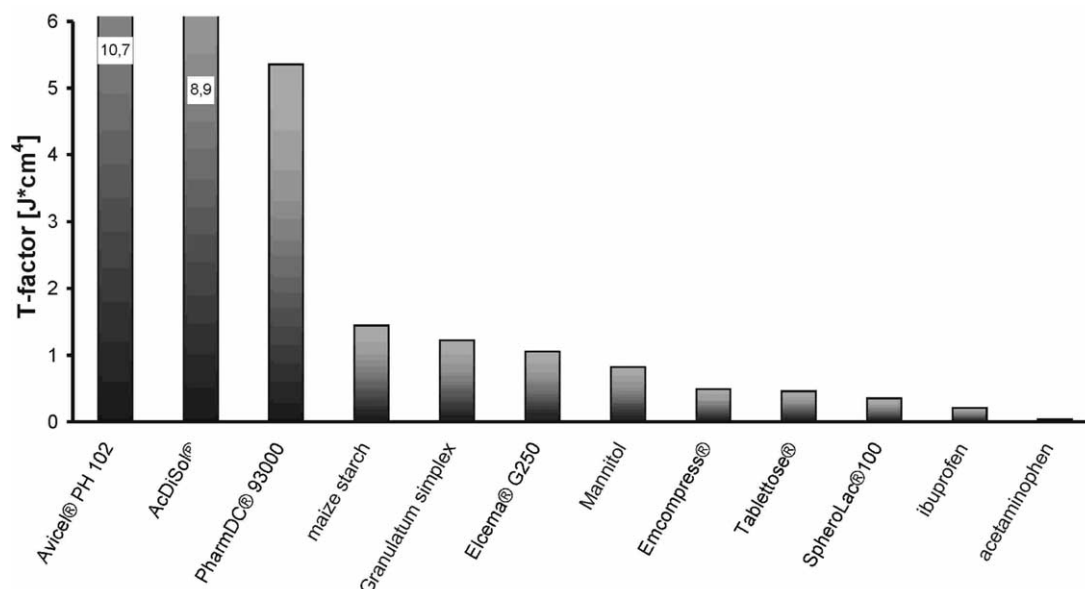
The excipients were chosen to represent a variety of deformation characteristics—microcrystalline cellulose (Avicel®) and pregelatinized starch (PharmDC® 93000) exhibit high plastic deformation. Even at low punch forces, they are able to form stable tablets. Dicalciumphosphate (Emcompress®), sieved lactose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

and preagglomerated lactose (Tablettose®) are brittle materials. Tablettose® shows better tableability than sieved lactose. The method employed for calculating the T -factor was able to show this difference (T -factor 0.35 for sieved and $T = 0.50$ for preagglomerated lactose, $P = 0.0012$). Granulatum simplex (lactose/potato

starch/PVP) is an example of a granulate. Fig. 1(b) shows the calculated T -factors for these excipients and some drugs. Characteristic force/displacement-profiles of excipients and acetaminophen are presented in Fig. 1(a). Same true volumes of each substance were tableted with same machine adjustments.



(a)

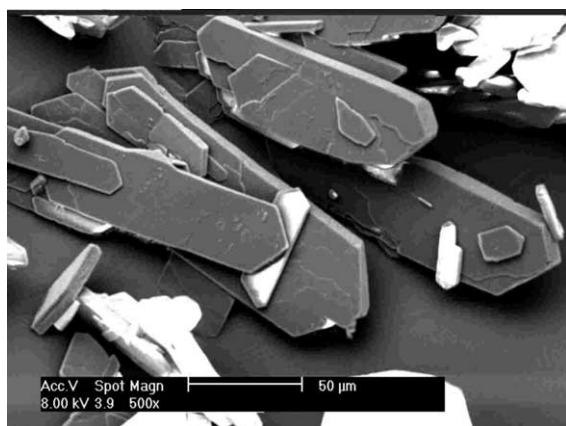


(b)

Fig. 1. (a) Force/displacement-profiles of excipients and the drug acetaminophen for comparison. Same true volumes of each substance were tableted with same machine adjustments. (b) Tableting properties of excipients and drugs.



(a)



(b)

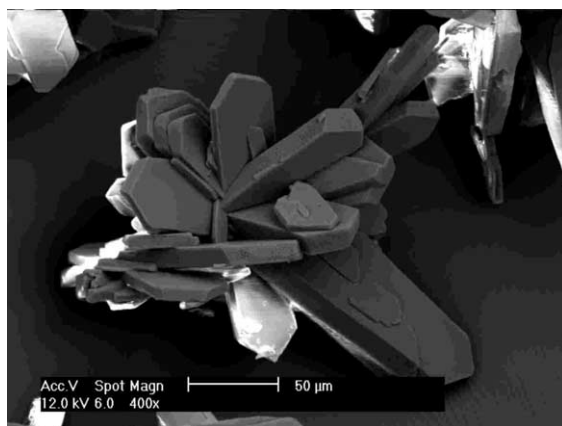


Fig. 2. SEM photographs of ibuprofen. (a) Habit I; (b) habit II.

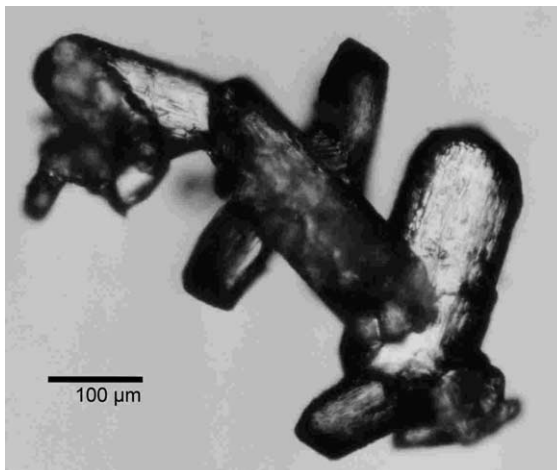
Table 3
DSC-data

	(a) DSC-data ibuprofen		(b) DSC-data acetaminophen				
	Needle-shaped habit	Plate-shaped habit	Habit I	Habit II	Habit III	Habit IV	Habit V
Onset of T_m (°C) (\pm S.D.)	75.2 ± 0.1	75.1 ± 0.1	169.5 ± 0.1	169.3 ± 0.1	169.4 ± 0.1	169.7 ± 0.1	169.2 ± 0.1
ΔH_f (J/g) (\pm S.D.)	125.8 ± 3.3	126.1 ± 2.9	177.7 ± 4.3	173.7 ± 5.6	175.7 ± 3.9	176.1 ± 5.4	172.7 ± 3.7

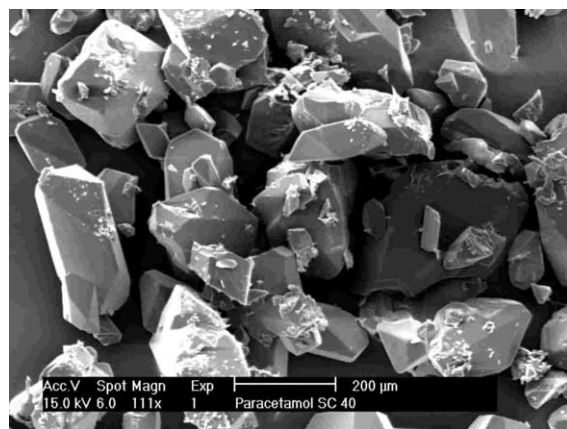
Results: mean of three measurements.



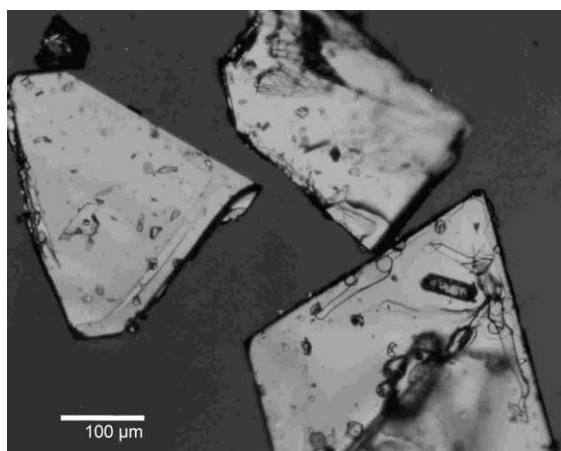
(a)



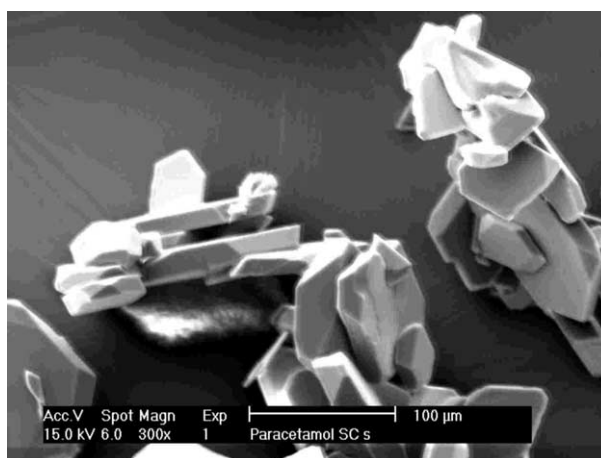
(b)



(c)



(d)



(e)

Fig. 3. SEM and microscope pictures of acetaminophen. (a) Habit I; (b) habit II; (c) habit III; (d) habit IV; (e) habit V.

4.2. Influencing of tableting properties by crystal habit: ibuprofen and acetaminophen

The analgesic drugs ibuprofen and acetaminophen show bad manufacturing behavior: ibuprofen is a cohesive and adhesive powder, the flow properties are poor and it has a high tendency to stick to the punches. The compacts are mechani-

cally unstable and consequently, for the production of tablets, a high amount of bonding agents and a granulation step are necessary. Tableability of acetaminophen is much worse than that of ibuprofen, as confirmed by the *T*-factor (Fig. 1). Therefore, both drugs mostly have to be granulated before tableting.

In this study, two habits of ibuprofen and five

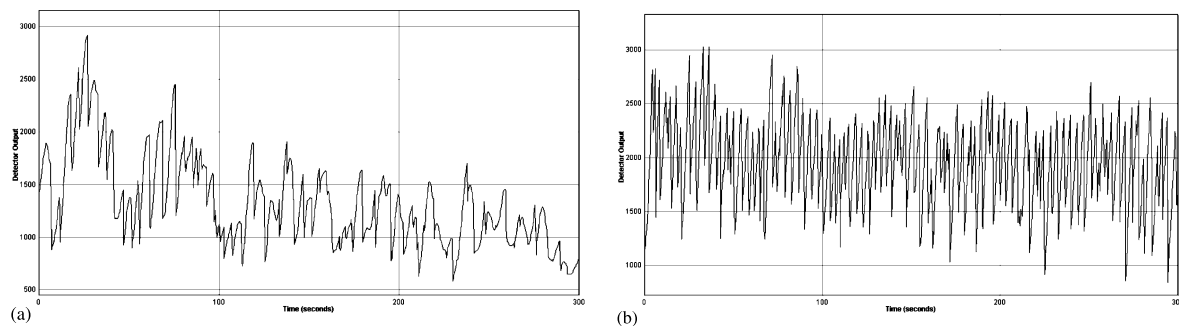


Fig. 4. Powder flow characteristics of ibuprofen. (a) Habit I; (b) habit II.

Table 4
Flowability

	(a) Flowability of ibuprofen		(b) Flowability of acetaminophen		
	Needle-shaped habit	Plate-shaped habit	Habit I	Habit III	Habit V
Mean (s)	4.9	3.1	3.9	3.7	3.2
Scatter (s)	2.3	1.0	1.1	0.8	0.8
Max (s)	12.0	5.0	6.2	5.0	5.0

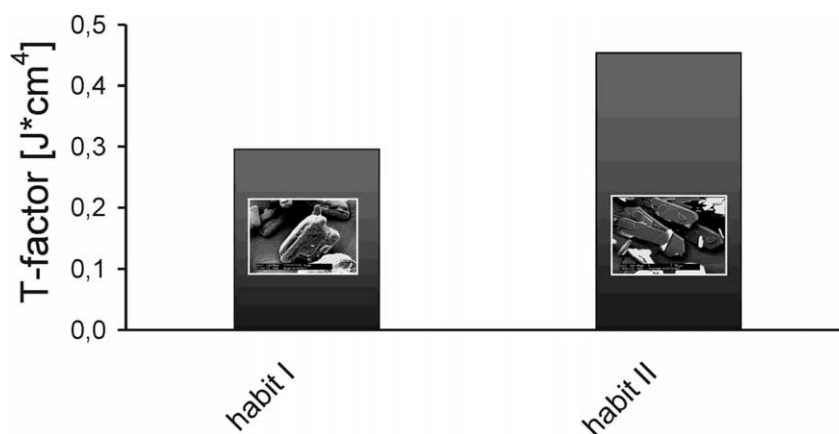


Fig. 5. Tableting properties of ibuprofen.

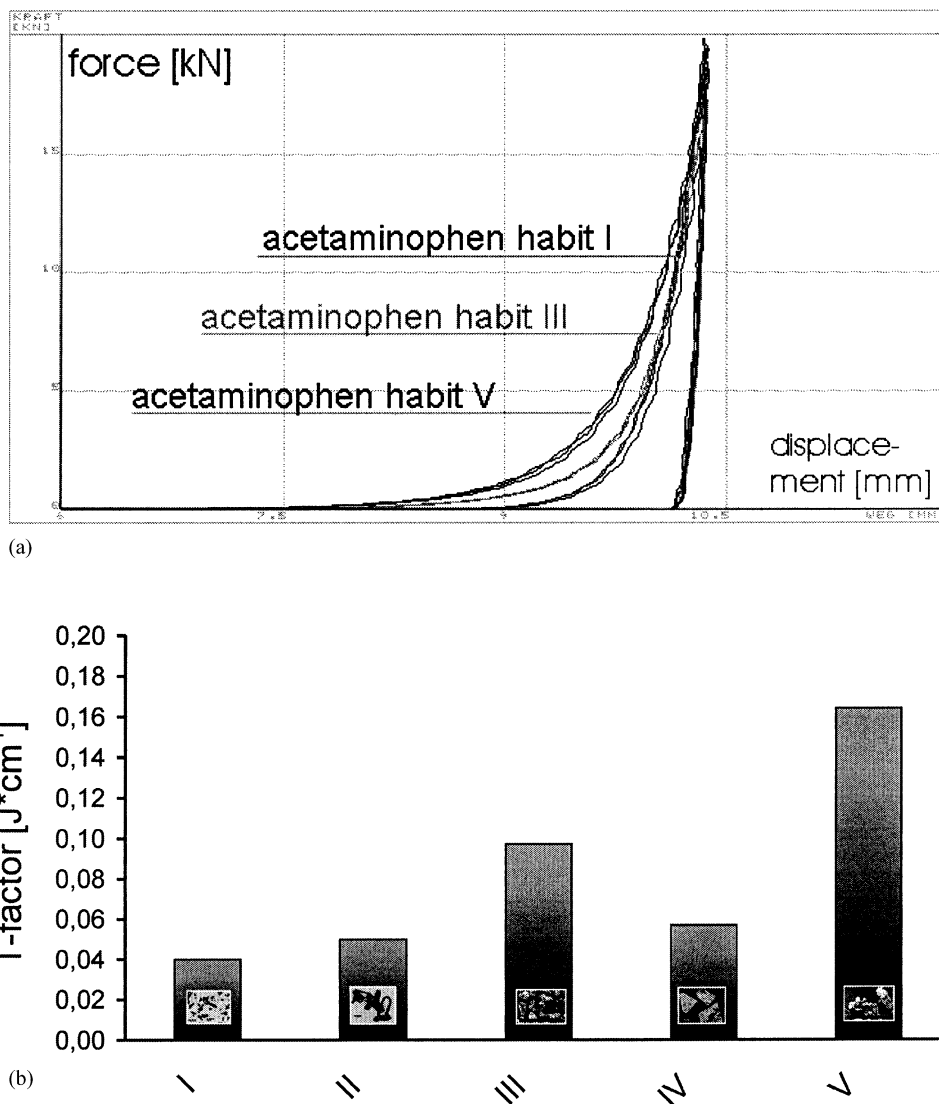


Fig. 6. Force/displacement-profiles of different crystal forms of acetaminophen. Same true volumes of each substance were tableted with same machine adjustments. (b) Tableting properties of acetaminophen.

different crystal forms of acetaminophen were compared (Figs. 2 and 3). These crystals were determined as isomorphs by DSC (Table 3) and powder X-ray diffraction.

Properties that affect the handling and manufacturing processes of these crystals vary dramatically. It was observed that different crystal forms have different flow characteristics (different adhesion/cohesion behavior). Because of the especially

bad flowability of ibuprofen-commodity (habit I) differences in flow-characteristics are particularly remarkable. In Table 4, the parameters of ibuprofen are presented and in Fig. 4, the profile of measured avalanches is shown. It is clear that the prepared crystals show a regular flowability. The flow characteristic of the common crystal form is irregular which represents cohesive behavior. Differences in flowability of acetaminophen are not

so dramatic because of the better flowability of the common crystals of this drug (Table 4).

Differences in tableting properties of the pure drug between the different habits are shown in Fig. 5 and Fig. 6(b). In the case of ibuprofen, the free flowing habit II (thin plates) shows the best compaction behavior. The properties of both compacts are compared in Table 5. The difference in mechanical strength of the compact of pure

drug at comparable punch forces in particular is remarkable. Because of the better flowability, the die is filled very homogeneously and the contact between the crystals is intensive. So, input of energy into the powder is much more effective. The total energy is higher and the elastic deformation lower. In the case of acetaminophen, small plates (habit V) or prismatic crystals (habit III) are preferable (force/displacement-profiles are

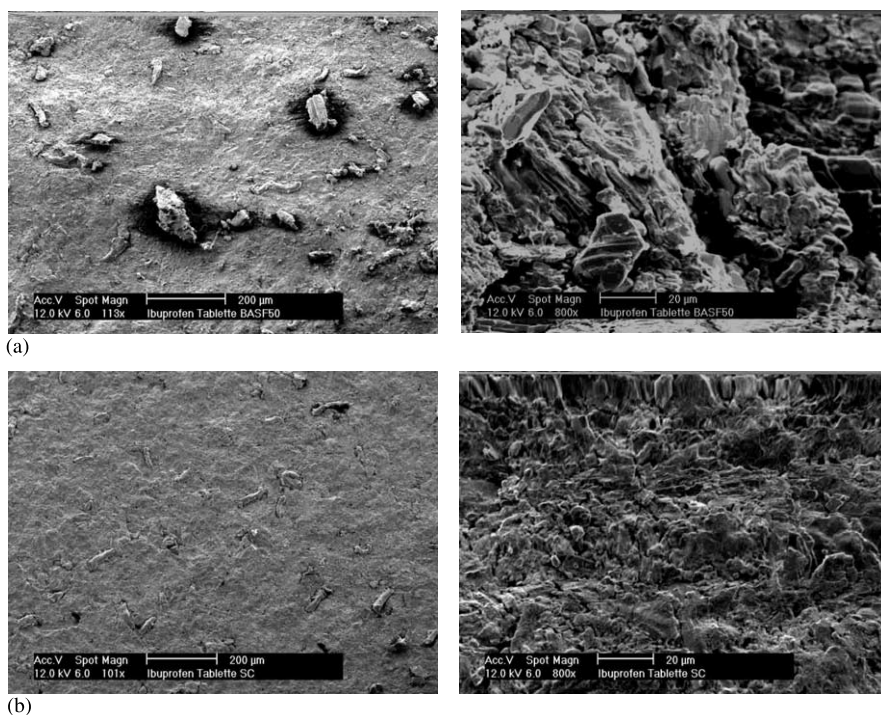


Fig. 7. SEM photographs of the ibuprofen tablet surface. (a) Habit I; (b) habit II.

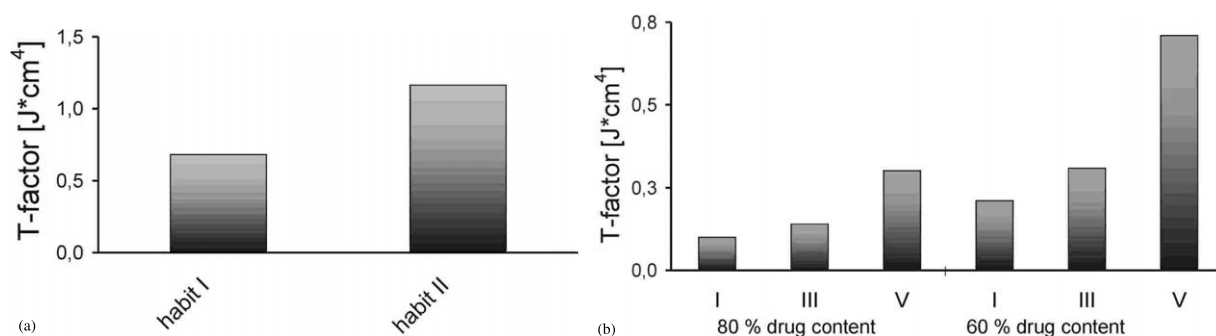


Fig. 8. Ibuprofen-tablets (drug content 91%). (b) Acetaminophen tablets.

Table 5
Comparison of ibuprofen compacts: characteristic data

	Needle-shaped habit	Plate-shaped habit
Flowability	Cohesive	Free flowing, not cohesive
Sticking to the punches	Adhesive	Not adhesive
Elastic recovery (%)	24	19
F_{\max} (kN)	16	15
Total energy (J)	4.2	4.9
Crushing strength (N)	32	55

Same true volumes of pure ibuprofen were tableted ten times with same machine adjustments.

shown in Fig. 6(a) and calculated T -factors in Fig. 6(b)).

To test the suitability for direct compression, a powder with 91% drug content with 4% Avicel® PH102, 4% AcDiSol®, 0.5% Aerosil® and 0.5% magnesium stearate was tableted. In the case of habit I, the flowability was lower which resulted in a higher S.D. (1.1%) of the tablet mass (S.D. = 0.4% in the case of ibuprofen habit II). The T -factors of the powder mixtures are shown in Fig. 8(a). Because of the good tableting behavior of the excipients, the T -factors are higher than those of the pure drug. Differences between the two crystal forms are still present in the powder mixture and are detected by the used method. During the tableting process in the case of habit I, there was substance sticking to the punches and the surface of the tablets was damaged. In the case of the plate-like habit, the surface of the tablets was even and there was no substance sticking to the punches. Pictures of the ibuprofen tablets are shown in Fig. 7. Holes can be detected in tablets prepared from the common crystal form (Fig. 7a).

To compare the tableting behavior of powder mixtures with excipients and acetaminophen, the drug was mixed with excipients (80% drug content: 15.5% Avicel® PH102, 4% AcDiSol® and 0.5% magnesium stearate; 60% drug content: 34% Avicel® PH102, 5.5% AcDiSol® and 0.5% magnesium stearate) and analyzed. The T -factor shows

higher values now because of the good compaction behavior of the excipients. However, in Fig. 8(b) it can be seen that the differences between the crystals still exist in the powder mixture.

5. Conclusions

Differences in crystal modification affect the properties of a drug even if, as in isomorphic drugs, there are only differences in the crystal habit. Tableting behavior, flowability and the tendency to stick to the punches can be affected by the choice of an optimal crystallization method— influencing the crystal habit of the drug. Even for drugs with bad compaction behavior, a habit can be developed that shows better tableting properties. In the case of ibuprofen, a directly compressible form was found (possible drug content 90%). Also, in the case of acetaminophen, differences in tableting properties were observed.

The importance of the choice of the optimal crystal form was demonstrated. This has to be carried out in the first steps of drug formulation development. Determination of the tabletability using the employed calculation allows a rapid, economic and reproducible comparison of pure drugs or powder-mixtures. Thus, the development of a suitable crystal form, which ideally is directly compressible, can be achieved.

Acknowledgements

We would like to thank BASF AG for financial support and for the supply of ibuprofen and acetaminophen.

References

- Carstensen, J.T., Ertell, C., Geoffroy, J.-M., 1993. Physico-chemical properties of particulate matter. *Drug Dev. Ind. Pharm.* 19, 195–219.
- Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R., 1999. Formation and compression characteristics of prismatic polyhedral and thin plate-like crystals of paracetamol. *Int. J. Pharm.* 187, 77–89.

- Heckel, R.W., 1961. Density-pressure relationships in powder compaction. *Trans. Metall. Soc. AIME* 221, 671–675.
- Jbilou, M., Ettabia, A., Guyot-Hermann, A.-M., Guyot, J.C., 1999. Ibuprofen agglomerates preparation by phase separation. *Drug Dev. Ind. Pharm.* 25, 297–305.
- Joiris, E., Martino, P., Berneron, C., Guyot-Herman, A.-M., Guyot, J.-C., 1998. Compression behavior of orthorhombic paracetamol. *Pharm. Res.* 15, 1122–1130.
- Martino, P., Guyot-Hermann, A.-M., Conflant, P., Drache, M., Guyot, J.-C., 1996. A new pure paracetamol for direct compression: the orthorhombic form. *Int. J. Pharm.* 128, 1–8.
- Panelli, R., Filho, F.A., 1998. Compaction equation and its use to describe powder consolidation behavior. *Powd. Metal.* 41, 131–133.
- Shell, J., 1963. X-ray and crystallographic applications in pharmaceutical systems. III: Crystal habit quantitation. *J. Pharm. Sci.* 52, 100–101.
- Staniforth, J.N., Rees, J.E., Kayes, J.B., Priest, R.C., Cotterill, N.J., 1981. The design of a direct compression tablet excipient. *Drug Dev. Ind. Pharm.* 7, 179–190.
- Rasenack, N., Müller, B.W., Einig, H., 2001. German Patent Application No. 0050/53009.