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# Development of mini-tablets with 1 mm and 2 mm diameter

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ABSTRACT

The feasibility of formulating mini-tablets with 1 mm diameter on a rotary-die press in comparison to mini-tablets of 2 mm was investigated. To gain insight into the production of 1 mm mini-tablets, three model drugs of different compression characteristics were chosen, namely quinine hydrochloride, ibuprofen and spray-dried gentian extract. A high drug load in combination with robust and reproducible mechanical properties was requested. Depending on the individual drug substance, mini-tablets were produced by direct compression or after roll-compaction/dry granulation. The tensile strength, mass, and their variation coefficients were determined to assess the mechanical properties of the tablets. The content uniformity and the dissolution behavior of selected batches were analyzed.

For the first time 1 mm mini-tablets could be successfully produced by direct compression (90% quinine hydrochloride; 90% dried gentian extract) and after roll compaction (70% ibuprofen). Depending on the applied compression pressure, 1 mm mini-tablets with quinine hydrochloride exhibited robust mechanical properties (e.g. median tensile strength of 2.02 N/mm$^2$) with equal or lower variance of distribution compared to the 2 mm compacts. With respect to content uniformity of dosage forms, 1 mm mini-tablets containing 80% quinine hydrochloride met the requirements of the European Pharmacopeia (AV = 6.8).



## 1. Introduction

Mini-tablets are used as multiple unit dosage forms and are equal or smaller than 3.0 mm in diameter (Lennartz and Mielck, 1998). Used as multiple unit dosage forms, mini-tablets exhibit several advantages like minor risk of dose dumping and independence of the rhythm of food transport compared to single unit dosage forms (Bechgaard and Nielsen, 1978; Follonier, 1992). For application, the compacts can be filled into hard gelatin capsules or can be administered with a dose dispenser for individual dosing (Bredenberg et al., 2003). With respect to a subsequent coating step, mini-tablets reveal several advantages compared to irregularly shaped units like granules. Mini-tablets can be coated reproducibly and require less coating material compared to granules, due to their constant specific surface area, smooth outer surface and robust mechanical properties (Munday, 1994).

To date, mini-tablets were developed serving for various applications. With respect to poorly compressible drugs, the reduction of tablet diameter from 10 mm to 2 mm enabled higher drug loads of pancreatin (Pich and Moest, 1989). Lennartz and Mielck (1998) supported this statement by comparing tablets of different sizes containing acetaminophen. Regarding modified drug delivery, matrix mini-tablets (De Brabander et al., 2000) and biphasic delivery systems (Lopes et al., 2006) were developed and investigated. Furthermore, ophthalmic inserts prepared by mini-tabletting are described in literature (Saettone et al., 1995) as well as sustained release floating dosage forms (Goole et al., 2008). Pich and Moest (1989) filed a patent concerning cylindrical pancreatin microtablets with a diameter of 1.0–2.5 mm. However, all mini-tablets described in this patent exhibited a diameter equal or larger than 1.5 mm.

All studies mentioned above were carried out with mini-tablets of at least 1.5 mm diameter. To our best knowledge, the manufacturing of mini-tablets of 1.0 mm diameter has not been described in scientific or patent literature yet. The reduction of the tablet diameter enables the manufacturing of multiple-unit solid dosage forms with defined dimensions, which are in size directly comparable to pellets and granules. A major interest was to investigate whether down-scaling of mini-tabletting to 1.0 mm compacts was possible and to compare the results to mini-tablets of 2.0 mm diameter.

The preparation of mini-tablets is of rising importance in paediatrics due to new European regulatory requirements on products for paediatric use (Regulation (EC) No. 1901/2006, 2006). First clinical studies revealed that even children of small age are able to swallow mini-tablets of 3.0 mm diameter (Thomson et al., 2009). Therefore, rational development of mini-tablets is of high impact with particular interest in robust mechanical properties and high drug loads.

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The aim of this study was to prepare 1 mm and 2 mm mini-tablets on a rotary die press, containing three model drugs with different compression characteristics. Quinine hydrochloride as a basic model drug, ibuprofen as a poor compressible drug and a spray-dried plant extract were used as active ingredients. The feasibility of preparing mini-tablets with high drug load and robust mechanical properties should be investigated. For the first time, mini-tablets with a diameter of 1 mm should be compressed for each model drug. Subsequently, mechanical properties and content uniformity of the mini-tablets should be evaluated.

## 2. Materials and methods

### 2.1. Materials

Quinine hydrochloride (Buchler, Braunschweig, Germany), ibuprofen (Ibuprofen 90, BASF, Ludwigshafen, Germany), dried gentian extract (Bionorica, Neumarkt, Germany), α-lactose monohydrate (Flowlac® 100, Meggle, Wasserburg, Germany), colloidal silicon dioxide (Aerosil® 200, Evonik Degussa, Essen, Germany), crospovidone (Kollidon® CL, BASF, Ludwigshafen, Germany), high density silicified microcrystalline cellulose (Prosolv® HD90, J.R.S. Pharma, Rosenberg, Germany), magnesium stearate (Welding, Hamburg, Germany), talcum (Talkum Pharma G, C.H.Erbslöh, Krefeld, Germany).

### 2.2. Preparation of mini-tablets

#### 2.2.1. Tabletting mixtures

All tabletting mixtures (Table 1) were compressed to 2 mm mini-tablets and grey labeled formulations were compressed to 1 mm mini-tablets, additionally.

Tabletting formulations for quinine hydrochloride mini-tablets are depicted in Table 1a. Quinine hydrochloride (quinine-HCl) was either used in powdered form (quinine direct) or after dry granulation (quinine gran). α-Lactose monohydrate (lactose) served as a filler, magnesium stearate as lubricant and colloidal silicon dioxide (c. silicon dioxide) was used to enhance the flowability of the mixtures. In order to accelerate the disintegration time of mini-tablets, crospovidone was added. In addition to the formulations containing powdered or granulated drug fractions, the whole tabletting mixtures were dry granulated (quinine mix gran) as described under Section 2.2.3.

Tabletting formulations containing ibuprofen are displayed in Table 1b. Ibuprofen was used as received (ibu direct) or dry granulated (ibu gran). Drug fractions of 70% were blended with high density silicified microcrystalline cellulose (SMCC) which served as a binder. Crospovidone was used to accelerate the disintegration and colloidal silicon dioxide to improve the flowability of the mixtures. Talcum was added as lubricant to minimize the tendency of sticking. Additionally, a mixture of ibuprofen (97.5%), magnesium stearate (0.5%) and crospovidone (2.0%) was dry granulated and subsequently mixed with SMCC, colloidal silica and talcum (mix gran ibu).

Tabletting formulations containing different concentrations of dried gentian extract (gentian) are shown in Table 1c. The dried gentian extract was used as received and was blended with different concentrations of SMCC, colloidal silicon dioxide, crospovidone and magnesium stearate.

Each tabletting mixture was blended for 20 min in a turbula mixer (W. Bachofen, Basel, Switzerland) at 42 rpm. Afterwards, lubricant was added and the formulations were blended for 2 min in addition.

#### 2.2.2. Flowability

Flowability of tabletting mixtures and drugs was determined using a computer controlled ring shear tester (RST-01.c, RST-CONTROL 95, Schulze Schüttgutmesstechnik, Wolfenbuettel, Germany) twice. The normal stress during pre-shearing was 5 kPa resulting in the consolidation stress. Afterwards, four different normal loads between 1 kPa and 4 kPa were applied. To terminate the measurement cycle, the first normal load (1 kPa) was repeated. A comparison of the two values should reveal changes of the sample during the measurement procedure. The relationship of the consolidation stress to the unconfined yield strength was calculated as the flowability factor ($ff_c$).

#### 2.2.3. Roll compaction/dry granulation

The active ingredients quinine hydrochloride, ibuprofen and mixtures of each drug were dry granulated using a roller compactor (Minipactor, GMP Gerteis + Processengineering, Jona, Switzerland), equipped with smooth rolls. A specific compaction force of 2 kN/cm

**Table 1**
Tabletting mixtures of 2 mm mini-tablets and 1 mm mini-tablets (grey) (a) formulations containing quinine hydrochloride, (b) formulations containing ibuprofen and (c) formulations containing gentian extract.

| Formulation | Powdered quinine-HCl | Granulated mixture | Granulated | Lactose | Magnesium stearate | Silicon dioxide | Crospovidone |
|---|---|---|---|---|---|---|---|
| *(a)* | | | | | | | |
| Quinine direct 70 | 70.0 | | | 24.5 | 3.0 | 0.5 | 2.0 |
| Quinine direct 80 | 80.0 | | | 14.5 | 3.0 | 0.5 | 2.0 |
| Quinine direct 90 | 90.0 | | | 4.5 | 3.0 | 0.5 | 2.0 |
| Quinine gran 70 | | 70.0 | | 24.5 | 3.0 | 0.5 | 2.0 |
| Quinine gran 80 | | 80.0 | | 14.5 | 3.0 | 0.5 | 2.0 |
| Quinine gran 90 | | 90.0 | | 4.5 | 3.0 | 0.5 | 2.0 |
| Quinine gran mix 70 | | | 70.0 | 24.5 | 3.0 | 0.5 | 2.0 |
| Quinine gran mix 80 | | | 80.0 | 14.5 | 3.0 | 0.5 | 2.0 |

| Formulation | Powdered ibuprofen | Granulated ibuprofen | Granulated ibuprofen-mixture | SMCC | Talcum | Silicon dioxide | Crospovidone |
|---|---|---|---|---|---|---|---|
| *(b)* | | | | | | | |
| Ibu direct 70 | 70.0 | | | 26.5 | 1.0 | 0.5 | 2.0 |
| Ibu gran 70 | | 70.0 | | 26.5 | 1.0 | 0.5 | 2.0 |
| Mix gran ibu 70 | | | 70.0[a] | 28.5 | 1.0 | 0.5 | – |

| Formulation | Gentian extract | SMCC | Magnesium stearate | Silicon dioxide | Crospovidone |
|---|---|---|---|---|---|
| *(c)* | | | | | |
| Gentian 50 | 50.0 | 44.5 | 3.0 | 0.5 | 2.0 |
| Gentian 70 | 70.0 | 24.5 | 3.0 | 0.5 | 2.0 |
| Gentian 90 | 90.0 | 4.5 | 3.0 | 0.5 | 2.0 |

[a] Granulated ibuprofen-mixture composed of 97.5% ibuprofen, 0.5% magnesium stearate and 2.0% crospovidone.

was applied for quinine hydrochloride and tabletting mixtures containing quinine hydrochloride. The speed of rolls was set to 3 rpm and the gap between the rolls was kept constant at 2.0 mm. Ibuprofen and the ibuprofen mixture were dry granulated with a specific compaction force of 3 kN/cm, the gap between the rolls was kept constant at 3.0 mm and speed of rolls was set to 2 rpm. The prepared ribbons were dry granulated using a star granulator with a 1.0 mm sieve.

#### 2.2.4. Laser light diffraction

Particle size distributions of ibuprofen and dry granulated ibuprofen were analyzed by laser light diffraction (Helos, Sympatec, Clausthal-Zellerfeld, Germany). Measurements were performed in triplicate with a dry dispersing unit (Vibri, Rhodos T4.1, Sympatec, Claustha-Zellerfeld, Germany) at 1.0 bar.

#### 2.2.5. Compression of mini-tablets

All formulations were compressed on a rotary die press (IMA Pressima, Kilian, Cologne, Germany) equipped with either one 1 mm or one 2 mm 19-tip mini tabletting tool. Biconvex mini-tablets were prepared at a tabletting speed of 10 rpm.

Different pressures were applied, depending on the size of the tablets and the compression behavior of the used drug. 2 mm quinine hydrochloride mini-tablets were compressed with compaction forces of 2.0, 4.0 and 6.0 kN. 1 mm mini-tablets were prepared with 0.5, 1.0 and 1.5 kN. The compaction forces of all quinine hydrochloride mini-tablets corresponded to pressures of 33, 67 and 100 MPa. Mean compaction forces of 3.0, 4.0 and 5.0 kN were applied for the 2 mm mini-tablets containing ibuprofen and forces of 0.75, 1.0 and 1.25 kN were used for the 1 mm tablets, respectively. Compaction forces complied with pressures of 50, 67 and 84 MPa, respectively. 2 mm mini-tablets containing herbal extract were compressed with 4.0, 6.0 and 8.0 kN, and forces of 1.0, 1.5 and 2.0 kN were employed for 1 mm mini-tablets. Compaction forces of both tablet sizes corresponded to 67, 100 and 134 MPa.

### 2.3. Characterization of the mini-tablets

#### 2.3.1. Tensile strength

Tensile strength was analyzed to compare the mechanical properties of different sized mini-tablets. All mini-tablets were stored at least 24 h at 21 °C/45% r.h. Thirty tablets of each batch were evaluated concerning height and crushing force. The mean value and the coefficient of variation were determined.

The height of mini-tablets of all batches was measured using image analysis (Leica Microsystems, Cambridge, UK). The system consists of a stereo microscope, a digital camera and computer software (Leica Qwin, Cambridge, UK).

The crushing resistance of each mini-tablet was evaluated with a texture analyzer (TA-XT2i Stable Micro Systems, Godalming, UK). A constant speed of 0.5 mm/s was set and the diametrical force needed to crush the tablet was detected with a sensitivity of 0.05 N. Subsequently, tensile strength was calculated using the equation for flat-faced tablets according to Fell and Newton (1970). Lennartz and Mielck (1998) discussed the applicability of the equation modification for convex discs (Pitt et al., 1988) for the characterisation of mini-tablets. This modification was invented for convex discs with a ratio of central cylinder thickness to diameter of 0.06–0.3. In contrast to biconvex tablets of bigger sizes, mini-tablets are almost spherical and the ratio of central cylinder thickness to diameter is often above 0.3. Therefore, Lennartz and Mielck (1998) decided not to use the modified equation but the tensile strength equation for flat-faced tablets.

**Table 2**
Flowability of quinine hydrochloride and quinine hydrochloride tabletting mixtures analyzed by the ring shear tester.

| Substance/formulation | ffc-values |
|---|---|
| Quinine hydrochloride | 2.7; 2.5 |
| Quinine hydrochloride granule | 5.6; 5.6 |
| Quinine direct 70 | 5.1; 5.2 |
| Quinine direct 80 | 4.8; 4.5 |
| Quinine direct 90 | 5.0; 5.0 |
| Quinine gran 70 | 11.2; 10.1 |
| Quinine gran 80 | 9.9; 9.5 |
| Quinine gran 90 | 8.6; 8.2 |
| Quinine gran mix 70 | 6.3; 6.5 |
| Quinine gran mix 80 | 6.1; 5.9 |

#### 2.3.2. Dissolution testing

Dissolution tests were performed using a basket apparatus (Sotax AT7, smart, Sotax, Loerrach, Germany) according to the Ph.Eur. monograph 2.9.3. The rotational speed of baskets was set to 100 rpm. Mini-tablets containing quinine hydrochloride were analyzed in 900 ml acetate buffer (pH 5.5) at 37 ± 0.5 °C. Phosphate buffer (pH 6.0) was used as dissolution medium for the compressed ibuprofen mini-tablets. The amount of released drug was detected using a UV–vis spectrometer (Lambda 40, PerkinElmer, Rodgau-Juedesheim, Germany) with a flow-through cuvette. Quinine hydrochloride was analyzed at a wavelength of 302 nm and ibuprofen at a wavelength of 221 nm.

#### 2.3.3. Uniformity of dosage units

The content uniformity of selected batches of quinine hydrochloride mini-tablets was evaluated according to the Ph.Eur. 7.1 (2.9.40).

## 3. Results and discussion

### 3.1. Development of mini-tablets containing quinine hydrochloride

#### 3.1.1. Effects of composition on the properties of 2.0 mm mini-tablets

The flowability of tabletting mixtures is a crucial parameter for successful mini-tabletting. Decreasing die orifices require good flow properties of the mixtures, to ensure rapid and homogenous die filling. Poor flow behavior of tabletting formulations can lead to inaccurate filling of the dies causing dosing variability of the tablets. Flemming and Mielck (1995) investigated the flow rates of several direct compressible excipients in order to facilitate the production of mini-tablets. Kachrimanis et al. (2005) extended the investigations and elucidated the effects of orifice dimensions and selected particle properties on the flow rate of some excipients into die orifices. Flowability was analyzed with a ring shear tester and the resulting values were evaluated according to the Jenike classification (1970). The higher the $ff_c$-value, the better is the flowability. The flow characteristics of quinine hydrochloride and tabletting mixtures are displayed in Table 2. The pure drug exhibited poor flow characteristics and was assessed as a cohesive powder according to Jenike (1970). To improve flowability of cohesive substances, tabletting excipients with free-flowing behavior may be added. Therefore, free flowing lactose was blended with different amounts of quinine hydrochloride and the flow behavior of all direct compressible mixtures could be improved to easy-flowing.

However, the flow properties of the tabletting mixtures were still challenging. Therefore, a previous roll compaction step was used as an attempt to improve flow properties of the active ingredient itself as suggested by Kleinebudde (2004). Dry granulated quinine hydrochloride exhibited improved flow properties and

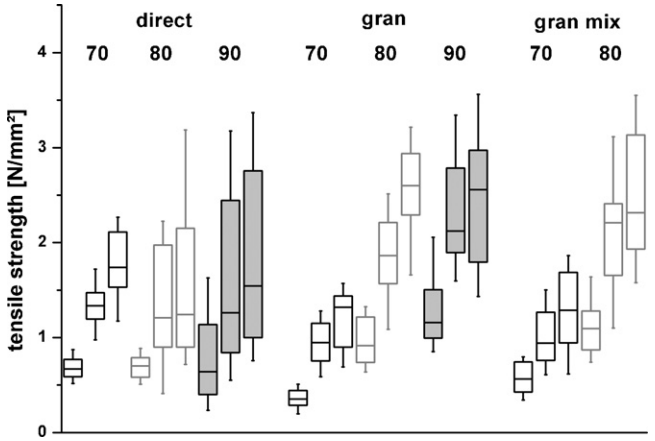


**Fig. 1.** Tensile strength of 2 mm quinine hydrochloride mini-tablets ($x_{10}$, $x_{25}$, $x_{50}$, $x_{75}$, $x_{90}$). Abbreviations indicate the used tabletting formulation and mini-tablets produced with rising compression pressures (33, 67, 100 MPa) were analyzed ($n = 30$).

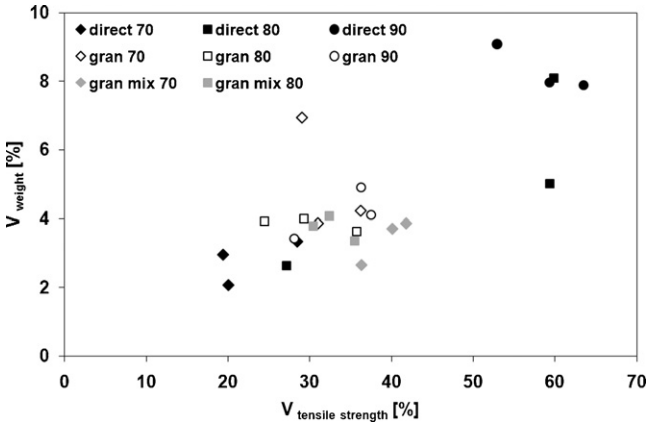


**Fig. 2.** Correlation of variation coefficients of weight and tensile strength of 2 mm quinine hydrochloride mini-tablets.

could be assessed as easy-flowing granules. The addition of a free-flowing lactose as a filler further increased the flowability of the tabletting mixtures. The higher the concentration of lactose, the better was the flow behavior. The tabletting mixture containing 70% (w/w) dry granulated active ingredient and 24.5% (w/w) lactose exhibited free-flowing behavior.

To achieve uniformity among the resulting tablets, the formulations containing 70% (w/w) and 80% (w/w) were additionally dry granulated. As expected, the flow properties decreased compared to the mixture containing dry granulated drug and the free-flowing filler due to the compaction of the filler. However, all analyzed tabletting formulations showed easy-flowing or free-flowing behavior and could be compressed to 2 mm mini-tablets with a smooth outer surface and no visible sticking or capping.

With respect to a subsequent coating step, the mechanical properties of the produced mini-tablets were of particular interest. The tensile strength as a function of compaction pressure for 2 mm mini-tablets is depicted in Fig. 1. The calculated values depended on the applied compaction pressure. The higher the compaction pressure, the higher was the tensile strength of the resulting mini-tablets and the wider was the distribution of the values.

It is already well known from literature, that tensile strength is affected by pre-treatment of the drug (Herting and Kleinebudde, 2008). Tablets compressed of granules usually exhibit lower values for tensile strength than direct compressed tablets. This phenomenon is widely known as loss of compactibility and described as work-hardening. Malkowska and Khan (1983) explained this effect with a consumption of binding sites during the granulation step. A different approach for explanation is particle size enlargement, which results in less available binding areas between the particles (Sun and Himmelspach, 2006). However, the mechanical properties of mini-tablets with quinine hydrochloride could not be explained by these hypotheses. The pre-treatment of the drug did not have a reproducible influence on the median of the tensile strength of the mini-tablets. In contrast, granulation of the active ingredient (gran 70, 80, 90) or the whole mixture (gran mix 70, 80) led to mini-tablets with more reproducible mechanical properties. With respect to the wide distribution of tensile strengths of mini-tablets made from powder mixtures (direct 70, 80, 90), no comparison of the mechanical properties was performed.

The calculated tensile strength of quinine hydrochloride mini-tablets depended on the drug load. Increasing quinine hydrochloride concentrations led to tablets with improved tensile strength (70% < 80% < 90%). The free-flowing filler did not lead to an increased compactibility and therefore served mainly for flowability enhancement. Mini-tablets prepared of the direct compressible formulations containing 80% and 90% active ingredient were the only exception from this observation. The resulting tablets exhibited mechanical properties which were comparable to those of direct compressed mini-tablets with 70% drug. However, this effect might be due to the considerably wide distributions of tensile strength in consequence of inaccurate die filling during the manufacturing process.

Coefficients of tensile strength and weight of the 2 mm mini-tablets were correlated (Fig. 2). Variation coefficients of tensile strength from 20 to 40% corresponded to variation coefficients of weight below 4.2%. In contrast, mini-tablets made of direct compressible mixtures with 80% and 90% drug exhibited high variation coefficients of tensile strength and weight. These mixtures also exhibited the poorest flowability (see Table 2), which might cause inaccurate die filling, resulting in mini-tablets with high weight and tensile strength variations.

To conclude, it was possible to develop high loaded 2 mm quinine hydrochloride mini-tablets with acceptable mechanical properties. Nevertheless, the formulation with 80% granulated drug let to mini-tablets with a high drug load, robust and reproducible mechanical properties and was evaluated as most appropriate for further studies.

Dissolution testing of quinine hydrochloride mini-tablets (quinine gran 80) resulted in 90% drug release within the first 23 min of dissolution (Fig. 3). Additionally, content uniformity of the same batch was evaluated. A mean of 98.3% and standard deviation of

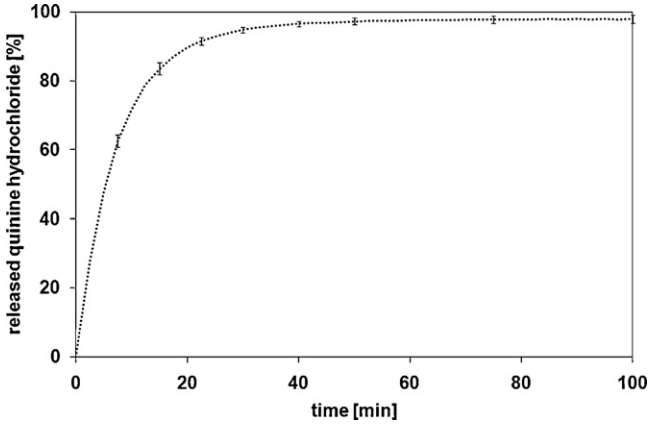


**Fig. 3.** Dissolution profile of quinine hydrochloride mini-tablets containing 80% (w/w) dry granulated drug ($n = 3$; mean ± SD).

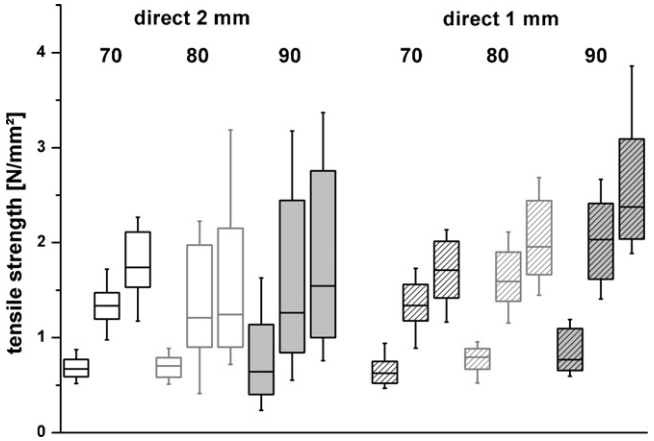


**Fig. 4.** Tensile strength of 2 mm and 1 mm quinine hydrochloride mini-tablets ($x_{10}$, $x_{25}$, $x_{50}$, $x_{75}$, $x_{90}$). Abbreviations indicate the used tabletting formulation and mini-tablets produced with rising compression pressures (33, 67, 100 MPa) were analyzed ($n = 30$).

5.5% were calculated to an acceptance value of 13.3 fulfilling the requirements of the Ph.Eur. monograph 2.9.40. Moreover, it can be assumed that content uniformity of a dose consisting of several mini-tablets would lead to lower values than the analyzed single mini-tablets.

### 3.1.2. *Effects of composition on the mechanical properties of 1 mm mini-tablets*

The direct compressible tabletting formulations with quinine hydrochloride were used to prepare 1.0 mm mini-tablets (Table 1a). Regarding the 2 mm mini-tablets, these formulations resulted in mini-tablets with the lowest (quinine 70) and mini-tablets with the highest variation coefficients of tensile strength (quinine 80 and quinine 90) (Fig. 2).

Besides a smooth manufacturing process, 25% of 1 mm mini-tablets were bisected by the scraper. With respect to manufacturing processes of industrial scale, the scraper needs modification to prevent bisection of the 1 mm mini-tablets.

The mechanical properties of the resulting 1 mm mini-tablets were determined. The calculated tensile strength is depicted in comparison to the tensile strength of the corresponding 2 mm compacts (Fig. 4). As expected, 1 mm mini-tablets exhibited increasing tensile strength due to increasing compaction pressures. Similar to the 2 mm mini-tablets, the 1 mm solids showed a dependence of tensile strength on the amount of quinine hydrochloride. The higher the drug concentration of the mini-tablets, the higher was their tensile strength. The dependence of the mechanical properties on the diameter of mini-tablets has been controversially discussed in literature before. Lennartz and Mielck (1998) detected an enhanced tensile strength with decreasing diameter of mini-tablets. However, the observations were also dependent on compression pressure and drug concentration. Mittwollen (2002) could not confirm an increase of tensile strength with decreasing tablet diameter. High loaded quinine hydrochloride mini-tablets analyzed in the current study revealed enhanced values for tensile strength with decreasing diameter. However, this effect might be due to the wide distribution of tensile strength values of 2 mm mini-tablets made of direct compressed mixtures. In contrast, the distribution of tensile strength of the 1 mm compacts was considerably smaller. Mini-tablets containing 80% and 90% quinine hydrochloride exhibited significantly lower variation coefficients than the 2 mm compacts. With decreasing tablet diameter, mechanical properties of the resulting tablets improved and were more reproducible. Pich and Moest (1989) were the first to describe advantages of small tabletting diameters on the tabletting behavior of formulations. Lennartz and Mielck (1998) supported their observations by successful tabletting of the poor compressible paracetamol in high quantities to tablets with decreasing diameter. In the present study, 1 mm mini-tablets with robust mechanical properties could be successfully developed. The resulting compacts showed even smaller variation coefficients of tensile strength than the corresponding 2 mm mini-tablets.

Exemplarily, the content uniformity of 1 mm mini-tablets compressed with 100 MPa and containing 80% powdered drug was evaluated. The mean drug content of 100.9% and the standard deviation of 2.8% resulted in an acceptance value of 6.8 meeting the requirements of the Ph.Eur. monograph 2.9.40.

### 3.2. *Effects of composition on the properties of 1 mm and 2 mm ibuprofen mini-tablets*

Ibuprofen is known as an active ingredient with poor solubility and challenging compaction properties (Rasenack and Muller, 2002). Several studies evaluated the influence of the ibuprofen crystal habit on its compressibility and flow properties and revealed needle-shaped particles as worst case, e.g. for compression behavior (Di Martino et al., 2002; Garekani et al., 2001). To minimize sticking-tendency, Roberts et al. (2004a,b) investigated the effect of lubricant type, punch tip geometry and surface roughness. In accordance to these studies, during this work mini-tablets were compressed with unused, convex mini tabletting tools which lower the sticking tendency. Various technological methods to improve flowability and compressibility of ibuprofen were summarized by Möller (1998). Following these studies, ibuprofen should be pretreated before compression. Silicified microcrystalline cellulose, known as an excellent flowing diluent with anti-sticking properties was used as filler (Gohel and Jogani, 2005).

Ibuprofen was either dry granulated or direct compressed to mini-tablets of 2 mm and 1 mm diameter. With respect to the poor solubility of ibuprofen, the mode of incorporating the superdisintegrant was varied to enhance the dissolution rate of the mini-tablets (Table 1b). However, the main purpose of the current study was the development of ibuprofen mini-tablets rather than gaining deeper insight into the relation between the mode of incorporation and the dissolution rate of active ingredients.

Mini-tablets with 70% dry granulated ibuprofen, containing the superdisintegrant crospovidone extragranularly were compressed (gran ibu 70). In addition, mini-tablets with 70% dry granule fraction, containing 97% ibuprofen, 0.5% lubricant and 2.0% disintegrant were prepared (mix gran 70). For comparison, mini-tablets containing 70% ibuprofen and 2.0% disintegrant were directly compressed (direct 70). In addition, the tabletting mixture with pure dry granulated ibuprofen was compressed to 1 mm mini-tablets. The particle size distribution of granulated ibuprofen was determined with laser light diffraction. The median particle size of the granules ranged between 60 and 71 μm, 10% were less than 5 μm and 90% of the granules were less than 460 μm.

The mechanical properties of the compressed mini-tablets are shown in Fig. 5. As expected, increasing compression pressures resulted in increased tensile strength of both 1 mm and 2 mm mini-tablets. The pre-treatment of the drug did not have any influence on the median and the distribution of tensile strength. Again, the resulting values could not be explained by the work hardening phenomenon. With respect to the wide distribution of tensile strength, no conclusion can be drawn. In contrast to the 1 mm mini-tablets containing quinine hydrochloride, 1 mm mini-tablets with ibuprofen exhibited lower tensile strength than the corresponding 2 mm tablets.

Irrespective of the challenging compaction properties of ibuprofen, the distribution of tensile strength was comparable to the values obtained for the quinine hydrochloride tablets. No differ-

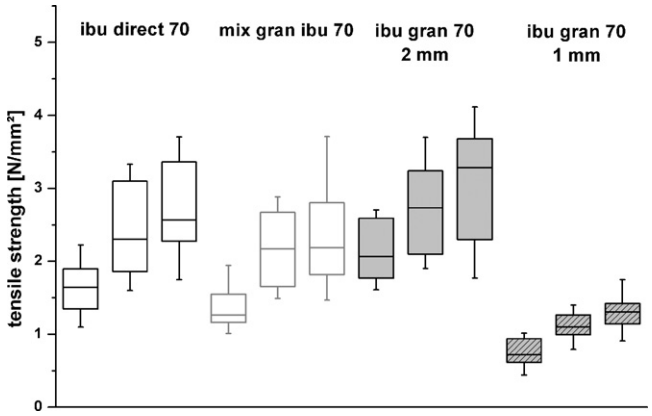


**Fig. 5.** Tensile strength of 2 mm and 1 mm ibuprofen mini-tablets ($x_{10}$, $x_{25}$, $x_{50}$, $x_{75}$, $x_{90}$). Abbreviations indicate the used tabletting formulation and mini-tablets produced with rising compression pressures (50, 67, 84 MPa) were analyzed ($n = 30$).

entiation between ibuprofen mini-tablets of different tabletting formulations could be made. Compared to the 2 mm mini-tablets, the compression of a tabletting mixture with dry granulated drug to 1 mm mini-tablets resulted in considerably narrower distributions.

Mini-tablets containing ibuprofen with a smooth surface and robust mechanical properties could be obtained. In addition to direct compressed 1 mm mini-tablets with quinine hydrochloride (see Section 3.1.2), also dry granulated ibuprofen could be processed to mini-tablets of 1 mm diameter for the first time.

The dissolution profiles of the 2 mm mini-tablets were recorded and are presented in Fig. 6. As expected, the direct compressed tablets exhibited the fastest drug release. Mini-tablets containing the superdisintegrant crospovidone extragranularly showed the slowest release and mini-tablets containing the superdisintegrant intergranularly exhibited faster dissolution. The influence of the mode of incorporation of superdisintegrants on the dissolution rate of active ingredients is controversially discussed. van Kamp et al. (1983) revealed no difference between the modes of incorporation. Gordon et al. (1993) described the extragranular mode as superior to all others. Khattab et al. (1993) found that equal distribution intragranularly and extragranularly lead to the fastest dissolution rates. The dissolution profiles obtained during the present study might not necessarily be correlated to the mode of incorporating the disintegrant but to differences in the tensile strength of the tablets. Mini-tablets with intergranulary incorporated superdisintegrant exhibited faster dissolution profiles than mini-tablets with extragranular superdisintegrant but also the lowest tensile strength.

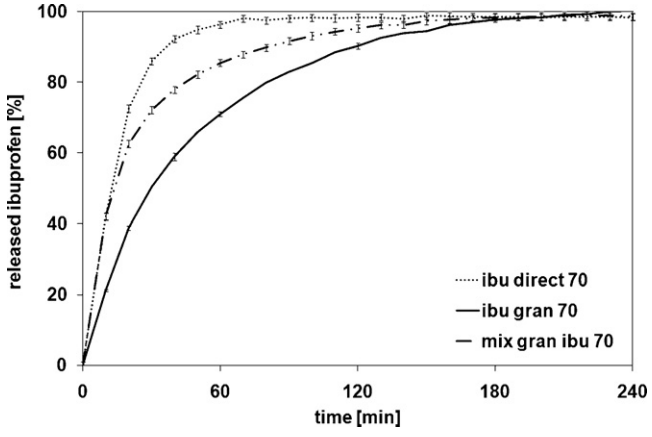


**Fig. 6.** Dissolution profile of 2 mm ibuprofen mini-tablets ($n = 3$; mean ± SD).

**Table 3**
Flowability of gentian extract and gentian extract tabletting mixtures analyzed by the ring shear tester.

| Substance/formulation | ffc-values |
|---|---|
| Gentian extract | 8.6; 8.7 |
| Gentian 50 | 20.0; 19.4 |
| Gentian 70 | 19.8; 21.0 |
| Gentian 90 | 17.5; 17.8 |

### 3.3. Effects of composition on the mechanical properties of 1 mm and 2 mm mini-tablets containing a spray-dried gentian extract

Dried herbal extracts often exhibit poor flowability and compression behavior. Due to the variable particle size distribution, hygroscopic behavior and low density of the substances, direct compression of the substances seemed to be inadequate. Wet-granulation with non-solvents (Díaz, 1996), dry granulation (Rocksloh, 1999; Soares et al., 2005; Von Eggelkraut-Gottanka, 2002), or even loading the extracts onto fumed silica as means to improve flowability and compaction behavior were described in literature. Spray-drying of herbal extracts usually leads to very fine and poorly compressible powders. However, spray-dried gentian extract was used to prepare mini-tablets of 1 mm and 2 mm during this study. The spherically formed herbal extract exhibited a narrow particle size distribution with particle sizes of $x_{10} = 16\ \mu m$, $x_{50} = 53\ \mu m$ and $x_{90} = 111\ \mu m$. These characteristics resulted in excellent flow properties (Table 3). In addition, silicified microcrystalline cellulose as spray-dried filler with free flowing behavior and enhanced compactibility was added to increase tensile strength of the mini-tablets. Consequently, tabletting mixtures exhibited free flowing behavior irrespective of the drug load.

Tensile strength as a function of compression pressure of the manufactured 2 mm and 1 mm mini-tablets is highlighted in Fig. 7. With increasing compression pressures, the mechanical properties of the mini-tablets were improved. The tensile strength of 2 mm mini-tablets decreased with increasing amounts of active ingredient. In contrast, the calculated tensile strength of the 1 mm mini-tablets increased with rising drug concentration. The contradictable behavior was probably due to the method for analyzing the mechanical properties of the mini-tablets. The 1 mm mini-tablets containing at least 70% dried gentian extract did not break, but were squeezed during tensile strength characterization. Therefore, the measurement method of analyzing the mechanical properties of 1 mm mini-tablets should be adjusted in further studies.

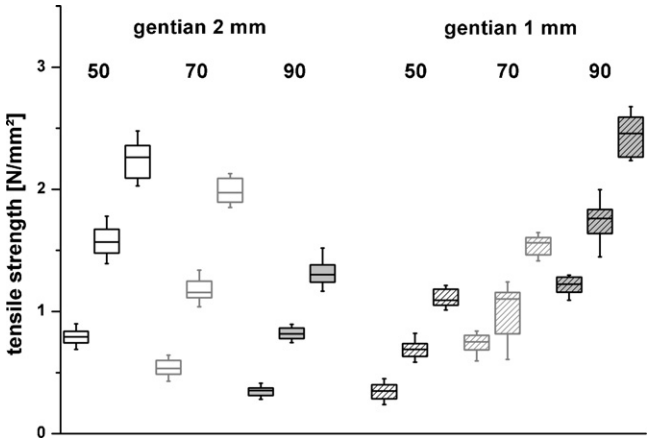


**Fig. 7.** Tensile strength of 2 mm and 1 mm gentian extract mini-tablets ($x_{10}$, $x_{25}$, $x_{50}$, $x_{75}$, $x_{90}$). Abbreviations indicate the used tabletting formulation and mini-tablets produced with rising compression pressures (67, 100, 134 MPa) were analyzed ($n = 30$).

In general, the variation coefficients of tensile strength of the gentian mini-tablets are remarkably lower compared to quinine hydrochloride or ibuprofen mini-tablets. Irrespective of the size of mini-tablets, high and reproducible values for tensile strength of gentian mini-tablets could be achieved.

## 4. Conclusions

For the first time, compression of mini-tablets with a diameter of 1 mm could be achieved on a rotary die press. The resulting 1 mm mini-tablets were compared to mini-tablets of 2 mm in diameter. Three model drugs with different compression behavior could be successfully compressed to mini-tablets and no visible sticking or capping occurred. Mini-tablets of 1 mm and 2 mm were directly compressed with high drug loads up to 90%. Even a tabletting mixture containing 70% dry granulated active ingredient was compressed to 1 mm mini-tablets and resulted in tablets with a smooth surface and reproducible mechanical properties. No general statement could be made regarding the influence of tablet size on tensile strength. Compared to the corresponding 2 mm compacts, 1 mm mini-tablets exhibited equal or even lower variation coefficients of tensile strength. With respect to manufacturing processes of industrial scale, the scraper needs modification to prevent the bisection of 1 mm mini-tablets during tabletting.

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