Research Article

X-RAY Spectrometry

Received: 13 January 2009 Revised: 17 June 2009 Accepted: 2 July 2009 Published online in Wiley Interscience: 11 August 2009

(www.interscience.com) DOI 10.1002/xrs.1205

X-ray computed microtomography for determination of relationships between structure and breaking of scored tablets

T. Sovány,[a] P. Kása Jr,[a] K. Vakli[b] and K. Pintye-Hódi[a]*

This paper reports on the relationship between the structure and halving properties of scored tablets. The results of the density measurements and structure determination by X-ray computed microtomography revealed that this analytical technique is very suitable for the investigation of porous structures and aggregates thanks to its noninvasive character. The results of the analyses show that besides various porosities also big differences exist in the arrangement of the particles inside the comprimates. These basic qualitative differences in the structure of tablets prepared with different tablet presses greatly influence their breaking, and must be taken into consideration during the production of dosage forms. Copyright © 2009 John Wiley & Sons, Ltd.

Introduction

The scored tablet is a widely used solid dosage form which combines the advantages of tablets (e.g. easy administration and stability) with dose flexibility.[1] This is very advantageous, particularly in pediatrics. However, very accurate breaking into halves is required to ensure the safe blood levels of the drug, in accordance with the guidelines of the drug authorities, which prescribe verification of the correct halving of scored tablets.

Such halving is a considerable problem in the pharmaceutical field,[2] but is a poorly studied topic in pharmaceutical technology. The halving properties depend greatly on the composition of the applied powder mixtures and the compression process.[3,4] These factors strongly influence the internal structure of the tablet, which governs its halving.

Two main problems can occur during the halving of tablets: breaking into halves with different masses and loss of mass (Fig. 1). Both problems are strongly linked with the internal structure of the tablets. Porosity and hardness seem to be good indicators of the prospective halving properties, but it is preferred to know the general density and force distribution inside the tablet. These parameters are determined by the material properties (which determine the type and strength of bonding at a given stress) and by the processes that occur during compression (which determine the stress acting on the powder).

The current analytical method for the measurement of tablet porosity is gas adsorption porosimetry. This is a useful, noninvasive method for determination of the skeletal density of the sample, but cannot provide appropriate information concerning the real structure. For hardness determination, the pharmacopeial method or three-bend hardness testing is widely used; these are useful, but destructive methods. Some authors have attempted to determine tablet hardness with spectroscopic methods, but the result depends appreciably on the penetration of the waves into the sample.[5] For samples with a high capping tendency, which usually contain significant structural defects, this method generally overestimates the real hardness of the sample. Hardness measurements can be combined with microscopic methods for study of the tablet or the breaking surface, but this method is also inappropriate for structure determination, because of the potential destruction of the sample.

X-ray computed microtomography (micro CT) is a rapid and noninvasive technique which can demonstrate the particle arrangement inside the tablet, and furnish useful information concerning its structure.[6,7] The theoretical background of this method is that X-rays are attenuated via absorption and/or scattering as they pass through a sample. From such the radiation attenuation, two-dimensional gray-scale projections of the sample can be detected, and the overall combination of these projection furnishes three-dimensional information. By repetition of this while the sample is rotated, the three-dimensional structure can be reconstructed from the data on the two-dimensional shadow images by means of a special algorithm.[7] The density distribution in scored tablets with different shapes was studied earlier and conclusions were drawn as regards the halving.[8] However, the effects of different compaction processes of the two main types of tablet presses on the tablet structure have not been investigated previously. The aim of the present paper, therefore, was thus to acquire information via micro CT on the qualitative differences in structure and density distribution of tablets with a given shape prepared with different tablet presses.

Materials and Methods

The tablets were compressed from a 1 : 1 binary mixture of two widely used pharmaceutical excipients, microcrystalline cellulose (Vivapur 102, J. Rettenmeier & Söhne, Germany) and spray-dried

* *Correspondence to: K. Pintye-Hódi, Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6., H-6721 Szeged, Hungary. E-mail: klara.hodi@pharm.u-szeged.hu*

a *Department of Pharmaceutical Technology, University of Szeged, H-6720, Eötvös u. 6., Szeged, Hungary*

b *Joó Katalin Analytical Trading and Supporting Ltd. H-2131, Alkotmány u. 7., Göd, Hungary*

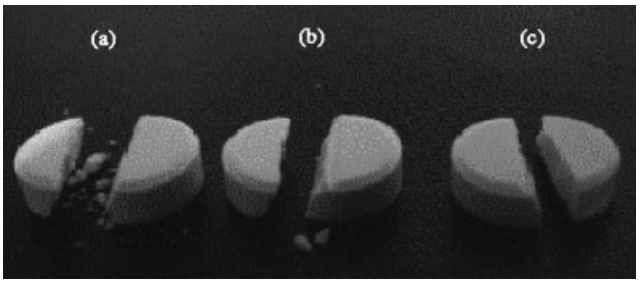

Figure 1. Pictures of a tablet with a crumbled breaking surface (a), a tablet broken into uneven halves (b), and an acceptably well-broken tablet (c).

Figure 2. Tablet hardness tester.

mannitol (Pearlitol SD 200, Roquette Pharma, Italy), lubricated by the addition of 1% magnesium stearate (Ph. Eur.).

A Turbula mixer (Willy A. Bachofen Machienenfabrik, Switzerland) was applied for 8 min to prepare the 1 : 1 powder mixture, and for 2 min after the addition of the lubricant, at 50 rpm.

Round and flat scored tablets with a diameter of 8 mm were compressed on a Korsch EK0 (E. Korsch Machienenfabrik, Germany) eccentric press or a Ronchi AM8S (Officine Meccanice F.lli Ronchi, Italy) rotary tablet press at compression forces of 5 and 15 kN. Eccentric presses are batch-type machines, where only the upper punch is active during the compression phase, with a relatively long compression time. In contrast, rotary presses operate in continuous running, and both punches are active during compression, resulting in a momentary load on the powder bed. The compression force was detected with strain gauges built into the punches. The other parameters were a temperature of 24 °C, an RH of 57%, and a compression speed of 30 tablets/min. Hundred

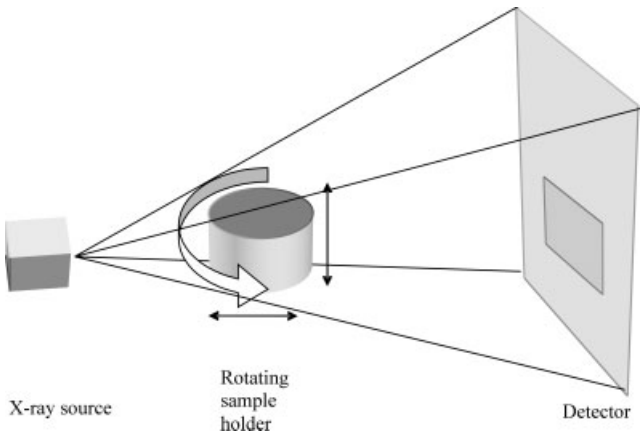

Figure 3. Schematic figure of a micro CT apparatus.

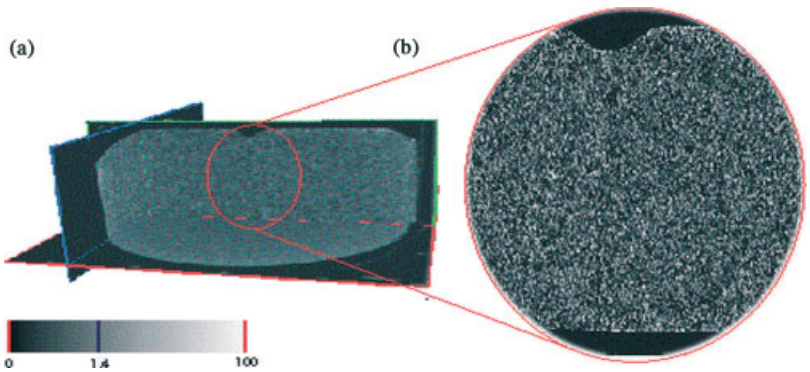

Figure 4. Density distribution in Tablet A (eccentric press, 5 kN).

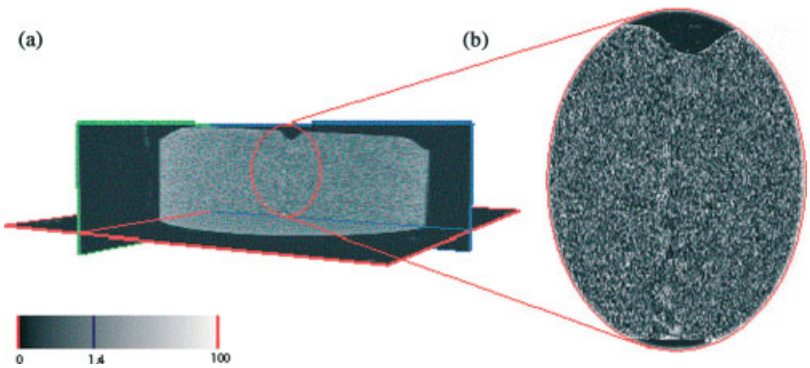

Figure 5. Density distribution in Tablet B (eccentric press, 15 kN).

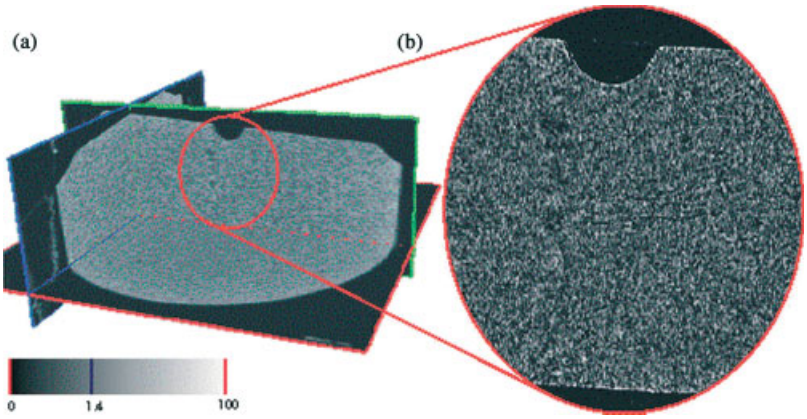

Figure 6. Density distribution in Tablet C (rotary press, 15 kN).

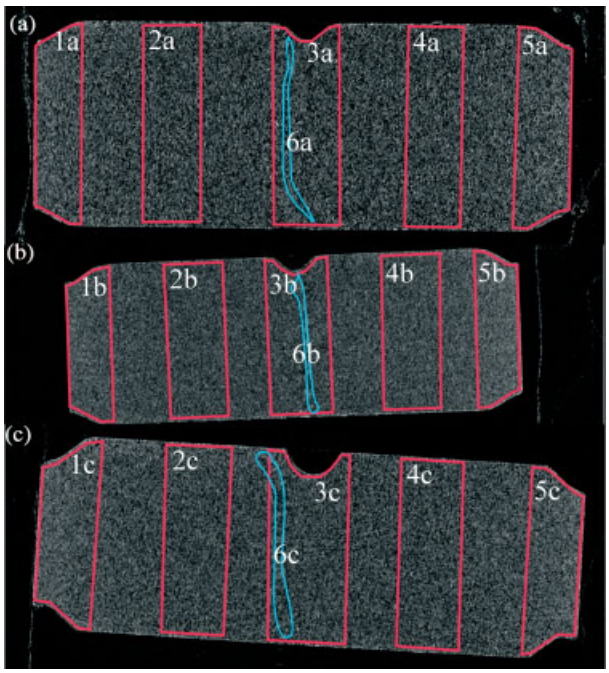

Figure 7. Regions of interest in different tablets (Tablet A (a), Tablet B (b) and Tablet C (c)).

tablets were compressed at each setting, without prelubrication of the die, for modeling of the industrial conditions.

Three-point bend testing was used for measurement of the force required to break the tablets into halves. Measurements were made with a laboratory-constructed tablet hardness tester; the elastic deformation occurring in the tablets was measured with strain gauges (Fig. 2).

The true density of tablets was determined with a Quantachrome helium stereopycnometer (Quantachrome GmbH., Germany). The porosity was calculated via the following equation (Eqn 1):

$$\phi = 1 - (\rho_{\text{apparent}}/\rho_{\text{true}}) \quad (1)$$

The structures of the tablets were analyzed with a SkyScan 1172 high-resolution micro CT apparatus. A schematic figure of a micro CT apparatus is displayed in Fig. 3. In this study, the X-ray source was set to 89 keV and 112 μA. All tablets were scanned in the whole 360° rotation range throughout 0.15° steps. The total duration

Table 1. Properties of the tablets

Sample Press	Tablet A Eccentric	Tablet B Eccentric	Tablet C Rotary
Compression force (kN)	5	15	15
Thickness (mm)	2.968	2.777	2.838
Diameter (mm)	7.933	7.927	8.042
True density (g/cm^3)	1.5202	1.5129	1.4658
Apparent density (g/cm^3)	1.2321	1.3253	1.2655
Porosity	0.189	0.124	0.137
Radial hardness (N)	72.20	118.0	88.0
Axial hardness (N)	57.72	81.89	9.50

Table 2. Gray-scale intensities in different regions of interest

Area	Mean	SD	Min	Max
Tablet A				
1a	75.533	41.961	0	255
2a	62.945	41.371	0	247
3a	62.339	42.593	0	255
4a	62.048	43.252	0	255
5a	74.969	45.250	0	255
6a	54.206	41.071	0	213
Tablet B				
1b	78.150	38.716	0	255
2b	64.946	37.563	0	247
3b	66.949	38.655	0	244
4b	69.361	37.165	0	234
5b	88.662	37.915	0	255
6b	59.013	37.569	0	196
Tablet C				
1c	81.121	36.108	0	255
2c	65.639	35.684	0	224
3c	63.665	36.737	0	252
4c	64.276	38.083	0	248
5c	79.358	38.319	0	255
6c	58.851	36.562	0	218

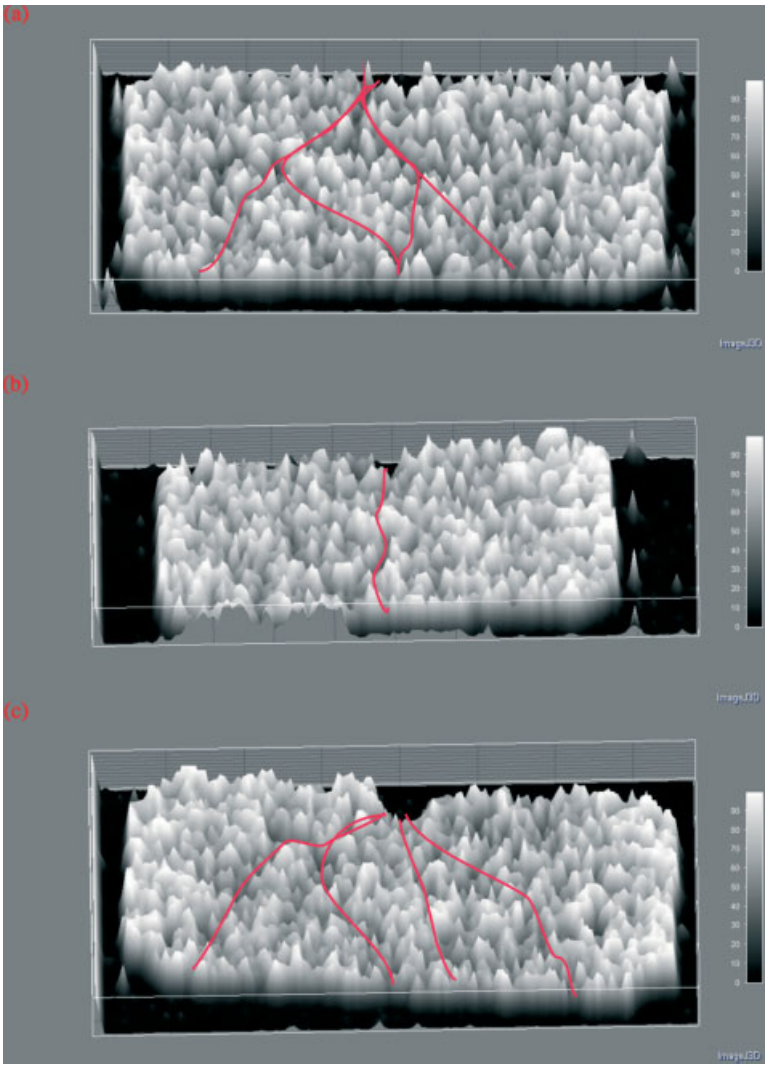

Figure 8. Gray-scale intensities and possible breaking directions in the cross sections of Tablet A (a), Tablet B (b) and Tablet C (c).

of scanning was approximately 3 h. The radiographs were then reconstructed with a standard cone-beam reconstruction program (NRecon) into 16-bit jpg pictures, each of 3120 × 3120 pixels.

The gray-scale intensities and optical densities in the regions of interests were determined with the ImageJ image-analyzing software (National Institute of Health, USA)

Results and Discussion

The aim of the present study was to clarify the reasons for the differences in mechanical behavior of tablets prepared with different tablet presses. The particles show bidirectional movement during compression. Rearrangement proceeds along the axial lines of the transmitted forces, and they provide some movement in the radial direction too, away from the punches. These radial components can result in considerable friction and adhesion to the die wall. A high level of friction can conduce to the formation of structural damage, which changes the mechanical behavior of the tablets. The quantity, duration and direction of the load determine the movement and rearrangement of the particles and cause significant differences in the structures of tablets compressed by different tablet presses. For structural investigation, three samples were selected from the tablets, compressed from the excipient mixture which displayed optimal compressibility in our previous studies.[3,4]

The results of the breaking studies revealed that the tablets prepared with the eccentric press at a compression force of 15 kN (Tablet B) demonstrated acceptable halving properties. However, the tablets compressed from the same material with rotary press under the same conditions (Tablet C) failed this test. These latter results were comparable only with those on the tablets prepared with the eccentric press at a compression force of 5 kN (Tablet A). The X-ray spectrometric pictures of Tablets A–C are presented in Figs 4–6, respectively. It is clearly visible that, despite the differences in the physicochemical parameters (Table 1), the tablets appear to have essentially similar structures. Their density increases from the center to the edges, which is a result of the radial movement of the particles. The gray-scale intensity data (Table 2) of different regions of interest (Fig. 7) indicate that the density gradient increases with increasing compression force. In general, it can be stated that, because of the friction on the die wall, the edge region is 1.1 to 1.4 times denser than the center region of the tablets. Moreover, because of the effects discussed above, a low-density pore (Fig. 7, regions 6a, 6b and 6c) is formed in the center

of the tablets, which exerts a significant effect on the breaking. However, in spite of these similarities, the microstructures of the samples reveal important differences. Tablet A, which has the highest porosity, exhibits poor breaking properties despite the particles being rearranged along vertical lines of force, i.e. the rich pore network allows breaking in many ways, which usually results in a rough breaking surface susceptible to crumbling. This is to be seen in Fig. 8(a), where the mean gray-scale intensities of 256 pixel^2 areas are displayed, with the marking of the possible ways of breaking.

The structure of Tablet B (Fig. 5) is much less porous, and there are more considerable differences in the density distribution. Similarly as for Tablet A, the low-density area visible under the score line (Fig. 5(b)) is of greater importance because of the lower porosity. This area associated with the vertically rearranged particles ensures that the breaking force will pass through the tablet vertically, resulting in a smooth breaking surface (Fig. 8(b)).

In the case of the tablets prepared with the rotary press, the main problem was the breaking into unequal parts. Our previous study suggested that a possible reason is the fact that rotary presses cause only half the stress on the powder bed relative to eccentric presses. However, the porosity of the tablet is unexpectedly not so much higher as compared with that of Tablet B. The structure reveals that the direction of the lines of forces has become deformed, probably because of the bidirectional compression force. This results in an oblique pore structure, which is clearly indicated by the mean gray intensities of the cross-sectional data (Fig. 8(c)). Moreover, the score line is hollower and this makes the low-density area wider. These structural properties lead the breaking force away from the score line and give rise to breaking into unequal halves.

Conclusions

The above results reveal that micro CT is a powerful noninvasive technique for the analysis of the microstructures of pharmaceutical solid dosage forms. They further indicate that the use of an eccentric or a rotary tablet press can give rise to variations in density distribution and have a significant impact on the mechanical properties of tablets, which influences their storage, transport and usage. The knowledge of the differences between the microstructures of scored tablets can help in the development of the production method and point to the optimal shapes of the punches and the score line; this can additionally facilitate data transfer between various tablet presses.

Acknowledgements

We would like to thank the SkyScan Company (B-2550, Kontich, Belgium) for measurements. This work was supported by a Sanofi-Aventis scholarship.

References

[1] N. Rodenhuis, P. A. G. M. De Smet, D. M. Barends, *Eur. J. Pharm. Sci.* **2004**, *21*, 305.
[2] E. van Santena, D. M. Barendsa, H. W. Frijlink, *Eur. J. Pharm. Biopharm.* **2002**, *53*, 139.
[3] T. Sovány, P. Kása jr., K. Pintye-Hódi, *AAPS PharmSciTech* DOI: 10,1208/s12249-009-9225-2.
[4] T. Sovány, P. Kása jr, K. Pintye-Hódi, *J. Pharm. Sci. – US* DOI: 10.1002/jps.21853.
[5] S. Virtanen, O. Antikainen, J. Yliruusi, *Int. J. Pharm.* **2008**, *360*, 40.
[6] D. Traini, G. Loreti, A. S. Jones, P. M. Young, *Microsc. Anal.* **2008**, *111*, 13.
[7] B. C. Hancock, M. P. Mullarney, *Pharm. Technol.* **2005**, *29*, 92.
[8] I. C. Sinka, S. F. Burch, J. H. Tweed, J. C. Cunningham, *Int. J. Pharm.* **2004**, *271*, 215.