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Shape and surface smoothness of pellets made in a rotary processor

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Abstract

The shape and surface smoothness of pellets made in a rotary processor by the wet granulation technique has been studied. Optical microscopy combined with image analysis was used to determine three shape parameters (circularity, roundness and elongation) and the fractal dimension, which is a characteristic for the surface smoothness of the pellets. This study reveals that pellets made in a rotary processor by the wet granulation technique are more variable in terms of their sphericity than in terms of their elongation. In order to obtain very spherical pellets, spheronization should go on for a long time with sufficient intensity. Furthermore, the spheronization enhancing properties of microcrystalline cellulose—thanks to its plastic properties when wetted—are confirmed. The fractal dimensions of the surface are close to 2, indicating that the pellets are characterized by a rather smooth surface. Nevertheless, small but significant differences in surface smoothness can be detected using this fractal approach. From the experiments performed in this study, it can be concluded that using the wet granulation technique in the rotary processor under the appropriate conditions, it is possible to produce excellent pellets in terms of sphericity and surface smoothness.

Keywords: Fractal dimension; Rotary processor; Pellets; Shape; Surface Smoothness; Image analysis

1. Introduction

One of the main purposes of pelletization is to produce spherical particles, which can then be successfully coated and, thus, are optimal for controlled release products. Moreover, spherical particles exhibit good flow characteristics, which aid the transfer of materials. And last but not least, good spherical properties are useful in processes which require an exact metering of granules such as capsule filling.

Different methods have been proposed for the determination of the shape. The most commonly

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used technique is the analysis of microscopic or non-microscopic pictures of the objects of interest (Chapman et al., 1988; Lövgren and Lundberg, 1989; Wan et al., 1993; Podczeck and Newton, 1994). This image analysis technique, however, has up till now only been used for the evaluation of pellets prepared by the extrusion–spheronization process. The first aim of this study is to look for appropriate shape factors, which can be calculated from data obtained by the image analysis. These shape factors should elucidate shape differences between the pellet batches made in a rotary processor. Once appropriate shape factors have been selected, the potential influence of the process and formulation factors on the final shape of the pellets can be examined.

On the other hand, microscopy combined with image analysis can be used to obtain the fractal geometry of a particle. In the pharmaceutical field, fractal geometry has mainly been used in the study of the surface smoothness of powders, either excipients or drugs (Holgado et al., 1995a,b). Since it has been revealed that powder or granule characteristics (Thibert et al., 1988; Cartilier and Tawashi, 1993), like flow and packing properties, are also related to the smoothness of the particle surface knowledge about the smoothness of the pellet surface is important. In this paper, the capability of fractal geometry to differentiate between the several pellet batches made in a rotary processor with respect to their surface smoothness is studied.

To support visually the conclusions on pellet shape and surface, scanning electron microscopic (SEM) pictures are taken.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate (Pharmatose®, type 200 M, DMV, Veghel, The Netherlands), microcrystalline cellulose (Avicel®, type PH-101, FMC, Cork, Ireland) and 1% riboflavin (Produits Roche, Brussel, Belgium) were used as starting materials. All materials were of Ph. Eur. grade. Geometric mean diameters on a weight basis of 42 μm and 44 μm were found for respectively the α-lactose monohydrate and the microcrystalline cellulose as determined with an air jet sieve (type A32OLS, Alpine, Augsburg, Germany). The geometric mean diameter on a volume basis of riboflavin was determined using the electrical sensing zone method (Coulter Multisizer II, Coulter Electronics, Luton, UK), and equalled 3.6 μm. Demineralized water was used as granulation liquid.

2.2. Methods

2.2.1. Pellet production method

The pellets were made in a rotary processor (MP-1, Niro-Aeromatic, Bubendorf, Switzerland) by the wet granulation technique. The equipment, preparation of pellets and experimental design to evaluate the influence of major process and formulation variables have been described earlier (Vertommen and Kinget, 1997). For a better understanding, the independent variables with their different levels are repeated in Table 1.

2.2.2. Image analysis

The method used for image capture and shape analysis by means of the software (PC Image, version 1.5, Foster Findlay Associates, Newcastle upon Tyne, UK) is based on the information provided by Lindner and Kleinebudde (1993) and Hellén and Yliruusi (1993). From the direct measurements, three shape factors were calculated as defined in Eqs. (1)–(3).

$$\text{circularity} = \frac{4 \cdot \pi \cdot \text{area}}{\text{perimeter}^2} \quad (1)$$

Table 1
Low and high levels for the independent variables

	Independent variable	Low level	High level
a	MCC content (%)	30	35
b	Water–MCC ratio	1.18	1.22
c	Rotor speed (rpm)	550	800
d	Spheronization time (min)	5	15
e	Water addition rate (ml/min)	30	60

Table 2
Shape parameters for the different pellet batches

Experiment	Circularity		Roundness		Elongation	
	Mean	CL[a] × 10^{-4}	Mean	CL[a] × 10^{-4}	Mean	CL[a] × 10^{-4}
(1)	0.8762	30	0.7339	58	1.2915	108
a	0.8994	25	0.7639	51	1.2506	86
	0.8887	29	0.7494	51	1.2714	92
b	0.8892	30	0.7614	61	1.2555	104
ab	0.9191	23	0.7791	52	1.2399	90
c	0.8973	29	0.7561	56	1.2711	100
ac	0.9221	25	0.7632	53	1.2749	100
bc	0.9035	30	0.7653	67	1.2662	118
	0.9096	25	0.7662	55	1.2628	98
abc	0.9239	25	0.7805	62	1.2537	110
d	0.8996	25	0.7668	55	1.2494	93
ad	0.9050	24	0.7786	54	1.2354	89
bd	0.9003	22	0.7674	50	1.2498	88
abd	0.9108	26	0.7778	57	1.2408	95
	0.9108	27	0.7848	66	1.2341	114
cd	0.9260	21	0.7864	57	1.2428	101
	0.9175	25	0.7561	58	1.2917	113
acd	0.9238	28	0.7858	73	1.2577	134
bcd	0.9252	21	0.7751	55	1.2649	105
abcd	0.9432	21	0.8107	57	1.2182	110
e	0.9005	25	0.7631	53	1.2565	96
ae	0.9141	33	0.7723	60	1.2542	109
be	0.9260	21	0.7789	51	1.2414	88
	0.9156	31	0.7712	66	1.2582	118
abe	0.9323	20	0.8001	52	1.2198	91
ce	0.9024	32	0.7621	68	1.2736	122
ace	0.9272	26	0.7652	68	1.3014	133
	0.9352	26	0.8012	71	1.2324	129
bce	0.9198	23	0.7728	54	1.2631	101
abce	0.9296	22	0.7742	61	1.2843	123
de	0.9189	21	0.7653	52	1.2590	89
	0.8945	35	0.7534	75	1.2826	136
ade	0.9225	22	0.7791	53	1.2459	94
bde	0.9101	26	0.7740	63	1.2488	108
abde	0.9407	16	0.8165	51	1.1967	86
cde	0.9218	28	0.7610	66	1.3103	140
acde	0.9431	22	0.8124	64	1.2361	128
bcde	0.9281	31	0.7794	78	1.2912	169
abcde	0.9495	19	0.8306	55	1.2025	104
	0.9461	22	0.8219	66	1.2209	130

[a] Value which has to be added to or subtracted from the mean in order to obtain the 95% confidence limits.

$$\text{roundness} = \frac{\text{area}}{\pi \cdot \frac{\text{maximum Feret diameter}^2}{4}} \quad (2)$$

$$\text{elongation} = \frac{\text{maximum Feret diameter}}{\text{minimum Feret diameter}} \quad (3)$$

The purpose of these parameters is to emphasise the spherical (circularity and roundness) or oblate (elongation) shape of pellets. These shape parameters have a theoretical value of one for a perfect round particle.

Table 3
Shape parameter characteristics of four different pellet batches

	Experiment			
	(1)	abe	acde	abcde
Circularity				
Mean	0.8762	0.9323	0.9431	0.9495
95% CI	0.8732--0.8791	0.9303--0.9343	0.9409--0.9453	0.9476–0.9513
Median	0.8851	0.9407	0.9537	0.9588
10%–90%	0.8231--0.9222	0.8884--0.9634	0.9023--0.9707	0.9146–0.9719
Roundness				
Mean	0.7339	0.8001	0.8124	0.8306
95% CI	0.7281--0.7396	0.7949--0.8053	0.8060--0.8189	0.8251–0.8362
Median	0.7409	0.8161	0.8328	0.8556
10%–90%	0.6238--0.8340	0.6792--0.8974	0.6753--0.9146	0.6997–0.9233
Elongation				
Mean	1.2915	1.2198	1.2361	1.2025
95% CI	1.2807--1.3022	1.2107--1.2288	1.2233--1.2489	1.1921–1.2128
Median	1.2570	1.1779	1.1756	1.1456
10%–90%	1.1318--1.4938	1.0769--1.4248	1.0687--1.4824	1.0600–1.4320

The fractal dimension of the contour for 30 pellets of each investigated batch was determined using the inswing structured walk technique (Koch, 1993). For each pellet the natural logarithm of the estimated perimeters, normalised with respect to the maximum Feret diameter, is plotted as a function of the natural logarithm of the stride lengths, normalised with respect to the maximum Feret diameter, resulting in a so-called Richardson plot. If a particle is 'self-similar', i.e. its degree of ruggedness is the same for all scales, one line can be drawn through all data points. Particle contours, however, rarely provide self-similarity and depending on the resolution, one or more linear segments can be found. In this study the linear segment between 3 and 13% of the maximum Feret diameter has been studied. A linear regression is performed between the stride lengths corresponding to 3 and 13% of the maximum Feret diameter of the pellet and the slope and correlation coefficient are determined. The mean of the slopes for the 30 pellets, the 95% confidence interval for this mean and the mean of the correlation coefficients are calculated. From this mean slope, the fractal dimension of the contour (D_l) and surface (D_s) are obtained according to Eq. (4) (Graf, 1991) and 5 (Farin and Avnir, 1992).

$$D_l = 1 + |slope| \quad (4)$$

$$D_S = D_l + 1 \quad (5)$$

2.2.3. SEM pictures

Before examining the pellets with a scanning electron microscope (SEM FEG, XL Series, Philips Electronics, Eindhoven, the Netherlands), the pellets were sputter coated with gold.

3. Results and discussion

3.1. Discriminative potential of the shape parameters

The results for the three shape parameters of the different pellet batches are tabulated in Table 2. The mean value for circularity varies between 0.8762 and 0.9495, and that for roundness between 0.7339 and 0.8306, implying that all pellets are reasonably spherical. In Table 3, the mean values with their 95% confidence interval and the 10, 50 (median) and 90% fractiles of the shape parameter distributions of four selected batches are presented. Using a quick visual evaluation, the pellet batch denoted by (1) was revealed to be a batch containing irregular granules rather than

Table 4
Analysis of variance: effect of the independent variables on the shape parameters of pellets

Factor or interaction	Circularity		Roundness		Elongation	
	F-ratio	Effect	*F*-ratio	Effect	*F*-ratio	Effect
a	54.07	(+) ***	36.31	(+)***	13.93	(—)**
b	20.20	(+)***	15.34	(+)***	6.23	(−)*
ab	0.06	—	0.28	—	0.36	—
c	46.92	(+)***	5.15	(+)*	4.57	(+)*
ac	0.27	—	0.51	—	0.12	—
bc	1.95	—	0.52	—	0.08	—
d	19.82	(+)***	16.47	(+)***	3.18	—
ad	0.73	—	3.61	—	4.82	(−)*
bd	1.52	—	0.00	—	0.14	—
cd	4.60	(+)*	2.52	—	0.08	—
e	38.09	(+)***	10.51	(+)**	0.07	—
ae	0.68	—	2.73	—	1.89	—
be	0.16	—	0.21	—	0.27	—
ce	6.94	(−)*	0.75	—	1.79	—
de	1.10	—	0.14	—	0.18	—

—, no effect; * $p<0.05$; ** $p<0.01$; *** $p<0.001$.

spherical pellets. The pellets of the batch denoted by abe seemed to be rather spherical and the pellets of the batches denoted by acde and abcde were judged as being 'perfect' spheres.

According to Hellén and Yliruusi (1993) circularity is less effective to elucidate shape differences between pellet batches made by extrusion–spheronization. A Kruskal-Wallis test indicates, however, a significant ($P(T>\chi^2)<0.001$) difference between the four pellet batches for both sphericity parameters. Furthermore, the statistical analysis revealed that all of the batches can be

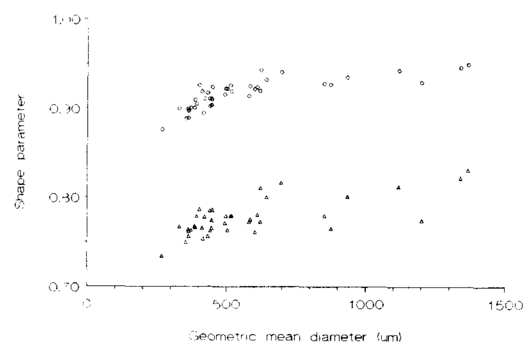

Fig. 1. Circularity (○) and roundness (△) as a function of the geometric mean diameter.

significantly differentiated (95% confidence level) from each other with respect to their sphericity (z-values > 2.638). It can therefore be concluded that pellets made in a rotary processor are more variable in terms of their sphericity than pellets made by the extrusion–spheronization technique under the conditions studied by Hellén and Yliruusi (1993). The range between the absolute mean values for roundness is something larger, but on the other hand it should be mentioned that the width of the distributions (10–90% fractiles) is wider too.

The results for the elongation are presented in Table 2. The mean value for the elongation varies between 1.1967 and 1.2915 indicating that the pellets are slightly elongated. As can be seen in Table 3 the width of the distributions, however, is relatively large and the distributions are skewed with elongation values close to 2 under all conditions studied, which leads to a higher mean elongation. A Kruskal-Wallis test indicates a significant ($P(T<\chi^2)<0.001$) difference between the batches, but batch abe and acde cannot be significantly (95% confidence level) differentiated from each other (z-value < 2.638).

On the other hand, Hellén and Yliruusi (1993) found that pellets made by extrusion–spheroniza-

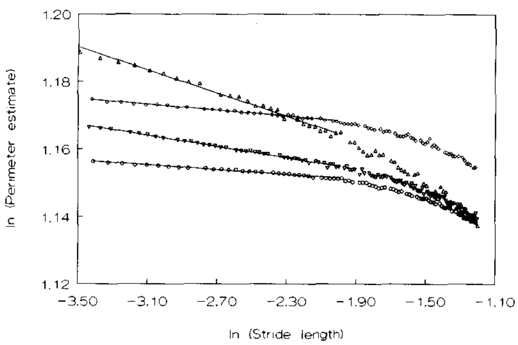

Fig. 2. Richardson plots for a pellet of batch: '(1)' (△), 'abe' (▽), 'acde' (○) and 'abcde' (◇). The perimeter estimate and the stride length have been normalised with respect to the maximum Feret diameter.

tion are more variable in terms of their elongation. This contradictory conclusion arises from the different pellet production method. In the extrusion–spheronization technique, extrudates, i.e. cylindrical segments characterized by a large maximum to minimum Feret diameter ratio, are broken and rounded off in a spheronizer to pellets, characterized by a low maximum to minimum Feret diameter ratio. In contrast to the extrusion–spheronization technique, the wet granulation technique in the rotary processor starts from fairly spherical powder particles, which are build up to spherical pellets and thus there is no transition from a large to small maximum to minimum Feret diameter ratio.

3.2. Influence of the independent variables on the pellet shape

In Table 4 the effect of the independent variables on the shape parameters of pellets are listed. Since second, third or fourth-order interactions are not likely to exist (Philippe, 1967), the results for these higher order interactions together with the replications were used to determine the experimental error. All the independent variables have a significant influence on the sphericity parameters. Increasing any of the independent variables increases the circularity and roundness of the pellets, i.e. the pellets become more spherical. This can be partially explained by the fact that circularity and roundness are linked to the pellet-size. In Fig. 1, the circularity and roundness are plotted against the geometric mean diameter. Larger pellets are generally more spherical due to the fact that they make contact with the rotor disk and inner wall more often. When increasing an independent variable leads to an increase in size (Vertommen and Kinget, 1997) and an increase in size means more spherical pellets, it is quite normal that these independent variables will influence the sphericity to a certain extent.

Taking in account the F-ratios found in the analysis of variance for the geometric mean diameter (Vertommen and Kinget, 1997), it can be concluded that the microcrystalline cellulose content, amount of water added, spheronization speed and time have a relative large F-value for the sphericity parameters. Moreover, a positive interaction between the rotor speed and spheronization time can be seen for the circularity parameter. The water addition rate, although revealed as a significant factor, has a relative low F-value for the sphericity parameters.

The large F-value for the microcrystalline cellulose content is not surprising since microcrystalline cellulose is known to enhance spheronization due to its plastic properties (O'Conner and Schwartz, 1989). To obtain its plastic properties, the microcrystalline cellulose should be sufficiently wetted, which explains the influence of the amount of added water on the sphericity parameters. Furthermore it can be seen that the pellets become more spherical as spheronization speed or time is increased. To obtain spherical pellets it is indeed necessary that pellets undergo the spiral rope-like movement in the rotary processor during an adequate period of time with sufficient intensity. This spiral rope-like movement removes bumps or flat spots on the pellet surface mainly by collision between the particles and the rotor disk or inner wall, or eventually by mutual collision between particles. The spiral rope-like movement is, however, not strong enough to break elongated pieces into smaller fragments. As a consequence, these elongated pieces persist throughout the entire process irrespective of the processing conditions used. Bumps or flat spots on the elongated pieces, which show enough plasticity, are removed reduc-

Table 5
Results of fractal analysis

Experiment	Number of pellets	Slope: mean	95% CL[a]	Correlation coefficient: mean
(1)	30	−0.0174	0.00129	−0.991
abe	30	−0.0083	0.00058	−0.986
acde	30	−0.0035	0.00013	−0.992
abcde	30	−0.0043	0.00019	−0.992

[a] Value which should be added to or subtracted from the mean to obtain the 95% confidence limits.

ing the elongation, but whatever the conditions used in this study, particles with an elongation close to 2 have been obtained.

3.3. Fractal geometry of four pellet batches

In Fig. 2, the Richardson plots obtained for a pellet from each of the four selected pellet batches are presented. The results for the linear regression of the Richardson plots of the 30 pellets of each of the four batches are listed in Table 5. The mean fractal dimensions calculated from the slopes of the Richardson plots are 1.0174, 1.0083, 1.0035, and 1.0043 for experiment (1), abe, acde and abcde. Using Eq. (5), fractal dimensions of the surface of 2.0174, 2.0083, 2.0035, and 2.0043 are obtained. Since these values are close to 2, which refers to the classical assumption of a smooth and flat area, it has to be concluded that these pellets are characterized by a rather smooth surface.

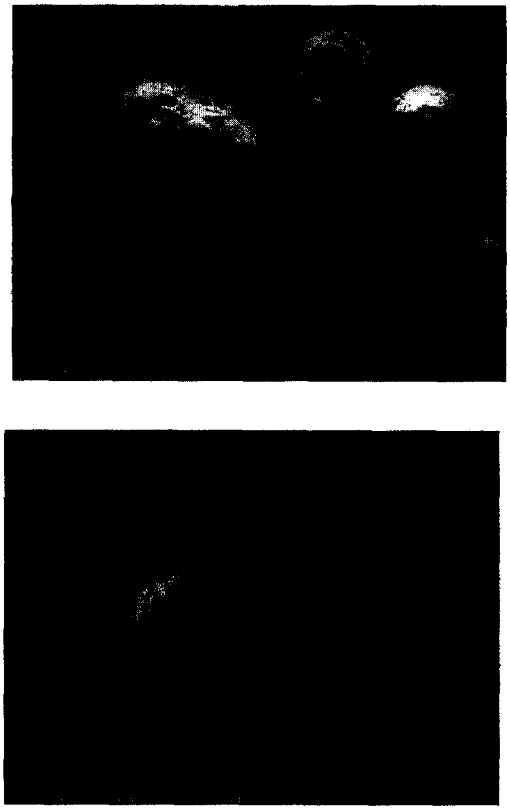

Fig. 3. Pellets with smallest geometric mean diameter. (experiment '(1)', sieve fraction 180–250 μm). Magnification: A, $\pm 100\times$; B, $\pm 400\times$.

Furthermore, and despite their rather smooth surface, it is still possible to differentiate between the pellet batches. A Mann-Whitney two sample test indicates for example a significant ($P(|z| > 5.574) < 0.0001$) difference between batch acde and abcde. The pellets of batch (1) have the roughest surface, while pellet batches acde and abcde are characterized by the smoothest surfaces. The pellets of batch (1) are the least spherical pellets, while pellets of batch acde and abcde are the most spherical ones. Generally, it can be concluded that sphericity and surface smoothness are to some extent linked to each other. Indeed, the same forces that make the pellets more spherical by removing bumps and flat spots, will smooth the pellet surface. However, although the pellets of batch abcde are the most spherical ones (circularity of 0.9495), they are not the smoothest ones (D_s of 2.0043), and the smoothest ones (D_s of 2.0035), i.e. pellet batch acde, are not the most spherical ones (circularity of 0.9431). Therefore, sphericity and smoothness are not completely coincident and the fractal dimension of the surface may even give a more accurate idea to what

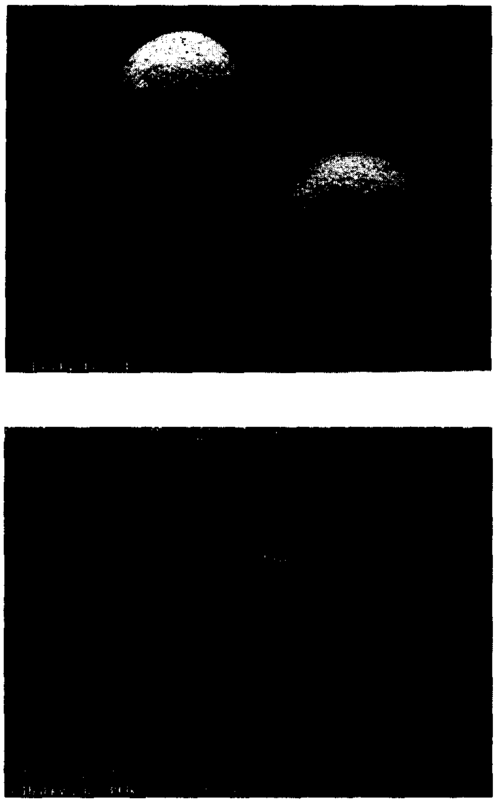

Fig. 4. Pellets with a large geometric mean diameter (experiment 'abcde', sieve fraction 1180–1400 μm). Magnification: A, ± 25 × ; B, ± 400 × .

extend the bumps or flat spots are removed by the forces acting in the rotary processor.

The differences between the pellet batches acde and abcde in terms of sphericity and surface smoothness are small, and one should, therefore, not expect to observe a different behaviour due to these small differences in sphericity and surface smoothness during further processing like for example, coating. If sphericity and surface smoothness deviate quite far from the ideal picture of a smooth sphere, like the pellets of batch (1), one should take this under consideration if for example these pellets are coated. The amount of coating mass needed to get a certain uniform coating thickness, will not be in agreement with the calculated one, which is based on the assumption of an ideal smooth sphere.

3.4. SEM photographs

The photographs shown in Fig. 3 are taken from the pellet sample characterized by the smallest geometric mean diameter (experiment (1)). It is clear from these photographs that the pellets or granulates are not perfectly spherical nor do they have a smooth contour and surface. This agrees with the lower value for the sphericity parameters and higher fractal dimension obtained for this pellet batch. Several individual subelements in the pellets as well as smaller particles adhering to the larger agglomerates can be observed in the pictures. Hence, it can be concluded that agglomeration with subsequent smoothing has not yet been finished. On the left hand side of Fig. 3A, a regular shaped particle with flat surfaces can be seen. Such pieces are rarely observed and are most probably pieces which have adhered to the rotary processor wall or baffle.

The photographs in Fig. 4 are taken from pellets characterized by a large geometric mean diameter (experiment abcde). In agreement with the values for the sphericity parameters and fractal dimension for this batch, spherical pellets with a smooth contour and surface can be observed in these photographs.

Fig. 5 shows the photograph of a pellet sample (experiment abe) with a geometric mean diameter situated between the two extremes discussed before. The pellets show characteristics of both extremes, i.e. semi-spherical to spherical particles

Fig. 5. Pellets with intermediate geometric mean diameter (experiment 'abe', sieve fraction 710–1000 μm). Magnification: ± 25 × .

with a rather smooth contour in which, however, still a few individual subelements can be detected. These observations agree with the values for the sphericity parameters and fractal dimension, which are situated between the two extremes discussed before.

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