Structure of Disintegrating Pellets with Regard to Fractal Geometry

Martin Schröder[1] and Peter Kleinebudde[1,2]

Received April 28, 1995; accepted July 25, 1995

Purpose. The aim of this study was to investigate the influence of the granulation liquid on pellet properties.

Methods. Pellets containing propyphenazone were obtained by extrusion/spheronization using different 2-propanol/water mixtures as granulation liquids. The pore structure of the pellets was determined by mercury porosimetry. The fractal dimension of the pore system was calculated according to the model of the Menger sponge. Further characterization included SEM-photographs, disintegration, dissolution and tensile strength.

Results. Fractions exceeding 40% 2-propanol in the fluid resulted in rapid dissolution rates of the pellets. This effect was caused by the rapid and complete disintegration of the pellets as compared to those obtained with less 2-propanol in the mixture. These phenomena were interpreted as being due to a change in the particle bonding of the pellets at concentrations of 40% 2-propanol. Evidence for this hypothesis resulted from the spheronization process, the tensile strength measurements and from SEM-photographs. The analysis of the pore system in terms of fractal dimensions implied a dependency of the fraction of 2-propanol in the granulation liquid on the pore structure. High fractions of 2-propanol resulted in lower fractal dimensions close to the dimension of the Menger sponge (2.727).

Conclusions. The structure of pellets can be markedly influenced by the composition of the granulation liquid. Investigations of the pore system in terms of fractal geometry are more useful for the explanation of pharmaceutical properties than if the pure values for the porosity are taken.

KEY WORDS: pellet structure; dissolution rate; porosity; fractal dimension; granulation liquid; tensile strength.

INTRODUCTION

The aim of a previous study (1) was to enhance the dissolution rate of propyphenazone from pellet formulations. The pellets did not disintegrate and the dissolution rate was only marginally influenced by the investigated formulations. This study deals with the development and characterization of a disintegrating pellet formulation to allow a rapid dissolution of propyphenazone.

Water is the most commonly used liquid in granulation technology. In the field of pellet technology only some studies have dealt with the effects of mixtures of water and alcohol as granulation liquid (2–4). There are some hints that the pellets resulting from this manufacture may disintegrate. This study focuses the attention on the effects of 2-propanol/water-mixtures as granulation liquid.

Furthermore the differences in the structure of disintegrating or not disintegrating pellets were compared. Recent literature has dealt with fractal geometry to describe the structure of a porous body (5–8). The complexity of the pore system is fixed in a single figure, that of the fractal dimension. The changes in the disintegration and dissolution behavior may correlate with changes in the fractal dimension of the pore system. Thus the concept of fractal dimensions was used to distinguish between the pellet batches. Furthermore SEM-photographs and tensile strength were used to characterize the pellet structure.

MATERIALS AND METHODS

Materials

Propyphenazone (BP, Oranienburger Pharmawerk, D-Oranienburg) was used as a model drug. Sodium starch glycolate (Primojel, BP; Bufa B.V., NL-Uitgeest) was used as disintegrant and microcrystalline cellulose (Avicel PH 102, USP/NF/EP, FMC-Corp., Pa USA) as filler. Colloidal silicon dioxide (Aerosil 200, Degussa, D-Frankfurt) was added to enhance the flowing properties. Mixtures of 2-propanol (Merck, D-Darmstadt) and demineralized water were used as granulation liquid.

Pellet Preparation

Mixtures of 30% (w/w) propyphenazone, 10% (w/w) sodium starch glycolate, 59.5% (w/w) microcrystalline cellulose, and 0.5% colloidal silicon dioxide with a batch size of 1.5 kg were blended for 15 minutes in a Turbula-blender (Type T10B, W.A. Bachhofen AG, CH-Basel). The weights of all substances were corrected for their moisture content. Mixtures of demineralized water and 2-propanol were used as granulation liquids; the concentrations of 2-propanol were varied between 0 and 60% (w/w) in steps of 5 or 10%.

The pellets were prepared by an extrusion/spheronization process as previously described (9). The content of granulation liquid was adjusted by running the power-consumption-controlled extruder (10) at 170 W. Some selected batches were repeated to estimate the experimental error.

The pellets were first dried in a fluid bed (Type TR2, Glatt, D-Haltingen) at 45°C for 30 min. The drying was completed on a tray in a forced-air oven at 35°C for 24 hours. Additionally pellets extruded with pure water as granulation liquid were freeze dried (Lyovac GT 3, Leybold-Heraeus, D-Köln)

All further characterizations were performed with the 900–1000 μm sieve fraction.

Dissolution Testing

The dissolution profiles were obtained as described earlier (1). Pellets with a sample mass of about 100 mg were used in the present study to meet sink conditions. Each batch was tested twice.

Disintegration Time

Disintegration time tests were carried out according to

[1] Department of Pharmaceutics and Biopharmaceutics, Christian-Albrechts University of Kiel, Kiel, Germany.

[2] To whom correspondence should be addressed at Christian-Albrechts University of Kiel, Department of Pharmaceutics and Biopharmaceutics, Gutenbergstr. 76-78, D-24118 Kiel, Germany.

0724-8741/95/1100-1694$07.50/0

the USP XXII (ZT4, Erweka-Apparatebau, D-Heusenstamm). Demineralized water was used as immersion fluid. Nevertheless, a modification was necessary because this apparatus is usually used to test tablets. The pellets were not placed directly in the basket-rack assembly. An amount of 100 mg pellets was filled in a Plexiglas cylinder with sieves of 710 μm on top and bottom. This cylinder weighted with a steel tube was placed in the basket-rack assembly. The disintegration time was set to the point at which no more particles were present on the sieve. All runs were performed in duplicate.

Porosity and Pore Structure

The true density (ρ_t) of the 900–1000 μm fraction was measured using a helium pycnometer (AccuPyc 1330, Micromeritics, USA-Norcross). The values of ρ_t were mean values of a minimum of 5 runs. The apparent density (ρ_a) was determined by mercury displacement (Macropores Unit 120, Carlo Erba Instruments, I-Milano). The porosity (ϵ) was calculated according to eq. 1.

$$\epsilon = \left(1 - \frac{\rho_a}{\rho_t}\right) \cdot 100\ [\%] \qquad (1)$$

Richardson plots were obtained from mercury intrusion data (Porosimeter 2000, Carlo Erba Instruments, I-Milano). The intruded mercury volume (V_i) was detected conductometrically and recorded from a computer. The relative density (ρ_r) was calculated using eq. 2. where V_a is the apparent volume. To avoid compressibility effects of mercury, pressures above 71 MPa were disregarded for further calculations. The corresponding pore diameter (d) was calculated according to the Washburn equation (11).

$$\rho_r = \frac{(V_a - V_i)}{V_a} \qquad (2)$$

Tensile Strength

At least 50 pellets of each batch were crushed with a texture analyzer (TA-XT2, Stable Micro Systems, GB-Haslemere, Surrey). The punch was moved with a speed of 1 mm/s down on the pellet. Following this the strain was 50% of the pellet height (d) while measuring the force as crushing strength (cs). The tensile strength (ts) was calculated for each individual pellet according to eq. 3. The arithmetic mean was set as tensile strength for the batch.

$$ts = \frac{4 \cdot cs}{\pi \cdot d^2} \qquad (3)$$

SEM-Photographs

The pellets were coated with a gold layer using a sputter (SCD 005, Bal-Tec AG, Fürstentum-Liechtenstein) with 50 mA for 180 s. Subsequently SEM-photographs were taken with a scanning electron microscope (XL 20, Philips, NL-Eindhoven).

RESULTS AND DISCUSSION

Spheronization Behavior

In preliminary investigations it was found that fractions of more than 70% (w/w) 2-propanol caused problems during the extrusion process. It was not possible to obtain steady state extrusion conditions and the resulting products were not homogenous. Thus the fraction of 2-propanol in the granulation liquid was only varied between 0–60% (w/w). These conditions of manufacture resulted in pellets with one exception. The extrudates manufactured with 40% (w/w) 2-propanol were not stable during spheronization and turned partially back into a powder. It was astonishing that this effect was not observed for 30% and 50% 2-propanol in the granulation liquid. Thus for further characterization only a sieve fraction of agglomerated particles could be gained from batches manufactured with 40% (w/w) 2-propanol.

Dissolution

The dissolution profiles are shown in Fig. 1. The dissolution rate is strongly dependent on the fraction of 2-propanol in the granulation liquid. Using water as granulation liquid the pellets stayed intact. The dissolution behavior could be described by the $\sqrt{t}$-law from Higuchi. For fractions of more than 20% 2-propanol remarkably higher dissolution rates were obtained. Fractions of 2-propanol from 40% to 60% in the granulation liquid led to very rapid dissolution. Similar dissolution profiles were found earlier for manually destroyed pellets (1). This is in accordance with the results from Bonny and Leuenberger (12) who found that destroying of the matrix resulted in a higher dissolution rate. Nevertheless destroying of the matrix here was not reached by exceeding a percolation threshold.

Disintegration

The disintegration times (Tab. 1) of the pellet batches were markedly influenced by the composition of the granulation liquid. Concentrations from 0% to 20% (w/w) 2-propanol resulted in disintegration times higher than 15 min.

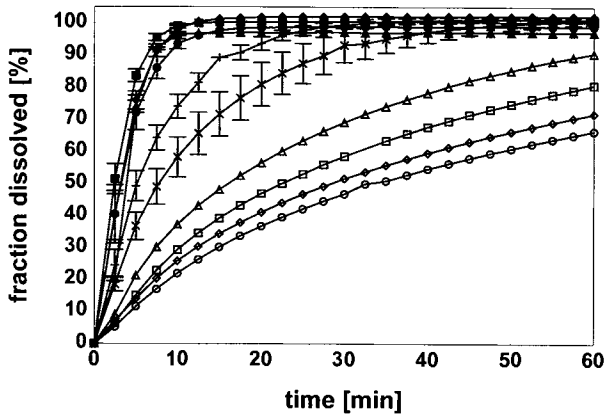

Fig. 1. Dissolution profiles: mean curves for pellets manufactured with different fractions of 2-propanol in the granulation liquid in % (w/w) (n = 2–6, standard deviations smaller than symbol size are not shown). ○: 0%, ◇: 10%, □: 15%, △: 20%, ×: 30%, +: 35%, ●: 40%, ◆: 45%, ■: 50%, ▲: 60%.

Table I. Influence of the Fraction of 2-Propanol in the Granulation Liquid on Disintegration Time, Porosity and Fractal Dimensions of the Pore Volume

2-propanol [% (w/w)]	dt (1. run) [s]	dt (2. run) [s]	ϵ [%]	D_1	D_2
0	>900	>900	5.3	2.98	2.88
0	>900	>900	3.8	3.00	2.86
0[1]	>900	>900	53.9	2.90	2.95
10	>900	>900	18.8	2.90	2.95
10	>900	>900	17.5	2.86	2.97
15	>900	>900	21.6	2.78	2.97
20	>900	>900	22.4	2.76	2.98
30	180	245	29.6	2.80	2.98
30	381	>900	31.3	2.84	2.98
35	170	67	33.5	2.81	2.98
40	28	31	46.3	2.77	2.96
40	25	24	47.0	2.76	2.95
45	55	52	42.9	2.70	2.93
50	73	90	40.8	2.77	2.92
50	65	122	39.5	2.70	2.92
50	70	60	35.7	2.83	2.92
60	117	74	38.0	2.78	2.92
60	121	135	33.7	2.68	2.92

[1] freeze dried.
dt: disintegration time.
ϵ: porosity.
D_1: fractal dimension of the between grain void space.
D_2: fractal dimension of the within grain void space.

which indicates no or only incomplete disintegration. Between 30% and 35% a transition took place and the resulting pellets disintegrated. First a distinct erosion was obvious. This erosion resulted in a higher dissolution rate indicating a partial destroying of the matrix. At fractions of more than 35% 2-propanol in the granulation liquid pellets were obtained with a disintegration time of about 1–2 min. Therefore the dissolution behavior can be explained by the disintegration of the pellets. The freeze dried pellets showed no disintegration within 15 min.

Porosity and Pore Structure

The porosity of the pellets is presented in fig. 2. Increasing fractions of 2-propanol resulted in higher values for the porosity. However, a kink is obvious at about 40% 2-propanol. This may indicate that a transition in the particle bonding took place. The pure value for the porosity could not be related with the disintegrating properties of the pellets. Although freeze-drying and therefore avoiding of shrinking (13) resulted in a total porosity of more than 50% a disintegration of these pellets could not be found.

Under the prerequisite of a constant formulation and therefore same particle size the pore system may give an impression of the changes in structure and bonding of the pellets. Ritter and Drake (14,15) introduced a mercury intrusion technique to get more detailed information about the structure of solid bodies. In the field of pellet technology e.g. Niskanen (16) used the mercury intrusion data to compare pellets consisting of theophylline of different particle sizes and binder-solution concentrations.

Fractal geometry is a new approach in the investigation of the complexity of a system and was established by Mandelbrot (17). In the meantime fractal geometry has been applied to many pharmaceutical fields as well (18). Mercury intrusion data are appropriate for calculating fractal dimensions of the pore system of a natural body (5–8,19). For this purpose a double-logarithmic presentation -so called Richardson-plot- was used by some authors (6,20) to visualize the complexity and fractal behavior of a system. Self-similarity and therefore fractal behavior resulted in a linear relationship in this plot.

The self-similarity of real objects such as the pellets investigated here was not invariant in the whole range of scale. Thus more than one linear segment and nonfractal segments appeared for these objects. Kaye (19) suggested using the slopes of the linear segments as fractal dimensions representing the between grain voids (D_1) and within grain

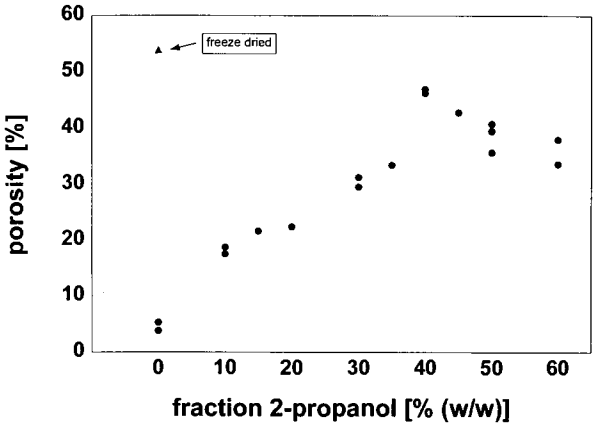

Fig. 2. Porosity of all pellet batches in dependence of the fraction of 2-propanol in the granulation liquid.

voids (D_2) volume space. Others (5,6) used the model of the Menger sponge to determine the fractal dimension leading to values between 2 and 3 which were closer to the more easily imagined Euclidean dimension.

The fractal dimension D of the pore volume was calculated according to the straight line relationship of eq. 4. This formula was derived in (6) regarding the model of the Menger sponge. The linear sections in the Richardson-plots for between grain voids and within grain voids were fixed visually and the slopes were obtained from linear regression.

$$\log(\rho_r) = (3 - D) \cdot \log(d) + C \quad (4)$$

ρ_r relative density
D fractal dimension
d pore diameter
C constant

The mercury intrusion data are presented as Richardson plots in fig. 3. Increasing fractions of 2-propanol in the granulation liquid resulted in changes in the Richardson-plot indicating changes in the structure of the pellets. A remarkable effect occurred when the granulation liquid contained more than 40% 2-propanol. Discrete changes in the mercury intrusion data were found for these pellets. While the powder mixture and therefore the particle size remained constant these changes might indicate a transition in the structure and particle bonding of the pellets. The freeze dried pellets were found to have a high porosity. However, the particle bonding mechanism should not be influenced by the drying process. The graph for the mercury intrusion data in fig. 3 proved that these pellets must have another structure than those granulated with high amounts of 2-propanol. Consequently pellets with high porosity could be distinguished by their pore structure.

Water as granulation liquid led to a fractal dimension D_1 of about 2.9–3 which is close to the Euclidean dimension of a three-dimensional body (Table I). D_1 was independent of the drying process as seen for the freeze-dried pellets. Increasing fractions of 2-propanol in the granulation liquid led to a decrease in the fractal dimension D_1 to values of about 2.7–2.8. This was closer to the fractal dimension of the Menger sponge (2.727). Leuenberger et al. (7) reported fast disintegrating tablets to have fractal dimensions of the porous network in the range from 2.82 to 2.88. The fractal dimension D_1 represents the between grain voids depending on the particle size distribution and the particle bonding. Under consideration that the powder mixture is constant it can be concluded that the composition of the granulation liquid had a remarkable influence on the particle bonding. The effect of the granulation liquid on the fractal dimension D_2 was smaller than expected.

The concept of fractal dimensions is suitable for detecting the differences resulting from the switch in granulation liquid from water to 2-propanol/water-mixtures. The transition in the range from 30–50% was not reflected well in the fractal dimensions because the slopes in the Richardson plots were very similar for higher fractions of 2-propanol in the granulation liquid. Nevertheless the whole shape of the curves in the Richardson plot changed discretely in this range of concentration and indicated a change in the structure of the pellets. This confirmed the other results.

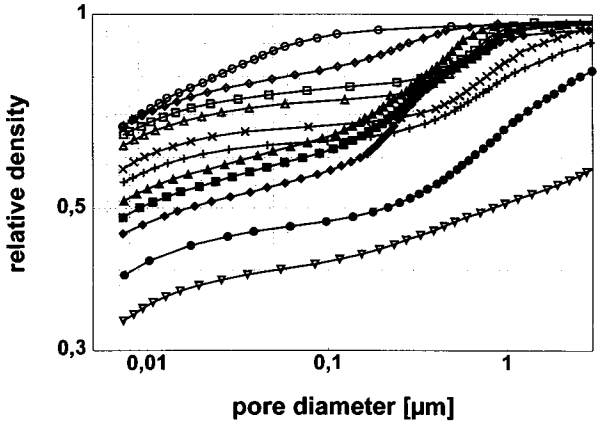

Fig. 3. Richardson-plots calculated from mercury intrusion data for pellets prepared with different fractions of 2-propanol in the granulation liquid in % (w/w) (For greater clarity only every 10th measured point is shown.). ○: 0%, ▽: 0%; freeze dried, ◇: 10%, □: 15%, △: 20%, ×: 30%, +: 35%, ●: 40%, ◆: 45%, ■: 50%, ▲: 60%.

Tensile Strength

Assuming a change in structure and particle bonding the tensile strength might be influenced. The results are presented in fig. 4. It is obvious that increasing fractions of 2-propanol led to lower values for the tensile strength. This suggested that the particle bonding was weakened by the addition of 2-propanol to the granulation liquid. Here again a kink appeared in the graph between 40% and 50% of 2-propanol indicating a transition in the structure of the pellets. The mechanical properties were markedly affected by the composition of the granulation liquid.

SEM-Photographs

SEM-photographs of some selected batches are presented in fig. 5A–5F. The change in structure and particle bonding, resulting from higher fractions of 2-propanol in the granulation liquid, is well documented here. Fractions of 2-propanol from 0% and 35% (5A,5C) resulted in a similar structure. Even the freeze dried pellets (5B) with the highest

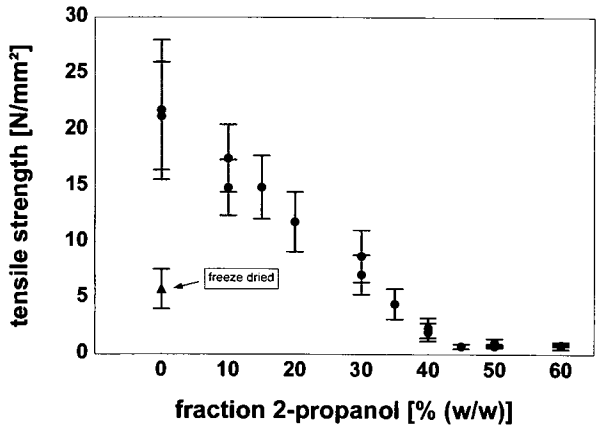

Fig. 4. Tensile strength of pellets prepared with different fractions of 2-propanol in the granulation liquid; arithmetic mean and standard deviation for each tested batch ($n \geq 50$).

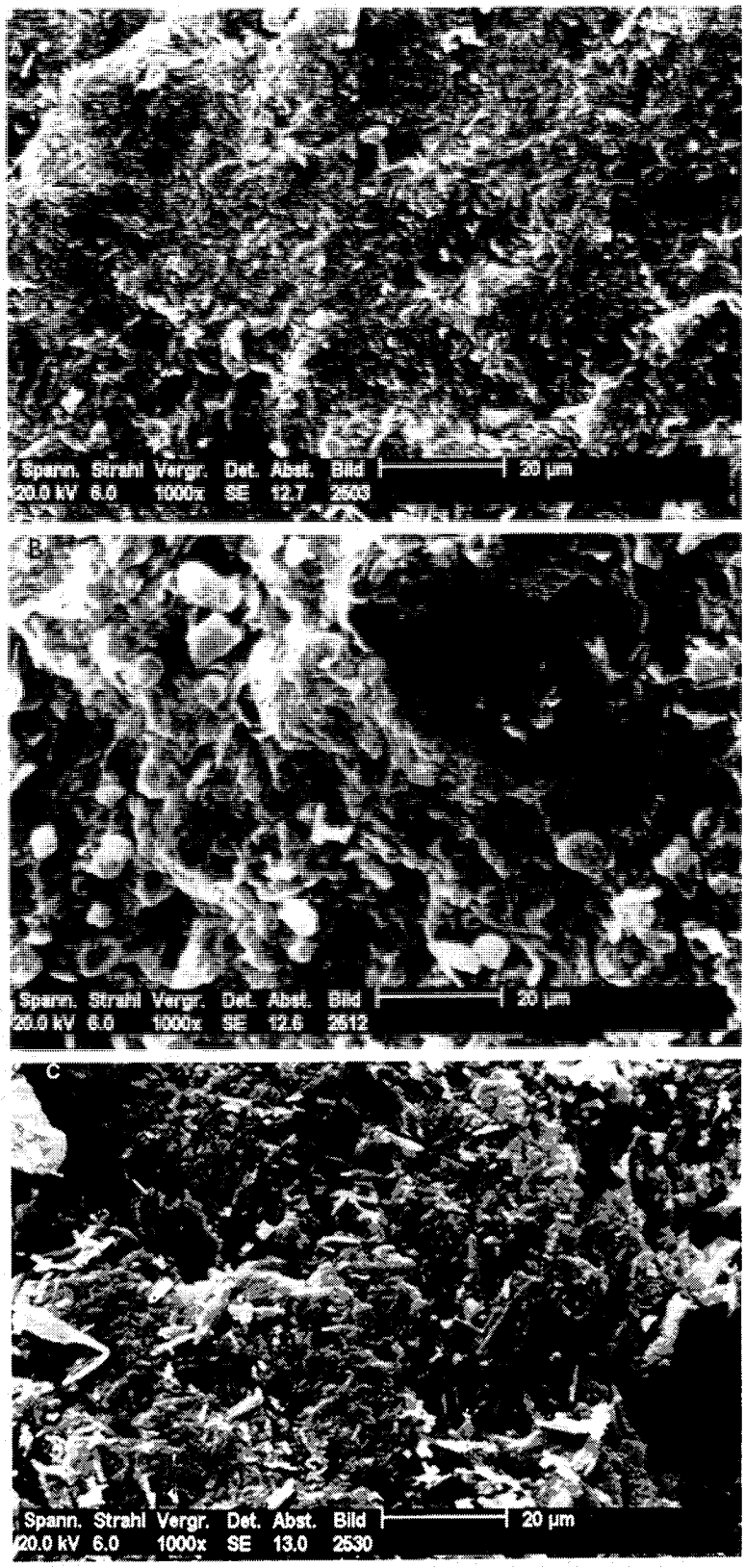

Fig. 5. SEM-photographs of pellets prepared with different fractions of 2-propanol in the granulation liquid in % (w/w) (magnification: 1000×).

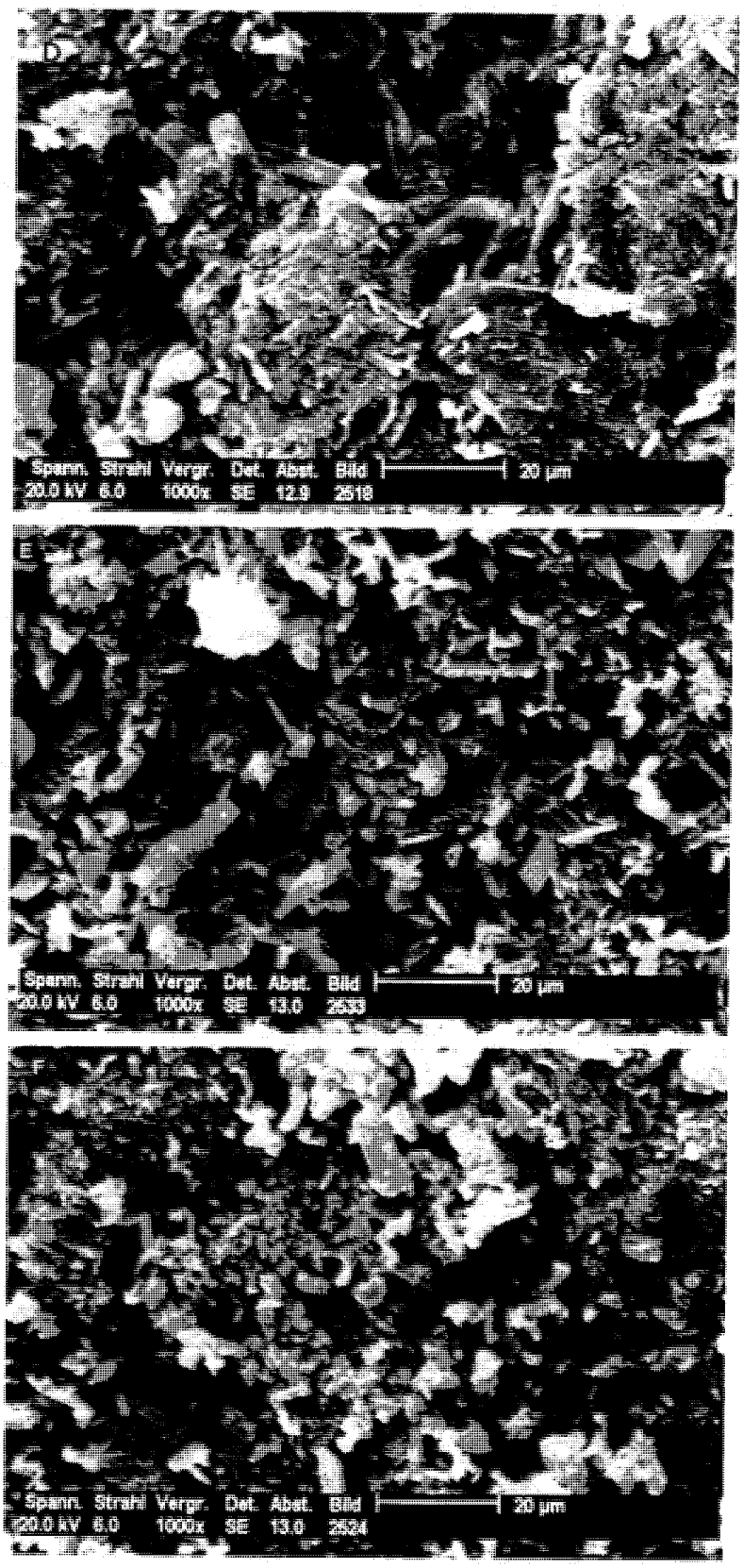

Fig. 5. Continued.

measured porosity showed a similar surface structure. A very different structure was observed for 45% and 60% (5E,5F) but within this range the structure was similar. The transition in the particle bonding can be illustrated by the pellets extruded with 40% 2-propanol (5D) where both kinds of structural elements predominate.

ACKNOWLEDGMENTS

The authors are indebted to Prof. B. Tillmann for giving the possibility to make SEM-photographs in his institute and Mr. H. Mrohs for the introduction in this method. Further thanks are due to the companies Oranienburger Pharmawerk, Lehmann & Voss and Bufa for the supply of materials.

REFERENCES

1. M. Schröder and P. Kleinebudde. Influence of formulation parameters on dissolution of propyphenazone pellets. *Eur. J. Pharm. Biopharm.* accepted
2. F. W. Goodhart, J. R. Draper and F. C. Ninger. Design and Use of a Laboratory Extruder for Pharmaceutical Granulations. *J. Pharm. Sci.* **62**:133–136 (1973).
3. G. P. Millili and J. B. Schwartz. The strength of microcrystalline cellulose pellets: The effect of granulating with water/ethanol mixtures. *Drug Dev. Ind. Pharm.* **16**:1411–1426 (1990).
4. J. A. C. Elbers, H. W. Bakkenes and J. G. Fokkens. Effect of amount and composition of granulation liquid on mixing, extrusion and spheronization. *Drug Dev. Ind. Pharm.* **18**:501–517 (1992).
5. W. I. Friesen and R. J. Mikula. Fractal Dimensions of Coal Particles. *J. Colloid Interface. Sci.* **120**:263–271 (1987).
6. M. Usteri, J. D. Bonny and H. Leuenberger. Fractal Dimension of Porous Solid Dosage Forms. *Pharm. Acta Helv.* **65**:55–61 (1990).
7. H. Leuenberger, R. Leu and J. D. Bonny. Application of percolation theory and fractal geometry to tablet compaction. *Drug Dev. Ind. Pharm.* **18**:723–766 (1992).
8. J. D. Bonny and H. Leuenberger. Determination of fractal dimensions of matrix-type solid dosage forms and their relation with drug dissolution kinetics. *Eur. J. Pharm. Biopharm.* **39**:31–37 (1993).
9. P. Kleinebudde and H. Lindner. Experiments with an instrumented twin-screw extruder using a single-step granulation/extrusion process. *Int. J. Pharm.* 94:49–58 (1993).
10. P. Kleinebudde, A. J. Sølvberg and H. Lindner. The Power-consumption-controlled Extruder: A Tool for Pellet Production. *J. Pharm. Pharmacol.* 46:542–546 (1994).
11. E. W. Washburn. Note on a method of determining the distribution of pore sizes in a porous material. *Proc. Nat. Acad. Sci.* 7:115–116 (1921).
12. J. D. Bonny and H. Leuenberger. Matrix type controlled release systems: I. Effect of percolation on drug dissolution kinetics. *Pharm. Acta Helv.* **66**:160–164 (1991), II. Percolation effects in non-swellable matrices. *Pharm. Acta Helv.* **68**:25–33 (1993).
13. P. Kleinebudde. Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: I. Shrinking properties. *Int. J. Pharm.* **109**:209–219 (1994), II. Swelling properties. *Int. J. Pharm.* **109**:221–227 (1994).
14. H. L. Ritter and L. C. Drake. Pore-Size Distribution in Porous Materials. *Ind. Eng. Chem.* 17:782–786 (1945).
15. H. L. Ritter and L. C. Drake. Macropore-Size Distributions in Some Typical Porous Substances. *Ind. Eng. Chem.* 17:787–791 (1945).
16. M. Niskanen. Explaining the Dissolution Properties of Theophylline Pellets by their Microstructure. *Pharm. Tech. Int.* (Sept.): 20–38 (1992).
17. B. Mandelbrot. *The Fractal Geometry of Nature*, Freeman & Co., New York, 1977.
18. H. P. Koch. The concept of fractals in the pharmaceutical sciences. *Pharmazie.* 48:643–659 (1993).
19. B. H. Kaye. *A Random Walk Through Fractal Dimensions*, VCH, Weinheim, Germany, 1989.
20. H. Leuenberger, L. Holman, M. Usteri and S. Winzap. Percolation Theory, Fractal Geometry, and Dosage Form Design. *Pharm. Acta Helv.* 64:34–39 (1989).