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Shrinking and swelling properties of pellets containing microcrystalline cellulose and low substituted hydroxypropylcellulose: I. Shrinking properties

Peter Kleinebudde

Department of Pharmaceutics and Biopharmaceutics, Christian-Albrechts-University, Gutenbergstrasse 76 / 78, 24118 Kiel, Germany

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Abstract

From a previous study it is known that pellets obtained from extrusion/spheronization containing microcrystalline cellulose (MCC) and/or low-substituted hydroxypropylcellulose (L-HPC) are able to shrink during drying. This phenomenon has important consequences for pellet properties. The pellet size is reduced while the shape remains constant. Densification during shrinking leads to a lower porosity. In the actual study, shrinking and swelling phenomena were analysed quantitatively. This paper (part I) describes the manufacturing of the pellets and their shrinking properties together with their porosities, friabilities and liquid saturations. The accompanying article (part II) investigates the swelling and dissolution properties of the resulting pellets. Drying methods are of great importance for the properties of resulting pellets. Parts of the same formulations were dried alternatively by fluid-bed, oven or freeze-drying techniques and analysed with the aid of image analysis. Additionally, image analysis of the wet pellets was performed before drying. Freeze-drying almost suppressed shrinking of pellets. The size distributions of freeze-dried pellets are comparable to those of wet (undried) pellets and their porosities are very high. Fluid-bed and oven drying led to identical shrinking phenomena. The influence of the presence of L-HPC in the formulation on the shrinking process was studied. The extent of shrinking is influenced by the amount of excipients which are able to absorb water, the water content of the extrudate and the manner of drying. Freeze-drying prevents shrinking.

Key words: Extrusion/spheronization; Pellet; L-HPC; MCC; image analysis; Porosity; Freeze-drying; Fluid-bed drying

1. Introduction

The width of pellets resulting from an extrusion/spheronization process should equal at least the die diameter. The length depends on the spheronization behaviour of the extrudate and equals the width under ideal circumstances. In a previous study (Kleinebudde, 1993), the sizes of pellets determined through image analysis were found to be smaller than expected. Pellets produced with 1 mm die diameters showed a width between 0.84 and 0.98 mm. Also, the projected area of the pellets was less than expected. It was suggested that this is due to the swelling proper-

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ties of L-HPC. Wet pellets were found to shrink during fluid-bed drying.

The aim of this study was to confirm the results of the former investigation and to explore the relations between formulation and process variables with respect to the shrinking and swelling behaviour of pellets. Pellets were alternatively dried via a standard fluid-bed technique, freeze-drying or oven drying. The formulation variables were the type of drug, the inclusion of L-HPC and the water content of the extrudate. For the determination of the extent of shrinking the size of wet pellets was measured by image analysis directly after spheronization. The same pellets were inspected again after drying in an oven. Additionally, the porosity and friability of some selected batches were examined.

2. Materials and methods

2.1. Materials

Acetaminophen USP (Mallinckrodt, Raleigh, U.S.A.), caffeine BP, USP (Merck, Darmstadt, Germany), propyphenazone BP (Oranienburger Pharmawerk, Oranienburg, Germany), microcrystalline cellulose (MCC, Avicel PH 101, FMC Inc., Philadelphia, U.S.A.) and Aerosil 200 (Degussa, Frankfurt, Germany) were used as received. Two types of low substituted hydroxypropylcellulose (L-HPC, Shin-Etsu Chemical Co., Tokyo, Japan) were used in this study: LH 20 with 13.3% hydroxypropyl content (Certificate of Analysis) has an average particle size of 40 μm (Shin-Etsu 1991) and LH 30 with 13.2% hydroxypropyl content 25 μm, respectively.

The moisture content of the different powders was determined by weighing before and after drying at 105°C for 18–24 h. Demineralized water was used as granulation liquid. Other materials were of analytical grade.

2.2. Experimental design

Pellets containing 30% (w/w) of acetaminophen (ace), caffeine (caf) or propyphenazone (pro), respectively, were manufactured. Batches coded no. 1 contained 30% drug, 69.5% microcrystalline cellulose (MCC, Avicel PH 101, FMC Inc., Philadelphia, U.S.A.) and 0.5% Aerosil 200 (Degussa, Frankfurt, Germany). In batches coded no. 2 low substituted hydroxypropylcellulose (L-HPC, Shin-Etsu Chemical Co., Tokyo, Japan) was substituted for 20% of MCC. The individual runs were identified by the drug, the absence or presence of L-HPC and the number of the run, e.g., ace1.2 denotes the second run with acetaminophen but without L-HPC. For acetaminophen a blend with L-HPC LH 30 was additionally made. Runs ace2.4–ace2.6 were performed with L-HPC LH30.

2000 g of each blend were extruded in three runs with different levels of water content in randomised order. The levels for the water contents depended on the composition.

2.3. Production procedure

Blending and extrusion were performed as described previously (Kleinebudde and Lindner, 1993) using a co-rotating twin-screw extruder. The axially mounted die plate had 48 dies of 1 mm diameter and 2.5 mm length. The batch size was 2000 g dry powder mass, corrected for moisture content of the raw materials. For all trials the dry powder feed rate was 25 g min^{-1} and the extrusion speed was fixed at 60 rpm. During extrusion several samples of extrudate were drawn in order to determine their water contents. After starting the extrusion process the extrudate of the first 200 s was discarded. Collection of the extrudate was then begun until 750 g had accumulated. Power consumption of the extruder, pressure and temperature of the extrudate at the die plate were automatically recorded on a computer and evaluated later.

The extrudate was spheronized immediately after production. The spheronizer with a diameter of 320 mm (Type S-320, Nica, Mölndal, Sweden) operated at 800 rpm (13.4 m s^{-1} radial velocity) with a residence time of 5 min. At the end of spheronization two samples of about 20 g were taken for image analysis of wet spheres and for freeze-drying. The sample for freeze-drying was frozen immediately at −18°C and later dried

in a freeze-dryer (Lyosystem I, Leybold-Heraeus, Köln, Germany). The remaining wet spheres were dried in a fluid bed dryer (Glatt TR 2, Binzen, Germany) at 45°C for 30 min.

2.4. Analytical methods

2.4.1. Image analysis

Image analysis (Leco 2001, Leco Instruments, St. Joseph, U.S.A.) was carried out in different steps. Pellets were inspected before and after drying. Four frames of wet spheres with 200–400 pellets in total were successively prepared on a glass plate lying on an illuminated desk and analysed immediately. Afterwards the pellets on the glass plate were dried at 50°C in an oven for at least 12 h and inspected again as dry pellets. The unsieved freeze-dried pellets were analysed in the same way. Shrinking of pellets was calculated for each parameter according to Eq. 1:

$$\text{shrinking}\ (\%) = 100 \times \left(\frac{\text{parameter}_{\text{wet}}}{\text{parameter}_{\text{dry}}} - 1 \right) \quad (1)$$

The volume of the pellets was calculated according to Eq. 2:

$$\text{volume} = \frac{\text{area}^2}{\text{length}} \quad (2)$$

For all studies the parameters, area, length (= longest of eight measured Ferets), width (= shortest Feret) and aspect ratio (AR = length/width), their respective standard deviations and coefficients of variation, were evaluated. All parameters were calculated individually for each inspected particle. Count distributions for the parameters can be presented graphically.

2.4.2. Porosity

The porosity of the pellets was calculated from Eq. 3:

$$\epsilon = 100 \cdot \left(1 - \frac{\rho_a}{\rho_t} \right) \quad (3)$$

The true density (ρ_t) was determined using a gas pycnometer (AccuPyc 1330, Micromeritics, Norcross, U.S.A.) with helium as gas. The apparent density (ρ_a) was determined using mercury intrusion porosimetry (Macropores Unit 120 and Porosimeter 2000, Carlo Erba Instruments, Milano, Italy). Measurements for apparent density were repeated twice.

The median of the pore radius-volume distribution from mercury intrusion was taken as the average pore radius.

2.4.3. Friability

For friability testing, dust was first removed from the pellets. 9 g were weighed into glasses and shaken on a Retsch Mill (Type MM, Retsch, Haan, Germany) for 13 min at maximum speed. The pellets were again freed of dust and weighed. Their friability was calculated from the difference between the two weights. Four replicates were prepared for each tested batch.

3. Results

3.1. Extrusion

Water content of the extrudate ($n = 6$), power consumption, pressure and end temperature during extrusion are listed in Table 1. Batch ace2.6 resulted in uncontrolled agglomeration ('snow balling') during spheronization due to overwetting of the extrudate. Run pro1.3 resulted in agglomeration of rounded spheres during fluid-bed drying, indicating a very wet extrudate for this particular formulation. Increasing the water content for a formulation resulted in lower power consumption, pressure and temperature.

Image analysis was performed on all batches (except run ace2.6), while for additional investigations only pellets obtained from optimally wetted extrudate were used.

3.2. Image analysis

The results of image analysis are consistent. Due to the amount of data they cannot be presented completely. The different effects found will be given for specific examples. For run pro1.3 an average width of 1.51 mm for wet pellets and 1.17 mm after oven drying was found. This again

Table 1
Extrusion results

Run	Water content (%)	c.v. (%)	Power consumption (W)	c.v. (%)	Pressure (bar)	c.v. (%)	End temperature (°C)
ace1.1	49.48	1.96	312.5	4.1	5.8	5.1	40.5
ace1.2	54.41	0.64	170.4	3.4	2.8	6.5	29.7
ace1.3	47.66	2.73	343.1	5.4	5.6	7.2	39.9
ace2.1	51.86	2.20	216.7	4.0	5.6	6.7	34.2
ace2.2	57.45	1.01	157.1	2.8	3.6	6.5	29.0
ace2.3	60.39	0.79	130.3	2.5	3.2	5.2	27.1
ace2.4	53.98	2.19	192.3	5.2	4.8	8.8	32.5
ace2.5	60.21	1.54	138.7	5.9	3.1	9.9	27.7
ace2.6	63.37	0.66	111.0	2.3	2.0	7.6	25.7
caf1.1	49.71	1.91	217.1	4.7	4.7	8.7	34.1
caf1.2	51.46	0.62	172.3	2.7	3.6	5.4	31.1
caf1.3	49.42	1.96	217.8	3.1	4.4	6.4	33.7
caf2.1	57.53	0.94	155.9	3.6	5.0	7.4	29.9
caf2.2	59.53	1.13	135.3	2.7	3.8	5.0	27.7
caf2.3	59.17	0.68	130.7	3.4	3.4	7.5	27.9
pro1.1	48.12	1.56	380.2	4.6	7.1	4.7	43.1
pro1.2	53.30	0.43	226.3	5.3	4.5	8.6	33.7
pro1.3	56.39	0.83	158.2	7.3	3.1	9.5	29.1
pro2.1	57.62	1.48	178.5	4.0	5.7	7.3	31.2
pro2.2	60.82	1.78	137.8	4.9	3.9	10.1	28.0
pro2.3	62.78	1.77	120.7	4.8	3.1	11.0	26.8

c.v., coefficient of variation.

indicates slight overwetting of the mass with the beginning of uncontrolled agglomeration.

The influence of water content on the pellet properties is shown for formulation ace2 in Fig. 1 and 2. The medians of the width distributions are clearly below 1 mm for all water contents (Fig. 1).

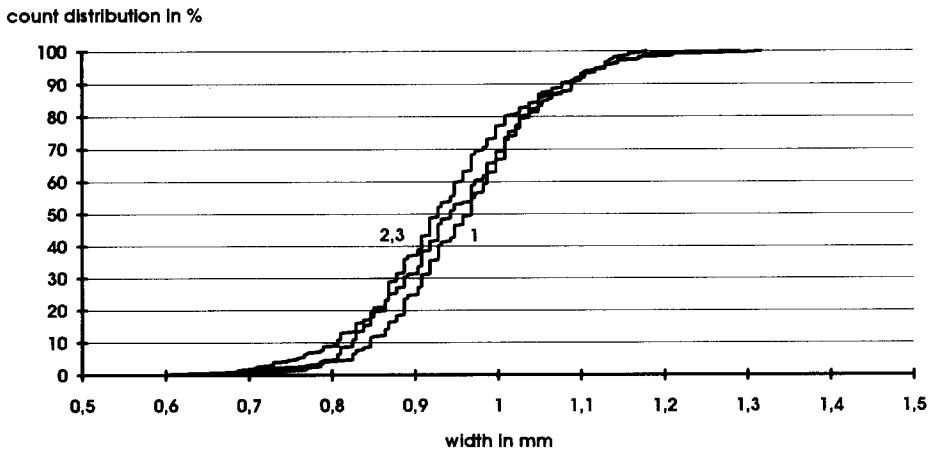

Fig. 1. Count distributions of width for three different water contents of formulation ace2: (1) ace2.1; (2) ace2.2; (3) ace2.3; (1–3) oven-dried.

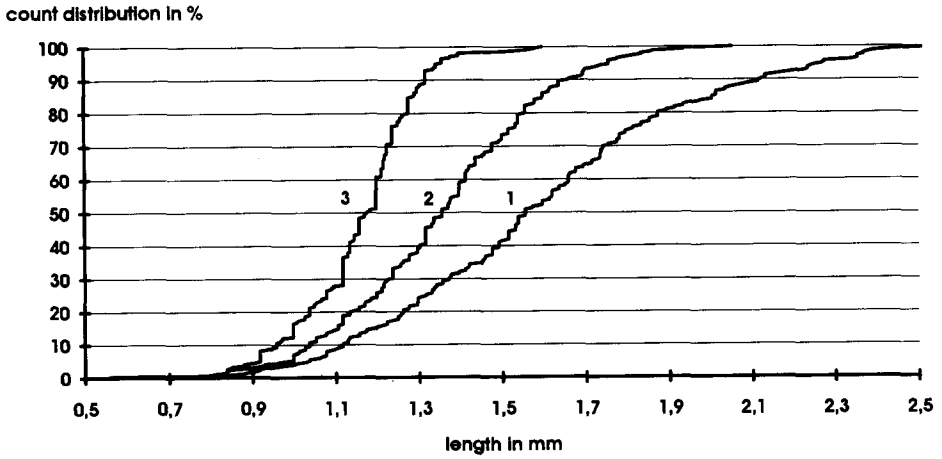

Fig. 2. Count distributions of length for three different water contents of formulation ace2: (1) ace2.1; (2) ace2.2; (3) ace2.3; (1–3) oven-dried.

The width distribution of the oven-dried pellets is almost the same for all three water contents. The length distribution is shifted towards higher values and broadened at lower water contents (Fig. 2). This leads to different aspect ratio distributions (not shown).

The influence of the addition of L-HPC is demonstrated for three different formulations with acetaminophen in Fig. 3 and 4. In this test series, the length distributions were nearly the same for the optimally wetted pellets of the three different formulations after oven drying (Fig. 3). Before drying the two formulations containing L-HPC showed greater lengths compared to L-HPC-free pellets while the width distributions were equal for all formulations. After oven drying the width distributions for the two formulations containing L-HPC shifted towards lower values (Fig. 4). Consequently, the aspect ratio distribution for dried L-HPC-free pellets (ace1.2) indicates the smallest values (not shown).

Comparison of the results between wet, oven-

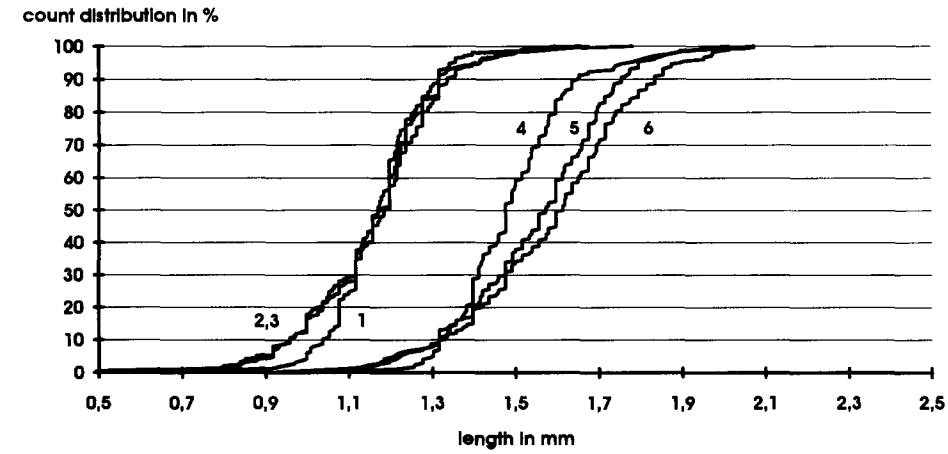

Fig. 3. Count distributions of length for the three different formulations containing acetaminophen: (1 + 4) ace1.2; (2 + 5) ace2.3; (3 + 6) ace2.5; (1–3) oven-dried; (4–6) wet pellets.

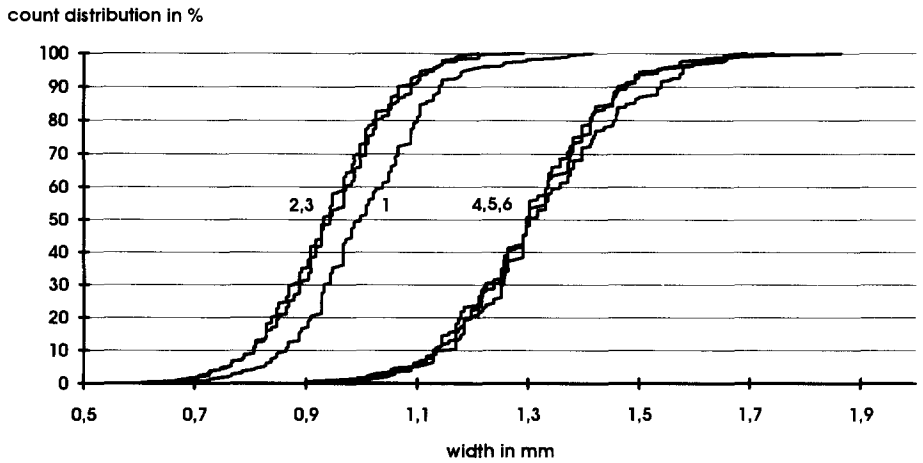

Fig. 4. Count distributions of width for the three different formulations containing acetaminophen: (1 + 4) ace1.2; (2 + 5) ace2.3; (3 + 6) ace2.5; (1–3) oven-dried; (4–6) wet pellets.

dried and freeze-dried pellets is shown in Fig. 5 and 6 for formulation ace2.3. Shrinking phenomena occurred for all pellets during oven and fluid-bed drying. The aspect ratio distribution was equal for wet, fluid-bed-dried and freeze-dried pellets and only marginally different for oven-dried pellets (Fig. 5). In all size parameters, such as width (Fig. 6), length and volume, the distributions for wet and freeze-dried pellets were very similar. The distributions for oven-dried pellets as well as for fluid-bed-dried pellets were shifted significantly towards lower values. The width median dropped from 1.30 to 0.93 mm.

Changing the type of drug demonstrated only a minor influence on the results of image analysis. The width distributions were identical for the formulations containing L-HPC. For length, the distributions were shifted towards higher values with increasing solubility of the drug (Fig. 7).

The extents of shrinking for different parameters of the pellets are listed in Table 2. For each parameter the extent of shrinking for oven-dried

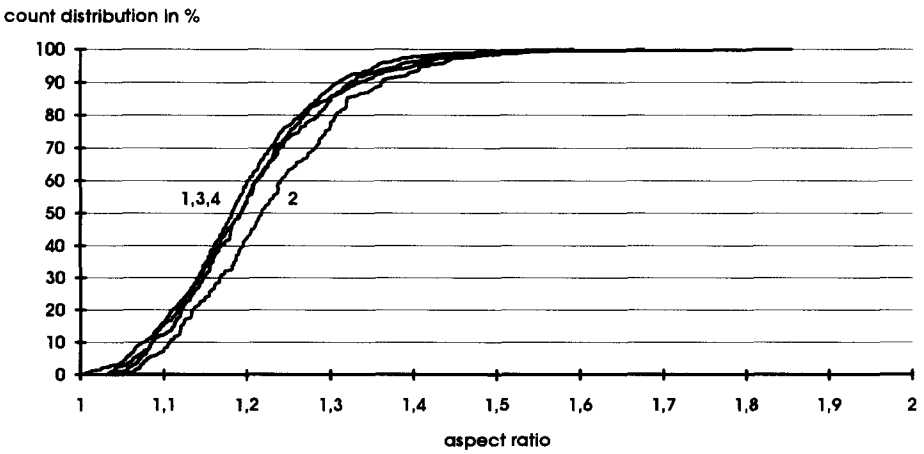

Fig. 5. Count distributions of aspect ratio for fluid-bed-dried (1), oven-dried (2), freeze-dried (3) and wet (4) pellets of formulation ace2.3.

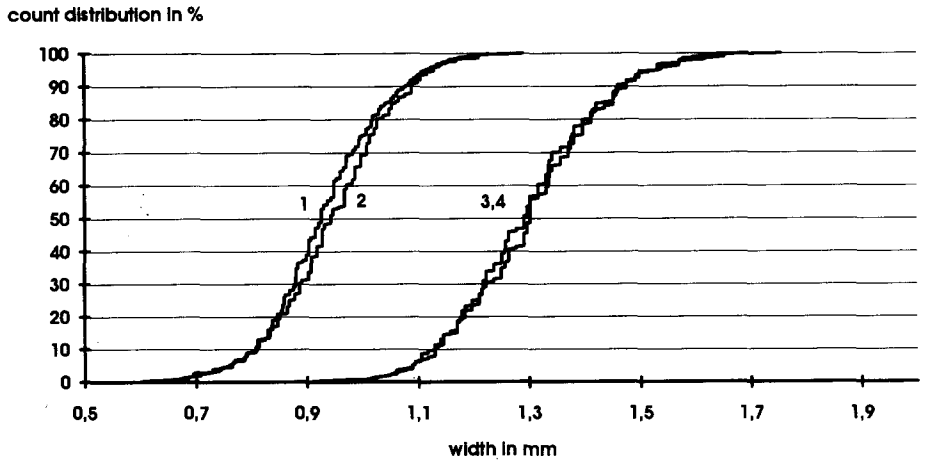

Fig. 6. Count distributions of width for fluid-bed-dried (1), oven-dried (2), freeze-dried (3) and wet (4) pellets of formulation ace2.3.

(o) and freeze-dried (f) pellets is shown. As illustrated in Fig. 6 the extent of shrinking during oven drying and fluid-bed drying was similar. Small negative results indicate greater values of the respective parameter for dry pellets compared to wet pellets.

3.3. Porosity

For fluid-bed-dried pellets differences in the porosities and average pore radii for the two compositions can be seen (Table 3). Without L-HPC, porosities between 3 and 7% were found while the addition of L-HPC led to porosities of 17–23%. The mean pore radii are much smaller for L-HPC-free pellets (17.2–43.5 nm) than for pellets containing L-HPC (150–330 nm).

Very high porosities were found for freeze-dried pellets. However, the porosities for L-HPC-free pellets were still lower than those for pellets including L-HPC. For freeze-dried pellets porosities can be estimated from the water con-

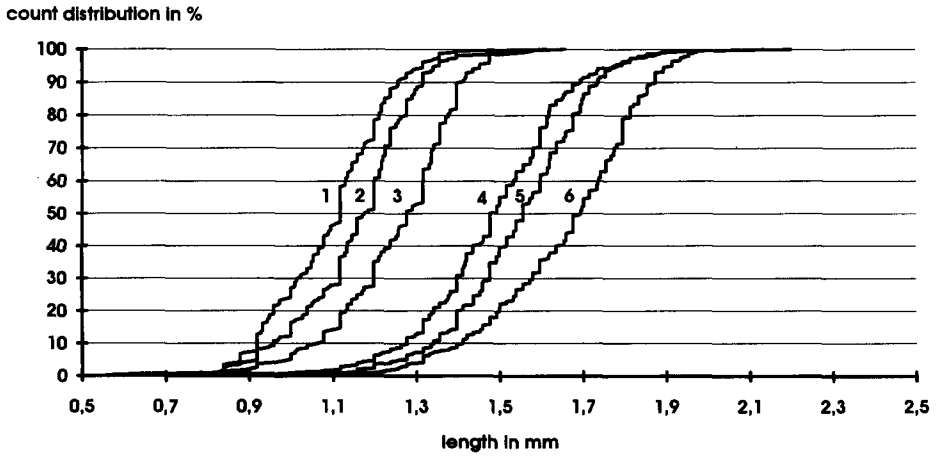

Fig. 7. Count distributions of length for pellets with three different drugs containing L-HPC LH20: (1 + 4) pro2.3; (2 + 5) ace2.3; (3 + 6) caf2.3; (1–3) oven-dried; (4–6) freeze-dried.

Table 2
Results of shrinking analysis

Run	Aspect ratio		Length		Width		Area	
	o	f	o	f	o	f	o	f
ace1.1	−4	−4	28	7	28	8	66	17
ace1.2	−3	0	27	−2	31	−1	67	−2
ace1.3	−1	−1	25	8	26	9	59	17
ace2.1	−3	−2	25	9	28	12	63	18
ace2.2	−3	−4	27	−3	33	1	70	−1
ace2.3	−2	0	34	1	38	1	87	1
ace2.4	−2	−3	29	6	32	8	72	13
ace2.5	−3	0	37	4	41	4	93	8
caf1.1	0	2	28	4	28	2	65	9
caf1.2	−2	1	27	2	30	1	66	7
caf1.3	0	2	26	5	26	3	62	10
caf2.1	−1	0	33	4	34	4	81	7
caf2.2	−1	1	35	4	36	3	85	8
caf2.3	−2	−2	34	1	36	3	84	4
pro1.1	−1	1	23	10	24	9	54	20
pro1.2	−1	1	36	2	38	0	83	4
pro1.3	−5	−5	26	−6	30	−2	62	−7
pro2.1	0	1	35	7	35	7	83	12
pro2.2	−1	−1	35	1	36	1	87	2
pro2.3	−2	−1	36	0	39	2	89	2

o, shrinking for oven-dried pellets in %; f, shrinking for freeze-dried pellets in %.

tent of the extrudate. The average sizes of pore radii were much greater for freeze-dried pellets compared to fluid-bed-dried pellets (Table 3).

Kristensen et. al. (1984) proposed the parameter, liquid saturation S (Eq. 4), for comparison of different agglomerates prepared in a high shear mixer. In Table 3 saturation S was calculated for the freeze-dried pellets according to Eq. 4:

$$S = \frac{H \cdot (1-\epsilon) \cdot \rho}{\epsilon} \quad (4)$$

where H is the moisture content on a dry basis, ϵ the intragranular porosity and ρ the particle density of feed material. The equation is based on the assumption that the liquid density is unity.

3.4. Friability

In all cases the friability of the pellets was below 1% (Table 3) with a high coefficient of variation.

4. Discussion

4.1. Influence of water content of the extrudate

The amount of liquid in the extrudate was found to be the key variable in wet extrusion/spheronization (Bains et al., 1991; Kleinebudde, 1993). Therefore, the water content of the extrudate must be taken into account for all interpretations of the data.

The water content of extrudate affects all extrusion process variables and determines the size and shape of the resulting particles. Power consumption, pressure and end temperature drop with increased water content. At an optimum water content nearly spherical particles are obtained. Insufficiently wetted extrudate leads to anisometric particles while overwetted extrudate gives nearly spherical, but very large particles. These well known facts are supported by the actual results. In the working range for a pellet formulation (Kleinebudde, 1993), optimal pellets in terms of sphericity are obtained with highly wetted extrudate.

Table 3
Results on porosity and friability

Run	ρ_t (g cm^{-3})	ε (fluid-bed) (%)	ε (freeze) (%)	H (%)	S (freeze) (%)	Pore radius (fluid-bed) (nm)	Pore radius (freeze) (nm)	Friability (fluid-bed) (%)	c.v. (%)
ace1.2	1.46	4.4	54.5	106	160	25.5	2855	0.43	21.6
ace2.3	1.44	16.8	64.0	147	121	330.3	2828	0.33	22.4
ace2.5	1.44	16.9	62.5	145	124	318.2	2402	0.65	12.9
caf1.2	1.50	6.8	49.9	119	146	43.5	1961	0.23	18.4
caf2.2	1.50	22.8	64.5	152	124	206.0	1702	0.22	27.5
caf2.3	1.49	17.1	63.6	151	131	149.7	1617	0.30	11.7
pro1.3	1.40	3.3	54.1	129	154	17.2	2346	0.16	14.5
pro2.3	1.38	22.6	65.2	169	124	175.4	2556	0.32	20.8

It is further evident that the amount of liquid required for the production of round spheres depends on the composition of the formulation. A comparison between different formulations is biased if the absolute water content of the different formulations is held constant. The liquid saturation S allows a possible approach to the comparison of relative water contents between different formulations. Eq. 4 is applicable, if the void space is not affected during the production process (Schubert, 1982). This is not true for the given experimental conditions. The drugs are more or less soluble in water which affects the liquid/solid ratio during the process. Furthermore, the excipients MCC and L-HPC are able to absorb water and therefore to swell (Fielden et al., 1992). The loss of water during drying will result in a shrinking process combined with a reduction in porosity. This densification during drying is usually observed in extrusion/spheronization, since most formulations contain a certain amount of MCC. In these cases, the calculated values for S can exceed several 100%.

Shrinking is suppressed by freeze-drying. In this case it appeared to be valid to calculate S. However, all calculated values for S exceeded 100% (Table 3). This can be due to several effects. For example, the pellets can also shrink to a certain extent during freeze-drying. This is supported by the results of image analysis (Table 2). On the other hand, Kristensen and Schaefer (1987) stated that measurements of intragranular porosity are biased because mercury can penetrate larger pores of the agglomerate. In both cases, the estimated values of S will exceed 100%. Although the calculated S values cannot be absolutely correct, they do provide some information about the process. Lindberg et al. (1987, 1988) and Kristensen et al. (1984) also reported values for S exceeding 100%.

4.2. Influence of L-HPC

The addition of L-HPC had no influence on the width distributions of wet pellets (Fig. 4). Mean width values are determined by the die diameter. After oven drying the width distribution for L-HPC-free pellets was less shifted to the left compared to the two distributions for the formulations including L-HPC. The wet pellets without L-HPC had a lower water content, therefore, the extent of shrinking was lower. However, the porosity of the pellets containing L-HPC was still higher. Differences can be seen in the length distributions of the pellets (Fig. 3). The smallest lengths were detected for the MCC/drug pellets leading to the lowest values for aspect ratio. The addition of L-HPC worsened the length distribution. This is caused by the greater elasticity of the extrudate. The extrudate is not brittle enough to break apart during spheronization into small particles of uniform length. Agglomerates containing L-HPC shrink more than others. In this study accidental length distributions after drying were nearly identical for all three optimal wetted extrudates. Comparing the results for wet and dried pellets may provide an explanation for this phenomenon.

The extent of liquid saturation is greater for L-HPC-free pellets when compared to pellets containing L-HPC (Table 3). This could either reflect a more pronounced shrinking of L-HPC-free pellets during freeze-drying or is a true indication of higher S values during manufacturing. Greater shrinking of pellets with L-HPC during freeze-drying is not supported by the data (Table 2). In the latter case, it could be explained by the fact that optimally wetted L-HPC-free pellets show better aspect ratio values than pellets with L-HPC (Kleinebudde, 1993).

4.3. Influence of drying technique

There is a remarkable difference between freeze-drying and fluid-bed drying as well as oven drying regarding pellet properties. Only a minor shrinking tendency can be seen during freeze-drying. Removing the water leaves a skeleton of solid material. These pellets are of similar size compared to the wet pellets. They are characterised by high porosities dependent on the initial high water contents of the extrudates. Extrudate with L-HPC needs more water for optimal wetting and the resulting freeze-dried pellets show higher porosities.

Evaporation of water in an oven or in a fluid

bed is accompanied by a shrinking process in the presence of excipients which can absorb water. The resulting pellets are smaller compared to undried pellets. The shrinking process leads to densification. The porosity no longer reflects the initial water content of the extrudate, but is more dependent on the formulation. Formulations containing only MCC and drug led to porosities of the dried pellets of less than 10%, indicating nearly complete shrinking (Table 3). Adding L-HPC, which absorbs more water than MCC, resulted in porosities between 16 and 23%.

Recently, Bataille et al. (1993) compared two drying processes for pellets made of 20% MCC and 80% lactose. The extrudate had a water content of 34% (m/m). Microwave drying led to higher porosities compared to oven drying. Oven drying is considered to be a slow and less traumatising process while microwave drying will lead to a quasi-immediate loss of water. During the fast microwave drying shrinking of the matrix may be incomplete. In the case of microwave drying shrinking may be inhibited due to the rapidity of the process. Using freeze-drying techniques the water movement is blocked and the structure of the solid backbone is preserved.

4.4. Influence of drug

Fig. 7 shows that with increased solubility of the drug the length distribution is shifted towards higher values. At the same time the water content differs for the three formulations. The lower the water solubility of the drug, the greater is the amount of water needed for adequate wetting (Alleva and Schwartz, 1986; Jayieoba and Spring, 1980; Baert et al., 1991). Higher water contents cause more pronounced shrinking. In this study the slight differences in image analysis results may be affected by slightly different extrusion conditions and cannot be unambiguously related to an influence of drug type.

5. Conclusions

From the results presented, it is obvious that the formation of the matrix in pellets is not finished after spheronization. The drying operation can strongly influence matrix formation. Densification of pellets can be caused by shrinking during drying as well as by the application of pressure during extrusion or the effect of mechanical forces during spheronization.

Spheronized extrudate containing MCC and/or L-HPC undergoes substantial changes during fluid-bed drying or oven drying. These changes have important effects on the apparent density, porosity, size, dissolution behaviour and mechanical stability of the resulting pellets. The shape of pellets is not affected by shrinking. As a consequence, the liquid saturation concept for the comparison of different formulations is not applicable for oven-dried and fluid-bed-dried pellets. The porosity of freeze-dried pellets depends on the water content of the extrudate and they can be denominated as 'skeleton' pellets. On the other hand, the porosity of fluid-bed dried 'shrinking' pellets depends almost entirely on the formulation. The presence of L-HPC increases porosity.

If shrinking phenomena occur during drying, the results of image analysis for dried pellets should be carefully interpreted. A comparison of pellets before and after drying can enhance the understanding of the drying step in pellet production.

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References

Alleva, D.S. and Schwartz, J.B., Granulation rheology: I. Equipment design and preliminary testing. *Drug Dev. Ind. Pharm.*, 12 (1986) 471–487.

Baert, L., Fanara, D., De Baets, P. and Remon, J.P., Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces. *J. Pharm. Pharmacol.*, 43 (1991) 745–749.

Bains, D., Boutell, S.L. and Newton, J.M., The influence of moisture content on the preparation of spherical granules

of barium sulphate and microcrystalline cellulose. *Int. J. Pharm.*, 69 (1991) 233–237.

Bataille, B., Ligarski, K., Jacob, M., Thomas, C. and Duru, C., Study of the influence of spheronization and drying conditions on the physico-mechanical properties of neutral spheroids containing Avicel PH 101 and lactose. *Drug Dev. Ind. Pharm.*, 19 (1993) 653–671.

Fielden, K.E., Newton, J.M. and Rowe, R.C., Movement of liquids through powder beds. *Int. J. Pharm.*, 79 (1992) 47–60.

Jaiyeoba, K.T. and Spring, M.S., The granulation of ternary mixtures: the effect of solubility of the excipients. *J. Pharm. Pharmacol.*, 32 (1980) 1–5.

Kleinebudde, P., Application of low substituted hydroxypropylcellulose (L-HPC) in the production of pellets using extrusion/spheronization. *Int. J. Pharm.*, 96 (1993) 119–128.

Kleinebudde, P. and Lindner, H., Experiments with an instrumented twin-screw extruder using a single-step granulation/extrusion process. *Int. J. Pharm.*, 94 (1993) 49–58.

Kristensen H.G. and Schaefer, T., Granulation. A review on pharmaceutical wet-granulation. *Drug Dev. Ind. Pharm.*, 13 (1987) 803–872.

Kristensen H.G., Holm, P., Jaegerskou, A. and Schaefer, T., Granulation in high speed mixers: 4. Effect of liquid saturation on the agglomeration. *Pharm. Ind.*, 46 (1984) 763–767.

Lindberg, N.-O., Hansson, E. and Holmquist, B., The granulation of a tablet formulation in a high-speed mixer, Diosna P25. Influence of intragranular porosity and liquid saturation. *Drug Dev. Ind. Pharm.*, 13 (1987) 1069–1079.

Lindberg, N.-O., Tufvesson, C., Holm, P. and Olbjer, L., Extrusion of an effervescent granulation with a twin screw extruder, Baker Perkins MPF 50 D. Influence on intragranular porosity and liquid saturation. *Drug Dev. Ind. Pharm.*, 14 (1988) 1791–1798.

Schubert, H., *Kapillarität in porösen Feststoffsystemen*, Springer Verlag, Berlin, 1982.

Shin-Etsu Chemical Co., Low-substituted hydroxypropyl cellulose, 1991.