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

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Abstract

Pellets containing microcrystalline cellulose (MCC) and low substituted hydroxypropylcellulose (L-HPC) are able to swell in contact with an aqueous phase. Swelling is the reverse to shrinking of wet pellets obtained by extrusion/spheronization during drying. This shrinking is only partially reversible. Shrinking and consequently swelling can be almost suppressed using freeze-drying. The pellets studied do not disintegrate during swelling and dissolution. For propyphenazone, caffeine and acetaminophen as model drugs, the dissolution rate is enhanced in the presence of L-HPC in the pellets. The dissolution rates of freeze-dried pellets are graeter compared with fluid-bed-dried pellets.

Key words: Extrusion/spheronization; Pellet; L-HPC; Image analysis; Dissolution; Scanning electron microscopy; Freeze-drying; Fluid-bed drying

1. Introduction

In the preceding paper (part I; Kleinebudde, 1994), pellets obtained from extrusion/spheronization containing different drugs were described. The pellet properties were shown to be highly dependent on the type of drying process.

The objectives of this part of the investigation were to determine whether or not the shrinking processes are reversible. The swelling properties of pellets in contact with an aqueous phase were determined using image analysis. Furthermore, the consequences of the shrinking and swelling properties of pellets with respect to the dissolution rate were investigated. The studies were completed by taking SEM photographs of different kinds of pellets.

2. Materials and methods

2.1. Materials

Details of the manufacturing of the pellets under study were described in the preceding paper (Kleinebudde, 1994). The pellets contained 30% (w/w) of acetaminophen (ace), caffeine (caf) or propyphenazone (pro), respectively. Batches coded no. 1 contained 30% drug, 69.5% microcrystalline cellulose (MCC, Avicel PH 101, FMC

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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 corresponds to the second run with acetaminophen but without L-HPC.

The runs for a specific formulation differ in the water content of extrudate. Each run represents a batch of identically prepared pellets including the spheronization step. Each batch was then divided into two parts which underwent different drying stages. A sample was freeze-dried while the main fraction was fluid-bed dried. The current investigations were not performed on all batches produced, but on the best runs of a formulation in terms of shape of the pellets.

Usually, L-HPC LH20 was used, only runs ace2.4 to ace2.6 being performed with L-HPC LH30. The two types of L-HPC have the same degree of substitution but different average particle size: 40 μm for LH20 and 25 μm for LH30 (Shin-Etsu 1991). All other materials used were of analytical grade.

2.2. Particle size analysis of drug powders

The particle size distributions of the drugs were measured with a laser diffractometer (Helos, Sympatec, Clausthal-Zellerfeld, Germany). The powdered drugs were suspended in air using a Rodos unit (Sympatec). The volume size distributions were calculated with a computer program (Sympatec). The 10, 50 and 90% quantiles (x_{10}, x_{50} and x_{90}) of the volume distributions are listed in Table 1.

2.3. Swelling studies

Image analysis (Leco 2001, Leco Instruments, St. Joseph, U.S.A.) was employed for swelling studies. Samples from 900–1000 μm fractions of fluid-bed-dried pellets or unsieved freeze-dried pellets, respectively, were placed on a petri dish. At first a field of pellets was measured. Water was added until the petri dish was filled completely and 2, 5, 10, 15 and 20 min after the addition of water one constant frame containing 15–70 particles was analysed. Length (longest of eight ferets), width (shortest of eight ferets), aspect ratio and (projected) area were used as parameters. Swelling of the pellets was calculated for each parameter according to Eq. 1:

$$\text{swelling}\ (\%) = 100 \times \left(\frac{\text{parameter}_{20\,\text{min}}}{\text{parameter}_{2\,\text{min}}} - 1 \right) \quad (1)$$

Table 1
Water solubility and results of particle size analysis of drugs; 10, 50 and 90% quantiles of volume distribution

Drug	Water solubility	x_{10}	x_{50} (μm)	x_{90}
Acetaminophen	1:70 [a]	5.84	38.07	138.79
Caffeine	1:60 [a]	5.65	110.67	399.38
Propyphenazone	1:400 [b]	1.85	8.59	27.77

[a] BP88.
[b] Merck Index.

2.4. Scanning electron microscope (SEM) studies

Pellets were fixed using conductive carbon cement (Plano, Marburg, Germany) and sputtered with gold under an argon atmosphere (Baltec SCD 005, Baltec AG, Balzers, Liechtenstein). Surfaces of the pellets were examined at different magnifications with a Philips XL 20 (Philips, Eindhoven, The Netherlands) scanning electron microscope.

2.5. Dissolution testing

Dissolution testing was performed using the paddle method at a rotation speed of 100 rpm. The dissolution apparatus (Apparatus 2, USP XXII, Type PTW S, Pharmatest, Hainburg, Germany) was interfaced to a spectrophotometer (Type HP 8452A, Hewlett Packard, Palo Alto, U.S.A.). The UV absorbances were measured automatically each 2.5 min up to 60 min.

For dissolution experiments on fluid-bed-dried pellets, fractions in the particle size range 900–1000 μm were used. The freeze-dried pellets were used unsieved. Each dissolution test was

performed on at least three samples of pellets with 900 ml of phosphate buffer pH 7.4 (USP XXII) heated to 37°C. The samples were tested in randomised order to obtain the average release profile and to determine the reproducibility of drug release. For parametrization of the dissolution curve, all data up to 80% release of acetaminophen were fitted to the Weibull function (RRSB plot) according to Langenbucher (1972, 1976). All fitted curves showed coefficients of determination higher than 0.99. The data showed no lag time of dissolution, therefore, only an estimation of the dissolution time, T_d, the time interval when 63.2% of drug is released, is necessary.

3. Results

3.1. Swelling studies

The kinetics of swelling were studied three times for pellets from run ace2.3 (Fig. 1). Swelling had almost finished 20 min after contact with water. For the length and width, similar swelling behaviour could be observed and therefore the aspect ratio was not affected, whereas the swelling of area was more distinct. The results of the swelling studies for a period of 20 min are summarised in Tables 2 and 3 for fluid-bed-dried and freeze-dried pellets, respectively. Some tests were repeated in order to gain information about the measurement error. Swelling could always be observed for fluid-bed-dried pellets (Table 2) and was more pronounced for L-HPC containing pellets. Freeze-dried pellets swelled only to a negligible extent (Table 3).

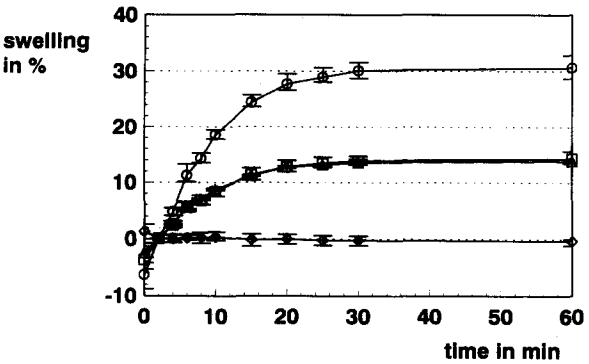

Fig. 1. Swelling kinetics for fluid-bed-dried pellets (ace2.3, $n = 3$, ±SD). Aspect ratio (◇), width (□), length (△) and area (○).

Table 2
Swelling results between 2 and 20 min after addition of water for fluid-bed-dried pellets in %

Run	Aspect ratio	Length	Width	Area
ace1.2	−1.1	7.7	9.6	18.0
ace2.3	0.1	13.0	13.8	28.0
ace2.5	−0.3	14.2	14.8	30.8
ace2.5	−0.1	12.8	13.2	28.4
caf1.2	0.7	2.1	6.5	6.6
caf1.2	0.0	5.8	6.2	12.1
caf2.2	0.7	11.7	10.9	24.6
caf2.2	4.6	13.3	9.7	27.8
caf2.3	1.4	14.3	13.1	30.0
pro1.3	−0.7	6.7	7.1	14.3
pro1.3	−2.0	4.5	6.8	12.8
pro2.3	−1.1	12.5	14.0	29.1
pro2.3	0.4	13.7	13.7	30.0

3.2. SEM images

SEM images are shown in Fig. 2 for pellets containing acetaminophen. Fig. 2a and b shows pellets without L-HPC (ace1.2) and Fig. 2c and d pellets with LH20 (ace2.3). The exchange of L-HPC LH 20 for LH 30 is of no detectable influence on the surface structure and is therefore not shown here. The differences between fluid-bed-

Table 3
Swelling results between 2 and 20 min after addition of water for freeze-dried pellets in %

Run	Aspect ratio	Length	Width	Area
ace1.2	0.5	1.3	1.5	2.6
ace2.3	1.3	1.5	0.6	2.1
ace2.5	1.2	0.3	−0.2	0.4
caf1.2	1.4	4.9	2.9	7.0
caf2.2	−0.7	1.8	1.8	3.0
caf2.3	1.1	1.6	0.7	2.1
pro1.3	2.2	1.4	0.2	2.0
pro2.3	3.5	2.7	−1.0	1.9
pro2.3	−1.1	0.8	1.2	1.3

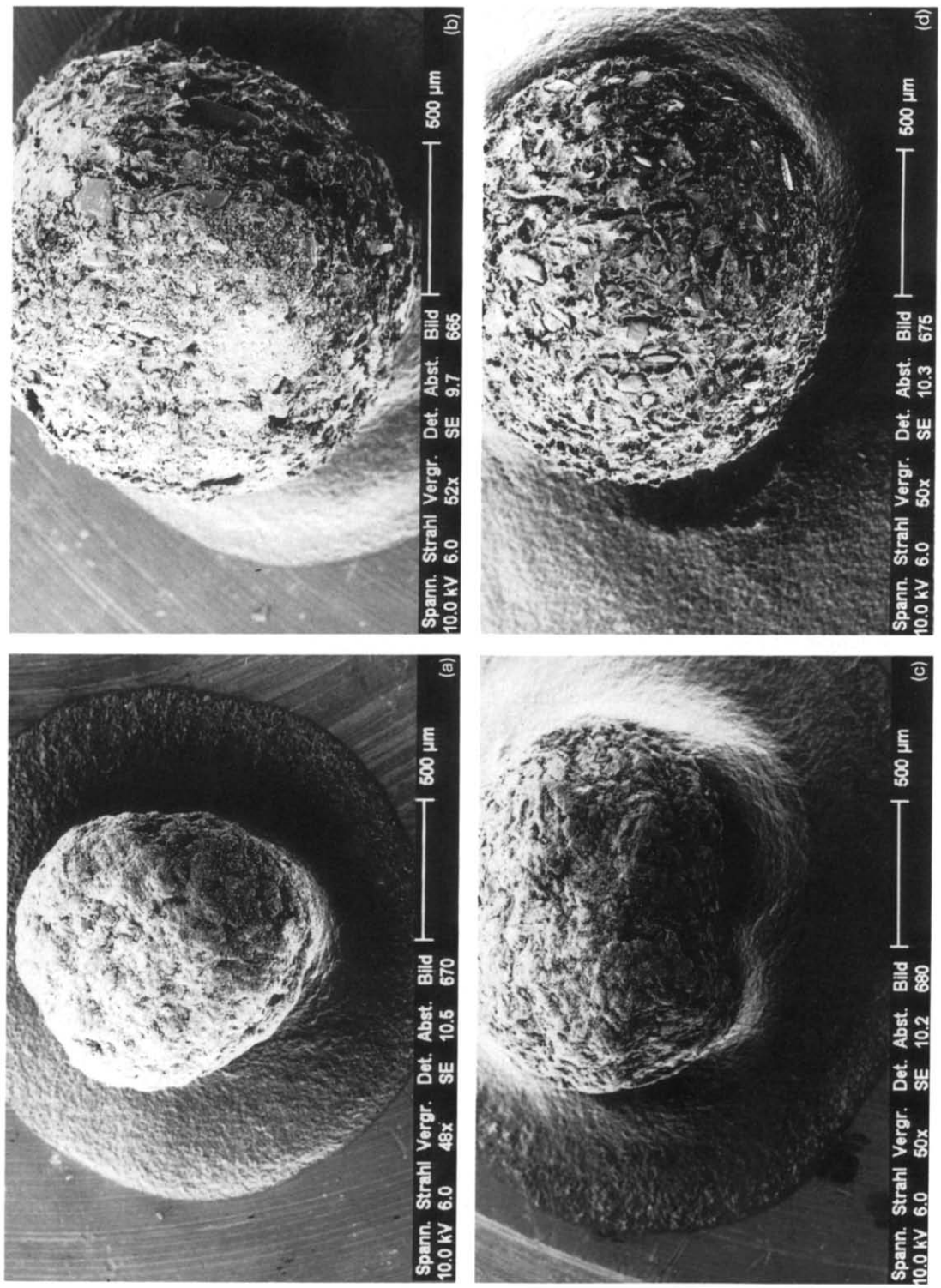

Fig. 2. SEM photos of acetaminophen containing pellets: (a) fluid-bed-dried pellet without L-HPC (ace1.2); (b) freeze-dried pellet without L-HPC (ace1.2); (c) fluid-bed-dried pellet with L-HPC LH20 (ace2.3); (d) freeze-dried pellet with L-HPC LH20 (ace2.3).

Table 4
Results for the parametrization of dissolution profiles up to 80% release

Run	Fluid-bed-dried pellets				Freeze-dried pellets			
	T_d (min)	s (min)	c.v. (%)	n	T_d (min)	s (min)	c.v. (%)	n
ace1.2	25.93	0.63	2.41	5	14.95	0.38	2.52	6
ace2.3	13.72	0.30	2.17	3	7.45	0.26	3.46	3
ace2.5	13.74	0.27	1.97	6	7.95	0.23	2.87	6
caf1.2	14.11	0.26	1.81	3	9.31	0.38	4.12	3
caf2.2	7.43	0.23	3.12	3	5.40	0.06	1.12	3
caf2.3	10.22	0.30	2.89	3	5.25	0.18	3.49	3
pro1.3	151.01	7.40	4.90	6	151.23	14.10	9.32	6
pro2.3	67.16	0.53	0.79	3	49.98	0.58	1.16	3

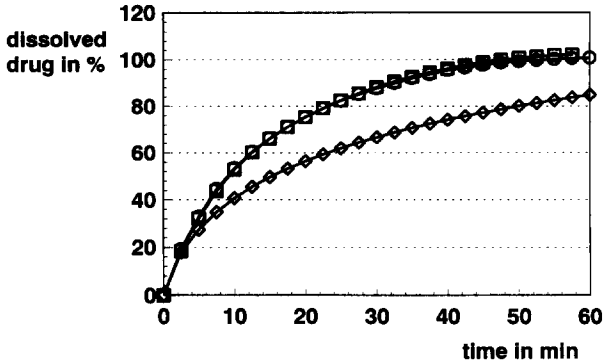

Fig. 3. Dissolution profiles for fluid-bed-dried acetaminophen pellets without L-HPC (ace1.2 (◇)), with LH20 (ace2.3 (○)) and with LH30 (ace2.5 (□)).

dried pellets (Fig. 2a and c) and freeze-dried pellets (Fig. 2b and d) are most striking. Pellets of nearly the same weight exhibit marked differences in size. The surface of the small fluid-bed-dried pellets appears to be much smoother and dense compared to the rough and fissured surface of freeze-dried pellets. The ruptured surface is even more pronounced for the pellet containing L-HPC (Fig. 2d). Typically, the L-HPC-containing pellet (Fig. 2c) is less round compared to the L-HPC-free pellet (Fig. 2a).

3.3. Dissolution

The results of dissolution trials are shown in Table 4. The addition of L-HPC enhanced dissolution for all drugs. For acetaminophen this is shown in Fig. 3. There is no significant difference between the two L-HPC types LH20 and LH30. The drying operation has a significant influence on dissolution behaviour. Freeze-dried pellets showed faster dissolution as compared to fluid-bed-dried pellets. As an example, this is demonstrated for run ace1.2 in Fig. 4. An exception are pellets containing propyphenazone without L-HPC, which exhibited the same dissolution profiles independent of the drying procedure (Table 4). The combination of freeze-drying and addition of L-HPC is additive and results in the most rapid dissolution for all drugs. There are marked

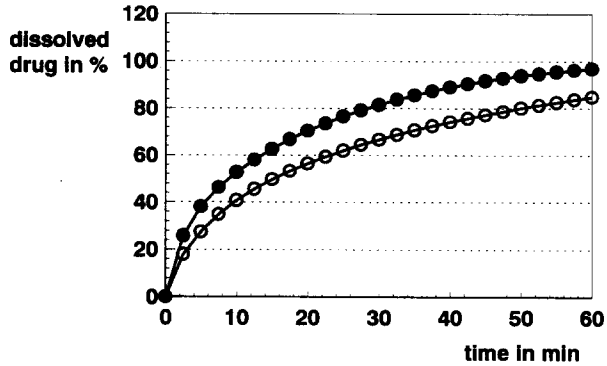

Fig. 4. Dissolution profiles for acetaminophen pellets (ace 1.2) obtained from freeze-drying (●) and fluid-bed-drying (○).

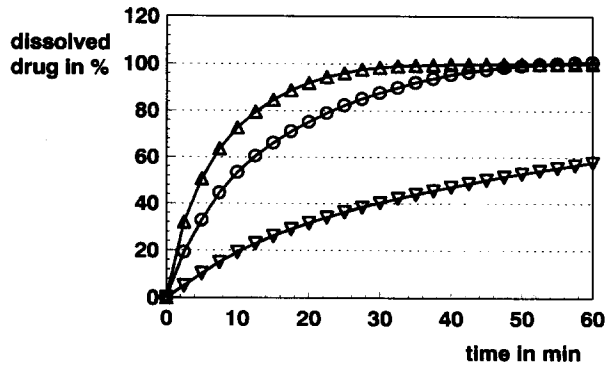

Fig. 5. Dissolution profiles of pellets containing L-HPC with caffeine (caf2.2 (△)), acetaminophen (ace2.3 (○)) and propyphenazone (pro2.3 (▽)).

differences in dissolution rates between the three investigated drugs (Fig. 5).

4. Discussion

4.1. Swelling studies

For reasons of experimental set-up, it was not possible to use the dry pellets as a basis for calculations of swelling. For each swelling study (Tables 2 and 3) only one frame containing 15–70 pellets could be used. This number is not representative of the particle size distribution, but for swelling only relative changes are observed (Eq. 1). If the same pellets are always inspected, even small sample sizes should be sufficient. Due to turbulence during the filling process after the addition of water, a different sample of pellets was inspected in the frame. For the rest of the time, the inspected pellet sample was kept constant. Therefore, swelling could only be related to pellets that had been in water for 2 min. Consequently, the extent of swelling is not completely recorded. However, a comparison of size for swollen pellets after 20 min with size for wet pellets directly after spheronization confirms that shrinking during drying is not completely reversible.

Three groups of pellets can be classified: (i) non-swellable freeze-dried pellets; (ii) slightly swellable fluid-bed-dried pellets without L-HPC; (iii) swellable fluid-bed-dried pellets containing L-HPC.

This classification corresponds to the shrinking behaviour during drying. Freeze-dried pellets have been referred to as 'skeleton' pellets, since they retain their size during drying. As expected only minor swelling was observed. This is due to a softening of the surface. All pellets kept their shapes during dissolution and swelling studies. Disintegration could not be observed. However, a substantial softening was observed after the completion of dissolution.

4.2. Dissolution

O'Connor and Schwartz (1993) demonstrated a square root of time relationship to be valid for the mechanism of drug release from pellets containing microcrystalline cellulose. This relationship is based on the equation of Higuchi (1963) for inert granular materials. In the case of propyphenazone with its relatively low solubility, the dissolution curves can be fitted well with the square root of time law. In the case of acetaminophen and caffeine, this model only results in poor fits. The dissolution profiles show deviations from linearity. The solubility of the drug and T_d are inversely ranked, irrespective of the drug particle size. Although propyphenazone is the drug with the smallest particles, it shows the highest T_d values (Table 1).

Several factors can affect the release behaviour. The initial porosity of pellets varies over a wide range. Fluid-bed-dried pellets without L-HPC have very low porosity while freeze-dried pellets containing L-HPC demonstrate the highest porosities (Kleinebudde, 1994). There is no simple correlation between (initial) porosity and dissolution time (T_d). At the same time, the pellet size does not remain constant. Freeze-dried pellets of the same formulation and weight have a much larger surface according to their low apparent density as compared to fluid-bed-dried pellets. An obvious correlation between pellet size and dissolution time (T_d) cannot be detected. On the other hand, fluid-bed-dried pellets undergo significant alteration during dissolution caused by swelling phenomena, whereas freeze-dried pellets are not affected by swelling. However, deviations from the square root of time law can be observed for fluid-bed-dried as well as freeze-dried pellets.

For propyphenazone pellets without L-HPC the dissolution rate of fluid-bed-dried pellets was as high as that for freeze-dried pellets, although the porosities of the pellets differed extremely (3.3 and 54.1%, respectively). At present, there is no explanation available for this phenomenon. The total porosity cannot be the variable uniquely influencing dissolution.

5. Conclusions

Fluid-bed-dried pellets can swell in contact with an aqueous phase. The ability to swell is

proportional to the extent of shrinking during drying. 'Skeleton' pellets, which do not shrink during drying, do not tend to swell in contact with water. Shrinking phenomena are found to be not completely reversible, therefore, swelling of pellets is less effective than shrinking.

Skeleton pellets show a higher dissolution rate compared to 'shrinking' pellets. This can be an effect of the different initial porosities. The influence of L-HPC can also be attributed to the different porosities of the pellets compared. Results for dissolution of propyphenazone containing pellets indicate that the total porosity cannot be the only variable influencing the dissolution rate.

The swelling properties of pellets can be used for the construction of time-controlled explosion systems for controlled drug release (Ueda et al., 1988). It is possible to obtain pellets with swelling properties from extrusion/spheronization.

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