J. Pharm. Pharmacol. 1994, 46: 2–7
Received December 5, 1992

Use of Powdered Cellulose for the Production of Pellets by Extrusion/Spheronization

H. LINDNER AND P. KLEINEBUDDE

Department of Pharmaceutics and Biopharmaceutics, Christian-Albrecht-University, Gutenbergstrasse 76/78, 2300 Kiel, Germany

Abstract—The use of powdered cellulose instead of microcrystalline cellulose in the extrusion/spheronization process was investigated. The aim of the study was to assess differences between two types of powdered cellulose using a 2^{4-1} fractional factorial design. Water content and amount of binder were found to be most important while type of cellulose and screw speed had only negligible influence on the extrusion process and the resulting pellets. Pellets obtained with powdered celluloses showed higher porosities and faster dissolution rates compared with those made with microcrystalline cellulose. Image analysis was found to be an appropriate method for the simultaneous characterization of pellet size and shape.

Pellets are increasingly used as multiple unit dosage forms. The shape of the pellets, their mechanical properties and dissolution behaviour are important factors for this application. Extrusion/spheronization is an appropriate method for producing pellets with desired qualities.

Microcrystalline cellulose is the standard excipient in extrusion/spheronization (Reynolds 1970; Conine & Hadley 1970; Rowe 1985). It leads to round spheres with a variety of different drugs. In some cases the addition of binders can be necessary to produce acceptable spheres (Funck et al 1991). Pellets produced with Avicel are reported to be strong and dense (Rowe 1985). Compared with pellets produced using other excipients, the drug release from pellets made of microcrystalline cellulose can be slow (O'Connor & Schwartz 1985; Zhang et al 1990).

There are several ways to accelerate the dissolution rate of the incorporated drug. One way is to change the drug-diluent ratio in the mixture (O'Connor & Schwartz 1985). Alternatively water soluble excipients, surfactants or disintegrants can be added (Harris & Ghebre-Sellassie 1989; Bianchini et al 1992). Increased porosity and drug release can be obtained by using ethanol-water mixtures during extrusion (Millili & Schwartz 1990). However, this results in pellets with lower strength and less uniform shape.

A different approach is to substitute another excipient for microcrystalline cellulose. Powdered celluloses have a chemical structure similar to microcrystalline cellulose but differ in their swelling behaviour. In this study different types of powdered celluloses were used instead of microcrystalline cellulose.

The objective of the current study was to assess the differences between two cellulose types, Elcema G 250 and P 100, with regard to pellet production. Using a fractional factorial design the influences of cellulose type, water content, extrusion screw speed and amount of additional binder on the extrusion process and the resulting pellet qualities were evaluated. Additionally, the pellets produced with powdered cellulose were compared with those made with microcrystalline cellulose (MCC).

Correspondence: P. Kleinebudde, Department of Pharmaceutics and Biopharmaceutics, Christian-Albrecht-University, Gutenbergstrasse 76/78, 2300 Kiel, Germany.

Materials and Methods

Materials

Paracetamol (acetaminophen USP, Mallinckrodt, Raleigh, USA) was used as a model drug. Sodium carboxymethylcellulose (carmellose sodium, Tylose C 6000, Hoechst, Frankfurt, Germany) was used as additional binder. Elcema G 250 (granulated powdered cellulose, particle size 200–300 μm), Elcema P 100 (fine powdered cellulose, particle size 50–100 μm) (Degussa, Frankfurt, Germany) and Avicel PH 101 (microcrystalline cellulose, mean particle size of 50 μm) (FMC-Corp., Philadelphia, USA) were the different celluloses used. Colloidal silicon dioxide (Aerosil 200, Degussa, Frankfurt, Germany) was used as a flow regulator.

Demineralized water was used as the granulating fluid. The water content of the powders was determined by the use of an infrared balance (Type 1212 MP, Sartorius, Göttingen, Germany).

Experimental design

The experiments were performed using a 2^{4-1} fractional factorial design. The investigated variables were: water content of the extrudate (A), type of cellulose (B), amount of binder (C) and screw speed of the extruder (D). The defining equation for confounding was I = ABCD.

Each variable was studied at two levels (Table 1). The resulting eight experiments were performed in randomized order. The complete experimental plan is listed in Table 2.

The response variables were particle size and shape, friability, true density, apparent density, porosity and dissolution behaviour. Additionally, the dependencies of the extrusion parameters, power consumption of the extruder and temperature of the extrudate on the influence variables were estimated. Analysis of experimental data was per-

Table 1. Levels and code of the influence variables (factors).

Factor	Low level (−1)	High level (+1)
Water content (A)	55%	45%
Type of cellulose (B)	Elcema G 250	Elcema P 100
Amount binder (C)	1%	2%
Screw speed (D)	80 rev min^{-1}	40 rev min^{-1}

Table 2. Experimental plan including experiments for comparison between powdered (Elcema) and microcrystalline celluloses (MCC).

		with Elcema	with MCC
Paracetamol	30%	30%	30%
Elcema G 250	67–68%	33·75%	
Elcema P 100	67–68%	33·75%	
Avicel PH 101			67·5%
Tylose C6000	2–1%	1·5%	1·5%
Aerosil 200	1%	1%	1%

formed by multiple linear regression using statistical software (SAS 6·03, SAS-Institute, Cary, USA). The analysis of the data was performed in several steps. A 2^3-model was initially calculated. For all observed response variables only a few influence variables had coefficients with large values. The (absolute) higher a value for an influence variable, the more important is the effect. To calculate the experimental error and to estimate significant effects, different models were fitted to the data. For most response variables it was possible to reduce the model to a 2^2-design. In that case the eight experimental runs could be seen as a full replicated 2^2-experimental design and the error for these models could be estimated.

In all other cases only rough estimations of the dependencies on the main factors without interactions were possible.

Comparison of powdered cellulose (Elcema) and microcrystalline cellulose (Avicel) pellets

One experiment (experiment 9 in Table 3) was performed at the center point of the experimental design with all influence variables at level zero. For this experiment the pellets were produced at an extrusion speed of 60 rev min^{-1} with water content of 50%. The amount of binder was 1·5% and both types of powdered celluloses were mixed. The composition of the powder blend is listed in Table 3. The pellets of this experiment were compared with pellets made with microcrystalline cellulose instead of powdered cellulose using the same process conditions (Table 3).

Table 3. Composition of the powder mixtures showing the percentage of the single components.

Experiment	Run no.	Water content A	Cellulose B	Binder C	Screw speed D
1	2	+1	−1	−1	+1
2	8	+1	+1	+1	+1
3	6	+1	−1	+1	−1
4	4	+1	+1	−1	−1
5	3	−1	+1	−1	+1
6	5	−1	−1	+1	+1
7	1	−1	−1	−1	−1
8	7	−1	+1	+1	−1
9	9	0	0	0	0
MCC	10	0	0	0	0

Pellet preparation

The composition of the powder mixture depended on the experiment (Table 3). Batch size for the experiments was 1000 g of dry powder blend. The dry powders were mixed in a Turbula mixer for 15 min (Type T 10 B, Bachofen, Basel, Switzerland). Extrusion was carried out using a laboratory scale twin-screw extruder (Berstorff ZE 25 × 18 D, Berstorff GmbH, Hannover, Germany). The extruder was equipped with two screws with a diameter of 25 mm and a length of 45 cm. The axial mounted die plate had 48 cylindrical holes of 1 mm diameter and 2·5 mm length. Power consumption of the motor and temperature of the extrudate were measured and data were collected using a personal computer. The single-step granulation-extrusion process was performed as described earlier (Kleinebudde & Lindner 1993). Dry powder blend was fed into the extruder at 25 g min^{-1} calculated as dry powder. Water was pumped at a rate according to the desired water content of the extrudate (Table 1) into the extruder barrel. In the production of the powdered cellulose (Elcema) and the microcrystalline cellulose pellets (MCC), the pump rate was adjusted to a water content of 50%.

About 800 g of extrudate was collected after the extrusion process reached steady-state conditions (constant power consumption). During the experimental run, power consumption of the extruder and temperature of the extrudate were recorded every 2 s. The mean values were calculated. The power consumption was corrected for the idle power consumption at the specified screw speed leading to the corrected power consumption. As a result of warming up of extrudate and extruder during the experimental run, the temperature measured is not constant. Therefore, only the mean of the last ten measured values for the temperature was calculated. This value is closest to the temperature level which would occur in a long-time run. During the experimental run, six samples of about 5 g extrudate were drawn and dried at 105°C to determine the total water content. Wet extrudate (750 g) was immediately processed to pellets on a spheronizer at 800 rev min^{-1} for 5 min. The spheronizer was equipped with a cross hatched plate of 320 mm diameter (Model 320 S, Nica, Mölndal, Sweden). The pellets were dried in a fluidized air bed at 45°C for 30 min (Glatt TR 2, Glatt, Binzen, Germany).

Test methods

Friability. The pellets were put on a 355 μm sieve to remove dust and smaller particles. About 5 g was weighed in a glass (m_1) and shaken for 3 min on a shaker at maximum amplitude (Retsch Mühle Type MM, Retsch, Haan, Germany). The pellets were sieved again and weighed (m_2). The friability was calculated as:

$$\text{Friability} = \frac{m_1 - m_2}{m_1} \cdot 100\ [\%]$$

Each batch was measured three times.

Density and porosity. The true density (ρ_t) was measured using an air-comparison pycnometer (model 930, Beckman Instrument, Fullerton, USA). Three measurements were taken from each batch. The apparent density (ρ_a) was determined by mercury intrusion porosimetry (Porosimeter 2000, Carlo Erba Instruments, Milano, Italy). Each batch was tested twice.

The porosity (ε) was calculated as:

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

Sieve analysis. Each pellet batch was divided into eight equal fractions using a sample riffler (Retsch PT, Retsch KG, Haan, Germany). A fraction of about 100 g was sieved on a sieve shaker (Type Vibrio, Retsch KG, Haan, Germany) for 5 min at 20% maximum amplitude. The sieve sizes were 1400, 1250, 1000, 900, 710 and 500 μm. Data from sieve analysis were processed using the RRSB-method (DIN 66145 1976) resulting in the two parameters d′ (RRSB diameter) and n (exponent) for the particle size distribution.

Image analysis. For image analysis (Leco 2001, Leco Instruments, St Joseph, USA), a fraction of unsieved pellets was distributed on an illuminated desk. The pictures of ten fields containing about 2000 pellets were taken by a macro camera. Each individual pellet was inspected and data were processed automatically. The feature parameters length (longest diameter), width (diameter rectangular to length), aspect ratio (ratio of length to width) and roundness ($4 \cdot \pi \cdot \text{area} \cdot \text{perimeter}^{-2} \cdot 100\%$) were determined. For an ideal round particle a roundness of 95–100% is obtained.

Mean values and their standard deviations were calculated.

Dissolution testing. Dissolution studies were performed according to the paddle method (USP XXII apparatus 2) at a rotational speed of 100 rev min^{-1}. Nine hundred millilitres phosphate buffer pH 7·5 at 37°C was used as the dissolution medium. The dissolution medium was continuously pumped through a spectrophotometer (Model DU 55, Beckman Instruments, Fullerton, USA). The amount of released drug was calculated by measuring the absorption at 280 nm. Measurements were taken every 5 min and 250 mg pellets (1000–1120 μm sieve fraction) were tested in each vessel. Three dissolution profiles were taken on each batch.

For characterization of the dissolution curve, all data up to 80% release of paracetamol were fitted to the Weibull function according to Langenbucher (1972, 1976). The data showed no dissolution lag time, so that only the estimation of T_d, the time when 63·2% of drug is released, was necessary. T_d can be estimated precisely making it possible to distinguish between various dissolution profiles.

Results and Discussion

The focus of the experiment was to assess the suitability of different types of cellulose powder in the extrusion/spheronization process. Two different powdered celluloses, a fine (Elcema P 100) and a granular type (Elcema G 250) were chosen.

In contrast to extrusion with microcrystalline cellulose it was necessary to use a binder in combination with the cellulose powder to obtain acceptable pellets. Therefore, the amount of binder was chosen as an additional influence variable. From previous studies it was known that the water content affects the extrusion process predominantly (Kleinebudde & Lindner 1993). Therefore, it was necessary to include the water content as the third influence variable. Moreover, it was not clear whether the screw speed is important. A significant effect of this variable was not expected. For this reason a 2^{4-1} design including the factor screw speed was chosen.

Table 4. Extrusion parameters, pellet densities, porosities, friability values and dissolution times (T_d) for the different experiments.

Experiment	Power consumption (W)	Temperature (°C)	True density (g cm^{-3})	Apparent density (g cm^{-3})	Porosity (%)	Friability (%)	T_d (min)
1	392	38·4	1·463	1·045	28·57	0·069	8·66
2	254	34·3	1·459	1·137	22·10	0·054	14·43
3	242	35·7	1·454	1·126	22·58	0·023	13·83
4	256	41·2	1·483	1·057	28·72	0·059	11·97
5	120	28·7	1·469	0·918	37·50	0·107	12·58
6	105	25·3	1·465	0·930	36·50	0·082	14·07
7	151	30·8	1·465	0·926	36·77	0·109	12·76
8	61	27·4	1·468	0·923	37·11	0·028	15·36
9	167	32·1	1·458	0·937	35·75	0·030	14·75
MCC	—	—	1·365	1·362	0·2	0·027	37·77

Table 5. Sieve and image analysis results for the different experiments.

	Sieve analysis		Image analysis						
				Aspect ratio		Length		Width	
Experiment	d′ (mm)	n	Roundness (%)		c.v. (%)	(mm)	c.v. (%)	(mm)	c.v. (%)
1	1·025	20·13	83·23	1·448	18·88	1·359	26·33	0·911	18·37
2	1·033	16·49	68·32	2·02	24·12	2·128	27·64	1·037	11·30
3	1·038	16·54	70·96	1·823	25·84	1·856	30·48	0·991	12·96
4	1·020	20·85	82·69	1·455	18·41	1·416	23·59	0·943	12·14
5	1·163	13·00	90·63	1·136	9·96	1·140	14·96	0·971	15·43
6	1·225	15·23	89·83	1·209	17·77	1·359	19·07	1·095	10·29
7	1·117	12·24	89·85	1·163	9·39	1·185	13·54	0·987	13·34
8	1·751	5·48	87·84	1·181	12·21	1·701	22·30	1·374	16·96
9	1·073	20·60	85·60	1·353	16·04	1·352	22·12	0·973	12·90
MCC	—	—	87·38	1·180	9·70	1·285	14·78	1·060	14·70

The results of the experiment are listed in Tables 4 and 5. Table 6 summarizes the significant effects for those responses described by a 2^2-model in the factors A and C. For the other responses the significant effects of the main factors without interactions are listed in Table 7.

Table 6. Significant effects for the model: response = A + C + AC.

Response	Water content A	Binder content C	Interaction AC
Apparent density	***	***	***
Porosity	***	***	***
Length	**	**	
Variation of length	***	**	
Aspect ratio	***	***	**
Roundness	***	***	***

* $P < 0{\cdot}1$, ** $P < 0{\cdot}05$, *** $P < 0{\cdot}01$.

Table 7. Significant effects for the model: response = A + B + C + D.

Response	Water content A	Cellulose B	Binder content C	Screw speed D
Power consumption	***		*	
Temperature	***		***	**
True density				
Friability			*	
d′				
n	**			
Width			*	
Dissolution time			**	

* $P < 0{\cdot}1$, ** $P < 0{\cdot}05$, *** $P < 0{\cdot}01$.

Extrusion parameters

Power consumption was significantly affected by water content and amount of binder only. Additionally the temperature was influenced by the screw speed (Table 7).

Higher water contents decrease power consumption. The binder content has a minor influence. In both cases a lubricating effect reducing the friction and power consumption can be assumed (Ovenston & Benbow 1968; Harris & Ghebre-Sellassie 1989).

Warming of the extrudate results from friction of the material. For this reason the temperature shows the same dependency as the power consumption. At low water content and a low amount of binder the temperature rises to 40°C. At high water and high binder content the temperature rises to only 26°C. The temperature is important for the following spheronization step. A warm extrudate will lose more water and the plasticity of the mass will be decreased.

Density and porosity

There were only minor deviations between the values for the true densities. They were slightly changed by the amount of added binder. The pellet densities were the same as the densities of the dry powder blends. As expected, the process variables had no influence on this parameter.

The apparent density and the porosity were dependent on the water content and the amount of binder (Table 6). Type of cellulose and screw speed showed no influence. The porosity varied from 22 to 36%.

Evaporation of water from the pellets leads to the formation of pores. Higher water content during the extrusion process will result in higher porosities. At low water content, the effect of the amount of binder is more pronounced. More binder results in a product with fewer pores. This effect is minimized at higher water contents.

Friability

Pellets produced by extrusion/spheronization techniques often have very low friability (Reynolds 1970). Common friability tests (Zhang et al 1990) led to friability values of less than 0·01% with an unacceptable reproducibility. The test method chosen for these experiments puts mechanical stress on the pellets. A similar test was described earlier (Körber & Moest 1990). The measured values were below 0·1%, but it was possible to differentiate between the batches with this method. However, the large variation in the data did not allow for a model to be fitted.

The data analysis only allowed a rough estimation of the influencing effects. Only the binder had a distinct effect on friability (Table 7). More binder resulted in lower friabilities. There was no evident correlation between porosity and friability.

Sieve analysis

Sieve analysis is a suitable method for the analysis of round or nearly round particles. Thus, it is a good method for comparing batch to batch variations in the production of an optimized pellet formulation. However, during development of a formulation the experiments will sometimes result in anisometric particles. The shape has an influence on the results for size distribution. For elongated particles, sieve analysis ideally measures only the width distribution. Even in this ideal case, sieve analysis seems to be of limited value because the interesting variations are to be seen in length rather than width.

The pellets produced in this trial were not of uniform shape. In Figs 1 and 2, pictures of the best and the worst batch in terms of isometry are given. The calculated equivalent diameter does not reflect the subjective impression of the pellet size. A simultaneous characterization of size and shape seems to be necessary to cover the whole range of experimental results. The statistical analysis of the data showed only an influence of the water content on the uniformity of the pellet size distribution expressed by the parameter n (Table 7). An explanation of this phenomenon is given below.

Image analysis

The shape and size of particles can be determined simultaneously by means of image analysis. In the extrusion/spheronization process the particles are formed during the spheronization step. The extrudate must break down into small pieces and form round pellets due to the forces in the spheronizer, and the mass has to fulfil several requirements. It must be brittle enough to break down into small cylinders but it must be sufficiently cohesive not to be powdered in the spheronizer. If the cohesive forces are too strong the extrudate only breaks down into long, anisometric pieces.

On the other hand, the rod-like fragments must have the required plasticity to be converted into spheres (Fielden et al 1992). If the plasticity is inadequate only cylinders with rounded ends are generated.

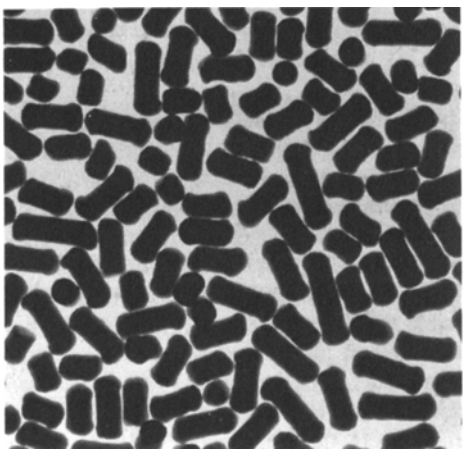

FIG. 1. Pellets of experiment 2, mean aspect ratio of 2·020.

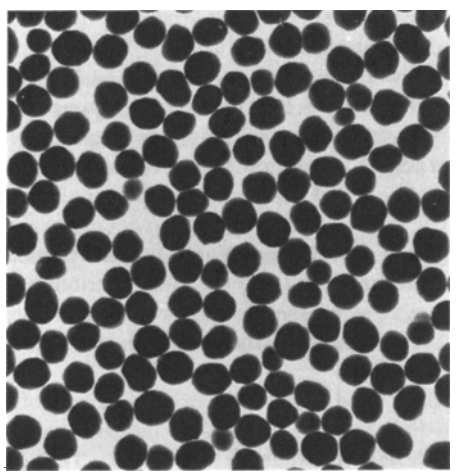

FIG. 2. Pellets of experiment 5, mean aspect ratio of 1·136.

Usually the length of the extrudate can be varied by spheronization while the width of the particles is mostly defined by the die. The width is changed only slightly during the process with the exception of agglomeration due to an overwetted extrudate. This is reflected in the results for the width. The overall variation was relatively small with the exception of experiment 8. In this case, the extrudate was very wet and soft. During spheronization, agglomeration was found to appear (Newton & Fielden 1992).

The experimental data for length, variation of length, aspect ratio and roundness are satisfactorily explained by a 2^2 model with the influence variables water content and amount of binder (Table 6). It could be shown that the remaining influence variables (screw speed and type of cellulose) were of no significance. The length of the pellets varied over a wide range. Pellets tended to be longer with lower water content and higher amounts of binder. The higher the water content the softer the material, leading to rounder and smaller particles. The binder has an opposite effect; more binder results in stronger and more elastic extrudates, which resist forces in the spheronizer leading to longer particles.

With increasing length the variation in the length was higher. If the extrudate breaks into nearly isometric pieces the resulting pellets will have a uniform size. In this case, small values for both length and variation of length are obtained. If the extrudate breaks down into longer fragments the probability of a uniform length is reduced.

The aspect ratio is a good indicator for the isometry or anisometry of a particle. In this trial, the aspect ratio exhibits the same dependencies as the length due to constant values of width. For optimal round particles, an aspect ratio close to one is obtained. In this case the variation in length and in aspect ratio is minimized.

The measured values for roundness exhibit the same dependencies as the values for aspect ratio. However, the roundness does not distinguish between round and less round pellets as exactly as the aspect ratio. The roundness is an important factor in the case of irregularly shaped particles. For these particles high perimeters are measured and low values for the roundness are calculated. In this trial all particles showed smooth surfaces with rounded ends (Figs 1, 2) and the aspect ratio was superior for characterizing the shape of the pellets.

Dissolution testing

The dissolution depends on the amount of binder. Higher amounts of binder led to slower dissolution rates resulting in higher values for the calculated dissolution time. An influence of type of cellulose, water content and screw speed could be detected. All batches had dissolution times of about 12 min with the exception of experiment 1, which had a shorter dissolution time. The pellets did not disintegrate during the dissolution test. Although the porosity varied from 22 to 36% this is not reflected in the dissolution data.

Comparison between cellulose and microcrystalline cellulose

The pellets made with microcrystalline cellulose were very dense and strong. The porosity for the pellets was found to be lower than 3%. The friability of these pellets was 0·027%. This value is as low as the lowest measured values for Elcema pellets.

The pellets prepared with Elcema had a faster dissolution than the pellets containing microcrystalline cellulose. The dissolution time for pellets with microcrystalline cellulose (experiment MCC) was 37·8 min and only 14·8 min for powdered cellulose (experiment 9). The dissolution profiles are shown in Fig. 3.

Neither type of pellet disintegrated during the test. This behaviour was reported for microcrystalline cellulose by O'Connor & Schwartz (1985). The low porosity might have been the reason for the longer dissolution time, although a direct relationship between porosity and dissolution data could not be shown for Elcema pellets.

Microcrystalline and powdered celluloses showed different behaviour during the drying process of the wet pellets. In the case of powdered cellulose the evaporating water left

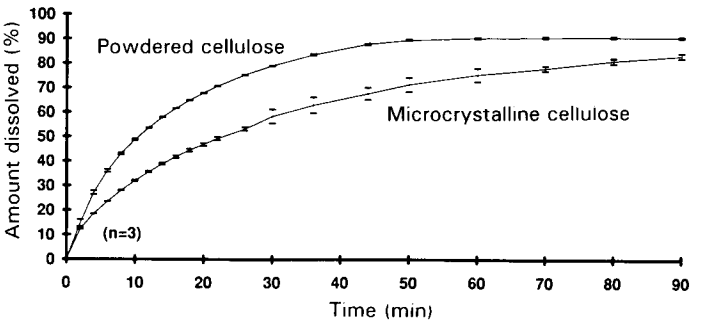

FIG. 3. Comparison of the dissolution profile of pellets with microcrystalline cellulose and powdered cellulose.

pores. The structure of the pellets was preserved resulting in high porosities. The total porosity was related to the amount of water in the wet material. In the case of microcrystalline cellulose the process was different. It may be that the internal structure of the pellets formed by the microcrystalline cellulose is weak and when the water evaporates the matrix collapses and only few pores are formed. Alternatively, the microcrystalline cellulose itself takes up the water; when the water is evaporated the microcrystalline cellulose shrinks and no pores are left. This behaviour of microcrystalline cellulose as a 'molecular sponge' was described by Fielden et al (1988).

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