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International Journal of Pharmaceutics 124 (1995) 231–239

international journal of pharmaceutics

Characterization of β-cyclodextrin for direct compression tableting: II. The role of moisture in the compactibility of β-cyclodextrin

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Received 15 January 1994; revised 25 January 1995; accepted 2 March 1995

Abstract

The role of moisture in the compactibility of β-cyclodextrin has been examined. A physically modified β-cyclodextrin (BCD-DC) was compared to a commercial β-cyclodextrin product (Kleptose®). The moisture sorption-desorption isotherms of both β-cyclodextrin samples showed considerable hysteresis. This can be attributed to the fact that water is associated to β-cyclodextrin in the form of a crystal hydrate. Both β-cyclodextrin samples lost their compactibility on removal of water, thus demonstrating that moisture is essential for the compactibility of β-cyclodextrin. A moisture content of about 14% appears to be optimum for maximum compactibility of samples studied.

Keywords: β-Cyclodextrin; Tablet; Direct compression; Filler-binder; Compactibility; Moisture; Sorption-desorption

1. Introduction

The interaction of water with powdered materials is a major factor in formulation, processing and product performance of solid dosage forms. For direct compression fillers, the moisture sorption and desorption isotherms are among the typical properties that have been tested and proposed as quality assurance specifications. Water associates with solids in a number of different ways, each with its own unique set of underlying mechanisms (Zografi, 1988). Phenomena relevant to pharmaceutical systems include adsorption to a surface as a monolayer and as multilayers, capillary condensation into micropores, crystal hydrate formation, deliquescence, and absorption into the bulk phase of amorphous solids. The interaction of water with crystalline solids is primarily due to its ability to hydrogen bond. The properties of water in the vicinity of a solid surface to which it is adsorbed, will appear to be different than that of bulk water. These properties will extend to about three molecular diameters away from the surface or when the space within which the water is confined approaches these molecular dimensions, e.g., micropores and thin films. Water can assume regular positions in

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Elsevier Science B.V.
SSDI 0378-5173(95)00093-3

the lattice of crystalline solids with a specific stoichiometry to form crystal hydrates. If water strongly interacts with the molecules of the solid then the hydrate formation will lead to distinctly different solid phases from the anhydrous phase. In other cases the formation of a hydrate has no effect on the crystal structure of the anhydrous form and the water can be removed without altering the crystal structure.

The moisture content of the powder mass before compaction may influence the tablet indirectly by affecting the volume reduction of the powder mass during compression. Studies on the effect of moisture on volume reduction behavior have been reported. Water has been suggested to act as a lubricant during compression and thereby reducing the friction, both interparticulate and between the particles and the die wall (Shotton and Rees, 1966). The compactibility of the powder mass and thereby the tablet strength can thus be influenced by water. Khan et al. (1981) reported that compactibility of microcrystalline cellulose progressively decreased with a reduction in its moisture content. It was proposed that water acts as an internal lubricant and facilitates slippage and flow within the microcrystals of microcrystalline cellulose thus promoting hydrogen bonding of the crystals. Increased moisture content has also been shown to give lower yield pressures during compaction (Ragnarsson and Sjögren, 1985). This was again attributed to the assumption that water facilitates the deformation of particles in combination with reduced interparticulate friction.

Characterization of a physically modified β-cyclodextrin (BCD-DC) sample for direct compression tableting has been reported earlier (Pande and Shangraw, 1994). The compactibility of BCD-DC was compared to a commercial β-cyclodextrin product (Kleptose®) and other commonly used direct compression fillers. BCD-DC showed superior compactibility compared to Kleptose® and excellent dilution potential. Compactibility and dilution potential of BCD-DC were comparable to microcrystalline cellulose. Since β-cyclodextrin contains 13–15% water, the role that this water plays in the compactibility of β-cyclodextrin has been investigated in this study.

2. Materials and methods

2.1. Materials

Two samples of BCD were used. Kleptose® is a commercial BCD product manufactured by Roquette, France. Roquette also supplied a BCD physically modified for direct compression (BCD-DC).

2.2. Methods

2.2.1. Sorption-desorption isotherms

For the sorption isotherm, three accurately weighed samples of BCD-DC and Kleptose® (100–200 mg) were placed in glass weighing bottles of 12 ml capacity and dried under vacuum at 35°C for 48 h. After drying, the bottles were transferred to tightly closed desiccators kept at 25°C and relative humidities of 11, 23, 33, 43, 52, 65, 75, 83 and 93% achieved with saturated salt solutions (Callahan et al., 1982). After standing for 10 days, the bottles were weighed and then dried at 105°C for 3 h. Weights of the bottles were determined after drying, and from the weight of the samples before and after drying, the equilibrium moisture content of the samples was calculated. These results were plotted against the respective relative humidity to obtain the sorption isotherm. A similar procedure was used to determine the desorption isotherm. However, the samples were initially equilibrated over saturated potassium nitrate (relative humidity of 93% at 25°C) for a period of 14 days and then transferred to the desiccators.

2.2.2. Surface area determination

Surface area of the BCD samples was determined by the BET method using the micromeritics FlowSorb II 2300 apparatus (Micromeritics Instrument Corp., USA). Krypton was used as the adsorbate gas (0.1% krypton in helium). Different sample treatment procedures were used to determine their effect on the surface area:

1. samples degassed by purging with helium-krypton mixture for 24 h at 25°C;
2. samples dried at 105°C for 3 h and degassed for 30 min;

3. samples dried at 35°C for 48 h and degassed for 30 min.

All the determinations were carried out in triplicate.

The surface areas of the 212–300, 90–125 and the 45–75 μm size fractions of both samples were also determined under the same conditions as the unseparated samples.

2.2.3. Preparation and tableting of β-cyclodextrin samples with varying moisture contents

The 212–300 and 90–125 μm size fractions of BCD-DC and Kleptose® were used in all the tableting studies. The powder samples (0.9–1.1 g) were spread out in thin layers in 25 ml glass weighing bottles. These powders were then dried either at 105°C for 3 h or at 35°C for 48 h. The dried samples were then stored at relative humidities of 11, 52, and 93% for 14 days which resulted in samples with different moisture contents. The moisture content of the samples was determined by drying at 105°C for 3 h. Tablets were compressed with the dried samples as well as the samples with different moisture contents. The procedure for tablet preparation and evaluation was described in an earlier article (Pande and Shangraw, 1994). Tablet tensile strength was plotted against the compression pressures for the various samples to determine the effect of moisture content on tablet strength.

3. Results and discussion

Drying under vacuum at 105°C for 3 h has been shown to be an effective method for removal of water from β-cyclodextrin (Nakai et al., 1986). With both BCD-DC and Kleptose® there was no further loss in weight after drying for 3 h at 105°C. Thus, this method can be used for the determination of moisture content of the β-cyclodextrin samples. Drying at high temperatures can sometimes lead to changes in powder characteristics. This is not a concern when just the moisture content of a sample is to be determined, but if the dried sample is to be tested further for its compactibility and surface area then the effect of drying temperature on these properties needs to be evaluated. Keeping this in mind, drying at lower temperatures was also attempted. Drying at room temperature (25°C) under vacuum would be preferred since no heat would be applied to the sample. However, this treatment did not result in complete water removal. Even after drying for 48 h approx. 1.5–2.0% of water was still retained by the sample. However, increasing the temperature to 35°C leads to complete water removal after 48 h. Moisture content results obtained by drying at 35°C are not significantly different from those obtained by drying at 105°C (Table 1). Therefore, this is the lowest temperature that can be used for complete water removal of the β-cyclodextrin samples. The moisture content of Kleptose® is slightly higher than that of BCD-DC (14.5% vs 14.0%).

Table 1
Moisture content of β-cyclodextrin samples

Sample	Drying temperature (°C)	Drying time (h)	% moisture
BCD-DC	105	3	13.99 (0.07) [a]
	35	48	13.64 (0.39)
	25	48	12.58 (0.06)
Kleptose®	105	3	14.53 (0.03)
	35	48	14.15 (0.22)
	25	48	12.69 (0.10)

[a] 95% confidence interval ($n = 3$).

3.1. Sorption-desorption isotherms

The experimentally measured sorption-desorption isotherms are shown in Fig. 1. It is clearly seen that both samples exhibit considerable hysteresis. During the sorption process, moisture uptake occurs for both samples up to 65% relative humidity. After this significant moisture uptake does not occur even at 93% relative humidity. Only a small amount of moisture is lost during the desorption process. After storage at 11% relative humidity for 10 days, BCD-DC retained 13.9% moisture while Kleptose® retained 13.1% moisture. The hysteresis observed with β-cyclodextrin can be explained by examining the form in which the water is associated with it.

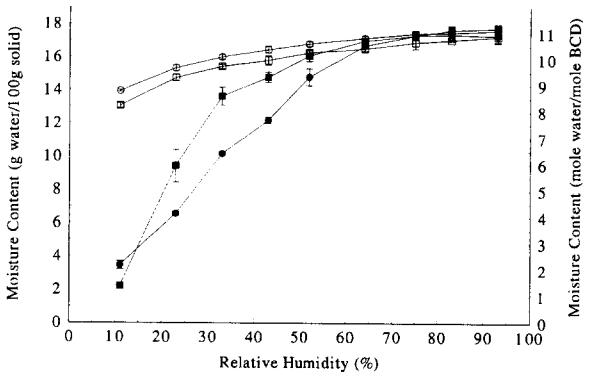

Fig. 1. Moisture sorption-desorption isotherms for BCD-DC and Kleptose®. BCD-DC, sorption (●); Kleptose®, sorption (■); BCD-DC, desorption (○); Kleptose®, desorption (□). Mean ± 95% confidence interval.

A survey of the available literature reveals that in the case of β-cyclodextrin, water is associated in the form of crystal hydrates (Lindner and Saenger, 1978, 1982; Fujiwara et al., 1983; Nakai et al., 1986). Lindner and Saenger (1978, 1982) reported from crystallographic studies that β-cyclodextrin is associated with 12 molecules of water to form a dodecahydrate. These 12 water molecules occupy regular positions within the β-cyclodextrin crystal lattice. The β-cyclodextrin cavity is filled with 6.5 water molecules distributed statistically over eight sites. The remaining 5.5 water molecules of the dodecahydrate are spread over eight sites between β-cyclodextrin molecules. Although the exact mechanism of the interaction of water with β-cyclodextrin was not clear from the study, the authors concluded that water in β-cyclodextrin is in an 'activated' state and can be easily pushed out by a guest molecule to become a part of the bulk water. Recently, Fujiwara et al. (1983) reported a new solvate form of β-cyclodextrin where 11 molecules of water associate with each molecule of β-cyclodextrin.

The right *y*-axis in Fig. 1 shows the moles of water taken up per mole of β-cyclodextrin. From this, it is seen that additional water is not taken up after 11 moles of water are associated with a mole of β-cyclodextrin. Thus, in case of both BCD-DC and Kleptose®, 11 molecules of water are associated with a molecule of the β-cyclodextrin, which agrees with the solvate form reported by Fujiwara et al. (1983). Nakai et al. (1986) have shown that anhydrous β-cyclodextrin has a completely different X-ray diffraction pattern compared to the hydrate form, indicating that when water leaves the β-cyclodextrin molecule, there is a collapse of the crystal structure leading to a new polymorph. Thus, the anhydrous β-cyclodextrin can be expected to behave differently than the hydrated form. Based on powder X-ray diffraction patterns, the authors also reported that on storage at a relative humidity of 48.3%, the anhydrous β-cyclodextrin was converted to the hydrated form although the crystallinity was lower than that of a recrystallized sample. The crystallinity increased on storage at higher humidities, and above a relative humidity of 79% the diffraction pattern was the same as that of recrystallized β-cyclodextrin.

The moisture sorption-desorption isotherms indicate the potential of water to be released from β-cyclodextrin under a given set of environmental conditions. If anhydrous β-cyclodextrin is exposed to the atmosphere, it will take up water depending on the relative humidity. The initial moisture content of both BCD-DC and Kleptose® can be achieved by storing the anhydrous samples between 40 and 50% relative humidity. This indicates that both samples could take up more water if stored at relative humidities higher than 50% based on the sorption isotherms. On the other hand, most of the water in the original samples will not be lost by storage below 50% relative humidity as indicated in the desorption isotherms. The initial moisture content of both BCD-DC (14%) and Kleptose® (14.5%) is lower than that of the hydrate containing 11 moles of water/mole of β-cyclodextrin (17%) due to a drying step following crystallization during the manufacture of these materials.

3.2. Role of water in surface area determinations

Before the surface area of a sample can be determined it is necessary to remove contaminating materials which can alter the surface potential and block or fill pores. Water present in a

sample can affect the surface area readings and lead to erroneous results and thus removal of water is necessary. Sample conditioning can be accomplished by vacuum pumping or purging with an inert gas. Quite often these methods require the use of elevated temperatures to hasten the rate at which water and other contaminants leave the surface. The procedure used for removal of water is not a major issue when water is primarily adsorbed onto the surface of a solid. Zografi et al. (1984) reported that for microcrystalline cellulose which contains adsorbed water, the surface area of microcrystalline cellulose samples was independent of sample pretreatment at temperatures varying from 25 to 100°C. Thus, adsorbed water leaves the solid without causing any structural changes. However, with crystal hydrates, dehydration caused by sample pretreatment can drastically alter surface properties. In case of β-cyclodextrin it has been reported that dehydration causes collapse of the original crystal structure and leads to the formation of a new polymorph (Nakai et al., 1986). The surface area of this polymorph could be entirely different from that of the original material.

For both BCD-DC and Kleptose®, surface area measurement without any sample pretreatment was not possible because the samples lost moisture during the surface area determination causing a drift in the surface area readings. However, a significant loss of moisture did not occur after the samples had been purged with the helium/krypton mixture for 24 h at 25°C. Hence, the initial surface area measurements were carried out using this method. The other sample pretreatment procedures used were drying at 35°C for 48 h and 105°C for 3 h. As indicated earlier, both these procedures resulted in an anhydrous product.

The surface area results for the unseparated BCD-DC and Kleptose® samples using the different sample pretreatment procedures are shown in Table 2. Clearly sample pretreatment has a very significant effect on the surface area of the samples. For the samples which were purged with the helium/krypton mixture, the surface area of BCD-DC is twice that of Kleptose®. The higher compactibility of BCD-DC has been attributed to its higher surface area (Pande and Shangraw, 1994). An increase in surface area is observed for both BCD-DC and Kleptose® after the samples are dried at 35°C. The difference in the surface area of the samples is also lower after drying at 35°C. Thus, loss of water is accompanied by a change in the powder characteristics of β-cyclodextrin. In fact, if the samples are dried at 105°C, the surface area of Kleptose® is higher than BCD-DC. Perhaps, the loss of water results in the cracking of the crystal and creation of newer surfaces and more cracks/laminations in the particles. Kuhnert-Brandstatter (1971) characterized solvates of pharmaceuticals using thermomicroscopy and reported that some of the crystal hydrates crack and 'jump' during dehydration.

Table 2
Effect of sample treatment on surface area of unseparated and size fractions of BCD-DC and Kleptose®

Sample	Surface area (m^2/g)		
	He/Kr purged	Dried at 35°C	Dried at 105°C
BCD-DC (unseparated)	0.43	0.54	0.74
BCD-DC (212–300 μm)	0.35	0.41	0.62
BCD-DC (90–125 μm)	0.52	0.55	0.68
BCD-DC (45–75 μm)	0.58	0.63	0.82
Kleptose® (unseparated)	0.21	0.41	0.92
Kleptose® (212–300 μm)	0.07	0.30	0.92
Kleptose® (90–125 μm)	0.14	0.37	0.87
Kleptose® (45–75 μm)	0.34	0.66	0.89

Note: 95% confidence intervals ($n = 3$) for all values are ≤ 0.03 m^2/g.

The difference in the surface area of the anhydrous samples prepared by heating at 35°C and 105°C indicates that the rate of water removal is also an important factor. Faster removal of water at 105°C results in a greater disruption of the crystal surface since water is removed at a faster rate. A similar behavior is seen with the various sieve fractions of BCD-DC and Kleptose® (Table 2). The most dramatic differences are seen in the case of the higher sieve fractions (212–300 μm). With the 212–300 μm size fraction of Kleptose® there is almost a ten fold increase in surface area when it is dried at 105°C. In all the size fractions for samples dried at 105°C, the anhydrous Kleptose® samples have a greater surface area than

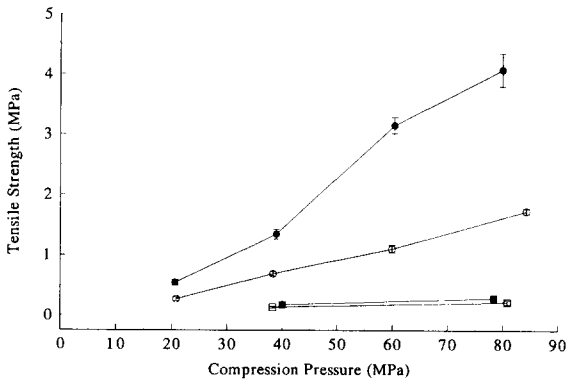

Fig. 2. Compactibility of anhydrous BCD-DC and Kleptose® (90–125 μm size fraction). Samples dried at 105°C for 3 h. Anhydrous BCD-DC (■); anhydrous Kleptose® (□); BCD-DC (●); Kleptose® (○). Mean ± 95% confidence interval.

the BCD-DC samples, which is the reverse of the surface area of the helium/krypton purged samples where BCD-DC has a higher surface area. In the case of Kleptose® which consists of more regular crystals a greater disruption of the crystal is caused by loss of water. In the case of BCD-DC which has been shown to contain numerous cracks/laminations, the loss of water occurs without as great a disruption of the crystals.

3.3. Tableting of β-cyclodextrin samples with varying moisture contents

Two size fractions of BCD-DC and Kleptose® were evaluated. The 212–300 μm size fraction was used because on drying at 105°C this size fraction showed almost a 10-fold increase in surface area of Kleptose®. The other size fraction evaluated was the 90–125 μm fraction which was dried at 35°C. β-cyclodextrin completely loses its compactibility on removal of water (Fig. 2). The significant differences in the compactibility of BCD-DC and Kleptose® are lost on removal of water. These results clearly show that moisture is essential for the compactibility of β-cyclodextrin. Giordano et al. (1990) reported that water plays a important role in the compactibility of β-cyclodextrin. The compactibility of anhydrous β-cyclodextrin was shown to be poor, but improved on sorption of increased amounts of water. The authors also noted that tablets made from rehydrated anhydrous β-cyclodextrin (14.5%) showed a decrease in their strength on storage. This was attributed to the transformation of the adsorbed water to water of crystallization. However, no evidence to support this conclusion was offered. In our opinion the decrease in tablet strength was probably caused by further uptake of moisture by the tablets leading to a breakage of bonds formed during compression.

This behavior is in contrast to that observed for α-lactose monohydrate. It has been reported that the compactibility of α-lactose monohydrate increases with increasing thermal or chemical dehydration of the solid (Lerk et al., 1983). These results have been explained by the increased fragmentation of the dehydrated lactose leading to tablets with a different pore size distribution. In another study, Lerk et al. (1984) have reported that this phenomenon is shown by other hydrates like dextrose monohydrate, citric acid monohydrate, calcium sulfate dihydrate, and calcium biphosphate dihydrate. The completely dehydrated samples of α-D-glucose monohydrate showed increased compactibility compared to that of the monohydrate. Moreover, the crushing strength of the tablets was found to increase with increasing temperatures of dehydration of the powder. The latter observation is indicative of a change in the texture of the particles during treatment. In all these samples, fragmentation is the major mode of deformation. This is not applicable to β-cyclodextrin since it has been shown to deform primarily by plastic flow. In the case of β-cyclodextrin, water helps in binding of the particles producing stronger tablets.

The decrease in porosity of tablets with compression pressure for the anhydrous and original β-cyclodextrin samples is shown in Fig. 3. At 40 and 80 MPa the porosity of the anhydrous β-cyclodextrin tablets is much higher than that for tablets made from the original material. This indicates that water probably acts as a plasticizer promoting the deformation of the particles and bringing them closer to each other, resulting in greater particle-particle interaction and ultimately producing stronger tablets. A similar explanation was offered by Khan et al. (1981) to explain the increase in the compactibility of mi-

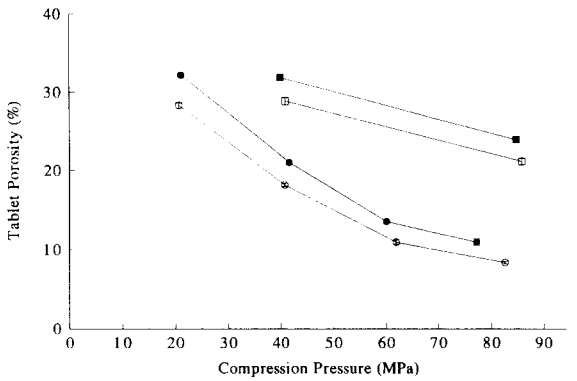

Fig. 3. Porosity vs compression pressure. Anhydrous BCD-DC and Kleptose® (90–125 μm size fraction). Samples dried at 35°C for 48 h. Legend same as Fig. 2. Mean ± 95% confidence interval.

crocrystalline cellulose with an increase in its moisture content. It was proposed that since microcrystalline cellulose compacts by plastic deformation, the moisture content within the pores acts as an internal lubricant and facilitates slippage and flow within the individual microcrystals. After plastic deformation, the particles are so close that hydrogen-bonding can occur and the presence of an optimum amount of water will prevent elastic recovery by forming bonds through hydrogen-bond bridges. Although the form of water associated with β-cyclodextrin (crystal hydrate) is not the same as that associated with microcrystalline cellulose, the available evidence indicates that it plays a similar role in producing stronger tablets.

In the case of α-lactose monohydrate and anhydrous α-lactose, Vromans et al. (1985) reported that despite the significant difference in compactibility between the two types of α-lactose, the tablets exhibited almost equal overall porosity at the same compaction load. Since the predominant mechanism for lactose is brittle fracture, it behaves differently from β-cyclodextrin.

The anhydrous BCD-DC and Kleptose® powders were stored at relative humidities of 11, 52 and 93%. The equilibrium moisture contents of these samples are shown in Table 3. These samples were then compressed into tablets and their tensile strength was evaluated. For BCD-DC, the samples stored at 11% relative humidity (moisture content 5.6%) produced tablets with slightly higher tensile strength than the anhydrous sample (Fig. 4). However, the sample stored at 52% relative humidity (moisture content 15.2%) shows a more significant increase in its compactibility. The sample stored at 93% relative humidity had a moisture content of 17.3% and shows a decrease in tablet strength. Thus, there seems to be an optimum level of moisture which results in the strongest tablets. It should be noted that the sample stored at 52% relative humidity (moisture content 15.2%) produced softer tablets than the original BCD-DC (moisture content 14.0%), therefore it has probably already passed the optimum level of water needed for compactibility. These results demonstrate that the moisture specifications for BCD-DC need to be controlled

Table 3
Moisture contents of anhydrous β-cyclodextrin samples stored under different relative humidity conditions

Sample	Storage condition (% R.H.)	% moisture content
BCD-DC	11	5.61
BCD-DC	52	15.21
BCD-DC	93	17.33
Kleptose®	11	7.68
Kleptose®	52	16.69
Kleptose®	93	17.42

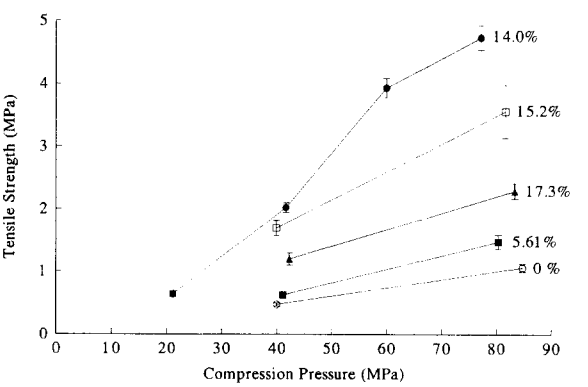

Fig. 4. Effect of moisture on compactibility of BCD-DC (90–125 μm size fraction). Original sample (●); anhydrous sample (○); stored at 11% R.H. (■); stored at 52% R.H. (□); stored at 93% R H. (▲). Numbers next to each data set indicate percent moisture content.

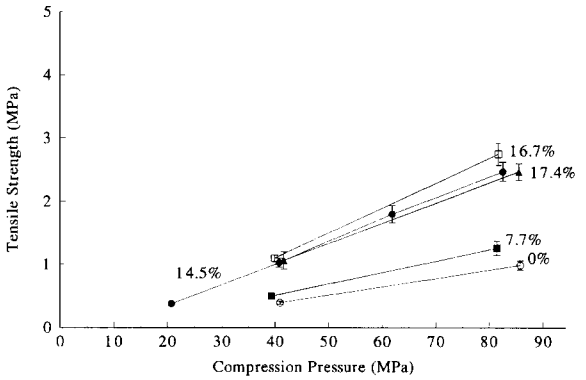

Fig. 5. Effect of moisture on compactibility of Kleptose® (90–125 μm size fraction). Legend same as Fig. 4. Numbers next to each data set indicate percent moisture content.

tightly and that a moisture level of about 14% is optimum for compactibility.

With Kleptose®, moisture plays a similar role as in the case of BCD-DC (Fig. 5). The only difference is that since its original compactibility is not as good as BCD-DC, the differences between the various levels are not as significant. The sample kept at 11% relative humidity has only a slightly lower compactibility than the original Kleptose® sample. The sample kept at 52 and 93% relative humidity had a compactibility almost equivalent to that of the original material.

4. Conclusions

These studies demonstrate that water plays a critical role in the performance of β-cyclodextrin as a filler. The moisture sorption-desorption isotherms of both β-cyclodextrin samples displayed considerable hysteresis. This can be attributed to the fact that water is associated with β-cyclodextrin in the form of a crystal hydrate. Crystal hydrates of BCD-DC and Kleptose® contain 11 moles of water per mole of β-cyclodextrin. Sample pretreatment conditions had a very significant effect on the surface area results obtained for both samples. This demonstrates that careful attention should be paid in the removal of water from crystal hydrates. Removal of water at higher temperatures than required could cause significant changes in powder characteristics and mask differences in the original samples. Both the β-cyclodextrin samples lost their compactibilities on removal of water. Thus, moisture is very essential for compactibility of β-cyclodextrin. A moisture content of about 14% appears to be optimum for maximum compactibility of samples studied.

Acknowledgements

This work was supported by Roquette.

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