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Technological properties of crystalline and amorphous α-cyclodextrin hydrates

L. Maggi, U. Conte *, G.P. Bettinetti

Department of Pharmaceutical Chemistry, University of Pavia, V. Taramelli 12, 27100 Pavia, Italy

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Abstract

In this study the technological properties of some crystalline and amorphous modifications of α-cyclodextrin (α-Cd) were investigated. The solid-state of α-Cd, as well as the amount and energy of crystal water and the presence of the α-Cd dehydrated form, play a role in the performance of the material as a pharmaceutical adjuvant. Common technological operations such as granulation, dehydration and rehydration, milling, compaction, etc. induce solid-state phase transformations of α-Cd which in turn influence the physical properties of the powder and of finished product (e.g. a tablet). The α-Cd solid phases considered were the hexahydrate polymorph I in the pure state (both old batch recrystallized from water, B, and new batch, H), and also the hexahydrate polymorph I containing small amounts of dehydrated α-Cd (old batch, A), the nonstoichiometric hydrate with 7.57 mol of crystal water (α-Cd·7.57H_2O form III, C), two rehydrated samples of dehydrated α-Cd (a new hydrated crystal form V, G, and α-Cd·6H_2O form I, E) and two amorphous products (D, F). The technological behaviour of each sample was evaluated in terms of flow properties, bulk and tapped density, compressibility and volume reduction for powders, and tensile strength, porosity and disintegration time for compressed tablets (produced at five different force levels, from 50 to 300 kN). α-Cd·7.57H_2O, and both amorphous α-Cd samples which all gave tablets whose characteristics were substantially independent of the compression force displayed the most suitable technological properties for a possible use as pharmaceutical adjuvants.

Keywords: α-Cyclodextrin; Hydrate; Dehydrated hydrate; Amorphous; Powder; Tablet; Technological properties

1. Introduction

Physico–mechanical properties (Bettinetti et al., 1994), characterization for direct compression tableting (Giordano et al., 1990; Pande and Shangraw, 1994) and performance as a pharma-

* Corresponding author. Tel.: + 39 382 507374; fax: + 39 382 507382.

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ceutical excipient (Martini et al., 1994) of β-cyclodextrin (β-Cd) have been reported. α-Cyclodextrin (α-Cd) is more soluble in water than β-Cd and may show for some drugs stronger inclusion properties (e.g. econazole and miconazole (Mura et al. 1992) and gangloside GM-1 (Ahmed et al., 1994), better stabilizing capacity (e.g. prostacyclin methyl ester (Hayashi et al., 1978; Uekama et al., 1981) and better absorption enhancing ability (e.g. morphine (Uekama et al., 1995) modified calcitonin and octreotide (Haeberlin et al., 1996). These features can be shown by α-Cd also α-Cd epichlorohydrin polymer, e.g. for indomethacin (Uekama et al., 1987).

Moreover, two of the approved and marketed pharmaceutical products in tablet form (Opalmon and Pansporin T) contain α-Cd (Stella and Rajewski, 1997) and a monography for α-Cd has been included, with that for β-Cd, in the Japanese Pharmaceutical Excipients (JPE) compendium (Thompson, 1997). Therefore, the possibility of pharmaceutical application of α-Cd similar to those of β-Cd (Giordano et al., 1990; Bettinetti et al., 1994; Martini et al., 1994; Pande and Shangraw, 1994) can be considered.

The solid-state properties at the molecular level of a material used in a tableting process can strongly influence some physico–chemical and technological characteristics of the formulation such as flowability, packing, cohesion, compressibility, etc. and hence the processability, as well as the quality and stability of the finished product (Lieberman and Lachman, 1981; Maggi et al., 1995; Muñoz-Ruiz and Paronen, 1997).

Various solid-states of α-Cd are reported, i.e. a number of hydrates both polymorphs and of different stoichiometry, a dehydrated-hydrate crystal form and an amorphous form (Chacko and Saenger, 1981; Nakai et al., 1986; Bettinetti et al., 1995a,b, 1996a,b; Maggi et al. 1997; Novak et al., 1997).

Untreated and handled samples may show different technological properties during the manufacturing process. For example, the crystalline or amorphous nature, and/or the water content of the products (e.g. after granulation) could be key factors for the production of tablets with the desired technological and biopharmaceutical properties.

The physico–chemical modifications of the solid phases of α-Cd induced by thermal or mechanical treatments such as sieving, grinding, granulation, drying, compaction were therefore investigated. Moreover, some technological parameters of the resulting α-Cd samples isolated under carefully controlled conditions, were assessed. In particular the sieve fraction, angle of repose, bulk and tapped density and true density of powder samples were measured. In a subsequent step, powders composed of each, individual α-Cd product were compacted at five different force levels from 50 to 300 kN, using an instrumented tablet machine described elsewhere (Conte et al., 1972). The tensile strength, apparent volume, porosity and disintegration time of the tablets of each series were evaluated.

2. Materials and methods

2.1. Materials

Using the first batch of a commercial product coded A: α-Cyclodextrin W6 (a generous gift from Wacker-Chemie Italia SPA, Milan, Italy), various α-Cd solid phases were prepared (Table 1). The starting material A was a mixture of

Table 1
Description of the α-Cd solid phases considered in this study

Code	Sample	Crystal form
A	Commercial sample 1	α-Cd · $6H_2O$ form I[a]
B	A recrystallized from water	α-Cd · $6H_2O$ form I
C	A recrystallized from 1.2 M $BaCl_2$	α-Cd · $7.57H_2O$ form III
D	A thoroughly ground	Amorphous
E	A dehydrated and rehydrated at 100% R.H., r.t.	α-Cd · $6H_2O$ form I
F	C thoroughly ground	Amorphous
G	B dehydrated and rehydrated at 45% R.H., r. t.	Form V
H	Commercial sample 2	α-Cd · $6H_2O$ form I

[a] Presence of dehydrated α-Cd evidenced by X-ray analysis (Bettinetti et al., 1995a).

Table 2
True density and particle size fractions of the α-Cd products considered

Code	True density (g/cm^3)	Particle size fraction (μm)
A	1.498	<45
B	1.483	<45
C	1.562	45–300
D	1.492	<45
E	1.506	<45
F	1.666	<45
G	1.496	<45
H	1.500	<45

hexahydrate polymorph I with dehydrated α-Cd as a minor component. The unique α-Cd·6H_2O form I (B) can be easily obtained by recrystallization from water of A. The product isolated by recrystallization from 1.2 M aqueous $BaCl_2$ was α-Cd·7.57H_2O (C). Amorphous α-Cd (D) was obtained by thorough grinding of A (mortar grinder RM 0, Retsch, Haan, D). The product E was isolated by rehydration under controlled condition (100% of relative humidity, room temperature) of the fully dehydrated, starting product A. Another amorphous product (F) was obtained by thorough grinding of C (mortar grinder RM 0, Retsch, Haan, D). The hydrated crystal form V (G), was prepared by rehydration (45% R.H., room temperature) of the dehydrated α-Cd form I (sample B). Details on the preparation of samples can be found in reference Bettinetti et al., 1995a, 1996b. A new batch of commercial α-Cd (same supplier) which consists of quite pure α-Cd·6H_2O form I (H) was also considered.

2.2. Methods

The particle size distribution of the samples was evaluated by sieving (ASTM E11-70 Series). Generally more than 95% of the powder was below 45 μm. Only in the case of the product C a broader sieve fraction was obtained and the 45–300 μm fraction was used (Table 2). On these samples the angle of repose, true density (AccuPyc 1330 Micromeritic, Norcross, GA), (Table 2) and bulk density were measured. The tapped density was determined at constant volume reduction that happens generally after 400–500 strokes (Grosso Vaschetti, Turin, Italy).

The tablets were prepared using a single-punch tableting machine (Kilian, Coln, D) instrumented with piezoelectric load washers (Kistler, Winterthur, CH) for compression force measurements (Conte et al., 1972) and equipped with flat punches of 11.28 mm in diameter. Accurately weighed 300 mg of powder were introduced into the dye and then the automatic compression cycle was activated. Whenever necessary, a mixture of microcrystalline cellulose (Avicel PH 102, FMC, PA) and magnesium stearate (9.5:0.5) was compressed between two consecutive cycles to clean the dye and punches. The thickness and diameter of the tablets produced were measured and their volume calculated. From tablets' volume and true density of the different products the porosity of the tablets was evaluated. The crushing strength of the tablets was measured with a suitable apparatus equipped with a high sensitive load washer (Kistler, Winterthur, CH) (Conte et al., 1972). The disintegration tests were carried out in deionized water at 37°C using the USP 23 apparatus without disks. The results are reported in graph as the average of six samples with standard deviation bars.

3. Results

Sample A shows the lower angle of repose, followed in the increasing order by the products H, B, C, D, E, F, G (Fig. 1). The products D, E, F, G have unfavourable angles of repose (i.e. higher than 50°C).

Both commercial products, A and H displayed the best flowability and settling characteristics in term of bulk and tapped density, (compared to other products) which were parallel with a reduced powder volume (Fig. 2). However, it must be stressed that very small amounts of colloidal silica are generally added by manufacturers to improve the flow properties of a bulk product. All other products examined were obtained through recrystallization or dehydration and rehydration process that easily remove such additives.

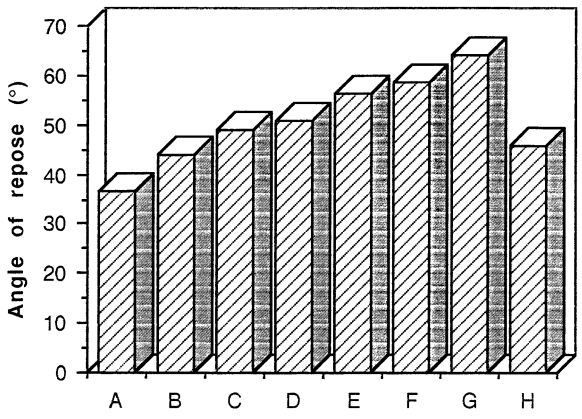

Fig. 1. Angle of repose of the eight solid forms of α-Cd considered (see Table 1).

A relatively high density and a good packing behaviour were also shown by products C, (probably due to its larger particle size) and F, followed in the decreasing order by E, B, G and D, which is the bulkier powder.

During the compression process all the samples showed a similar behaviour, i.e. a tendency to bind and seize. The product E, indeed could not be compressed at all due to very serious seizure problems. Moreover the tablets obtained using the A, B, G and H powders often underwent a lamination process, even at the lowest compression force. Although none of the α-Cd forms tested appears 'per se' suitable for direct compression, C and D samples displayed the more favourable compression behaviour.

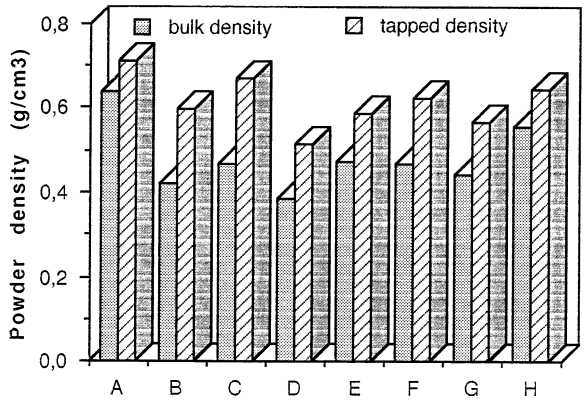

Fig. 2. Bulk density and tapped density of the eight solid forms of α-Cd considered (see Table 1).

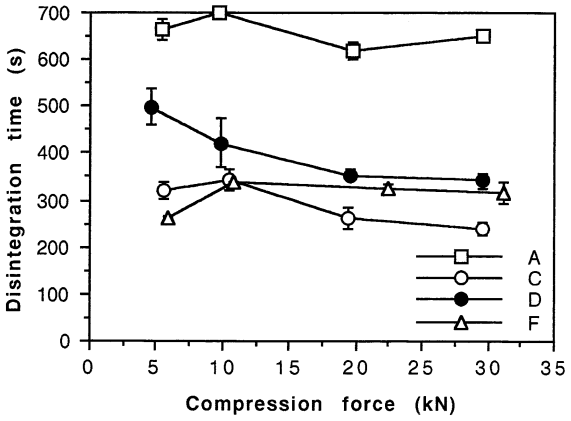

Fig. 3. Disintegration times of the tablets obtained from the α-Cd forms A, C, D, and F (see Table 1), as a function of the compression force applied.

Disintegration tests showed that for four out of seven compacted products (i.e. A, C, D, F) the disintegration time was not influenced by the level of compression force, though for the tablet A it was about twice that of the other three samples (Fig. 3). On the other hand, the tablets from B, G and H showed a remarkable increase in the disintegration time (from 20–30 s to 9–10 min) as a function of the compression force (Fig. 4).

The crushing strength was quite high for all the tablets tested and still two distinct groups, in light of the technological properties, can be outlined.

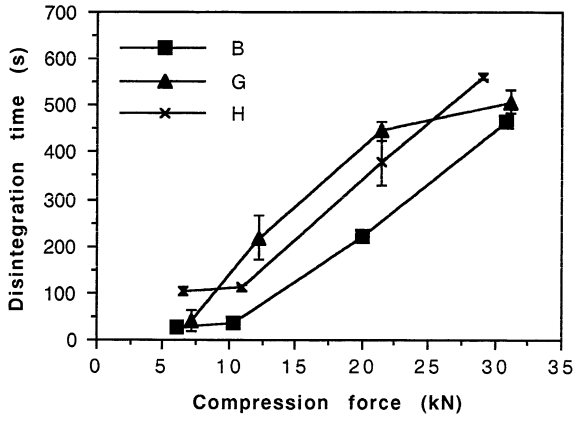

Fig. 4. Disintegration times of the tablets obtained from the α-Cd forms B, G, and H (see Table 1), as a function of the compression force applied.

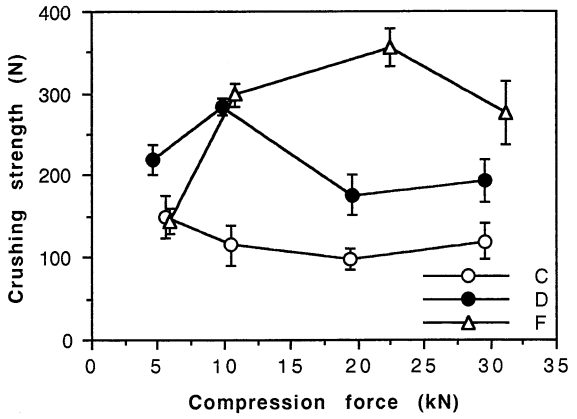

Fig. 5. Crushing strength of the tablets obtained from the α-Cd products C, D, and F, versus the compression force applied.

For C tablets the tensile strength was almost independent of the compression force (Fig. 5), the crushing strength of D was higher but similar to C, although a very high value was obtained at 10 kN of compression force. The tablets made of F showed an increase in strength until 20 kN followed by a decrease at 30 kN (Fig. 5). A, B, G and H tablets, instead, showed a typical linear dependence of the crushing strength as a function of the compression force with a plateau at about 200 N only in the case of the product B (Fig. 6).

As for the deformation properties under compression in terms of tablets' volume reduction the

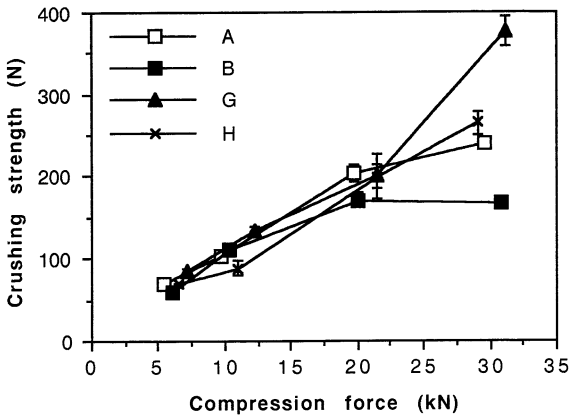

Fig. 6. Crushing strength of the tablets obtained from the α-Cd products A, B, G, and H versus the compression force applied.

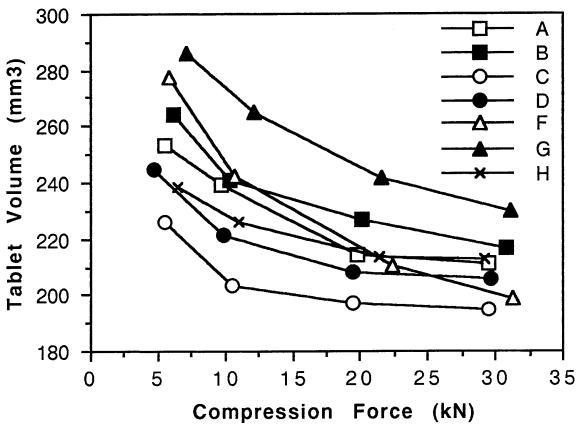

Fig. 7. Volume of the tablets obtained from the α-Cd sample considered as a function of the compression force applied (S.D. < 1%).

highest values were shown by the sample C followed by the amorphous sample D, and the commercial products, A and H (Fig. 7). Crystalline samples B and G, had less deformation ability and the amorphous sample F, the highest degree of variability in terms of the tablet volume, which was almost linearly related to the compression force.

The products C and F, at same level of volume reduction, were characterized by the higher porosity (Fig. 8), though the disintegration time of the tablets (see Fig. 3) did not appear to be signifi-

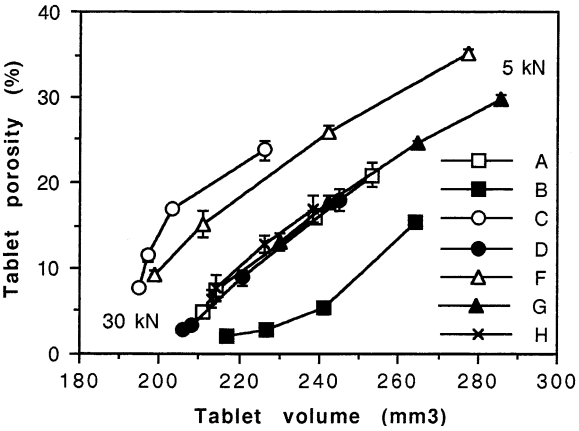

Fig. 8. Porosity of the tablets obtained from the α-Cd sample considered as a function of the volume reduction at the different force levels.

cantly influenced by this parameter. A, D, E, F and H showed a comparable trend, and a linear correlation can be found in terms of both deformation and porosity relationships as a function of the compression force. The powder B which gave tablets characterized by the higher volume and a very low porosity, displayed a limited ability to accommodate volume reduction during the compression phase (Fig. 8). This behaviour was more pronounced at the compression forces which are usually applied in the manufacturing process, e.g. 200–300 kN. The less dense powder B gave compressed tablets with a very low porosity. Instead, the powder C, with the higher true density value gave tablets of good porosity which was reflected by the decrease in the disintegration–dissolution time as a consequence of the promotion of the hydration process.

The tableting behavior of formulation can reasonably be ascribed to the characteristics of Cds (e.g. crystallinity changes and water sorption and desorption) if they are present in larger amounts. Due to the overall better compaction properties of amorphous α-Cd, a decrease in crystallinity resulted in good tablet hardness and disintegration times as in the case of β-Cd (Nakai et al., 1985).

Total dehydration of the intial α-Cd crystal form, for example in the drying process, had instead to be avoided because of the poor compaction properties of the rehydrate material, whose crystal structure depends on the humidity and temperature condition of rehydration. To be noted that anhydrous β-Cd rehydrates to the same monoclinic crystal form as the initial hydrate containing 14.5% of water as mass fraction (Steiner and Koellner, 1994), though the cohesive properties of the rehydrated material are distinctly stronger than those of the initial hydrate (Giordano et al., 1990).

4. Conclusions

Considering that through this study the sole, intrinsic characteristics of the individual α-Cd products were considered, none of them shows optimal technological properties 'per se'. Obviously some properties may be improved by mixing each product with suitable excipients and compression adjuvants. Moreover all products, except C, were used as a very fine granulometric fraction, i.e. in a physical form usually not suitable for direct compression. The technological behaviour of α-Cd samples can be however related to their crystalline or amorphous nature and the amount and state of crystal water present. The dehydration followed by rehydration at 100% R.H. has a strongly adverse effect on the compression properties of the crystalline hexahydrate α-Cd form I causing seizure.

The processability of the same crystal form recrystallized from water and of the sample obtained by rehydration at 45% R.H. (form V) is also rather limited because of an excessive powder cohesion and sticking and lamination phenomena during tableting. Tablets obtained from the other different materials show overall acceptable technological properties, since the crushing strength is rather high and the disintegration time quite short.

Both batches of the commercial products tested display good flow characteristics but unfavourable compression properties. The more suitable α-Cd crystal forms for technological applications are the hydrate at the higher water content ($7.57H_2O$), C, and the amorphous samples D and F. Important characteristics of the respective tablets are mostly independent of the compression force applied, and the scaling up of the formulation should be accordingly easier.

The use of α-Cd in tablet formulation is not necessarily limited by its small cavity which can not allow the monomolecular inclusion of some therapeutic molecules as the cavity of β-Cd or γ-Cd. Actually, noncomplexing applications of Cds where some biopharmaceutical and technological advantages can be obtained even with simple drug-Cd ground mixtures are reported (Frömming and Szejtli, 1994; Mitrevej et al., 1996), though the improvement of drug stability generally requires the inclusion of the drug in the Cd cavity.

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