ELSEVIER

International Journal of Pharmaceutics 148 (1997) 33–39

international journal of pharmaceutics

Particle and powder properties of cyclodextrins

Angel Muñoz-Ruiz [a,b,*], Petteri Paronen [a]

[a] *Department of Pharmaceutics, University of Kuopio, P.O. Box 1627, Kuopio 70211, Finland*
[b] *Department of Pharmaceutical Technology, Facultad de Farmacia, University of Sevilla, C/Tramontana S/N, Sevilla 41012, Spain*

Received 20 August 1996; accepted 20 November 1996

Abstract

The particle and powder properties of α-, β-, γ- and hydroxypropyl-β- (HPβ) cyclodextrins (CDs) were examined. Special attention was paid to water interaction and thermal properties of CDs. The CDs studied showed big differences in particle size distribution and particle shape. In all cases, with the exception of βCD, the log-normal distribution described adequately the particle size distribution. However, the beta-distribution characterized well particle shape factor distribution. The typical α and β parameters obtained from the beta-distribution fitting are related to sphericity and shape uniformity of the particles. Water content results for CDs, obtained by loss on drying at 160°C and Karl Fisher methods, yielded similar results; thus, it was possible to evaporate practically all the water at 160°C. Water content of CDs 'as received' was dependent on the storage history of the samples after manufacturing. The DSC profiles of the CDs showed a broad, intense endothermic effect in the range 20–130°C, this asymmetric peak was ascribed to water removal. αCD showed a characteristic peak with an onset temperature 138°C. This peak seems to be independent of water content, and only small modifications are observed after drying at high temperature. Thus, a feasible structural change is associated with this peak. © 1997 Elsevier Science B.V.

Keywords: Cyclodextrin; Water-content; Particle size and shape; Thermal properties

---

1. Introduction

Cyclodextrins (CDs) are a family of three well known, industrially produced, major cyclic oligosaccharides, and several minor, rare ones. The three major cyclodextrins are crystalline, homogeneous, relatively nonhygroscopic substances with have a torus-like macro-ring shape, built up from glucopyranose units (Frömming and Szejtli, 1994). The α-cyclodextrin (αCD) comprises six glucopyranose units, the β-cyclodextrin (βCD) seven, and the γ-cyclodextrin (γCD) eight units. For pharmaceutical purposes numerous derivatives have been prepared. Because of the molecular dimensions, more exactly the cavity diameter, the βCD derivatives have attained more practical

---

[*] Corresponding author.

PII S0378-5173(96)04820-X

importance in pharmacy. One of the most studied derivative is the hydroxypropyl-β-cyclodextrin (HPβCD).

Physical characterization of raw materials used in the formulation of solid dosage forms is demanded, especially when these materials are employed in direct compression tabletting. There are, however, a few information about physical properties of cyclodextrins. The earliest paper in relation with binding properties of a β-cyclodextrin polymer pilot product was published by Fenyvesi et al. (1984). The β-cyclodextrin polymer was found to be well suitable for direct compression, own relatively advantageous binding and disintegrating properties. The compaction capacity of βCD and the influence of water content were studied by Giordano et al. (1990) and more recently by Pande and Shangraw (1995). Also the application of CD polymers as a disintegrant (Fenyvesi et al., 1984) and the effect on bioavailability in comparison with other disintegrants constitute the other aspect of the studies of cyclodextrin in tabletting.

The purpose of the present work was the physical characterization of α-, β- and γ-CDs and HPβCD, especially those properties more related to tabletting, including particle size and shape, water interaction, as well as thermal properties.

2. Materials and methods

2.1. Materials

The cyclodextrins used were: α-cyclodextrin (αCD), β-cyclodextrin (βCD), γ-cyclodextrin (γCD) all manufactured by Cyclolab, Budapest, Hungary, and hydroxypropyl-β-cyclodextrin (HPβCD)—Encapsin® HPB, manufactured by Janssen Biotech, Stockholm, Sweden. According to the information from the manufacturer, the substitution of hydroxylgroups in HPβCD was random owning an average value of 0.4.

2.2. Methods

The scanning electron micrographs of the particulate samples, covered with gold, were made using a Jeol JSM-35 electron micoscope (Jeol, Tokyo, Japan) using an accelerating voltage of 15 KeV. The scanning electron micrographs were taken at a magnification adequate for particle size. The particle size distribution of the cyclodextrins was examined using the digitalized images of the micrographs where the dimensions of the contained approximately 400 particles were analysed. The equivalent diameter used was the Martin diameter, determined from the chord parallel to the direction of measurements which bisected the projected area (Rumpf, 1990).

The shape factor defined as the ratio between equivalent diameters (Rumpf, 1990) was calculated using the following equation:

$$\frac{X_a}{X_{pe}} \tag{1}$$

where X_a was the equivalent diameter of the sphere having the same area, and X_{pe} the equivalent diameter of the sphere having the same perimeter. The values of the shape factor were larger as the particle shape became more regular. The relation $X_a \leq X_{pe}$ always applied, where the equal sign was valid only for spherical particles.

The water content of powders as received was determined with a Karl Fischer titrator Mettler DL 35(Mettler-Toledo, Greinfesee, Switzerland). Water content was also measured, after storing the materials for 4 days at 20°C in desiccators above saturated salt solutions of potassium acetate and sodium bromide which maintained relative humidities of 22% and 60%, respectively, and after storing for 24 h in an oven at 160°C.

Differential scanning calorimetry (DSC) was performed on a Perkin Elmer (Perkin Elmer, CT, USA) DSC-7 instrument. All DSC runs with samples as received and stored under conditions above mentioned were performed under an atmosphere of dry nitrogen (flow 23 ml/min) using the heating rate of 5°C/min. Powder samples of 1–3 mg in weight were crimped in perforated 50 μl aluminum pans.

3. Results and discussion

3.1. Particle properties

The particle size distributions of CDs are presented in Fig. 1. According to the figure, γCD and HPβCD are the material consisting of very small particles. βCD consisted of much larger particles and a wider particle size distribution than any of the other CDs. αCD was intermediate in particle size. In all cases, with the exception of βCD, the lognormal-distribution fitting has a significance level higher than 0.95. This significance level was obtained from the χ^2-test for 14 degrees of freedom (Yamane, 1973). However, normal distribution fitting was not adequate as can be seen in Fig. 1.

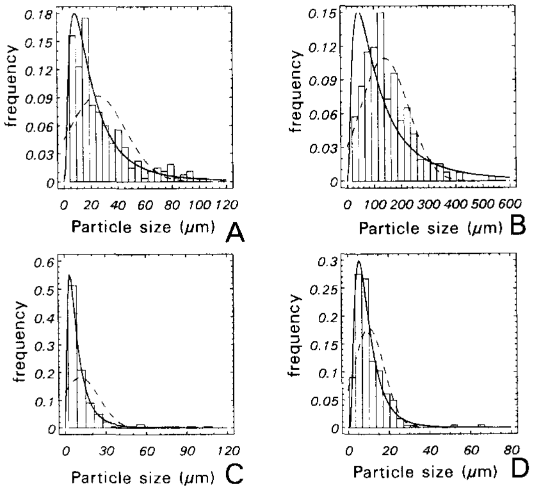

Fig. 1. Particle size histogram and distribution fitting. Dotted line: normal distribution. Discontinous line: log-normal distribution. Continous beta-distribution. A, αCD; B, βCD; C, γCD; D, HPβCD

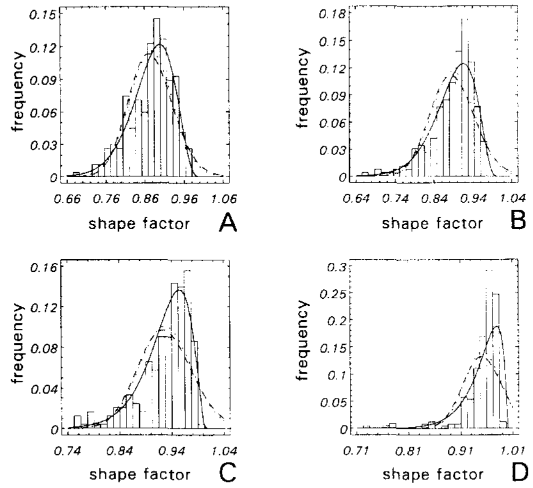

Fig. 2. Particle shape factor histogram and distribution fitting. Continous line: normal distribution. Discontinous line: log-normal distribution. A, αCD; B, βCD; C, γCD; D, HPβCD.

Fig. 2 shows particle shape factor histograms. In all cases, the beta-distribution fitting has a significance level higher than 0.95 (χ^2-test, 14 df). However, normal distribution as well as log-normal distribution fittings were not adequate to describe the data, as can be seen in Fig. 2. Beta-distribution is defined by the following density function:

$$B(\lambda;\alpha,\beta)=\frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\Gamma(\beta)}\left(\frac{\lambda}{1-\lambda}\right)^{\alpha-1}\left(\frac{1-2\lambda}{1-\lambda}\right)^{\beta-1} \qquad (2)$$

where λ is the variable under study, and α and β are the typical parameters of this distribution.

This distribution is only valid for variables which values are comprised between 0 and 1, obtained usually from ratios between two related variables (Cramér, 1971). Particle shape factor complies with these two conditions. The typical values obtained from the beta-distribution fitting for the α parameter were 30.5, 28.5, 31.0 and 33.5 for αCD, βCD, γCD and HPβCD, respectively. The meaning of this parameter is mainly related with the mean or the highest value of the probability function. Mean in beta-distribution, however, is obtained from a ratio which consist of α and β parameters. Thus, the higher α values, the more spherical particles. According to this parameter, the increasing rank order observed in sphericity was βCD < αCD < γCD < HPβCD. The values obtained for the β parameter were 4.3, 3.5, 2.5 and 1.6 for αCD, βCD, γCD and HPβCD, respectively. The value β in the beta-distribution describes the probability of a large deviation from the mean. Variance, however, in beta-distribution is calculated from an equation which includes α and β parameters. The higher β

Table 1
Water content (%) and loss of drying (%) and the corresponding number of H_2O mol by 1 CD mol for CD powders stored under different conditions

Material	Water content 'as received'	H_2O mol by CD mol 'as received'	Water content at 20% RH	H_2O mol by CD mol at 20% RH	Water content at 60% RH	H_2O mol by CD mol at 60% RH	Loss on drying at 160°C	H_2O mol by CD mol (loss on drying at 160°C)
α-CD	9.26	5.51	9.60	5.72	10.71	6.38	9.49	5.65
β-CD	13.48	9.82	13.29	9.68	14.48	10.55	13.85	10.09
γ-CD	7.69	6.00	8.45	6.59	10.55	8.23	7.22	5.64
HPβCD	4.75	3.60	4.94	3.74	10.68	8.09	4.61	3.49

values, the larger deviations. According to this parameter, the increasing rank order observed in shape uniformity was αCD < βCD < γCD < HPβCD.

3.2. Powder properties

Water content results for CDs in Table 1, obtained by loss on drying and Karl Fisher methods, yielded similar results, thus, practically all the water was possible to evaporate at 160°C. This supports the finding of Marini et al. (1993), the dehydration of CDs is completed near 150°C. All the CDs 'as received' as well as after storing over 20% RH, have a relatively high water content, being the highest in the βCD, and lowest in HPβCD. The water contents of αCD and βCD were consistent with the previously reported values of 10% and 13%, respectively (Duchêne and Wouessidjewe, 1990). Water content of γCD, however, was clearly lower than the 16% reported. The obtained value can be explained on the basis that the received γCD was probably stored after manufacturing at relative dry humidity conditions. The water vapour sorption isotherms for α-, β- and γCDs were previously reported by Frömming and Szejtli (1994). According to their study, only a small increase in the degree of hydration with increasing humidity from 20 to 60% RH was expected for αCD. The results in this paper confirm this tendency. An increase of approximately 4 H_2O mol by 1 CD mol was expected for β- and γCDs. In this study the increase, however, was only 0.87 and 1.64 H_2O mol by one CD mol for β- and γCD, respectively. Thus, previous storage history of materials and possibly also the limited time to reach the equilibrium (4 days) were probably the reasons for that. It is also possible that the physical structure and the water binding properties of CDs used in this study were different than those of the samples referred by Frömming and Szejtli (1994). At least, in the case of βCD the water content is important because this substance is not stable with higher water content than 12%, according to the Japanese Pharmacopoeia.

On the basis of the previous studies (Marini et al., 1993) six water molecules in the βCD are occupying intramolecular positions (inside the cavity), the other molecules occupying partially two bindings sites inside the cavity and eight sites outside (intermolecular water). The involved hydroxyl groups (outside of the cavity) of βCD are partially substituted by hydroxypropyl groups in HPβCD, this fact explains the lower number of water molecules in this derivative than in βCD itself. It is interesting to remark that, under 60% RH, the difference between water mol in βCD and in HPβCD is 2.46, being only slightly lower than the 2.8 sites which, according to the manufacturer's information, are substituted by hydroxypropyl groups. Giordano et al. (1990), however, reported that the transformation from adsorbed to bonded water in βCD is a process in which the migration from the water adsorbed from ambient atmosphere onto the surface to the molecular network and formation of hydrates occurs in approximately 20 days.

The DSC profiles of the CDs showed a broad, intense endothermic effect in the range 20–130°C with onset temperatures comprised in this range (Table 2). This asymmetric peak has been ascribed to water removal (Giordano et al., 1992) since in a similar temperature range a weight loss can be recorded. Only αCD showed major differences in

Table 2
Enthalpies (ΔH) (J/g) and onset temperature based on DSC measurements

Material	Storage conditions	ΔH (J/g)	Onset temperature (°C)
αCD	'As received'	239.6	58.6
	20% RH	257.3	70.4
	60% RH	308.7	69.8
	160°C	164.0	65.7
βCD	'As received'	323.6	63.4
	20% RH	337.1	68.5
	60% RH	348.5	67.7
	160°C	106.2	19.8
γCD	'As received'	159.2	28.1
	20% RH	208.6	55.3
	60% RH	256.8	45.9
	160°C	121.9	67.4
HPβCD	'As received'	78.6	25.1
	20% RH	102.8	35.2
	60% RH	163.4	23.2
	160°C	48.3	39.3

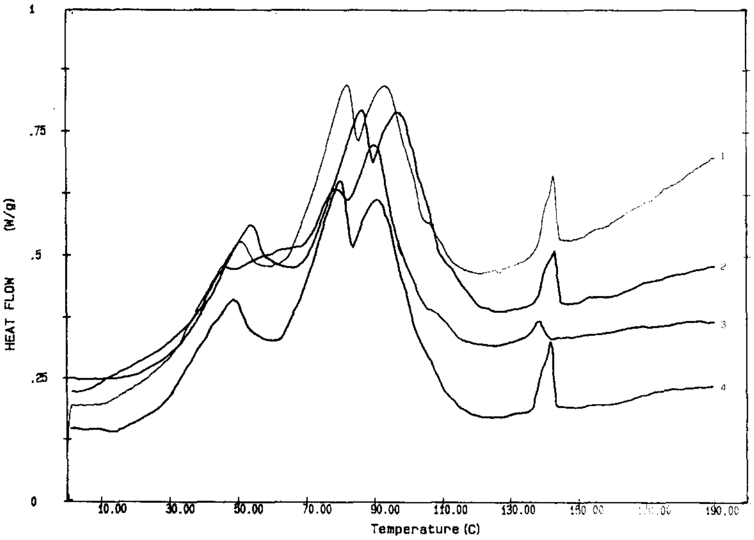

Fig. 3. DSC runs for αCD. 1, 'as received'; 2, 20% RH; 3, 60% RH; 4, 160°C.

the DSCs (Fig. 3). Thus, in this range appeared four peaks around 54, 86, 92 and 110°C. The enthalpies for these peaks were not possible separately to calculate, and the value in Table 2 corresponds with the four peak integration areas. The αCD showed also a characteristic peak (Fig. 3) with an onset temperature of 138°C and an enthalpy of 5.7 J/g for the 'as received' and stored at 20% RH, 6.1 J/g for the sample stored at 60%RH, and 1.8 J/g for the sample after drying at 160°C. This peak seems to be independent of water content, and only small modifications are observed after drying at high temperature. Thus, a feasible structural change is associated with this peak.

α- and γCDs showed an increase higher than 10°C in the onset temperature when the samples were stored at 20% RH. Processes, such as the loose or transition from intermolecular or intramolecular water can be involved in these changes (Marini et al., 1993). The endothermic peaks of αCD looked rather irregular and indented. This tendency was observed previously by Giordano et al. (1992) for βCD exposed to moisture saturated atmosphere for short times.

The integration of the endothermic peak was difficult because of the lack of a suitable starting baseline previously observed by Giordano et al. (1992). The values founded for the entalphies were related with the amount of mol of water presented by 1 mol of CD. However, suggestive differences were found for the enthalpies, after stored the samples at 20% RH, while only small variation in water content was found with regard to the samples 'as received'. It appears that a water independent energy contribution as well as the previous storage history of materials and the limited time to reach the equilibrium must be claimed to account for experimental results.

Acknowledgements

The experimental work in this study was carried out in the Department of Pharmaceutics, University of Kuopio, Finland. The authors thank the Ministerio de Educación y Ciencia, Spain for the mobility grant, the Technology Development Centre of Finland (TeKes) and the Research and Science Foundation of Farmos, Finland for financial support, Ms. M. Simonen and Ms. M de la Matta (University of Kuopio, Finland) for the skillful experimental assistance.

References

Cramér, H., *Mathematical Methods of Statistics*. Princeton University Press, Princeton, 1971, pp. 241–244.

Duchêne, D. and Wouessidjewe, D. Physicochemical characteristics and pharmaceutical uses of cyclodextrin derivatives. Part I. *Pharm. Technol. Int.*, 2 (1990) 21–29.

Fenyvesi, E., Shirakura, O., Szejtli, J. and Nagai, T. Properties of cyclodextrin polymer as a tabletting aid. *Chem. Pharm. Bull.*, 32 (1984) 665–669.

Frömming, K.H. and Szejtli, J. Cyclodextrin derivatives. In: K.H. Frömming and J. Szejtli (Eds.), *Cyclodextrin in Pharmacy*, Kluwer Academic, Dordrecht, 1994, pp. 19–32.

Giordano, F., Gazzaniga, A., Bettinetti, G.P. and La Manna, A. The influence of water content on the binding capacity of β-cyclodextrin. *Int. J. Pharm.*, 62 (1990) 153–156.

Giordano, F., Bruni, G., Marini, A., Berbenni, V., Gazzaniga, A. and Bettinetti, G.P. Thermodynamics of water–β-cyclodextrin interactions. *Boll. Chim. Pharm.*, 131 (1992) 185–188.

Marini, A., Berbenni, V., Massaroti, V., Mustarelli, P., Riccardi, R., Gazzaniga, A. Giordano, F., Bruni, G. and Vila, M. Thermal study of water/βcyclodextrin interactions. *Solid State Ionics*, 63 (1993) 358–362.

Pande, G.S. and Shangraw, R.F. Characterization of β-cyclodextrin for direct compression tableting. II. The role of moisture in the compactability of β-cyclodextrin. *Int. J. Pharm.*, 124 (1995) 231–239.

Rumpf, H., The characteristics of system and their changes of state. In: Scarlett, B. (Ed.), *Particle Technology*. Chapman and Hall, London, 1990, pp. 14–15.

Yamane, T., *Statistics. An Introductory Analysis*, Chpt. 21. Harper, New York, 1973, pp. 761–795.