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Complexation with tolbutamide modifies the physicochemical and tableting properties of hydroxypropyl-β-cyclodextrin

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Abstract

The physicochemical and tableting properties of hydroxypropyl-β-cyclodextrin (HP-β-CD) and its tolbutamide (TBM) complex were studied. The kinetics of TBM/HP-β-CD inclusion complex formation in solution were determined by the phase solubility method. Solid complexes were prepared by freeze-drying and spray-drying. Water sorption–desorption behaviour of the materials were studied and compacts were made using a compaction simulator. TBM and HP-β-CD formed 1:1 inclusion complexes in aqueous solution with an apparent stability constant of 63 M^{-1}. HP-β-CDs and TBM/HP-β-CD complexes were amorphous whereas the freeze-dried and spray-dried TBMs were polymorphic forms II and I, respectively. Sorption–desorption studies showed that HP-β-CDs were deliquescent at high relative humidities. TBM/HP-β-CD complexes had slightly lower water contents at low relative humidities than the physical mixtures. However, at high humidities their water sorption and desorption behaviours were similar to those of corresponding physical mixtures, indicating a glass transition of the complexed materials. TBM/HP-β-CD complexes demonstrated a worse compactibility than similarly prepared HP-β-CDs or physical mixtures. Also particle properties that resulted from these preparation methods affected the compactibility of the materials. In conclusion, the physicochemical and tableting properties of HP-β-CD were modified by complexation it with TBM.

Keywords: Hydroxypropyl-β-cyclodextrin; Tolbutamide; Freeze-drying; Spray-drying; Moisture sorption–desorption; Tableting

1. Introduction

Cyclodextrins (CDs) have several well established pharmaceutical applications (Thompson, 1997). Particularly β-CD, which is the most

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widely used CD in oral drug delivery, is considered to be a promising material as a direct compression excipient because of its favourable compactibility and dilution potentials, and low lubricant sensitivity (Pande and Shangraw, 1994). It has been used, for example, to modify the physical and tableting properties of microcrystalline cellulose (Tsai et al., 1998). Various CD derivatives have been synthesized in order to improve the usefulness of the parent β-CD (Thompson, 1997). Hydroxypropyl-β-CD (HP-β-CD) is one of the most commonly used β-CD derivatives in this class, due to its high water-solubility, parenteral safety and complexation ability. In the solid state, it readily lends itself to plastic deformation, which is beneficial for successful tablet formation (Muñoz-Ruiz and Paronen, 1996). However, complexation of HP-β-CD with tolbutamide increased resistance towards plastic deformation, which might cause some changes in tablet formation properties (Suihko et al., 2000).

Tolbutamide (TBM) is used clinically in tablet form as an oral hypoglycemic agent. It is practically insoluble in aqueous solutions, which is considered to be a rate-limiting step in its oral absorption (Miralles et al., 1982). The inclusion complex of TBM with β-CD or HP-β-CD increases its aqueous solubility, dissolution rate and rate of oral absorption (Kedzierewicz et al., 1993; Veiga et al., 1996), which makes such combinations suitable candidates for more efficacious formulations.

Both the preparation method of solid drug–CD complexes and the nature of the particular CD play important roles in the performance of a drug–CD formulation application (Mura et al., 1999). Among several frequently used techniques, both freeze-drying and spray-drying been have shown to be suitable for the preparation of solid drug–CD inclusion complexes (Veiga et al., 1996; Mura et al., 1999).

Although the benefits and pharmaceutical applications of CDs are well established, little attention has been paid to the tableting properties of HP-β-CD, and how these properties change in drug–HP-β-CD complexes. The aim of this study was to investigate the physicochemical and tableting properties of HP-β-CD and its TBM complex. Spray-drying and freeze-drying were used to prepare solid TBM/HP-β-CD complexes, and their properties were compared to identically prepared pure TBMs, HP-β-CDs and TBM/HP-β-CD physical mixtures.

2. Materials and methods

2.1. Materials

Tolbutamide (TBM) was purchased from Sigma Chemicals (USA), 2- hydroxypropyl-β-cyclodextrin (HP-β-CD) (Encapsin® HPB) from Janssen Biotech (Belgium), disodium phosphate dihydrate from Merck (Germany), sodium chloride and methanol (HPLC-grade) from J.T. Baker (The Netherlands), hydrochloric acid and ammonium from Riedel-de Haën AG (Germany), and sodium hydroxide from Eka Nobel AB (Sweden). All the materials were of analytical grade.

2.2. Apparatus

The high pressure liquid chromatographic (HPLC) system consisted of a Beckman solvent module (Model 116), UV detector (at 215 nm), a System Gold data module (Beckman Instruments, USA), a Marathon autosampler equipped with a column thermostat (Spark Holland, The Netherlands), a Rheodyne 7080-080 20 μl loop injector (Rheodyne, USA), and a Supelcosil LC8-DB (15 cm × 4.6 mm i.d., 5 μm) reversed-phase column (Supelco). Chromatographic conditions were as follows; column temperature 40°C, flow rate was isocratic at 1.0 ml/min, the mobile phase consisted of a 40% aqueous monobasic potassium phosphate buffer (0.2 M, pH 4.0) in methanol. An Orion SA 520 pH meter (Orion research Inc., USA) equipped with a combination pH electrode, was used to determine pH.

2.3. Solubility studies

The complexation of TBM with HP-β-CD in aqueous solution was determined by the phase-solubility method (Higuchi and Connors, 1965).

Excess amounts of TBM were added to phosphate buffer solutions (0.16 mol, pH 7.4, ionic strength 0.5) which contained various concentrations (3.6–144.6 mmol) of HP-β-CD. The suspensions were shaken at room temperature for 72 h and pH was monitored throughout equilibration. The pH of the suspensions was adjusted to pH 7.4 with HCl or NaOH, if necessary. After equilibration, the suspensions were filtered through 0.45 μm membrane filters and analyzed by HPLC. The determination of intrinsic solubility (S_o) of TBM in CD-free phosphate buffer (0.16 mol, pH 7.4) was made in triplicate.

2.4. Preparation of freeze-dried and spray-dried materials

TBM/HP-β-CD complexes were prepared as solutions by adding an excess amount of TBM to a 244.6 mmol HP-β-CD solution (20% w/w) at pH 8.0, equilibrated, filtered and freeze-dried (Multi-Dry, FTS-Systems) (Suihko et al., 2000). Both TBM and HP-β-CD were also freeze-dried as pure materials from aqueous solutions at pH 8.0.

Similarly prepared TBM/HP-β-CD, TBM and HP-β-CD solutions were spray-dried (Büchi 190 Mini Spray Dryer, Büchi Labortechnik AG, Switzerland) under the following conditions (reported as inlet and outlet temperatures, respectively, ± 10°C); TBM/HP-β-CD solution, 145 and 100°C; HP-β-CD, 160 and 110°C; TBM, 150 and 95°C (Suihko et al., 2000).

The freeze-dried and spray-dried samples were passed through a 297 μm sieve and stored at least 72 h at 20°C and 33% relative humidity (Suihko et al., 2000). The physical mixture was made by mixing TBM and HP-β-CD powders with a Turbula 2P mixer (Turbula, Switzerland) at a 1:5 w/w ratio, which is equal to the theoretical TBM/HP-β-CD molar ratio of a 1:1 inclusion complex.

2.5. Solid state identification

Powder X-ray diffraction patterns were obtained from a Philips PW1820, ADP1700 Automated Powder diffractometer System (Philips, The Netherlands) under the following conditions; Ni filtered CuK_a radiation ($\lambda = 0.15418$ nm), 50 kV voltage, 40 mA current, and peak angle range 3.00–35.00°. Data were collected and analyzed by the Philips ADP1700 software package.

KBr disks of the powdered samples were analyzed by a FT-IR Spectrometer (Nicolet 510P FT-IR Spectrometer, Nicolet Instruments Corp., USA). The data were averaged from 32 scans over the range of 400–4000 cm^{-1} for each sample.

2.6. Water sorption studies

For water sorption study, powder samples were dried in a vacuum oven (Heraeus Instruments, Germany) at 40°C for 24 h, and then placed in a desiccator at a relative humidity (RH) of 22%. After 24 and 48 h the samples were weighed and transferred to a second desiccator maintained at RH 33%. This procedure was repeated over a range of increasing RHs (i.e. 22, 33, 45, 58, 70, 85 and 95%), which was achieved with saturated salt solutions (Nyqvist, 1983). Desorption studies were made by repeating the sorption procedure over the same series of RHs, but in the reverse order.

2.7. Determination of powder surface area

The specific surface areas of the powders were measured using a single point BET gas adsorption apparatus (Flowsorb 2300, Micromeritics, GA). Nitrogen was used as absorbent gas. Before the analysis samples were dried in a vacuum oven (Heraeus Instruments) at 40°C for 24 h and also degassed in the BET apparatus. The expressed values were means of three parallel measurements.

2.8. Compaction studies

Compacts were prepared with a compaction simulator (PuuMan, Finland). Quantities of powder were manually filled into a 10 mm (diameter) die to produce tablets having a theoretical thickness of 1.4 mm at zero porosity. A single-sided sawtooth profile with an upper-punch velocity of 60 mm/s and compression pressure of 150 MPa was used. The tablets were made with a die-wall lubricant by treating the punches and die wall with a 2% w/w suspension of magnesium stearate in acetone before each test.

Diametral crushing strength of the compacts was determined by a CT5 universal tester (Engineering Systems) with a constant cross-head velocity of 1 mm/s. Thickness and diameter of the compacts were measured with a micrometer screw before the crushing strength determinations, and compact porosity was calculated from both the weight and dimensions of the compacts and the material density. The tensile strength of compacts was derived according to the method reported by Fell and Newton (1970). The results presented as the means of 20 or 21 determinations, except for spray-dried HP-β-CD where the results are the mean of 13 determinations.

3. Results and discussion

3.1. Solubility studies

The solubility studies were performed at pH 7.4 where TBM (pKa 5.3) is in its ionized form. The aqueous solubility of TBM increased linearly as a function of increasing HP-β-CD concentration (Fig. 1). The phase-solubility diagram was classified as an A_L-type (Higuchi and Connors, 1965), which indicates the formation of 1:1 TBM/HP-β-CD complexes at pH 7.4 over the investigated HP-β-CD concentration range. The apparent stability constant ($K_{1:1}$) for these complexes was calculated according to Equation 1:

$$K_{1:1} = \text{Slope}/\{[S_0]^*(1 - \text{Slope})\} \quad (1)$$

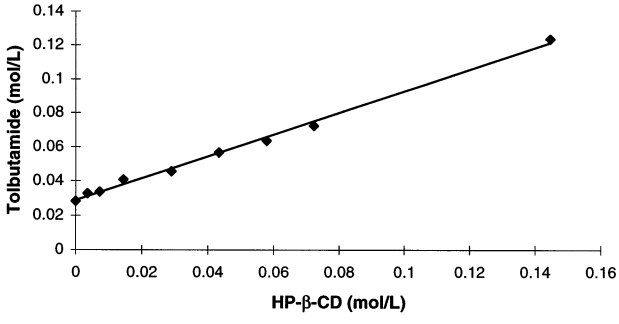

Fig. 1. Phase-solubility diagram of tolbutamide with hydroxypropyl-β-cyclodextrin at pH 7.4.

where $K_{1:1}$ is the apparent stability constant for the complex and S_0 the solubility of TBM in the absence of HP-β-CD. The intrinsic solubility (S_0) of TBM in phosphate buffer solution (pH 7.4) at room temperature was 7.62 ± 0.19 mg/ml (mean $\pm$ S.E., $n = 3$), and the $K_{1:1}$ for the TBM/HP-β-CD complex was 63 M^{-1}. These results are in good agreement with earlier reported values (Veiga et al., 1996).

3.2. Solid-state properties

According to phase-solubility studies, the complexed materials contained 14.3% of TBM and 85.7% of HP-β-CD. Theoretical amounts of free and complexed TBM and HP-β-CD in equilibrium were calculated according to Equation 2:

$$K_{(1:1)} = SL/\{(S_{tot} - SL)\ (L - SL)\} \quad (2)$$

where SL, S_{tot} and L are molar concentrations of the inclusion complex, TBM and HP-β-CD, respectively. Thus, the degree of complexation of TBM and HP-β-CD in freeze-dried and spray-dried materials were 76 and 65% w/w, respectively. In practice, the freeze-dried and spray-dried complexed materials contained 17.2 and 16.2% w/w of TBM, respectively, as determined by HPLC. The minor differences between the values obtained from the solubility studies and the measured values from powders probably results from differences in pH between the phase solubility studies (pH 7.4) and sample preparation (pH 8.0).

The inclusion complex formation between TBM and HP-β-CD in the freeze-dried and spray-dried materials were also confirmed by XRPD and FTIR. The freeze-dried and spray-dried HP-β-CD and complexed materials had diffuse X-ray diffraction patterns, which indicates the formation of an amorphous phase during these processes (Fig. 2). The physical mixtures showed typical characteristics of TBM. The freeze-dried and spray-dried TBM samples had X-ray diffraction patterns matching those of polymorphic forms II and I, respectively (Kimura et al., 1999).

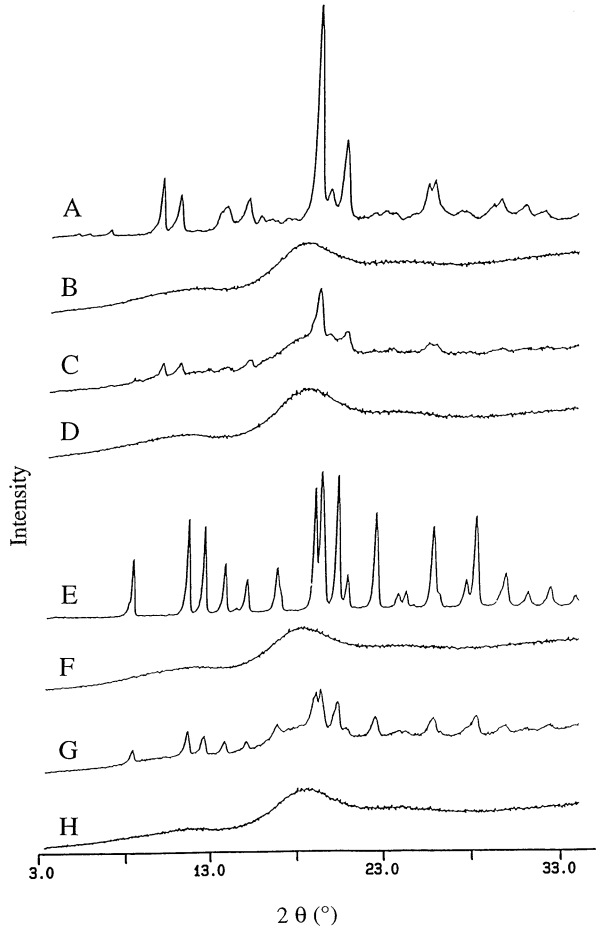

Fig. 2. X-ray powder diffraction patterns of freeze-dried tolbutamide (A), hydroxypropyl-β-cyclodextrin (B), physical mixture (C), complexed material (D), and spray-dried tolbutamide (E), hydroxypropyl-β-cyclodextrin (F), physical mixture (G), and complexed material (H).

Differences between the FTIR spectra of freeze-dried and spray-dried complexed materials and physical mixtures indicate a solid-state interaction between TBM and HP-β-CD. In particular, the characteristic carbonyl (C=O) absorption bands at 1659 and 1701 cm^{-1} for freeze-dried TBM, and 1663 and 1703 cm^{-1} for spray-dried TBM (Fig. 3) appeared as one broad band at 1701 cm^{-1} in both complexed materials. Both freeze-dried and spray-dried complexed materials showed similar changes in the FTIR spectra, which might be attributed to the dissociation of intermolecular hydrogen bonds in the TBM crystal lattice that are replaced by weaker forces in the complexed materials (Gandhi and Karara, 1988). Spectra of the freeze-dried and

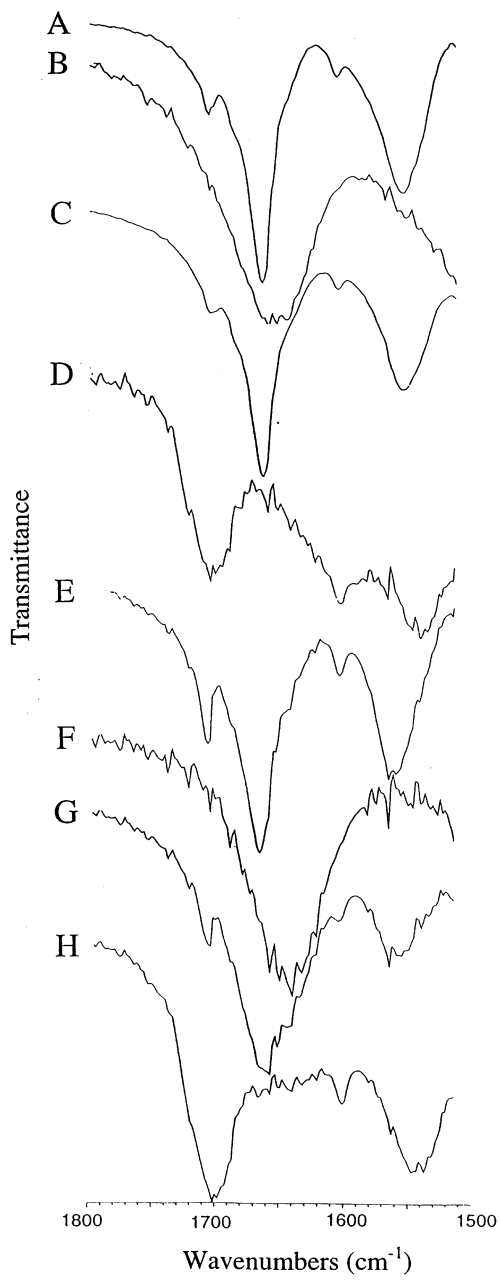

Fig. 3. FT-IR spectra of freeze-dried tolbutamide (A), hydroxypropyl-β-cyclodextrin (B), physical mixture (C), complexed material (D), and spray-dried tolbutamide (E), hydroxypropyl-β-cyclodextrin (F), physical mixture (G), and complexed material (H).

Table 1
The specific surface areas of powders, porosities, tensile strengths and surface specific tensile strengths of compacts made of freeze-dried (FD) and spray-dried (SD) tolbutamide (TBM), hydroxypropyl-β-cyclodextrin (HP-β-CD), their physical mixtures and complexed materials[a]

	Specific surface area (m^2/g)		Porosity (%)		Tensile strength (MPa)		Surface specific tensile strength	
	FD	SD	FD	SD	FD	SD	FD	SD
TBM	0.76 (0.02)	1.42 (0.10)	12.9 (0.4)	9.8 (0.2)	2.1 (0.2)	2.3 (0.1)	2.8	1.6
HP-β-CD	1.00 (0.02)	1.63 (0.02)	14.0 (0.3)	14.1 (1.1)	5.1 (0.5)	4.0 (1.7)	5.1	2.5
Physical mixture	0.80 (0.05)	1.82 (0.04)	14.7 (0.2)	13.1 (0.4)	4.6 (0.3)	5.3 (1.4)	5.8	2.9
Complexed material	0.69 (0.06)	1.64 (0.09)	14.2 (0.7)	14.4 (0.5)	1.7 (0.8)	3.6 (1.2)	2.5	2.2

[a] Compacts were made by using an applied load of 150 MPa. Standard deviations are listed in parentheses.

spray-dried physical mixtures showed unchanged carbonyl absorption bands for TBM. Freeze-dried and spray-dried TBM had absorption bands equivalent to those of polymorphic forms II and I, respectively (Kimura et al., 1999).

The results by both XRPD and FTIR demonstrated that the freeze-dried and spray-dried complexed materials were amorphous and primarily contained mostly TBM-HP-β-CD inclusion complexes. However, the actual amount of solid inclusion complexes in the complexed materials could not be accurately determined by these methods. The oligosaccharide structure of HP-β-CD enables a molecular interaction with TBM in ways that are not distinguishable in the amorphous state. During spray-drying, for example, the equilibrium between solvent, free and complexed TBM and HP-β-CD changes and, therefore, the fractions of complexed TBM and HP-β-CD could be somewhat different than the theoretical values. During freeze-drying, the formation of new inclusion complexes is hindered due to the continuous solid phase, as the amount of inclusion complexes should not change during the drying process.

3.3. Physical properties

The basic physical properties, e.g. particle size and shape, material density and specific surface areas of powders of the freeze-dried and spray-dried materials have been reported in a previous study (Suihko et al., 2000). However, specific surface area of the powders which were used in compacts was measured and the results are presented in Table 1. The values show similar trend with respect to material and preparation method as reported earlier (Suihko et al., 2000).

All the sorption-desortion isotherms of the studied materials were type II and had open hysteresis loops, except those of the TBMs (Fig. 4). This type of isotherm is characteristic of hydrophilic polymers having both surface adsorption and also absorption in the solid phase (Umprayn and Mendes, 1987). The spray-dried HP-β-CD absorbed slightly more water than the freeze-dried material, presumably due to the smaller particle size and greater specific surface area of spray-dried HP-β-CD (Suihko et al., 2000). However, both materials were hygroscopic at higher humidities and became to deliquescent at RH 95%. The freeze-dried and spray-dried physical mixtures absorbed 1 to 2 additional moles of water (per mole of HP-β-CD) during, and more water during the sorption phase (up to RH 85 and 70%, respectively) when compared to similarly prepared complexed materials. At high humidities the water content of the similarly prepared physical mixtures and complexed materials were equivalent. In both complexed materials the hysteresis loop was greater than that of the physical mixtures, indicating that water is more tightly bound in the complexed materials during desorption.

A lower particle surface area that is available for water sorption could partly explain the lower water content and reduced water uptake of the complexed materials at low humidities. This difference could, however, also result from disordered water molecules in the HP-β-CD cavity, where there are 11 partially occupied positions for seven water molecules in the cavity of $11H_2O \cdot$ β-CD (Saenger et al., 1998), which are partially replaced by TBM. Uncomplexed TBM could also reduce available binding sites for water outside the central torus of the HP-β-CD ring. On the other hand, homo-inclusion of the hydroxypropyl-chains into the HP-β-CDs cavity, as reported by Harata et al. (1993), partly explains the small difference observed in water content between the physical mixtures and complexed materials. Complex formation of TBM with HP-β-CD increased structural rigidity, resulting in lower deformability of the complexed materials when compared to the HP-β-CDs or physical mixtures (Suihko et al., 2000). This molecular rigidity could also hinder the moisture sorption of the complexed materials at low humidities. At high humidities moisture adsorption and desorption behaviours of complexed materials resembled to that of the physical mixtures. This behaviour is presumably related to a glass transition of the complexed materials, which increases molecular mobility and releases more sites for hydrogen bonding with water. This suggestion is also supported by the fact that the complex formation of aspirin with HP-β-CD at high humidity decreases the glass transition temperature of solid aspirin/HP-β-CD complex more than that of HP-β-CD (Duddu and Weller, 1996).

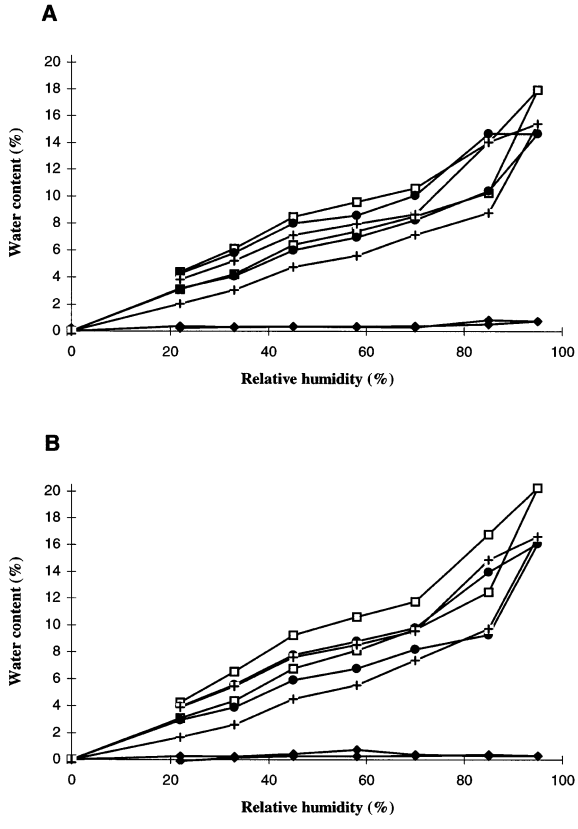

Fig. 4. The water sorption-desorption isotherms of the freeze-dried (A), and spray-dried (B), powders. TBM (◆), HP-β-CD (□), physical mixture (●), and complexed materials (+).

3.4. Tableting properties

Porosities of the compacts of freeze-dried and spray-dried materials were almost the same, except for the TBM polymorphs, whose compact porosities were lower (Table 1, Fig. 5). Spray-dried materials yielded stronger compacts than freeze-dried materials, except in case of the HP-β-CDs. The tensile strength of compacts produced from freeze-dried and spray-dried complexed materials were lower than that of the HP-β-CDs or physical mixtures. Tensile strength of spray-dried TBM (form I) compacts was slightly higher than that of the less-stable freeze-dried TBM (form II) compacts. This is in accordance with earlier reports which have concluded that the stable polymorph generally forms stronger interparticulate bonds and, thus, stronger compacts than the less stable form (Ragnarsson and Sjögren, 1984). However, this difference could also result from the slightly smaller particle size and lower porosity of the compacts resulting from spray-dried TBM (Suihko et al., 2000).

There also seemed to be a correlation between tensile strength of compacts and specific surface areas of the powders (Table 1). Therefore, surface specific tensile strength (SSTS), which has been

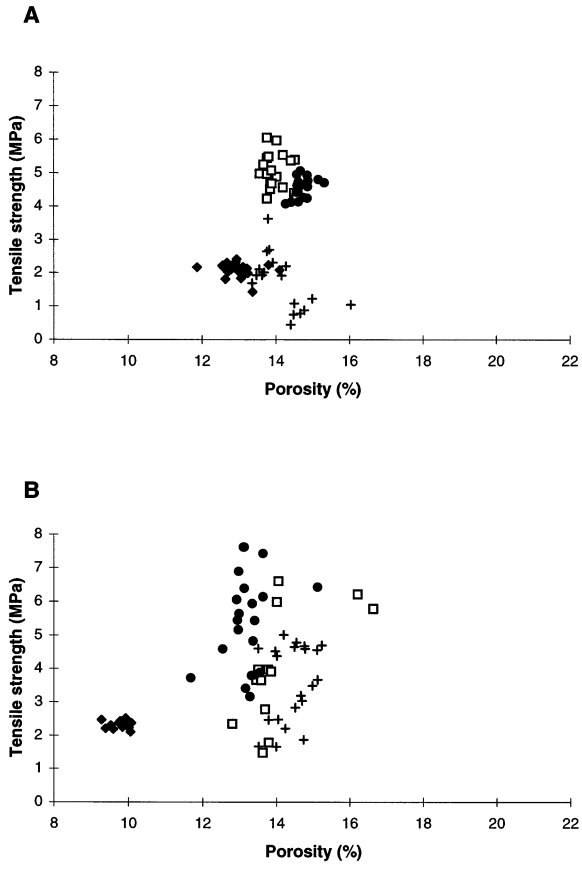

Fig. 5. Tensile strength of freeze-dried (A) and spray-dried (B) TBM (◆), HP-β-CD (□), physical mixture (●), and complexed materials (+) compacts as a function of compact porosity. Compacts were prepared at 150 MPa.

used to distinguish between different interparticulate bonding mechanisms in compacts (Nyström et al., 1993), was used to estimate the effect of available particle surface area for the effect of interparticulate bonding on compact strength:

$$SSTS = TS/SSA \quad (3)$$

where TS is the tensile strength of compacts and SSA is the specific surface area of prepared powders. The rank-order of surface specific tensile strength for the freeze-dried materials was essentially the same as for tensile strength (Table 1).

The observed trend towards a slightly lower tensile strength of compacts that were compressed from complexed materials could be a consequence of an inclusion complexation with TBM and HP-β-CD, and subsequent increased molecular rigidity and resistance against particle deformation as reported earlier (Suihko et al., 2000). Even a subtle decrease in the deformability of particle asperities could decrease the particle surface area that is available for interparticulate bonding, and thus, diminish desired compactibility properties when compared to compacts of HP-β-CDs. In addition, the low water content of the complexed materials at the RH 33% might also diminish their compactibility to some extent. The lowest tensile strength and surface specific tensile strength of the freeze-dried complexed material showed that, in this case, the compact strength was mostly dependent on complex formation between TBM and HP-β-CD. On the other hand, the spray-dried materials had small differences in surface specific tensile strengths. This indicates that also particulate properties, and especially the available surface area for interparticulate bonding, determines the compact strength.

4. Conclusions

Little attention has been paid to the tableting properties of HP-β-CD and its drug complexes. The present study demonstrates that the formation of freeze-dried or spray-dried TBM/HP-β-CD complexes change water sorption-desorption and tableting properties of the materials when compared to HP-β-CDs or physical mixtures made of the same materials. These subtle changes could substantially affect stability and tableting performance of a tablet formulation containing drug/CD complexes.

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