Deformation Behaviors of Tolbutamide, Hydroxypropyl-β-Cyclodextrin, and Their Dispersions

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Purpose. The deformation behaviors of compressed freeze-dried and spray-dried tolbutamide/hydroxypropyl-β-cyclodextrin molecular dispersions were evaluated and compared with similarly prepared tolbutamides (TBM), hydroxypropyl-β-cyclodextrins (HP-β-CD) and as their physical dispersions.

Methods. TBM, HP-β-CD, and their 1:1 molecular dispersions were prepared by freeze-drying and spray-drying, and physical dispersions of TBM and HP-β-CD were blended. Deformation properties of the prepared materials were evaluated by using a compaction simulator and constants derived from Heckel plots. Molecular dynamics (MD) simulations were performed in order to gain a molecular-level view on the deformation behavior of TBM-HP-β-CD inclusion complex.

Results. The freeze-dried TBM polymorphic form II was less prone to overall particle deformation than the spray-dried stable form I. Formation of molecular dispersions decreased the plastic and elastic behaviors of these materials. Also, the MD simulations showed a reduced molecular flexibility of the TBM-HP-β-CD inclusion complex, as compared to HP-β-CD.

Conclusions. The formation of TBM and HP-β-CD molecular dispersion resulted in more rigid molecular arrangements, which were less prone to deformation than either HP-β-CDs or physical dispersions. The results showed how differing molecular, solid, particle, and powder state properties affect the deformation properties of the materials studied.

KEY WORDS: Hydroxypropyl-β-cyclodextrin; tolbutamide; inclusion complex; physico-technical properties; deformation properties; molecular dynamics simulation.

INTRODUCTION

The oral administration of solid drug-cyclodextrin (CD) complexes has received a considerable amount of attention in recent years, and tablet dosage forms of drug-CD complexes are of great interest. However, surprisingly few studies have dealt with the deformation properties of CDs or drug-CD inclusion complexes. Muñoz-Ruiz and Paronen reported that CDs, and especially hydroxypropyl-β-CD (HP-β-CD), are highly prone to plastic deformation (1). Similar observations have been made of commercial and physically modified β-CDs, particularly concerning the significant role of moisture content on compactibility (2,3). Recently, β-CD has been used to modify the physico-technical properties of both excipients and drugs. For example, the co-drying of β-CD with microcrystalline cellulose improved powder and tabletting properties of microcrystalline cellulose (4), and the compressional properties of paracetamol were improved by preparing solid dispersions of paracetamol with an excess of β-CD (5).

Computational chemistry, e.g., molecular dynamics (MD) simulations, have also been used to study CDs and drug-CD inclusion complexes (6). Koehler *et al.* (1988) were among the first to use MD in order to study the conformational differences of α-cyclodextrin in both aqueous solution and crystalline form (7).

In our preliminary studies, we used spray-drying and freeze-drying to prepare 1:1 molar molecular dispersions of TBM and HP-β-CD, and evaluated their solid-state, physical and tableting properties by comparing to similarly prepared TBMs, HP-β-CDs and their physical dispersions (8,9). Freeze-drying and spray-drying produced amorphous TBM-HP-β-CD dispersions that were assumed to contain solid inclusion complexes. This assumption has been verified recently in another study, where a spray-dried amorphous dispersion of TBM preferably formed 1:1 solid-state complexes with HP-β-CD (10). Our preliminary studies also revealed that freeze-dried TBM crystallized into a thermodynamically less stable polymorphic form II and spray-dried TBM resulted in a stable polymorphic form I (8,9). Both were comparable to the results reported earlier (11). Tablet strengths of both molecular dispersions were poor, and was associated with a complex formation between TBM and HP-β-CD, which increased molecular rigidity and reduced the interparticulate bonding capacity. Moreover, all of the prepared materials primarily deformed by plastic flow, even though the TBM-HPβ-CD molecular dispersions had somewhat greater resistance towards particle deformation under compression.

The aim of the present work was to study the effect of complex formation and deformation properties of both freeze-dried and spray-dried TBM and HP-β-CD. Deformation behavior of the prepared materials was analyzed by using constants derived from the Heckel equation. MD simulations of TBM-HP-β-CD inclusion complex and HP-β-CD were performed to evaluate the mechanical properties on the molecular level.

MATERIALS AND METHODS

Materials

Tolbutamide was purchased from Sigma Chemicals Co. (USA). Hydroxypropyl-β-cyclodextrin (Encapsin HPB) was purchased from Janssen Biotech (Belgium).

Preparation of the Samples

Sample preparation was performed as described earlier (8,9). Briefly, molecular TBM-HP-β-CD dispersions, plain TBMs and HP-β-CDs were prepared by freeze-drying (Multi-Dry, FTS-Systems Inc., NY) and spray-drying (Büchi 190 Mini spray-dryer, Büchi Labortechnik, Switzerland). Physical dispersions (1:5 w/w) of the materials were blended with a Turbula mixer (Turbula, Switzerland). All samples were passed through a 297 μm sieve and stored at 20°C and 33% relative humidity (RH).

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Physical Properties

Mean particle size of the powders, coated with gold, was determined from scanning electron micrographs taken with a JEOL JSM-35 scanning electron microscope (JEOL Ltd., Japan). The equivalent Martin diameter was determined for 380–411 particles from each sample. The ratio between equivalent diameters of a sphere having the same area, and a sphere having the same perimeter was referred to as the shape factor (12). Larger values of the shape factor indicated that particles became more regular, where unity represented a totally spherical particle. The material densities were determined with a helium-pycnometer (Multipycnometer MVP-1, Quanta Chrome, NY) using helium as the inert measurement gas. Specific surface areas were measured with a single point BET gas adsorption apparatus (Flowsorb 2300, Micromeritics, GA) using nitrogen as the adsorbent gas. The water content of the samples was determined with a Karl Fischer titrimeter (Mettler DL 35 Karl Fischer titrimeter, Mettler Toledo AG, Switzerland).

Compression Studies

Densification properties of the powders were studied with a compaction simulator (Puuman Ltd., Finland). Quantities of powder were manually filled into a die (10 mm in diameter) to produce flat faced tablets having a theoretical thickness of 1.4 mm at zero porosity. Single-sided sawtooth profiles and upper-punch velocities of 6, 60 and 300 mm/s, at compression pressures of 50, 100 and 150 MPa, were used. The tablets in the compression experiments were made with die-wall lubrication by treating the punches and die wall with a 2% (w/w) suspension of magnesium stearate in acetone before every test. During compression, both the upper and lower punch forces and displacements were recorded, and the obtained compression displacement data were corrected according to upper and lower punch deformations.

Evaluation of the consolidation mechanism of the powders was determined form the Heckel equation (13,14):

$$\ln 1/(1 - D) = KP + A \quad (1)$$

which relates the packing fraction, or relative density, D, (i.e., the ratio between the apparent density of a powder bed and the material density) to the applied pressure, P. The slope of the linear portion of the graph, K, was expressed as a reciprocal, and considered as the mean of the yield pressure, P_y. Both the Heckel tablet-in-die and ejected-tablet methods were used (15). In the tablet-in-die method, the applied pressure and packing fractions of the powder column were determined during the loading phase of the compression process, i.e., both the upward part of the Heckel plot and the yield pressure (Py, as the reciprocal of the slope) were determined from the linear portion of the Heckel plot from four parallel measurements. When using the ejected-tablet method, the packing fractions were determined by measuring the dimensions and weights at 24 h after ejection from the die from four parallel compacts stored at 20°C and RH 33%. Time-dependent densification behavior of the powders was evaluated on the basis of the variation of yield pressure, at different punch velocities, and using the strain-rate-sensitivity (SRS) index (16). SRS was calculated by using the following equation:

$$SRS = \{(P_{y2} - P_{y1})/P_{y2}\} * 100\ (\%) \quad (2)$$

where P_{y1} is the mean yield pressure at 6 mm/s and P_{y2} the mean yield pressure at 300 mm/s.

Molecular Dynamic Simulations

All molecular modeling studies were carried out an a SGI O2 workstation using the Sybyl 6.5 software package. The crystal structures of TBM (17) and β-CD (18) were obtained from the Cambridge Crystallographic Data Centre. Four randomly chosen hydroxyl groups on the β-CD were substituted with hydroxypropyl side chains to simulate the average structure of HP-β-CD, which was used in the experimental section. TBM was manually docked within the CD cavity, and the subsequent inclusion complex was minimized by using MMFF94 prior to MD simulations in vacuo at 300 K. The length of the simulation was 10 ns, and data were collected every 0.5 ps. The root mean square (RMS) deviation in molecular deformation of a CD structure, as compared to the last frame of trajectory, was calculated for each frame.

RESULTS

Physical Properties

The physical properties of the materials are presented in Table I. The mean Martin's particle diameter of freeze-dried materials were fairly close to each other and somewhat greater than diameters of the spray-dried materials. The freeze-dried materials had an irregular and "flaky" particle shape, i.e., a smaller particle shape factor than the spray-dried materials, whose particles shape were more spherical and typical of the spray-dried materials. Both forms of TBM powders consisted of larger particles when compared to the other similarly prepared materials. However, their particle surface structures were more irregular than those of the other materials, eventhough they resembled the characteristic flaky and spherical features of the freeze-dried and spray-dried materials, respectively. This irregular surface structure of TBM particles is also indicated by relatively high specific surface areas. Freeze-dried powders had smaller specific surface areas than the corresponding spray-dried materials. Both molecular dispersions had significantly smaller specific surface areas than the similarly prepared physical dispersions or HP-β-CDs. Freeze-dried and spray-dried molecular dispersion powders contained 18 and 14% less water, respectively, than physical dispersions made by using the same method. The hydrophilic HP-β-CDs water content was related to the relative humidity (33%) of the stored samples, whereas the low water content of TBM was a consequence of its hydrophobicity.

Packing Fractions

The packing fraction of a powder, D_0, was defined as the relative density of the powder bed at the point where an upper punch force of 100 N appeared. For TBM and molecular dispersions, D_0-values tended to decrease slightly, and for HP-β-CD and physical dispersions D_0-values remained constant with increasing punch velocity (Table II). Unexpectedly, small particles of both molecular dispersions densified more easily in the pre-compression phase than either HP-β-CDs or physical dispersions. Both HP-β-CDs had low D_0-values, in line with values reported earlier (1).

Table I. Physical Properties of Freeze-dried (FD) and Spray-dried (SD) Tolbutamide (TBM), Hydroxypropyl-β-cyclodextrin (HP-β-CD), and Their Physical and Molecular Dispersions. Standard Deviations in Parentheses

	Material density (g/cm^3)		Mean Martin's diameter (μm)		Particle shape factor		Specific surface area (m^2/g)		Water content (%)	
Material	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD
TBM	1.34 (0.01)	1.30 (0.00)	38.3 (28.9)	27.3 (19.3)	0.85 (0.07)	0.85 (0.06)	0.96 (0.17)	0.97 (0.02)	0.2 (0.1)	0.1 (0.0)
HP-β-CD	1.48 (0.00)	1.49 (0.01)	39.3 (39.8)	4.2 (2.8)	0.80 (0.09)	0.95 (0.06)	0.59 (0.05)	2.40 (0.01)	7.4 (0.1)	7.3 (0.1)
Physical dispersion	1.45[a]	1.45[a]	24.5 (25.7)	4.3 (3.2)	0.83 (0.08)	0.94 (0.05)	0.68 (0.04)	2.01 (0.02)	6.0 (0.0)	5.7 (0.0)
Molecular dispersion	1.45 (0.00)	1.46 (0.01)	20.8 (23.1)	3.9 (2.5)	0.81 (0.08)	0.96 (0.05)	0.49 (0.04)	1.47 (0.06)	4.9 (0.1)	4.9 (0.1)

[a] Calculated values.

Densification arising from die filling and particle rearrangement was described by the D_A-values. The extent of this phase for the freeze-dried and spray-dried materials showed the same tendency as D_0-values in the pre-compression (bulk) stage (Table II). The D_A-values of both TBM forms, and freeze-dried physical and molecular dispersions decreased as the punch velocity increased. For other materials, the D_A-values were nearly constant with increasing punch velocity. Freeze-dried materials, except TBM, had greater D_A-values than spray-dried materials. Both HP-β-CDs had the lowest D_A-values, while TBM the highest. The freeze-dried physical dispersion had slightly greater D_A-values. To the contrary, the spray-dried physical dispersion had smaller D_A-value than the corresponding molecular dispersions.

D_B-values described the particle rearrangement in the die, and were obtained as the difference between D_A and D_0. Spray-dried materials had low D_B-values, which are characteristic for plastic materials (19), whereas the freeze-dried materials had somewhat higher D_B-values (Table II). D_B of the freeze-dried materials tended to be slightly decreased, except for the molecular dispersions, which increased with increasing punch velocity for the spray-dried materials. Both TBM forms had relatively high D_B-values. The physical dispersions, HP-β-CDs and molecular dispersions, in decreasing sequence, had relatively low D_B-values.

Deformation Properties

The Heckel tablet-in-die plots of the freeze-dried and spray-dried materials are presented in Fig. 1, which show short initial curvatures, especially for the spray-dried materials. This type of Heckel plots are typical for plastically deforming materials (20). Thus, according to the shape of the Heckel tablet-in-die plots, all the materials had a predominant deformation propensity towards plastic flow. The tendency of materials towards total deformation, with both plastic and elastic components, was demonstrated by the mean yield pressure values obtained from the upward portion of the Heckel plot, using the tablet-in-die method (Table III). The mean yield pressures of the freeze-dried HP-β-CD and its physical dispersion with TBM were lower than those of the freeze-dried molecular dispersion and TBM. Similarly, the spray-dried TBM and physical dispersion had lower mean yield pressures than the corresponding HP-β-CD and molecular dispersion.

Both of the molecular dispersions had slightly lower moisture contents than the corresponding physical dispersions (Table I). Therefore, we examined the effect of absorbed moisture on the deformation behavior of HP-β-CD in order to determine if water possessed a more critical role in deformation of the CDs than inclusion complex formation. The freeze-dried and spray-dried HP-β-CDs were vacuum dried at 40°C for 24 h, and thereafter stabilized for one week at relative humidities of near 0% (silica gel) and 70% (saturated KI solution). Dry freeze-dried and spray-dried HP-β-CDs contained 3.1 and 2.9% (w/w) water, and had high tablet-in-die mean yield pressure values of 117.6 ± 3.3 and 105.9 ± 3.5 MPa, respectively. Both freeze-dried and spray-dried HP-β-CDs, stored at 70% relative humidity, contained 12.6% (w/w) water and had low mean yield pressure values of 58.3 ± 4.9 and 50.7 ± 4.7 MPa, respectively.

Table II. Packing Fractions of the Freeze-dried (FD) and Spray-dried (SD) Tolbutamide (TBM), Hydroxypropyl-β-cyclodextrin (HP-β-CD), and Their Physical and Molecular Dispersions Obtained from the Heckel Tablet-in-die Method

	Compression speed (mm/s)																	
	6						60						300					
	D_0[a]		D_A[b]		D_B[c]		D_0		D_A		D_B		D_0		D_A		D_B	
Material	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD
TBM	0.44	0.52	0.67	0.71	0.23	0.20	0.44	0.50	0.65	0.68	0.21	0.18	0.41	0.49	0.60	0.69	0.19	0.19
HP-β-CD	0.37	0.34	0.54	0.40	0.17	0.06	0.37	0.33	0.53	0.39	0.16	0.06	0.38	0.34	0.54	0.41	0.16	0.08
Physical dispersion	0.37	0.38	0.60	0.44	0.23	0.06	0.37	0.37	0.59	0.43	0.22	0.06	0.38	0.37	0.56	0.45	0.18	0.08
Molecular dispersion	0.43	0.47	0.57	0.51	0.13	0.05	0.41	0.46	0.54	0.50	0.13	0.05	0.38	0.43	0.53	0.51	0.15	0.08

[a] D_0 describes the relative density of the powder bed under 100 N load.
[b] D_A describes the densification arising from the die filling and particle rearrangement.
[c] D_B descrubes the particle rearrangement in the die.

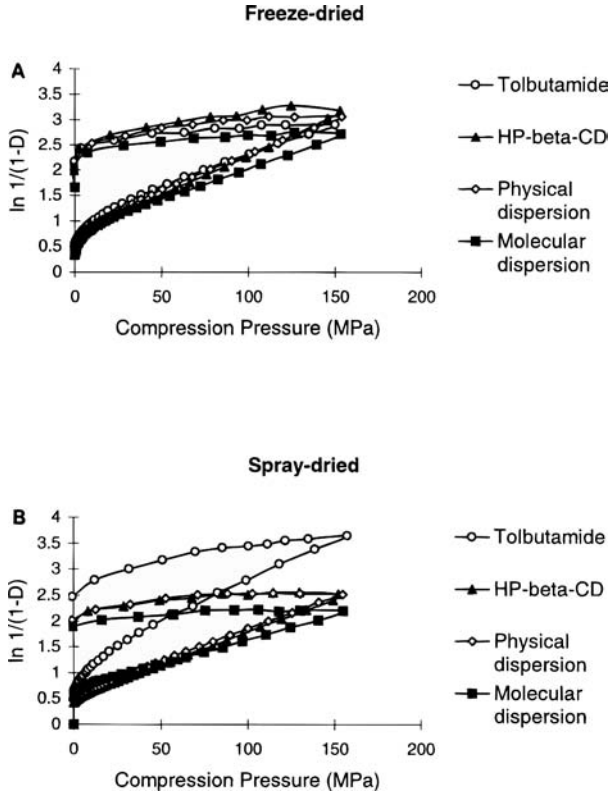

Fig. 1. Heckel tablet-in-die plots of freeze-dried (A) and spray-dried (B) tolbutamide, hydroxypropyl-β-cyclodextrin, and their physical and molecular dispersions.

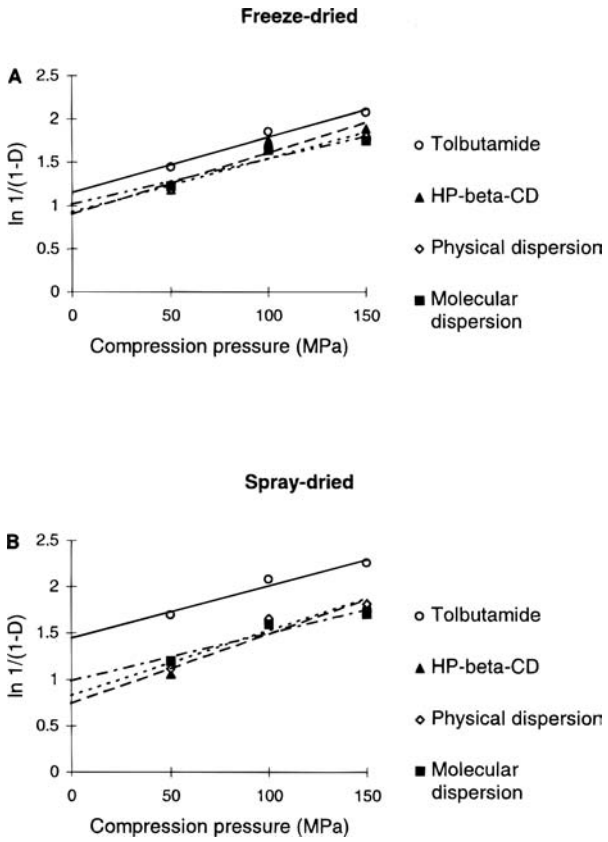

Fig. 2. Heckel ejected-tablet plots of freeze-dried (A) and spray-dried (B) tolbutamide, hydroxypropyl-β-cyclodextrin, and their physical and molecular dispersions.

The tendency of a material to deform in a plastic fashion, i.e., undergo permanent deformation, is shown by the mean yield pressure obtained from the Heckel ejected-tablet plots (Fig 2). Freeze-dried and spray-dried molecular dispersions showed a decreased propensity towards plastic flow when compared to ordinary TBMs, HP-β-CDs or physical dispersions (Table III). The freeze-dried TBM form II showed slightly higher plasticity than the spray-dried form I.

The reciprocal of the difference between the Heckel tablet-in-die and ejected-tablet upward plot slopes can be used as a parameter to describe the tendency of a material to deform elastically (20). The results from the present study pointed out that both of the molecular dispersions were less elastic than similarly prepared HP-β-CDs or physical dispersions as seen in the Combined-values in Table III. TBM polymorphs have opposite elastic characteristics, where TBM form II was the least elastic of the freeze-dried materials, and the spray-dried TBM form I showed highest elasticity. The freeze-dried HP-β-CD seemed to be more elastic than the spray-dried material. These differences overlapped each other in both of the physical dispersions, where elastic behavior was a mean of the counterparts.

Typically plastic materials with an elastic component in

Table III. Yield Pressure Values (MPa) and Strain Rate Sensitivities (SRS %) Derived from Heckel Plots for Freeze-dried (FD) and Spray-dried (SD) Tolbutamide (TBM), Hydroxypropyl-β-cyclodextrin (HP-β-CD) and Their Physical and Molecular Dispersions

	Tablet-in-die						Ejected-tablet		Combined		SRS %	
	6 mm/s		60 mm/s		300 mm/s							
Material	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD	FD	SD
TBM	83 (5)[a]	59 (3)[b]	83 (7)[a]	57 (6)[b]	69 (2)[a]	60 (9)[b]	156[a]	175[b]	176[a]	83[b]	<0[a]	0.5[b]
HP-β-CD	58 (1)	63 (1)	59 (2)	68 (2)	69 (1)	86 (5)	143	133	101	140	15.9	26.1
Physical dispersion	64 (2)	62 (1)	66 (1)	65 (2)	65 (1)	83 (2)	161	143	112	117	1.3	25.9
Molecular dispersion	76 (1)	93 (1)	77 (2)	96 (10)	78 (1)	109 (11)	192	196	128	187	2.6	14.9

Note: Standard deviation in parentheses and correlation coefficient was always >0.986.
[a] Polymorph II.
[b] Polymorph I.

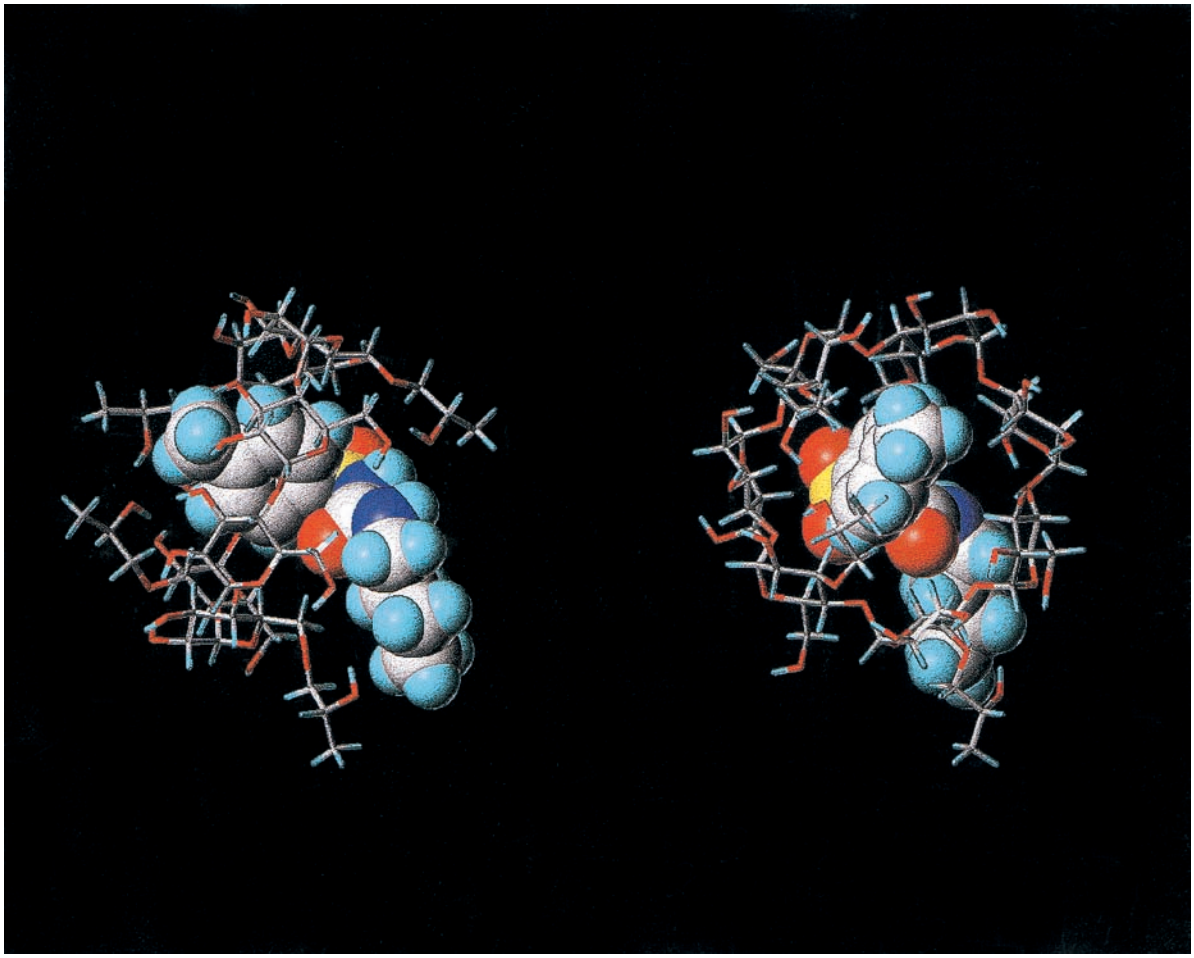

Fig. 3. Orthographic views of the most probable molecular structure of the 1:1 molar tolbutamide-hydroxypropyl-β-cyclodextrin inclusion complex.

their deformation behavior have high strain rate sensitivity (16). In general, the freeze-dried materials had lower SRS values than the spray-dried (Table III). The SRS of the both freeze-dried and spray-dried TBMs were negligible, as the molecular dispersions and physical dispersions had intermediate values, and HP-β-CDs had the highest SRS values.

Molecular Dynamics Simulations

In the case of TBM there were two different ways to dock the ligand within HP-β-CD, as either the aromatic ring or the lipophilic chain had favorable interactions with the hydrophobic cavity. MD simulations indicated, that the aromatic ring was more probable as the interacting structure for TBM, with an energy difference between the two possibilities of 20 kJ/mol. During the simulations, the aromatic ring of TBM was firmly located within the CDs cavity. The NH and SO_2-groups in the chain of TBM formed hydrogen bonds with the hydroxyl groups and hydroxypropyl side chains of HP-β-CD. A molecular model showing the most probable structure of the 1:1 stochiometric TBM-HP-β-CD inclusion complex is illustrated in Fig. 3. In all MD simulations, the TBM-HP-β-HP inclusion complex resulted in a lower molecular deformation than ordinary HP-β-CD or TBM (Table IV). For HP-β-CD, it could be suggested that its loss of deformation is due to increased molecular rigidity of the hydroxypropyl side chains. However, a similar effect is also seen with β-CD, which suggest this idea that this phenomenon is caused by the inclusion complexation.

DISCUSSION

The packing fractions and observed mean yield pressure values indicate that all of the studied powders underwent densification rather easily and were primarily deformed by plastic flow. However, deformation of the freeze-dried materials was less time-dependent, indicating partial fragmentation propensity, which was also seen as relatively high D_B-values, presumably resulting from their greater mean particle size and irregular particle shape. These particle properties of the amorphous freeze-dried HP-β-CD, physical dispersion (mostly amorphous HP-β-CD) and molecular dispersion could explain the lower observed mean yield pressure values when compared to the smaller and more spherical particles of the corresponding amorphous spray-dried materials. Also, Wong and Pilpel had reported similar behavior with plastically deforming excipients (21).

Both of the amorphous molecular dispersions were less prone to plastic and elastic particle deformation, when compared with similarly prepared HP-β-CDs and physical dispersions,

Table IV. Molecular RMS Deformation in nm for β-cyclodextrin (β-CD), Hydroxypropyl-β-cyclodextrin (HP-β-CD), Tolbutamide (TBM), and CD-TBM Inclusion Complexes

	β-CD	β-D/TBM inclusion complex	HP-β-CD	HP-β-CD/TBM inclusion complex	Hydroxypropyl-chains of HP-β-CD	TBM	TBM included in HP-β-CD
RMS deformation	0.13 (0.04)	0.11 (0.04)	0.14 (0.02)	0.09 (0.02)	0.12 (0.03)	0.41 (0.12)	0.10 (0.02)

Note: Standard deviation in parentheses.

although they were not purely fragmenting either. This indicates that the flexibility of TBM and HP-β-CD molecules was diminished in the molecular dispersions, making the materials more rigid and less prone to deformation than HP-β-CDs or physical dispersions. This phenomenon can be explained by the inclusion complexation, which causes rigid molecular arrangements. However, the primary deformation mechanism of the amorphous molecular dispersions seems to be plastic flow. Similarly, the amorphous structure of lactose is known to facilitate particle deformation by plastic flow (22).

CDs mainly deform by plastic flow and the yield pressure values of HP-β-CD obtained in this study are of the same magnitude reported earlier (1,2). Water plays a critical role in the deformation of HP-β-CD, which is shown by a great difference in mean yield pressure values between dry and "moist" HP-β-CDs. The dry HP-β-CDs probably exist in their glassy state, i.e., below their glass transition temperature (23). Thus, the low water content could result in low molecular mobility and high interparticulate friction, both of which result in high resistance against particle rearrangement and deformation during compression. This is seen as high mean yield pressure values. In moist HP-β-CDs, absorbed water in the interior of the CD cavity does not reinforce the molecular structure in the same way as a guest molecule would, but acts as a plasticizer together with the adsorbed water. Thus, high water content could increase molecular mobility and reduce interparticulate friction under compression, which results in low mean yield pressure values. In short, moist HP-β-CD is easily compressed. This behavior is in agreement with that of hydroxypropylmethylcellulose, where increases in moisture content affects densification and deformation properties by enhancing particle deformation and reducing interparticulate friction (24).

Both freeze-dried and spray-dried TBMs were of different polymorphic forms. The differences in particle size and polymorphism created dissimilarities in their resulting densification and deformation performances. Large particles of the both freeze-dried and spray-dried TBM had lowest interparticulate cohesive forces and friction and thus became more dense in the pre-compression phase. During compression, both TBM forms primarily deformed by plastic flow. In the case of form I these results are in line with the results of Humbert-Droz *et al.* (25). However, the freeze-dried form II had some fragmentation propensity, presumably due to its larger mean particle size and slightly flaky particle shape. In general, a decrease in particle size of partially fragmenting materials lead to an increased deformation stress until a plateau value at the brittle-ductile transition point was achieved (26). Also, particle deformation behavior that was independent of particle size was typical for plastically deforming materials.

In this study the less stable freeze-dried TBM form II was less prone to overall densification and particle deformation than the spray-dried stable form I, which also showed some elasticity. Initially, these results seem to be contradictory with earlier reports, where the less stable polymorph was reported to deform more easily (27,28). However, the volume reduction mechanism of freeze-dried TBM form II could change during compression from brittle, as seen in the precompression phase, to ductile, with a greater propensity towards plastic flow when compared to spray-dried TBM form I. The lower tendency towards plastic flow and the higher elasticity of the form I could indicate higher stability and strength of the intermolecular bond network within the crystal lattice, when compared to the less stable form II. Thus, the thermodynamically more stable form I is also mechanically more stable to irreversible lattice deformation.

In the inclusion complex, the phenyl ring of TBM is protruding from the wider end of the hydrophobic cavity of HP-β-CD in most cases, and the structure has a lower energy than the other inclusion complex studied. Similar observations have also been made in solid-state NMR studies of TBM and HP-β-CD (10). The MD simulations indicate that formation of the inclusion complex decreases the molecular deformability of the system, when compared to free HP-β-CD. This phenomenon has been theoretically characterized by MD simulations of a self-included β-CD derivative (29), and experimentally by Muñoz-Botella (30). Muñoz-Botella found that β-CD nanotubes deformed more easily by atomic force microscopy in the tapping mode, because of its lower local rigidity when compared to retinal-β-CD inclusion complex nanotubes. This change in the elastic properties was explained as a consequence of retinal-β-CD inclusion process. Our results from the compression studies and the MD simulations affirm that the inclusion complex formation of guests molecules with CDs reduces the flexibility of the complex when compared with free CDs or guest-CD physical dispersions.

CONCLUSIONS

This study examined how physico-technical properties of materials are affected by different molecular, solid, particulate and bulk state properties. In the freeze-dried and spray-dried amorphous molecular dispersions, the flexibility of TBM and of HP-β-CD molecules was decreased, and these materials became more rigid and less prone to deformation in the particulate and bulk state than HP-β-CDs or physical dispersions. The TBM polymorphs demonstrated how crystalline structure affects the deformation properties of materials under compression. The stable TBM form I had higher resistance against irreversible particle deformation than the less stable form II. Freeze-drying and spray-drying resulted in different particle

and bulk state properties, which also affect the deformation behavior of these materials.

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