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Research Paper

Crystal Structure Changes of γ-cyclodextrin After the SEDS Process in Supercritical Carbon Dioxide Affect the Dissolution Rate of Complexed Budesonide

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Purpose. The present study describes the crystal structure changes of γ-cyclodextrin (γ-CD) during the solution enhanced dispersion by supercritical fluids (SEDS) process and its effect on dissolution behaviour of complexed budesonide.
Materials and Methods. γ-CD solution (10 mg/ml in 50% ethanol) was pumped together with supercritical carbon dioxide through a coaxial nozzle with or without a model drug, budesonide (3.3 mg/ml). The processing conditions were 100 b and 40, 60 or 80°C. γ-CD powders were characterised before and after vacuum-drying (2–3 days at RT) with XRPD, SEM and NMR. Budesonide/γ-CD complexation was confirmed with DSC and XRPD. The dissolution behaviour of complexed budesonide was determined in aqueous solution (1% γ-CD, 37°C, 100 rpm).
Results. During the SEDS process (100 b, 40 and 60°C), γ-CD and budesonide/γ-CD complexes crystallized in a tetragonal channel-type form. The vacuum-drying transformed crystalline γ-CD into amorphous form while the complexes underwent a tetragonal-to-hexagonal phase transition. The increase in the processing temperature decreased the crystallinity of γ-CD. At 80°C, amorphous γ-CD was obtained while the complexes crystallized in a hexagonal channel-type form. The dissolution behaviour of budesonide/γ-CD complexes was dependent on their crystal structure: the tetragonal form dissolved faster than the hexagonal form.
Conclusions. The crystal structure of γ-CD and subsequently, the dissolution rate of complexed budesonide, can be modified with the processing conditions.

KEY WORDS: amorphicity; budesonide; channel structure; complex; γ-cyclodextrin; dissolution; hexagonal; SEDS; supercritical fluids; tetragonal.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides that have been used to improve the physicochemical and biopharmaceutical properties of drugs in various pharmaceutical dosage forms (1–4). The natural α-, β- and γ-CDs are cyclic molecules consisting of six, seven or eight glucopyranose units, respectively. The CD derivatives are formed when the free hydroxyl groups of natural CDs are chemically substituted. The three-dimensional structure of a CD molecule resembles a truncated cone with a hydrophilic outerior and lipophilic interior. Due to their structure, CDs are able to form inclusion complexes with lipophilic drug molecules.

The crystal structures of natural CDs have been described as channel-type (tetragonal or hexagonal) and cage-type (herringbone or brick-wall) alignments (5–7). In the columnar channel-type structure, the CD molecules are orientated to form a continuous channel of the linearly aligned CD cavities (Fig. 1a and b). In the cage herringbone and brick-wall alignments (Fig. 1c and d), the cavities of the CD molecules are blocked with the adjacent CD molecules. The crystals of γ-CD may consist either of cage herringbone or of columnar channel-type packing (6,7). The tetragonal and the hexagonal channel-type structures are distinguished based on the different close packing of the γ-CD molecules in the respective two-dimensional unit cells (Fig. 1a and b).

Solid drug/CD complexes have been prepared by various methods in solution and in solid state (6,8). Freeze-drying and spray drying of aqueous solutions, containing spontaneously formed drug/CD complexes, are among the most commonly used methods to produce solid drug/CD complexes. If the aqueous solubility of the complexes is limited, methods involving the precipitation of the complexes from supersaturated solutions can be used as well. Typically, the

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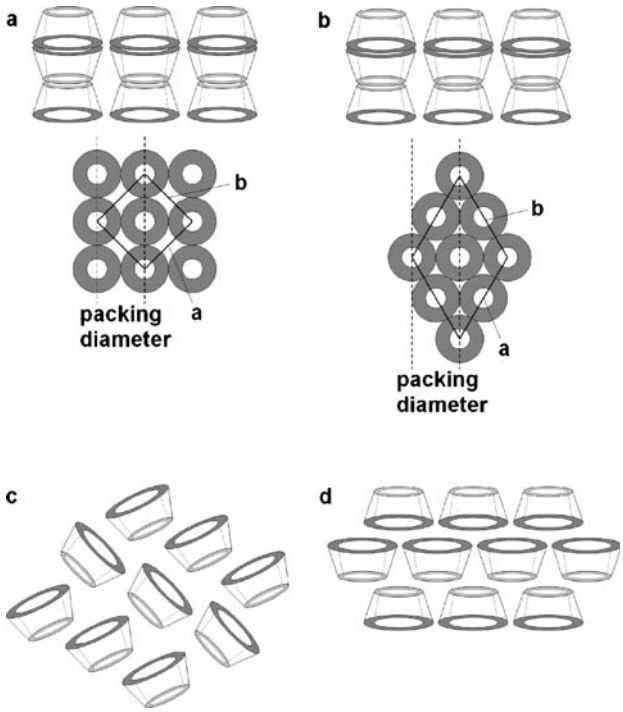

Fig. 1. Schematic representation of the crystal structures of cyclodextrins: (**a**) tetragonal columnar channel-type, (**b**) hexagonal columnar channel-type, (**c**) cage herringbone-type and (**d**) cage brick-wall-type structures.

complex formation takes place in aqueous environment. However, it has been reported recently that supercritical fluids may act as an alternative medium for complex formation (9–14). According to these studies, the solid drug/CD complexes have been formed during a static equilibration of drug-CD physical mixtures in supercritical fluids.

In our previous work, we described a novel method for preparation of budesonide/γ-CD complexes by using the solution enhanced dispersion by supercritical fluids (SEDS) process (15). The aim of the present study was to clarify the effect of the SEDS processing conditions on the properties of γ-CD particles and to further discuss the effect of crystal structure changes of γ-CD, induced by the SEDS process, on the dissolution rate of complexed model drug (budesonide).

MATERIALS AND METHODS

Materials

γ-cyclodextrin (Cavamax® W8 Pharma, MW: 1297) was purchased from Wacker–Chemie GmbH (Burghauser, Germany). Micronised budesonide (MW 430.5, d_{50}= 1.9 μm) was kindly donated by LAB Pharma, Ltd (Turku, Finland). Carbon dioxide (99.9%) was purchased from AGA Gas AB (Sweden). Ethanol (99.5%, Ph. Eur.) was purchased from Solveco Chemicals AB (Tåby, Sweden) and methanol (HPLC grade) from Labscan, Ltd (Dublin, Ireland). Dimethyl sulfoxide (DMSO-d6) and trimethyl silane (TMS) were purchased from Cortecnet (Paris, France). All chemicals were used as received.

Description of the SEDS-process

The SEDS apparatus and processes have recently been described in our previous work (15). In the present study, solid γ-CD particles were prepared with the conventional SEDS method. Briefly, during the experiment, the liquid-state CO_2 was pumped from the cylinder through a cooler (−10°C; flow rate 25 ml/min), after which it was pressurised and heated to achieve supercritical conditions. The processing conditions to produce γ-CD particles were 100 b and 40, 60 or 80°C (conventional method). γ-CD solution (10 mg/ml γ-CD in 50% v/v ethanol) was continuously pumped through the coaxial nozzle (flow rate 0.1 ml/min) together with supercritical carbon dioxide (SC-CO_2). The antisolvent-effect of SC-CO_2 caused the precipitation of γ-CD particles in the particle formation chamber. At the end of the experiment, the produced powders were rinsed with SC-CO_2 for 10 min (25 ml/min CO_2). The recovery of γ-CD powders were calculated as the percentage ratio of collected powder (mg) to the amount of γ-CD (mg) in the pumped solution.

The budesonide/γ-CD complexes were prepared by the conventional and modified SEDS methods as described earlier (15). Briefly, with the conventional method, budesonide (3.3 mg/ml) and γ-CD (10 mg/ml) were dissolved in the same solution (50% v/v ethanol) and processed at 100 b and 40 or 60°C (flow rates: 0.1 ml/min of the solution and 25 ml/min of SC-CO_2). With the modified method, budesonide (3.3 mg/ml in 99.5% v/v ethanol) and γ-CD (10 mg/ml in 50% v/v ethanol) were dissolved in separate solutions and processed at 100 b and 60 or 80°C (flow rates: 0.1 ml/min of each solution and 25 ml/min of SC-CO_2). At the end of the experiment, the produced powders were rinsed with SC-CO_2 for 10 min.

Characterisation of SEDS-processed Powders

The stability of γ-CD chemical structure was confirmed by a nuclear magnetic resonance (NMR) analysis of SEDS-processed γ-CD before and after the vacuum-drying. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 at 303 K, operating at 500.1 and 125.6 MHz, respectively. DMSO-d6 was used as the solvent. Chemical shifts (δ) were reported in ppm using TMS as the internal standard. SEDS-processed γ-CD samples were measured before and after the vacuum-drying.

The particle size and morphology of unprocessed and SEDS-processed γ-CD powder samples were evaluated before and after drying (2–3 days under vacuum in room temperature) with scanning electron microscopy (SEM) (XL30 ESEM TMP microscope, FEI Company/Oy Philips Ab). The powder samples were fixed onto a copper tape and sputter coated with gold for 2.5 min (Advanced Sputter Coater, Series II-E5100, Polaron Equipment Ltd, UK). The acceleration voltage was set to 15 kV, spot size to 2.5–3.0 and working distance to 10 mm.

The crystallinity of the SEDS-processed powders was determined by x-ray powder diffraction (XRPD) before and after drying (2–3 days under vacuum in room temperature). The XRPD measurements were conducted with a Bragg–Brentano $\theta/2\theta$ reflection geometry based Philips PW1820 diffractometer using CuK_{α}(λ= 1.54184 A)

radiation. The X-ray tube voltage was set to 40 kV and the current to 50 mA. The divergence of the primary X-ray beam was limited by an automatic divergence slit (ADS) and a 15 mm mask. The irradiated sample length was fixed at 12 mm. The diffracted beam was nickel K_β filtered and limited by a 0.2 mm receiving slit and a 1° anti-scatter slit. The samples were measured on a copper sample holder in a round sample cavity with a diameter of 6 mm and a depth of 0.3 mm. The samples were measured between the angular range of 3–30° (2θ) using 0.02° steps and a 1 s counting time per step. The measured diffractograms were analysed using X'Pert HighScore software (Philips, 2001).

The formation of budesonide/γ-CD complexes during the SEDS-process was confirmed previously by differential scanning calorimetry (DSC) and XRPD (15). The DSC study revealed that no crystalline budesonide was present in the SEDS-processed budesonide/γ-CD powders and the XRPD study indicated that their diffractograms were comparable to that of drug/γ-CD complexes. The dissolution behaviour of budesonide/γ-CD complexes (powder samples corresponded to 280–410 μg of budesonide) was determined in sink conditions by using 1% w/V γ-CD aqueous solution (37°C, 100 rpm) as a reservoir. The samples of 1.0 ml were withdrawn at 0.5; 1, 2, 3, 4, 5 and 10 min. The budesonide concentration of the samples was analysed with HPLC-UV (Purospher® RP-18e, 125×4 mm (5 μm), mobile phase: methanol-water 72:28 v/v, 1.0 ml/min, λ=250 nm). The retention time of budesonide was 4 min.

RESULTS AND DISCUSSION

Recovery of SEDS-processed γ-CD

The processing conditions had no effect on the extraction of hydrophilic γ-CD as the recovery of γ-CD was 75, 83/63 (n=2) and 74% in 40, 60 and 80°C at 100 b, respectively. These results are in agreement with previous findings: in general, the presence of hydroxyl groups in a molecule reduces its solubility in SF (16) and thus, the hydrophilic CDs are considered to be practically insoluble in SF (9).

Stability of γ-CD Chemical Structure

The stability of γ-CD chemical structure during the SEDS-process was confirmed by the ^{1}H and ^{13}C decoupled NMR spectra (see supplementary material). All of the spectra corresponded to those of unprocessed γ-CD. These results indicate that the chemical structure of γ-CD remained unchanged during the SEDS process and the subsequent vacuum-drying.

In addition to the peaks corresponding to γ-CD, the ^{1}H spectra of SEDS-processed γ-CD samples (both undried and vacuum-dried) showed a triplet signal at 4.31 ppm, a multiplet signal at 3.44 ppm and a triplet signal at 1.06 ppm. Furthermore, the ^{13}C decoupled spectra showed signals at 55.97 and 18.49 ppm. These ^{1}H and ^{13}C shifts are typical for ethanol in DMSO-d6. The addition of absolute ethanol to

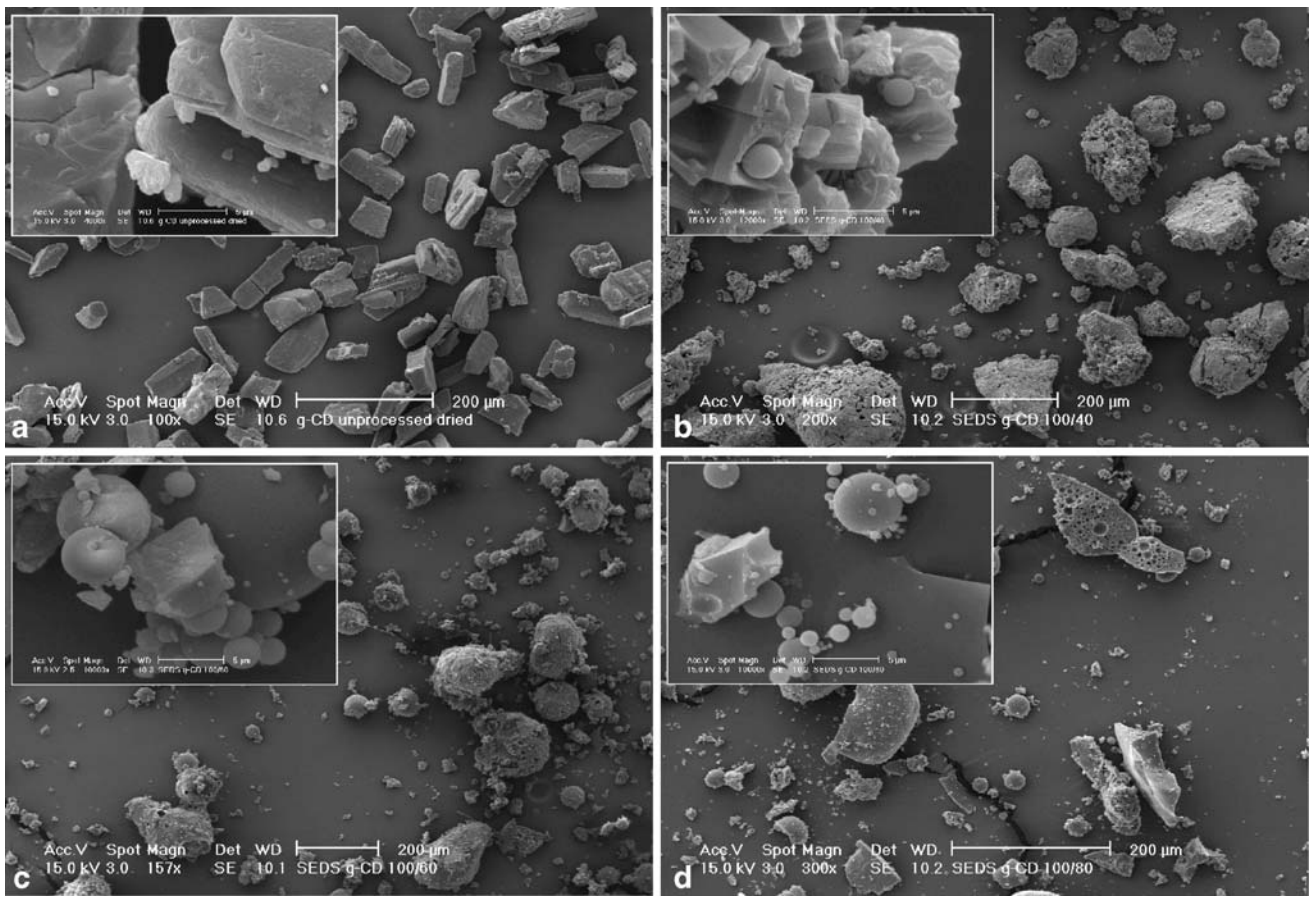

Fig. 2. SEM images of (**a**) unprocessed, vacuum-dried γ-cyclodextrin and (**b**)–(**d**) SEDS-processed, undried γ-cyclodextrin powders. Processing conditions: (**b**) 100 b, 40°C, (**c**) 100 b, 60°C, (**d**) 100 b, 80°C. Scale bar: 200 and 5 μm (inset).

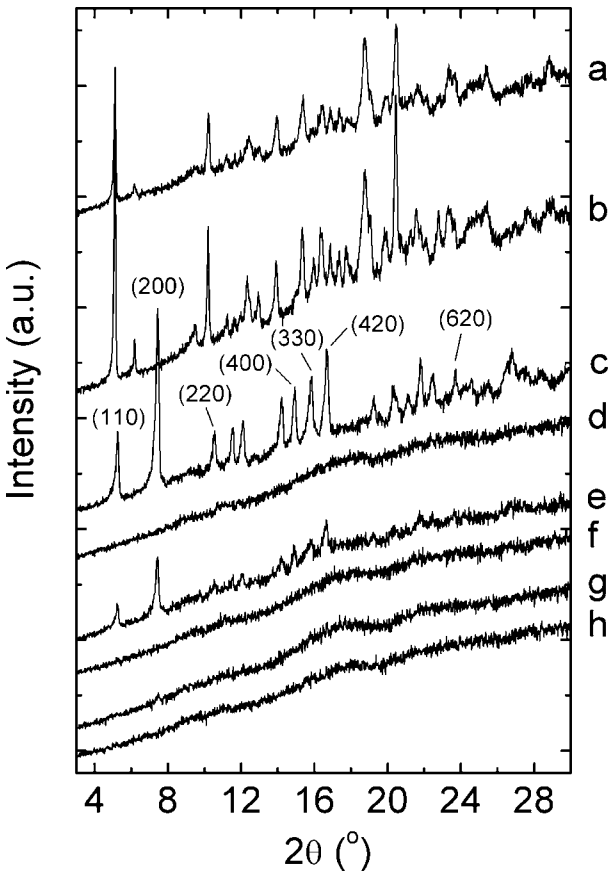

Fig. 3. X-ray powder diffractograms of (**a**) unprocessed, undried γ-cyclodextrin, (**b**) unprocessed, vacuum-dried γ-cyclodextrin and (**c**)–(**h**) SEDS-processed γ-cyclodextrin powders. Processing conditions: (**c**) 100 b, 40°C (undried), (**d**) 100 b, 40°C (vacuum-dried), (**e**) 100 b, 60°C (undried), (**f**) 100 b, 60°C (vacuum-dried), (**g**) 100 b, 80°C (undried), (**h**) 100 b, 80°C (vacuum-dried).

each sample increased the intensities of these peaks but no other peaks were observed compared to the original spectra. The relative amount of residual ethanol in the SEDS-processed powders was evaluated by comparing the integrals of the protons of the ethanol methyl group and the γ-CD acetal carbon (4.89 ppm) in the ^{1}H spectra (see supplementary material). It was observed that all of the γ-CD powders contained residual ethanol (ethanol:γ-CD molar ratio from 1:4.6 to 1:2; corresponding to 0.8–1.7% w/w). However, no correlation between the processing conditions or vacuum-drying and the amount of ethanol in the γ-CD powder was observed in the present study.

In order to determine the amount of residual ethanol in the budesonide/γ-CD complex powders, the additional ^{1}H and ^{13}C spectra were measured. In the ^{1}H spectrum, the ethanol peaks were overlapped with the budesonide peaks and in the ^{13}C spectrum, the high background noise complicated the integration of budesonide and ethanol peaks (data not shown). Therefore, the quantitation of ethanol in the budesonide/γ-CD complex powders was not possible.

Particle Morphology Changes of γ-CD

The SEDS-processes produced micron-sized γ-CD particles together with larger-sized aggregates (Fig. 2b–d). The SEDS-processed γ-CD particles showed a remarkable change in particle morphology compared to the initial state. While the unprocessed γ-CD particles were considered as regular-shaped crystals (Fig. 2a), the SEDS-processed γ-CD particles were mostly irregular or spherical in shape (Fig. 2b–d). The particle morphology was comparable to that of SEDS-processed budesonide/γ-CD complexes (15). The increase in the processing temperature (i.e. the decrease in the solvent power of SC-CO_2) seemed to increase the sphericity of the micron-sized γ-CD particles. The vacuum-drying did not alter the particle morphology of any γ-CD powder sample (data not shown).

Crystal Structure Changes of γ-CD

The crystal structure of free γ-CD molecules, crystallized from water, typically represents a cage herringbone alignment (6–8,17,18) though the formation of channel-type γ-CD with only water as the guest molecule has also been reported (19,20). Anyhow, in general, only uncomplexed hydrated γ-CD can form a cage-type packing while the complexation with another guest molecule induces the formation of a channel-type packing (7,21). For example, the inclusion of lipophilic molecules (n-propanol, potassium 12-crown-4, methanol and various benzene derivatives) induced the formation of a channel-type γ-CD structure (7,21–23).

Table I. Diffraction Data for the As-received γ-cyclodextrin Powder Before and After Vacuum-drying

Unprocessed γ-CD, Undried		Unprocessed γ-CD, Vacuum-dried		Reference Cage γ-CD
$2\theta_{meas}$ (deg)	d_{meas}(Å)	$2\theta_{meas}$ (deg)	d_{meas} (Å)	$2\theta_{ref}$[a] (deg)
5.1	17.28	5.1	17.24	
6.2	14.29	6.2	14.25	
9.5	9.27	9.5	9.29	
10.2	8.66	10.2	8.66	
11.2	7.88	11.2	7.87	
12.4	7.12	12.3	7.17	12.4
13.0	6.82	13.0	6.82	
14.0	6.34	13.9	6.36	
15.4	5.76	15.3	5.78	15.2
15.9	5.59	16.0	5.54	
16.4	5.39	16.4	5.41	16.5
16.9	5.24	16.9	5.25	
17.4	5.10	17.4	5.10	
17.8	4.99	17.8	4.99	
18.7	4.74	18.8	4.73	18.8
19.0	4.66	19.1	4.65	
20.0	4.44	19.8	4.48	
20.5	4.33	20.5	4.34	
21.6	4.11	21.6	4.12	
22.7	3.91	22.8	3.90	
23.4	3.81	23.3	3.81	23.4
23.7	3.76	23.7	3.76	
25.4	3.51	25.4	3.50	
27.7	3.22	27.7	3.22	
28.8	3.10	28.9	3.09	

[a] Literature values for cage-type γ-CD structure are taken from reference (20)

Table II. Crystallographic Characteristics of the SEDS-processed γ-cyclodextrin Powders Before Vacuum-drying (Undried)

Crystallographic Characteristics				
Processed at 100 b, 40°C	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[a](Å)
	(110)	5.28	16.75	16.75
	(200)	7.46	11.84	11.84
	(220)	10.57	8.37	8.37
	(400)	14.96	5.92	5.92
	(330)	15.82	5.60	5.58
	(420)	16.64	5.33	5.30
	(620)	23.69	3.76	3.75
Processed at 100 b, 60°C	Hkl	$2\theta_{meas}$ (deg)	d_{meas}(Å)	d_{calc}[b](Å)
	(110)	5.25	16.82	16.82
	(200)	7.43	11.89	11.89
	(220)	10.52	8.39	8.41
	(400)	14.89	5.94	5.95
	(330)	15.78	5.61	5.61
	(420)	16.65	5.32	5.32
	(620)	23.62	3.77	3.76

[a] Calculated assuming a tetragonal unit cell with $a=b=23.69$ Å, packing diameter 16.75 Å
[b] Calculated assuming a tetragonal unit cell with $a=b=23.78$ Å, packing diameter 16.82 Å

In the present study, the SEDS process induced the precipitation of tetragonal channel-type γ-CD (processed at 100 b and 40 or 60°C). While the XRPD powder diffractogram of the unprocessed γ-CD (Fig. 3a) was comparable to the one described for crystalline, cage-structured γ-CD (diffraction data compared in Table I) (20), the powder diffractograms of the SEDS-processed samples (at 100 b, 40 and 60°C) before vacuum-drying (Fig. 3c and e) corresponded to the tetragonal channel-type γ-CD (20,24). Therefore, the diffraction patterns of the SEDS-processed γ-CD powders (at 100 b, 40 and 60°C) were indexed on the basis of a two-dimensional tetragonal unit cell with dimensions $a=b=23.69$ Å and $a=b=23.78$ Å, respectively (Table II). The d-spacings of the hkl(200) reflection were used to calculate the unit cell dimensions (indicated in Fig. 3c). The calculated d-spacings were in excellent correlation with those observed, confirming the tetragonal structure of the SEDS-processed γ-CD powders (Table II). In the present study, the formation of tetragonal channel-type γ-CD was probably induced by the inclusion of ethanol in the crystal structure during the SEDS process, as indicated by NMR.

The SEDS processing conditions strongly affected the crystallinity of γ-CD. The increase in the processing temperature from 40 to 60°C decreased the intensities of the XRPD diffraction peaks (Fig. 3c and e), indicating a decreasing crystallinity of the powder. The increase in temperature up to 80°C resulted in the disappearance of the diffraction peaks (Fig. 3g) indicating the formation of amorphous material during the process.

The vacuum-drying did not alter the crystal structure of unprocessed γ-CD as indicated by the similar XRPD pattern before and after the drying (Fig. 3a and b). In contrast, the SEDS-processed vacuum-dried γ-CD powders were amorphous (Fig. 3d, f and h) regardless of their initial state of crystallinity (Fig. 3c, e and g). This result is in good agreement with studies of Hunt *et al.* (20) and Rusa *et al.* (19) who described the phase transition of γ-CD from a crystalline tetragonal channel-type to an amorphous form during a vacuum-drying period (90°C, 15 h).

The γ-CD phase transition during the vacuum-drying has been explained to occur due to the removal of loosely bound interstitial water (i.e. water residing between CD columns) and the subsequent destruction of structure-stabilizing hydrogen bonds between CD and water (20). On the other hand, a rapid precipitation of a solute can also lead to formation of amorphous particles in general (25). In the present study, the increase in formation of amorphous γ-CD during the SEDS-process with an increase in processing temperature may have resulted from the increased water evaporation due to the elevated processing temperature and/or from the faster particle formation due to the decreased solvent power of SC-CO_2. Furthermore, the γ-CD crystal structure changes observed after the vacuum-drying could be explained by the facilitated evaporation of the structure-stabilizing water during the vacuum-drying period.

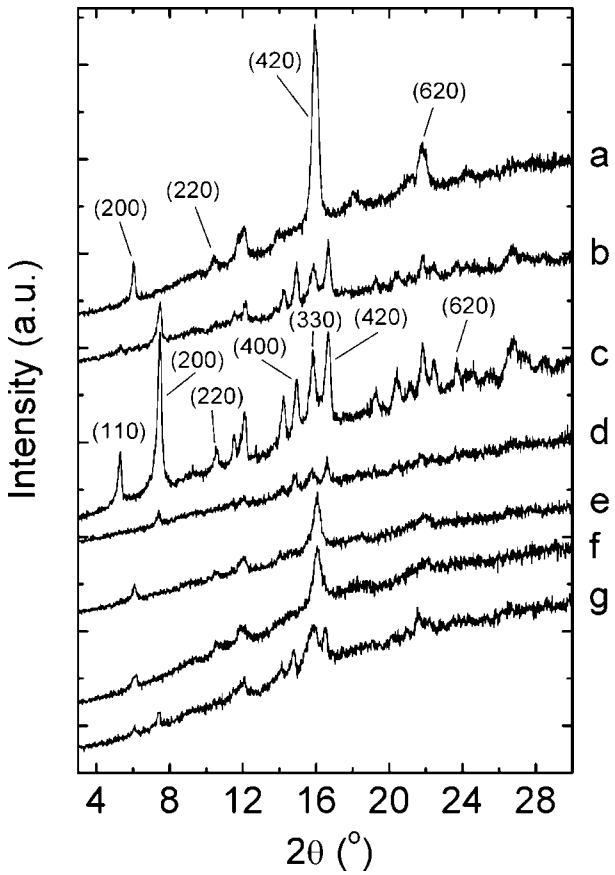

Fig. 4. X-ray powder diffractograms of budesonide/γ-cyclodextrin complex powders prepared (**a**) by precipitation method (26) and (**b**)–(**g**) by SEDS process. Processing conditions: (**b**) 100 b, 40°C (conventional method, undried), (**c**) 100 b, 60°C (modified method; undried), (**d**) 100 b, 60°C (conventional method, undried), (**e**) 100 b, 80°C (modified method, undried), (**f**) 100 b, 60°C (modified method, vacuum-dried), (**g**) 100 b, 60°C (conventional method, vacuum-dried).

Table III. Crystallographic Characteristics of the SEDS-processed and Precipitated Budesonide/γ-cyclodextrin Complex Powders with (Prominently) Hexagonal Structures

Crystallographic Characteristics				
Precipitation Method [a]	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[b](Å)
	(200)	6.01	14.70	14.70
	(220)	10.43	8.48	8.48
	(420)	15.92	5.57	5.55
	(620)	21.75	4.09	4.08
Modified SEDS method 100 bar, 60°C; vacuum-dried	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[c](Å)
	(200)	6.079	14.53	14.53
	(220)	10.545	8.38	8.39
	(420)	16.098	5.50	5.49
	(620)	22.017	4.03	4.03
Modified SEDS Method 100 b, 80°C; Undried	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[d](Å)
	(200)	6.0837	14.53	14.53
	(220)	10.532	8.39	8.39
	(420)	16.102	5.50	5.49
	(620)	21.962	4.04	4.03
Conventional SEDS Method 100 b, 60°C; Vacuum-dried	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[e](Å)
	(200)	6.10	14.48	14.48
	(220)	–	–	8.36
	(420)	16.04	5.52	5.47
	(620)	22.12	4.01	4.02
	Hkl	$2\theta_{meas}$	d_{meas}	d_{calc}[f]
	(110)	–	–	16.87
	(200)	7.41	11.93	11.93
	(220)	10.48	8.43	8.43
	(400)	14.80	5.98	5.96
	(330)	15.70	5.64	5.62
	(420)	16.57	5.34	5.33
	(620)	–	–	3.77

[a] Preparation described in (26)
[b] Calculated assuming a hexagonal unit cell with $a=b=33.94$ Å, packing diameter 16.97 Å
[c] Calculated assuming a hexagonal unit cell with $a=b=33.55$ Å, packing diameter 16.77 Å
[d] Calculated assuming a hexagonal unit cell with $a=b=33.55$ Å, packing diameter 16.78 Å
[e] Calculated assuming a hexagonal unit cell with $a=b=33.44$ Å, packing diameter 16.72 Å
[f] Calculated assuming a tetragonal unit cell with $a=b=23.86$ Å, packing diameter 16.87 Å

Crystal Structure Changes of Budesonide/γ-CD Complexes

In the present study, budesonide/γ-CD complexes were prepared with the precipitation, conventional SEDS and modified SEDS methods as described earlier (15,26). The XRPD pattern of the precipitated budesonide/γ-CD complex powder (Fig. 4a) closely resembled the patterns of γ-CD complex powders with a hexagonal channel-type packing of the crystal structure (5,21,27). Therefore, the diffraction pattern of the precipitated budesonide/γ-CD complexes was indexed on the basis of a two-dimensional hexagonal unit cell with dimensions $a=b=33.94$ Å (Table III). The d-spacings of the hkl(200) reflection were used to calculate the unit cell dimensions (indicated in Fig. 4a). The calculated d-spacings were in excellent correlation with those observed, confirming the hexagonal channel-type structure of the precipitated budesonide/γ-CD complex powder (Table III).

The preparation of budesonide/γ-CD complexes with the conventional SEDS method (processed at 40 and 60°C; Fig. 4b and d) and with the modified SEDS method (processed at 60°C; Fig. 4c) yielded tetragonal channel-type γ-CD complexes before drying. The patterns could be indexed with high correlation on the basis of a tetragonal unit cell with dimensions $a=b=23.60$–23.86 Å (Table IV). It was noted that the budesonide/γ-CD complexes prepared with modified SEDS method (100 b, 60°C) showed a much higher crystallinity compared to the complexes prepared with conventional SEDS method at the same processing conditions (Fig. 4c,d).

Thus, so far both conventional and modified SEDS processes (at 100 b and 40 or 60°C) have produced tetragonal

Table IV. Crystallographic Characteristics of the SEDS-processed Budesonide/γ-cyclodextrin Complex Powders with Tetragonal Structures

Crystallographic Characteristics				
Conventional SEDS Method 100 b, 40°C; Undried	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[a](Å)
	(110)	5.28	16.72	16.72
	(200)	7.48	11.81	11.82
	(220)	10.57	8.36	8.36
	(400)	14.96	5.92	5.91
	(330)	15.87	5.58	5.57
	(420)	16.70	5.30	5.29
	(620)	23.71	3.75	3.74
Modified SEDS Method 100 b, 60°C; Undried	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[b](Å)
	(110)	5.29	16.68	16.69
	(200)	7.48	11.80	11.80
	(220)	10.60	8.34	8.34
	(400)	14.99	5.91	5.90
	(330)	15.89	5.57	5.56
	(420)	16.75	5.29	5.28
	(620)	23.71	3.74	3.73
Conventional SEDS Method 100 b, 60°C; Undried	Hkl	$2\theta_{meas}$(deg)	d_{meas}(Å)	d_{calc}[c](Å)
	(110)	–	–	16.87
	(200)	7.41	11.93	11.93
	(220)	–	–	8.44
	(400)	14.84	5.97	5.96
	(330)	15.75	5.63	5.62
	(420)	16.63	5.33	5.33
	(620)	23.60	3.77	3.77

[a] Calculated assuming a tetragonal unit cell with $a=b=23.64$ Å, packing diameter 16.72 Å
[b] Calculated assuming a tetragonal unit cell with $a=b=23.60$ Å, packing diameter 16.69 Å
[c] Calculated assuming a tetragonal unit cell with $a=b=23.86$ Å, packing diameter 16.87 Å

Table V. Correlation between the Crystal Structure of SEDS-processed and Precipitated Budesonide/γ-cyclodextrin Complex Powders and the Dissolution Behaviour of Complexed Budesonide

Complex Preparation Method (Processing Conditions)	Packing Type of the Columnar Channel Crystal Structure	Packing Diameter (Å) [a]	Amount of Budesonide Dissolved in 1 min (n=3) (%, mean ± SD)	Amount of Budesonide Dissolved in 5 min (n=3) (%, mean ± SD)
Conventional SEDS Method (100 b, 40°C; Undried)	Tetragonal	16.72 (#5)	93±1	97±0
Modified SEDS Method (100 b, 60°C; Undried)	Tetragonal	16.69 (#6)	87±1	89±1
Conventional SEDS Method (100 b, 60°C; Undried)	Tetragonal	16.87 (#2)	84±1	88±0
Modified SEDS Method (100 b, 60°C; Vacuum-dried)	Hexagonal	16.77 (#4)	65±9	90±3
Precipitation Method [b]	Hexagonal	16.97 (#1)[c]	62±10	80±3
Conventional SEDS Method (100 b, 60°C; Vacuum-dried)	Hexagonal[d]	16.72 (#5)	57±1	84±2
Modified SEDS Method (100 b, 80°C; Undried)	Hexagonal	16.78 (#3)	54±4	80±1

[a] Calculated according to Takeo and Kuge (5), indicated in Fig. 1a and b
[b] Preparation described in (26)
[c] Size order, largest diameter indicated with #1
[d] A minor tetragonal phase was also detected in the sample

channel-type budesonide/γ-CD complex powders before the vacuum-drying of the samples. However, when the processing temperature was increased from 60 to 80°C (100 b; modified method), not tetragonal but hexagonal channel-type budesonide/γ-CD complex powder was obtained (Table III and Fig. 4e). It was also observed that the tetragonal channel-type structures of the undried SEDS-processed samples (Table IV and Fig. 4c,d) were transformed into hexagonal channel-type structures after the vacuum-drying (Table III and Fig. 4f,g). These phase transitions can be explained by the removal of water from the interstitial sites between the CD columns (20,21). Thus, it seems that the SEDS processing temperature of 80°C was high enough to remove the interstitial water from the tetragonal crystal structure and transform it into the more closely packed hexagonal channel-type form without the need of vacuum-drying. However, the tetragonal-to-hexagonal phase transition of budesonide/γ-CD complex powder processed with conventional SEDS method (100 b, 60°C) seems to have occurred only in part, as the diffraction pattern showed the peaks of both the tetragonal and the hexagonal forms after the vacuum-drying (Table III and Fig. 4d and g).

Correlation between γ-CD Crystal Structure and Dissolution Behaviour of Complexed Budesonide

γ-CD crystal structure in the complex powder was found to correlate with the dissolution behaviour of complexed budesonide (Table V, Fig. 5a). The powder samples could be separated into two distinct groups ("fast" and "slow") based on their crystal structure and dissolution rate. The "fast" group which consisted of budesonide/γ-CD complex powders representing the tetragonal channel-type packing of the crystal structure showed an enhanced dissolution rate compared to the "slow" group which consisted of complex powders with the hexagonal channel-type structure.

The calculated packing diameters were very similar irrespective of the γ-CD crystal structure (Fig. 1a,b, Table

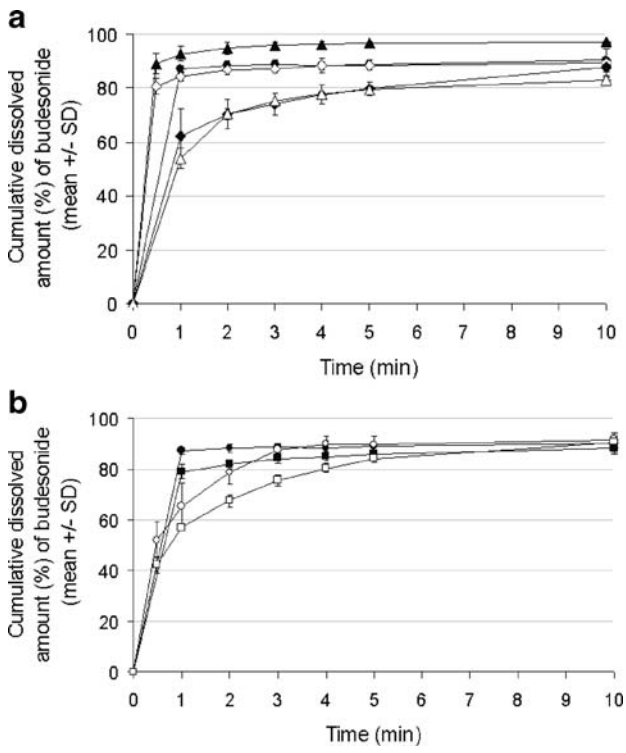

Fig. 5. (**a**) Dissolution behaviour of undried budesonide/γ-cyclodextrin complex powders (mean ± SD; n=3). Preparation method and processing conditions: SEDS 100 b, 40°C (conventional method, undried) (*black triangles*); SEDS 100 b, 60°C (modified method; undried) (*black circles*); SEDS 100 b, 60°C (conventional method, undried) (*white diamonds*); SEDS 100 b, 80°C (modified method, undried) (*white triangles*) and precipitation method (26) (*black diamonds*). (**b**) Dissolution behaviour of SEDS-processed budesonide/γ-cyclodextrin complexes before (filled symbols) and after drying (*open symbols*) (mean ± SD; n=3). Processing conditions: 100 b, 60°C (conventional method) (*squares*) and 100 b, 60°C (modified method) (*circles*).

V). Thus, the possible removal of water and/or ethanol molecules from the interstitial positions of the tetragonal unit cells (Fig. 1a) had produced a close packing of the columns of the γ-CD molecules in the hexagonal unit cell (Fig. 1b) without changing the diameter of the γ-CD molecules themselves. Thus, the divergent dissolution behaviours of the "fast" (tetragonally packed) and "slow" (hexagonally packed) sample groups (Fig. 5a) could be explained by the closeness ("tightness") of the packing of the columns of γ-CD molecules in the different unit cells. It seems feasible that the tetragonal packing with more space between the γ-CD molecules could facilitate the penetration of water molecules into the crystal structure and, thus, improve the dissolution rate of the complexed drug from the tetragonal channel-type complexes.

In the present study, the divergent dissolution behaviours cannot simply be explained by the possible differences in the particle size or the budesonide content of the complex powders since the differences in budesonide dissolution behaviour are observed even within the same batch of powder, depending on its state of drying after the SEDS-process at specific conditions (that is to say, the compared pair of samples had a similar particle morphology and budesonide content). The budesonide dissolution from SEDS-processed complexes was faster before the vacuum-drying (Fig. 5b, filled symbols) from the samples with the tetragonal packing of the crystal structure than after the vacuum-drying (Fig. 5b, open symbols) from the samples with the hexagonal close packing of the γ-CD molecules in the crystal structure. This result was in good agreement with the aforementioned dissolution behaviour of the "fast" and "slow" groups of samples.

As discussed previously (15), the SEDS-processed budesonide/γ-CD complex powders with a 1:2 (drug:CD) molar ratio may consist either of 1:2 (drug:CD) complexes alone or of 1:1 complexes with uncomplexed γ-CD. Thus, the XRPD patterns of the undried SEDS-processed complexes (processed at 40 and 60°C; Fig. 4b–d), with the tetragonal channel-type structures, might also represent the overlapped reflections of uncomplexed tetragonal channel-type γ-CD and hexagonal 1:1 budesonide/γ-CD complexes. Furthermore, the vacuum-drying of SEDS-processed complexes could have lead to the disappearance of the reflections of the tetragonal channel-type γ-CD (due to its phase transition from crystalline to amorphous state, as discussed in "Crystal Structure Changes of γ-CD") and thus, the reflections of the hexagonal budesonide/γ-CD complexes had become more evident in the diffractograms of the dried samples (Fig. 4f,g). Likewise, the absence of the tetragonal channel-type γ-CD reflections in the XRPD pattern of undried, SEDS-processed complexes (processed at 80°C; Fig. 4e) could also be explained by the phase transition of tetragonal uncomplexed γ-CD into an amorphous form due to the elevated processing temperature. Therefore, it could be suggested that the differences in the dissolution rate might depend on the crystallinity of the hexagonal channel-type of the budesonide/γ-CD complex structures as well, as amorphous compounds often dissolve faster compared to more crystalline ones. Thus, the slower dissolution rate of the budesonide/γ-CD complexes exhibiting the clear hexagonal channel-type structure peaks in the XRPD (Fig. 4e–g) would have been caused by the higher crystallinity of the hexagonal complex structure. However, this theory is not supported by the experimental results considering the dissolution rate of the samples within the "fast" or "slow" dissolving group. For example, considering the relative dissolution rates of the samples within the "fast" group (Fig. 5a; Fig. 4b–d), it can be noted that the most amorphous (proposed) hexagonal channel-type structure of the sample (produced with the conventional SEDS method (100 b, 60°C, undried; Fig. 4d)), did not release the complexed drug faster compared to the two more crystalline (proposed) hexagonal channel-type structures (Fig. 4b,c). This observation contradicts the proposed effect of the crystallinity of the hexagonal channel-type budesonide/γ-CD complex structure on the dissolution rate of complexed drug. Thus, based on the data available, it was concluded that the different close packings of the γ-CD molecule columns in the tetragonal or the hexagonal unit cells of the channel-type crystal structures were responsible for the divergent dissolution behaviour of budesonide.

CONCLUSIONS

In conclusion, the present SEDS-processes can be used to produce crystalline channel-type and amorphous γ-CD particles and crystalline channel-type γ-CD complexes in a single-step process. The crystal structure of solid γ-CD and budesonide/γ-CD complex powders can be modified by the processing conditions. The formation of budesonide/γ-CD complex powder with a tetragonal channel-type crystal structure improved the dissolution rate of the complexed drug compared to a hexagonal channel-type structure of the complexes. However, additional studies are needed to clarify the precise mechanism of the dissolution rate enhancement of the tetragonal channel-type γ-CD complex crystal structure compared to the hexagonal channel-type structure with various poorly water-soluble compounds.

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