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Hygroscopicity, phase solubility and dissolution of various substituted sulfobutylether β-cyclodextrins (SBE) and danazol–SBE inclusion complexes

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Abstract

The aim of the present work was to characterize hygroscopicity, phase solubility and dissolution properties for various substituted sulfobutylether β-cyclodextrins (SBEs) and danazol–SBE inclusion complexes. Moisture sorption was measured using a symmetric gravimetric analyzer. The complexes were characterized by powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC). Moisture sorption isotherms for the SBEs and the complexes showed low moisture sorption at RH $< 60\%$. The moisture absorption desorption isotherms for the various SBEs showed very little hysteresis, indicating almost complete desorption. Moisture adsorbed by the various SBE was in the order SBE $7 >$ SBE $4 >$ SBE 5 at 95% RH. Powder XRD data for complexes showed the disappearance of characteristic crystalline peaks for danazol or the formation of amorphous entities and DSC showed the disappearance of the peak of fusion of danazol indicating complex formation. Phase solubility of danazol with various substituted SBEs indicated 1:1 stoichiometry of complexes. The apparent stability constant, as determined by the method of Higuchi and Connors, increased as the degree of substitution of SBEs increased and decreased as the temperature increased. The dissolution of the complexes was significantly greater than that of the corresponding physical mixtures indicating that the formation of amorphous complex increased the solubility of poorly soluble danazol. More than 85% of danazol was released in < 10 min, compared to 15% danazol release from the physical mixtures.

Keywords: Sulfobutylether β-cyclodextrins (SBE); Danazol; Inclusion complexes; Moisture sorption desorption isotherms; Surface area analysis; Porosity; X-ray diffraction; Differential scanning calorimetry; Phase solubility analysis; Dissolution

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides containing 6, 7 or 8 glucopyranose units and are referred to as α, β and γ CD, respectively. A number of modified CDs have been developed, as shown in various reports (Muller and Brauns,

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1985; Thompson, 1997) to have applications, such as solubilization and stabilization of drugs. However only a few derivatives, such as hydroxypropyl and sulfobutylether β-cyclodextrins, are being investigated for pharmaceutical applications.

Presently, there are many commercially viable cyclodextrin formulations in the Japanese and European markets. These formulations comprise of intra-arterial infusion, sublingual tablets, capsules, suppositories and gargling solution (Thompson, 1997). In the US, only one formulation, Itraconazole (Sporanox®) oral solution has been approved (François et al., 1998). Recently, Captisol® (sulfobutyl ether β-cyclodextrin) is being investigated in drug delivery technology for specific ophthalmic uses and in the formulation development of new anticancer compounds. All these indicate the growing interest in the pharmaceutical industry to exploit the many advantages of cyclodextrin.

The newly developed sulfoalkyl ether derivatives of cyclodextrin have been reported to possess some advantages over parent cyclodextrin and other cyclodextrin derivatives (Fig. 1). One such derivative, sodium salt of sulfobutyl ether β-cyclodextrin (SBE), forms highly water soluble complexes with many poorly water soluble drugs, thus improving the stability (Torricelli et al., 1991) solubility, dissolution (Ventura et al., 1997; Yu and Streng, 1997) and bioavailability (Jarvinen et al., 1995) of these drugs. Okimoto et al. (1996) reported that the anionic SBEs often exhibits a 1:1 binding constants with neutral form of drugs, such as indomethacin and naproxen, that are comparable to or higher than those observed for the neutral HPCD. The better binding may be due to the butyl micellar arms that extended the depth of the hydrophobic cavity of the CD.

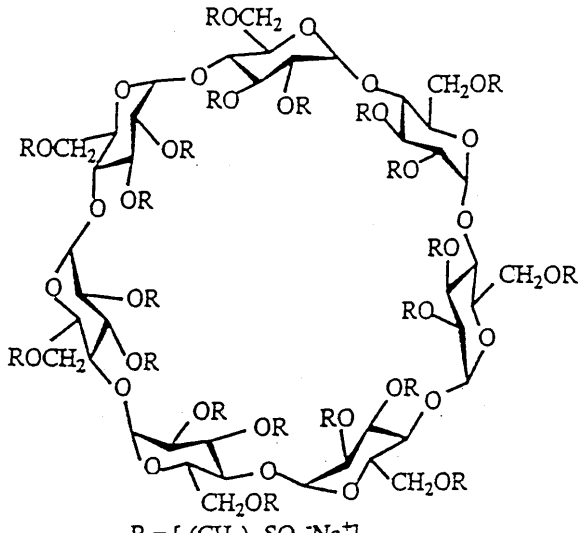

Fig. 1. Structure of sulfobutylether β-cyclodextrins.

Sulfobutyl ether β-cyclodextrin are a mixture of positional and regional isomers containing from one to as many as twelve sulfobutyl ether groups per CD. These mixtures are generally characterized by an average degree of substitution calculated on the basis of elemental analysis and/or NMR data (Luna et al., 1997a,b). The relationship between the degree of substitution, hydrophilicity and affinity for moisture has not been investigated.

Moisture levels in a solid influence the crystallinity of drugs, affect chemical and physical instabilities and powder processing operations, such as metering and compaction. For drugs and excipients, the residual water associated in solid state can significantly affect the successful development of pharmaceutical solid dosage forms, such as tablets, capsules etc. Hence, humidity conditions under which drugs and excipients are stored should be carefully controlled (Ahlneck and Zografi, 1990) and this must be based on a prior knowledge of critical relative humidity.

The possibility of using β-cyclodextrin as direct compression filler-binder has been previous reported by Pande and Shangraw (1995). These authors studied the role of moisture in the compactibility of β-cyclodextrin and concluded that a moisture level of 14% appears to be optimum for maximum compaction. Adeyeye et al. (1996) reported that danazol-sulfobutyl ether β-cyclodextrin 7 (SBE 7) complexes showed greater hygroscopicity than danazol-hydroxy propyl β-cyclodextrin (HPCD). However, the other variably substituted SBE derivatives have not been characterized for its moisture sorption characteristics.

The aim of the present work was to investigate moisture sorption characteristics of various substituted sulfobutyl ether β-cyclodextrin and the complexes formed with danazol, a steroid having low oral bioavailability due to dissolution rate limiting solubility and extensive first pass metabolism. The dissolution of danazol from these complexes was also determined. Three different SBEs with varied average degree of substitution — SBE 4, SBE 5 and SBE 7 — were used in the study. The 4, 5 or 7 indicate the average number of substituted sulfobutyl ether groups per CD.

2. Materials and methods

2.1. Materials

Various sulfobutyl ether derivatives SBE 4 (average MW = 1798), SBE 5 (average MW = 1857) and SBE 7 (average MW = 2160) were kindly donated by Cydex L.C. (Overland Park, KS). Danazol was purchased from Pharmrite North America Corporation. All other solvents used were of HPLC grade unless noted otherwise.

2.2. Methods

2.2.1. Preparation of solid danazol–SBE inclusion complexes

The inclusion complexes between danazol and the various substituted SBEs were prepared by solvent evaporation method, as reported previously by Badawy et al. (1996). Briefly, danazol (1 mol) and SBEs (3 mol) were dissolved in 90% methanol separately and then the two solutions were mixed. The solutions were stirred at ambient temperature and evaporated to dryness. The resulting complexes were screened through a No. 100 sieve and stored in a desiccator. The corresponding physical mixtures were prepared by physically mixing danazol with SBE.

2.2.2. Powder X-ray diffraction of danazol–SBE complexes

Powder X-ray diffraction patterns of various danazol–SBE complexes and physical mixtures were determined between $2\theta = 10–35°$ using a Philips PW 3710 scanner/PW 1830 generator with a Cukα anode at 40 kV and 30 mA.

2.2.3. Differential scanning calorimetry (DSC) of danazol–SBE complexes

DSC scans of the powder samples of SBEs, complexes and physical mixture were recorded on a Dupont 2910/TA DSC using Thermal Analyst software for data acquisition. Each sample (5 mg) was scanned at a rate of 10°C/min from 25 to 300°C. Nitrogen was used as a purge gas and an empty aluminum pan was used as a reference.

2.2.4. Particle size analysis

Particle size of the various SBEs and complexes were measured using Leica® microscope and analyzed using Quantimet Image Analyzer®. The SBE 4 and 5 were analyzed 'as received' from the company, while SBE 7 received as flakes, was ground in a glass mortar and then analyzed. The complexes were analyzed after sieving through No. 100 sieve.

2.2.5. Porosity and specific surface area analysis

Porosity and specific surface areas of the samples were determined by high-pressure porosimeter (Poremaster 60, Quantachrome Corp.). Specific surface area and total intruded volume of the mercury was calculated from the intrusion data with Quantachrome Poredata for Windows Software, Version 1.07.

2.2.6. Moisture sorption–desorption study

Moisture sorption–desorption isotherms for the various SBEs and the danazol–SBE complexes were measured using a SGA-100 Symmetric Gravimetric Analyzer (VTI Corp., FL). The samples were dried at 60°C for 2 h and then subjected to various humidity conditions. Typically, 5 mg of the sample was placed in a quartz sample holder. The sample holder was then attached to a hang down wire connected to an ultra sensitive microbalance. The temperature was maintained at 25 ± 0.01°C using a constant temperature bath. The relative humidity was increased from 1 to 95% RH in steps of 10% RH for the adsorption isotherm and decreased from

95 to 1% RH in steps of 10% for the desorption isotherm. At each relative humidity step, the system controls the RH and monitors the sample weight until it reaches equilibrium conditions. The equilibrium weight and temperature at the RH step were then recorded.

2.2.7. Phase solubility analysis

Phase solubility measurements using various SBEs and danazol were performed using the method described by Higuchi and Connors (1965). Briefly, an excess of danazol was added to various concentrations of SBEs. The system was shaken for 24 h in a constant temperature water bath at 22 ± 1 and 37 ± 1°C. Samples were filtered using a 0.22 μm filter and analyzed by HPLC as described below.

The apparent stability constants ($K_{1:1}$) for the various danazol–SBE complexes were determined using the slope and the intercept of the line obtained from the phase solubility diagram. The stability constant was calculated using Eq. (1)

$$K_{1:1} = \frac{\text{slope}}{\text{intercept}(1 - \text{slope})} \quad (1)$$

where the intercept corresponds to the intrinsic solubility (S_o) of danazol at 22 or 37°C.

Also the change in enthalpy (ΔH°) on complexation was determined using Van't Hoff equation

$$\ln\left(\frac{K_2}{K_1}\right) = \Delta H^\circ \frac{T_2 - T_1}{RT_2T_1} \quad (2)$$

The Gibbs free energy changes (ΔF°) were determined using the following equation

$$\Delta F^\circ = -RT \ln K \quad (3)$$

and the change in entropy (ΔS°) upon complexation was determined by the equation

$$\Delta S^\circ = \frac{(\Delta H^\circ - \Delta F^\circ)}{T} \quad (4)$$

2.2.8. Dissolution of the danazol–SBE complexes

An accurately weighed amount of the complexes or physical mixture containing 10 mg of danazol were filled in size No. 0 capsules. The dissolution studies were performed using USP XXIII apparatus 1 (Basket method). Phosphate buffer (500 ml, pH 6.8) was used as the dissolution medium, which was maintained at 37°C and stirred at 50 rpm. Samples (1 ml) were removed at regular intervals and analyzed using HPLC as described below.

2.2.9. HPLC assay

The concentrations of danazol in the phase solubility and dissolution studies were analyzed using a reverse phase HPLC method. Fifty microliters of standards and samples were injected into C 18 column (Phenomenex, Torrance, CA). Flow rate of 1 ml/min (Shimadzu Liquid Chromatography LC 10AS) was used for the mobile phase consisting of acetonitrile:water (68:32). Danazol was detected at 286 nm using an UV detector (Shimadzu UV-VIS Detector SPD 10A). Chromatograms were recorded and analyzed using EZChrom Software (Shimadzu Scientific Instruments Inc., Columbia, MD).

3. Results and discussion

3.1. Powder X-ray diffraction

Powder X-ray diffraction (XRD) of various SBEs showed a single broad peak indicating the amorphous nature of these compounds. Powder XRD for danazol and physical mixture of danazol with various SBEs showed characteristic crystalline peaks of danazol at $2\theta = 13.5°$, 15.5° and 17.5°. These peaks disappeared in the SBE 4–danazol complexes indicating amorphous nature of danazol due to the formation of inclusion complexes (Fig. 2). Previous studies performed in our laboratory (Badawy et al., 1996) using NMR have confirmed the inclusion of danazol into cyclodextrin cavity. Similar kind of diffraction patterns were observed for SBE 5– and SBE 7–danazol complexes (data not shown).

3.2. Differential scanning calorimetry

The DSC thermograms for SBE 4, danazol, SBE 4–danazol complex and the physical mixture are shown in Fig. 3. DSC curve for the physical mixture showed peaks, characteristic of the pure

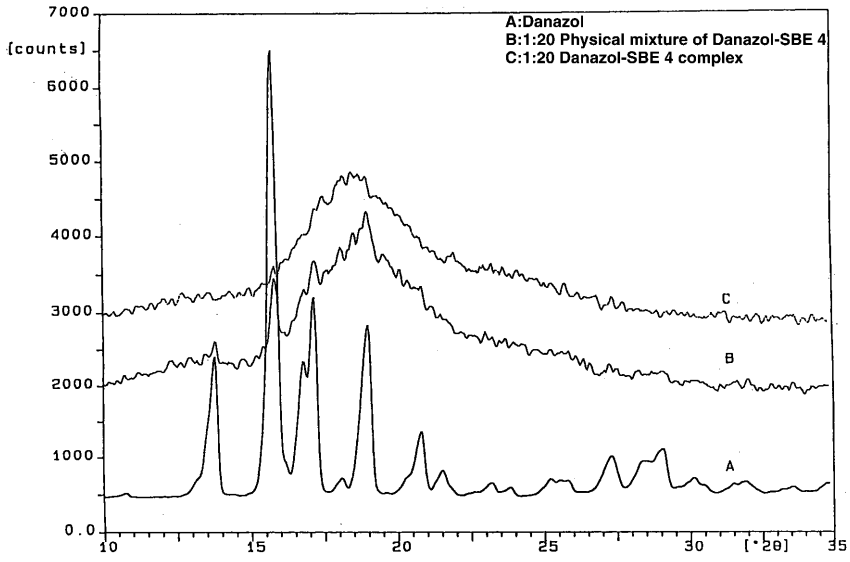

Fig. 2. Typical powder X-ray diffraction profiles for danazol, physical mixture of danazol and SBE 4 and SBE 4–danazol complex.

components. The broad endothermic peak in the range of 50–100°C in the physical mixture was due to the dehydration of SBE, while the sharp peaks at 224 and 275°C were due to fusion of danazol and fusion of SBE 4, respectively. In the SBE 4–, SBE 5– and SBE 7–danazol complex thermograms, danazol peak disappeared, indicating interaction between the two components, probably complexation.

3.3. Moisture sorption desorption study

Fig. 4(A–C) and Fig. 5(A–C) show the moisture sorbed (grams of water sorbed/gram of solid) versus percent relative humidity at 25°C. The various SBEs and SBE–danazol complexes showed ≈ 0.01–0.2 g of water absorbed per gram of SBEs when the humidity was increased from 20 to 60%. This corresponds to $< 17\%$ weight change at 60% RH. Further increase in RH resulted in a drastic increase in moisture sorption. At 95% RH, the moisture sorbed by various SBEs were in the order SBE 7 > SBE 4 > SBE 5 (Fig. 4A–C). Similarly, the moisture sorbed by the corresponding SBE–danazol complexes at 95% RH followed the same rank order (Fig. 5A–C). It is noteworthy that both SBE and SBE–danazol complexes exhibit similar adsorption–desorption profiles, indicating that the presence of danazol in the complexes does not affect moisture uptake.

The rate of moisture uptake by the various substituted SBEs and the various danazol–SBE complexes were determined at each relative humidities. A biphasic rate profile was obtained in which up to a relative humidity of 50%, $< 1\%$ weight change per hour, was observed in all the cases and after 50% RH, the rate of moisture uptake increased drastically. Critical relative humidity, the point at which the curve intersects the x-axis on the uptake rate versus %RH profile could not be determined due to the biphasic nature of the profiles. However, this critical humidity could be estimated to lie within 20–40% RH. Also the samples start to deliquesce at RH levels $> 80\%$. The first hysteresis loop (between 95 and 70 or 80% RH as the case may be) is primarily due to drying of the saturated solution. At some point < 70 or 80% RH, the adsorption and desorption isotherms coincide. Below 60% RH, the desorption branch of the isotherm starts to deviate slightly from the adsorption branch and the difference persists until low RH values were reached. This second hysteresis is probably due to the formation of a skin around the sample with

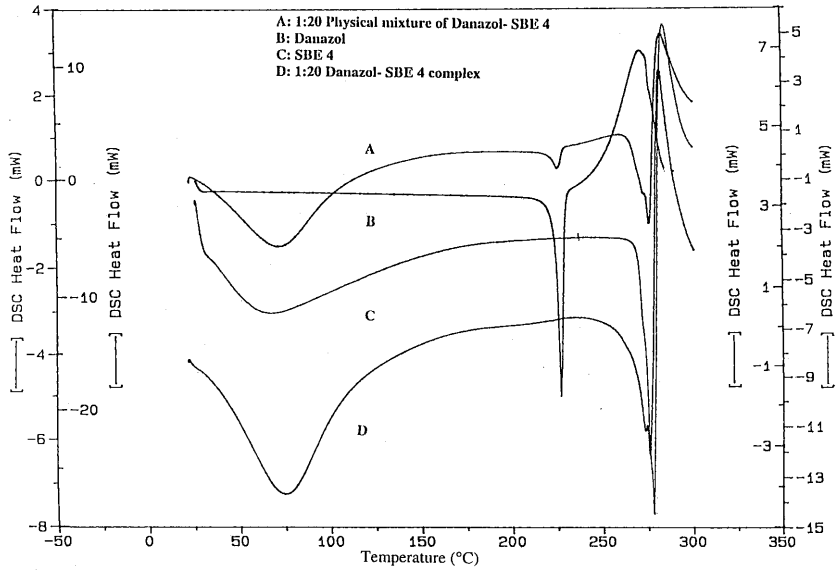

Fig. 3. Typical differential scanning thermograms for danazol, SBE 4, physical mixture of danazol and SBE 4 and SBE 4–danazol complex.

lower diffusivity for water. Since, in case of amorphous material, water acts as a plasticizer, the rate of diffusion of water will be a strong function of the water concentration, the lower the concentration, the lower the diffusion constant.

The SBEs and their complexes with danazol exhibited a Type III adsorption isotherm, as classified by Brunauer, (1943). Comparing the relative moisture sorbed by HPCD–danazol complex, as reported earlier by Adeyeye et al. (1996), the moisture sorbed by the various SBEs, i.e. SBE 4, SBE 5 and SBE 7 and their complexes with danazol, in our study was greater. This observed difference between HPCD and SBE is due to the presence of anionic charged sulfonic acid group in SBE making the polarizability of the SBEs greater than that of HPCD. Thus, more adsorption of water occurred on the adsorbent surface because of the hydrogen bonding propensity of a water molecule (Gregg and Sing, 1982).

3.4. Size distribution, surface area analysis and porosity

The SBEs and SBE–danazol complexes showed log normal particle size distribution. The surface areas of the differently substituted SBEs ranked in the order SBE 7 > SBE 4 > SBE 5 while those of the complexes were in the order SBE 4–danazol complex > SBE 7–danazol complex > SBE 5–danazol complex (Table 1). There was correlation between the moisture sorbed and the surface area of the individual SBE, but not generally with the complexes. SBE 7 having greater surface area than SBE 5 also had greater moisture sorbed compared to SBE 5 at 95% RH. This is due to the greater polarizability of SBE 7, the result of a greater number of anionic charges, as explained earlier. The porosities of SBE 4–danazol and SBE 5–danazol complexes were identical and thus, the moisture absorbed was similar. The highest moisture absorbed by SBE 7–danazol complex at 95% RH despite the lowest porosity is probably due to the greater polarizability of the SBE 7, as explained earlier.

3.5. Phase solubility analysis

Fig. 6 shows the phase solubility diagram of various SBEs with danazol at two different temperatures, 22 and 37°C. Solubility diagrams of danazol in various SBE solutions were linear A_L

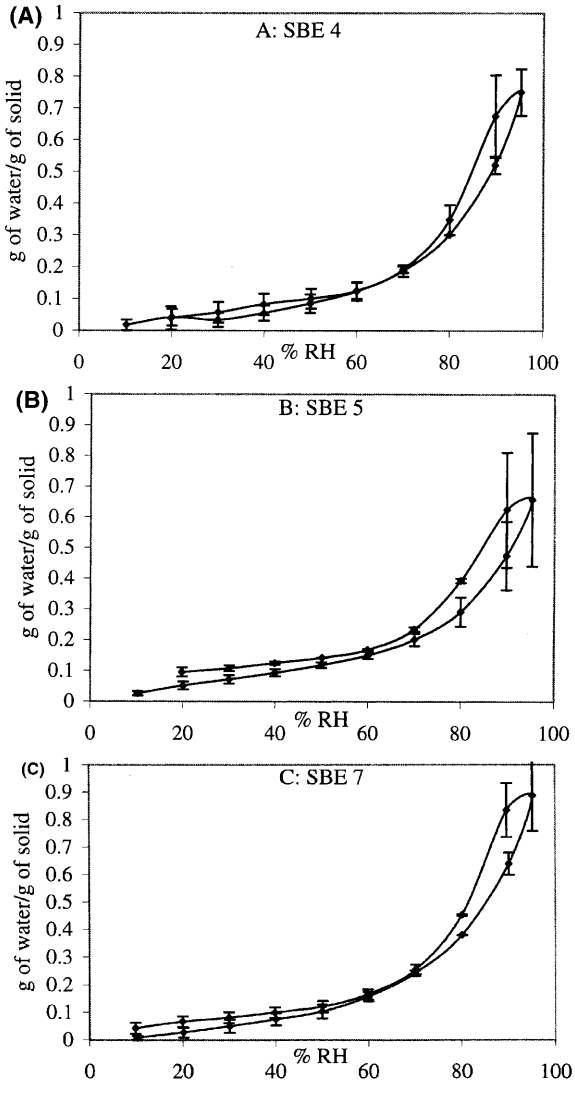

Fig. 4. Moisture sorption–desorption isotherms for SBE 4 (A), SBE 5 (B) and SBE 7 (C) [$n = 2$, bar represents S.D.] (lower curve in all graphs represent adsorption and upper curve represents desorption).

type, as classified by Higuchi and Connors (1965). This suggests a 1:1 stoichiometry of the complexes over the concentration range studied. The solubility of danazol in the presence of various substituted SBEs increased. The higher the degree of substitution, the greater the solubility of danazol and the stability constants. The apparent stability constants for complexes of danazol with SBE 4, SBE 5 and SBE 7 at 22 and 37°C are reported in Table 2.

Stability constants increased in the order SBE 7 > SBE 5 > SBE 4 at both temperatures. This is in agreement with previously reported data of

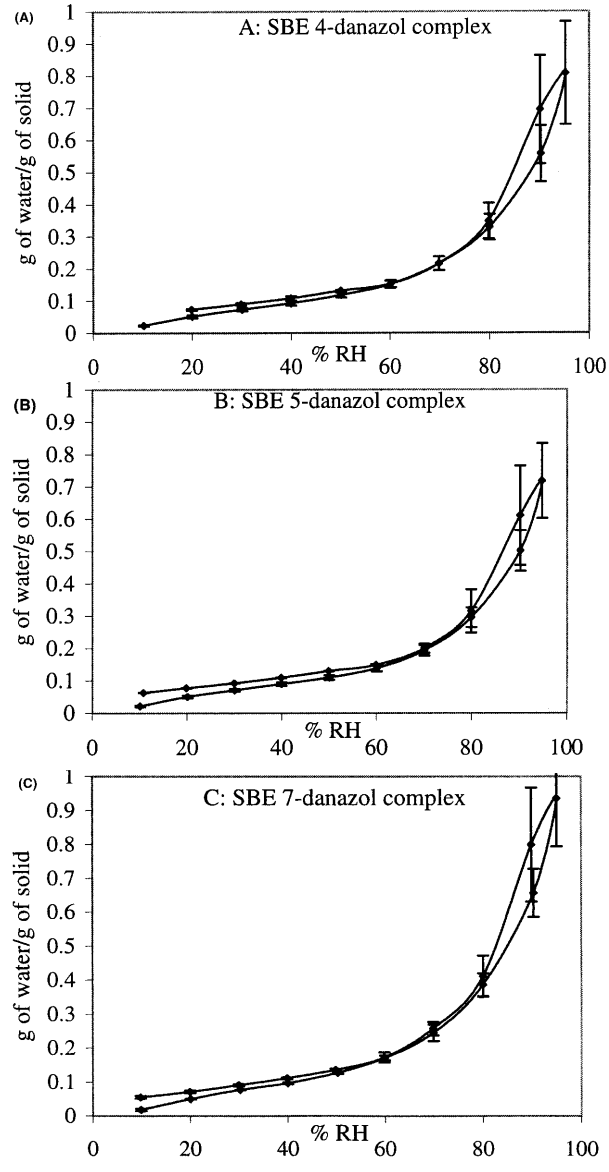

Fig. 5. Moisture sorption–desorption isotherms for SBE 4–danazol (A); SBE 5–danazol (B); and SBE 7–danazol complexes (C) [$n = 2$, bar represents S.D.] (lower curve in all graphs represent adsorption and upper curve represents desorption).

Table 1
Surface area, porosity and particle size analysis data of various SBEs and SBE–danazol complexes

Sample	Specific surface area (m^2/g)	Pore volume (cc/g)	Geometric mean diameter (μm)	Geometric S.D. (μm)
SBE 4	0.1213	0.8100	24.78	3.74
SBE 5	0.06537	1.0260	34.66	5.51
SBE 7	0.1588	0.8721	26.51	4.10
SBE 4–danazol complex	0.2107	0.7730	30.92	4.04
SBE 5–danazol complex	0.03233	0.7135	39.88	3.54
SBE 7–danazol complex	0.1392	0.5628	39.98	3.26

Muller and Brauns (1985), who observed a decrease in the stability constant of diazepam upon increasing the degree of substitution of methyl derivatives of β-cyclodextrin. Zia et al. (1997) reported that as the degree of substitution of SBEs increased, the stability constant increased for testosterone, however, for progesterone, the stability constant were similar as the degree of substitution increased. Specific guest–cyclodextrin interactions appear to play an important role in determining stability constants, i.e. guest molecular structure determines the magnitude of stability constant. It is proposed that chemical substitution of the hydroxy group on the β-CD molecules may also cause a distortion in the CD torus, such that a guest molecule may exhibit compromised stability constant. Furthermore, it was observed that the stability constant decreased with increasing temperature, probably due to the decrease in the interaction forces, such as van der Waals and hydrophobic forces.

Changes in thermodynamic parameters during complexation is an intricate phenomenon and is a result of changes in van der Waals interaction energy, hydrogen bonding and hydrophobic interaction between the guest and cyclodextrin. Various thermodynamic parameters, such as changes in enthalpy, Gibb's free energy and entropy of complexation are listed in Table 2. The negative enthalpies indicate that complexation phenomenon is exothermic, i.e. there was release of energy that favored formation of the complex. Furthermore, the inclusion of guest molecule would displace the 'enthalpy rich' water from the cyclodextrin cavity resulting in a favorable enthalpy of association. In all cases, the entropy change is negative indicating that complexation of danazol with SBEs resulted in an increase in the order of system. Strong interactions, as reflected in higher stability constants as the degree of substitution increases, may apparently cause an increase in hydrophobic interactions and large conformational changes due to an increase in the number of sulfobutyl ether groups attached to the β-cyclodextrin cavity. This, in turn, will decrease

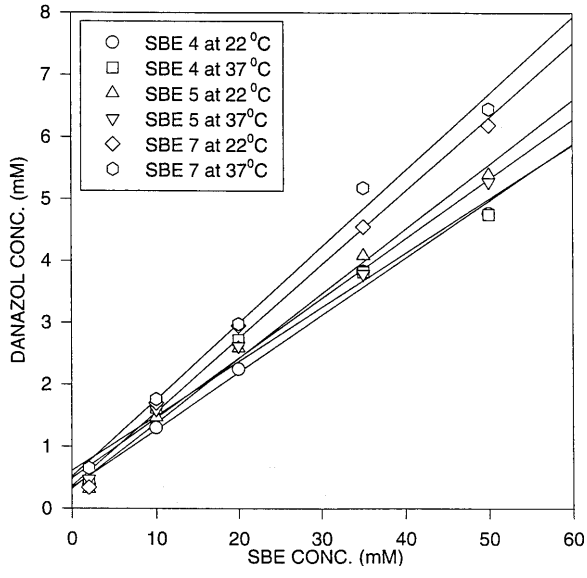

Fig. 6. Phase solubility of danazol with various substituted SBE derivatives.

Table 2
Stability constants and the thermodynamic parameters for complexation of danazol with SBE 4, SBE 5 and SBE 7

Temperature (°C)	K (M^{-1})	ΔH° (kJ/mole)	ΔF° (kJ/mole)	ΔS° (J/mole/°K)
SBE 4–danazol complex				
22	301.21	−32.758	−14.00	−63.55
37	157.95		−12.42	−65.57
SBE 5–danazol complex				
22	359.55	−25.083	−14.44	−36.05
37	219.32		−13.23	−38.22
SBE 7–danazol complex				
22	374.63	−15.802	−14.54	−4.28
37	274.38		−13.78	−6.52

the entropy of the system as reflected in lower negative ΔS° as the degree of substitution increases. Moreover, due to the probable increase in the hydrogen bonding of the sulfobutyl ether groups as the degree of substitution increases from 4 to 7 with the surrounding environment (water), lower negative enthalpy of complexation was observed.

3.6. Dissolution analysis

The dissolution profiles of the various danazol–SBE complexes and the corresponding physical mixtures are shown in Fig. 7. Due to the reduction in molecular crystallinity and an increase in water solubility following complexation, all the complexes showed significantly higher dissolution rates compared to the corresponding physical mixtures. More than 85% of danazol was released in <10 min, compared to 15% danazol release from the physical mixtures. No measurable quantity of danazol was detected when the dissolution of pure danazol was carried out due to the poor solubility of danazol in aqueous medium.

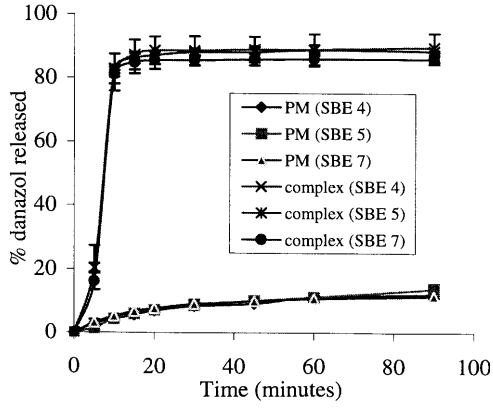

Fig. 7. Dissolution of various SBE–danazol complexes and SBE–danazol physical mixtures (PM).

4. Conclusions

Moisture sorbed by the various SBEs and their complexes was smaller at relatively lower humidity conditions (0–60%), but at $>60\%$ RH sorption of moisture increased drastically. Therefore, necessary care should be taken not to expose the excipients to humidities $>40\%$. Moisture sorption increased as the degree of substitution increased. Stability constant decreased with increasing temperature, while increasing degree of substitution on SBE increased stability constant. The various complexes showed higher dissolution compared to the physical mixtures of danazol with SBEs. The characterization of newer excipients is critical in the development of first products and the understanding of potential stability problems. The SBEs are very useful excipients in improving the aqueous solubility of steroids such as danazol. Further studies will focus on developing solid oral formulation using danazol–SBE complexes and evaluating the feasibility of improving the bioavailability of danazol.

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