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Evaluation of various properties of alternative salt forms of sulfobutylether-β-cyclodextrin, $(SBE)_{7M}$-β-CD

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Abstract

The goal of this study was to evaluate alternative salt forms of $(SBE)_{7M}$-β-CD (currently the sodium salt). The potential salt form would ideally decrease the rate of $(SBE)_{7M}$-β-CD release from osmotic pump formulations and result in an increase in the rate and extent of drug release in osmotic pump tablet and pellet dosage forms. Several $(SBE)_{7M}$-β-CD salt forms (potassium, calcium, and two ethylene diamine salt forms) were prepared by either titration or ultrafiltration and characterized by elemental analysis and capillary electrophoresis, CE. The physical properties (water uptake behavior, osmolality, complexation characteristics, etc.) were then compared to the sodium salt form. Although the water isotherm and the binding characteristics using various model drugs were similar among all the salt forms, the calcium salt form appeared to be the best alternative candidate due to its lower osmolality and slower intrinsic dissolution rate.

Keywords: Salt form; Sulfobutylether-β-cyclodextrin; Development

1. Introduction

Sulfobutylether-β-cyclodextrin, $(SBE)_{7M}$-β-CD, has been one of the most popular β-CD derivatives used as a pharmaceutical excipient due to an improved toxicity profile and ability to solubilize several poorly water-soluble drugs (Rajewski and Stella, 1996; Irie and Uekama, 1997; Stella and Rajewski, 1997; Thompson, 1997). SBE-β-CD is a negatively charged β-CD derivative prepared by the addition of sulfobutylether (SBE) groups to β-CD. The SBE groups variably substitute at the 2-, 3-, and 6-positions of the total 21 hydroxyl groups of β-CD (Fig. 1). $(SBE)_{7M}$-β-CD as the sodium salt form is commercially known as Captisol®. The subscript of 7M indicates an average total degree of substitution (TDS) of seven SBE groups per CD molecule.

The high solubility and osmotic properties of $(SBE)_{7M}$-β-CD has led to its use as a solubilizing and/or osmotic agent for developing controlled porosity osmotic pump tablets. Controlled release tablets of several poorly water-soluble drugs, such as testosterone (Okimoto et al., 1999b), chlorpromazine (Okimoto et al., 1999a), prednisolone (Okimoto et al., 1998; Rao et al., 2001), methylprednisolone (Zannou, 2000) and in general (Okimoto et al., 2004) have been reported. Occasional incomplete drug release was observed in certain osmotic pump tablet or pellet formulations containing the $(SBE)_{7M}$-β-CD sodium salt form (Captisol®) when physical mixtures of drug and $(SBE)_{7M}$-β-CD are used. That is, the relatively fast release of the $(SBE)_{7M}$-β-CD sodium salt form leads to incomplete complex formation between the drug and $(SBE)_{7M}$-β-CD inside the device over time with the fast release of the $(SBE)_{7M}$-β-CD sodium salt form attributed to its high solubility (and dissolution rate) and high osmolality.

Therefore, the work described here involves the preparation of several different salt forms of $(SBE)_{7M}$-β-CD. A salt form with slower dissolution rate and lower osmotic properties may help to achieve the goal of more complete release of poorly water-soluble drugs. Several physicochemical properties, such as solubility, osmolarity, and hygroscopicity, as well as some tableting properties were evaluated and compared to those of the sodium salt form.

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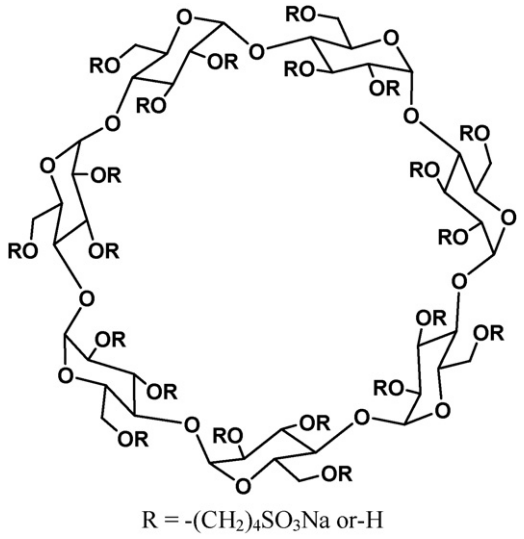

Fig. 1. Chemical structure of $(SBE)_{7M}$-β-CD sodium salt form (Captisol®).

2. Materials and methods

2.1. Materials

All chemicals were analytical grade or ACS reagents. A stirred ultrafiltration system (Amicon Model 2000) with a cellulose acetate membrane (500 molecular weight cut-off (MWCO), diameter 150 mm, filter code YC 05) was obtained from Amicon, Inc. (Beverly, MA). Cationic exchange resin (AG 50W-X2, mesh size 100–200) was purchased from Bio-Rad Laboratories, Inc. (Hercules, CA).

Sulfobutylether-β-cyclodextrin ($(SBE)_{7M}$-β-CD or Captisol®) in its sodium salt form was a generous gift from CyDex, Inc. (Lenexa, KS). This material was milled through a round-hole 0.94 mm screen on a Quadro®Comil® mill (Quadro, Inc., Millburn, NJ) at 3800 rpm (80% of maximum). Deuterium oxide (99.9–100.0%), sodium hydroxide, potassium hydroxide, ethylene diamine (EDA), calcium hydroxide, calcium chloride, benzoic acid, Trizma® base (tris(hydroxymethyl)aminomethane), potassium carbonate, prednisolone, testosterone, papaverine, and prazosin were purchased from Sigma–Aldrich Co. (St. Louis, MO). Lithium chloride was obtained from Spectrum Chemical Mfg. Corp. (Gardena, CA). Acetonitrile, hydrochloric acid, potassium acetate, and magnesium nitrate were purchased from Fischer Scientific (Pittsburgh, PA). 2,6-TNS (6-*p*-toluidinylnaphthalene-2-sulfonate) was purchased from Acros Organics (Pittsburgh, PA).

2.2. Titration method for the preparation of the $(SBE)_{7M}$-β-CD potassium and ethylene diamine (EDA) salt forms

One hundred and fifty grams of new cationic exchange resin in its acid form was loaded into a column (3.5 cm in diameter and 38 cm in height) and rinsed with double-distilled water (about 1 L) for equilibration, which resulted in a pH value of about 6.0. A 0.1 M solution of $(SBE)_{7M}$-β-CD sodium salt (150 mL) was passed through the cationic exchange resin at a flow rate of 15 mL/min to obtain the acid form of $(SBE)_{7M}$-β-CD. One exchange was required for the complete conversion to the acid form after the conditions had previously been optimized. The acid form was immediately titrated to the endpoints listed in the following pH values with 1 M potassium hydroxide or 0.1 M EDA (pK_{a_1} 6.85; pK_{a_2} 10.97) solutions to obtain potassium salt forms (pH 5) or two EDA salt forms (pH 5 and pH 9) of $(SBE)_{7M}$-β-CD, respectively. The potassium and EDA salts were isolated by freeze-drying.

2.3. Ultrafiltration method for the preparation of the $(SBE)_{7M}$-β-CD calcium salt form

Calcium chloride (30 g) was added to the $(SBE)_{7M}$-β-CD sodium salt form solution (30 g) in 250 mL of double-distilled water to optimize the cation exchange. Excess sodium, calcium, and chloride ions were removed by passing them through a cellulose acetate ultrafiltration membrane under a pressure of 30 psi while the calcium salt form of $(SBE)_{7M}$-β-CD was retained. The process was repeated 3–4 times by adding more calcium chloride. The retentate was finally rinsed with double-distilled water until chloride ions were no longer detected in the filtrate by a silver nitrate assay (0.05 M). The total process for optimal exchange took longer than 3 weeks. The calcium salt form of $(SBE)_{7M}$-β-CD solution was lyophilized and subsequently characterized.

2.4. Capillary electrophoresis (CE)

The average total degree of substitution (TDS) of each salt form was determined by CE. The alternative salt forms of $(SBE)_{7M}$-β-CD (10 mg/mL) were separated using a Beckman P/ACE 2210 capillary electrophoresis system consisting of a fused silica capillary (of a 50 μm internal diameter with total length and effective length of 37 and 30 cm, respectively) and detected at 230 nm (Tait et al., 1992; Luna et al., 1996). The running buffer contained 30 mM of benzoic acid in water adjusted to a pH between 6 and 7 with a 0.1 M Tris solution. All the solutions were filtered through a 0.45 μm PTFE membrane before running in the CE system. The capillary was conditioned with 0.1 M NaOH solution for 1 min, double-distilled water for 2 min, and finally by the running buffer solution for 2 min. Each alternative salt form of $(SBE)_{7M}$-β-CD was injected with 0.5 psi of pressure for 2 s and separated at 30 kV for 15 min.

2.5. Water sorption/desorption studies

Water sorption isotherms of each $(SBE)_{7M}$-β-CD salt form were determined using a VTI MB300 W (VTI Corporation, Hialeah, FL) with an integrated microbalance system to measure the uptake or loss of water. Weight measurements were taken over a 240-min equilibration period at each relative humidity level studied. The water sorption isotherms were then plotted as the percent change in sample weight as a function of relative humidity (RH).

Table 1
Drug properties and conditions for UV analysis

Drug	MW	pK_a	λ (nm)	Solvent	Concentration (μg/mL)
Prednisolone	360.4	–	246	Water	15
Testosterone	288.4	–	248	Water	15
Papaverine HCl	375.9	8.1	250	10 mM HCl (pH 3.0)	6
Prazosin HCl	419.9	6.5	245	10 mM HCl (pH 3.0)	7

2.6. Osmolality measurement

A freezing point osmometer (Micro-Osmette™ Model 5004, Precision Systems, Inc., Natick, MA), was used to measure the osmolality of 0.05 M aqueous solutions of each $(SBE)_{7M}$-β-CD salt form. The osmometer was calibrated with sodium chloride standard solutions, and the osmolality of each salt form solution (50 μL) was measured in triplicate.

2.7. UV method to determine drug-$(SBE)_{7M}$-β-CD binding constants

Appropriate aqueous solutions of each drug (Table 1) were prepared to give an absorbance value in the range of 0.6–0.8 units. Stock solutions of $(SBE)_{7M}$-β-CD (0.05 or 0.1 M) were used. All solutions were then filtered through a 0.45 μm PVDF filter prior to use. Drug properties and conditions for UV analysis are shown in Table 1. The drug solution (800 μL) was analyzed in a semi-micro quartz cuvet (1.5 mL; 1 cm path length) and measured against a reference cell that contained either water or buffer solutions, depending on the drug solvent. All measurements were performed at 25 °C using a controlled temperature water bath connected to the cell compartment of a Perkin-Elmer double beam UV/Vis Lambda 6 (Perkin-Elmer Life and Analytical Science, Inc., Boston, MA). The absorbance of the drug solution was taken as the initial value. A solution of $(SBE)_{7M}$-β-CD solution (1 μL) was added to both reference and sample cells using a Hamilton® syringe, mixed well, and allowed to reach the desired temperature for 8 min before measurements. The binding constants (K) were determined using the following equations (Scatchard, 1949; Connor, 1987):

$$\frac{\Delta A}{L_f} = -K\Delta A + S_L K \Delta\varepsilon_b \quad (1)$$

$$\Delta\varepsilon_b = \varepsilon_b - \varepsilon_s - \varepsilon_L \quad (2)$$

$$\Delta A = A_L - A_0 \quad (3)$$

where A_L and A_0 are the absorbance of the substrate in the presence and absence of ligand, respectively; L_f is the free ligand concentration; S_L is the ligand concentration; ε_L, ε_b, and ε_s are the molar extinction coefficients of the ligand, bound substrate, and substrate, respectively.

2.8. Flow studies

The angle of repose was determined using a ring stand and funnel setup. The plastic funnel had the following dimensions: upper diameter, 10 cm; lower diameter, 0.7 cm; total height, 12 cm. Fifty grams of $(SBE)_{7M}$-β-CD were poured into the funnel while holding a piece of cardboard at the end of the funnel and then the cardboard was released. The height of the powder heap (h) and the diameter of the powder heap base (D) were measured to calculate the angle of repose (θ) using the equation $\tan\theta = 2h/D$.

The bulk density of the milled material was determined by pouring the material into a 100 mL fluted graduated cylinder to 100 mL (V_1). The weight (w) was measured. Then the cylinder containing the same amount of sample was tapped for 1000 strokes using a VanKel® Tapped density tester (Model 50-120, Varian, Inc., Cary, NC) and the final volume (V_2) was read, and the tapped density was determined. The Carr index (C) was calculated using the equation $C = [1 - (V_2/V_1)] \times 100$.

2.9. Effect of residual moisture on tablet hardness at different relative humidities

Saturated salt solutions of lithium chloride, potassium acetate, potassium carbonate, and magnesium nitrate (Callahan et al., 1982) were prepared to maintain constant relative humidity conditions of 11, 23, 43, and 53%, respectively. The milled $(SBE)_{7M}$-β-CD was equilibrated with the saturated salt solutions in dessicators at room temperature (25 °C). The water content after equilibration was determined by a Karl Fischer titration technique (Brinkmann® 652KF-Coulometer). The material, which had been lubricated with 0.5% magnesium stearate, was compressed into tablets using a Stokes® tablet press with 1/4-in punches. Physical tests for thickness, weight variation, hardness, and friability were performed.

2.10. Intrinsic dissolution studies

The apparatus for intrinsic dissolution (Wood's apparatus, Varian, Inc., Palo Alto, CA) consisted of a punch and die. About 200 mg of $(SBE)_{7M}$-β-CD was compressed with a Carver tablet press at 1 tonne of compression force for 1 min to obtain a single face of defined area (0.5 cm^2) exposed on the bottom of the die. The top of the die was attached to a holder of the dissolution apparatus with a controlled rotation speed.

The release of $(SBE)_{7M}$-β-CD was followed using a Perkin-Elmer 650-40 fluorescence spectrophotometer (Oak Brook, IL). The addition of 2,6-TNS to a $(SBE)_{7M}$-β-CD solution gave rise to a fluorescent peak at 455 nm (excitation at 325 nm) and $(SBE)_{7M}$-β-CD was determined from a calibration plot (Zannou, 2000). The intrinsic dissolution rate, defined as the dissolution rate of pure substance with constant surface area, was determined from the slope of the cumulative amount of $(SBE)_{7M}$-β-CD released per unit of surface area over time.

Table 2
Elemental analysis of all the salt forms of $(SBE)_{7M}$-β-CD

Salt forms of $(SBE)_{7M}$-β-CD	Elemental analysis (theoretical values), $n = 6.5$							
	$\%Na^+$	$\%Ca^{2+}$	$\%K^+$	%C	%H	%N	%S	%C/%S
Na^+	5.93 (6.47)			36.00 (35.39)	5.89 (5.75)	0.00 (0)	8.52 (9.03)	4.22 (3.92)
K^+	0 (0)		10.09 (10.71)	34.09 (34.41)	5.76 (5.40)	<0.5 (0)	8.85 (8.78)	3.84 (3.92)
Ca^{2+}	0 (0)	5.19 (5.48)		34.56 (34.38)	6.22(5.99)	<0.5 (0)	8.38 (8.77)	4.12 (3.92)
EDA, pH 5.0 (1:2)				37.83 (38.13)	6.89 (6.98)	3.73 (3.88)	8.37 (8.88)	4.52 (4.29)
EDA, pH 9.0 (1:1)				37.50 (38.90)	7.63 (7.42)	6.64 (7.28)	7.55 (8.33)	4.97 (4.67)

2.11. Viscosity measurement

Viscosity measurements of dilute solutions of the $(SBE)_{7M}$-β-CD sodium and calcium salt forms from 0.01 to 0.1 M in double-distilled water were determined using an Ostwald viscometer (Cannon Instrument Company, State College, PA), whereas those of more concentrated solutions from 0.15 to 0.35 M were determined using a cup and bob Brookfield viscometer with a small adapter SC4-18/13R (Brookfield Engineering Laboratories, Inc., Middleboro, MA). All the measurements were conducted at 37 °C using a controlled temperature water bath. The viscometer had been calibrated with a standard prior to use.

2.12. Diffusion coefficient measurement

A pulsed field gradient ^1H NMR (Bruker 500 MHz AM spectrophotometer (Bruker, Inc., Germany)) was used to measure the diffusion coefficients of the $(SBE)_{7M}$-β-CD sodium and calcium salt forms. Solutions were prepared in D_2O at the following concentrations: 0.01, 0.05, 0.10, 0.15, and 0.25 M. The sample solutions were equilibrated at 37 °C, and the instrument was calibrated with 10 mM β-CD. Twelve spectra with determined peak heights were obtained at different gradient amplitudes using the bipolar longitudinal eddy delay sequence of Wu et al. (1995). The diffusion coefficients (D) were determined from the slope of semi log plots of peak height versus gradient power.

3. Results and discussion

3.1. Characterization of $(SBE)_{7M}$-β-CD salt forms

The total degree of substitution (TDS) of all salt forms were characterized by elemental analysis (Table 2) and by CE. The ratio of carbon to sulfur from the elemental analysis can be used to determine the TDS, which was found to be consistent with the results from CE experiments. The CE electropherograms of all salt forms are illustrated in Fig. 2 and the area under the curve of each peak is integrated to calculate the TDS value. Due to various degrees of substitution of SBE groups per CD molecule with negative charges on the CD molecules, each peak represents the degree of substitution of SBE groups with the lower degree of substitution eluted at an earlier time due to the smaller amount of negative charges on the overall CD molecule. All the salt forms had TDS values similar to the sodium salt form, which was the starting material, indicating no significant loss of $(SBE)_{7M}$-β-CD molecules with lower degrees of substitution during the processing.

3.2. Comparison of the physical properties of several salt forms of $(SBE)_{7M}$-β-CD

3.2.1. Water sorption/desorption studies

Water sorption was analyzed from 0 to 90% RH, then in reverse for water desorption. Only a slight hysteresis was observed upon water desorption, which was similar for all salt forms. Fig. 3 represents an example of the water sorption/desorption isotherms of the sodium salt. It should be noted that the EDA (pH 5, 1:2) salt form had the lowest water uptake compared to the sodium salt form, but the difference was not highly significant (Fig. 4). As a result, all the salt forms had similar water uptake behavior. Calcium salts are often less hygroscopic than sodium salt forms of crystalline materials. However, because all the current salts were amorphous glassy solids, the resulting similarity in water uptake should not have been surprising.

3.2.2. Osmolality measurement

Osmolality is a measure of osmotic pressure created by a solution, and such pressure can be used as a driving force to deliver drugs in controlled osmotic-pump formulations. Typically, the osmolality value of body fluids is in the range of 285–295 mOsm/kg (Martin and Bustamante, 1993). In general, pharmaceutical solutions such as parenteral and ocular solutions should be adjusted to approximately the same osmotic pressure as that of body fluids to avoid any membrane damage or irritation, but that is less of a concern for oral formulations.

The osmolality values of solutions of $(SBE)_{7M}$-β-CD salt forms are listed in Table 3. The calcium and EDA (pH 5, 1:2) salt forms had the lowest osmolality values compared to the

Table 3
Osmolality of different salt forms of 0.05 M $(SBE)_{7M}$-β-CD using an osmometer

Salt forms of $(SBE)_{7M}$-β-CD	Measured pH	Osmolality (mOsm/kg) (S.D.)
Sodium	5.36	292 (5)
Potassium	4.31	286 (3)
Calcium	4.61	132 (2)
EDA, pH 5 (1:2)	4.60	121 (2)
EDA, pH 9 (1:1)	8.84	293 (8)

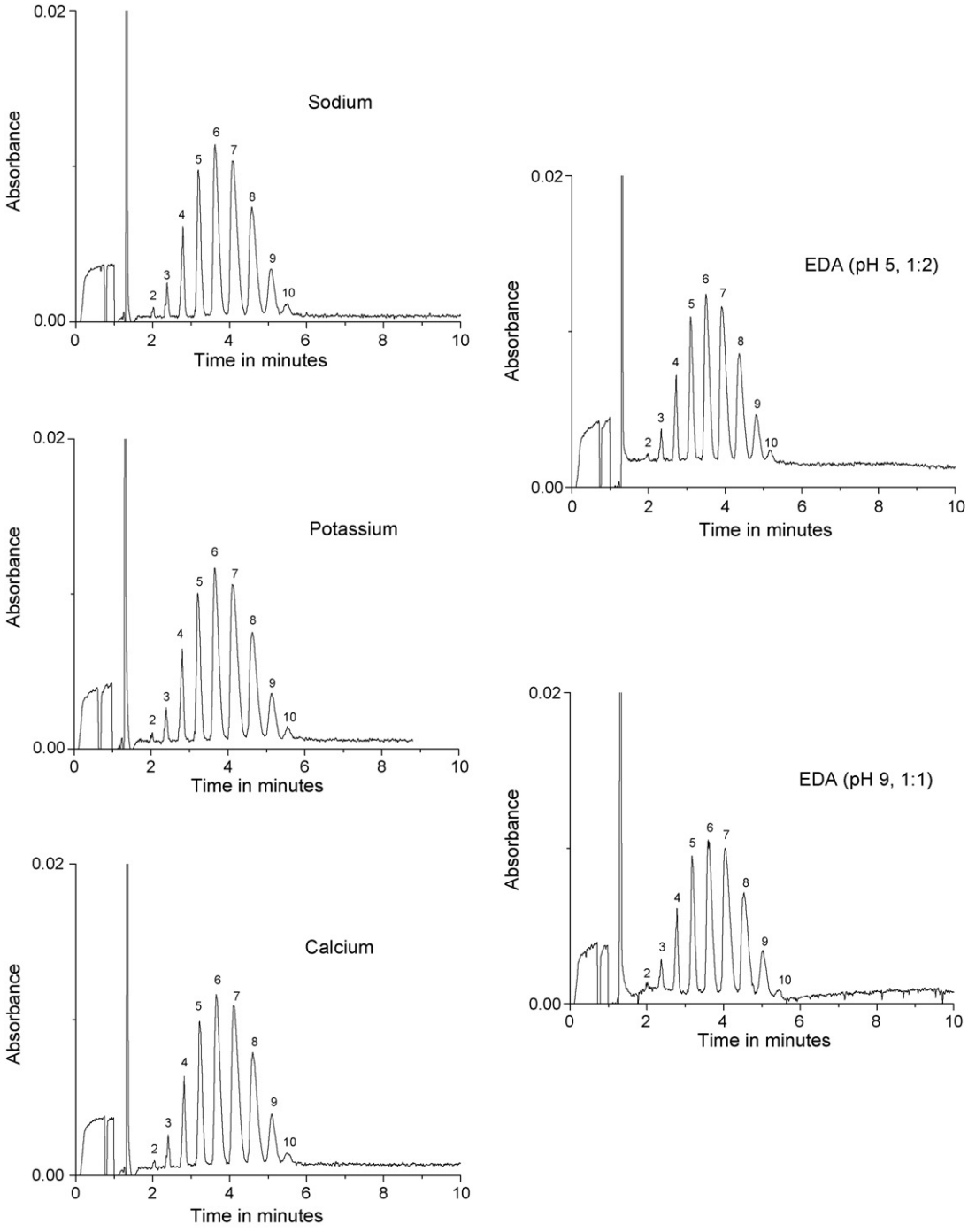

Fig. 2. Electropherograms of the sodium, potassium, calcium, and two EDA salt forms of $(SBE)_{7M}$-β-CD after ultrafiltration.

sodium salt form. An advantage of this lower osmolality is that a larger amount of cyclodextrin can be added to solubilize certain drugs without exceeding the desired osmotic properties values. In microporous osmotic pump tablet and pellet dosage forms, release rate from such a device is a function of the difference in the osmotic pressure inside the dosage form to that in the bulk solution. Thus, a lowering of the internal osmotic pressure in such a device should lead to slowing of the drug release rate relative to the use of the sodium salt.

3.2.3. Complexation characteristics

The binding constants of each salt form with neutral model drugs (prednisolone and testosterone) and ionizable model drugs (papaverine HCl and Prazosin HCl) were evaluated using the UV method (Table 4). No significant differences in the binding constants were observed for any of the $(SBE)_{7M}$-β-CD salt forms. The binding constants of the EDA (pH 9, 1:1) salt forms with ionizable drugs could not be determined due to the pH change during the experiment.

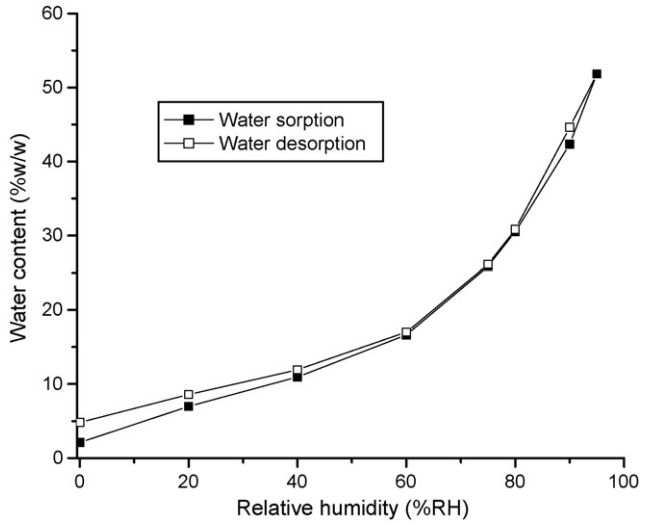

Fig. 3. Water sorption/desorption isotherm of $(SBE)_{7M}$-β-CD sodium salt form (■, water sorption; □, water desorption).

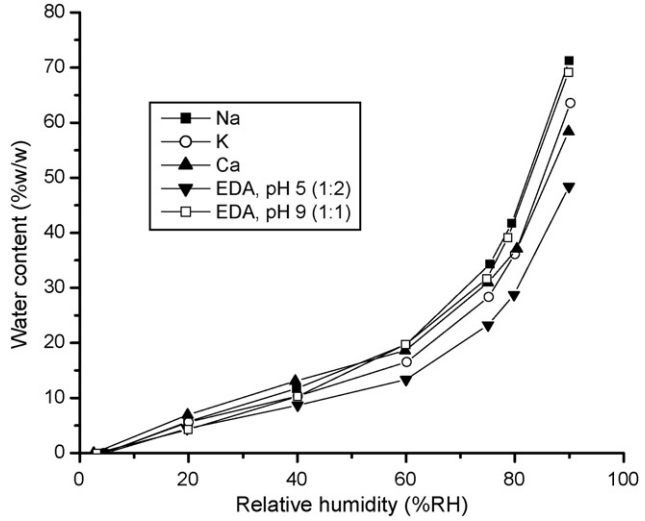

Fig. 4. Water uptake behavior of all salt forms of $(SBE)_{7M}$-β-CD (■, Na; ○, K; ▲, Ca; ▼, EDA, pH 5 (1:2); □, EDA, pH 9 (1:1)).

Based on the physical property evaluation of all the $(SBE)_{7M}$-β-CD salt forms, the calcium salt form having the lowest osmolality was chosen for further studies. Although the EDA salts showed some promise, they were not chosen due to the possible chemical reactivity of the EDA and the pH dependency of the physical form of the salt. A comparison of the sodium and calcium salt forms (e.g., flow properties, tableting properties, moisture effect on tablet hardness, intrinsic dissolution rate, etc.) were performed as described below.

3.3. Comparison of the bulk and tableting properties of the sodium versus the calcium salt forms of $(SBE)_{7M}$-β-CD

3.3.1. Flow studies

Two indicators, angle of repose and the Carr index, were used to indicate the flow properties of the $(SBE)_{7M}$-β-CD sodium and calcium salt forms. A coarse particle typically flows better than a fine particle. Angle of repose values less than 40° generally indicate adequate flow properties for materials, whereas Carr index values greater than 25% indicate poor flow characteristics (Gordon et al., 1990).

The angle of repose and Carr index for the sodium salt were 40.5° and 24.2%, respectively, both of which were borderline values with some tendency toward poor flow properties (Sotthivirat et al., 2000). In addition, the size distribution (data not shown here) would appear to potentially cause some flow problems. However, there was no significant variation in tablet weight achieved on the Stokes® model F Press, indicating fairly good flow during actual tablet compression (Sotthivirat et al., 2000).

The angle of repose and Carr index for the calcium salt were 39.6° and 35.0%, respectively. The angle of repose yielded borderline values, whereas the Carr index indicated poor flow characteristics. Like the sodium salt form, the particle size distribution was mostly fine (in the 0–500 μm size range) with a lesser amount of coarse materials (>500 μm). Even though the poor flow characteristics were indicated based on the Carr index, there were no flow problems observed during tablet compression. Thus, the measurement of the angle of repose and Carr index can be indicative of flow characteristics, but may not totally indicate actual flow problems in the tablet manufacturing process with the Stokes® tablet press.

3.3.2. Effect of residual moisture on tablet hardness at different relative humidities

After equilibrium was established, the water content of the sodium and calcium salt forms of $(SBE)_{7M}$-β-CD material stored in desiccators was determined using a Karl Fischer titration technique (Table 5). A significant increase in tablet hardness was observed for both salt forms of the $(SBE)_{7M}$-β-CD equilibrated at 23, 43, and 52% RHs, compared to that stored at 11% RH due to the greater association of water. The sodium salt

Table 4
Complexation ability of different salt forms of $(SBE)_{7M}$-β-CD toward neutral and cationic drugs at 25 °C using the UV method

Salt forms of $(SBE)_{7M}$-β-CD	Binding constants (M^{-1}) (S.D.)			
	Prednisolone	Testosterone	Papaverine HCl	Prazosin HCl
Sodium	1691 (98)	25,855 (87)	885 (30)	21,315 (818)
Potassium	1718 (85)	26,393 (291)	959 (22)	22,330 (1154)
Calcium	1884 (73)	24,884 (439)	924 (45)	22,634 (1110)
EDA, pH 5 (1:2)	1766 (151)	28,304 (224)	1064 (28)	21,187 (1810)
EDA, pH 9 (1:1)	1684 (155)	25,455 (215)	N/A	N/A

Table 5
Moisture contents of $(SBE)_{7M}$-β-CD stored under different relative humidity conditions

Storage condition (%RH)	Water content (%)	
	$(SBE)_{7M}$-β-CD (Na)	$(SBE)_{7M}$-β-CD (Ca)
11	2.8	7.2
23	8.8	10.1
43	10.7	13.5
52	14.2	15.7

form showed a dependency on compression force. Tablet hardness increased as the samples equilibrated at higher RHs (11, 23, and 43% RH), as shown in Fig. 5. In contrast, no increase in tablet hardness was observed for the samples equilibrated at 52% RH at the compression forces studied. Unlike the sodium salt form, the calcium salt form stored at 43 and 52% RHs indicated no dependency on compression force affecting tablet hardness, while for the samples stored at 11 and 23% RHs, compression forces up to 1 tonne had a significant influence on tablet hardness (Fig. 6).

3.4. Comparison of additional physical properties of the sodium and calcium salt forms of $(SBE)_{7M}$-β-CD

3.4.1. Intrinsic dissolution studies

Intrinsic dissolution rates of both the sodium and calcium salt forms were not dependent on the degree of agitation. This is probably due to the highly viscous layer present at the interface of the salt form tablets, thus the aqueous diffusion layer thickness was unaffected by higher agitation rates. The intrinsic dissolution rate of the calcium salt form (TDS of 7.1) was lower than that of the $(SBE)_{7M}$-β-CD sodium salt form (TDS of 6.4; Table 6). Likewise, with the similar TDS values of both salt forms, the intrinsic dissolution rate of the calcium salt was approximately half the rate of that of the sodium salt at 50 rpm. However, due to the limited amount of the calcium salt available, experiments were performed at only one agitation rate.

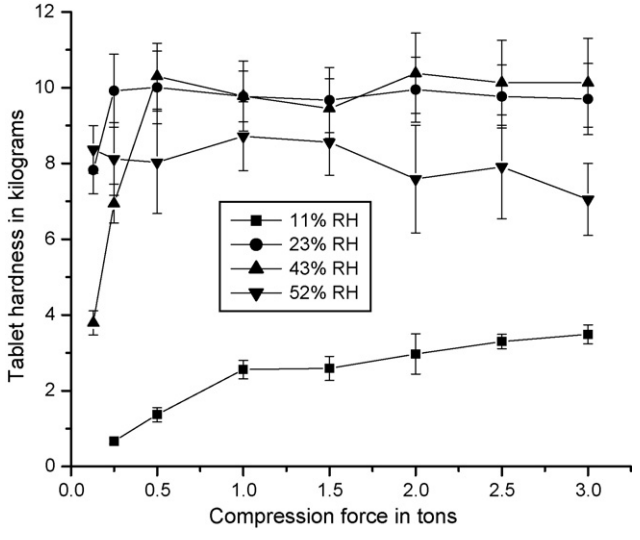

Fig. 5. Influence of residual water (■, 11% RH; ●, 23% RH; ▲, 43% RH; ▼, 52% RH) on tablet hardness of the sodium salt form of $(SBE)_{7M}$-β-CD at different compression forces.

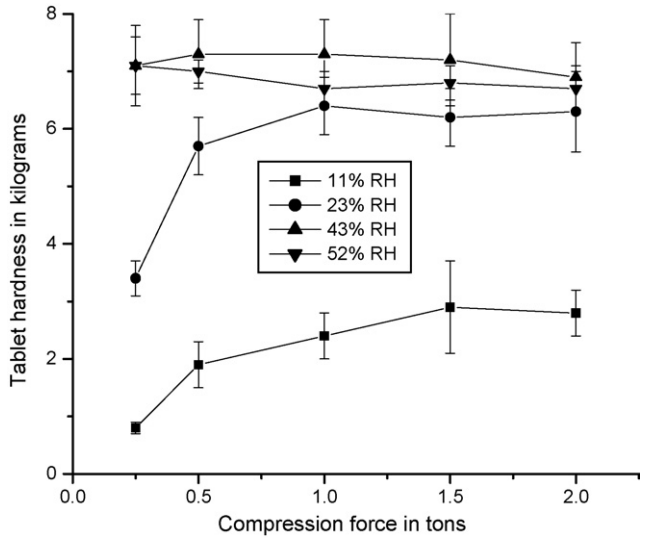

Fig. 6. Influence of residual water (■, 11% RH; ●, 23% RH; ▲, 43% RH; ▼, 52% RH) on tablet hardness of the calcium salt form of $(SBE)_{7M}$-β-CD at different compression forces.

Table 6
Intrinsic dissolution rates (IDR) of sodium and calcium salt forms of $(SBE)_{7M}$-β-CD at various agitational speeds at 37 °C

Salt forms of $(SBE)_{7M}$-β-CD	Intrinsic dissolution rate (mg/(min cm^2)) (S.D.)		
	50 rpm	100 rpm	150 rpm
Sodium (TDS 6.4)	34.0 (3.8)	32.3 (2.6)	37.9 (0.2)
Calcium (TDS 7.1)	26.1 (0.8)	26.0 (1.2)	27.8 (0.5)
Calcium (TDS 6.5)	17.4	N/A	N/A

3.4.2. Viscosity and diffusion coefficient measurements

The viscosity and diffusivity of both sodium and calcium salt forms were dependent on their concentrations, as summarized in Tables 7 and 8. As expected, the viscosity of the solution increased with the concentration of the salt forms, leading to the retardation of the diffusion process.

Table 7
Viscosity measurements of the sodium and calcium salt forms of $(SBE)_{7M}$-β-CD at various concentrations at 37 °C

Concentration (M)	Viscosity (cP) in H_2O (S.D.)	
	$(SBE)_{7M}$-β-CD (Na)	$(SBE)_{7M}$-β-CD (Ca)
0.01	0.8 (0.0)	0.7 (0.0)
0.05	1.0 (0.0)	1.2 (0.0)
0.10	1.6 (0.0)	1.9 (0.0)
0.15	3.5 (0.0)	4.1 (0.0)
0.20	7.1 (0.0)	8.6 (0.1)
0.25	16.8 (0.0)	21.0 (0.1)
0.30	47.1 (0.1)	61.0 (0.3)
0.35	172.3 (0.4)	188.6 (0.8)

Table 8
Diffusion coefficient measurements of the sodium and calcium salt forms of $(SBE)_{7M}$-β-CD at various concentrations at 37 °C (diffusion coefficient of 10 mM β-CD = 7.8×10^{-6} cm^2/s)

Concentration (M)	Diffusion coefficient ($\times 10^{-6}$ cm^2/s)	
	$(SBE)_{7M}$-β-CD (Na)	$(SBE)_{7M}$-β-CD (Ca)
0.01	4.6	4.7
0.05	3.1	2.8
0.10	1.9	1.9
0.15	1.4	1.1
0.25	0.31	0.33
0.30	0.087	0.094

The sodium and calcium salt forms had similar diffusion coefficient values in the range of concentrations studied. The calcium salt forms, however, were slightly more viscous than the sodium salt forms, especially at concentrations above 0.25 M. It is possible that a decreased diffusion coefficient was not observed for the calcium salt form because the hydration radius of the sodium salt ions may be larger than that of the calcium salt ions, which counterbalances the viscosity effect. Another possible explanation is that the diffusion coefficient may be a measure of the diffusion rate of the negatively charged $(SBE)_{7M}$-β-CD molecule which is much larger than the corresponding cation. Thus, the diffusion coefficient of $(SBE)_{7M}$-β-CD would be similar for any salt forms regardless of cations.

4. Conclusion

All the $(SBE)_{7M}$-β-CD salt forms were prepared by either titration or ultrafiltration methods and subsequently characterized by elemental analysis and CE. Water uptake behavior, osmolality, and complexation characteristics using different drugs were evaluated among all the salt forms and compared to the sodium salt form. The calcium salt form showed promise although, apart from the osmotic properties, it was not greatly different from the sodium salt.

The flow and tableting properties of both sodium and calcium salt forms of $(SBE)_{7M}$-β-CD were evaluated using angle of repose and the Carr index. Based on these observations, flow properties should not have been ideal. However, neither salt form had actual flow problems during tableting process with a Stokes® single punch press. The residual water content in the material appeared to play an important role in the production of hard tablets for both salt forms. The intrinsic dissolution rate of calcium salt was significantly different from that of the sodium salt at an agitation speed of 50 rpm. The calcium salt form showed slightly higher viscosity values than the sodium salt form at concentrations above 0.25 M while their diffusion coefficient values were similar.

Based on the preset criteria for the best candidate to be used as an osmotic and solubilizing agent in oral controlled release formulations (e.g., osmotically-controlled tablets and pellets) as well as other possible formulations, the calcium salt form of $(SBE)_{7M}$-β-CD has lower osmolality and a slower intrinsic dissolution rate, compared to the sodium salt form. Furthermore, the calcium salt form possesses adequate but not ideal flow properties during the actual tableting process. Use of the calcium salt also prevents high sodium exposure for those patients where this is undesirable.

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