Osmotic Properties of Sulfobutylether and Hydroxypropyl Cyclodextrins

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Purpose. The purpose of this study was to determine the osmolality of sulfobutylether (SBE) and hydroxypropyl (HP) derivatives of cyclodextrins (CDs) via vapor pressure osmometry (VPO) and freezing point depression (FPD). (SBE) and HP-CDs are efficient excipients capable of solubilizing and stabilizing poorly water-soluble drugs in parenteral formulations. (SBE)-CDs have also been used as solubility enhancers and osmotic agents for the sustained release of poorly water-soluble drugs from osmotic pump tablets. The knowledge of the CD's osmolality in solution or inside such tablets would allow one to further characterize the release mechanisms.

Methods. Experiments were conducted at 37°C with eight types of HP and (SBE)-CDs. The aqueous solutions ranged from 0.005–0.350 mol l^{-1}. Methods were developed to allow the measurement of high osmolalities using a vapor pressure osmometer or a differential scanning calorimeter.

Results. The osmolality calculations from the VPO and FPD measurements correlated well. The osmolality of (SBE)-CDs was significantly higher than the osmolality of HP-CDs and increased with the total degree of substitution (TDS). All CDs showed deviations from ideality at high concentrations.

Conclusions. Empirical correlations of osmolality with concentration and TDS allowed the prediction of osmolality over a wide concentration range. This study also gave some useful insights into the behavior of CD derivatives in solution.

KEY WORDS: cyclodextrins; osmotic pressure; vapor pressure osmometry; freezing point depression; glass transition temperature.

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ABBREVIATIONS: A, membrane surface area; B, second virial coefficient; C, third virial coefficient; CD(s), cyclodextrin(s); ΔR, vapor pressure osmometer voltage signal output; DSC, differential scanning calorimeter; ϕ, osmotic coefficient; FPD, freezing point depression; h, membrane thickness; HP-CD, hydroxypropyl cyclodextrin; K′, vapor pressure osmometer cell constant; $L_p\sigma$, fluid permeability; m, solution molality; M_1, M_2, molecular weight of the solvent and the solute, respectively; ν, number of particles which a compound can dissociate into in solution; ξ_m, osmolality; Π, osmotic pressure; ΔΠ, difference in osmotic pressure across the membrane; Π/c, reduced osmotic pressure; P, effective membrane permeability of the solute; ΔR, measuring effect of the vapor pressure osmometer; R, gas constant; S, solute saturation solubility; (SBE)-CD, sulfobutylether cyclodextrin; T, temperature; TDS, total degree of substitution; Tg′, glass transition temperature of the frozen solution; T_m, melting temperature of ice water; $\overline{V_1^0}/\overline{V_1}$, ratio of partial molar volumes for the solvent at infinite dilution and in the solution; VPO, vapor pressure osmometry.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides used as pharmaceutical excipients mainly to solubilize and stabilize drugs *via* complexation (1,2). The parent CDs, α-, β-, and γ-CDs, contain six, seven, and eight glucopyranose units, respectively. These CDs have been widely derivatized to optimize their solubility and safety. Two of the most pharmaceutically relevant derivatives are the 2-hydroxypropyl (HP-) and the sulfobutylether (SBE-) CDs (2). They differ by their substituent type and ionic state. HP-CDs are uncharged, whereas (SBE)-CDs are negatively charged polyelectrolytes and have sodium as the counter cation. These derivatives are defined by their total degree of substitution (TDS) or average number of substituents per CD molecule (3), which may affect the CD properties.

As with any dissolved molecule, CDs generate osmotic pressure in aqueous solution. They are used in parenteral formulations to solubilize and/or stabilize drugs, as well as to decrease irritation at the administration site (4). The CD containing parenteral formulations should preferably be isoosmotic with blood (286 ± 4 mOsm/kg [5]). The knowledge of the osmotic pressure of CD solutions as a function of their concentration is thus necessary. In oral formulations, CDs have mainly been used as solubilizing and stabilizing agents to improve drug bioavailability (4). $(SBE)_{7M}$-β-CD has also been specifically used as solubility enhancer and osmotic agent for the sustained release of poorly water-soluble drugs from osmotic pump tablets (6,7). The release rate out of these drug delivery devices is usually described by Eq. 1 (8,9):

$$\frac{dm}{dt} = \frac{AS}{h}(L_p\sigma \cdot \Delta\Pi + P) \tag{1}$$

where A and h are the membrane surface area and thickness, respectively, S is the solute solubility, $L_p\sigma$ is the fluid permeability. ΔΠ is the difference in osmotic pressure across the membrane, and P is the solute permeability across the membrane. The main driving force to the release is osmotic pumping, represented by ΔΠ (9). Under sink conditions, the release will be mainly dependent on the osmotic pressure generated by the CD inside the tablet. The osmotic pressure, therefore, will be a function of the CD concentration in the tablet and of the CD type (10). (SBE)-CDs of various TDS are indeed expected to exhibit significant differences in their osmotic properties. Thus, in these CD osmotic pump tablets, knowing the osmotic pressure generated inside would allow one to more fully characterize the release mechanisms (10).

Osmotic pressure is a measure of the difference in solvent activity between the pure and solution state. It is a colligative property and, therefore, depends on temperature and on the number of particles in solution (5,11). A more accurate description of solvent activity in the presence of solute is given by osmolality (ξ_m in Osm/kg), defined in Eq. 2 (12):

$$\xi_m = \nu \cdot m \cdot \phi \cdot \frac{\overline{V_1^0}}{\overline{V_1}} = \frac{\Pi}{\left(\frac{RT}{\overline{V_1^0}}\right) \cdot \left(\frac{M_1}{1{,}000}\right)} \tag{2}$$

where ν is the number of particles that a compound can dissociate into in solution, m is the molality of the solution, ϕ is the osmotic coefficient, $\overline{V_1^0}/\overline{V_1}$ is the ratio of partial molar

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volumes for the solvent at infinite dilution and in the solution, Π is the osmotic pressure (in atm), R is the gas constant ($=0.0821$ l atm K^{-1} mol^{-1}), T is the temperature (in K), and M_1 is the solvent molecular weight. In aqueous solution, the relationship between osmolality (ξ_m) and osmotic pressure (Π) is described by Eq. 3 (13):

$$\xi_m \approx \frac{\Pi}{RT} \tag{3}$$

The direct measurement of osmolality is often problematic. It is most often determined indirectly *via* the measurement of other colligative properties, mainly vapor pressure lowering (vapor pressure osmometry, VPO) and freezing point depression (FPD) (5). Many apparati and semi-empirical models are available to both measure and describe the osmolality and osmotic pressure as a function of the solute concentration in dilute conditions. Solution properties at higher concentrations are not very well understood; measurements and model predictions become a challenge, especially for polyelectrolytes (5,14). More specifically, the (SBE)-CD solutions, in the concentration range of interest, generate osmolality and viscosity too high for their osmolality to be measured using the standard osmometers. Additionally, their polyelectrolyte nature renders model predictions unreliable at high concentrations.

The objective of this study was thus 2 fold: to measure the osmolality of HP and (SBE)-CD solutions over the large concentration range relevant to tablet formulations (10), and to develop a model capable of describing the osmolality generated in CD solutions as a function of concentration. The study was conducted in water with eight CDs: HP-β-CD, HP-γ-CD, $(SBE)_{4M}$-β-CD, $(SBE)_{7M}$-β-CD, $(SBE)_{9M}$-β-CD, $(SBE)_{4M}$-γ-CD, $(SBE)_{9M}$-γ-CD, and $(SBE)_{12M}$-γ-CD. Both HP-CDs had a TDS of four. The TDS in the (SBE)-CD nomenclature was indicated by the number in subscript, followed by the letter M indicating that these materials were composed of mixtures of (SBE)-CDs of various degrees of substitution.

MATERIALS AND METHODS

Materials

Sodium chloride was obtained from Sigma Chemical Co. (St. Louis, MO). HP-β-CD and HP-γ-CD were donated by Wacker Biochem Corp. (Adrian, MI). $(SBE)_{7M}$-β-CD was donated by Cydex, Inc. (Overland Park, KS). $(SBE)_{4M}$-β-CD, $(SBE)_{9M}$-β-CD, $(SBE)_{4M}$-γ-CD, $(SBE)_{9M}$-γ-CD, and $(SBE)_{12M}$-γ-CD were synthesized in our laboratory. Table I contains technical information on these CDs.

Cyclodextrin Solutions Preparation

The aqueous solutions, ranging from 0.005–0.350 mol l^{-1} were prepared 1 day prior to measurement. The concentrations were corrected for the CD water content. The CD and double-glass distilled water amounts in each solution were carefully weighed and the exact molar and molal concentrations were calculated. The same solutions were used for VPO and FPD determinations.

Very dilute $(SBE)_{7M}$-β-CD and $(SBE)_{9M}$-γ-CD solutions were also needed to verify some of the working hypotheses. Aqueous solutions, ranging from 1.25×10^{-3}–5.00×10^{-3} mol l^{-1}, were prepared similarly as described above and measured *via* an automatic osmometer.

Osmolality Measurements by Vapor Pressure Osmometry

The osmolality of CD aqueous solutions was determined at 37°C as a function of CD concentration using the Osmomat™ 070 Vapor Pressure Osmometer (UIC, Inc., Joliet, IL). For optimum operating conditions, the instrument was placed in a thermostated chamber (25.0°C ± 0.5°C) and was protected against air flow disturbances. The difference in water vapor pressure between the reference and tested solutions was measured by two thermistors arranged in a Wheastone bridge. The change in resistance was output as a voltage, the measuring effect, ΔR (V). For each tested solution, measurements were repeated until three consecutive reproducible ΔR values were obtained. Below 1.5 Osm/kg, double-distilled wa-

Table I. Technical Data on Studied Cyclodextrin Derivatives

Cyclodextrin type	Molecular weight	Substitution		Water (%)	Tg′[f] (°C)
		Total degree	Range[a]		
HP-β-CD	1,424[b]	4.97[b]		6.28[c]	–11.6 ± 0.0
HP-γ-CD	1,553[b]	4.40[b]		5.75[c]	–10.7 ± 0.2
$(SBE)_{4M}$-β-CD	1,871[d]	4.66[d]	1–9	6.26[e]	–22.6 ± 0.1
$(SBE)_{7M}$-β-CD	2,163[d]	6.50[d]		4.00[e]	–25.9 ± 0.0
$(SBE)_{9M}$-β-CD	2,489[d]	8.56[d]	5–11	3.47[e]	–30.5 ± 0.1
$(SBE)_{4M}$-γ-CD	2,125[d]	5.23[d]	1–10	2.65[e]	–21.5 ± 0.2
$(SBE)_{9M}$-γ-CD	2,827[d]	9.67[d]	7–13	2.99[e]	–29.4 ± 0.0
$(SBE)_{12M}$-γ-CD	3,151[d]	11.72[d]	8–13	3.47[e]	–33.3 ± 0.01

[a] Determined by capillary electrophoresis.
[b] Determined by NMR.
[c] Determined by loss on drying.
[d] Determined by elemental analysis.
[e] Determined by Karl-Fisher.
[f] Determined by DSC at 5°C/min in 0.1 mol/kg solutions.

ter was used as the reference. For higher osmolalities, the vapor pressure difference between pure and CD-containing water was too high for the instrument to measure. NaCl standard solutions (of known osmolalites [15] and previously measured ΔR) were then used as the reference to reduce the difference in vapor pressure between the standard and test solutions. The measuring effect was then calculated as shown in Eq. 4:

$$\Delta R_t = \Delta R_r + \Delta R_o \quad (4)$$

where the subscripts *t, r,* and *o* stand for total, reference, and observed, respectively.

The solution osmolality was obtained using Eq. 5:

$$\xi_m = \frac{\Delta R}{K'} \quad (5)$$

where K' is the osmometer cell constant obtained from calibration using standard solutions of NaCl (15). For each measured concentration, a K' value was calculated using Eq. 6 obtained by combination of Eqs. 2 and 5:

$$K' = \frac{\Delta R}{\nu \cdot m \cdot \phi \cdot \frac{\overline{V_1^0}}{\overline{V_1}}} \quad (6)$$

where $\nu = 2$ for NaCl solutions (13), m and ξ_m are known (15), and $\phi \times (\overline{V_1^0}/\overline{V_1})$ is calculated using Eq. 2. The K' values obtained by measurement against the same standard solutions were averaged and used to calculate the CD solution osmolality (Eq. 5).

Osmolality Measurements by Differential Scanning Calorimetry

The FPD of water with increasing CD concentration was measured using the differential scanning calorimeter (DSC) Pyris 1 (The Perkin-Elmer Corporation, Norwalk, CT). The instrument temperature scale was calibrated at 5°C/min with cyclohexane and n-decane (T_m = 6.54 and −29.66°C, respectively). The 5–15-mg samples were frozen to −50°C and were melted by heating at 5°C/min. All measurements were conducted in triplicate. The freezing or melting point of ice (T_m) was determined during the warming phase as the extrapolated onset temperature of the melting endotherm (pre-eutectic endotherm for NaCl, which crystallized upon freezing; International Confederation for Thermal Analysis convention [16,17]). The glass transition temperature of the frozen CD solutions (Tg' – midpoint of the endothermal baseline shift) was also noted. The FPD of CD-containing water was calculated relative to the T_m of double-glass distilled water. The osmolality scale was calibrated using NaCl standard solutions of known osmotic pressures (15). This curve relating directly FPD and osmolality was used to calculate the osmolality of the CD solutions.

Osmolality Measurements in Dilute Solutions

The osmolality of dilute solutions of $(SBE)_{7M}$-β-CD and $(SBE)_{9M}$-γ-CD was determined by FPD using the Micro-Osmette™ (Precision System, Inc., Natick, MA). The osmometer was calibrated using NaCl standard solutions. The measurements were performed with 50 μl of solution and the osmolality was directly read off the osmometer output screen.

RESULTS AND DISCUSSION

Vapor Pressure Osmometry vs. Freezing Point Depression: Method Validation

The calibration parameters for the VPO measurements are indicated in Table II. The VPO method was validated up to 7.5 Osm/kg (correlation between published [15] and measured values: r^2 = 1.00, slope = 1.001 ± 0.002, intercept = 0.003 ± 0.008). The measurements were very reproducible, but, as expected, less accurate at low osmolalities where differences in vapor pressure between water and CD solutions were very small and the K' value was more variable.

Overall, FPD values of water in the presence of NaCl were of larger amplitude than the literature values (15). The discrepancy was attributed to the method used. Measurements by DSC have indeed been reported as highly dependent on experimental conditions such as the heating rate (16). At low NaCl concentrations, T_m values were less reproducible. Above 4.6% (w/w) NaCl, T_m was identical to the NaCl-water mixture eutectic point and could not be determined. The calibration could thus be performed only from 0.2–1.5 Osm/kg and all the FPD data were compared to the VPO data for which the calibration curve was defined up to 7.5 Osm/kg. *A posteriori,* different measurement conditions (change in heating rate) might have allowed the calibration with a larger range of NaCl concentrations.

From 0.2–6.0 Osm/kg, the VPO and FPD data were in good agreement (Fig. 1). All measurements were highly reproducible. The FPD measurements were, however, overall more scattered than the VPO determinations. Between 2.5 and 6.0 Osm/kg, FPD values underestimated the VPO values (within a 10% error). Beyond 6.0 Osm/kg, the FPD calculations were significantly lower than the VPO ones. This was attributed, for each CD derivative, to the proximity of the Tg' to the T_m, which interfered with accurate detections of the onset of the meling peak. Table I reports the Tg' values for all the CDs. As reported elsewhere, Tg' for $(SBE)_{7M}$-β-CD was not significantly affected by concentration (18). The HP- and (SBE)-β-CDs exhibited a lower Tg' than the γ-CD derivatives. A decrease in Tg' is usually associated with an increase in the molecule flexibility (19), thus the β-CD derivatives seemed more flexible than the γ-CD derivatives. This was quite surprising since the parent β-CD is more rigid than γ-CD due to intramolecular hydrogen bonding inside the cavity (20). These interactions are disrupted due to the substitution of some hydrogen atoms by HP or SBE groups. For the

Table II. Calibration of the Vapor Pressure Osmometer

Osmolality range	Reference solution	NaCl standard solutions (%)	Cell constant K′	Cell constant Std (%)
0.0–1.5	Water	0.3, 0.9, 1.2, 1.6, 4.3, 4.6	2.340	4.0
1.5–3.0	NaCl 4.3%	4.6, 5.0, 6.2, 7.4, 8.4	2.377	3.3
3.0–4.5	NaCl 8.4%	8.8, 10.0, 11.5, 12.0	2.466	1.1
4.5–6.0	NaCl 12.0%	13.0, 14.5, 15.0	2.483	0.5
6.0–7.5	NaCl 15.0%	16.0, 17.0	2.514	0.3

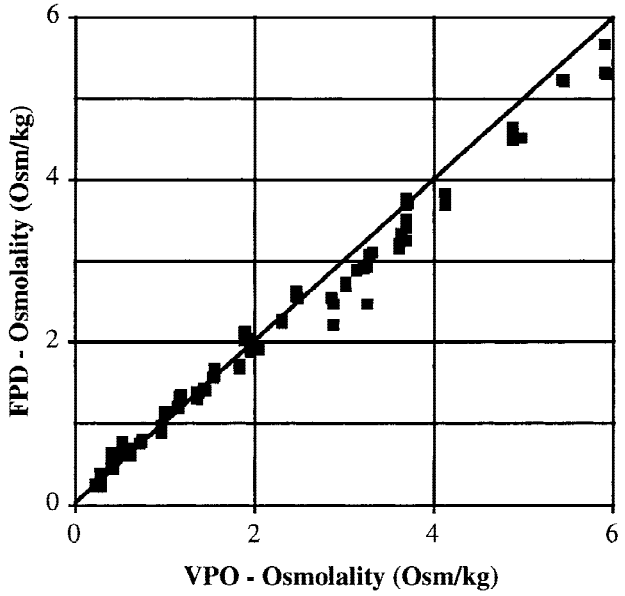

Fig. 1. (SBE)-CD osmolality. Correlation between freezing point depression (DSC) and vapor pressure lowering (VPO) values. (n = 3; r^2 = 0.989; slope = 0.896 ± 0.097; intercept = 0.110 ± 0.025).

(SBE)-CDs, Tg' also decreased with an increase in TDS. The hydrated SBE chains on the CD molecule are often pictured as an extension of the CD cavity (21). The Tg' values could be an indication of the mobility of these chains.

VPO was the method of choice based on the accuracy and reproducibility of the results. DSC is, however, a more readily available technique and does provide reasonably reliable values over a more narrow concentration range. The measurements were easier and faster to perform, and required a minimum sample amount. This method would not be recommended for the measurement of low osmolalities, and is limited in its range by the solute properties (eutectic or glass transition temperature of the frozen system).

Osmolality vs. Cyclodextrin Concentration in Solution

An objective of the present study was to develop a model (theoretical or empirical) capable of describing the osmolality of CD solutions with increasing concentration. For uniformity, the following analysis was based solely on the VPO data.

Two semi-empirical models have been mainly used to describe the osmolality of solutions with increasing molality. The first is the van't Hoff model, mathematically described by Eq. 2, with $\overline{V_1^0}/\overline{V_1}$ assumed to be constant and equal to 1. This model has been shown useful for concentrated solutions of nonelectrolytes and dilute solutions of electrolytes (5). At higher concentrations, the van't Hoff model becomes invalid due to solute-solvent and solute-solute interactions (22). The second model is the virial equation (Eq. 7) (11,23):

$$\frac{\Pi}{c} = \nu \cdot RT \cdot \frac{\overline{V_1^0}}{\overline{V_1}} \left(\frac{1}{M_2} + Bc + Cc^2 + \ldots \right) \tag{7}$$

with Π/c (l atm/g) the reduced osmotic pressure, M_2 (g/mol) the solute molecular weight, $\overline{V_1^0}/\overline{V_1}$ the ratio of partial molar volumes of the solvent in the pure state and in the solution, and B (mol l g^{-2}) and C (mol l^{-2} g^{-3}) the second and third virial coefficients, respectively. In dilute solutions ($\overline{V_1^0}/\overline{V_1} \approx 1$), Eq. 7 simplifies to Eq. 2 and is often used to determine solute molecular weight. At higher concentrations, the virial coefficients, B in particular, are used as indicators of the solute excluded volume and the type and degree of interaction of all the species present in solution (11,24,25).

The osmolality of HP-β-CD solutions is shown in Fig. 2. The same osmolality values were observed with HP-γ-CD solutions at similar concentrations. As reported by Huber *et al.* (5,26), nonionic sugar solutes osmolality depended on the concentration (or number of particles in solution) only. As with dextrose, mannitol, and sorbitol (26), the osmolality was ideal up to 0.6 mol/kg (which corresponded to HP-β-CD and HP-γ-CD solutions of about 0.4 and 0.3 M, respectively). The positive deviations from ideality have been associated with solute-solvent and solute-solute interactions (22). The data for the HP-CDs were fit to the virial equation (Eq. 8) using Sigma Plot® (version 4.14, SPSS Science, Chicago, IL). There were no prior assumptions made on the number of particles that HP-CDs can dissociate into the solution and the molecular weight:

$$\frac{\Pi}{c} = A' + B'c + C'c^2 \tag{8}$$

with

$$A' = \frac{\nu \cdot RT}{M_2} \frac{\overline{V_1^0}}{\overline{V_1}},\ B' = \nu \cdot RT \frac{\overline{V_1^0}}{\overline{V_1}} B, \text{ and } C' = \nu \cdot RT \frac{\overline{V_1^0}}{\overline{V_1}} C.$$

The results were in close agreement with the independently determined molecular weights (Table I): at low concentration, the equation collapsed to the expected value of RT/M_2 (Fig. 3). The viral equation described adequately the osmotic pressure over the entire HP-CD concentration range. The assumption of constant $\overline{V_1^0}/\overline{V_1}$ was thus valid in HP-CD so-

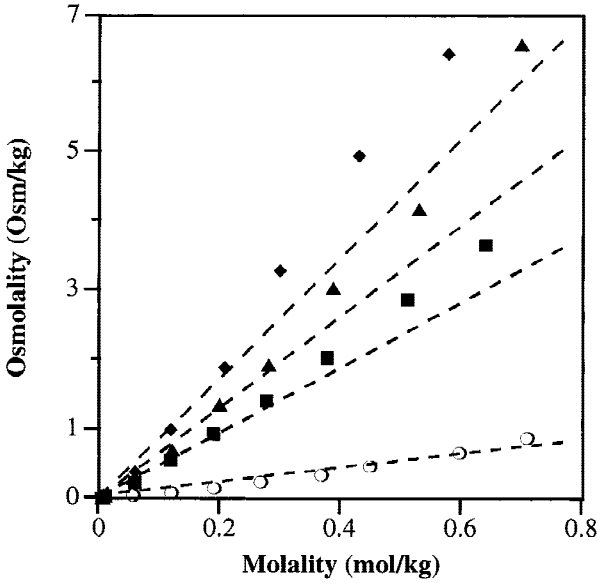

Fig. 2. Osmolality as a function of cyclodextrin molality. The symbols represent the data (n = 3): ○, HP-β-CD, ■, $(SBE)_{4M}$-β-CD; ▲, $(SBE)_{7M}$-β-CD; and ◆, $(SBE)_{9M}$-β-CD. The dashed lines (----) represent the expected osmolality in the presence of ideal solutes (calculated based on the van't Hoff equation [Eq. 2] with $\phi = \overline{V_1^0}/\overline{V_1} = 1$).

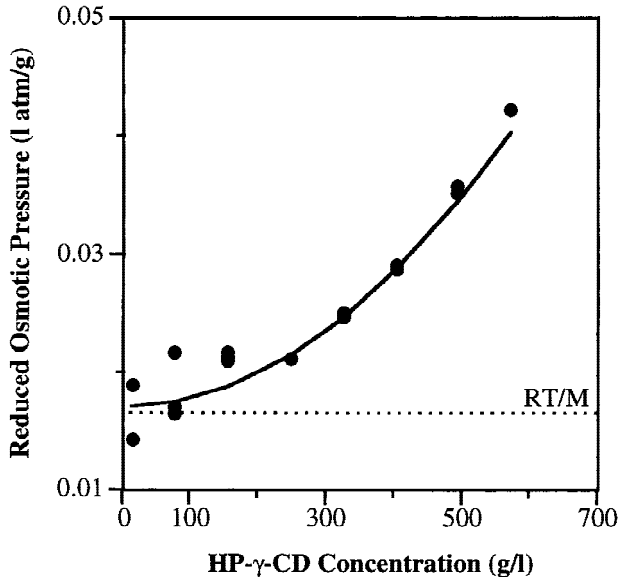

Fig. 3. Reduced osmotic pressure of HP-γ-CD solutions of increasing concentration with ● data (n = 3) and —— fit (virial equation parameters obtained from fitting the data: $A' = (0.017 \pm 0.009)$ 1 atm g^{-1}, $B' = 0$ l atm^2 g^{-2}, $C' = (7.051 \pm 1.148)$ E^{-8} 1 atm^{-3} g^{-3}. The (*RT/M*) dotted line has been constructed based on the independently determined molecular weight (see Table I).

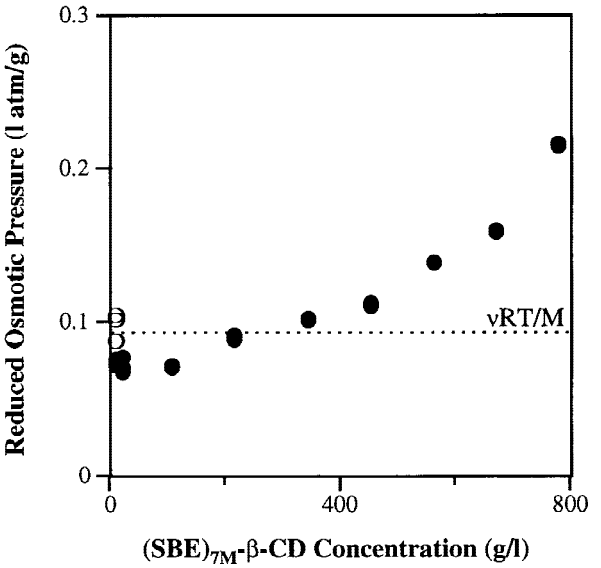

Fig. 4. Reduced osmotic pressure (Π/*c*) of $(SBE)_{7M}$-β-CD solutions of increasing concentration (n = 3): ○, very low concentrations (automated FPD osmometer), and ●, higher concentrations (VPO). The (*νRT/M*) dotted line has been constructed based on the independently determined TDS and molecular weight (see Table I).

lutions at least up to 0.350 mol l^{-1}. Both HP-CDs appeared to have identical behavior in solution. The second virial coefficient, *B,* was equal to zero for the HP-γ-CD and was slightly negative for the HP-β-CD (-5.97×10^{-7} mol l g^{-2}); *C* was equal to 2.77×10^{-9} and 2.92×10^{-9} mol l^2 g^{-3}, respectively. This suggested small deviations from ideality at higher concentrations, most probably due to repulsive interactions between CD molecules (11).

For the (SBE)-β-CD solutions, the osmolality increased with the TDS [indicator of the number of particles that (SBE)-β-CD can dissociate into in solution: ν = TDS + 1; Fig. 2]. Similar behavior was observed in (SBE)-γ-CD solutions. The osmolality appeared somewhat ideal only up to 0.2 mol/kg, beyond which significant positive deviations were observed. This was consistent with the published deviations from ideality for solutions of osmolalities exceeding 0.5–0.8 Osm/kg (26). The reduced osmotic pressure (Π/*c*) exhibited an unusual behavior and could not be fit satisfactorily to Eq. 8 (Fig. 4). At very dilute concentrations (measured by the automated FPD osmometer), the equation collapsed to the expected value of $\nu RT/M_2$ and thus confirmed the independently determined molecular weight and TDS (Table I). At low concentrations, Π/*c* exhibited a minimum that could be attributed to the predominance of attractive forces (11): solvation, hydrogen bonding, and/or electrostatic interactions between the negatively charged (SBE)-CDs and their Na^+ counter-ions. At low concentration of (SBE)-CD, the osmotic pressure generated was less than the osmotic pressure at the same concentration of ideal molecules. With increase in CD concentration, these attractive forces were compensated and dominated by repulsive forces, most probably electrostatic in nature. The osmolality of (SBE)-CD solutions could not be fit to any of the two models discussed above due to the fact that $\overline{V_1}^0/\overline{V_1}$ is not constant over the studied concentration range.

As an alternative to the virial equation, an empirical model was then developed based on the solution ionic concentrations ($\nu \times m$ in mol/kg):

$$\xi_m = \beta \cdot (\nu \cdot m)^a \quad (9)$$

The osmolality behavior for each of the six (SBE)-CD solutions, ranging from 0.005–0.350 mol l^{-1}, could be described by the unified equation (Fig. 5):

$$\xi_m = 0.916 \cdot ([\text{TDS} + 1] \cdot m)^{1.075} \quad (10)$$

Moreover, similar equations could be developed for NaCl (Eq. 11) and HP-CDs (Eq. 12):

$$\xi_m = 0.935 \cdot (2 \cdot m)^{1.012} \quad (11)$$

$$\xi_m = 1.154 \cdot (m)^{1.043} \quad (12)$$

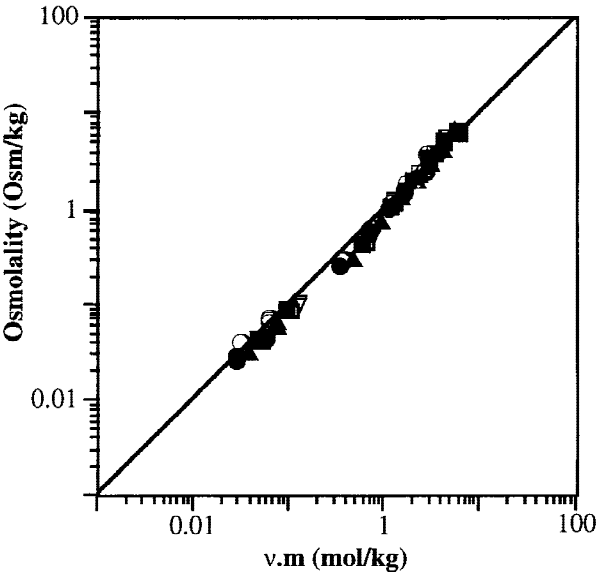

Fig. 5. Osmolality versus ionic concentration (ln-ln plot): ●, $(SBE)_{4M}$-β-CD; ○, $(SBE)_{4M}$-γ-CD; ▲, $(SBE)_{7M}$-β-CD; ■, $(SBE)_{9M}$-β-CD; □, $(SBE)_{9M}$-γ-CD; and ▽, $(SBE)_{12M}$-γ-CD.

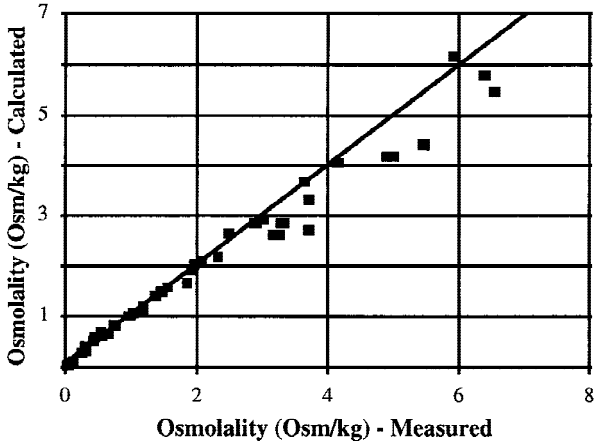

Fig. 6. Prediction accuracy of the empirical model. Correlation between measured (VPO) and calculated (Eq. 9) osmolalities of (SBE)-CD aqueous solutions. (n = 3; r^2 = 0.981; slope = 0.909 ± 0.008).

Eqs. 10–12 described the osmolality with an accuracy of 9%, 6%, and 3%, respectively (the coefficient of variation of the preexponential factor and the power were less than 2.5% in each case; Fig. 6). This unified empirical model could be rationalized based on the van't Hoff theory. As expected, it showed that osmolality was directly dependent on the number of particles in solution. This dependence was affected by both the α and β factors. The pre-exponential factor, β, seemed to be dependent on the type of molecule in solution: a value of 1 would be expected for an ideal solute, higher than 1 for nonelectrolytes, and lower than 1 for electrolytes. This was consistent with the osmotic coefficient behavior, which has been similarly classified (23); β could then be considered as an effective osmotic coefficient. The power, α, represents some correction factor that could account for the variation in $\overline{V}_1^0/\overline{V}_1$, and ϕ with concentration. This factor seemed molecule-dependent, but was similar for the same type of CD derivative. This term may be related to the effect of the solute addition on water structure and could be considered as an indicator of the amplitude of deviation from ideality. This unified empirical model (Eq. 9) was of significance in our case study of the osmotic properties of CDs for use in osmotic pump tablets (6,7,10): it reasonably predicted the osmolality of the HP- and (SBE)-CD solutions solely based on solution concentration and TDS.

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