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Applicability of $(SBE)_{7m}$-β-CD in controlled-porosity osmotic pump tablets (OPTs)

Kazuto Okimoto[a], Yuji Tokunaga[a], Rinta Ibuki[a], Tetsumi Irie[b], Kaneto Uekama[b], Roger A. Rajewski[c,*], Valentino J. Stella[c]

[a] *Technological Development Laboratories, Fujisawa Pharmaceutical Co. Ltd., 1–6, Kashima 2-chome, Yodogawa-ku, Osaka 532-8514, Japan*
[b] *Department of Pharmaceutics, Faculty of Pharmaceutical Science, Kumamoto University, 5–1 Oe-honmachi, Kumamoto 862-0973, Japan*
[c] *Department of Pharmaceutical Chemistry and the Center for Drug Delivery Research, The University of Kansas, Lawrence, KS 66047, USA*

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Abstract

The purpose of this study was to investigate the general application of a controlled-porosity osmotic pump tablet (OPT) utilizing $(SBE)_{7m}$-β-CD as both a solubilizer and an osmotic agent for drugs with varying physical properties. OPTs utilizing $(SBE)_{7m}$-β-CD were prepared for five poorly soluble and two highly water-soluble drugs. The Japanese Pharmacopoeia dissolution method was used to study the drug and $(SBE)_{7m}$-β-CD release from the OPTs. The drug concentration in the OPT core after the OPT was placed in the release medium for two hours was assayed gravimetrically and by HPLC. An appropriate composition ratio (ACR) of $(SBE)_{7m}$-β-CD to drug at which drug release from the OPT was complete and pH-independent within the physiological pH range of the GI tract was determined for each drug. The ACR values correlate to the drug concentration in the OPT core when the OPTs were placed in the release medium for two hours. The release profiles of prednisolone (a poorly water-soluble drug) and sodium chloride (a water-soluble compound) from the OPTs were almost the same as that of $(SBE)_{7m}$-β-CD. Also, the release rate of each drug per unit membrane surface area from the OPTs was similar, regardless of the differences in drug solubility. The present results confirmed that $(SBE)_{7m}$-β-CD serves as both a solubility modulator and as an osmotic pumping agent for OPTs, from which the release rate of both water-soluble and poorly water-soluble drugs can be controlled.

Keywords: Osmotic pump; Controlled-porosity osmotic pump tablet; $(SBE)_{7m}$-β-CD; Cyclodextrins; Chlorpromazine; Prednisolone; Estradiol; Indomethacin; Naproxen; Diltiazem hydrochloride; Sulbutamol sulfate; pH-independent release

* Corresponding author. Tel.: +1 785 864 5158; fax: +1 785 749 7393.
E-mail address: rajewski@ku.edu (R.A. Rajewski).

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1. Introduction

The controlled-porosity osmotic pump tablet (OPT) concept was developed as an oral drug delivery system by Zentner et al. (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and McClelland et al. (1991). This OPT is a spray-coated tablet with a semipermeable membrane containing leachable pore former materials. In this system, the drug, after dissolution inside the core, is released from the OPT by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created by an osmotic agent, the drug itself or a tablet component, after water is imbibed across the semipermeable membrane. This system is generally applicable for only water-soluble drugs. Poorly water-soluble drugs cannot dissolve adequately in the volume of water drawn into the OPT, making release from OPTs incomplete.

Recently, this problem was overcome by adding sulfobutyl ether-β-cyclodextrin ($(SBE)_{7m}$-β-CD), a β-cyclodextrin derivative which is variably substituted by an average of seven sulfobutyl ether groups on the 2-, 3- and 6- positions of the glucose unit of β-cyclodextrin (Stella and Rajewski, 1992). $(SBE)_{7m}$-β-CD has a high solubilizing (Okimoto et al., 1996, 1998, 1999a; Zia et al., 1997) and osmotic pressure effect because it includes seven sulfonic acid sodium salt moieties per molecule (Okimoto et al., 1999; Zannou et al., 2001). The advantages of controlled-porosity osmotic pump tablets (OPT) utilizing $(SBE)_{7m}$-β-CD were reported earlier (Okimoto et al., 1998, 1999a, 1999b; Stella et al., 2002; Zannou, 2000; Rao, 2000). The advantages include, controlled and complete release for poorly water-soluble drugs such as testosterone and prednisolone (PDL), and pH-independent release for cationic drugs, such chlorpromazine (CLP) free base (Okimoto et al., 1998, 1999a, 1999b) and dipyridamole (Rao, 2000). For complete and pH-independent release of CLP or PDL from the OPT, however, it was necessary to use an excess molar ratio of $(SBE)_{7m}$-β-CD to the drug. Although both PDL and CLP form 1:1 inclusion complexes with $(SBE)_{7m}$-β-CD, the appropriate composition ratios (ACR) were 2:1 and 10:1, cyclodextrin to drug, respectively.

In the present study, the role of the $(SBE)_{7m}$-β-CD to drug ratio in the OPT core with seven model drugs, including both highly and poorly water-soluble drugs, was studied with the goal of evaluating if $(SBE)_{7m}$-β-CD could be used for drugs with a variety of physical properties.

2. Materials and methods

2.1. Materials

The synthesis and characterization of $(SBE)_{7m}$-β-CD have been described previously (Stella and Rajewski, 1992). HP-β-CD (Encapsin™; mw 1338; total degree of substitution, 4.2) was supplied by American Maize Products Co. (Hammond, IN, USA). Chlorpromazine hydrochloride (CLP), prednisolone (PRD), estradiol (EST), indomethacin (IND), naproxen (NPX), diltiazem hydrochloride (DIL), sulbutamol sulfate (SAL), lactose, fructose and sodium chloride were purchased from Wako Pure Chemical Company (Osaka, Japan). CPL free base was obtained by converting salts to the free base using aqueous sodium bicarbonate. Cellulose acetate (CA-398-10) was purchased from Eastman Chemical Company (Kingsport, TN, USA). Micronized lactose was purchased from DMV (The Netherlands). Triethyl citrate (TEC) was purchased from Pfizer (New York, NY, USA).

2.2. Preparation of tablet cores

The cores of the osmotic pump tablets (equivalent to 10 mg drug) were prepared by using an eccentric tableting machine (Okada Seikou Company) using 5–10 mm round punches with granules prepared by kneading the drugs and the respective osmotic pump agents, $(SBE)_{7m}$-β-CD, HP-β-CD or a sugar mixture (lactose:fructose, 1:1 as the weight ratio) with 50% w/v ethanol followed by drying. The specific procedures have been described previously (Okimoto et al., 1998, 1999b). The drug to β-CD derivatives ratios were from 1:1 to 1:15 as a molar ratio and the sugar to drug ratios were quantitatively the same as the drug to β-CD derivatives ratios. The composition of the tablet cores for each drug may be found in Table 1. The percentage of free drug versus that in complex form for those studies involving the β-CD derivatives was not determined in the present study. Ongoing studies are addressing this issue.

Table 1
Composition[a] of tablet cores prepared at appropriate composition ratio (ACR)[b]

Drug	Amount of osmotic pump agent in OPT[c] (mg)	
	$(SBE)_{7m}$-β-CD	HP-β-CD
Prednisolone	111.8	82.7
Estradiol	369.7	273.6
Chlorpromazine	631.7	461.1
Naproxen	1311.8	970.7
Indomethacin	844.3	624.8
Diltiazem hydrochloride	44.8	33.2
Salbutamol sulfate	34.9	25.8

[a] The amount of drug in the tablet core is fixed at 10 mg.
[b] ACR is for $(SBE)_{7m}$-β-CD/drug tablet core.
[c] For OPTs prepared using a sugar mixture, the amount of sugar mixture used in the core tablets is the same as that of the $(SBE)_{7m}$-β-CD in the tablet cores.

2.3. Preparation of OPTs

Each OPT tested was prepared by spray coating the tablet cores using a Flow Coater Mini® (Floint Company). Coating conditions were as follows: inlet air temperature, 50 °C; out let air temperature, 45 °C; fluidizing airflow rate, 65 m^3/h; spray rate, 8 g/min; spray pressure, 1 kg/cm^2. The composition of the film liquid was cellulose acetate (CA-398-10)/micronized lactose/triethyl citrate (TEC) equal to 1/1/0.5 as a weight ratio with the total concentration of ingredients in the liquid of 10.6 w/w (%) using dichloromethane and ethanol in a 75/25 weight ratio.

2.4. Release studies

The release of drugs from the core or OPT (equivalent to 10 mg drug) was determined using the paddle method of the Japanese Pharmacopoeia (JP) XIII dissolution test (50 rpm, 37 °C). The dissolution medium (900 mL) was the JP first fluid (pH 1.2), the JP second fluid (pH 6.8) or distilled water. The released drugs were monitored over a 12 h period by an automatic dissolution tester (Hewlett 8451A Diode Array Spectrophotometer), by which the test medium was sampled through a 10–20 μm metal filter and measured at 250–300 nm depending on the spectral properties of the drug. Sodium chloride release was monitored by sodium quantitation by inductively coupled plasma atomic emission spectrophotometry (Hitachi ICPAES Spectrophotometer, Japan) and was corrected for sodium present in the release medium and from $(SBE)_{7m}$-β-CD. The release of $(SBE)_{7m}$-β-CD was analyzed according the post column complexation method for HP-β-CD described by Szathmary (1989). In this assay the retention time of the $(SBE)_{7m}$-β-CD peak was about 2.7 min.

2.5. Phase solubility studies

The intrinsic solubilities and the stability binding constants of PDL, CLP, IND and NPX with the β-CD derivatives were reported previously by Okimoto et al. (1996, 1998, 1999a, 1999b). McClelland et al. (1991) and Bonferoni et al. (1992) previously reported the intrinsic solubilities of DIL and SAL, respectively. Because of their high solubilities, the complexation constants of DIL and SAL with the β-CD derivatives were not determined. The stability constants for EST with the β-CD derivatives were determined using the same phase solubility method (Higuchi and Connors, 1965). An excess of each drug was added into 0–0.05 M $(SBE)_{7m}$-β-CD or HP-β-CD solutions and agitated at 25 °C for 72 h. The equilibration time was confirmed by preliminary studies. After centrifuging the suspensions at 10,000 rpm, the isolated supernatants were fractionated on a Hypersil ODS column with detection at 254 nm using a mobile phase of 60% acetonitrile–water. The stability constants of the drug with $(SBE)_{7m}$-β-CD were calculated by the method of Higuchi and Connors (1965).

2.6. Analysis of OPT core contents following release media exposure

After exposing each OPT to the release medium for two hours, the solution phase inside the OPT was removed as completely as possible by pipette after slicing the coating with a knife. Preliminary studies confirmed that the core contents were dissolved at two hours and the sampled solution was assumed to be homogeneous. The total mass of dissolved solids was gravimetrically determined from the weight of the retrieved sample before and after vacuum drying for 12 h. The solubility of the drug in the solution was determined by HPLC assay. The amount of $(SBE)_{7m}$-β-CD in the solution phase was calculated from the total dissolved solids minus the analytically determined drug content. The

HPLC assays for the drugs except for SAL and DIL were the same as those for the phase solubility studies. DIL and SAL were analyzed using the methods of McClelland et al. (1991) and Bonferoni et al. (1992), respectively.

3. Results and discussion

3.1. Appropriate composition ratio of drug to $(SBE)_{7m}$-β-CD in OPT

In this study, the neutral drugs prednisolone (PDL) and estradiol (EST), the basic drug chlorpromazine (CLP) and the acidic drugs naproxen (NPX) and indomethacin (IND) were used as models of poorly water-soluble drugs. Diltiazem hydrochloride (DIL) and salbutamol sulfate (SAL) were used as models of water-soluble drugs as was sodium chloride. Table 2 shows the appropriate composition ratio (ACR) of $(SBE)_{7m}$-β-CD to drug which insures the complete and pH-independent release of the respective drug from the OPT. For example, data for determination of ACRs for PDL and CLP are shown in Figs. 1 and 2, respectively. That is, ACRs were estimated from plots of the relationship between the final percent of the drug release determined at the time independent portion of the release profile (12 h) as a function of varying the molar ratio of $(SBE)_{7m}$-β-CD to the drug. For DIL and SAL, release in the absence of $(SBE)_{7m}$-β-CD was not determined. A ratio of 1:1 drug to $(SBE)_{7m}$-β-CD gave complete release for both drugs. Therefore, reported in Table 2 is the presumed ACR of 1:1. For all the drugs studied, release was time independent after approximately 6–7 h with variation between 8 and 12 h of less than 2%.

Table 2
Appropriate composition ratio (ACR) of core tablet in the OPTs for complete release over 12 h (dose, 10 mg)

Drug	pH of medium	Appropriate composition ratio (ACR) $(SBE)_{7m}$-β-CD (M):Drug (M)
Prednisolone	1.2–6.8	2:1
Estradiol	1.2–6.8	5:1
Chlorpromazine	1.2–6.8	10:1
Naproxen	1.2–6.8	15:1
Indomethacin	1.2–6.4	ND[a]
	6.5–6.8	15:1
Diltiazem hydrochloride	1.2–6.8	1:1
Salbutamol sulfate	1.2–6.8	1:1

[a] No release at a cyclodextrin:drug ratio of 15:1.

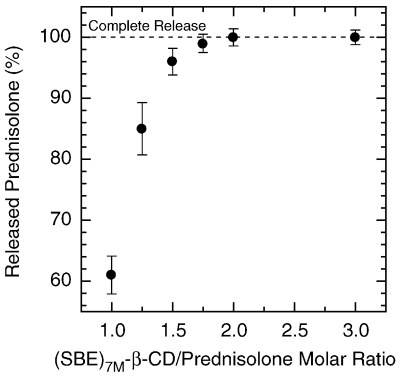

Fig. 1. Relationship between the composition ratio of $(SBE)_{7m}$-β-CD to prednisolone and percent release of prednisolone from the OPT over 12 h used to determine the appropriate composition ratio (ACR) for prednisolone (n = 3).

3.2. Relationship between appropriate composition ratio and drug solubility

At composition ratios less than their ACR, it is assumed that drugs that require a high ACR for complete release exhibit incomplete dissolution/release of the drug when the OPT was placed in the release medium. To define what controls the ACR value for each drug

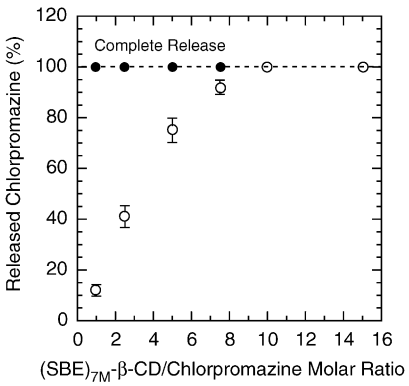

Fig. 2. Relationship between the composition ratio of $(SBE)_{7m}$-β-CD to chlorpromazine and percent release of chlorpromazine from the OPT in pH 1.2 medium (●) and pH 6.8 medium (○) (n = 3). This was then used to determine the appropriate composition ratio (ACR) for chlorpromazine.

Table 3
Intrinsic solubility (S_0), pK_a, stability constant and calculated solubility of each drug in 0.05 M $(SBE)_{7m}$-β-CD mediums

Drug	S_0 (mg/mL)	pK_a	Stability constant (M^{-1})			Calculated solubility[a]	Medium
			K	K_1[b]	K_2[c]	(mg/mL)	
Prednisolone	2.1×10^{-1}	–	1513	–	–	8.5	Water
Estradiol	3.1×10^{-3}	–	73799	–	–	6.2	Water
Chlorpromazine	8.7×10^{-4}	9.30	–	73100	32100	15.7	pH 6.8 buffer
Naproxen	4.2×10^{-2}	4.81	–	3600	432	4.6	pH 1.2 buffer
Indomethacin	3.1×10^{-3}	4.81	–	1590	312	2.5×10^{-1}	pH 1.2 buffer
Diltiazem hydrochloride	>590	8.91	–	ND	ND	ND	Water
Salbutamol sulfate	230	9.22	–	ND	ND	ND	Water

[a] These values are calculated as the solubility in 0.05 M $(SBE)_{7m}$-β-CD medium.
[b] Binding constant of uncharged drug with $(SBE)_{7m}$-β-CD.
[c] Binding constant of charged drug with $(SBE)_{7m}$-β-CD.

it is important to investigate the drug's solubility improvement by $(SBE)_{7m}$-β-CD in the OPT. Table 3 lists the intrinsic solubility, pK_a, stability constant and the solubility of each drug in 0.05 M $(SBE)_{7m}$-β-CD (except for DIL and SAL) with 0.1 M buffer solutions of different pH values or water. Table 4 shows the w/w (%) of each drug, $(SBE)_{7m}$-β-CD and the total dissolved solids in solutions produced in OPTs that were placed in release media for two hours and assayed for content. Reported are those pH values where release would be most limiting for drugs with a strong pH dependency, NPX (pH 1.2) and CPL (pH 6.8). The importance of pH and ACR on release of CPL was extensively discussed in an earlier paper (Okimoto et al., 1999b). The total dissolved content of the OPTs (w/w, %) was gravimetrically calculated from the difference of the weight of the solution and the solids remaining after drying. In addition, the w/w (%) of the respective drugs in the solution was determined after HPLC analysis. The amount of $(SBE)_{7m}$-β-CD present in the solution was calculated from the difference between the concentration of the dissolved solids and the drug concentration. Stella et al. (2002) showed that $(SBE)_{7m}$-β-CD concentration can be as high as 0.3 M in OPTs so the solubility of the drugs is expected to be greater in the OPTs than in the 0.05 M $(SBE)_{7m}$-β-CD solution reported in Table 3. The approximate 60–65 w/w (%) $(SBE)_{7m}$-β-CD in the OPTs at 2 h corresponds to about 0.3–0.35 M. Fig. 3 shows the relationship between the drugs in the OPTs (w/w, %) to their ACR values. The amount of $(SBE)_{7m}$-β-CD needed to solubilize a drug is determined by the intrinsic solubility of the drug and the strength of inclusion complex formation. Therefore the drug content as a w/w (%) in the OPTs decreases with increasing ACR. Also, as shown in Table 4, the amount of dissolved solids in the OPT for each drug was almost identical at two hours (the mean = 65 w/w (%), S.D. = 2.6) and, apparently, independent of drug solubility. This is not surprising as most of the solid was $(SBE)_{7m}$-β-CD. Additionally, the cyclodextrin:drug mole ratio (data not included) in the OPTs at two hours was equivalent to the ACR.

As shown in Table 3, the intrinsic solubility of the water-soluble drugs was 10^3 to 10^6 times greater than

Table 4
Concentration of drug, $(SBE)_{7m}$-β-CD and total dissolved solids in the solution phase in OPTs exposed to release media for two hours

Drug	Medium	Concentration (w/w, %)			Molar ratio of $(SBE)_{7m}$-β-CD drug
		Drug	$(SBE)_{7m}$-β-CD	Dissolved solids	
Predinisolone	Water	4.8	57.1	61.9	2:1
Estradiol	Water	1.6	61.5	63.1	5.1:1
Chlorpromazine	pH 6.8 buffer	0.9	64.2	65.2	10.1:1
Naproxen	pH 1.2 buffer	0.7	62.3	62.9	15.4:1
Indomethacin	pH 6.8 buffer	0.7	62.4	63.1	15.1:1
Diltiazem hydrochloride	Water	11.9	57.0	68.9	1.1:1
Salbutamol sulfate	Water	13.7	51.3	65.1	0.9:1

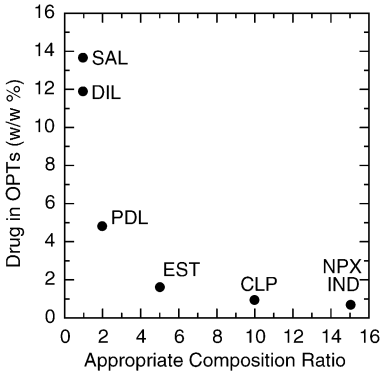

Fig. 3. Relationship between w/w (%) of drug in the solution phase in the OPT core after exposure of the OPT to release media for two hours (n = 3) vs. the appropriate composition ratio (ACR).

the solubility of the poorly water-soluble drugs in the absence of cyclodextrin. However, in the presence of 0.05 M $(SBE)_{7m}$-β-CD in the OPT, the difference in concentration between the water-soluble and the poorly water-soluble drugs is significantly decreased. The differences would be even closer if solubilities had been determined in 0.3 M $(SBE)_{7m}$-β-CD.

3.3. Applicability of drugs to OPT using $(SBE)_{7m}$-β-CD

Fig. 4 shows the comparison of the release of PDL, a poorly water-soluble drug (Fig. 4A) and sodium chloride (NaCl), a water-soluble molecule (Fig. 4B) to the release of $(SBE)_{7m}$-β-CD from OPTs. The mole ratio of $(SBE)_{7m}$-β-CD to NaCl and PDL in the OPTs in both cases was 2:1. Also, two different membrane thicknesses (0.25 and 0.5 mm) for the OPTs were used in this study. The release rates of PDL or NaCl and $(SBE)_{7m}$-β-CD from the OPTs in the respective experiments were almost identical. Since PDL forms an inclusion complex with $(SBE)_{7m}$-β-CD, this result suggests that PDL is released from the OPT as the complex with $(SBE)_{7m}$-β-CD. This is consistent with earlier findings for PDL (Okimoto et al., 1998), testosterone (Okimoto et al., 1999a), and PDL from a matrix dosage form that utilized $(SBE)_{7m}$-β-CD as a solubilizing agent (Rao et al., 2001). However, NaCl, which has a high polarity and a small molecular size, is not expected to form an inclusion complex with $(SBE)_{7m}$-β-CD. Therefore, the fact that NaCl and $(SBE)_{7m}$-β-CD are released from the OPT at the same rate might be surprising. A logical conclusion is that the release rates are controlled by the presence of $(SBE)_{7m}$-β-CD.

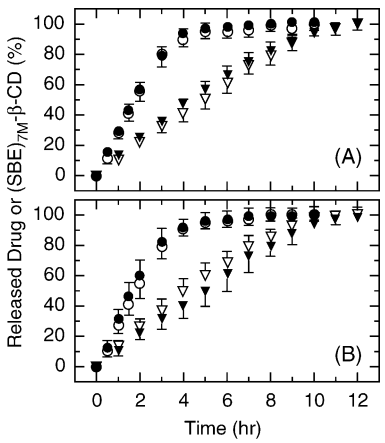

Fig. 4. Comparison of release rate in water of prednisolone (A) or NaCl (B) to $(SBE)_{7m}$-β-CD from OPTs of different membrane thickness. 0.25 mm of membrane thickness; circle, 0.5 mm of membrane thickness; triangle, prednisolone or NaCl; closed symbols, $(SBE)_{7m}$-β-CD; open symbols (n = 3).

Table 5 lists the release rates of all the drugs from OPTs corrected for tablet surface area. For these OPTs, PDL, CLP, DIL and SAL were used as the model drugs and $(SBE)_{7m}$-β-CD, HP-β-CD, and a sugar mixture of lactose and fructose (1:1 as a weight ratio) were chosen as the osmotic pump agents. Because of the differences in the ACRs values among the drugs, the tablet size varies. Therefore, to compare drug release rates from the OPTs, dividing A/h (surface area of the OPT/membrane thickness) normalized the release rates for each respective tablet.

The normalized release rates of the water-soluble or poorly water-soluble drugs from the OPTs utilizing both β-CD derivatives were similar across all drugs for each CD. The release rate from the $(SBE)_{7m}$-β-CD based OPTs was about double those for the HP-β-CD OPTs consistent with greater osmotic pressure from $(SBE)_{7m}$-β-CD (Zannou et al., 2001). The release of the drugs from the sugar mixture OPTs varied significantly across all drugs. Compared to the sugar mixture, for CLP at pH 6.8 and PDL, $(SBE)_{7m}$-β-CD and HP-β-CD significantly increased the release rates consistent with their solubilizing effects but decreased the release rate of the polar drugs, CLP at pH 1.2 and DIL. This later observation suggests an inhibitory effect consistent with the release

Table 5
Comparison of the normalized release rates of drug from OPTs containing $(SBE)_{7m}$-β-CD or other potential osmotic pump agents

Drug	Medium	Normalized release rate (mg/cm/h)		
		$(SBE)_{7m}$-β-CD	HP-β-CD	Sugar mixture
Prednisolone	Water	91.2	45.5	0.7
Chlorpromazine	pH 1.2 buffer	85.7	37.9	195.7
	pH 6.8 buffer	62.7	30.0	ND[a]
Diltiazem hydrochloride	pH 1.2 buffer	61.5	32.7	82.7
	pH 6.8 buffer	62.1	33.2	84.1
Salbutamol sulfate	pH 1.2 buffer	63.2	37.8	22.2
	pH 6.8 buffer	62.2	38.6	22.0

For both $(SBE)_{7m}$-β-CD and HP-β-CD the CDs were at their respective ACR values.
[a] Not detectable.

rates being controlled by the osmotic, diffusion and viscosity properties (Zannou et al., 2001) of the cyclodextrins and not the drugs themselves. By effectively controlling the internal properties of the OPTs, namely osmotic pressure and viscosity, similar release rates of a variety of drugs with varying and pH-dependent solubility and osmotic properties can be achieved.

4. Conclusion

$(SBE)_{7m}$-β-CD serves as both a solubility modulator and as an osmotic pumping agent for OPTs, from which the release rate of both water-soluble and poorly water-soluble drugs can be controlled. An ACR, or appropriate composition ratio, was determined for $(SBE)_{7m}$-β-CD to drug (those requiring solubility enhancement) for complete release of drugs over 12 h from the OPTs. For soluble drugs $(SBE)_{7m}$-β-CD acts primarily as an osmotic and an OPT control agent. Significantly, $(SBE)_{7m}$-β-CD not only enhances the delivery of poorly soluble drugs from OPTs but acts as a controlling excipient for soluble drugs such that the release rate, corrected for table surface area, of both poorly soluble and soluble drugs are similar.

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