Department of Pharmacy[1], Tokyo Women's Medical University Medical Center East, Nishiogu-2-1-10, Arakawa-ku; Department of Pharmaceutics[2], Faculty of Pharmaceutical Sciences, Hoshi University, Ebara, Shinagawa-ku, Tokyo, Japan

Sustained release of highly water-soluble drugs with micelle forming ability from polyionic matrix tablets

Y. Tanaka[1], Y. Miyazaki[1, 2], S. Yakou[1], K. Takayama[2]

Received April 3, 2006, accepted April 28, 2006

Yoichi Tanaka, Department of Pharmacy, Tokyo Women's Medical University Medical Center East, Nishiogu-2-1-10, Arakawa-ku, Tokyo 116-8567, Japan
tanakaph@dnh.twmu.ac.jp

Pharmazie 62: 41–45 (2007) *doi: 10.1691/ph.2007.1.6059*

The aim of present study was to evaluate the application of a hydrophilic matrix tablet capable of polyion complex (PIC-tablet) to a controlled-release device for highly water-soluble drugs. The PIC-tablet was prepared from a mixture of dextran sulfate and [2-(diethylamino)ethyl] dextran chloride, and diltiazem hydrochloride was used as a model drug. Release tests revealed that the drug release was sustained even in 50% drug loading and was influenced by ionic strength but not by pH in medium. The drug release mechanism was thus investigated from the viewpoint of drug micelle forming property. The micelle forming ability of diltiazem was examined by the conductivity method, and was found to be influenced by ionic strength but not by pH value in accordance with the release tests. The results suggested that the drug's micelle interacted with the polyionic matrix. Further studies were conducted using metoprolol tartrate and thiamine hydrochloride as cationic drugs and sodium cloxacillin and sodium salicylic acid as anionic ones. The release profiles of the micelle-forming drugs metoprolol tartrate and sodium cloxacillin were also suppressed in spite of different solubility or opposite ionic charge from diltiazem hydrochloride. These findings demonstrated that the PIC-tablet is a promising device for oral controlled release delivery of water-soluble drugs with good micelle-forming ability.

1. Introduction

Compressed hydrophilic matrix tablets are widely used as modified release dosage forms owing to their simplicity of formulation, inexpensiveness of matrix polymer and their versatility of release characteristics (Melia 1991). Studies on the *in vivo* drug release from these matrices, however, have indicated a few drawbacks. Sako et al. (1996a) reported that orally administered hydrophilic matrix tablets were partially broken down by gastrointestinal destructive forces and the *in vivo* drug release from them was remarkably accelerated. In contrast, on the arrival of hydrophilic matrix tablets to the colon without full swelling, the drug in the tablet was hardly absorbed because of suppression of the drug release (Sako et al. 1996b).

In order to overcome these problems, we developed a hydrophilic matrix tablet capable of forming polyion complex (PIC-tablet), which was prepared from a mixture of oppositely charged dextran derivatives (Miyazaki et al. 2003). PIC-tablet would form a durable gel layer resistant to gastrointestinal destructive forces which could swell in the colon where only a small amount of water exists, resulting in good *in vitro*/*in vivo* correlation. The *in vivo* performance of PIC-tablets was confirmed by the studies on human volunteers, showing good drug release behavior beyond a variety of gastrointestinal environments (Miyazaki et al. 2006).

In the course of studies on PIC-tablets, however, we have only used theophylline, which has relatively low water-solubility, as a model drug. In general, the drug release from a hydrophilic matrix is controlled by two mechanisms. While poorly soluble drugs are released solely by erosion of the gel layer, water-soluble drugs are released both by diffusion out of the gel layer and by erosion of the gel (Lee 1985). Therefore, the release rate of highly water-soluble drugs from the hydrophilic matrix is hardly suppressed because of rapid diffusion through the gel layer (Ford et al. 1991). In order to fully realize the versatility of PIC-tablets, the tablets needed to be applied to highly water-soluble drugs without additional modifications such as an increase in matrix thickness.

The objective of the present study was to evaluate the possibility of application of PIC-tablets to highly water-soluble drugs. A PIC-tablet incorporating diltiazem hydrochloride (DTZ) as the model drug was prepared and investigated for drug release. In addition, to confirm the drug release mechanism, *in vitro* drug release studies were conducted using metoprolol tartrate (MTP) and thiamine hydrochloride (TA) as cationic drugs, and cloxacillin sodium (MCIPC) and sodium salicylic acid (SA) as anionic drugs.

2. Investigations and results

2.1. Diltiazem release from PIC-tablet

A highly water-soluble drug, diltiazem (DTZ), was incorporated into the PIC-tablet. Fig. 1 shows the effect of drug

Table: Drug properties

Drug	Molecular weight	Solubility (mg/mL)	Charge state	CMC* (mol/L)
DTZ	414.53	558–678[a)]	cation	0.103
MTP	342.41	1000[b)]	cation	0.125
TA	300.81	≒1000[b)]	cation	0.251
MCIPC	475.88	100–1000[b)]	anion	0.072
SA	161.12	1150[c)]	anion	0.705

[a)] Bodmeier, R. et al., 1996, Pharm. Res., 13 (1), 52–56
[b)] Japanese Pharmacopoeia XIV
[c)] Product Information Sheet, Wako Pure Chemical Industries. Ltd
* Critical micelle concentration

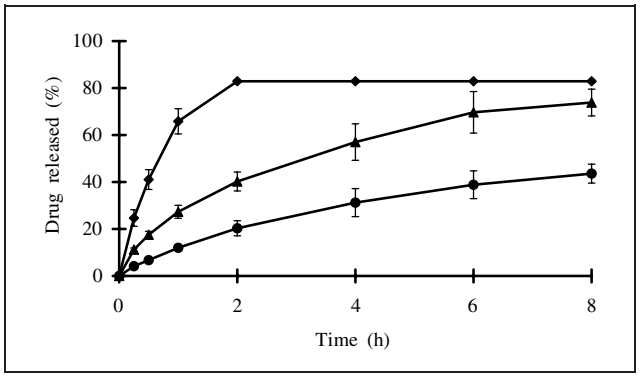

Fig. 1: DTZ release profiles from PIC-tablets (200 mg) containing 75 mg (●), 100 mg (▲) or 125 mg (◆) of drug in JP XIV 2nd fluid (pH 6.8). Each result shows the mean ± S.D. (n = 3)

loading amount on the release profiles of DTZ from PIC-tablets. As the drug content increased, the drug release rate increased. DTZ release was extremely depressed even in the case of 50% drug loading. In general, the release rate of highly water-soluble drugs from hydrophilic matrices was hardly suppressed because the drugs diffused rapidly through the gel layer (Ford et al. 1991). Although DTZ has high water solubility as shown in the Table, its release is suppressed to the same extent as that of theophylline (solubility 11 mg/mL, Miyazaki et al. 2003). This result indicated that DTZ could interact with the polyionic matrix of PIC-tablet in the diffusion process. We thus investigated the factors affecting DTZ release from PIC-tablet focusing on pH and ionic strength in the dissolution medium.

The influence of the pH value of the dissolution medium on the DTZ release is shown in Fig. 2a. Three kinds of dissolution medium, namely, JP XIV 1st fluid (pH 1.2), 2nd fluid (pH 6.8) and acetate buffer (pH 4.0) were used after adjusting the ionic strength to be 0.1 mol/kg by addition of sodium chloride. The release profiles were similar to each other, indicating that the drug release was not affected by pH. In contrast, DTZ release profiles were altered by the ionic strength of the medium as shown in Fig. 2b. As the ionic strength was increased from 0.025 to 0.1, DTZ release rate increased. In the previous report, polyion complex formation between dextran sulfate (DS) and [2-(diethylamino)ethyl] dextran (EA) was hardly influenced by these factors (Miyazaki et al. 2001). In contrast, there were several reports that the critical micelle concentration (CMC) of micelle forming drugs was affected by ionic strength in medium (Attwood and Fletcher 1986, Taboada et al. 1999). Thus, the effects of pH and ionic strength in the medium on DTZ properties was investigated.

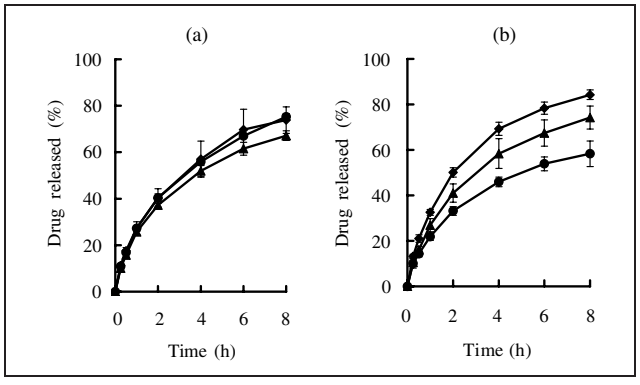

Fig. 2: DTZ release profiles at various pH with same ionic strength (a); pH 1.2 (●), pH4.0 (▲), pH6.8 (◆), and at various ionic strength (b); 0.025 (●), 0.05 (▲), 0.1 (◆). Each result shows the mean ± S.D. (n = 3)

2.2. Micelle forming property of diltiazem

The CMC of DTZ in the solutions having various pH values and ionic strengths was analyzed by the conductivity method. Fig. 3a shows the CMC of DTZ in the medium with pH 1.2, 4.0, and 6.8. The ionic strength in all solutions was adjusted to be 0.1 mol/kg. The CMC of DTZ was determined to be approximately 0.1 mol/L (41.4 mg/mL) in all media. These results indicated that the micelle-forming ability of DTZ was not affected by pH. Fig. 3b shows the CMC of DTZ in the sodium chloride solution having 0.025, 0.05, or 0.1 of ionic strength. The CMC of DTZ increased with increasing ionic strength in the solution. These results showed that the CMC of DTZ was affected by ionic strength (0.025–0.1), but not by pH (1.2–6.8). This trend was in good agreement with the DTZ release rate from PIC-tablets. According to a previous study for oral extended release of highly water-soluble drugs (Kojima et al. 2003), drug diffusion was controlled utilizing the drug's micelle-forming property and

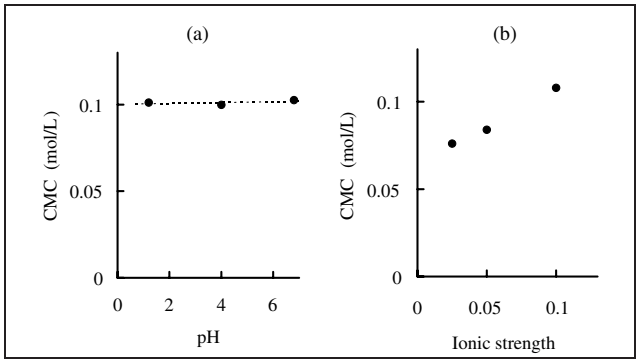

Fig. 3: Relationship between the CMC of DTZ and pH value (a), and between the CMC of DTZ and ionic strength (b)

counter polymers. Therefore, micelle formation of DTZ could relate to the release mechanism from PIC-tablets.

2.3. Release behavior of various drugs with different properties

In order to confirm that the micelle forming ability of drugs incorporated into PIC-tablets influences the drug release behavior, several model drugs with different properties were selected, as summarized in the Table, and evaluated for their release profiles. Fig. 4 displays the release profiles of sodium salicylic acid (SA) and thiamine hydrochloride (TA) used as an anionic and a cationic drug, respectively. Irrespective of its charge state, almost all of the loading drug was released from PIC-tablet within 0.5 h. This was due to rapid diffusion of the drugs and pore-forming in the tablet by drug leaching out. Although SA and TA each had an electronic charge in the medium, they did not sufficiently interact with the polyionic matrix of PIC-tablet because of their poor ability to form micelle (Table).

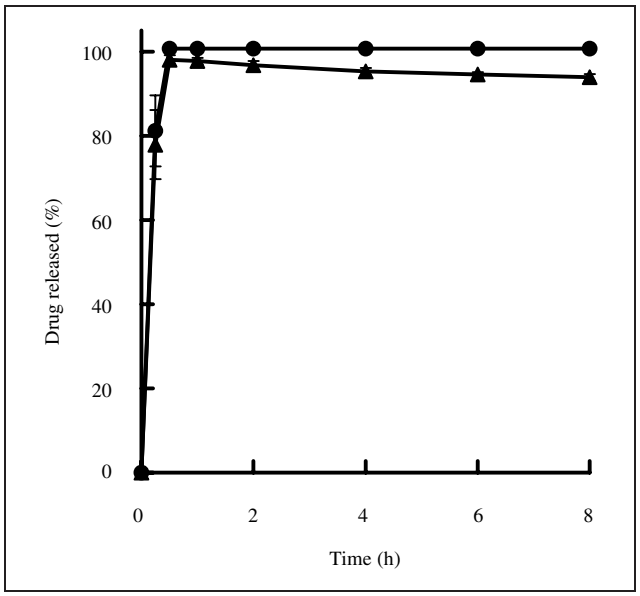

Fig. 4: Release profiles of SA (▲) and TA (◆) from PIC-tablets in JP XIV 2nd fluid (pH 6.8). Each result shows the mean ± S.D. (n = 3)

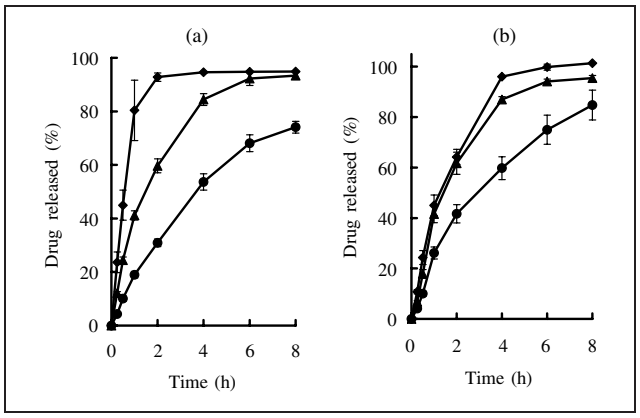

Fig. 5: Release profiles of MTP (a) and MCIPC (b) from PIC-tablets in JPXIV 2nd fluid (pH 6.8). Each result shows the mean ± S.D. (n = 3).
Drug contents: ●, 25 mg; ▲, 50 mg; ◆, 75 mg

Fig. 5 shows the drug release of metoprolol tartrate (MTP) and cloxacillin sodium (MCIPC), known as micelle-forming drugs (Attwood and Agarwal 1979, 1984), from PIC-tablets with various drug contents. The release profiles of both drugs were suppressed compared with SA and TA. The MTP release rate was delayed in 25% of drug content (Fig. 5a), while the solubility of MTP was about 1000 mg/mL. MCIPC release was also prolonged up to 6 h (Fig. 6b). The CMC of MTP and MCIPC in JP XIV 2nd fluid was determined to be 0.125 mol/L (42.8 mg/mL) and 0.072 mol/L (34.3 mg/mL), respectively. These results demonstrated that the highly water-soluble drugs with good micelle forming ability would interact with the polyionic matrix irrespective of their charge state, leading to sustained release from the tablets. This was due to the amphoteric nature of the gel layer composed from polyion complex between DS and EA.

3. Discussion

This study was carried out to apply a PIC-tablet to highly water-soluble drugs. Release times of DTZ, MTP and MCIPC were prolonged compared with those of SA and TA (Figs. 1 and 5). Whether or not the drug could form a stable micelle in the gel layer during the diffusion process was an important factor. Fig. 6 represents an illustration of the proposed release mechanism, and the matrix and drug state on the release process. When in contact with the dissolution medium, the PIC-tablet forms a gel layer with a three-dimensional network structure. Simultaneously, drugs dissolve in the dissolution medium penetrated into the gel layer at a higher concentration than CMC The drug molecules thereby form micelles, which have an electronic charge outside. Due to the increase in net charge and in size, the micelles could more efficiently interact with the polyionic matrix than monomolecular drugs. On further swelling the micelles disintegrate into monomolecular drugs, and then the drug molecules diffuse out of the matrix.

In the detailed comparison, the release rate of DTZ was lower than that of MTP (Figs. 1 and 5a). The CMC values of DTZ and MTP in JP XIV 2nd fluid were 0.103 and 0.125 mol/L, respectively. Since the CMC of DTZ was lower than that of MTP, DTZ could form a stable micelle in the polyionic matrix and interact with DS more efficiently due to the increase in net charge. This explanation holds true for MCIPC. In this case, anionic MCIPC interacted with EA having diethylaminoethyl residues. Thus, PIC-tablets allowed a highly water-soluble drug with good micelle forming ability to undergo sustained-release irrespective of its charge state. This is a great advantage for application of PIC-tablets to a controlled release device. The inherent electronic charge of the matrix polymers contributed to achieving sustained release of incorporated drugs. These findings confirmed that PIC-tablet is a promising device for oral controlled release of highly water-soluble drugs with micelle forming property, and not only for poor water-soluble drugs.

In general, the conventional hydrophilic matrix tablet such as a hydroxypropylmethylcellulose tablet is poorly adapted to highly water-soluble drugs because such drugs can rapidly diffuse out of the matrix. There have been various attempts to make sustained-release systems for water-soluble drugs by use of hydrophilic matrix tablets, such as the incorporation of electrolytes with drug in the tablets expecting electrostatic interaction (Pillay et al. 1999, 2000), and the use of an oppositely charged polymer intended to invoke ionic bonding (Bonferoni et al. 1993,

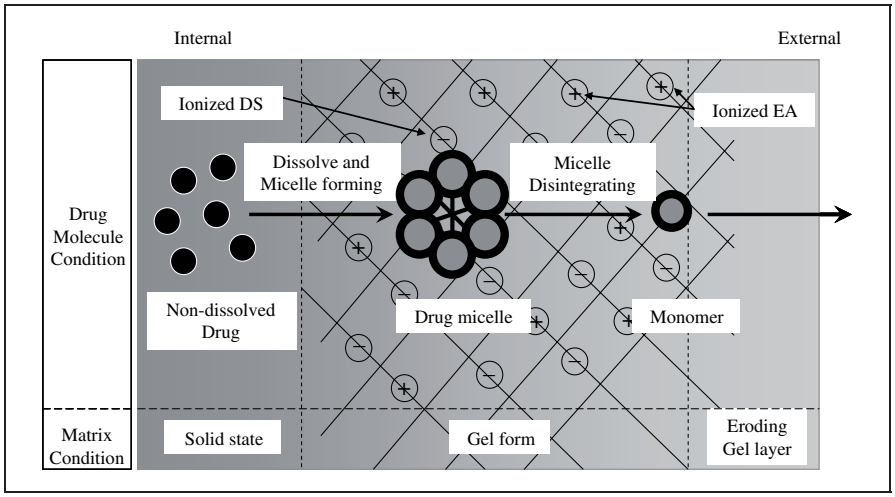

Fig. 6:
Schematic description of drug release mechanism from PIC-tablets

2000). These controlled release systems, however, required additional ingredients such as electrolytes or counter polymers, so the tablet size became larger and unsuitable for clinical use. Furthermore, the release mechanism was still questionable. In DTZ tablets containing lambda-carrageenan, ionic bonds between DTZ and lambda-carrageenan were involved in the release mechanism (Bonferoni et al. 2000). According to Kojima et al. (2003), DTZ's micelle formation contributed to prolongation of DTZ release from the hydrophilic matrix using carbopol^{TM} 971 and iota-carrageenan as counter polymers.

The findings of our study supported the involvement of a drug's micelle forming in the drug release mechanism. However, the detailed relationship between micelle properties and drug release rate remained unclear. More systematic studies of this issue are in progress.

In conclusions, PIC-tablets controlled the release rate of drugs having high water-solubility and stable micelle forming ability such as DTZ, MTP and MCIPC. Moreover, irrespective of the drug's charge state, the drug release rate was prolonged due to amphoteric nature of the polyionic matrix. Various drugs with different water-solubilities and charge states could be applied without any additive such as a counter polymer. These results indicated that a PIC-tablet is a useful device for oral controlled delivery of highly water-soluble drugs with good micelle forming ability.

4. Experimental

4.1. Materials

Dextran sulfate (DS), [2-(diethylamino)ethyl] dextran (EA) and MTP were obtained from Sigma. Co. (St. Luis, United States). DTZ, TA, and SA were obtained from Wako Pure Chemical Industries. Ltd. (Osaka, Japan). MCIPC was obtained from MP Biomedicals. Inc. (California, United States). All of the chemicals described above were sifted through a 100 mesh sieve (less than 150 μm) before use. All other chemicals were of reagent grade and were used as received. The model drugs and their aqueous solubility are listed in the Table.

4.2. Preparation of tablets

All ingredients were mixed using pestle and mortar by hand. Flat-faced tablets 8 mm in diameter were prepared by direct compression under 150 kgf/cm^2 for 30 s on a hydraulic press (Shimadzu Co. Ltd., Kyoto, Japan).

In all formulations, a 3 : 7 mixture of DS and EA was employed as the matrix polymer. The formulation consisted of 100 mg of drug and 100 mg of the mixture except as mentioned.

4.3. Drug release study

Drug release from tablets was tested by the paddle method (200 rpm) at 37 ± 0.5 °C using 900 mL of Japanese Pharmacopoeia (JP) XIV 1st fluid (pH 1.2, 0.07 M HCl and 0.0342 M NaCl), JP XIV 2nd fluid (pH 6.8, 0.05 M H_2KPO_4 and 0.0236 M NaOH) and three kinds of sodium chloride solution (ionic strength 0.025, 0.05, and 0.1). The samples were withdrawn and filtered at 0.25, 0.5, 1, 2, 4, 6, and 8 h. The drug concentration was analyzed by a spectrophotometer at wavelength of 209, 234, 236, 274 and 296 nm for MCIPC, TA, DTZ, MTP and SA, respectively.

4.4. Determination of critical micelle concentration

The critical micelle concentration (CMC) of drugs was determined by the conductivity method (Attwood and Natarajan 1980) using a conductance meter (Hanna Instrument Inc., Rhode Island, United States). Adequate amounts of drug were dissolved in solutions at predetermined concentrations within 0.0–0.2 mol/L (10 points for each drug). The conductivity of the solutions was plotted against drug concentration in the solutions. In both low and high drug concentration ranges, linear regression curves were determined by showing the maximum correlation coefficient values (R^2) on each. The CMC was calculated by the intersection point of two linear regression curves. The solutions used in this section were the same as the dissolution medium described above.

References

Attwood D, Afarwal SP (1979) The surface activity and self-association of some beta-adrenoceptor blocking agents in aqueous solution. J Pharm Pharmacol 31: 392–395.

Attwood D, Natarajan R (1980) Micellar properties and surface activity of some bolaform drugs in aqueous solution. J Pharm Pharmacol 32: 460–462.

Attwood D, Afarwal SP (1984) Light scattering studies on micelle formation by some penicillins in aqueous solution. J Pharm Pharmacol 36: 563–564.

Attwood D, Fletcher P (1986) Self-association of local anaesthetic drugs in aqueous solution. J Pharm Pharmacol 38: 494–498.

Bonferoni MC, Rossi S, Tamayo M, Pedraz JL, Dominguez-Gil A, Caramella C (1993) On the employment of lambda-carrageenan in a matrix system. I. sensitivity to dissolution medium and comparison with Na carboxymethylcellulose and xanthan gum. J Control Release 26: 119–127.

Bonferoni MC, Rossi S, Ferrari F, Bettinetti GP, Caramella C (2000) Characterization of a diltiazem-lambda carrageenan complex. Int J Pharm 200: 207–216.

Ford JL, Mitchel K, Rowe P, Armstrong DJ, Elliott PNC, Rostron C, Hogan CR (1991) Mathematical modeling of drug release from hydroxylpropylmethylcellulose matrices: effect of temperature. Int J Pharm 71: 95–104.

Kojima H, Sawada T, Sako K (2003) Innovative oral controlled drug release system utilizing the micelle-forming property of highly water-soluble drugs. Prog Drug Delivery Sys 7: 13–22.

Lee PI (1985) Kinetics of drug release from hydrogel matrices. J Control Release 2: 277–288.

Melia CD (1991) Hydrophilic matrix sustained release systems based on polysaccharide carriers. Critical Rev Ther Drug Carrier Sys 8: 395–421.

Miyazaki Y, Yakou S, Takayama K (2001) The investigation for the formation of complexes between opposite-charged dextran derivatives. J Pharm Sci Technol, Jpn 61: 59–70.

Miyazaki Y, Yakou S, Nagai T, Takayama K (2003) The effect of polyion complex formation on *in vitro*/*in vivo* correlation of hydrophilic matrix tablets. J Control Release 91: 315–326.

Miyazaki Y, Tanaka Y, Yakou S, Takayama K (2006) *In vivo* drug release from hydrophilic dextran tablets capable of forming polyion complex. J Control Release: submitted.

Pillay V, Fassihi R (1999) Electrolyte-induced compositional heterogeneity: a novel approach for rate-controlled oral drug delivery. J Pharm Sci 88: 1140–1148.

Pillay V, Fassihi R (2000) A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system. J Control Release 67: 67–78.

Sako K, Mizumoto T, Kajiyama A, Ohmure T (1996a) Influence of physical factors in gastrointestinal tract on acetaminophen release from controlled-release tablets in fasted dogs. Int J Pharm 137: 225–232.

Sako K, Nakashima H, Sawada T, Fukui M (1996b) Relationship between gelation rate on controlled-release acetaminophen tablets containing polyethylene oxide and colonic drug release in dogs. Pharm Res 13: 594–598.

Taboada P, Attwood D, Ruso JM, Garía M, Sarmiento F, Mospuera V (1999) Effect of electrolyte on the surface and thermodynamic properties of amphiphilic penicillins. J Colloid Interface Sci 220: 288–292.