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Drug–Organic Electrolyte Complexes as Controlled Release Systems

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A water-insoluble complex between diltiazem HCl and Na deoxycholate was prepared to achieve sustained release dosage forms. Physicochemical characterization of the drug complex was carried out with differential scanning calorimetry, ^{1}H-nuclear magnetic resonance, and Fourier transform infrared spectroscopy. These techniques showed that the characteristic peaks in both the drug and the complexing agent (protonated amine and carboxylate) disappeared and new peaks appeared upon formation of the ionic complex. The release of diltiazem from drug-complex tablets was sustained for a long period of time (>24 h) and was dependent on the pH of the dissolution medium. However, the dependence of drug release on pH was eliminated at pH 6–8 and minimized at pH 1.5 when drug-complex powders were incorporated in hydroxypropylmethylcellulose (HPMC) drug carriers. Unlike the release of diltiazem HCl from HPMC drug carriers, drug release from drug-complex/HPMC tablets was linear or near linear irrespective of the viscosity grade of the polymer (E15 to K4M). This is due to a shift in the controlling mechanism of drug release from drug diffusion to erosion of polymer. Also, drug release kinetics was not significantly affected by the water solubility of cationic drugs (diltiazem HCl, verapamil HCl, propranolol HCl, and labetalol HCl) ranging from 1.6 to 62% and the type of amine (i.e., secondary or tertiary). The same release characteristics were observed from the complexes between anionic drugs (Na salicylate, naproxen Na, and tolmetin Na) and benzathine diacetate as found from the complexes between cationic drugs and Na deoxycholate.

Keywords complex; controlled release; erosion; diffusion; solubility

INTRODUCTION

Many mechanistic principles have been used to design controlled release dosage forms (Kim, 1999; Kydonieus, 1992): matrix, membrane-reservoir, swelling, ion exchange resin, osmosis, and so on. Matrix-controlled systems, especially compressed tablets, are one of the favorable designs because of simple, reliable manufacturing processes and costs. Drug release kinetics from matrix systems consisting of an active drug and a hydrophobic polymer or a mixture of polymers is governed by drug diffusion through the drug carrier, resulting in square root of time kinetics. Although release kinetics may depart from square root of time kinetics by using water-soluble polymers as drug carriers, drug diffusion still plays a significant role in release kinetics as drug loading increases. However, ion exchange resins composed of sulfonated crosslinked poly(styrene/divinyl benzene) afford high loading capacity with a negligible change in release kinetics ($\sqrt{t}$).

Several attempts were made in our laboratory to increase the rate of drug diffusion with time by synthesizing highly swellable polymers or to eliminate the effect of drug diffusion by designing water-soluble high molecular weight polyelectrolytes that would decrease the dissolution rate enough to allow prolonged drug release (Kim, 1994; Nujoma & Kim, 1996). Kim reported a linear release of propranolol HCl from a poly(acrylate K) (PA) bead, the degree of swelling of which in size was 2.7 (Kim, 1994). When an oppositely charged active drug binds to a water-soluble polyelectrolyte, it forms an ionic complex: drug release through ion exchange from the drug complex in the presence of electrolytes is slow but complete. The dissociated polyelectrolyte then dissolves in water without swelling. Kim and coworkers demonstrated near zero-order release kinetics by binding and releasing cationic drugs to strongly anionic polyelectrolytes: poly(sulfopropylmethacrylate potassium-co-methyl methacrylate) (PSPMK/MMA) (Nujoma & Kim, 1996) and poly(acrylamido-2-methyl-1-propanesulfonate sodium-co-methyl methacrylate) (PAMPSNa/MMA) (Konar & Kim, 1999). Konar and Kim reported analogous results using anionic drugs bound to strong cationic polyelectrolytes: poly(trimethylammonium ethyl methacrylate chloride-co-methyl methacrylate) (PTMAEAC/MMA) (Konar & Kim, 1998), poly(methacrylamidopropyl trimethylammonium chloride-co-methyl methacrylate) (PMAPTAC/MMA) (Konar &

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Kim, 1998), and pol(diallydimethyl ammonium chloride) (PDADMAC) (Konar & Kim, 2001). Zero-order release or near zero-order release kinetics with high drug loading capacity (>40%) has been reported using these drug–polyelectrolyte complex tablets. Recently, lamda carrageenan has been used to form a complex with the cationic drug, diltiazem HCl (Bonferoni, Rossi, Ferrari, & Caramella, 2004). Lee et al. (2005) evaluated a cationic analog of deoxycholate (deoxycholylethyleneamine) as a physical complexing agent for ceftriaxone.

Another way to eliminate or minimize drug diffusion in matrix-controlled systems is to reduce the solubility of a drug so that the rate of drug diffusion is very small or negligible compared with the rate of drug dissolution. Chang and Himmelstein showed that zero-order drug release kinetics was not obtained for a system having a high dissolution rate constant, whereas a system having a low dissolution rate yielded zero-order release even for a spherical geometry (Chang & Himmelstein, 1990). Gurney et al. demonstrated zero-order release kinetics of KCl from an ethyl cellulose tablet followed by a first-order kinetics after the complete dissolution of KCl in the matrix (Gurney, Doelker, & Peppas, 1982). If a water-soluble polymer is used as the drug carrier and there is no diffusion, one expects that drug release kinetics is controlled by the erosion of the polymer and zero-order release kinetics is anticipated for a slab geometry (Lee, 1980).

In this study, water-soluble cationic and anionic drugs were used to form complexes with an excipient of opposite charge. These complexes were water-insoluble. However, they were soluble only in the presence of salts. The anionic bile surfactant, Na deoxycholate, was used in this study for cationic drugs, because it is native to the body and thus, is unlikely to induce any adverse reaction. Benzathine diacetate was used for anionic drugs, because it has been used in pharmaceutical applications (Budavari, 1989). The preparation, characterization, and drug release study of cationic drug–deoxycholate and anionic drug–benzathine complexes are given herein.

MATERIALS AND METHODS

Materials

All materials were used as received. Na deoxycholate and benzathine diacetate were purchased from Mann Research Laboratories (New York, NY, USA) and NBS Biologicals (Cambridge, England), respectively. Sodium phosphate monobasic, potassium phosphate dibasic, dibasic calcium phosphate, hydrochloric acid, and sodium chloride were obtained from Fisher Scientific (Fair Lawn, NJ, USA). Diltiazem HCl, propranolol HCl, verapamil HCl, labetalol HCl, Na salicylate, naproxen Na, and tolmetin Na were purchased from Sigma Chemical (St. Louis, MO, USA). Different viscosity grades of hydroxypropylmethylcelluloses (HPMCs) were generously supplied by Dow Chemical (Midland, MI, USA). Water was distilled and de-ionized through a Milli Q Synthesis A10 (Waters, Boston, MA, USA). Simulated intestinal fluids were prepared with 0.01 M phosphate buffer at pH 6, 7, and 8 in 0.1 M NaCl. Simulated gastric fluids were prepared with concentrated HCl at pH 1.5 in 0.1 M NaCl.

Preparation of Drug–Deoxycholate and Drug–Benzathine Complexes

An aqueous drug solution (5%) was added to an aqueous solution of Na deoxycholate or benzathine diacetate (5%) to precipitate a cationic drug–deoxycholate or anionic drug–benzathine complex, respectively. The precipitate was washed free of soluble ingredients, dried, and triturated in a mortar and pestle. Tablets of 150 mg drug–deoxycholate complex (9.5 mm diameter) or tablets of 300 mg containing the complex and HPMC (10.5 mm diameter) were compressed under 2,000 lb compression force using a flat punch in a Carver press (Wabash, IN, USA).

CHARACTERIZATION OF DILTIAZEM–DEOXYCHOLATE COMPLEX

Differential Scanning Calorimetry

The differential scanning calorimetric studies were carried out on differential scanning calorimetry (DSC 30) (Mettler Toledo, Columbus, OH, USA), using STAR software, that was calibrated using the melting points of indium (156 ± 0.2°C) and zinc (419.5 ± 0.3°C) standards. Samples of diltiazem HCl, Na deoxycholate, and diltiazem–dexoycholate complex were weighed (Mettler MT5 microbalance) directly in aluminum crucibles (40 μL), crimped with a lid without a pinhole. The samples were scanned from 25 to 300°C at a heating rate of 10°C/min under a stream of dry nitrogen (flow rate of 50 mL/min).

^{1}H-Nuclear Magnetic Resonance

The 400-MHz ^{1}H-nuclear magnetic resonance (NMR) spectra of diltiazem HCl, Na deoxycholate, and diltiazem–dexoycholate complex were carried out on Varian Mercury 400-MHz NMR spectrophotometer (Palo Alto, CA, USA). The conditions for NMR measurement were as follows: relaxation delay time of 1 s, pulse angle 45.0°, and acquisition time of 1.995 s. All spectra were recorded in methanol—d_4. The probe temperature was regulated at 25°C.

Fourier Transform Infrared Spectroscopy

Infrared spectra were obtained using a Thermo Nicolet Fourier transform infrared spectroscopy (FTIR) spectrophotometer Model 100 (Thermoelectron Corp., Waltham, MA, USA). All spectra were determined as KBr pellets by scanning from 4,000 to 400 cm^{-1}.

Drug Release Study

Drug release kinetics from tablets of drug–deoxycholate and drug–benzathine complexes was carried out in simulated gastric and intestinal fluids at 37°C by the USP basket method (900 mL) at 100 rpm. The concentration of drug in dissolution media was measured on Agilent 8453A diode-array UV/Vis spectrophotometer (Wilmington, DE, USA) at 278 (diltiazem HCl), 287 (propranolol HCl), 296 (verapamil HCl), 306 (labetalol HCl), 315 (Na salicylate), 330 (naproxen Na), and 360 nm (tolmetin Na).

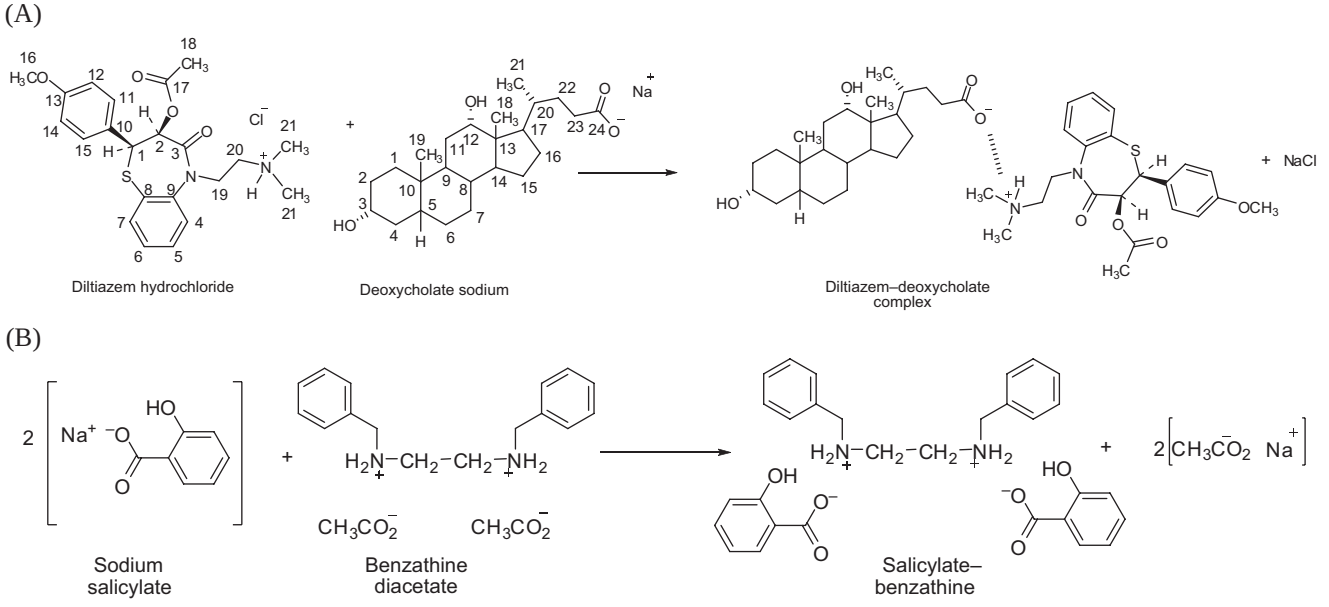
RESULTS AND DISCUSSION

On mixing aqueous solutions of Na deoxycholate with diltiazem HCl, a diltiazem–deoxycholate complex is formed as a sticky, thick, white precipitate (Scheme 1A). The precipitated complex could be dissolved in methanol and then spray-dried. In this study, the complex was dried under vacuum.

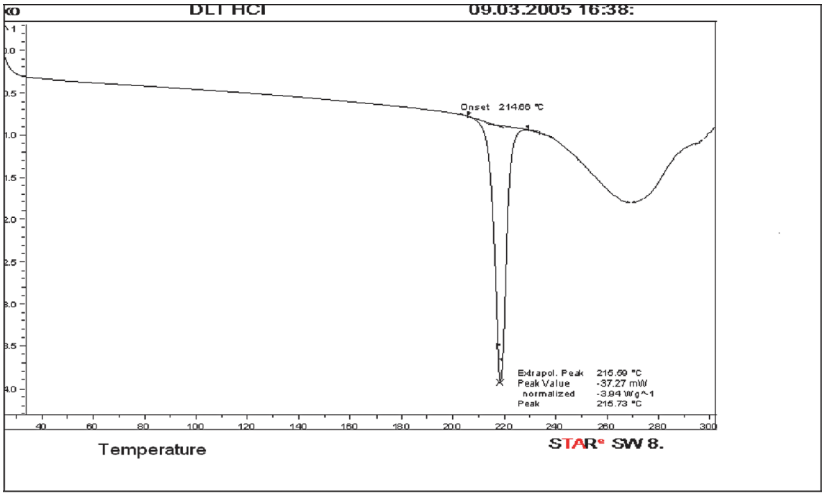
DSC thermograms of diltiazem HCl, Na deoxycholate, and diltiazem–deoxycholate complex are shown in Figure 1. The DSC thermogram of diltiazem HCl follows a typical, endotherm with an onset temperature at 214.6°C and a peak at 215.6°C that is associated with the melting point, as reported by Mazzo, Obetz, and Shuster (1994). The DSC thermogram of Na deoxycholate showed a broader melting endotherm ranging from 62 to 140°C, which could be due to a greater disorder in the crystallinity of Na deoxycholate. The absence of the characteristic melting peak of diltiazem at 215.6°C was strong evidence of the formation of diltiazem–deoxycholate complex. The complex showed a new peak at 69.5°C because of a shift in the endotherm of deoxycholate. Decomposition occurred at 140°C. These findings confirmed the formation of a new solid or drug–deoxycholate complex with a different thermal property.

^{1}H-NMR spectra of diltiazem HCl, Na deoxycholate, and drug–deoxycholate complex are shown in Figure 2. Table 1 summarizes the chemical shifts of important peaks in the diltiazem HCl, Na deoxycholate, and diltiazem–deoxycholate complex. Protons alpha to the ionized amine of diltiazem HCl give a singlet at 2.99 ppm, corresponding to the C-21 methyl groups, and multiplets centered at 3.36 and 3.65 ppm, corresponding to the protons on the C-20 methylene group. The ionic interaction of the diltiazem–deoxycholate complex reduces the deshielding of these protons relative to that in pure diltiazem HCl. This results in an upfield shift for each of these peaks in the complex, with the C-21 methyl protons appearing at 2.48 ppm and the C-20 methylene protons appearing as multiplets centered at 2.76 and 3.04 ppm. The ionic interaction in the complex has the opposite effect on the chemical shift of the protons alpha to the ionized carboxyl group, C-23, of deoxycholate. These protons show greater deshielding in the complex (2.15 and 2.35 ppm) than in pure Na deoxycholate multiplets centered at 2.17 and 2.31 ppm.

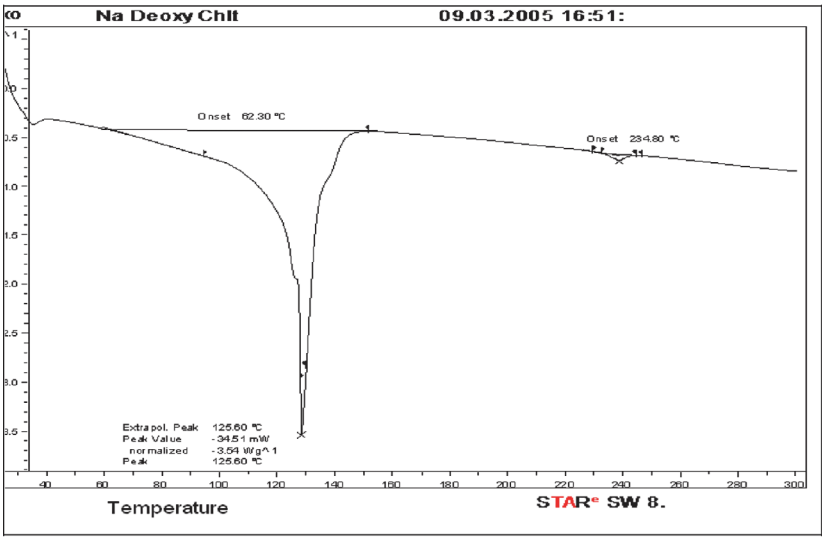
Figure 3 shows the FTIR spectra of Na deoxycholate, diltiazem HCl, and the complex. The hydroxyl stretching band of Na deoxycholate at 3,368 cm^{-1} slightly weakened and shifted to 3,408 cm^{-1} in the complex. Carboxylate stretching bands at 1,565 and 1,409 cm^{-1} in Na deoxycholate were not present in the complex. The protonated tertiary amine band of diltiazem HCl at 2,387 cm^{-1} disappeared upon formation of the complex. However, the secondary alcohol stretching band at 1,042 cm^{-1} and aliphatic stretching peaks at 2,938 and 2,864 cm^{-1}



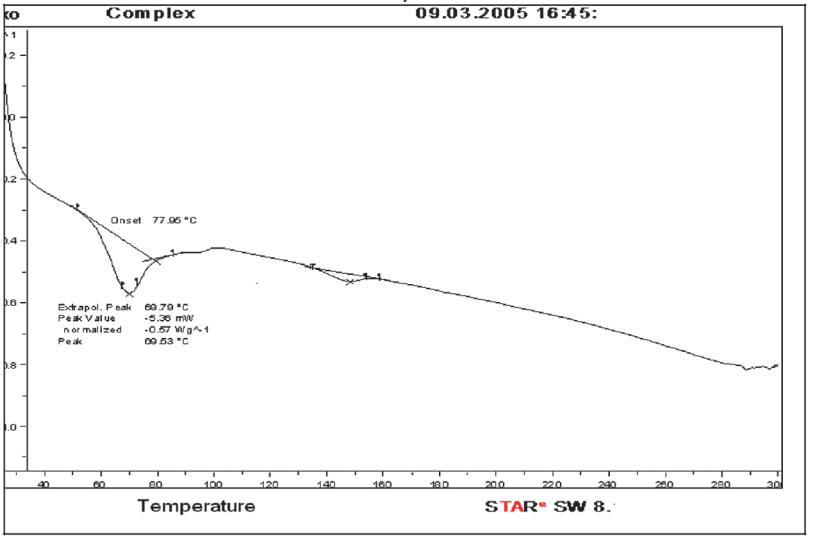
SCHEME 1. Drug complex formation: (A) diltiazem–deoxycholate; (B) salicylate–benzathine.



Diltiazem HCl



Na deoxycholate



Diltiazem–deoxycholate

FIGURE 1. Differential scanning calorimetry (DSC) thermograms of diltiazem HCl, Na deoxycholate, and diltiazem–deoxycholate.

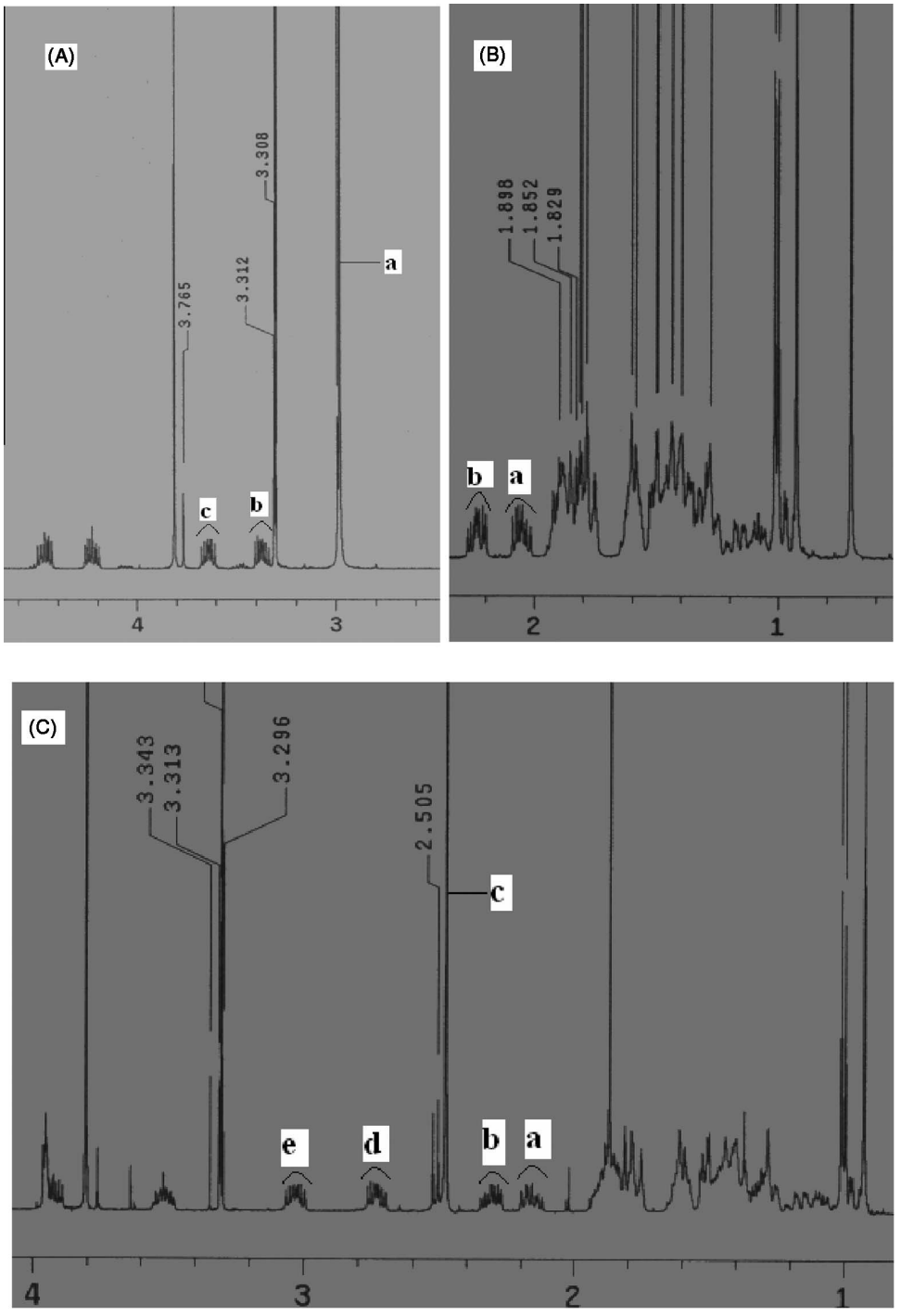


FIGURE 2. ^{1}H-nuclear magnetic resonance (NMR) spectra of diltiazem HCl, Na deoxycholate, and diltiazem–deoxycholate: (A) diltiazem HCl (a) C-21, CH_3, (b and c) C-20, CH_2; (B) Na deoxycholate (a and b) C-23, CH_2; and (C) diltiazem–deoxycholate complex (a and b) deoxycholate C-23, (c) diltiazem C-21, (d and e) diltiazem C-20.

were present in the spectra of both Na deoxycholate and the complex. In addition, ester and amide stretching peaks of diltiazem HCl at 1,742 and 1,640 cm^{-1}, respectively, were not changed in the complex. The disappearance of the carboxylate and the ammonium peaks from the spectrum of the complex indicates an ionic interaction between two groups in the complex.

Effect of pH on the release of diltiazem from diltiazem–deoxycholate complex tablets is shown in Figure 4. At pH 1.5, drug release was significantly retarded and then gradually

TABLE 1
Chemical Shifts for Protons of Diltiazem HCl in Free Drug, Na Deoxycholate in Free State, and in Diltiazem–Deoxycholate Complex

Proton	Diltiazem HCl (ppm)	Na Deoxycholate (ppm)	Diltiazem–Deoxycholate Complex (ppm)
C-20	3.36 and 3.65	—	2.76 and 3.04
C-21	2.99	—	2.48
C-23	—	2.05 and 2.25	2.17 and 2.31

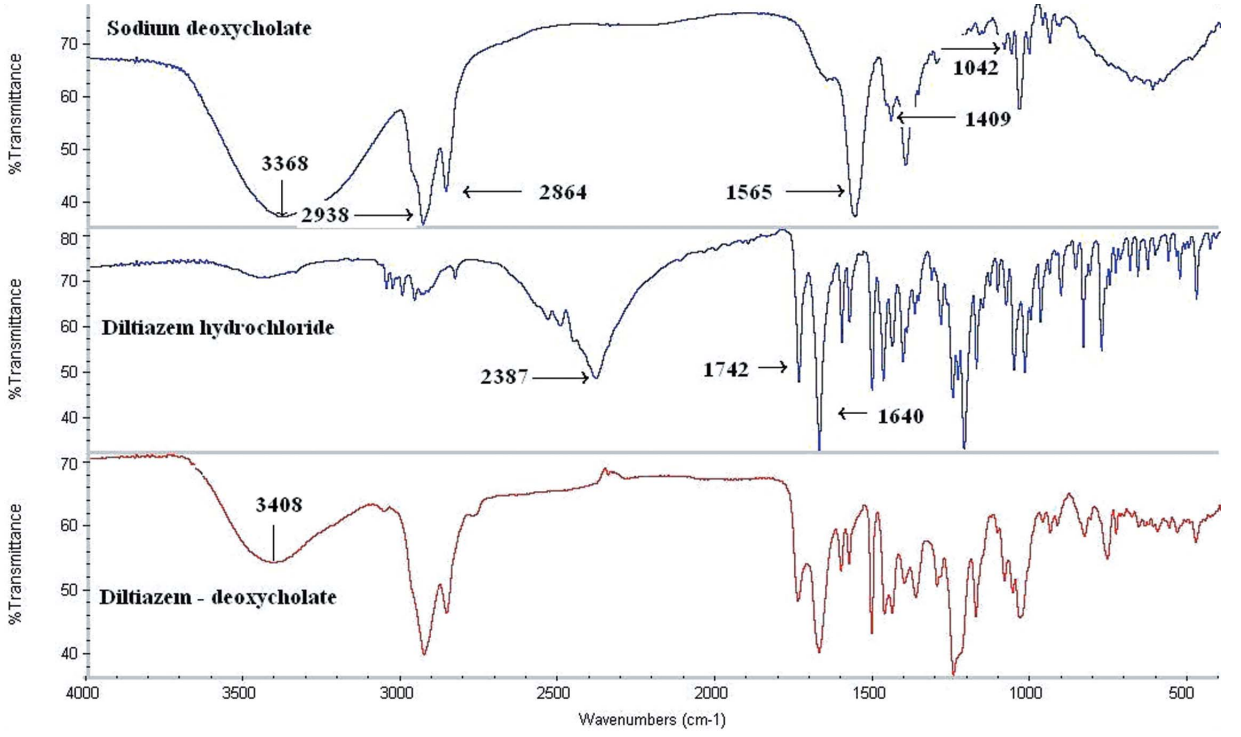


FIGURE 3. Fourier transform infrared (FTIR) spectra of Na deoxycholate, diltiazem HCl, and diltiazem–deoxycholate.

increased. At this pH, the complex dissociated, and protonation of deoxycholate gave the water-insoluble deoxycholic acid (Suzuki, Ogawa, Hironda, Ito, & Sunada, 2001). Thus, the dissociated diltiazem HCl became entrapped within the insoluble deoxycholic acid matrix and then slowly diffused out of the matrix. As the pH increased, the rate of dissolution of deoxycholate increased, and thus, a faster rate of drug release was observed. The dependence of drug release on pH was due to the dissociation of the slug-type complex tablet. One may anticipate much less dependence on pH if the complex is in a powder form. Figure 5 shows the effect of pH on the release of diltiazem from the complex/HPMC K-100LV (50 wt%) tablets. The effect of pH on drug release was greatly reduced at pH 6–8 because other governing mechanisms of drug release (e.g., polymer erosion and swelling) were added to drug release kinetics by the incorporation of HPMC. At pH 1.5, drug release was still slower than at other pHs because of the low solubility of deoxycholic acid. One may explain that drug release from the complex/HPMC tablets is governed by erosion of HPMC rather than dissociation of the complex. Upon erosion of swollen HPMC, the diltiazem–deoxycholate complex powder was added into the dissolution medium and the complex (powder) quickly dissociated. Even though incoming electrolyte might cause dissociation of the drug complex within the swollen gel, the amount of dissociation is very small, thus, one would not observe drug diffusion within the gel layer. Thus, drug release kinetics was linear or near linear except at pH 1.5. However, drug release kinetics from the

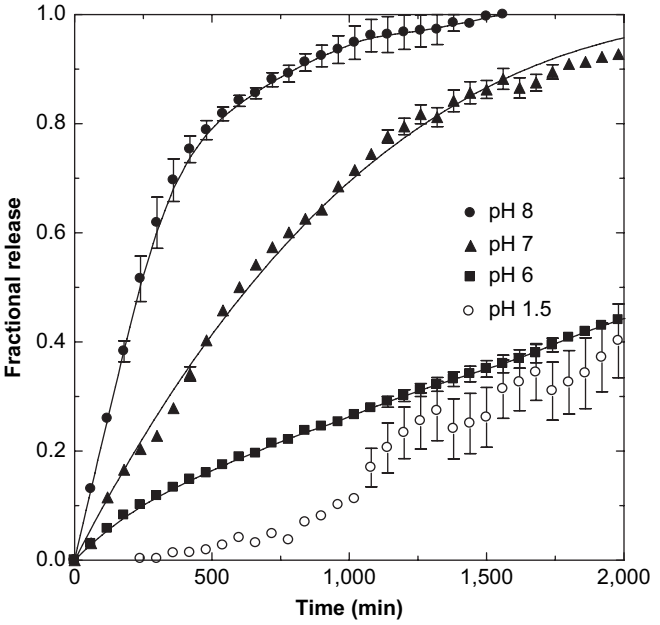


FIGURE 4. Effect of pH on the release of diltiazem from diltiazem–deoxycholate complex tablets.

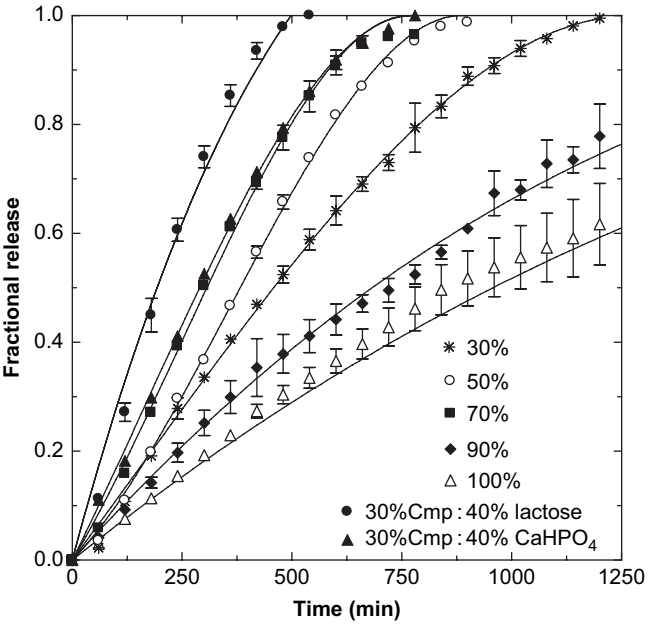


FIGURE 6. Effect of loading on the release of diltiazem from diltiazem–deoxycholate/hydroxypropylmethylcellulose (HPMC) K-100LV tablets.

diltiazem HCl/HPMC K-100LV tablets showed a rapid release followed by a slow release, indicating that drug release was based on the swelling of HPMC and drug diffusion through the swollen matrix (Narashinhan & Peppas, 1997; Pham & Lee, 1993). Figure 5 shows that linear or near linear drug release kinetics is obtained by reducing the solubility of the drug through complexation.

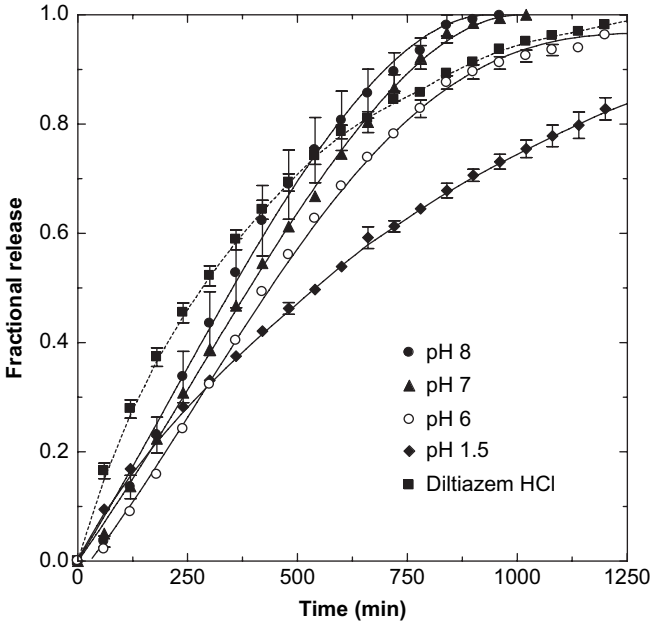


FIGURE 5. Effect of pH on the release of diltiazem from diltiazem–deoxycholate complex/hydroxypropylmethylcellulose (HPMC) K-100LV tablets.

Figure 6 shows the effect of drug loading on the release of diltiazem from the drug-complex/HPMC tablets. It has been reported that drug release kinetics moved from zero order at low loading toward first order as drug loading increased (Kim, 1998). As drug loading increased from 30 to 70%, the rate of drug release increased because of a polymer erosion-controlled system. Increasing drug loading to 90% shifted the release mechanism from a polymer erosion-controlled system to a complex dissociation-controlled system like that from 100% complex tablets, because there was a limited amount of the polymer to control drug release kinetics. Thus, drug release was slower at 90% loading than at 70%. When water-soluble polyelectrolytes are used to form a drug-polyelectrolyte complex (Konar & Kim, 1998, 1999, 2001; Nujoma & Kim, 1996), and the complex is incorporated in water-soluble drug carriers (e.g., HPMC), it is difficult to control drug release kinetics, because the drug carriers and polyelectrolytes simultaneously dissolve to release the drug. However, complexes between drugs and simple organic electrolytes allow drug release kinetics to be governed by the erosion of water-soluble polymers without involvement of drug diffusion.

When designing extended release dosage forms with different drug doses, it is better if they are of the same size, hence release kinetics will not change. In this way, one may anticipate a linear dose response—pharmacokinetic profiles. Normally, one is able to obtain superimposable release profiles

when a portion of high drug dose is replaced with a water-soluble excipient such as lactose (Kim, 1998). As shown in Figure 6, drug release profiles from 70% complex and from 30% complex with 40% lactose were not superimposable, because the complex is not water-soluble but lactose is. The water-soluble lactose excipient enhances the influx of water into the matrix so that the rate of matrix erosion becomes faster. When the water-insoluble excipient, dibasic calcium phosphate, was used instead of lactose, the two drug release profiles were superimposable.

As molecular weight or intrinsic viscosity of water-soluble polymeric drug carriers increases, drug release kinetics of water-soluble drugs moves toward nonlinear kinetics, because the synchronization process between polymer erosion and drug diffusion is not achieved in high molecular weight drug carriers (Narashinhan & Peppas, 1997; Pham & Lee, 1993). However, in this study, drug release was linear or near linear in all the cases irrespective of the viscosity grades of the polymer. This is because the controlling mechanism of drug release was by the erosion of the polymer (not drug diffusion) although drug release was found to be dependent on the different viscosity grades of HPMC (Figure 7). If one wishes to use only one polymer grade to control drug release kinetics, both HPMC K-100LV and E50 given once a day extended release tablet.

Figure 8 shows drug release profiles from different amine drugs complexed with Na deoxycholate and 50% HPMC K-100LV. Diltiazem HCl and verapamil HCl are the salts of tertiary amines, whereas propranolol HCl and labetalol HCl are the salts of secondary amines. The aqueous solubilities of diltiazem HCl, verapamil HCl, propranolol HCl, and labetalol HCl are 62, 14, 7, and 1.6%, respectively (Bari & Kim, 2006). It has been reported that the drug release rate increases with the increasing drug solubility when water-soluble drugs are incorporated into water-soluble drug carriers (e.g., HPMC and polyethyleneoxide) (Kim, 1998). For cationic drugs whose solubility is greater than 7% in water, drug release kinetics was not significantly affected by solubility and the type of amine (i.e., secondary or tertiary). However, with a water solubility of 1.6%, drug release kinetics of labetalol slightly slowed over time. This is because the rate of dissociation of labetalol/deoxycholate complex in the dissolution medium is slightly slower than the dissociation rates of other drug–deoxycholate complexes. This finding of indifferent release kinetics among cationic drugs is attributable to the water insolubility of the drug–deoxycholate complex. Thus, for drugs with solubility greater than 1.60%, drug diffusion in a drug carrier matrix becomes negligible, and drug release is controlled by the erosion of the polymer. However, for drugs with solubility less than 1.60%, one may expect slower drug release because of the slower rate of dissociation of drug–deoxycholate complex in the dissolution medium. It has been reported, however, that drug release from complexes is influenced by drug solubility when water-soluble polyelectrolytes such as PSPMK/MMA (Nujoma & Kim, 1996) and PAMPSNa/MMA (Konar & Kim, 1999) were used to form drug complexes. When bile salts are used to make drug complex for extended release dosage forms, one should take into consideration their cytotoxicity (Sakai, Imai, Ohtake, & Otagari, 1998; Shah, Palamakula, & Khan, 2004).

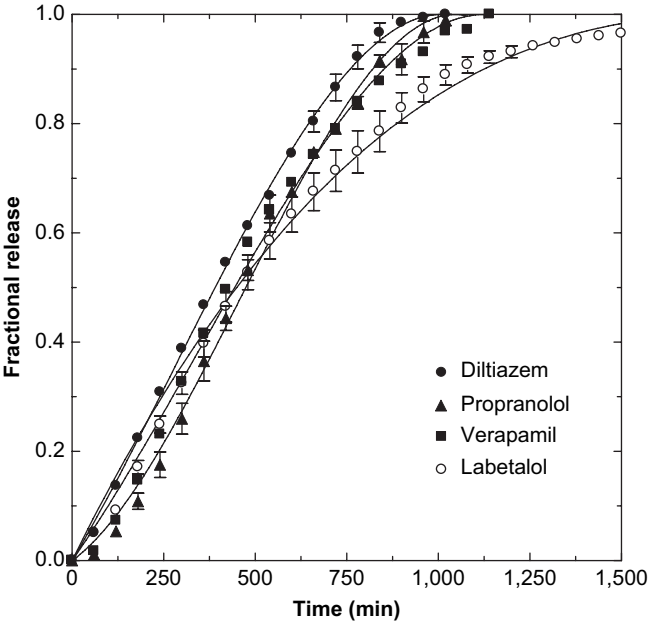


FIGURE 8. Effect of different cationic drugs on the release of the drugs from drug–deoxycholate complex/hydroxypropylmethylcellulose (HPMC) K-100LV tablets.

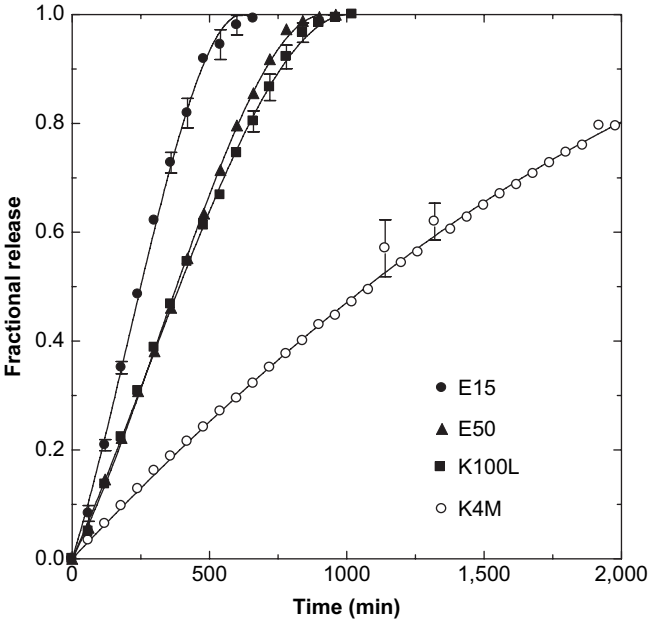


FIGURE 7. Effect of various viscosity grade hydroxypropylmethylcelluloses (HPMCs) on the release of diltiazem from diltiazem–deoxycholate/hydroxypropylmethylcellulose (HPMC) tablets.

The same approach was used for anionic drugs. In this case, *N*,*N*-dibenzene diamine diacetate (benzathine diacetate) was used to form complexes with anionic drugs (Na salicylate, naproxen Na, and tolmetin Na), as shown in Scheme 1B. As expected, the salicylate–benzathine complex precipitated upon mixing aqueous solutions of Na salicylate and benzathine diacetate. The release of Na salicylate from salicylate–benzathine complex tablets is shown in Figure 9. Unlike diltiazem–deoxycholate complex tablets, release rates of salicylate from salicylate–benzathine complex tablets at pH 1.5 and 7 were very close to each other. The dissociated salicylate became protonated (salicylic acid) at pH 1.5. However, the solubility of salicylic acid in water (0.41%) (Bari & Kim, 2006) was sufficient to quickly dissolve in the dissolution medium, whereas the solubility of deoxycholic acid at pH 1.5 for the diltiazem–deoxycholate complex was nil. As expected, release of naproxen from naproxen–benzathine complex tablets at pH 1.5 was not observed because of the negligible solubility of unionized naproxen. Superimposable release profiles at pH 1.5, 5, and 7 were obtained when the complex powders were incorporated into HPMC K-100LV carrier (data not shown). The release characteristics of salicylate–benzathine complex/HPMC K-100LV tablets were the same as those for the diltiazem–deoxycholate complex system shown earlier (Figures 6 and 7) with respect to the effects of polymer grades (HPMC E50, K-100LV, K4M) and drug complex loading in HPMC K-100LV (data not shown). Figure 10 shows the effect of anionic drugs on drug release from drug–benzathine complex/HPMC K-100LV. As observed earlier for diltiazem–deoxycholate complex/HPMC K-100LV tablets, no difference in release kinetics was observed among anionic drugs because of the drug releasing mechanism (i.e., polymer erosion) and the rapid dissociation of the complex upon casting into the dissolution medium. It has been reported, however, that drug release from anionic drug complexes is dependent on the solubility of the drugs when cationic polyelectrolytes such as PTMAEAC/MMA (Konar and Kim, 1998), PMAPTAC/MMA (Konar and Kim, 1998), and PDADMAC (Konar and Kim, 2001) are used to form the drug complexes.

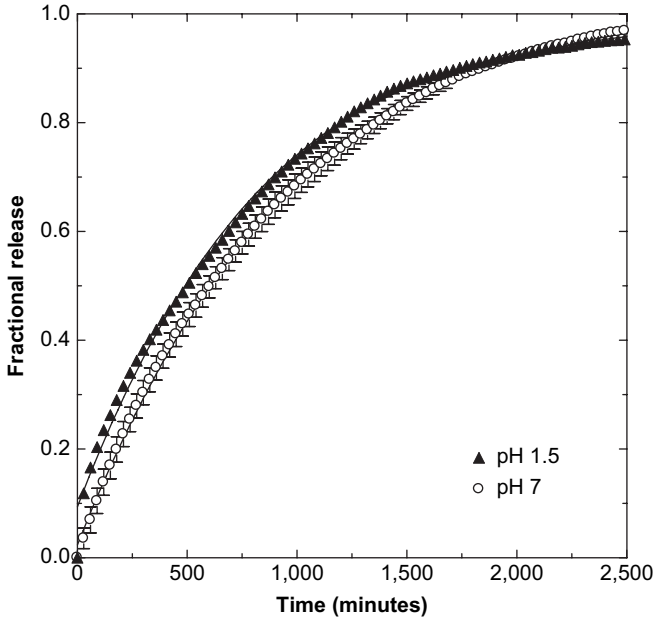


FIGURE 9. Effect of pH on the release of salicylate from salicylate–benzathine complex tablets.

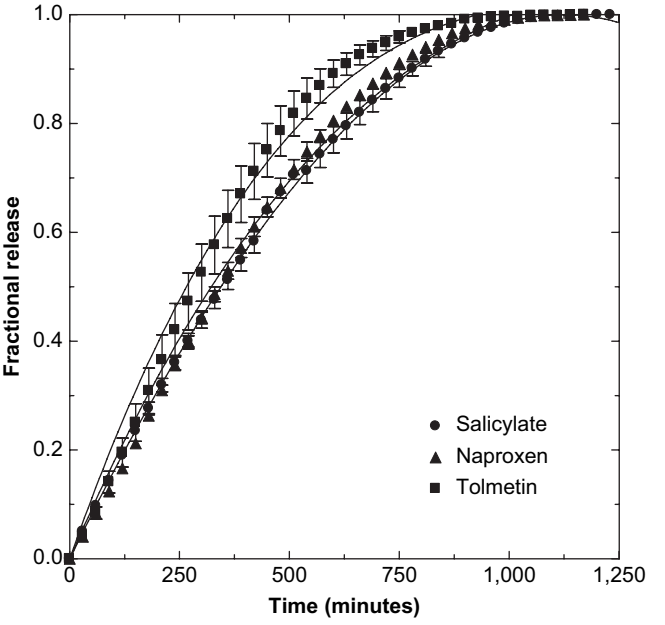


FIGURE 10. Effect of different anionic drugs on the release of the drugs from drug–benzathine complex/hydroxypropylmethylcellulose (HPMC) K-100LV tablets.

The linearity of drug release in Figures 4–10 was assessed by fitting the release data up to 60% to the phenomenological equation (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n, \tag{1}$$

where M_t, M_∞, k, and n are the amounts of drug release at time t, the total amount of drug in a tablet, a constant, and a release exponent, respectively. For diltiazem–deoxycholate complexes, the release exponent ranged from 0.71 to 1.59, as shown in Table 2, whereas for diltiazem HCl HPMC cases, the release exponent was 0.69. Excluding pH 1.5 and 6, the release exponent ranged from 0.82 to 1.59, indicating that drug release kinetics was linear or near linear. Sigmoidal release profiles were observed for the release exponent much greater than 1.0 (e.g., propranolol deoxycholate, verapamil deoxycholate, and labetalol deoxycholate). For salicylate–benzathine complexes, the release exponent was 0.53 and 0.75 for pH 1.5 and 7,

TABLE 2
Release Exponents of Drug–Organic Electrolyte Complex Tablets

	Drug/OR[a] Complex	DM[b]	n[c]
1[d]	Diltiazem/deoxycholate	pH 6	0.71 ± 0.019[e]
2[d]	Diltiazem/deoxycholate	pH 7	0.99 ± 0.051
3[d]	Diltiazem/deoxycholate	pH 8	0.99 ± 0.166
4	Diltiazem/deoxycholate	pH 6	1.28 ± 0.060
5	Diltiazem/deoxycholate	pH 7	1.09 ± 0.045
6	Diltiazem/deoxycholate	pH 8	1.24 ± 0.302
7	Diltiazem/deoxycholate	pH 1.5	0.73 ± 0.026
8	Diltiazem HCl	pH 7	0.69 ± 0.066
9[f]	Diltiazem/deoxycholate	pH 7	1.25 ± 0.244
10[g]	Diltiazem/deoxycholate	pH 7	1.08 ± 0.075
11	Diltiazem/deoxycholate (100%)	pH 7	0.85 ± 0.088
12	Diltiazem/deoxycholate (90%)	pH 7	0.82 ± 0.083
13	Diltiazem/deoxycholate (70%)	pH 7	1.26 ± 0.052
14	Diltiazem/deoxycholate (50%)	pH 7	1.26 ± 0.060
15	Diltiazem/deoxycholate (30%)	pH 7	1.04 ± 0.087
16	Diltiazem/deoxycholate K-100LV	pH 7	1.09 ± 0.045
17	Diltiazem/deoxycholate K4M	pH 7	0.90 ± 0.039
18	Diltiazem/deoxycholate E50	pH 7	1.08 ± 0.039
19	Diltiazem/deoxycholate E15	pH 7	1.23 ± 0.111
20	Propranolol/deoxycholate	pH 7	1.59 ± 0.178
21	Verapamil/deoxycholate	pH 7	1.38 ± 0.121
22	Diltiazem/deoxychoalte	pH 7	1.09 ± 0.045
23	Labetalol/deoxycholate	pH 7	1.10 ± 0.109
24[d]	Salicylate/benzathine	pH 1.5	0.53 ± 0.006
25[d]	Salicylate/benzathine	pH 7	0.75 ± 0.044
26	Salicylate/benzathine	pH 7	0.90 ± 0.040
27	Naproxen/benzathine	pH 7	1.03 ± 0.035
28	Tolmetin/benzathine	pH 7	1.08 ± 0.157

[a]Organic electrolyte.
[b]Dissolution medium.
[c]Release exponent of Equation 1.
[d]No hydroxypropylmethylcellulose (HPMC).
[e]95% confidence interval.
[f]30% complex and 40% lactose.
[g]30% complex and 40% $CaHPO_4$.

respectively. When drug–benzathine complexes were incorporated into HPMC tablets, the release exponent became 0.91–1.08, indicating linear drug release kinetics.

This concept of complexation of drug with organic electrolytes is limited to water-soluble drugs whose solubility is greater than 1.60%. If drug solubility is less than 1.60%, one may expect the slower drug release. In addition, if there is a stronger complexation between drugs and organic electrolytes, drug release rate is greatly decreased and thus once a day extended release tablets cannot be achieved. For example, we made attempts to form complexes between diltiazem HCl and disodium pamoate and atorvastatin calcium and benzathine diacetate. However, the releases of diltiazem and atorvastatin from diltiazem pamoate and benzathine atorvastatin complexes, respectively, were negligible because the ionic complex bonds were so strong that the rate of dissociation was very slow.

CONCLUSIONS

A poorly water-soluble, ionic complex was formed between diltiazem HCl and Na deoxycholate. It was characterized using DSC, ^{1}H-NMR, and FTIR. Using each technique, it was observed that key identifiable peaks from the drug and the complexing agent disappeared and new peaks

appeared upon formation of the ionic complex. Upon incorporation of the drug complex powder into hydrophilic drug carriers, such as HPMC, the influence of drug diffusion within the carrier became negligible, and drug release kinetics were governed by erosion of the carriers, leading to a linear or near linear release kinetics. Because of this erosion-controlled mechanism, linear or near linear drug release kinetics of various cationic drugs (e.g., verapamil HCl, propranolol HCl, labetalol HCl) from hydrophilic drug carrier tablets was independent of the type of amine (i.e., secondary and tertiary) but was affected by the water solubility when the drug's solubility was below 1.6%. Similar release characteristics were obtained using anionic drug–benzathine complexes.

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