In Situ Complex Systems of Drug and Organic Electrolyte for Extended Release Tablets Using HPC

Rajesh Vadlapatla, E. Kim Fifer and Cherng-ju Kim*

College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W. Markham St. Little Rock, AR 72205, USA

Abstract: *In situ* drug and organic electrolyte complex tablets were investigated as extended release dosage forms. Incorporating a 1:1 molar ratio of diltiazem HCl and an anionic organic electrolyte (i.e., Na deoxycholate) into HPC tablets extended the total release time with a near zero – order release rate (release exponent, n = 0.85 – 0.97) due to *in situ* complex formation of the drug and the organic electrolyte. When the molar ratio was less than 1 (e.g., 0.5), drug release was faster and the effect of drug diffusion was only slightly observable with n = 0.82 due to the availability of uncomplexed free drug to diffuse out of the swollen HPC gel layer. Little effect was observed for the type of amine in the drug or drug solubility on release kinetics for diltiazem HCl, verapamil HCl, and propranolol HCl. Benzathine diacetate was used as the organic electrolyte, *in situ* complexing agent for anionic drugs (e.g., Na salicylate). Even though the total extended release time was increased from 500 min to 1600 min, drug release kinetics for the *in situ* salicylate benzathine complex HPC tablets (n = 0.54 – 0.59) was not much improved compared to those of Na salicylate HPC tablets (0.40 – 0.41). Anionic drugs with low solubility (e.g., naproxen Na and tolmetin Na) showed slightly sigmoidal release profiles with n = 1.09 and 1.13, respectively. No difference in release kinetics among different cationic organic electrolytes (e.g., benzathine diacetate, aminodiphenylmethane HCl, and *N*-benzyl-2-phenethylamine HCl) for Na salicylate was found. It was found that more linear release kinetics was obtained when organic electrolytes were present in tablets more than the amount required to form 1:1 complexes with oppositely charged drugs.

Keywords: Complexation, diffusion, erosion, organic electrolytes, linear kinetics.

INTRODUCTION

Matrix-controlled drug delivery systems such as compressed tablets are common designs that are favored because they are inexpensive to manufacture. Incorporation of water-insoluble polymers into oral controlled release tablets affords Fickian release kinetics because of drug diffusion through the drug carriers. Water-soluble polymers exhibit advantages over water-insoluble polymers because the former have additional controlling mechanisms (i.e., swelling and erosion) that are lacking in the latter [1-4]. However, as drug loading and/or solubility increase, drug diffusion still plays an important role in release kinetics even with water-soluble polymers, resulting in non-linear release kinetics. Even though ion exchange resin delivery systems exhibit the square-root-time kinetics, they can load very high dose without a burst release [5].

In our laboratory several attempts were made to optimize ion exchange resin delivery systems by increasing or eliminating the rate of drug diffusion. Kim demonstrated that zero-order release kinetics were obtained for a highly water-soluble drug by synthesizing highly swellable polymer beads, the volume swelling of which was close to 20 times in size [6]. However, release time was short (6 hours). Kim and co-workers reported that water-soluble polyelectrolytes formed ionic complexes with oppositely charged: [7-10] poly(sulfopropylmethacrylate potassium/methyl methacrylate) (PSPMK/MMA), poly(acrylamido-2-methyl-1-propanesulfonate sodium/methyl methacrylate) (PAMPSNa/MMA), poly(trimethylammoniumethylmethacrylate chloride/methyl mathacrylate) (PTMAEAC/MMA), poly(methacrylamidopropyl trimethylammonium chloride/methyl methacrylate) (PMAPTAC/MMA), and poly(diallyldimethylammonium chloride) (PDADMAC). One was able to load water-soluble drugs greater than 40% and achieve zero-order release kinetics from these drug-polyelectrolyte complex tablets. However, drug release kinetics was dependent upon the water solubility of drugs and the type of amine in the drug moiety. Recently, we demonstrated that it is possible to form much less water-soluble drug complexes with organic electrolytes such as Na deoxycholate and benzathine diacetate [11]. These drug-organic electrolyte complex tablets provided not only zero-order release kinetics but also solubility and drug type independent kinetics when the complexes were incorporated in a hydrophilic drug carrier (hydroxypropylmethylcellulose, HPMC). One disadvantage of preformed drug-complex forming technique obtaining zero-order release controlled release matrices is that the drug-complex becomes a new chemical entity that vigorous clinical evaluation should be carried out.

Pillay and Fassihi showed that zero-order release kinetics of diltiazem HCl from HPMC tablets were obtained when alkali salts (e.g., Na_2HPO_4) were incorporated in a tablet formulation [12]. The presence of the alkali salt in the HPMC tablets raised the internal pH within the tablets, and

*Address correspondence to this author at the College of Pharmacy, University of Arkansas for Medical Sciences, 4301 W. Markham St. Little Rock, AR 72205, USA; Tel: (501) 686-5090; Fax: (501) 526-6510;
E-mail: ckim@uams.edu

1874-1266/10

thus diltiazem HCl became a deprotonated diltiazem free base, the solubility of which is very low, and the rate of polymer erosion governed release kinetics. It has been shown that zero-order release kinetics was obtainable for a system having a low drug dissolution rate and a high drug diffusion rate [13, 14]. Sriwongjanya and Bodmeier incorporated ion exchange resins as a physical mixture with a drug in HPMC matrix tablets to modify release kinetics of oppositely charged drugs [15]. Upon contact with water, a swollen gel layer formed around the drug carrier (HPMC), and a complex between the drug and the resin formed *in situ* within the swollen gel, resulting in the same release kinetics as HPMC tablets containing preformed drug-resin complexes. Thus, drug diffusion through the gel layer became negligible and release kinetics was controlled by erosion of the drug carrier with a near zero-order rate.

In this study the effect of *in situ* complex of organic electrolytes on the release of oppositely charged drugs in HPC-based hydrophilic matrix tablets was investigated.

MATERIALS AND METHODS

Materials

All materials were used as received. Na deoxycholate and benzathine diacetate were purchased from Mann Research Laboratories (New York, NY) and NBS Biologicals (Cambridge, England), respectively. Aminodiphenylmethane (ADPM) HCl and *N*-benzyl-2-phenethylamine (NBPEA) HCl were purchased from Aldrich Chemical (Milwaukee, WI). Sodium phosphate monobasic, potassium phosphate dibasic, hydrochloric acid, and sodium chloride were obtained from Fisher Scientific (Fair Lawn, NJ). Diltiazem HCl, propranolol HCl, verapamil HCl, Na salicylate, naproxen Na, and tolmetin Na were purchased from Sigma Chemical (St. Louis, MO). Hydroxypropylcelluloses M (HPC) was generously supplied by Nisso Nippon Soda Co., LTD (Tokyo, Japan). Water was distilled and de-ionized through a Milli Q Synthesis A10 (Waters, Boston, MA). Simulated intestinal fluids were prepared with 0.01 *M* phosphate buffer at pH 7 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. The precipitate was washed free of soluble ingredients, dried, and triturated in a mortar and pestle.

PREPARATION OF TABLETS

Tablets (10.5 mm diameter) of 300 mg total weight containing the preformed complex (153.6 mg) and HPC or 300 mg total weight containing 146.4 mg HPC and drug with or without excipient (e.g., organic electrolyte) were compressed under 2000 lb compression force using a flat punch in a Carver press (Wabash, IN). Detailed tablet compositions are listed in Table **1**.

Aqueous Solubility of Preformed Complexes

Solubility studies of preformed complexes (diltiazem deoxycholate and salicylate bezathine) and tolmetin Na were carried out in an aqueous solution at 25°C using an Agilent 8453A diode-array UV/Vis spectrophotometer. An excess amount of complex powder was dissolved in purified water with vigorous shaking. After allowing for settling for 10 days to attain equilibrium, the mixture was centrifuged. The supernatant was collected, diluted, and the UV/Vis spectrum was analyzed.

DRUG RELEASE STUDY

Drug release kinetics from tablets was carried out in simulated gastric and intestinal fluids, as well as in water, at 37° C by the USP basket method (900 mL) at 100 rpm. The concentration of drug in dissolution media was measured on an Agilent 8453A diode-array UV/Vis spectrophotometer (Wilmington, DE) at 278 nm, 287 nm, 296 nm, 315 nm, 330 nm, and 360 nm for diltiazem HCl, propranolol HCl, verapamil HCl, Na salicylate, naproxen Na, and tolmetin Na, respectively. Linearity of drug release was assessed by fitting the release data up to 60% to the phenomenological equation: [16].

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

where M_t is the amount of drug released at time t, M_∞ is the total amount of the drug in the tablet, k is a constant, and n is the release exponent.

When drug release kinetics is controlled by erosion of a swollen gel layer with no drug diffusion, the following kinetic expression may be used: [17].

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_e}{r_o}t\right)^2 \left(1 - \frac{2k_e}{l}t\right) \tag{2}$$

where r_o, l, and k_e are the tablet radius, tablet thickness, and the erosion rate constant, respectively. The later portion of drug release profile greatly affects release kinetic shape and the determination of erosion rate constant. Thus, up to 90% release data were used to evaluate whether release data might be expressed by Equation (2). Regression analysis (Graph Pad, San Diego, CA) of Equations (1) and (2) was performed and a 95% confidence level was calculated.

RESULTS AND DISCUSSION

One of the problems associated with matrix controlled systems is that drug release is controlled by drug diffusion through polymeric drug carriers (i.e., water – soluble and water – insoluble polymers), resulting in non – zero order release kinetics. In order to eliminate or minimize drug diffusion on the overall release kinetics, preformed complex tablets had been employed to achieve zero – order or near zero – order release kinetics [11]. However, a pre-formed complex between an ionic drug and an oppositely charged organic electrolyte (e.g., Na deoxycholate) creates a new chemical entity that must be completely tested before it can be introduced as a drug into the market whereas the physical mixture of drug and Na deoxycholate, which is a GRAS

Table 1. Detailed Tablet Compositions and Release Exponents

Composition							
	HPC	**Drug**		**Lactose**	**OE[c]**	**Dis. Med[e]**	**n[q]**
1	146.4[a]	Dlt[b]	153.6	0	NDC[d] 0	pH 1.5	0.63±0013[f]
2	146.4	Dlt	153.6	0	NDC 0	pH 7	0.65±0.013
3	146.4	Dlt	153.6	0	NDC 0	water	0.64±0.093
4	146.4	Dlt	80.0	0	NDC 73.6	pH 1.5	0.67±0.021
5	146.4	Dlt	80.0	0	NDC 73.6	pH 7	0.89±0.027
6	146.4	Dlt	80.0	0	NDC 73.6	water	0.85±0.014
7	146.4	PFDD[g]	153.6	0	0	pH 1.5	0.63±0.025
8	146.4	PFDD	153.6	0	0	pH 7	0.98±0.034
9	146.4	PFDD	153.6	0	0	water	1.00±0.029
10	129.4	Dlt	45.5	104.3	NDC 20.8	pH 7	0.82±0.035
11	129.4	Dlt	45.5	83.4	NDC 41.7	pH 7	0.85±0.080
12	129.4	Dlt	45.5	41.7	NDC 83.4	pH 7	0.86±0.038
13	129.4	Dlt	45.5	0	NDC125.1	pH 7	0.97±0.082
14	146.4	Dlt	80.0	0	NDC 73.6	pH 7	0.89±0.027
15	146.4	Vpm[h]	83.3	0	NDC 70.3	pH 7	1.04±0.027
16	146.4	Prp[i]	64.0	0	NDC 89.6	pH 7	0.86±0.016
17	146.4	Nsl[j]	153.6	0	BNZ[k] 0	pH 7	0.41±0.026
18	146.4	Nsl	153.6	0	BNZ 0	pH 1.5	0.59±0.030
19	146.4	Nsl	153.6	0	BNZ 0	water	0.40±0.031
20	146.4	Nsl	72.3	0	BNZ 81.3	pH 7	0.54±0.030
21	146.4	Nsl	72.3	0	BNZ 81.3	pH 1.5	0.56±0.018
22	146.4	Nsl	72.3	0	BNZ 81.3	water	0.59±0.038
23	146.4	SBNZ[l]	153.6	0	0	pH 7	0.97±0.042
24	146.4	SBNZ	153.6	0	0	pH 1.5	0.70±0.008
25	146.4	SBNZ	153.6	0	0	water	0.91±0.045
26	146.4	Nsl	47.3	0	BNZ106.3	pH 7	0.82±0.028
27	146.4	Nsl	47.3	53.2	BNZ 53.1	pH 7	0.62±0.047
28	146.4	Nsl	47.3	79.7	BNZ 26.6	pH 7	0.53±0.039
29	146.4	Nsl	72.3	0	BNZ 81.3	pH 7	0.60±0.063
30	146.4	Tmn[m]	71.7	0	BNZ 81.9	pH 7	1.13±0.039
31	146.4	Npn[n]	63.3	0	BNZ 90.3	pH 7	1.09±0.035
32	146.4	Nsl	72.3	0	BNZ 81.3	pH 7	0.60±0.063
33	146.4	Nsl	64.8	0	ADPM[o] 88.8	pH 7	0.54±0.030
34	146.4	Nsl	60.3	0	NBPEA[p] 93.3	pH 7	0.60±0.027

a: mg; b: diltiazem HCl; c: organic electrolyte; d: Na deoxycholate; e: dissolution medium;
f: 95% confidence interval; g: preformed diltiazem deoxycholate; h: verapamil HCl; i: propranolol HCl;
j: Na salicylate; k: benthazine diacetate; l: salicylate benzathine; m: tolmetin Na; n: naproxen Na;
o: aminodiphenylmethane HCl; p: N-benzyl-2-phenethylamine HCl; q: release exponent of Eq.(1).

material, does not require. Therefore, in this study ionic drugs and their counter ionic organic electrolytes are directly formulated into a water – soluble polymer in order to obtain extended release dosage forms. As shown in Fig. (**1a**), non-linear drug release profiles were obtained from HPC tablets containing only diltiazem HCl. In this study HPC M was chosen because it gives a viscosity of 400 cps in 2% solution in water whereas HPMC does not have this viscosity grade. As shown in Table **1**, the release exponent, n, was 0.63 – 0.65 because drug diffusion through a swollen gel layer of HPC contributed greatly to drug release kinetics. Drug release in water was faster than in buffered media (pHs 1.5 and 7) because the buffered media had higher ionic strength than water, so that higher osmotic forces exerted to the tablets. However, when a portion of diltiazem HCl was replaced with Na deoxycholate and the molar ratio of the drug and Na deoxycholate was 1, drug release was greatly slowed and its kinetics was close to near zero – order rate with a slight initial burst and release exponent of n = 0.85 – 0.89, as shown in Fig. (**1b**). Even though the *in situ* complex system involves simultaneously drug diffusion, swelling, complex formation, polymer dissolution, one is able to pinpoint which mechanisms are dominant for release kinetics based on the preformed complex and non-complex tablets. However, a single, exact release mechanism cannot be known. When the HPC tablets were in contact with an aqueous medium, HPC, the water – soluble drug, and the excipient absorbed water, and HPC became a gel at the surface allowing water to penetrate further into the matrix. As soon as the drug and Na deoxycholate were in contact with each other in an aqueous environment inside the tablets, they formed an *in situ* complex as shown in Scheme **1**. Thus, drug diffusion was retarded compared to those from HPC tablets containing no Na deoxycholate. Because the *in situ* complex was already hydrated in an aqueous environment, a small portion diltiazem deoxycholate was dissolved and dissociated by the incoming electrolyte and diffused out to the dissolution medium. Even if the complex was dissociated, there was an interaction between the two ingredients before the swollen gel eroded because of superimposibility with drug release profiles from *in situ* complex HPC tablets in water and pH 7. Unlike Fig. (**1a**), drug release from HPC tablets at pH 1.5 was much faster than at pH 7 and water, because at pH 1.5 Na deoxycholate became deoxycholic acid and would not form a complex. Thus, the dissociated drug diffused out of the tablet at a faster rate, showing a release exponent of n = 0.67. When multi-valent electrolytes (e.g., $CaCl_2$) replaced NaCl in the release medium, the similar release profiles (Fig. **1b** at pH 1.5) were expected due to the formation of Ca(deoxycholate)$_2$ that did not allow forming a complex.

Drug release from *in situ* complex HPC tablets was faster than from preformed complex HPC tablets, Fig. (**1c**), because the preformed complex (i.e., diltiazem deoxycholate) tablets absorbed water at a slower rate than the *in situ* drug and Na deoxycholate tablets. The addition of Na deoxycholate enhanced the water penetration into the tablets and thus polymer swelling and erosion rates became faster. The finding that drug releases at pH 7 and water from *in situ* and preformed complex tablets were superimposable suggests that drug release was controlled by polymer erosion once the drug and Na deoxycholate formed *in situ* complexes. As

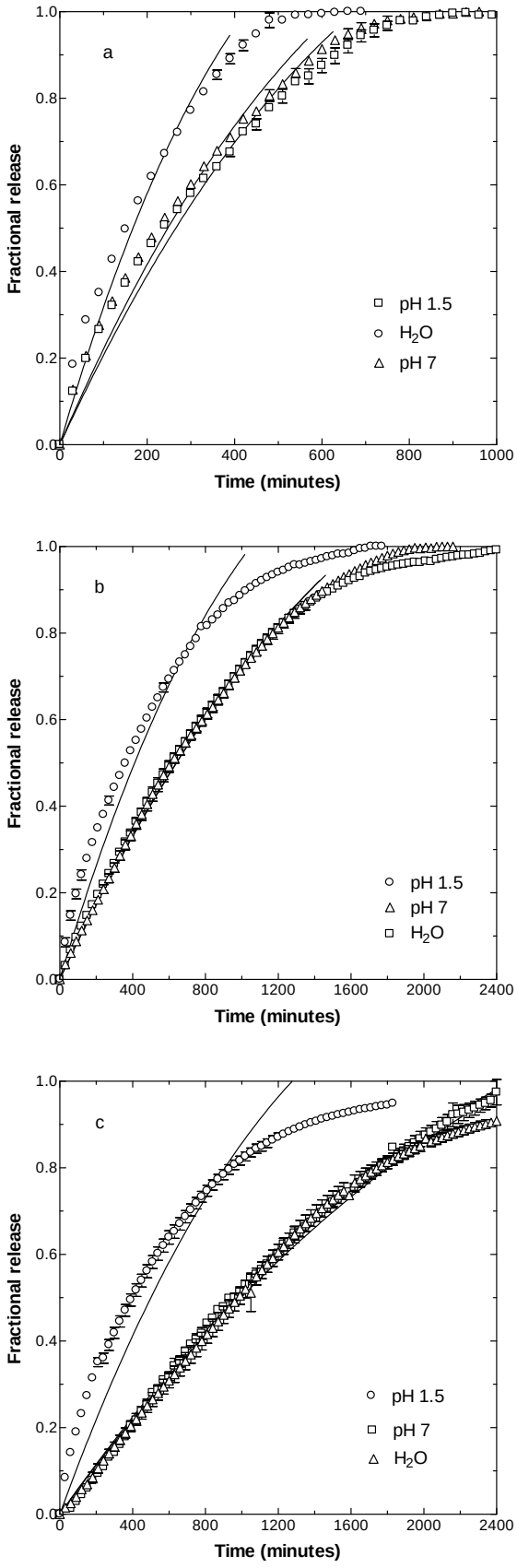
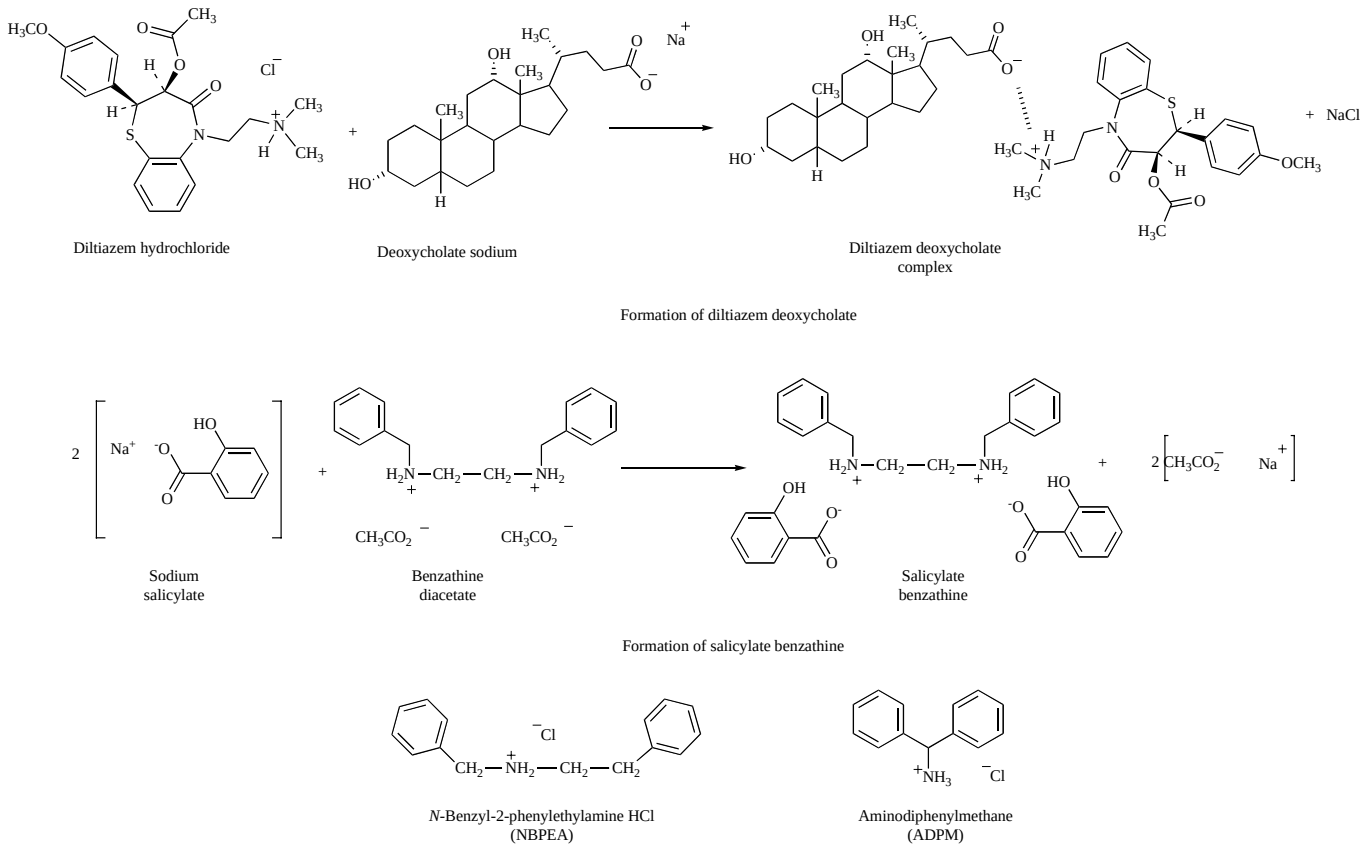


Fig. (1). Release of diltiazem HCl from HPC tablets: **a**) without Na deoxycholate; **b**) with Na deoxycholate; **c**) preformed diltiazem deoxycholate (lines calculated by Eq. (2)).



Scheme 1. *In situ* complex formation and organic electrolytes.

shown in Fig. (**1b**, **1c**), drug release kinetics from preformed complex tablets were rendered more linear, with n = 0.98 – 1.00, than that from *in situ* complex tablets (n = 0.85 – 0.89) because drug diffusion took place slightly before complexation, and the complex was already hydrated. The concept of using a simple organic electrolyte to lower the solubility of drug and achieve near zero –order release kinetics is very similar to the incorporation of alkaline salts or ion exchange resins into water – soluble polymer drug carriers [12, 15]. Pillay and Fassihi [12] reported that the release of diltiazem HCl from HPMC tablets incorporated with alkaline salts such as, Na_2HPO_4, etc. became a zero – order because Na_2HPO_4 in the tablets raised the internal pH upon the influx of water into so that diltiazem HCl became the poorly soluble diltiazem free base. Sriwongjanya and Bodmeier [15] employed ion exchange resins in HPMC tablets containing diltiazem HCl. When the tablets were placed in the dissolution medium, the dissolved drug in the matrix formed complexes with oppositely charged resins, and thus, there were not much free drugs in the matrix. Drug release kinetics was controlled by the erosion of HPMC because there was no contribution of drug diffusion toward the overall drug release kinetics. In the present study, a highly water – soluble drug (i.e., diltiazem HCl) whose solubility is 63% [18] was bound to deoxycholate upon the hydration of HPC tablets, leading to the formation of much less water – soluble complex (i.e., diltiazem deoxycholate) whose solubility is 0.12%. The rate of dissolution of diltiazem deoxycholate is very low and thus, drug release kinetics was governed by the erosion of the HPC matrix. Equation (2) expresses the release profiles of *in situ* complex and preformed complex HPC tablets (Fig. **1b**, **1c**), indicating that drug release kinetics is governed by the erosion of swollen polymer. When drug diffusion through a swollen gel layer is a dominating factor, Equation (2) predicts much lower values than those experimentally observed (Fig. **1a**).

The effect of molar ratio of Na deoxycholate to diltiazem HCl on the release of the drug from *in situ* complex HPC tablets at pH 7 is shown in Fig. (**2**). Release of the drug from tablets containing the molar ratio of 0.5 was faster than those from the other ratios (1 to 3). When the amount of Na deoxycholate was less than that required to form a 1:1 complex with the drug, the excess uncomplexed drug diffused out of the tablets *via* Fickian diffusion kinetics like Fig. (**1a**). However, the contribution of Fickian diffusion from tablets of the uncomplexed drug to the overall release kinetics was smaller than those having no Na deoxycholate because only half of diltiazem HCl in the HPC tablets was released *via* drug diffusion (n = 0.82). Drug release profiles from tablets containing a molar ratio greater than one were nearly superimposable because the entire drug present in the tablets was complexed and there was no excess free drug. As the molar ratio increased over 1, more linear release kinetics was obtained (n = 0.85, 0.86, and 0.97 for the ratio of 1, 2, and 3, respectively). In this experiment (Fig. **2**) the amounts of HPC and drug were fixed as 129.4 mg and 45.5 mg, respectively and the rest was Na deoxycholate and lactose to make up the total weight of tablet of 300 mg. The data used in Fig. (**1b**) were obtained with 146.4 mg of HPC and the molar ratio of 1 between diltiazem HCl and Na deoxycholate to make up the total weight of 300 mg. Fig. (**1b**, **2**) show that extended

release tablets may be designed such that once the drug dose is chosen, the equi- or higher molar amount of Na deoxycholate is determined and the amount of HPC (in this case) and viscosity grade determine the total release time. Equation (2) slightly underestimated release profile of the molar ratio of 0.5 due to the early drug diffusion of uncomplexed free drug.

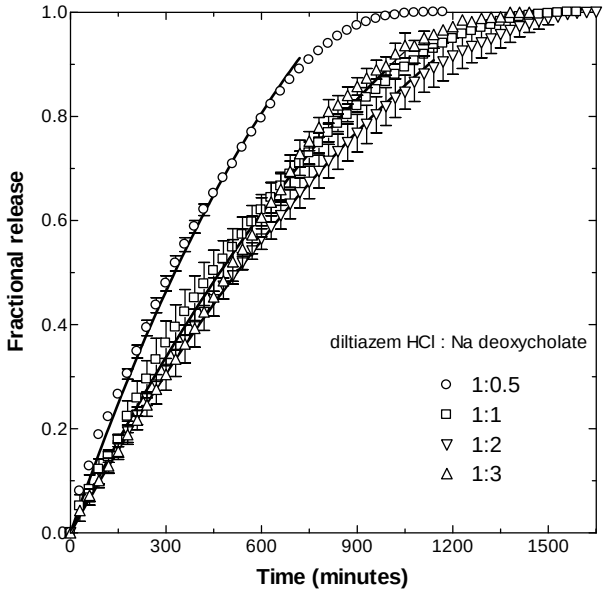


Fig. (2). Effect of molar ratio of diltiazem HCl to Na deoxycholate on the release of diltiazem HCl from *in situ* complex HPC tablets (lines calculated by Eq. (2)).

The effect of the type of amine drug and solubility on drug release from *in situ* complex HPC tablets in pH 7 is shown in Fig. (**3**). The drugs tested in this study have a wide range of solubility (7% - 63%) [18] and are basic drugs containing secondary or tertiary amine functional groups. As shown in Fig. (**3**), there is little variation in release among the drugs tested. For example, drug release kinetics is very similar between the secondary amine propranolol HCl and the tertiary amine verapermil HCl and their solubilities are 7% and 14%, respectively. The release exponents were n = 0.86 and 0.89 for propranolol HCl and verapamil HCl, respectively. While diltiazem HCl and verapamil HCl are both tertiary amine drugs, their solubilities differ greatly (63% and 14%, respectively) but little difference on drug release kinetics was observed. *In situ* verapamil deoxycholate gave better linear release kinetics (n = 1.04) than *in situ* propranolol deoxycholate (n = 0.88). It has been reported that drug release profiles from preformed complex tablets were superimposable among the drugs tested in this study [11]. Equation (2) was well suited for release profiles for different amine drugs. Kim and co-workers found that drug release kinetics from complex tablets made between amine drugs and anionic polyelectrolytes was dependent on drug solubility and amine type [7-10]. Unlike a simple organic electrolyte such as Na deoxycholate, polyelectrolytes have many ionic functional pendant groups that can form complexes with oppositely charged drugs. The physicochemical properties and drug release kinetics of polyelectrolyte complexes may be dependent on the type and solubility of the drug.

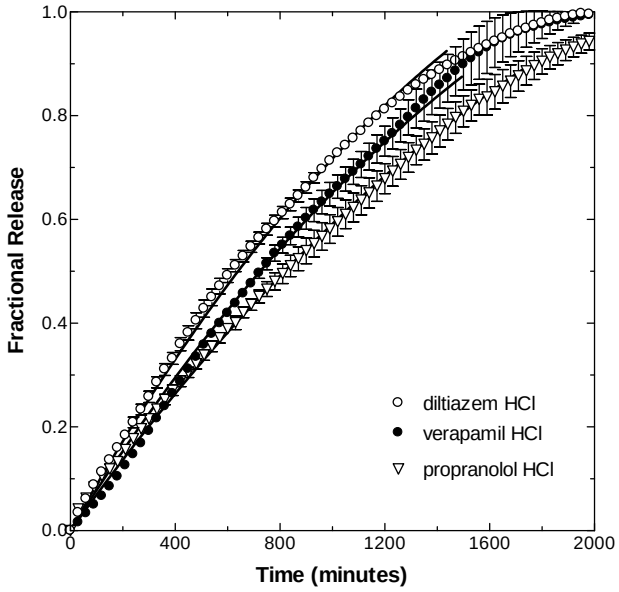


Fig. (3). Effect of drug's amine type and solubility on the drug release from *in situ* complex tablets (line calculated by Eq. (2)).

The same concept of lowering the solubility of a drug by complexation with an oppositely charged organic electrolyte may also be applied to anionic drugs. In this case, benzathine diacetate, NBPEA, and ADPM, as shown in Scheme **1**, were used. The release of Na salicylate from HPC tablets at pH 1.5 and 7 and water is shown in Fig. (**4a**) and release exponents ranged from 0.40 to 0.56 for both water and pH 7. For diltiazem HCl tablets, drug release was faster in water than at pHs 1.5 and 7. Whereas for Na salicylate the release of drug was slower at pH 1.5 than in either water or pH 7. At pH 1.5, Na salicylate (solubility is 45.7%) [18] in HPC tablets, became salicylic acid (solubility is 0.41%) [18], resulting in a slower release. Benzthine diacetate has two secondary amines, and thus, it requires two moles of Na salicylate for one mole of benzthine diacetate. When benzathine diacetate was incorporated at a 2 (Na salicylate) :1 (benzathine diacetate) molar ratio in HPC tablets, salicylate release was much slower than from tablets without benzathine diacetate (Fig. **4b**), and release exponents were in the range of 0.54 to 0.59. Upon infiltration of water into HPC tablets, benzathine diacetate reacts with Na salicylate to form an ionic complex precipitate (i.e., salicylate benzathine) whose solubility is 0.14%. Once the complex has formed, drug release was governed by erosion of HPC and drug diffusion through swollen HPC gel. Unlike Fig. (**1b**) where release of diltiazem was faster at pH 1.5, release of Na salicylate was superimposable at pHs 1.5, 7, and in water. At pH 1.5, Na salicylate became salicylic acid whose solubility is close to the solubility of the salicylate bezathine complex and thus, the release of Na salicylate at pHs 1.5 and 7 or water was superimposable. However, one postulates that an ionic bond between benzathine and salicylate is weaker than the ionic bond between diltiazem and deoxycholate, and thus, initially faster drug release was observed for *in situ* salicylate benzathine complexes. In addition, it seems that the rate of formation of *in situ* complex between Na salicylate and benzathine diacetate was slower than between diltiazem HCl and Na deoxycholate and more drug diffusion was observed. Thus, Equation (2) did not express well the release profiles of *in situ* complex HPC

tablets. The release of salicylate from preformed complex HPC tablets extended longer and was more linear (n = 0.91 and 0.97 in water and pH 7, respectively) than that from *in situ* complex HPC tablets because the in – situ complex was already hydrated and the preformed complex must become hydrated before it can dissociate.

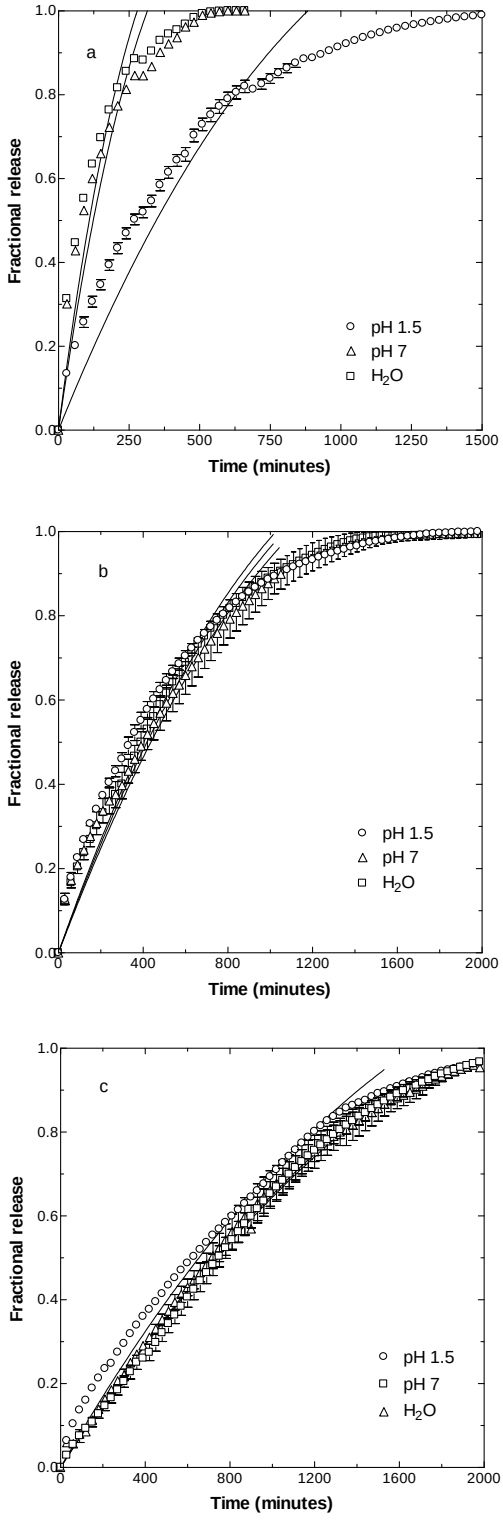


Fig. (4). Release of salicylate from HPC tablets: **a**) without benzathine diacetate; **b**) with benzathine diacetate; **c**) preformed salicylate benzathine (lines calculated by Eq. (2)).

The effect of the molar ratio of Na salicylate and benzathine diacetate on release of salicylate from *in situ* complex HPC tablets at pH 7 is shown in Fig. (**5**). When the molar ratio was 4, there was excess free uncomplexed drug available to diffuse through the swollen HPC gel, and thus, the initial burst release rate increased as the molar ratio increased. As observed for the *in situ* diltiazem – deoxycholate complex, drug release kinetics for the *in situ* salicylate benzthine complex system became more linear when excess cationic organic electrolytes was present than the amount required to form a 2:1 complex with Na salicylate. Molar ratio of 1:1 has more protonated amine functional groups available than required to form a complex with Na salicylate. Equation (2) describes the *in situ* complex tablet of 1:1 molar ratio. Thus, n = 0.53, 0.62, and 0.82 were obtained for the ratio of 4, 2, and 1, respectively. As the molar ratio increased, drug release kinetics was governed more by a drug diffusion mechanism than by polymer erosion.

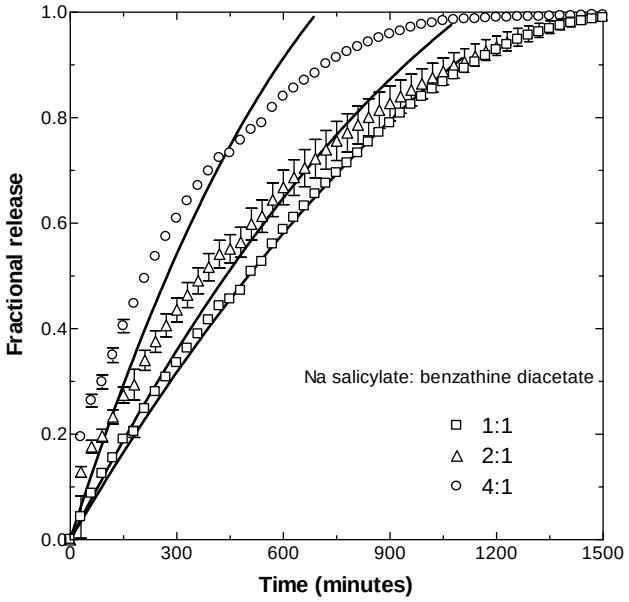


Fig. (5). Effect of molar ratio of Na salicylate to benzathine diacetate on the release of Na salicylate from *in situ* complex HPC tablets (lines calculated by Eq. (2)).

The effect of drug solubility on drug release from benzathine drug complex HPC tablets at pH 7 is shown in Fig. (**6**). Release of salicylate from *in situ* complex HPC tablets was faster than that for naproxen or tolmetin. The solubility of Na salicylate (49.7%) is greater than that of naproxen Na (14.7%) and tolmetin Na (14.9%), which leads to the weaker complex formation of Na salicylate over naproxen Na and tolmetin Na. Thus, the initial burst release of salicylate (n = 0.60) and slightly sigmoidal release of naproxen Na and tolmetin Na (n = 1.09 and n = 1.13, respectively) were observed. Eq. (2) overestimated drug release at early time due to the sigmoidal profile of naproxen Na and tolmetin Na.

Drugs with different types of amine functional groups were evaluated for use with Na deoxycholate as shown in Fig. (**4**). However, there are not many types of acidic functional groups in bioactive drugs, with the most common

being the carboxylic acid. For anionic drugs, organic electrolytes having primary or secondary amines were evaluated as shown in Fig. (**7**). ADPM HCl and NBPEA HCl are cationic primary amine and secondary amines, respectively, and benzathine is a cationic organic electrolyte having a secondary diamine. As shown in Fig. (**3**) for Na deoxycholate, where cationic amines did not have much effect on much drug release kinetics. For anionic drugs release kinetics was superimposable for different cationic organic electrolytes with release exponents ranging from n = 0.54 to n = 0.60.

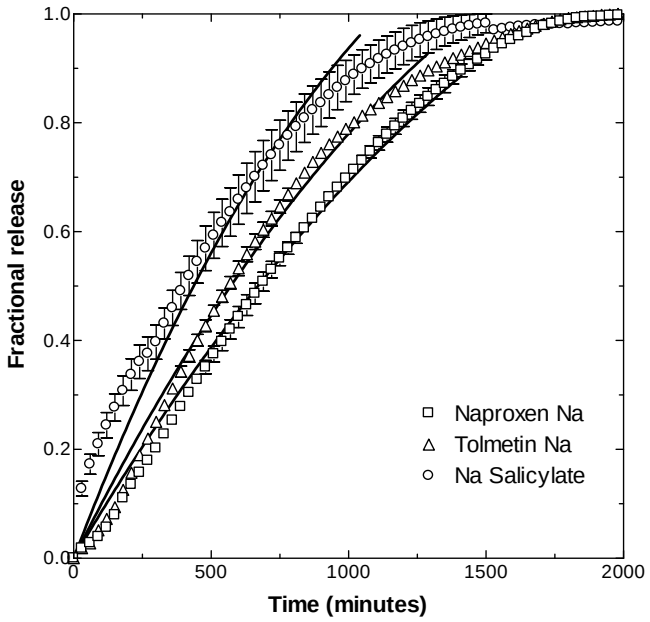


Fig. (6). Effect of drug solubility on the drug release from *in situ* complex tablets (lines calculated by Eq. (2)).

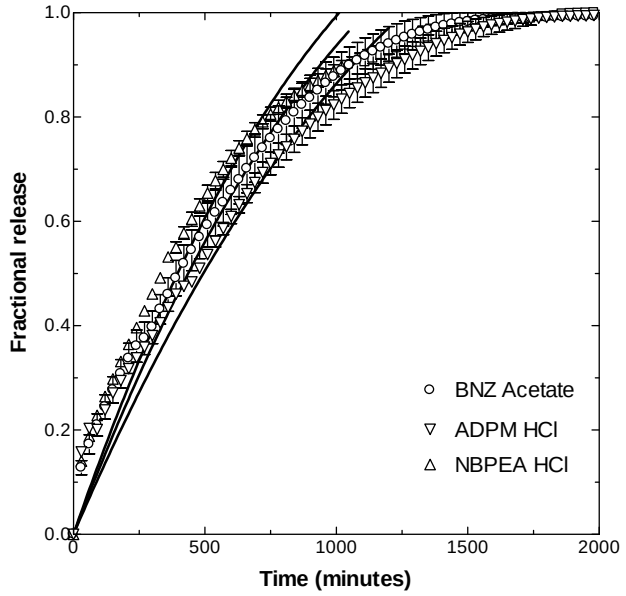


Fig. (7). Effect of cationic organic electrolytes on the release of salicylate from *in situ* complex tablets (lines calculated by Eq. (2)).

CONCLUSIONS

Incorporation of organic electrolytes into extended release tablets containing oppositely charged drugs further extended the total release time. Diltiazem HCl tablets with a Na deoxycholate produced more linear release kinetics than those without it. This linear release kinetics is due to formation of *in situ* complex in the tablets that leads to decreased drug solubility, and at the same time, drug diffusion through the swollen gel layer becomes negligible. As found in the case of preformed complex, drug release from these *in situ* complex tablets is governed by the erosion of polymers. Because the *in situ* complex forms in an aqueous environment, less linearity was observed than with preformed complex HPC tablets because *in situ* complex was already hydrated. However, cationic organic electrolytes did not increase the linearity of the drug release kinetics even though the total release time was greatly extended. One may postulate that the ionic interactions between anionic drugs and cationic organic electrolytes are weaker than that between these cationic drugs and anionic organic electrolytes (i.e., Na deoxycholate). The former gives less linear release kinetics than the latter. This approach can be extended to combination systems of cationic drugs and anionic organic excipients, and anionic drugs and cationic organic excipients.

REFERENCES

[1] Kydonieus, A., Ed. *Treatise on Controlled Drug Delivery;* Marcel Dekker: New York, **1992**.

[2] Kim, C. J. *Controlled Release Dosage Form Design;* Technomic Publishing Co.: Lancaster, PA, **1999**.

[3] Pham, A. T.; Lee, P. I. Probing the mechanism of drug release from hydroxypropylmethyl cellulose (HPMC) matrices. *Proc. Int. Symp. Control Release Bioact. Mater.*, **1993**, *20*, 220-221.

[4] Narashinhan, B.; Peppas, N. A. Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier. *J. Pharm. Sci*., **1997**, *86*, 297-305.

[5] Raghunathan, Y.; Amsel, L.; Hinsvark, O.; Bryant W. Sustained-release drug delivery system I: Coated ion-exchange resin system for phenylpropranolamine and other drugs. *J. Pharm. Sci*., **1981**, *70*, 379-382.

[6] Kim, C. J. Hydrogel beads for oral drug delivery. *Chemtech.*, **1994**, *24*(8), 36-39.

[7] Nujoma, Y. N.; Kim, C. J. A designer's polymer as an oral drug carrier (tablet) with pseudo zero-order release kinetics. *J. Pharm. Sci*., **1996**, *85*, 1091-1094.

[8] Konar, N.; Kim, C. J. Water-soluble quaternary amine polymers as controlled release carriers (tablets). *J. Appl. Polym. Sci*., **1998**, *69*, 263-265.

[9] Konar, N.; Kim, C. J. Drug release from drug-polyanion complex tablets: poly(acrylamido-2-methyl-1propanesulfonate sodium -co-methyl methacrylate). *J. Control Release*, **1999**, *57*, 141-145.

[10] Konar, N.; Kim, C. J. Drug release of ionic drugs from water-insoluble drug-polyion complex tablets. In: *Polymeric Drugs & Drug Delivery Systems*, Ottenbrite, R. M., Kim, S. W., Eds.; Technomic Publishing Co.: Lancaster, PA, **2001**; pp. 69-85.

[11] Vadlapatla, R.; Fifer, E. K.; Alexander, K. S.; Kim, C. Drug – organic electrolyte complexes as controlled release systems. *Drug Dev. Ind. Pharm*., **2009**, *35*, 1-11.

[12] Pillay, V.; Fassihi, R.. Electrolyte-induced compositional heterogeneity: A novel approach for rate-controlled oral drug delivery. *J. Pharm. Sci*., **1999**, *88*, 1140-1148.

[13] Chang, N. J.; Himmelstein, K. J. Dissolution-diffusion controlled constant-rate release from heterogeneously loaded drug-containing materials. *J. Control Release*, **1990**, *12*, 201-211.

[14] Kim, C. J. Effects of drug solubility, drug loading, and polymer molecular weight on drug release from POLYOX tablets. *Drug. Dev. Ind. Pharm*., **1998**, *24*, 645-654.

[15] Sriwongjanya, M., Bodmeier, R. Effect of ion exchange resins on the release from matrix tablets. *Eur. J. Pharm. Biopharm*., **1998**, *46*, 321-327.

[16] Ritger, P. L.; Peppas, N. A. A simple equation for description of solute release II. fickian and anomalous release from swellable devices. *J. Control Release*, **1987**, *5*, 37-43.

[17] Zhang, G. H.; Vadimo, W. A.; Chaudy, I. Drug release from erodible tablets. *Proc. Int. Symp. Control Release Bioact. Mater*., **1990**, *17*, 331-332.

[18] Bari, M. M. *Noncross-Linked And Cross-Linked Ampholytic Polymers For Controlled Release Carriers*. Ph.D. Thesis, Temple University, Philadelphia, PA, **2001**.

Received: October 07, 2009 Revised: November 30, 2009 Accepted: November 30, 2009