Iranian Journal of Pharmaceutical Research (2009), 8 (4): 241-249
Received: October 2008
Accepted: May 2009

Original Article

In Situ Cross-Linking of Polyanionic Polymers to Sustain the Drug Release from Theophylline Tablets

Majid Saeedi[a,b*], Jafar Akbari[a], Reza Enayatifard[a], Katayoun Morteza-Semnani[b, c], Masoumeh Tahernia[a] and Hadi Valizadeh[d]

[a]*Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.* [b]*Pharmaceutical Sciences Research Center, Mazandaran University of Medical Sciences, 20th km. of Khazar road, Sari, Iran.* [c]*Department of Medicinal Chemistry, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.* [d]*Department of Pharmaceutics, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.*

Abstract

The aim of this study was to develop an extended-release tablet formulation using a new in situ cross-linking method. The effects of polyvalent cations on theophylline release from tablets made with the polyanionic polymers sodium alginate and sodium carboxymethylcellulose, were investigated. Different miliequivalents of the di and tri-valent cation, Ca^{2+} and Al^{3+}, were added to tablet formulations. The results of the dissolution study showed that incorporation of cations sustained the drug release. This is due to an in situ cross-linking between the polyanionic polymers and the added cation in tablet formulation. The drug release prolongation and the release kinetics were dependent on the nature of the polymers and the cations' concentrations and valences. The drug release rate decreased by an increase in cation concentration. The combination of the two investigated polymers decreased the drug release rate to a higher extent in comparison with formulations containing each polymer alone. A zero-order drug release kinetic was observed in formulations containing 1:1:1 ratio of drug: Na alginate: NaCMC, and the investigated cations. These results showed that the in situ cross-linking by polyanionic polymers can be used for controlling the drug release rate.

Keywords: In situ cross-linking; Theophylline; Sodium alginate; NaCMC; Release; Kinetic.

Introduction

Theophylline, an alkaloid found in the leaves of the *Cameliai sinesis* is used clinically as a bronchodilator in management of Chronic Obstructive Pulmonary Disease (1). Conventional dosage forms of theophylline are administered 3-4 times a day to avoid large fluctuations in plasma concentration (2). Sustained-release dosage forms, on the other hand, provide desirable serum concentrations for prolonged period, thereby providing better patient compliance.

Hydrophilic gel-forming matrix tablets are widely used for oral controlled-release dosage forms, owing to the ease of manufacturing and their cost effectiveness. Numerous polymer, such as polysaccharides, have been used in the tablets. They relax in the presence of water to form a gel layer around the tablet (3). In these formulations, factors affecting the in vitro drug release such

* Corresponding author:
E-mail: majsaeedi@yahoo.com

as drug/polymer ratio, polymer viscosity, and the amount of additives have been studied from the view point of formulation design (4).

Recently, the use of natural polymers in designing the drug delivery systems has received much attention due to their excellent biocompatibility and biodegradability (5). Sodium alginate is a biopolymer that is widely used as an encapsulation matrix due to its ability to form hydrogel upon cross-linking. Its ability of gel forming under mild conditions makes alginate the polymer-of-choice in food, pharmaceutical and biotechnological applications. Alginates are linear unbranched copolymers of β-D-manuronic acid (M) and α-L-guluronic acid (G) units. The M and G monomers are 1→4 linked by glycosidic bonds, forming homopolymeric M- or G-blocks and heteropolymeric MG blocks. In the presence of polyvalent cations such as Ca^{2+} or Al^{3+}, cross-linking occurs to form gels. The cations act as bridges between the anionic polymer chains, constituting junction zones, forming a hydrogel network (6). Ca^{2+}, a commonly used cross-linker, preferentially interacts with G-blocks due to structurally favorable chelation sites formed by the corrugated chains (7). Hence, selective ion binding is formed with the of G-blocks (8). Due to the selective ion binding, cross-linking of alginates of different chemical compositions results in gels with different properties (9).

Sodium carboxymethylcellulose (NaCMC), another polyanionic polymer, is widely used in oral controlled-release matrices (10-14). Its good compression properties, nontoxic nature, and the ability to accommodate a large percentage of drugs are some of the reasons for its popularity (15).

Researchers have used cross-linking as a means to retard the drug release from alginate matrix tablets. Azarmi et al. (16) have reported a reduced drug release rate at pH 7.4 with increasing calcium chloride dihydrate concentration (0.75-19% w/w) incorporated into alginate matrices of Acetazolamide. Nokhodchi and Tailor (5) observed slower theophylline release only at high (21% w/w) calcium salt content. At intermediate calcium salt contents (11.8 and 16.7% w/w), initial burst release was observed followed by a slower drug release. Drug release was rapid at low calcium salt concentration (3.8% w/w) and this was attributed to insufficient cross-linking to produce an insoluble barrier.

The objective of the present work was to demonstrate the ability of Ca^{2+} and Al^{3+} to induce an in situ inter- and intra-cross-linking of polyanionic polymers in tablet formulations. We investigated the effects of the in situ cross linking on the release rate of theophylline.

Experimental

Materials

The tablets were prepared using the following ingredients: theophylline (Daru-pakhsh Co., Tehran, Iran), sodium alginate (Fluka, Switzerland), sodium carboxymethylcellulose (NaCMC) (viscosity of the 1% solution at 25°C is 1240 cps) (Daicel Chemical, Osaka, Japan), calcium chloride di-hydrate ($CaCl_2.2H_2O$) and aluminium chloride hexa-hydrate ($AlCl_3.6H_2O$) (Riedel-de Haen, Seelze, Germany), NaOH, KCl, HCl, magnesium stearate (Merck, Germany) and potassium di-hydrogen phosphate (Fluka, Switzerland).

Methods

Preparation of matrix tablets

A series of formulations containing a fixed amount of theophylline (100 mg), different amounts of sodium alginate (50-100 mg) and/or NaCMC (50-100 mg), and increasing amounts of $CaCl_2.2H_2O$ or $AlCl_3.6H_2O$ were sufficiently blended for 10 min. Magnesium stearate (1% w/w) was then added, followed by further mixing for 2 min. The resultant powder mixture was then compressed into tablets using a single punch machine (Korsch, Germany), with 10-mm diameter flat punch. All matrices were stored in a desiccator for at least 3 days to allow for tablet relaxation before use.

Dissolution studies

The United State Pharmacopoeia (USP) basket method was used for all the in vitro dissolution studies. In this method, a solution of HCl in distilled water (pH=1.2), and phosphate buffer (pH 6.8) both without enzymes, were used as dissolution media. The dissolution profile of theophylline was studied according to the USP basket method at 100 rpm, in 900 ml of medium maintained at 37.0 ± 0.5°C in a dissolution tester

(Caleva 8ST). The amount of theophylline was 100 mg in all formulations. The matrices were placed in 900 ml of the HCl solution (pH=1.2) for 2 h. Samples were withdrawn at predetermined time intervals (0.5, 1, 1.5, and 2 h), filtered and assayed specterophotometerically at 271.5 nm by using UV/Visible spectrophotometer (Varian, Australia). After 2 h, the dissolution medium was changed to phosphate buffer (pH=6.8). Samples were withdrawn at predetermined time intervals (3, 4, 5, 6, 7, and 8 h), and analyzed according to the perviously mentioned method. The mean of four determinations was used to calculate the drug release from each formulation.

Data treatment

Various mathematical equations have been proposed for kinetic analysis of drug release from the formulations. The zero order Eq. 1 describes the systems where the drug release rate is independent of the drug concentration (17). The first order Eq. 2 describes the release from systems where the release rate is concentration dependent (18). According to Higuchi model Eq. 3, the drug release from insoluble matrix is directly proportional to the square root of time and is based on Fickian diffusion (19).

$$Q_t = k_0 t \quad \text{(Eq. 1)}$$

$$Ln\ Q_t = ln\ Q_0 - k_1 t \quad \text{(Eq. 2)}$$

$$Q_t = k_H t^{1/2} \quad \text{(Eq. 3)}$$

In these equations, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in tablet and k_0, k_1 and k_H are the release rate constants for zero order, first order and Higuchi models, respectively.

In order to define a model which representing the best, dissolution data can be further analyzed by Ritger and Peppas and Korsemayer equation (20, 21).

$$M_t / M_\infty = K_p t^n \quad \text{(Eq. 4)}$$

Where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, K_p is a constant and "n" is the release exponent indicating the type of drug release mechanism. In cylindrical shape matrices, a release exponent of 0.45 can serve as an indication for Fickian diffusion. If $0.45 < n < 0.89$ anomalous transport could be concluded, and if "n" approaches to 0.89 the release mechanism can be described as polymer swelling. Criteria for selecting the most appropriate model based on best goodness of fit and smallest sum of squared residuals (22).

Statistical analysis

ANOVA followed by Tukey test was used to determine significant differences between groups and "$P < 0.05$" was considered as significant.

Results and Discussion

Table 1 shows the composition of the individual formulations. Figure 1 shows the drug release from sodium alginate formulations. As seen in Figure 1, Al^{3+} and Ca^{2+} caused a prolonged drug release in these formulations till 3 hours ($P < 0.0001$), but after 4 h this effect was not significant. Increasing the amount of cations in formulations did not show any decrease in theophylline release rate after 3 h ($P = 0.825$ for formulations containing Al^{3+} and $P = 0.517$ for formulations containing Ca^{2+}). In these formulations, comparison of the tablets containing similar miliequivalents of the two cations showed that Al^{3+} decreased the drug release rate to a higher extent compared to Ca^{2+} before 3 h ($P = 0.003$ and $P = 0.001$ for comparing F5 to F7 and F6 to F8, respectively).

The dissolution rate data were analyzed based on Eqs. 1-4 and their results were listed in Table 2. The results showed that in formulations containing sodium alginate in a sodium alginate: drug ratio of 1:1 (F1 and F5-F8), the addition of Al^{3+} and Ca^{2+} had no effect on the release kinetic of theophylline, and the highest correlation coefficients were achieved with the first-order model. By increasing the amounts of the cations, the release exponent (n) increased compared to F1. The lowest value ($n = 0.503$) was obtained for formulation F1 containing no cation, and adding the amount of the cation increased this value. The values of n showed that in F1, the release of theophylline was only controlled by diffusion, whereas in the presence of cations, the mechanism of release was slightly complex.

The presence of cations was able to extend the

Table 1. Composition of theophylline matrix formulations.

Code No.	Formulation constituents (mg)				
	Theophylline	Na alginate	NaCMC	$AlCl_3$	$CaCl_2$
F1	100	100	-	-	-
F2	100	-	100	-	-
F3	100	50	50	-	-
F4	100	100	100	-	-
F5	100	100	-	14.7	-
F6	100	100	-	50	-
F7	100	100	-	-	13.3
F8	100	100	-	-	45.2
F9	100	-	100	14.7	-
F10	100	-	100	50	-
F11	100	-	100	-	13.3
F12	100	-	100	-	45.2
F13	100	50	50	14.7	-
F14	100	50	50	50	-
F15	100	50	50	-	13.3
F16	100	50	50	-	45.2
F17	100	100	100	14.7	-
F18	100	100	100	50	-
F19	100	100	100	75	-
F20	100	100	100	100	-
F21	100	100	100	-	13.3
F22	100	100	100	-	45.2
F23	100	100	100	-	67.8
F24	100	100	100	-	90.4

drug release process. This phenomenon is related to an in situ gel formation between the cations and the anionic polymer. The occurrence of in situ gel formation depends on concentrations of the cations (23). In optimum concentration, the calcium chloride is able to cross-link more efficiently with the sodium alginate because a greater quantity of calcium ions is available to bind. As there is more calcium ions to bind, a better and stronger gel is formed around the matrix and this strong gel does not allow the dissolution medium to penetrate into the matrix at a high speed, resulting in a reduction in release rate (5).

Figure 2 shows the drug release from NaCMC formulations. As seen in Figure 2, Al^{3+} and Ca^{2+} caused a prolonged drug release from these formulations ($P < 0.0001$). The formulation series F9-F10 and F11-F12 contain equal miliequivalents of Al^{3+} and Ca^{2+}. In these formulations, Al^{3+} decreased the drug release to a higher extent compared to formulations containing Ca^{2+}.

The results of kinetic analysis showed that in formulations containing NaCMC in 1:1 ratio of NaCMC: drug in 1:1 ratio (F2 and F9-F12), the addition of Al^{3+} changed the release kinetic of theophylline. In F2, which contained none of the cations, the highest correlation coefficient was achieved with the first-order model. Al^{3+} did not change the drug release kinetic in F9, but by increasing the amount of this cation in F10, the best fitting was observed in Higuchi model and based on n value (n = 0.4304) the mechanism of drug release was based on Fickian diffusion. Ca^{2+} caused no change in the release kinetic of

Table 2. The release kinetic data of different formulations.

Formulation code	Zero-order model			First-order model			Higuchi model			Peppas model			
	K_0	r^2	*ss*	K_1	r^2	*ss*	K_H	r^2	*ss*	K_p	*n*	r^2	*ss*
F1	0.0012	0.691	51937	-0.0132	0.954	187	0.0366	0.823	16430	0.0669	0.5036	1.000	0.0
F2	0.0009	0.461	64389	-0.0086	0.919	6160	0.0272	0.599	33292	-	-	-	-
F3	0.0016	0.910	31646	-0.0083	0.959	1539	0.0466	0.969	515	0.0559	0.4613	0.979	49
F4	0.0017	0.935	28547	-0.0086	0.960	2520	0.0481	0.978	415	0.0421	0.5220	0.966	188
F5	0.0013	0.754	47769	-0.0119	0.966	245	0.0392	0.874	11671	0.0562	0.5363	0.996	6.3
F6	0.0014	0.781	44636	-0.0117	0.949	258	0.0413	0.895	8298	0.0499	0.5519	0.995	8.6
F7	0.0014	0.786	42207	-0.0111	0.949	263	0.0431	0.898	5880	0.0395	0.5958	0.993	14.6
F8	0.0015	0.782	40781	-0.0101	0.972	115	0.0440	0.895	4623	0.0285	0.6644	1.000	0.1
F9	0.0014	0.977	26727	-0.0032	0.992	5878	0.0383	0.987	569	0.0500	0.4301	0.963	201
F10	0.0013	0.962	24092	-0.0028	0.985	6318	0.0361	0.975	472	0.0454	0.4304	0.938	472
F11	0.0015	0.854	34025	-0.0050	0.953	3753	0.0432	0.939	1135	0.0377	0.5474	0.946	183
F12	0.0013	0.893	34099	-0.0036	0.976	7507	0.0389	0.965	1157	0.0360	0.5446	0.966	199
F13	0.0014	0.985	25861	-0.0035	0.975	4832	0.0392	0.985	706	0.0510	0.4276	0.970	160
F14	0.0014	0.985	22646	-0.0032	0.978	4432	0.0389	0.983	2611	0.0339	0.4969	0.965	374
F15	0.0016	0.921	28703	-0.0066	0.969	11571	0.0467	0.974	558	0.0466	0.4822	0.972	73
F16	0.0017	0.971	22471	-0.0061	0.961	1966	0.0479	0.989	3298	0.0326	0.5420	0.984	141
F17	0.0014	0.992	4564	-0.0023	0.962	3610	0.0373	0.956	91969	0.0051	0.7760	0.981	733
F18	0.0011	0.960	9149	-0.0017	0.917	3016	0.0298	0.921	45828	0.0065	0.7103	0.973	1055
F19	0.0009	0.974	7890	-0.0013	0.945	2947	0.0253	0.936	54106	0.0050	0.7224	0.972	1097
F20	0.0009	0.983	6512	-0.0012	0.962	2846	0.0237	0.943	68688	0.0042	0.7365	0.959	1656
F21	0.0014	0.985	13593	-0.0029	0.967	1007	0.0403	0.985	26113	0.0106	0.6923	0.988	270
F22	0.0014	0.992	4843	-0.0025	0.958	4200	0.0390	0.955	87044	0.0063	0.7405	0.979	572
F23	0.0012	0.995	4938	-0.0020	0.971	3375	0.0343	0.955	86538	0.0050	0.7688	0.969	1367
F24	0.0009	0.986	8283	-0.0012	0.964	3211	0.0243	0.949	48634	0.0053	0.7076	0.972	1010

theophylline in comparison with F2.

In formulation series F13-F16, both polymers (sodium alginate and NaCMC) were used in a ratio of 1:1:2 to the drug. The effect of cations on the release profile of Theophylline is shown in Figure 3. These profiles show that the mixture of the two investigated polymers decreased the drug release rate more than the F1 and F2 (each containing only one polymer). Also, Al^{+3} decreased the drug release rate more prominently than Ca^{2+}. This decrease in release rate was more than those in F5-F8 which contained sodium alginate, and less than those in F9-F12 which contained NaCMC.

The kinetic analysis showed that in formulations containing sodium alginate: NaCMC: drug in 1:1:2 ratio (F3 and F13-F16), the presence of Al^{3+} changed the release kinetic of theophylline. In F3, which contained none of the investigated cations, the highest correlation coefficient was achieved with the Higuchi model and based on the n value (n = 0.461), the drug release can be expressed as Fickian mechanism. Al^{3+} did not change the drug release kinetic in F13 (n = 0.428), but by increasing the amount of this cation in F14, the anomalous transport was observed (n = 0.497). Ca^{2+} caused no change in the release kinetic of theophylline in comparison with F3.

The next formulations (F4 and F17-F24) were designed with equal amounts of the two polymers and the drug (1:1:1, sodium alginate: NaCMC: drug). Figures 4 and 5 show the drug release from these formulations. The decreasing effect of the investigated cations on drug release rate was proved to be significant in these formulations (P < 0.001). Al^{3+} decreased the drug release rate to a higher extent compared to Ca^{2+} (P = 0.002 for

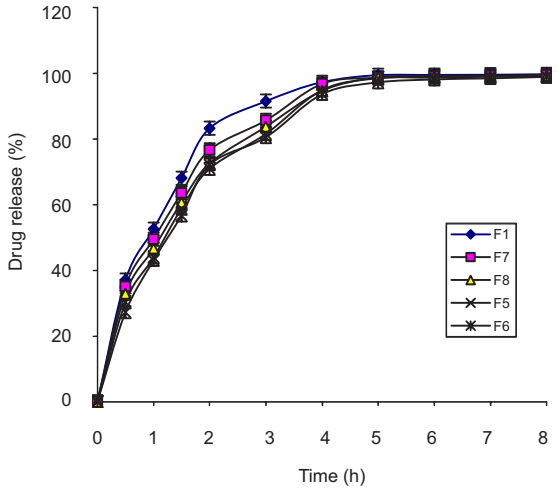

Figure 1. Drug release from the sodium alginate: theophylline (1:1) formulations containing Al^{3+} and Ca^{2+}.

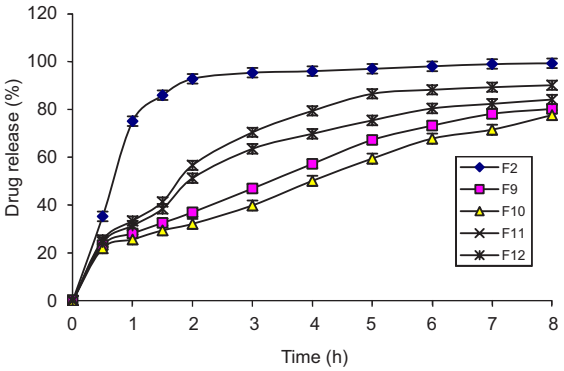

Figure 2. Drug release from the NaCMC: theophylline (1:1) formulations containing Al^{3+} and Ca^{2+}.

comparison of F20 and F24).

The kinetic analysis showed that in these formulations, adding of Al^{3+} changed the release kinetic of theophylline. In F4, which contained none of the investigated cations, the highest correlation coefficient was achieved with the Higuchi square root of time model. By increasing the amount of Al^{3+} (F17-F20), the fitted model was the in zero-order. In the presence of Ca^{2+} the anomalous mechanism was observed in drug release kinetic in F21 (n = 0.692). However, by increasing the amount of this cation in F22-F24, the best fittings were observed in zero-order model.

The release exponents (n) were increased in comparison with F4 by an increase in the amounts of the cations. The lowest value (n = 0.522) was obtained for formulation F4 containing no cation, and the presence of the cations increased this value. The values of n showed that in F4, the release of drug was only controlled by diffusion, whereas in the presence of cations, the mechanism of release was slightly complex.

The interaction between polyvalent cations like Al^{3+} and Ca^{2+} and negatively charged polymers like NaCMC or sodium alginate has been used in the past to prepare drug loaded microspheres (24, 25). We investigated the effects of the inclusion of low amounts of cations into Theophylline tablet formulations containing polyanionic polymers individually and in combination. The addition of Al^{3+} and Ca^{2+} extended the drug release process. This phenomenon is related to an in situ gel formation between the cations and the anionic polymers. The occurrence of in situ gel formation depends on concentrations of the cations (24-29). The mechanism of gelation of sodium alginate with calcium was studied by Vauthier et al. using rheological measurements (26). They reported that alginate solution with a concentration just below the gel point formed swollen aggregates of alginate molecules in the continuous phase in presence of calcium ion. The gelation progress seemed to pass through a pre-gel state corresponding to clusters of alginate molecules before a continuous and infinite gel was formed. Remunan-Lopez and coworkers showed that the drug permeability from sodium alginate films varied with the calcium chloride concentration used (27). Dave et al. showed that the release of indomethacin from sustained release pellets of sodium alginate was dependent on the concentration of calcium chloride: a slower drug release was obtained when the concentration of calcium chloride increased (28). Bodmeier and coworkers showed that the disintegration time of alginate beads was a function of the counter-ion concentration (29). In another study, Hosny et al. showed that the release rates of diclofenac sodium from sodium carboxymethylcellulose and sodium alginate beads were dependent on concentrations of the calcium and aluminum ions in solution (25). Azarmi and coworkers

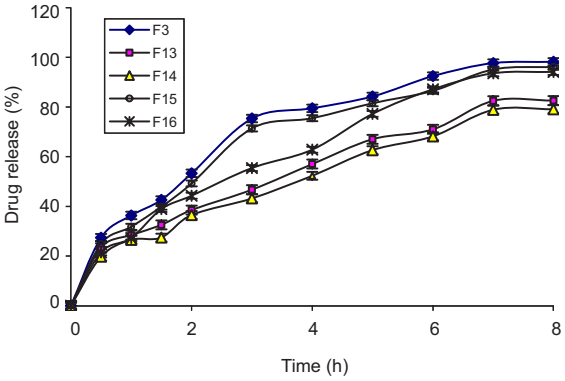

Figure 3. Drug release from the sodium alginate: NaCMC: theophylline (1:1:2) formulations containing Al^{3+} and Ca^{2+}.

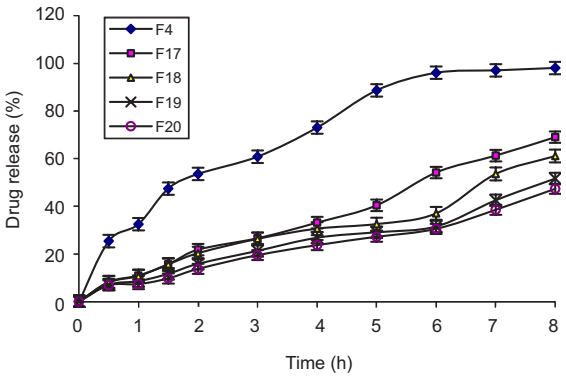

Figure 4. Drug release from the sodium alginate: NaCMC: theophylline (1:1:1) formulations containing Al^{3+} .

reported the same results in acetazolamide matrix tablets (16).

Our study showed that the NaCMC formulation (F2) had a burst drug release during the first 60 min. The burst release was also observed in sodium alginate formulation (F1). The occurrence of the burst release can be attributed to the time needed for gel formation. This phenomenon was observed for other formulations except for formulations F17-F24, presumably due to the higher polymer contents.

After the tablet is brought into contact with an aqueous medium, the calcium and aluminum salts and the drug dissolve from the tablet surface and diffuse into the bulk solution. Water penetrates through the pores left by the dissolved drug molecules and calcium and aluminum salts. The anionic polymer chains of the NaCMC and sodium alginate begin to swell. Molecules, which now dissolve from the tablet body, have to diffuse through the swelled polymer chains. The polyvalent cations can cross-link the anionic polymer chains:Ca^{2+}can cross-link two and Al^{3+} up to three strains of polymer chains. A viscous gel is formed on surface of the tablets. In all the investigated formulations, Al^{3+} decreased the drug release rate more than the same miliequivalents of Ca^{+2}. This might be due to the higher valence of Al^{3+}. As shown in Figure 1 to 3 the cross-linking and gel formation was faster in case of higher cation concentrations. Evaluation of the effects of these cations on the both polymers showed that Al^{3+} and Ca^{2+} were more effective on NaCMC. This is in accordance with the results reported by Hosney et al. (24). The same results were also reported by Azarmi and coworkers. Their results showed that aluminum and calcium ions caused a prolonged drug release for acetazolamide matrices containing NaCMC. Increasing the amounts of the cations in formulations decreased the release rate of acetazolamide. The study showed that the formulations containing Al^{3+} decreased the drug release rate to a higher extent compared to formulations containing Ca^{2+} (16).

Nokhodchi and Taylor showed that formulations of theophylline (with different amounts of the drug and sodium alginate) containing equal moles of $AlCl_3$ and $CaCl_2$, produced different release profiles. The formulation containing aluminum chloride decreased the drug release rate to a higher extent compared to formulations containing calcium chloride. Aluminum ions have an extra positive charge compared to calcium ions thus each molecule of aluminum is able to bind to one more alginate molecule. Because of this, the aluminum was capable of forming a gel, which did not allow the dissolution medium to quickly enter the tablet, more quickly. Thus, the dissolution rate was lower compared to the formulation containing the same number of moles of calcium chloride (5). It seems that Al^{3+} can produce cross-linking in three sites but Ca^{2+} produce it in two sites. This difference in valence should affect the gel network, and the drug release rate.

In our study, the combinations of the two polyanionic polymers were also evaluated. The results showed that the decreasing effect on the

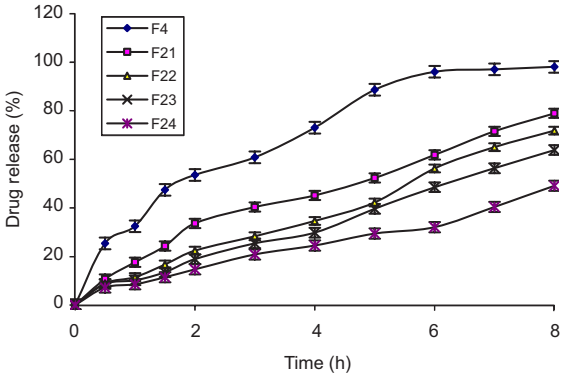

Figure 5. Drug release from the sodium alginate: NaCMC: theophylline (1:1:1) formulations containing Ca^{2+} .

release rate from the combination formulations with the same ratio to drug (F13-F16) were significantly higher ($P < 0.01$) in comparison with formulations containing only sodium alginate (F5-F8). Increasing the polymer content in F17-F24 resulted in the highest decrease in release rate ($P < 0.0001$). This also resulted in a change in the release kinetic. Nokhodchi et al. showed that the addition of HPMC can alter the drug release profile by an additional mechanism. They showed that the presence of HPMC in alginate matrices containing various concentrations of calcium chloride and aluminum chloride had a considerable effect on the release profile of theophylline. Their results showed that in producing a sustained release formulation by cross-linking, with the aid of HPMC a lower concentration of cation can be used to get the same or better release profile (5). In our study, it seems that combination of the two polyanionic polymers led to inter- and intra-cross-linking between the polymeric chains. This explains the stronger decrease in release rate and the kinetic behaviour of the related formulations.

References

(1) Soeterboek AM and Jonkman JHG. Clinical pharmacokinetic aspects of theophylline. In: Merkus FWHM. (ed.) *The Serum Concentrations of Drugs: Clinical Relevance, Theory and Practice.* 8th ed. Excerpta Medica Press, Amsterdam (1980) 250-259.

(2) Mellstand T, Svedmyr N and Fagerstorm PO. Absorption of theophyllinee from conventional and sustained release tablets. *Eur. J. Respir. Dis. Suppl.* (1980) 109: 54-61.

(3) Lotfipour F, Nokhodchi A, Saeedi M, Nouruzi-sani S, Sharbafi J and Siahi-Shadbad MR. The effect of hydrophilic and lipophilic polymers and fillers on the release rate of atenolol from HPMC matrices. *IL Farmaco*. (2004) 59: 819-825.

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

(5) Nokhodchi A and Tailor A. *In situ* cross-linking of sodium alginate with calcium and aluminum ions to sustain the release of theophylline from polymeric matrices. *IL Farmaco*. (2004) 59: 999-1004.

(6) Ching AL, Liew CV, Heng PWS and Chan LW. Impact of cross-linker on alginate matrix integrity and drug release. *Int. J. Pharm.* (2008) 355: 259-268.

(7) Braccini I, Grasso RP and Pérez S. Conformational and configurational features of acidic polysaccharides and their interactions with calcium ions: a molecular modeling investigation. *Carbohydr. Res.* (1999) 317: 119-130.

(8) Smidsrød O. Molecular basis for some physical properties of alginates in the gel state. *J. Chem. Soc. Faraday Trans.* (1974) 57: 263-274.

(9) Skjåk-Bræk G. Alginates: biosynthesis and some structure-function relationship relevant to biomedical and biotechnological applications. *Biochem. Soc. Trans.* (1992) 20: 27-33.

(10) Ford JL, Rubinstein MH and Hogan JE. Formulation of sustained release promethazine hydrochloride tablets using HPMC matrices. *Int. J. Pharm.* (1985) 24: 327-338.

(11) Ford JL, Rubinstein MH and Hogan JE. Propranolol hydrochloride and aminophyline release from matrix tablets containing HPMC. *Int. J. Pharm.* (1985) 24: 339-350.

(12) Ford JL, Rubinstein MH, McCaul F, Hogan JE and Edgar PJ. Importance of drug type, tablet shape and added diluents on drug release kinetics from HPMC matrix tablets. *Int. J. Pharm.* (1987) 40: 223-234.

(13) Baveja SK, Rao Ranga KV and Devi Padmalatha K. Zero order release hydrophylic matrix tablets of β-adrenergic blockers. *Int. J. Pharm.* (1987) 39: 39-45.

(14) Dabbagh MA, Ford JL, Rubinstein MH, Hogan JE and Rajabi-Siahboomi AR. The release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and HPMC. *Pharm. Dev. Technol.* (1999) 4: 313-324.

(15) Doelker E. Water-swollen cellulose derivatives in pharmacy, hydrogels in medicine and pharmacy. In: Peppas NA. (ed.) *Hydrogels in Medicine and Pharmacy.* Vol. 2, CRC Press, Boca Raton (1987) 115-161.

(16) Azarmi Sh, Valizadeh H, Barzegar-Jalali M and Lobenberg R. *In situ* cross-linking of polyanionic polymers to sustain the drug release of acetazolamide tablets. *Pharm. Ind.* (2003) 9: 877- 881.

(17) Najib N and Suleiman M. The kinetics of drug release from ethyl cellulose solid dispersions. *Drug Dev. Ind. Pharm.* (1985) 11: 2169-2181.

(18) Desai SJ, Singh P, Simonelli AP and Higuchi WI.

Investigation of factors influencing release of solid drug dispersed in inert matrices. III. Quantitative studies involving the polyethylene plastic matrix. *J. Pharm. Sci.* (1966) 55: 1230-1234.

(19) Higuchi T. Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* (1963) 52: 1145-1149.

(20) Korsemayer RW, Gurny R, Doelker EM, Buri P and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *J. Pharm. Sci.* (1983) 15: 23-35.

(21) Seipman J and Seipman F. Mathematical modeling of drug delivery. *Int. J. Pharm.* (2008) 364: 328-343.

(22) Prabakaran D, Singh P, Kanaujia P and Vyas SP. Effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps. *J. Pharm. Sci.* (2003) 259: 173-179.

(23) Saeedi M, Akbari J, Morteza-Semnani K and Asgarirad H. Interpolymer complexation in hydrophilic polymers. *Chem. Indian J.* (2005) 2: 17-21.

(24) Hosny EA, Al-Helv AR and Al-Dardiri MA. Comparative study of *in vitro* release and bioavailability of sustained release diclofenac sodium from certain hydrophilic polymers and commercial tablets in beagle dogs. *Pharm. Acta Helv.* (1997) 72: 159-164

(25) Badwan AA, Abumalooh A, Sallam E, Abukalaf A and Jawan O. Sustained release drug delivery system using calcium alginate beads. *Drug Dev. Ind. Pharm.* (1985) 11: 239-256.

(26) Vauthier C, Rajaonarivony M, Couarraze G, Couvreur P and Puisieux P. Characterisation of alginate pregel by rheological investigation. *Eur. J. Pharm. Biopharm.* (1994) 40: 218-222.

(27) Remunan-Lopez C and Bodmeier R. Mechanical water uptake and permeability properties of crosslinked chitosan glutamate and alginate films. *J. Control. Rel.* (1997) 44: 215-225.

(28) Dave A, Patel MM, Jani JK and Gohel MC. Study of indomethacin release from formulated controlled release capsules. *Indian J. Pharm. Sci.* (1993) 55: 168-171.

(29) Bodmeier R, Chen H and Paeratakul O. Novel approach to the oral delivery of micro- or nanoparticles. *Pharm. Res.* (1989) 6: 413-417.

This article is available online at http://www.ijpr-online.com