AAPS PharmSciTech 2007; 8 (3) Article 51 (http://www.aapspharmscitech.org).

Modification of Theophylline Release With Alginate Gel Formed in Hard Capsules

Submitted: October 17, 2006; Accepted: January 26, 2007; Published: July 6, 2007

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ABSTRACT

The aim of this work was to establish whether alginate gel formed spontaneously in hard gelatin capsules which modifies release of a model drug, theophylline. The effects of the alginate composition, the calcium addition, and the dissolution medium on drug release were also investigated. After the capsule shell dissolved in water, at neutral pH the gel layer of sodium alginate was formed immediately as the sodium alginate hydrated and swelled on contact with the aqueous medium. In acidic pH, the contents remained intact and the matrix shape was the same. Theophylline release from capsules containing different grades of alginate demonstrated different release patterns, depending on alginate composition and the pH of the medium. The capsules containing sodium/calcium salts of alginate showed the slowest drug release at neutral pH but the fastest in acidic medium. The presence of calcium acetate in the formulations influenced the drug release kinetics. The drug release in acidic medium showed a non-Fickian diffusion-controlled release, while those in water at neutral pH exhibited a Super Case II transport mechanism. The study also provides evidence that the behavior of alginate in forming the hydrated gel layer may explain the drug release behavior at different pHs.

KEYWORDS: Alginate, hydrogel matrices, hard capsules, controlled release, sustained release, theophylline.

INTRODUCTION

Alginic acid and its various inorganic salt forms are derived from brown seaweeds (*Phaeophyceae)*. The monovalent salts, often referred to as alginates, are hydrophilic colloids widely used in the food industry. Sodium alginate's use is especially widespread. Alginate is a linear copolymer composed of 2 monomeric units, D-mannuronic acid and L-guluronic acid. These monomers occur in the alginate molecule as regions made up exclusively of one unit or the other—M blocks or G blocks—or as regions in which the monomers approximate an alternating sequence (MG blocks).[1,2] The D-mannuronic acid exists in the 1C conformation and in the alginate polymer is connected in the β-configuration through the 1- and 4- positions; the L-guluronic acid has the 1C conformation and is α-1, 4-linked in the polymer. Because of the particular shapes of the monomers and their modes of linkage in the polymer, the geometries of the G-block regions, M-block regions, and alternating regions are substantially different, as shown in Figure 1.

Commercial alginates are derived from a variety of weed sources. Since different weeds yield alginates that differ in monomeric composition and block structure, a given alginate has its own characteristic calcium reactivity and gelation properties. Although the M/G ratio can be obtained relatively easily, the detailed molecular compositions of alginates in terms of block lengths and block distributions are much more difficult to determine.[2] As a result, alginates are usually referred to as high M or high G, depending on the proportions of M and G they contain. Most commercial products are of the high-M type, the best example being the alginate obtained from giant kelp, *Macrocystis pyrifera*. *Laminaria hyperborea* provides a high-G alginate. In general terms, high-G alginates produce strong, brittle gels that are heat-stable, while high-M alginates provide weaker, more elastic gels that have less heat stability but more freeze/thaw stability. Specifically, the G blocks are buckled while the M blocks have a shape referred to as an extended ribbon. If 2 G-block regions are aligned side by side, a diamond-shaped hole results. This hole has dimensions that are ideal for the cooperative binding of calcium ions. When calcium ions are added to a sodium alginate solution, such an alignment of the G blocks occurs, and the calcium ions are bound between the 2 chains like eggs in an egg box.[3,4] Thus, the calcium reactivity of alginate is the result of a calcium-induced dimeric association of the G-block regions. Depending on the amount of calcium present in the system, these

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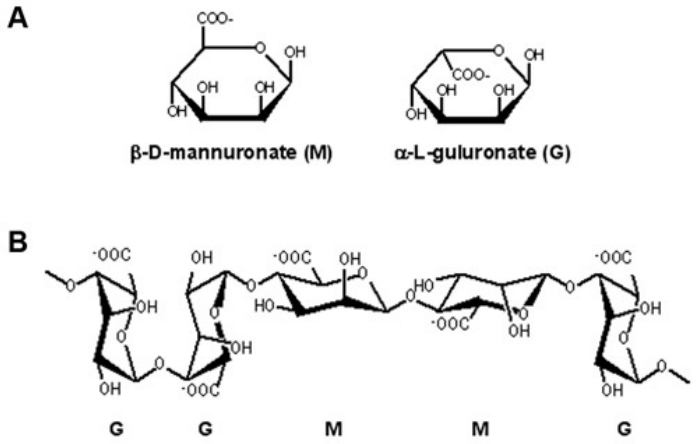

Figure 1. Structural data for alginates: (a) the monomers in alginate; (b) the alginate chain.

interchain associations can be either temporary or permanent. With low levels of calcium, temporary associations are obtained, giving rise to highly viscous, thixotropic solutions. At higher calcium levels, precipitation or gelation results from permanent associations of the chains.[5]

Hydrophilic polymer matrix systems (eg, polymeric matrix tablets or polymer powders in hard capsules) are flexible and widely used in oral controlled drug delivery because they assist in achieving the goals of a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance.[6-8] The ability of the hydrophilic polymer matrices to release entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross-linking makes the matrices particularly suitable for controlled-release applications.[7] These matrices can be applied for the release of both hydrophilic and hydrophobic drugs and charged solutes. The ability of alginate, sodium salt, to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry in sodium alginate's wide application as a carrier in hydrophilic matrix controlled-release oral dosage forms. Matrices incorporating alginate salts have been employed to successfully prolong the release of many drugs.[9-12]

The present work deals with a hydrophilic matrix based on the alginate gel system that has been characterized in relation to its possible use in modified drug delivery formulations. This kind of approach can be very useful both for interpreting the behavior of the alginate hydrogel when it is used as a sustained-/controlled-release matrix, and for optimizing modified-release dosage forms. For this purpose, the drug release from hard capsules containing an alginate gel system was determined. As a model drug we used slightly water-soluble theophylline, which has been widely used in studies because of its ready availability, relatively low cost, ease of assay, and chemical stability.

Scientists tend to use the term "alginate" without qualification. However, there are many different types of alginate on the market, with different chemical and physical characteristics. Therefore, the aim of this article was to investigate the effect of various grades of alginate (with different chemical composition)—especially a combination of alginate salts (ie, sodium/calcium alginate and ammonium/calcium alginate, which are self-gelling alginates)—on drug release from hard gelatin capsules. The effects of the amount of calcium added to some sodium alginate formulations (ie, Manucol and Manugel) and dissolution medium were also studied.

Materials and Methods

Materials

Six different grades of alginate were a generous gift from ISP (Thailand) Co (Bangkok, Thailand). The properties of the alginate samples are shown in Table 1. Theophylline (180-250 μm) was obtained as a gift sample from BASF (Thai) Limited (Bangkok, Thailand) and was used as received without further purification. All other chemicals were of reagent or food grade and used as supplied.

Table 1. Properties of Alginates Used for Hard Capsule Formulations*

Designation	Registered Trademark	Alginate Type	Approximate Particle Size (μm)	Form	Viscosity† (mPa s)	M/G Ratio	Bulk Density‡ (g/mL)
Manucol	Manucol DMF	Sodium alginate	106	Granular	300	0.59	0.845
Manugel	Manugel DMB	Sodium alginate	106	Granular	300	1.56	0.781
Keltone LV	Keltone LVCR	Sodium alginate	106	Fibrous	35	1.50	0.606
Keltone HV	Keltone HVCR	Sodium alginate	180	Fibrous	400	1.50	0.706
Kelset	Kelset	Sodium/calcium alginate	180	Fibrous	Gel at 2%	1.50	0.753
Keltose	Keltose	Ammonium/calcium alginate	180	Granular	Semi-gel	1.50	0.688

*Size, form, viscosity, and M/G ratio are specified and reported by the manufacturer. M/G ratio indicates mannuronic acid to guluronic acid ratio.
† 1% as is viscosity except where noted. Viscosity is generally measured using a Brookfield LV viscometer at 60 rpm with a No 2 spindle.
‡Average of 3 repeated tests.

Bulk Density Measurement

The bulk density of all alginate and theophylline samples was measured in a cylinder by the tapping method. The bulk density was calculated according to Equation 1.

$$\text{Bulk density } (\text{g/mL}) = \frac{\text{Weight}}{\text{Bulk volume}} \qquad (1)$$

Preparation of Alginate-Based Hard Capsules

The powder formulation composed of theophylline and alginate (1:6) was prepared by mixing in a blender at a speed of 50 rpm for 10 minutes. The powder blend was filled into No 1 hard gelatin capsules using a semiautomatic capsule-filling machine (Yeo Heng, Bangkok, Thailand). The filling weight for each capsule was calculated from the bulk density of powders (~324.2-386.9 mg/capsule, which is equivalent to 50 mg of active drug). In some cases, calcium acetate of either 3 or 30 mg per capsule was added to the formulations.

Weight Uniformity Testing

To determine capsule fill weights and variation in the batch, 30 capsules were sampled and accurately weighed using a Mettler analytical balance (Griefensee, Switzerland). The results were expressed as mean values of 30 determinations. The coefficient of variation was calculated from Equation 2:

$$\text{Coefficient of variation } (\%) = \frac{\text{Standard deviation}}{\text{Mean}} \times 100 \qquad (2)$$

In Vitro Release Studies

To examine the effects of the various grades of alginate, the calcium added to the formulation, and the dissolution medium on drug release, the dissolution studies were performed using US Pharmacopeia (USP) dissolution apparatus II. The paddle was operated at a speed of 50 rpm. One liter of either water or simulated gastric fluid (SGF) as the dissolution medium was placed in the glass vessel. The apparatus was assembled and the dissolution medium equilibrated to 37°C. The amount of drug release was measured at suitable time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours) and was then determined spectrophotometrically (model Lambda 2, PerkinElmer, Wellesley, MA) in a 1-cm cell at 270 nm. Each in vitro release study was performed in triplicate.

Analysis of Release Data

The mechanism of drug release from hard capsules during dissolution tests in water and SGF was determined using zero-order kinetics, first-order kinetics, and the Higuchi equation. But these models fail to explain the drug release that was due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data were also fitted to the well-known exponential equation, the Korsmeyer-Peppas equation, which is often used to describe the drug release behavior from polymeric systems[13]:

$$\frac{M_t}{M_f} = k \cdot t^n \qquad (3)$$

where k is a constant incorporating the structural and geometric characteristics of the matrix pellets, n is the release exponent, indicative of the drug release mechanism, and M_t / M_f represents the fraction of drug dissolved at time t. To clarify the release exponent for different batches of matrices, the log value of percentage drug released was plotted against log time for each batch according to Equation 4:

$$\log\left[\frac{M_t}{M_f}\right] = \log k + n \log t \qquad (4)$$

In the case of Fickian release (diffusion-controlled release), n has a limiting value of 0.45 and 0.43 for release from cylinders and spheres, respectively. In the case of Case II transport or relaxation-controlled delivery, the exponent n is 0.89 and 0.85 for release from cylinders and spheres, respectively. The non-Fickian release or anomalous transport of drug occurred when the n values fell between the limiting values of Fickian and Case II transport for both shapes. The non-Fickian kinetics correspond to coupled diffusion/polymer relaxation. Occasionally, values of $n > 0.89$ or $n > 0.85$ for release from cylinders and spheres have been observed and considered to be Super Case II kinetics.[13] This mechanism could result from increased plasticization at the relaxing boundary (gel layer).

Mean dissolution time (MDT) is used to characterize the drug release rate from a dosage form and indicates the drug-release-retarding efficiency of the polymer. In this study, MDT was calculated from dissolution data using the following equation[14]:

$$\text{MDT} = \left(\frac{n}{n+1}\right) \cdot k^{\left(\frac{-1}{n}\right)} \qquad (5)$$

where n is the release exponent and k is the release rate constant.

Results and Discussion

Controlled drug release from hard gelatin capsules (eg, hard capsules containing polymer powders) is commonly used in oral drug delivery systems because it allows for flexibility to obtain a desirable drug release profile, is cost-effective,

Table 2. Weight Uniformity and Mean Dissolution Time of Theophylline From Hard Capsules Containing Alginate

	Weight Uniformity			Mean Dissolution Time (hrs)	
Formulation	Mean* (mg)	Standard Deviation	Coefficient of Variation (%)	In Simulated Gastric Fluid	In Water
Manucol	371.4	23.1	6.22	2.33	2.79
Manugel	334.8	19.2	5.73	2.16	2.21
Keltone LV	330.0	17.4	5.27	3.46	2.03
Keltone HV	324.2	18.5	5.71	4.08	2.27
Kelset	355.4	21.4	6.02	0.10	5.96
Keltose	341.1	16.8	4.93	0.07	1.06
Manucol + Ca 3 mg	386.9	19.1	4.94	2.27	3.59
Manucol + Ca 30 mg	367.4	13.9	3.78	0.06	1.89
Manugel + Ca 3 mg	370.0	17.3	4.68	2.31	3.15
Manugel + Ca 30 mg	373.6	23.5	6.29	0.15	3.40

*The mean values are an average of 30 capsules.

and has broad regulatory acceptance. Hard capsule formulations for controlled release are easily produced by adding a suitable hydrophilic polymer (eg, sodium alginate) to the formulation.[10-12]

The powder formulations of theophylline and alginate were prepared, and the filling dose was then calculated according to their bulk density (Table 1). The powder blend was put into No 1 hard capsules. The weight uniformity of hard capsules containing theophylline and different grades of alginate is shown in Table 2. All formulations met the specifications for uniformity of dosage units of the USP. The coefficient of variation varied from 3.78% to 6.29%.

The ability of different grades of alginate (with different chemical compositions, forms, particle sizes, and viscosity) to form a hydrophilic matrix and modify the drug release from hard capsule formulations was investigated. It is known that the release of drug molecules from hydrophilic matrices is affected by changing the pH, because of the presence of an acidic group (ie, carboxylic acids) in the alginate chains that releases protons in response to changes in environmental pH. The acidic pH in the stomach (pH 1.2 of SGF) is quite different from the neutral pH in the intestine, and such a difference is large enough to induce different release profiles/kinetics. Thus, the release of theophylline from alginate matrices was investigated in physiological pH (ie, at gastric pH and at neutral pH) in relation to the matrices' degradation.

After the capsule shell dissolved in water, at neutral pH, the gel layer of sodium alginate was formed immediately as the sodium alginate hydrated and swelled (depending on the grades of sodium alginate) on contact with the aqueous medium. As the pK_a of alginic acid (by virtue of the carboxyl groups on the components of uronic acid residues) is ~4, it can dissolve and then form a viscous solution at neutral pH. In acidic pH, the contents remained intact and the matrix shape was the same (Figure 2). It is expected that formation of insoluble alginic acid would prevent the formation of a coherent gel layer. A previous study[15] showed that the alginate matrices, in the matrix tablet forms, swelled more in neutral medium (pH 6.8 buffer) than in acidic medium. In acidic medium, the outer hydrated surface layer formed around the matrices could be seen to possess a consistency that was very different from that formed around sodium alginate matrices that were hydrated in neutral medium. The hydrated layer (in acidic medium) was not viscous and adhesive but had a tough and rubbery texture (Figure 2), probably because at pH 1 to 2, sodium alginate is rapidly converted to alginic acid, which has the ability to swell on hydration but is virtually insoluble. This is in good agreement with a previous report.[15]

Figure 2. Hard capsules containing sodium alginate (Manucol): (a) intact capsule; (b) capsule immersed in water for 30 minutes; (c) capsule immersed in water for 5 hours; and (d) capsule immersed in simulated gastric fluid for 5 hours.

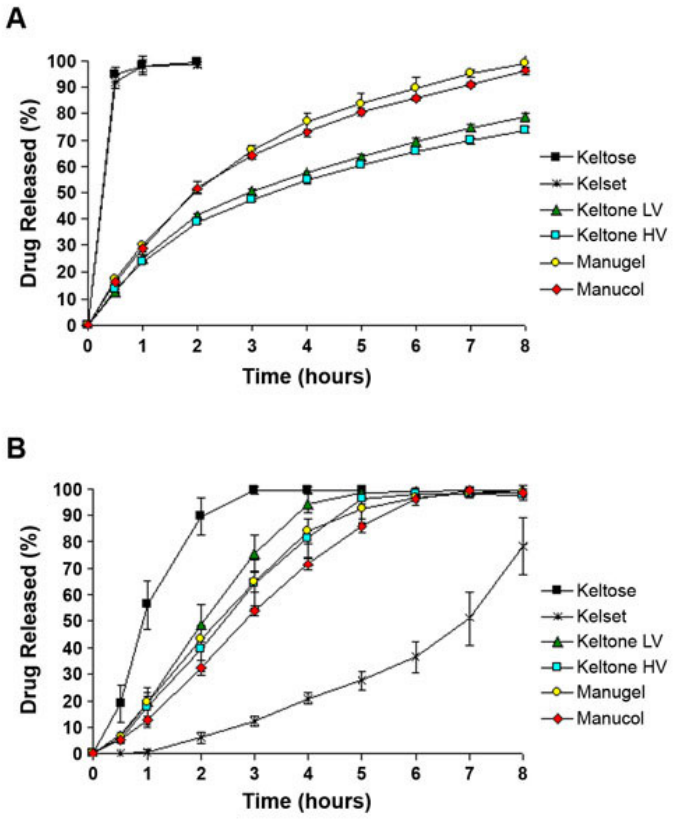

Figure 3. Theophylline released in SGF and water from hard capsules containing different grades of sodium alginate (n = 3). SGF indicates simulated gastric fluid.

Figure 3 shows the effect of different grades of alginate and of the pH of the medium on the release of theophylline from hard capsules containing alginate. In acidic conditions, although the 6 different grades of alginate did not significantly influence the matrices' swelling,[15] there was a significant difference in the drug release profiles from hard capsules containing different grades of alginate. The results showed that dose dumping was likely to occur from hard capsules containing a combination of alginate salts (ie, sodium/calcium alginate [Kelset] and ammonium/calcium alginate [Keltose]). This is due to the insolubility of alginic acid formed in acidic medium, resulting in disintegration of capsule components. The use of sodium alginate alone reduced the chances of dose dumping. The carboxyl groups in sodium alginate chains could be transformed into carboxylic acids. The alginate chains underwent a process of association, at pH < 3, resulting in the formation of a thick network of inter- and intramolecular hydrogen bonds.[16] The hard capsules containing sodium alginate alone did not show any burst release in gastric fluid (in vitro), indicating a reduced likelihood of unwanted toxic effects of theophylline, which has a narrow therapeutic index.

At neutral pH, the sodium alginate matrices swelled and then eroded (Figure 1), which is consistent with the previous report on alginate matrix tablets.[15] As a result, the drug release depended on how fast the swollen portion of sodium alginate eroded. At neutral pH, drug release from hard capsules containing alginate was controlled by the formation of a hydrated viscous layer around the capsules, which acted as a barrier to drug release by opposing the penetration of water into the matrices and the movement of dissolved solutes out of the matrices. The contribution of each release mechanism to the overall drug release process was influenced by the physical and mechanical properties of the gel barrier that formed around the capsules.[17] The capsules of alginate that contained a combination of sodium and calcium salts showed the slowest drug release at neutral pH but the fastest in acidic medium (Figure 3). The results suggest that the structure of capsules containing sodium alginate in water at neutral pH was markedly different from that of capsules formed in SGF. The effect of different grades of alginate on the drug release will be discussed later, along with the release parameter (ie, MDT).

The effect of the amount of calcium added on drug release in water and SGF is shown in Figures 4 and 5, respectively.

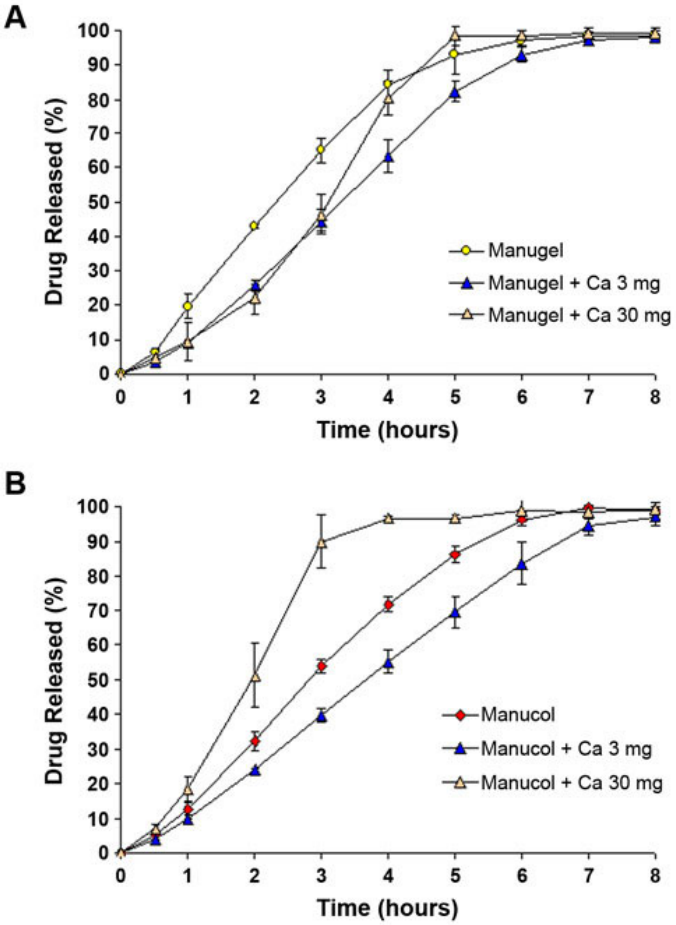

Figure 4. Effect of amount of calcium added on theophylline released in water from hard capsules containing Manugel or Manucol (n = 3).

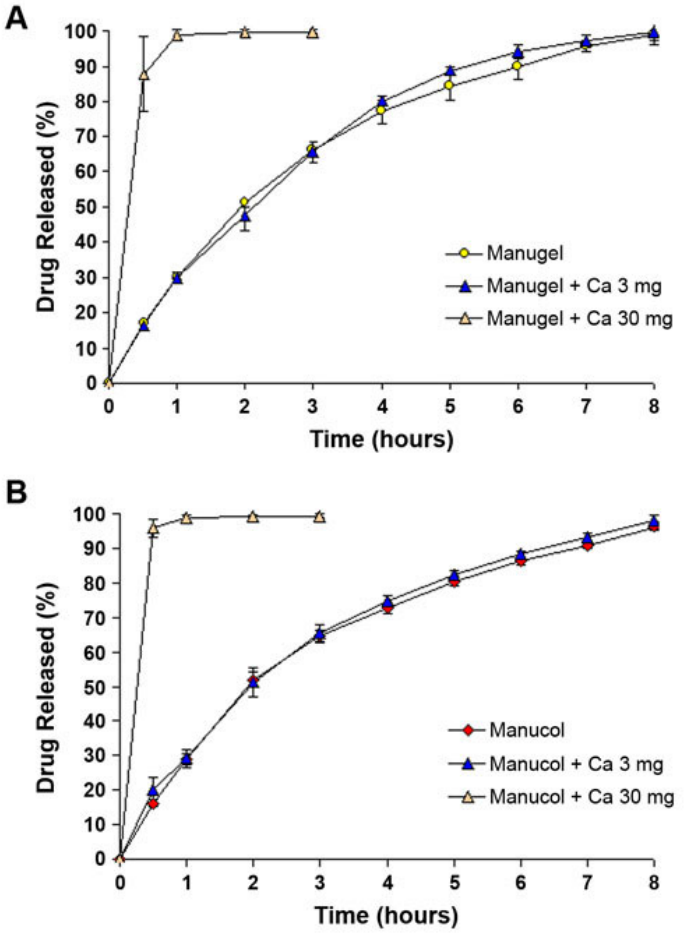

Figure 5. Effect of amount of calcium added on theophylline released in simulated gastric fluid from hard capsules containing Manugel or Manucol (n = 3).

At neutral pH, the drug release decreased apparently when 3 mg of calcium acetate was added into the formulations. The possible explanation is that sodium alginate could form a rigid gel with calcium ions[5] during the dissolution test. Water penetrates into matrices and dissolves calcium acetate. Furthermore, the dissolved calcium ions interact with alginate, thus forming a calcium alginate gel matrix. Therefore, the slower drug release from capsules with calcium acetate was due to the retention of the drug in the calcium alginate gel matrix. This result was consistent with findings from previous studies.[18] However, a large amount of added calcium (30 mg/capsule) produced a faster drug release (Figure 4). This can be explained by the influence of calcium on the gel formation. The gel strength increases with the addition of calcium up to a critical concentration.[18] Above this concentration, the gel strength weakens. This weakening is due to excessive cross-linking by the calcium and hence formation of a nonhomogeneous gel matrix. The capsules disintegrated partially, and the larger surface area created resulted in the faster drug release. In SGF, the drug release was insignificantly decreased in the alginate-based matrix capsules containing a small amount of calcium acetate (ie, 3 mg/capsule), as shown in Figure 5, probably because the added calcium ions were replaced by protons in the medium. Increasing the calcium amount in the formulations to 30 mg per capsule clearly increased the release rate. The complete disintegration (within 30 minutes) of matrices would cause the faster drug release in an acidic medium.

The release kinetics for all the models are shown in Table 3. A previous report showed that the release of ibuprofen (in pH 7.2) from hard capsules containing different grades of alginate followed zero-order kinetics.[10] However, in this study, the drug release data for hard capsules containing different grades of alginate showed a good fit into both the Higuchi equation and the Korsmeyer-Peppas equation, except that the capsules disintegrated rapidly (within 30 minutes) in the SGF. The Higuchi model is applicable if the drug release is largely governed by diffusion through water-filled pores in the matrix. A good fit to the Korsmeyer-Peppas equation indicated a combined effect of diffusion and erosion mechanisms for drug release.[13]

The value of the release exponent n determined from various formulations ranged from 0.623 to 0.762 in SGF, and from 1.129 to 2.273 in water. The k value ranged from 0.23 to 0.31 in SGF, and from 0.01 to 0.46 in water (Table 3). The value of n and k was found to vary with the type of alginate and the addition of calcium. The release exponents for the formulations that released rapidly are not shown because there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values. The hard capsules containing alginate with or without calcium acetate exhibited an anomalous (non-Fickian) diffusion-controlled release in SGF. In water, the release from capsules demonstrated Super Case II transport. It is evident that dissolution or erosion of the alginate matrices (at neutral pH) would account for the increasing values of n. This type of transport has also been reported by Sujja-areevath et al.[19]

MDT was used to characterize the drug release rate from hard capsules containing alginate and indicated the drug-release-retarding efficiency of alginate. Hard capsules containing different alginates showed different MDTs (Table 2). The formulations that disintegrated in SGF showed very low MDT (eg, 0.06-0.15 hours). Drug release in water produced a higher MDT value than drug release in SGF. This finding can be attributed to the swelling properties of alginate salts in a neutral medium. The addition of a small amount (3 mg) of calcium acetate into the formulation resulted in a reduced release rate in water (Table 3) and a higher MDT (Table 2). Similar results have been reported in matrix formulations containing pectin, which is the epimer of the G unit of alginate.[18] However, a large amount of added calcium (30 mg/capsule) produced a faster drug release and a lower MDT, as discussed above. The capsules containing a large amount of calcium acetate did not remain

Table 3. Mathematic Modeling and Drug Release Kinetics of Theophylline From Hard Capsules Containing Alginate*

Formulation	Correlation Coefficient, r^2				Kinetic Constant, k	Diffusional Exponent, n	Order of Release
	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas Model			
In SGF							
Manucol	0.9120	0.7628	0.9891	0.9887	0.28	0.737	Non-Fickian
Manugel	0.9163	0.8023	0.9955	0.9985	0.29	0.757	Non-Fickian
Keltone LV	0.9313	0.7690	0.9894	0.9756	0.23	0.685	Non-Fickian
Keltone HV	0.9347	0.7944	0.9912	0.9873	0.23	0.623	Non-Fickian
Kelset	NA	0.6178	NA	NA	NA	NA	NA
Keltose	NA	0.8286	NA	NA	NA	NA	NA
Manucol + Ca 3 mg	0.9263	0.8048	0.9937	0.9944	0.31	0.680	Non-Fickian
Manucol + Ca 30 mg	NA	0.6144	NA	NA	NA	NA	NA
Manugel + Ca 3 mg	0.9099	0.8158	0.9966	0.9974	0.28	0.762	Non-Fickian
Manugel + Ca 30 mg	NA	0.5209	NA	NA	NA	NA	NA
In water							
Manucol	0.9313	0.7659	0.9836	0.9984	0.12	1.309	Super Case II
Manugel	0.8678	0.6827	0.9940	0.9854	0.17	1.325	Super Case II
Keltone LV	0.7949	0.6475	0.9850	0.9961	0.18	1.372	Super Case II
Keltone HV	0.8629	0.6828	0.9902	0.9874	0.15	1.418	Super Case II
Kelset	0.9565	0.9698	0.8711	0.9585	0.01	2.273	Super Case II
Keltose	0.7003	0.5868	0.9830	0.9488	0.46	1.129	Super Case II
Manucol + Ca 3 mg	0.9870	0.8288	0.9726	0.9993	0.10	1.254	Super Case II
Manucol + Ca 30 mg	0.7313	0.6183	0.9610	0.9998	0.19	1.440	Super Case II
Manugel + Ca 3 mg	0.9554	0.7885	0.9636	0.9994	0.09	1.406	Super Case II
Manugel + Ca 30 mg	0.8851	0.7922	0.8825	0.9842	0.10	1.251	Super Case II

*Analyzed by the regression coefficient method. SGF indicates simulated gastric fluid; NA, not applicable.

intact during the experiment. The matrix disintegrated rapidly in water. The larger surface area created partly explains the faster drug release. The formulations containing Kelset (calcium/sodium alginate) showed the highest MDT, suggesting that the optimal amount of calcium content was added in the commercial formula. The ammonium salt (in Keltose) did not help to retard the drug release; it actually sped up the release. A previous study[15] suggested that, in neutral medium, ammonium salts may create pores in tablets to facilitate a slow disintegration, resulting in the fast drug release from matrix tablets.

In SGF, the addition of calcium did not extend the drug release, as the cross-linked calcium could be replaced by the protons in the acidic medium, forming the more permeable acid gel.[20] The hard capsules containing a combination of alginate salts (ie, Kelset and Keltose) demonstrated similar results. The calcium or ammonium salts in the formulations can also be replaced by protons in the SGF. Similar results were reported in alginate matrix tablets,[15] in which the rapid drug release from matrix tablets containing sodium/calcium alginate (Kelset) and ammonium/calcium alginate (Keltose) in acidic medium resulted from the disintegration of the matrix tablets. The likely reason is that ammonium and/or calcium salts of alginate were replaced by protons in the acidic medium to form alginic acid, which induced the matrices' disintegration.[15]

The effect of the M/G ratio on the release of theophylline from alginate-based hard capsules was determined using sodium alginate with a different M/G ratio but similar median particle sizes and viscosities (Table 1). The results showed that the capsules containing sodium alginate with high M content (ie, Manucol) had a higher MDT value than those with high G content (ie, Manugel), in both SGF and water. It is possible that high-M alginate hydrated faster and built up the diffusion barrier more rapidly, resulting in slower release. These results are in good agreement with Liew et al,[21] who reported a more sustained action of high-M alginate in sustaining drug release from matrix tablets. The alginate with the high viscosity grade also produced the higher MDT in both media. The higher-viscosity alginate slowed the drug release and exhibited less erosion.[22] These results, however, are different from those of the previous study,[21] which reported that higher alginate viscosity slowed down the drug release rate at neutral pH but enhanced the release rate in the acidic medium.

CONCLUSION

Alginate hydrated and generated a gelatinous layer on the capsule surface after contact with water at neutral pH, which is markedly different to that formed in acidic medium. Drug releases, in both acidic and neutral media, from hard capsules

containing different grades of alginate with or without calcium acetate were significantly different from each other. Drug release in an acidic medium showed a non-Fickian diffusion-controlled release, while drug release in water at neutral pH exhibited a Super Case II transport mechanism ($n > 1$). The study also provides evidence that the behavior of alginate in forming the hydrated gel layer may explain the drug release behavior at different pHs.

Given the results of this study, it is clear that hard capsules containing hydrophilic polymer enable the formation of oral controlled-release matrices using a process that is easy and inexpensive and does not require special production equipment. It is, therefore, possible to achieve a firmer basis for the use of alginate gel formed in hard capsules to control the drug release.

ACKNOWLEDGMENTS

The authors wish to thank ISP (Thailand) Co., which kindly provided the alginate samples. Thanks also to BASF (Thai), which kindly provided the sample of theophylline.

REFERENCES

1. Haug A, Larsen B. Quantitative determination of the uronic acid composition of alginates. *Acta Chem Scand A.* 1962;16:1908–1918.

2. Haug A, Larsen B, Smidsrod O. Studies on the sequence of uronic acid residues in alginic acid. *Acta Chem Scand A.* 1967;21: 691–704.

3. Grant GT, Morris ER, Rees DA, Smith PJA, Thom D. Biological interactions between polysaccharides and divalent cations: the egg-box model. *FEBS Lett.* 1973;32:195–198.

4. Braccini I, Perez S. Molecular basis of Ca^{2+}-induced gelation in alginates and pectins: the egg-box model revisited. *Biomacromolecules.* 2001;2:1089–1096.

5. Clare K. Algin. In: Whistler RL, BeMiller JN, eds. *Industrial Gums.* 3rd ed. New York, NY: Academic Press; 1993.

6. Kudela V. Hydrogels. In: Kudela V, ed. *Encyclopedia of Polymer Science and Engineering.* vol. 7. New York, NY: Wiley; 1987: 703–807.

7. Graham NB, McNeill ME. Hydrogels for controlled drug delivery. *Biomaterials.* 1984;5:27–36.

8. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. *AAPS PharmSciTech.* 2003;4:E31[serial online].

9. Stockwell AF, Davis SS, Walker SE. In vitro evaluation of alginate gel systems as sustained release drug delivery systems. *J Control Release.* 1986;3:167–175.

10. Veski P, Marvola M. Sodium alginate as diluents in hard gelatin capsules containing ibuprofen as a model drug. *Pharmazie.* 1993;48:757–760.

11. Ojantakanen S, Hannula A-M, Marvola M, Klinge E, Makioaa M. Bioavailability of ibuprofen from hard gelatin capsules containing sucralfate or sodium alginate. *Eur J Pharm Biopharm.* 1993;39:197–201.

12. Veski P, Marvola M, Smal J, Heiskanen I, Jurjenson H. Biopharmaceutical evaluation of pseudoephedrine hydrochloride capsules containing different grades of sodium alginate. *Int J Pharm.* 1994; 111:171–179.

13. Korsmeyer RW, Gurny R, Docler E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25–35.

14. Mockel JE, Lippold BC. Zero order release from hydrocolloid matrices. *Pharm Res.* 1993;10:1066–1070.

15. Sriamornsak P, Thirawong N, Korkerd K. Swelling, erosion and release behavior of alginate-based matrix tablets. *Eur J Pharm Biopharm.* 2007;66:435–450.

16. Dentini M, Rinaldi G, Barbetta A, Risica D, Skjak-Braek G. Acid gel formation in (pseudo) alginates with and without G blocks produced by epimerizing mannuronan with C5 epimerases. *Carbohydr Polym.* 2006;63:519–526.

17. Hodsdon AC, Mitchell JR, Davies MC, Melia CD. Structure and behaviour in hydrophilic matrix sustained release dosage forms, III: the influence of pH on the sustained-release performance and internal gel structure of sodium alginate matrices. *J Control Release.* 1995;33:143–152.

18. Sungthongjeen S, Sriamornsak P, Pitaksuteepong T, Somsiri A, Puttipipatkhachorn S. Effect of degree of esterification and calcium amount on drug release from pectin-based matrix tablets. *AAPS PharmSciTech.* 2004;5:E9[serial online].

19. Sujja-areevath J, Munday DL, Cox PJ, Khan KA. Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations. *Int J Pharm.* 1996;139:53–62.

20. Sriamornsak P, Kennedy RA. Development of polysaccharide gel coated pellets for oral administration, II: calcium alginate. *Eur J Pharm Sci.* 2006;29:139–147.

21. Liew CV, Chan LW, Ching AL, Heng PWS. Evaluation of sodium alginate as drug release modifier in matrix tablets. *Int J Pharm.* 2006;309:25–37.

22. Efentakis M, Koutlis A. Release of furosemide from multiple-unit and single-unit preparations containing different viscosity grades of sodium alginate. *Pharm Dev Technol.* 2001;6:91–98.