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Calcium alginate matrices for oral multiple unit administration: IV. Release characteristics in different media

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Abstract

The release properties of calcium alginate minimatrices were studied in media of various compositions. Three drugs with different aqueous solubility (paracetamol, theophylline and chloramphenicol) were incorporated as model substances and their release rates were investigated in 0.1 M HCl and water. The theophylline release was also studied in simulated gastric fluid (SGF), simulated intestinal fluid (SIF), 0.034 M NaCl and 0.1 M NaCl. Additionally, the simultaneous liberation of calcium ions from the carrier material into the different media was analysed and illustrated by means of calcium release curves. Only when pure water was applied as release medium were the matrices able to extend the release of the two least soluble model drugs, theophylline and chloramphenicol. In all other media the drug release proceeded much more rapidly, due to various transformations in the carrier material. The cross-linking calcium ions were rapidly discharged from the matrices in the presence of acid, and the carrier material was converted to alginic acid. Although the transformation did not change the morphology or the swelling behaviour of the matrices, it destroyed their ability to provide retarded drug release. In the NaCl solutions and SIF, the calcium ions were partly exchanged by the non-gelling sodium ions or sequestered by the phosphate. This caused swelling and, in the latter case, dissolution of the matrices, and induced a rapid release of the encapsulated drug. Due to the pronounced sensitivity towards the composition of the release medium and the rapid drug release in media of physiological relevance, it was concluded that the minimatrices do not seem applicable as an oral controlled release system.

Keywords: Alginate; Calcium-induced gelation; Oral drug delivery system; Extended release; Release medium; Paracetamol; Theophylline; Chloramphenicol

1. Introduction

Alginate is currently being investigated as a carrier material for different controlled release systems. Hydrophilic matrix tablets have been based on sodium alginate alone (Balz et al., 1992) or in combination with sodium calcium alginate (Horder et al., 1986) or HPMC (Timmins et al., 1992). Sodium alginate has also been evaluated as a release-controlling diluent in sustained-release capsules (Ojantakanen et al., 1993; Veski and

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Marvola, 1993). In addition, the ability of alginate to form gels with divalent cations has been utilized in the production of small calcium alginate matrices, intended for multiple unit administration (Østberg and Graffner, 1992; Shiraishi et al., 1993; Tateshita et al., 1993).

Alginate is a family of polysaccharides composed of α-L-guluronic acid (G) and β-D-mannuronic acid (M) residues in varying proportions and sequential arrangements. The alginate monomer composition is reported to have a major impact on the drug release properties of the different formulation systems (Timmins et al., 1992; Østberg and Graffner, 1994). Being a polyelectrolyte, alginate can exhibit swelling properties that are sensitive to the pH, ionic strength and specific ionic composition of the medium. This might also affect the release properties of alginate-based formulations. For example, drug release from the matrix tablets has been reported to be more rapid in acidic medium than in phosphate buffer (Fu Lu et al., 1991; Timmins et al., 1992), and the release of theophylline from calcium alginate minimatrices has been shown to proceed much faster in 0.1 M HCl than in water (Østberg and Graffner, 1994).

The aim of this study was to investigate the drug release properties as well as the behaviour of small calcium alginate matrices in media of various compositions. The liberation of calcium ions from the carrier material was analysed simultaneously. Three model drugs with different aqueous solubility, i.e., paracetamol, theophylline and chloramphenicol, were incorporated into the matrices.

2. Materials and methods

2.1. Materials

A sodium alginate (Protanal LF 10/60) with a G content of 68% and an average molecular weight of 200 000 was utilized throughout most of the study. In addition, four other alginates with a G content varying between 46 and 64%, and a mean molecular weight ranging from 200 000 to 270 000 (Østberg and Graffner, 1994), were applied in some of the experiments. The alginates were kindly donated by Pronova Biopolymer A/S, Drammen, Norway.

Paracetamol (BP), theophylline monohydrate (Ph. Eur.) and chloramphenicol (Ph. Eur.) were used as model drugs. All other chemicals were of analytical grade. Deionized water was used throughout the study.

Some physicochemical properties of the drug substances are listed in Table 1. The pK_a and pK_b values are taken from the literature (Florey, 1974, 1975). The solubilities were determined by suspending an excess of drug in the medium and stirring until equilibrium was established. The samples were filtered and diluted before the concentrations were determined spectrophotometrically.

2.2. Methods

2.2.1. Production of calcium alginate minimatrices

Calcium alginate gel beads were prepared using the method described earlier (Østberg and Graffner, 1992). A suspension of 7.0 g drug in 250

Table 1
Physicochemical properties of the investigated drug substances

Drug	pK_a	pK_b	Solubility (mg/ml)			Particle size
			In water (20.0°C)	(37.0°C)	In 0.1 M HCl (37.0°C)	
Paracetamol	9.5		12.7	21.4	21.4	85% < 100 μm [a]
Theophylline monohydrate	8.6	11.5; 13.5	5.3	13.1	10.7	95% < 100 μm [a]
Chloramphenicol			3.6	5.3	5.4	mostly < 10 μm [b]

[a] Sieve analysis.
[b] Microscopy.

g 2.0% alginate solution was extruded as droplets into 500 ml of 0.08 M $CaCl_2$ solution, saturated with drug. The extrusion flow rate was approx. 30 ml/min. The droplet size was controlled by applying a coaxial air stream of 7.2 l/min over the cannulae. After 45 min the beads were separated from the cross-linking solution, washed and air-dried. Blank matrices were prepared using the same procedure but without the addition of drug. Matrices containing theophylline were also produced by gelation in 0.05 M and 0.15 M $CaCl_2$ or by using different alginates as carrier material.

2.2.2. Characterization of the minimatrices

2.2.2.1. Drug content. The content of paracetamol, theophylline or chloramphenicol was assayed spectrophotometrically at 243, 272 and 278 nm (UV-160A, Shimadzu Corp., Kyoto, Japan), respectively, after dissolution of the matrices in phosphate buffer (Østberg and Graffner, 1992). Each determination was performed in triplicate.

2.2.2.2. Calcium content. 200–250 mg matrices were dissolved by boiling in 10 ml concentrated nitric acid. After dilution the calcium content was determined by atomic absorption spectroscopy (Spectr AA 10, Varian Techtrom Pty Ltd, Mulgrave, Victoria, Australia). The determinations were made in triplicate.

2.2.2.3. Drug release rate. The drug release properties of the matrices were studied using the USP XXII paddle apparatus at a rotation speed of 50 rpm. An amount of matrices containing 110 mg of drug was placed in 900 ml of degassed medium (37 ± 0.5°C). The drug release from all the formulations was determined in deionized water and in 0.1 M HCl. Matrices containing theophylline were also tested in 0.034 M NaCl, 0.1 M NaCl, simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4), USP XXII. Enzymes were not added to the latter two media. SGF consists of 0.086 M HCl and 0.034 M NaCl, whereas SIF is a 0.05 M phosphate buffer in which 0.05 M potassium and 0.04 M sodium ions are present. 2 ml samples were withdrawn at predetermined time intervals and assayed after dilution. The samples taken from SIF were filtered immediately after being drawn. Six replicates were made for each batch. The times for release of 50% ($t_{50\%}$) and 80% ($t_{80\%}$) of the drug were calculated.

2.2.2.4. Calcium release rate. The liberation of calcium from the matrices produced using 0.08 M $CaCl_2$ for gelation was investigated in all release media except SIF. The test conditions were identical to those described for the drug release studies. The calcium content of the withdrawn samples was determined directly by atomic absorption spectroscopy. Only the samples taken from 0.1 M NaCl were diluted with 0.1 M HCl before measurement. Three replicates were made for each batch.

2.2.2.5. Scanning electron microscopy (SEM). Morphological examination of the surfaces and the cross-sections of the matrices was carried out using SEM as described in a previous study (Østberg and Graffner, 1992). Cross-sections were obtained by cutting the matrices with a razor blade. The SEM studies of the matrices after completion of drug release were performed after the tested products had been freeze-dried.

3. Results and discussion

The drug release properties in water and 0.1 M HCl of minimatrices containing paracetamol, theophylline and chloramphenicol are shown in Fig. 1. In addition, the release of theophylline in SGF, SIF and two saline solutions is illustrated by the release profiles in Fig. 2. The release parameters $t_{50\%}$ and $t_{80\%}$ obtained in the various media from theophylline matrices made using different calcium concentrations are shown in Table 2.

Calcium ions were also liberated from the matrices during the drug release studies. Fig. 3 depicts the calcium release vs time curves in water and 0.1 M HCl for blank matrices and for matrices containing different model drugs. These formulations were made of an alginate which consisted of 68% G residues. The calcium release

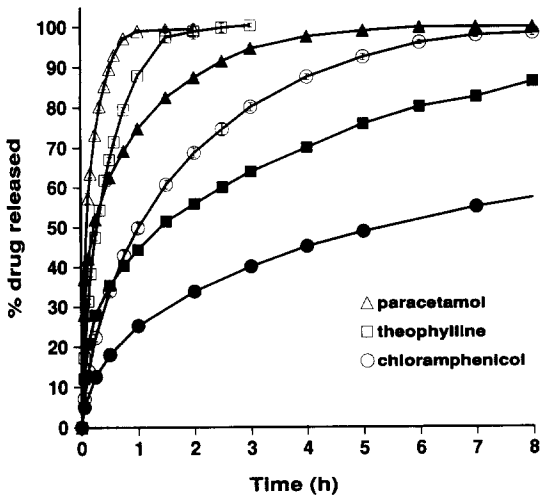

Fig. 1. Release of different model drugs in 0.1 M HCl (open symbols) and water (closed symbols); mean values ± SD, $n = 6$.

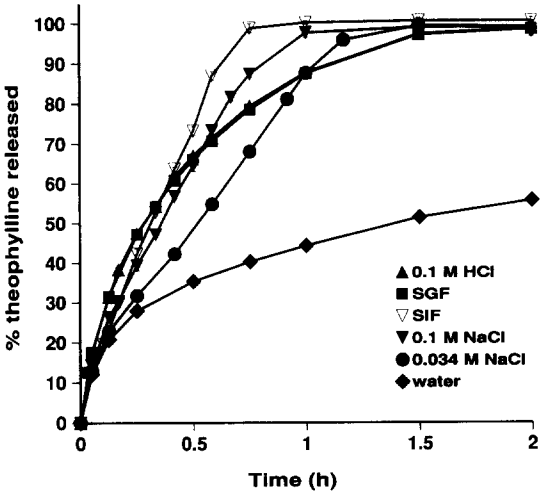

Fig. 2. Release of theophylline in different media from matrices prepared using 0.08 M $CaCl_2$; mean values ± SD, $n = 6$.

profiles of matrices made of alginates with lower G contents were similar to those in Fig. 3 and are therefore not shown. Fig. 4 demonstrates the release of calcium from the theophylline matrices in all the investigated media, except SIF.

3.1. Release properties in pure water

In water, the release rates of the different model drugs could be ranked according to the drug solubility (Fig. 1 and Table 1). The most soluble model drug, paracetamol, was released relatively rapidly whereas the release of the less soluble theophylline and, especially, chloramphenicol was more extended. A similar relationship between solubility and release rate was previously reported when various herbicides were incorporated into the calcium alginate matrices (Pfister et al., 1986).

The calcium concentration used for matrix production had a marked influence on the drug release rate in water (Table 2). As reported in an earlier study (Østberg and Graffner, 1994), the strongest retardation was achieved by matrices produced at an intermediate concentration.

During the drug release studies, between 10 and 14% of the calcium content left the matrices in water (Fig. 3). This occurred instantaneously and was independent of the encapsulated drug substance and the monomer composition of the alginate. Matrices made of alginates with different G contents produced identical calcium re-

Table 2
Release parameters $t_{50\%}$ and $t_{80\%}$ (± SD, $n = 6$) of matrices containing theophylline prepared using different calcium concentrations for gelation

Release medium	$[CaCl_2] = 0.05$ M		$[CaCl_2 = 0.08$ M		$[CaCl_2] = 0.15$ M	
	$t_{50\%}$ ± SD (min)	$t_{80\%}$ ± SD (min)	$t_{50\%}$ ± SD (min)	$t_{80\%}$ ± SD (min)	$t_{50\%}$ ± SD (min)	$t_{80\%}$ ± SD (min)
Water	73 ± 3	317 ± 7	84 ± 2	358 ± 7	62 ± 2	279 ± 7
0.1 M HCl	15 ± 1	43 ± 2	17 ± 1	46 ± 1	15 ± 1	43 ± 1
SGF	16 ± 1	45 ± 1	17 ± 1	47 ± 2	15 ± 1	45 ± 1
SIF	17 ± 1	33 ± 1	19 ± 0	32 ± 0	24 ± 1	39 ± 1
0.1 M NaCl	18 ± 1	35 ± 0	22 ± 0	39 ± 1	21 ± 1	39 ± 1
0.034 M NaCl	27 ± 1	49 ± 1	31 ± 0	54 ± 0	31 ± 1	56 ± 1

lease curves although they were previously shown to give quite different drug release profiles (Østberg and Graffner, 1994).

None of the formulations swelled visibly in water and they remained as firm bead structures even after drug release had reached completion. The calcium lost to this medium is believed to represent unbound ions that had failed to be washed out during the preparation procedure. The calcium involved in the cross-linking of the alginate probably remained in the matrices and kept the carrier material intact during the whole course of the release process.

3.2. Release properties in acidic dissolution media

The release rates of all the model drugs were considerably higher in 0.1 M HCl than in water (Fig. 1). The inability of the matrices to retard theophylline release in 0.1 M HCl has already been reported (Østberg and Graffner, 1994), but was obviously a property that applied for other incorporated drugs as well. Even for the least soluble model drug, chloramphenicol, the $t_{50\%}$ and $t_{80\%}$ values did not exceed 1 and 3 h, respectively.

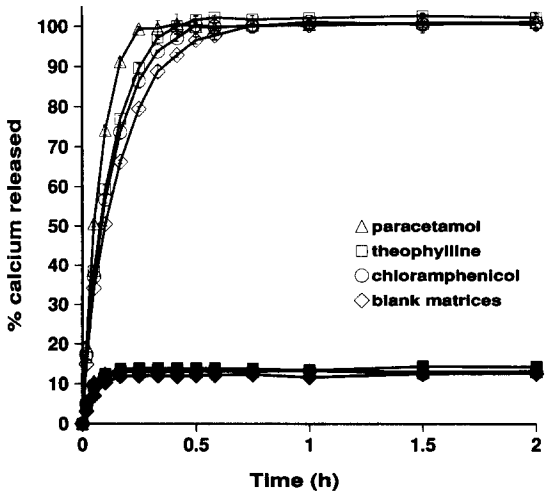

Fig. 3. Release of calcium from blank matrices and matrices containing different drugs in 0.1 M HCl (open symbols) and water (closed symbols); mean values ± SD, $n = 3$.

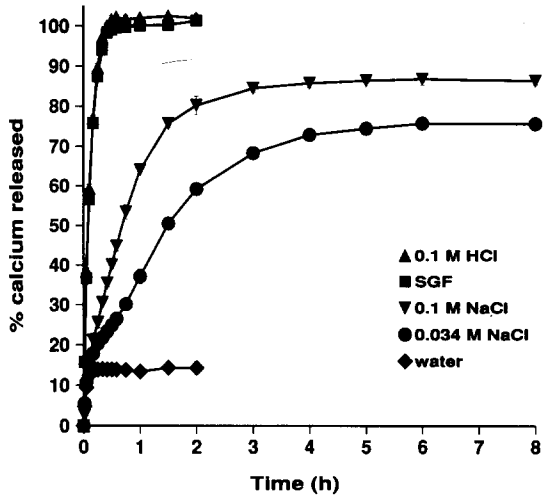

Fig. 4. Release of calcium in different media from theophylline matrices prepared using 0.08 M $CaCl_2$; mean values ± SD, $n = 3$.

The three different theophylline formulations gave identical release rates in 0.1 M HCl and SGF (Table 2 and Fig. 2). Apparently, neither the calcium concentration used for matrix production nor the presence of NaCl (0.034 M in SGF) affected the drug release in acidic medium.

In both the acidic release media, the matrices were entirely depleted of calcium ions within 0.5 h (Fig. 3 and 4) and the carrier material was converted to insoluble alginic acid. As in water, the calcium release rate was independent of the encapsulated drug (Fig. 3) and of the monomer composition of the alginate in the matrices (data not shown). The transformation did not induce any visible changes in the morphology or swelling behaviour of the matrices. No disintegration or swelling could be observed in 0.1 M HCl or SGF, and SEM micrographs after completion of drug release revealed the same honeycomb surface structure and porous interior as after release in water (Fig. 5). Thus, the rapid drug release in the presence of acid can only be explained by a change in the microstructure of the carrier material.

Draget et al. (1994) recently reported a reduced gel strength following the conversion of a calcium alginate gel to an alginic acid gel. This was ascribed to the weaker hydrogen bonds

cross-linking the alginic acid gel. Similarly to the calcium alginate gels, the mechanical properties of the acid gels were found to be determined by the chemical composition of the alginate. In both the acid gels and the calcium alginate gels, the G blocks were most effective in building junctions. The findings of Draget et al. (1994) might explain why, in our studies, drug release proceeded much faster from the transformed alginic acid matrices than from the calcium alginate matrices. They also provide a possible reason for why the matrices made of high G alginates produces the lowest drug release rates in both 0.1 M HCl and water, as reported in a previous study (Østberg and Graffner, 1994).

3.3. Release properties in media containing non-gelling cations

In the two NaCl solutions the theophylline release proceeded rapidly and was complete within 1.5 h (Fig. 2). The matrices swelled extensively during the release testing, and became loose gel structures which kept their integrity even after 24 h in the media. Drug release was more rapid in the 0.1 M solution than in the 0.034 M solution, but was little affected by the calcium concentration used for matrix production (Table 2).

The swelling of the matrices was caused by the exchange of the cross-linking calcium ions with

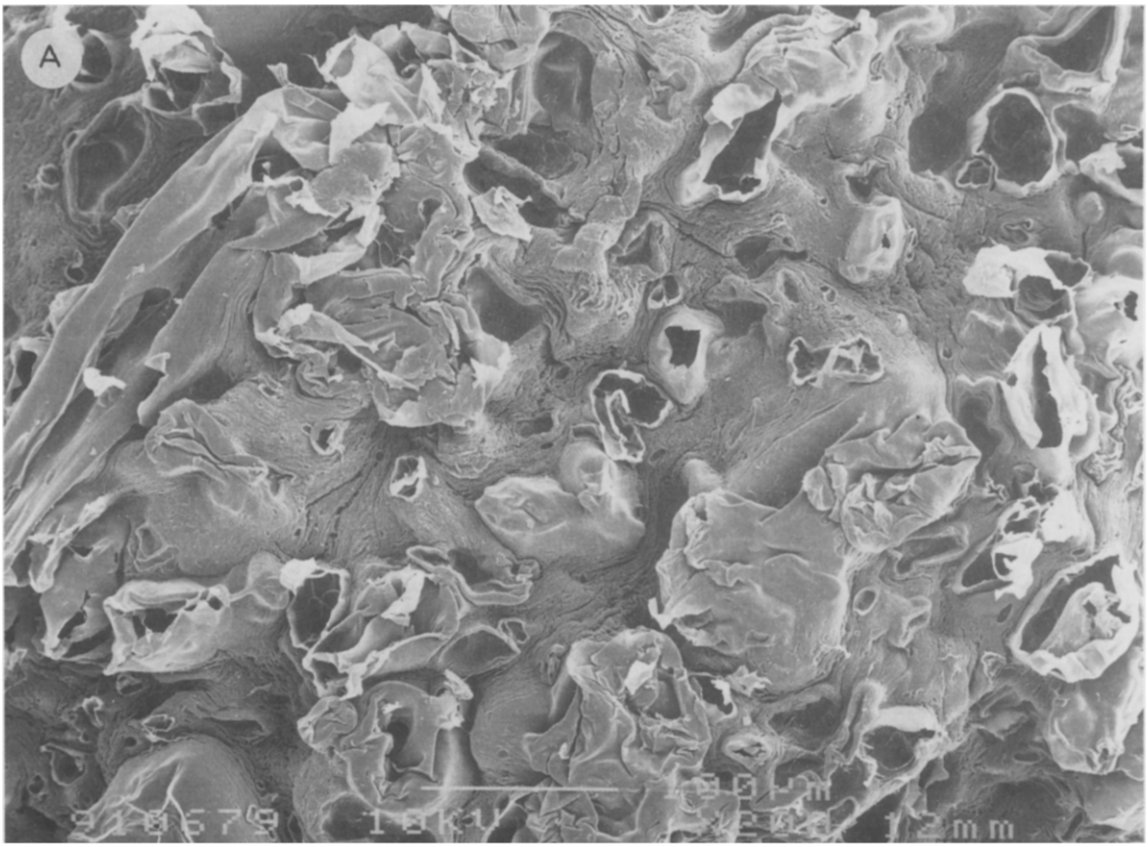

Fig. 5. Typical SEM pictures of a matrix surface (a) and cross-section (b) after completion of drug release in water, 0.1 M HCl or SGF.

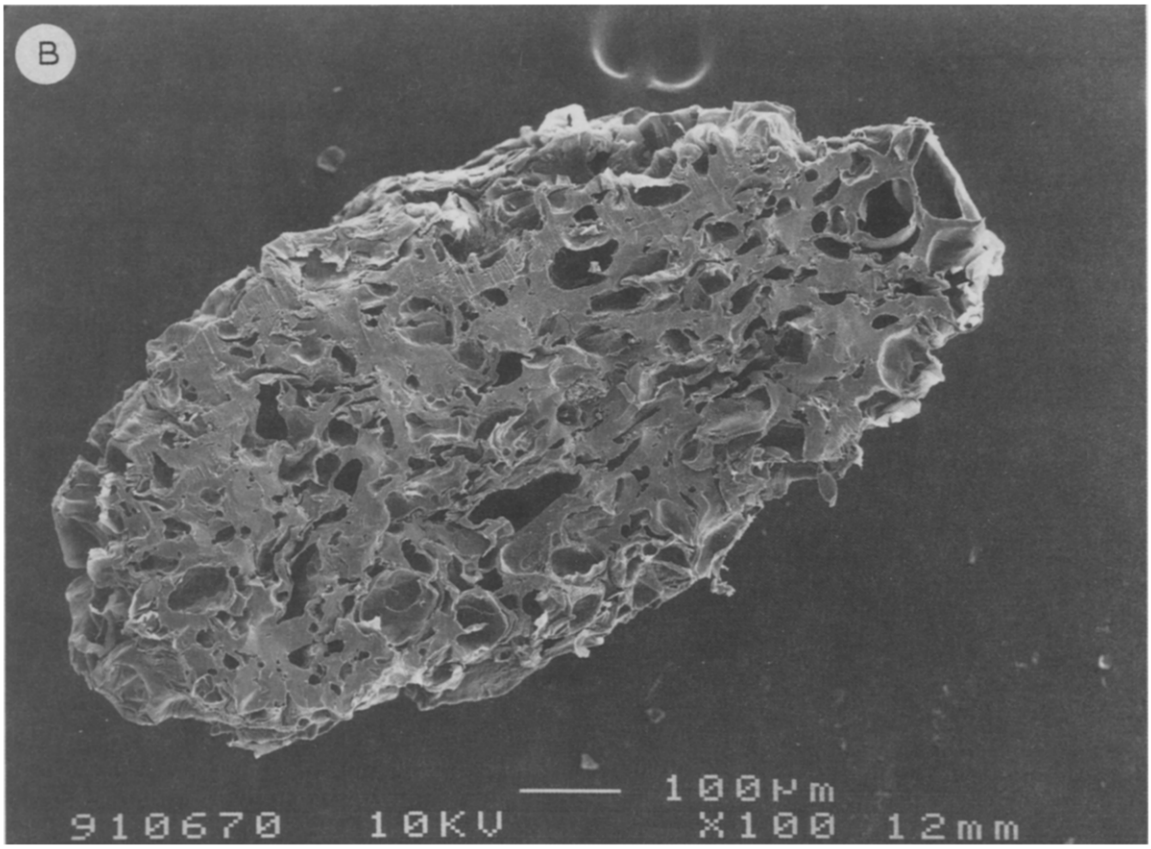

Fig. 5 (continued).

the non-gelling sodium ions. The partial formation of soluble sodium alginate, induced water uptake in the dehydrated gels. The calcium release curves in Fig. 4 show that ion exchange proceeded more slowly than drug release and that the replacement was not complete. In 0.1 M NaCl, $t_{50\%}$ for calcium release was 41 min and the amount released comprised 86% of the total calcium content. The corresponding figures obtained in 0.034 M NaCl were 89 min and 75%, respectively. Obviously, the amount of calcium remaining in the swollen polymer was sufficient to prevent total destruction of the gel bead structure.

The simultaneous presence of acid in a 0.034 M NaCl solution prevented swelling of the matrices as demonstrated by the lack of swelling in SGF. In SGF the release process was governed by the transformation of the carrier material to alginic acid rather than to the soluble sodium alginate. Addition of calcium or other gel-inducing cations to the NaCl solutions will also suppress matrix swelling (Smidsrød and Skjåk-Bræk, 1990).

3.4. Release properties in the presence of a calcium sequestrant

In SIF, which is a 0.05 M phosphate buffer, the matrices swelled and eventually dissolved, producing theophylline release rates that were even higher than in the NaCl solutions (Fig. 2 and Table 2). The swelling and destruction of the matrices were due to the sequestration of the cross-linking calcium ions by the phosphate. Insoluble calcium phosphate was formed, which made the medium turn slightly turbid during the release studies. Other substances with high affinity for calcium, for example, carbonate, citrate

and lactate, can also be expected to affect the release behaviour of the matrices in the same way.

Because of possible interference with phosphate, calcium release was not studied in SIF. Nevertheless, it was assumed to be both rapid and complete due to the rapid swelling and total dissolution of the matrices. In addition to phosphate, SIF also contained non-gelling cations like potassium and sodium ions. The effects of the simultaneous presence of these ions on the matrix behaviour were, however, not explained.

4. Conclusions

The drug release properties of the calcium alginate minimatrices are very sensitive to the composition of the dissolution medium. The calcium ions cross-linking the alginate are readily exchanged with H^+ and non-gelling cations like sodium. They are also rapidly sequestered by solutes with a high affinity for calcium. In media containing any of these substances, the encapsulated drugs are released quite rapidly due to changes that occur in the carrier material of the matrices. Pure water seems to be the only medium in which the matrices are able to provide extended release of the two least soluble model drugs tested in the present study. Hence, without modifications, the minimatrices do not seem worthy of further investigation as a possible oral controlled release system for low molecular weight drugs.

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References

Balz, E., Einig, H. and Dresen, P., Arzneimittel-Depotform auf Alginatbasis. *European Patent Application, 0 366 868 A1*, 1990.

Draget, K.I., Skjåk-Bræk, G. and Smidsrød, O., Alginic acid gels; The effect of alginate chemical composition and molecular weight. *Carbohydr. Polym.*, (1994) in press.

Florey, K., *Analytical Profiles of Drug Substances*, Vol. 3, Academic Press, New York, 1974.

Florey, K., *Analytical Profiles of Drug Substances*, Vol. 4, Academic Press, New York, 1975.

Fu Lu, M., Woodward, L. and Borodkin, S., Xanthan gum and alginate based controlled release theophylline formulations. *Drug Dev. Ind. Pharm.*, 17 (1991) 1987–2004.

Horder, R., Banks, M. and Hoadley, T.H., Slow release solid preparation. *European Patent Application, 0 188 040 A1*, 1986.

Ojantakanen, S., Hannula, A.-M., Marvola, M., Klinge, E. and Mäkipää, M., Bioavailability of ibuprofen from hard gelatin capsules containing sucralfate or sodium alginate as a diluent. *Eur. J. Pharm. Biopharm.*, 39 (1993) 197–201.

Østberg, T. and Graffner, C., Calcium alginate matrices for oral multiple unit administration: I. Pilot investigations of production method. *Acta Pharm. Nord.*, 4 (1992) 201–208.

Østberg, T. and Graffner, C., Calcium alginate matrices for oral multiple unit administration: III. Influence of calcium concentration, amount of drug added and alginate characteristics on drug release. *Int. J. Pharm.*, (1994) in press.

Pfister, G., Bahadir, M. and Korte, F., Release characteristics of herbicides from Ca alginate gel formulations. *J. Controlled Release*, 3 (1986) 229–233.

Shiraishi, S., Imai, T. and Otagiri, M., Controlled release preparation of indomethacin using calcium alginate gel. *Biol. Pharm. Bull.*, 16 (1993) 1164–1168.

Smidsrød, O. and Skjåk-Bræk, G., Alginate as immobilization material. *Trends Biotechnol.*, 8 (1990) 71–78.

Tateshita, K., Sugawara, S., Imai, T. and Otagiri, M., Preparation and evaluation of a controlled-release formulation of nifedipine using alginate gel beads. *Biol. Pharm. Bull.*, 16 (1993) 420–424.

Timmins, P., Delargy, A.M., Minchom, C.M. and Howard, J.R., Influence of some process variables on product properties for a hydrophilic matrix controlled release tablet. *Eur. J. Pharm. Biopharm.*, 38 (1992) 113–118.

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