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# Evaluation of Alginate Compressed Matrices as Prolonged Drug Delivery Systems

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**ABSTRACT** This research investigated the use of sodium alginate for the preparation of hydrophylic matrix tablets intended for prolonged drug release using ketoprofen as a model drug. The matrix tablets were prepared by direct compression using sodium alginate, calcium gluconate, and hydroxypropylmethylcellulose (HPMC) in different combinations and ratios. In vitro release tests and erosion studies of the matrix tablets were carried out in USP phosphate buffer (pH 7.4). Matrices consisting of sodium alginate alone or in combination with 10% and 20% of HPMC give a prolonged drug release at a fairly constant rate. Incorporation of different ratios of calcium gluconate leads to an enhancement of the release rate from the matrices and to the loss of the constant release rate of the drug. Only the matrices containing the highest quantity of HPMC (20%) maintained their capacity to release ketoprofen for a prolonged time.

**KEYWORDS:** Sodium alginate, Calcium gluconate, Ionic interaction, Prolonged release, Hydrophilic matrix

## INTRODUCTION

Compressed hydrophilic matrices are commonly used in preparing oral prolonged release dosage forms. They are usually easy and economical to formulate [1].

Sodium alginate (NaAlg), a water soluble salt of alginic acid, is a natural polysaccharide extracted from marine brown algae. It contains 2 uronic acids, β-D-mannuronic acid (M) and α-L-guluronic acid (G), and it is composed of homopolymeric blocks MM or GG, and blocks with an alternating sequence (MG blocks) [2,3]. NaAlg has been used as a matrix for entrapment of drugs [4, 5] and macromolecules [6-8]). Some of NaAlg's applications relate to a particular property: it can form hydrophilic gels by interaction with bivalent metal ions [9]. Since alginate gel can easily be formed by this ionic interaction in aqueous medium, gel beads are commonly obtained by dropping solutions of sodium alginate into solutions of calcium chloride [7, 10, 11].

The research investigated the use of NaAlg for the preparation of hydrophilic matrix tablets intended for prolonged drug release, using ketoprofen as a model drug. Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) used for relief of acute pain and in chronic diseases such as rheumatoid arthritis. Ketoprofen's plasma elimination half-life is 1 to 3 hours [12], so it must be administered at least twice daily to maintain therapeutic plasma level. Ketoprofen is therefore a good candidate for controlled release dosage forms.

Formulations containing ketoprofen and NaAlg, alone or in combination with calcium gluconate (CaGlu) and hydroxypropylmethylcellulose (HPMC), were prepared. The presence of calcium gluconate was in relation to the importance of calcium ions to the alginate gelling mechanism: in fact the ionic interactions between guluronate blocks and calcium ions determine the formation of a cross-linked gel. The matrices (containing 100 mg of drug) were obtained by direct compression of mixtures of the components at different compression forces. In vitro release tests (phosphate buffer pH 7.4) and in vitro erosion studies were carried out.

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# MATERIALS AND METHODS

## Materials

The following materials were used: ketoprofen, MW = 254.3, melting point, (m.p.) = 93 to 95°C and sodium alginate, high viscosity, 2.0% wt/vol aqueous solution at 25°C had viscosity of approximately 14 000 cPs (manufacturer value), (Sigma Chemical Co, St Louis, MO); calcium D-gluconate (Aldrich Chemical Company Inc, Milwaukee, WI); hydroxypropylmethylcellulose, Metolose¨ 90SH, 15,000 cPs (Shin-Etsu Chemicals, Tokyo, Japan).

## Preparation of compressed matrices

To assess the influence of the materials used (NaAlg, CaGlu, and HPMC) on the release of the drug, the matrix tablets were prepared without other excipients, and they were used as model formulations.

The matrices contain 20% of drug, corresponding to 100 mg of ketoprofen, and are divided into groups A, B, and C(**Table 1**). Each group is characterized by a different HPMC content: 0% (A), 10% (B), and 20% (C). Within each group there are 6 formulations, each characterized by a different NaAlg:CaGlu weight ratio: 1:0 (A1, B1,C1); 5:1 (A2, B2, C2); 2:1 (A3, B3, C3); 1:1 (A4, B4, C4); 1:2 (A5, B5, C5); and 0:1 (A6, B6, C6).

**Table 1.** Compositions of Matrices Prepared by Direct Compression*

| Matrix | Ketoprofen | NaAlg | CaGlu | HPMC |
|---|---|---|---|---|
| A1<br>B1<br>C1 | 20.0 | 80.0<br>70.0<br>60.0 | 0.0 | 0.0<br>10.0<br>20.0 |
| A2<br>B2<br>C2 | 20.0 | 66.7<br>58.3<br>50.0 | 13.3<br>11.7<br>10.0 | 0.0<br>10.0<br>20.0 |
| A3<br>B3<br>C3 | 20.0 | 53.3<br>46.7<br>40.0 | 26.7<br>23.3<br>20.0 | 0.0<br>10.0<br>20.0 |
| A4<br>B4<br>C4 | 20.0 | 40.0<br>35.0<br>30.0 | 40.0<br>35.0<br>30.0 | 0.0<br>10.0<br>20.0 |
| A5<br>B5<br>C5 | 20.0 | 26.7<br>23.3<br>20.0 | 53.3<br>46.7<br>40.0 | 0.0<br>10.0<br>20.0 |
| A6<br>B6<br>C6 | 20.0 | 0.0 | 80.0<br>70.0<br>60.0 | 0.0<br>10.0<br>20.0 |

*All values are percentages. Each matrix contains 100 mg of ketoprofen; total weight 500 mg. NaAlg =sodium alginate; CaGlu = calcium gluconate; HPMC = hydroxypropylmethylcellulose.

The drug and the corresponding quantities of the other components (NaAlg, HPMC, and CaGlu) were mixed in a Turbula apparatus (W.A. Bachofen, Basel, Switzerland) at 90 rpmfor 15 minutes; the empty volume of the jar used for the mixing process was about 40%. The total weight of the powder mixture used to prepare each batch was always 100 g. The matrix tablets were prepared by direct compression at 3 different levels of compression force (1000, 2000, and 3000 kg) using a hydraulic press (Perkin Elmer, Bucks, UK) equipped with 13-cm flat punches.

## In vitro release tests

In vitro release tests were carried out using the USP 23 n.1 dissolution test apparatus (basket). The basket apparatus was used in order to reduce the variability due to the hydrodinamic conditions of the test and to overcome the problem due to possible sticking of the gelled matrix on the wall of the dissolution container. The dissolution medium was USP phosphate buffer, pH 7.4 (1000 mL, 37°C), and the speed of rotation was 100 rpm. An automatic sampling and analysis system was used (Erweka DT 70, Erweka GmbH, Heusenstamm, Germany) and ketoprofen concentration was spectrophotometrically determined at 255 nm (Hitachi spectrophotometer, model U-2001, Hitachi Instruments, Tokyo, Japan). All release tests were run in triplicate, and mean values are reported (SD within about 4%).

## Erosion / release studies

In vitro erosion / release studies were carried out on the compressed matrices using the USP n.1 dissolution test apparatus (basket) according to the procedure described by Ranga Rao et al. [13]. The tests were performed under the conditions described above. After different intervals of time, the content of ketoprofen released in the dissolution medium was spectrophotometrically determined when each basket containing the gelled/partially eroded matrix was taken out of the dissolution medium and placed in a circulating hot air oven (about 60°C). The matrix was left in the oven until the residual was dried to constant weight. Percentage of residual matrix weight and corresponding percentage of drug released vs time (h) are reported. The test was run in triplicate; mean values are reported (SD within about 5%).

## RESULTS AND DISCUSSION

**Figures 1** , **2** , and **3** show the in vitro release profiles of A, B, and C matrices, respectively.

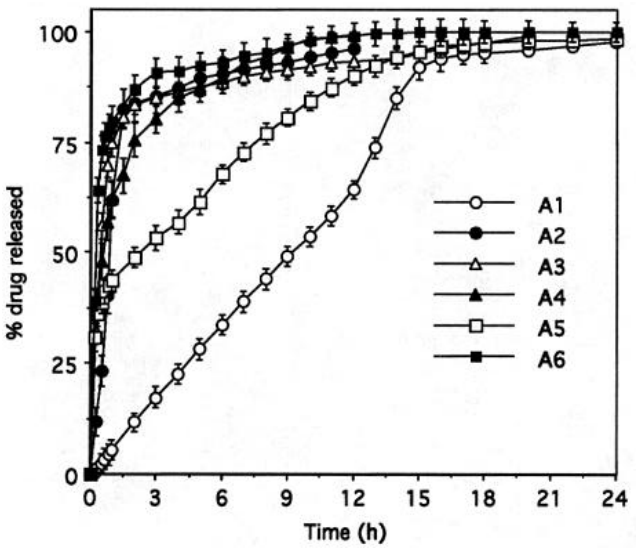


**Figure 1.** Release profiles (pH 7.4) of A matrices (applied compression force 3000 kg).

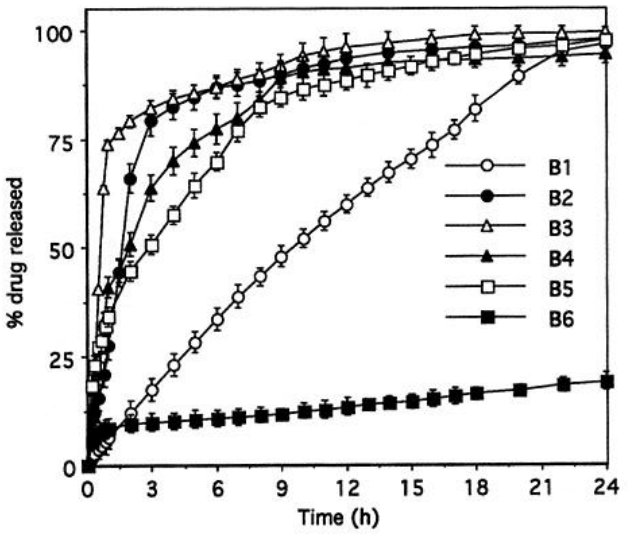


**Figure 2.** Release profiles (pH 7.4) of B matrices (applied compression force 3000 kg).

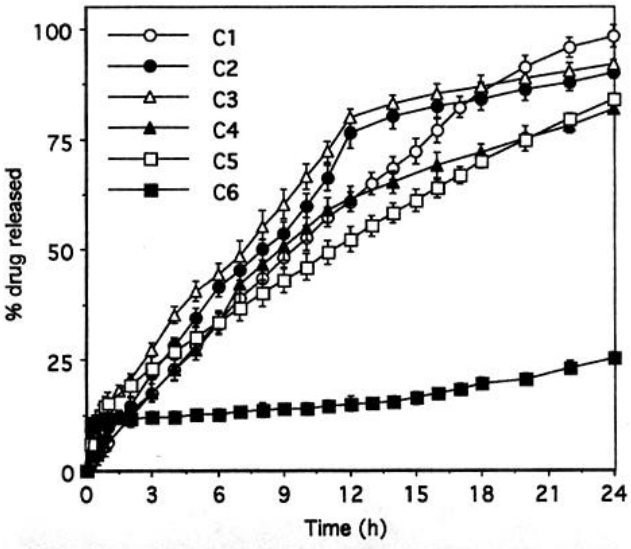


**Figure 3.** Release profiles (pH 7.4) of C matrices (applied compression force 3000 kg).

A1, B1, and C1 matrices were prepared with NaAlg and contained 0% (A1), 10% (B1), and 20% (C1) of HPMC, but no CaGlu. Despite their different compositions, the matrices had similar release behavior: in all cases a sustained drug release was reached. For the first 12 hours of dissolution, which corresponds to about 60% of released drug, the 3 matrices had almost identical profiles, characterized by a fairly constant rate.

The drug release data were fitted to the following equation [14]:

$$\mathbf{Mt/M = Kt^n}$$

where Mt/M is the fractional release of the drug at time t, k is a constant incorporating structural and geometric characteristics of the release device. and n is the release exponent, indicative of the mechanism of release. The data were fitted for 60% of drug released. The values of n and the coefficient of determination r2 obtained for A1-C1 systems are reported in **Table 2.**

These formulations had values of n very close to unity, particularly in the case of A1 matrices, containing only NaAlg, indicating that they behave as zero-order release systems. After 12 hours, the matrices constituted by NaAlg alone (A1) became quicker in their release, while the other 2 formulations containing

**Table 2.** Exponents (n) and coefficient of determination ($r^2$) according to $Mt/M = K t^n$

| Matrix | n | $r^2$ |
|---|---|---|
| A1 | 1.045 | 0.998 |
| B1 | 0.904 | 1.000 |
| C1 | 0.901 | 1.000 |
| C2 | 0.835 | 0.998 |
| C3 | 0.645 | 0.991 |
| C4 | 0.811 | 0.990 |
| C5 | 0.465 | 0.991 |

HPMC (B1 and C1) continued their release at an almost constant rate. These results may be related to their different behavior in the dissolution medium. During the in vitro tests all the systems were subjected to both a gelation process and to a slow a progressive erosion process. After about 12 hours of dissolution, the gelled matrices of the A1 formulations began to disintegrate more irregularly, which led to an increase in drug release and a consequent loss of the constant release rate. B1 and C1 were subjected to the slow and progressive erosion process until almost all the drug was released.

CaGlu was chosen as an additional excipient because calcium ions are important to the alginate gelling mechanism. The presence of CaGlu caused a notable change in the release behavior of the systems. In fact, a comparison of the release profiles of A2-C2 matrices, containing NaAlg and CaGlu in the ratio 5:1, respectively with 0% (A2), 10% (B2), and 20% (C2) of HPMC shows that the matrices containing 0% and 10% HPMC released about 80% of ketoprofen in less than 3 hours; C2 matrices, containing 20% HPMC extended the drug release over about 20 hours, but the corresponding release rate pattern was not linear.

A3-C3 formulations were characterized by an NaAlg:CaGlu 2:1 weight ratio. An increase in the quantity of CaGlu produced results similar to those seen for A2-C2 matrices. In fact, A3 (0% HPMC) and B3 (10 % HPMC) did not provide a sustained drug release: about 80% of ketoprofen was released within 2 hours. Only C3 matrices were able to extend release of ketoprofen but, as with C2, not in a linear way (**Table 2**).

The other 2 groups of formulations, A4-C4 and A5-C5, were prepared using NaAlg:CaGlu ratios of 1:1 and 1:2, respectively. As shown in **Figures 1**, **2**, and **3**, only C4 and C5 systems were able to give a sustained drug release; C4 matrices showed a release rate pattern nearly identical to those of formulations containing no CaGlu. After an initial burst effect, C5 matrices showed an almost constant drug release that was slower than the reference formulations containing no CaGlu: in 24hours, only 75% of ketoprofen was released.

All these results showed that the presence of CaGlu in combination with sodium alginate generally led to a lower capacity of the systems in controlling the release of the drug for a prolonged time and only the systems containing the highest quantity of HPMC (20%) maintained this capacity. The observation that uncross-linked systems had slower release rates than systems cross-linked with calcium can be at first sight somewhat surprising. However it should be remembered that the hydrated layer of the matrix and its subsequent physical properties were critical in determining the drug release. Sodium alginate was effective as a carrier with or without HPMC, but internal calcium ions, which ionically cross-link alginate at a molecular level, gave rise to changes in its characteristics and particularly in its hydration. After placing the matrix in contact with the dissolution medium, calcium crosslinking that occured in the gelled layer of the matrices probably determined inhomogeneities in the structure of the hydrated gel. The presence of the calcium salt could also have a channelling effect that determined more rapid media penetration into the inner layers of the matrix. Such an open structure may do little to affect diffusional pathways. All this caused irregular disintegration (instead of slow and progressive erosion) and in some cases a catastrophic failure of the systems: the final result of this process was a drug release rate which occured quicker and not in linear way.

A comparison of the release profiles of matrices containing CaGlu alone (A6), with 10% HPMC (B6) and with 20% HPMC (C6) showed a very rapid release rapid rate of drug in tablets containing only ketoprofen and CaGlu (A6). This particular behavior was due to the rapid disintegration of the matrix tablet constituted only by CaGlu and drug. A very slow release rate was observed in the tablets containing 10% and 20% HPMC (B6 and C6). In these 2 cases only the outer layer of the tablets was gelled and when they were recovered at the end of the test they

showed their inner part almost dry.

The matrices were subjected to both to a gelation process and an erosion process during the release tests, erosion/release studies were carried out on some the formulations. The results obtained from C5 matrices for the first 9 hours of the test, are presented in **Figure 4** as percentage residual (wt/wt) of eroded matrix and percentage of drug released at the corresponding times vs time (h). These results show that the matrix erosion process followed a pattern that corresponded to the profile of the drug release process.

The influence of compression force on the drug release rate was almost negligible. As shown in **Figure 5**, the release curves obtained from C4 matrices and prepared at 3 different compression forces were almost identical. Analogous results were obtained from the other matrices (data not reported).

These results indicate that applied compression force has little effect on drug release profiles over this range. It may be that the formation of the gel layer following immersion of these systems in the dissolution medium was the first step; drug release then proceeded via a combination of diffusion and erosion. The properties of the gelled layer seem less dependent on the state of the dry polymer matrix in the tablet, and thus of applied compression force, as observed previously [1].

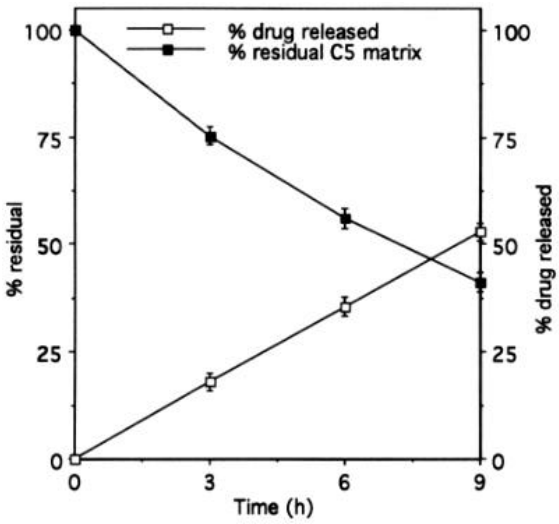


**Figure 4.** Erosion / release studies of C5 matrices (applied compression force 3000 kg).

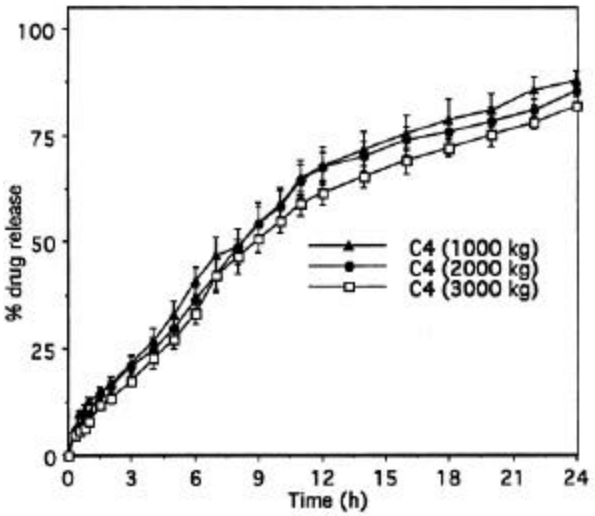


**Figure 5.** Influence of compression force on in vitro drug release from C4 matrices (applied compression forces: 1000, 2000, and 3000 kg).

## CONCLUSIONS

This research shows that sodium alginate can be used to modify release rates in hydrophilic matrix tablets prepared by direct compression. The results showed that the sustained release effects of sodium alginate matrices and of mixed matrices of sodium alginate and hydroxypropylmethylcellulose were the best among the formulations studied. They behave as zero-order release systems. The addition of calcium gluconate leads to a change in the release capacities of the matrices. Despite the presence of calcium ions and thus the possibility of an ionic interaction, the main effect of this excipient is an increase in ketoprofen release from the matrices. Also, only the formulations containing the highest quantity of hydroxypropylmethylcellulose are able to give a prolonged drug release.

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