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Release characteristics of ibuprofen from excipient-loaded alginate gel beads

Sung-Joo Hwang [a,*], Gye Ju Rhee [a], Ki Myung Lee [a], Kyoung-Hee Oh [b], Chong-Kook Kim [b]

[a] *College of Pharmacy, Chungnam National University, 220, Kung-Dong, Yousung-Gu, Taejon 305-764, South Korea*
[b] *College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Gu, Seoul 151-742, South Korea*

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Abstract

Ibuprofen-loaded alginate beads were prepared and found to optimize in vitro release with zero-order kinetics. The release of ibuprofen could be controlled by adding excipients or by adjusting the NaAlg/ibuprofen ratio.

Keywords: Alginate bead; Ibuprofen; Excipient; In vitro release

Polysaccharides such as alginic acid (Kim and Lee, 1992), agar (El-Helw and El-Said, 1988), chitin and chitosan (Kawashima et al., 1985; Bodmeier et al., 1989) have been used to agglomerate drugs for controlled drug delivery systems. When an aqueous solution of sodium alginate (NaAlg) is added dropwise to an aqueous solution of calcium chloride, spherical alginate beads with regular shape and size are produced, since an insoluble calcium alginate matrix is formed by the cation exchange between Na^+ and Ca^{2+} (Haug and Smidsrod, 1965). Alginate beads have the following advantages: (1) Alginate is known to be nontoxic as taken orally and to protect the mucous membrane of the upper gastrointestinal tract from the irritation of chemicals (Daigo et al., 1982). (2) Since dried alginate beads have the property of reswelling, they can act as a controlled-release system. (3) Since the property of reswelling is susceptible to the environmental pH, acid-sensitive drugs incorporated into the beads would be protected from gastric juice (Segi et al., 1989). Therefore, drug-loaded alginate beads might provide these advantages for nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen which leads to gastric irritation. Ibuprofen is a well-known hydrophobic NSAID administered orally (Wilson et al., 1989). Due to its short biological half-life and the hazards of gastric irritation, ibuprofen is a potential candidate for preparing prolonged or controlled release drug products (Dubernet et al., 1990).

This work was aimed the development of ibuprofen-loaded alginate beads as a controlled release oral delivery system. Ibuprofen-loaded alginate beads were prepared and the effects of the addition of excipients and the NaAlg/ibuprofen

* Corresponding author.

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ratios on the loading efficiency and the drug release were investigated.

Microcrystalline cellulose (Avicel® PH102, Asahi Chemical Co., Tokyo, Japan), sodium starch glycolate (Primojel®, sodium carboxymethylstarch, KSH-Deuschland GmbH, Germany), crospovidone (Kollidon® CL, cross-linked polyvinylpyrrolidone, BASF AG, Ludwigshafen, Germany), cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®, croscarmellose, FMC Co., Philadelphia, USA) and polyvinylpyrrolidone (PVP K-30, Kollidon® 30, BASF AG, Ludwigshafen, Germany) were used as excipients.

For the preparation of alginate beads, ibuprofen was added to 10 g of 2.0% NaAlg solution with NaAlg/ibuprofen ratios of 1:0, 1:0.5, 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10; if necessary, excipient (Ac-Di-Sol, Avicel PH102, Kollidon CL, Primojel, PVP K-30) was added and completely dispersed with a homogenizer. Using a 50 ml burette, this suspension was transferred dropwise to gently agitated calcium chloride solution (0.1 M, 50 ml) within a period of 20 min. The droplets were slowly stirred for 1 h to cross-link the alginate gel beads. The alginate beads were then separated from the solution and dried at 60°C for 12 h. The amount of PVP K-30 added was half of that of the other excipients, since NaAlg-PVP K-30 solution did not form drops due to its high viscosity.

The swelling test was performed in pH 6.8 simulated intestinal fluid (600 ml), using USP XXII dissolution apparatus I (basket method) at 100 rpm. The baskets containing the beads were removed from the dissolution medium at designated time intervals. The swelling percentages were calculated as a weight percentage based on the weight change of the swollen bead kept in the basket.

It was observed that the excipient-loaded alginate beads were very spherical and elegant even after drying compared with the beads without excipients. It was also noted that the higher loading dose of ibuprofen produced more regular and spherical beads. This might be due to the fact that ibuprofen is insoluble and uniformly dispersed in the matrix of alginate polymer. The amounts of ibuprofen incorporated into alginate beads with NaAlg/ibuprofen ratios of 1:0.5, 1:1,

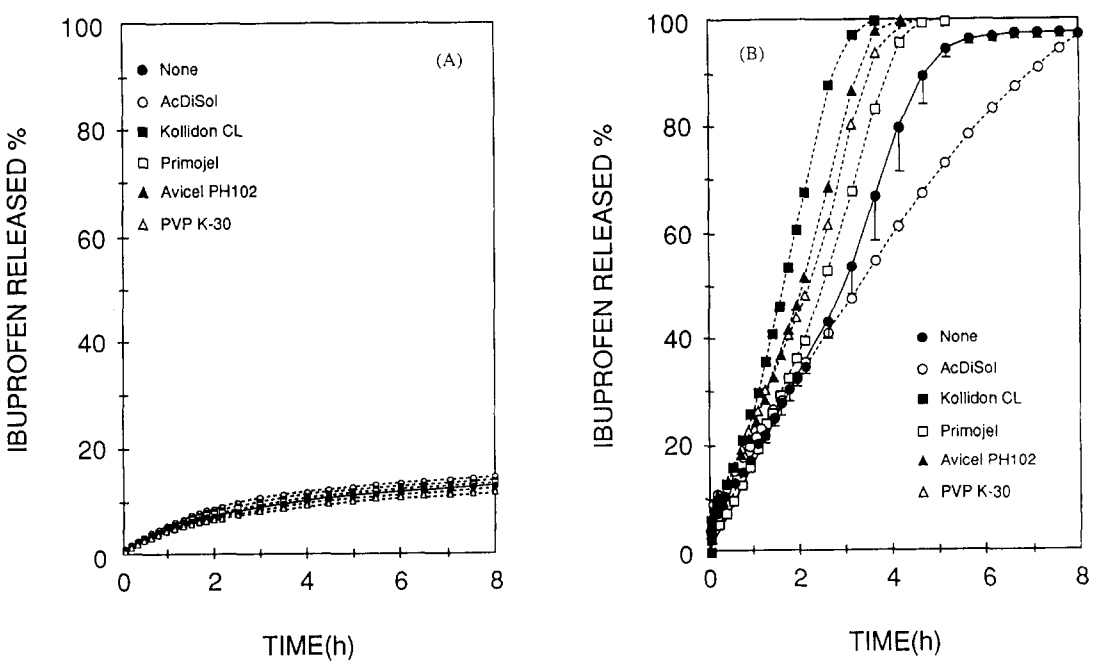

Fig. 1. In vitro release of ibuprofen from alginate beads with NaAlg/ibuprofen ratio of 1:10 at pH 1.2 (A) and pH 6.8 (B).

1:2, 1:4, 1:6, 1:8 and 1:10 were determined by UV spectrophotometry (Uvikon 860, Kontron Instruments Co., Basel, Switzerland) at 274 nm after dissolving the beads in pH 7.2 phosphate buffer. The incorporation efficiencies of ibuprofen in alginate beads with various excipients added were also determined. The actual contents of ibuprofen were very close to the theoretical values. All the loading efficiencies (% of the actual content compared to the theoretical content) were greater than 93% and were not affected by the ratio of NaAlg to ibuprofen and the added excipient under the current experimental conditions.

As shown in Fig. 1, the release of ibuprofen from alginate beads at pH 6.8 was more rapid than that at pH 1.2. 10–15% of ibuprofen was released at pH 1.2, while almost 100% of ibuprofen was released at pH 6.8 for 8 h. At pH 1.2, ibuprofen was released by diffusion only, since at this pH alginate beads scarcely swelled and eroded. On the other hand, at pH 6.8, since the alginate beads swelled to a great extent and eroded thereafter, zero- or first-order release kinetics resulted for both diffusion and swelling of the matrix.

Ibuprofen-loaded alginate beads containing various excipients were prepared and the effect of these excipients on the release behavior of ibuprofen from alginate beads was investigated as shown in Fig. 1. The release patterns of ibuprofen were not significantly changed by adding excipients at pH 1.2, however, the release rate generally increased at pH 6.8. Acceleration of ibuprofen release by excipients conformed to the descending order: Kollidon® CL > Avicel® PH102 > PVP K-30 > Primojel® > Ac-Di-Sol®. Kollidon® CL increased ibuprofen release greatly due to its high capillary activity and low viscosity (Kornblum and Stoopak, 1973). Ac-Di-Sol® demonstrated no effect on the release rate nor delay in the release of ibuprofen, possibly due to the high viscosity of the hydrated and gelled matrix in aqueous medium (Shah et al., 1981). Therefore, if excipients are to be employed in order to obtain a regular and spherical dried alginate bead, their effects on the drug release should be investigated.

Finally, the rate constants of ibuprofen from the beads at pH 6.8 with different ratios of NaAlg/ibuprofen were calculated (Table 1). For beads with a high NaAlg/ibuprofen ratio, first-order kinetics predominate since the path length of diffusion increases with time to a greater extent compared to the extent of erosion of the beads due to the considerable swelling. However, for the beads with a low NaAlg/ibuprofen ratio, both a moderate increase in diffusion path length and a moderate erosion of alginate beads led to

Table 1
Effect of the ratio of NaAlg to ibuprofen on the in vitro release rate constants of ibuprofen from alginate beads containing 150 mg of ibuprofen in pH 6.8 simulated intestinal fluid

NaAlg/ibuprofen	First-order (k [a] ± SE [b]) ($\times 10^{-3}$) (h^{-1})	Zero-order (k ± SE) (mg h^{-1})	Adequate model
1:1	432.6 ± 10.37 (0.989) [c]	26.06 ± 1.530 (0.734)	first-order
1:2	402.7 ± 10.39 (0.988)	25.44 ± 0.903 (0.919)	first-order
1:4	377.2 ± 7.30 (0.991)	24.16 ± 0.763 (0.933)	first/zero-order
1:6	422.1 ± 29.89 (0.913)	27.99 ± 0.235 (0.997)	zero-order
1:8	369.3 ± 33.07 (0.868)	26.04 ± 0.233 (0.996)	zero-order
1:10	490.8 ± 47.21 (0.850)	28.96 ± 0.481 (0.987)	zero-order

[a] Rate constant.
[b] Standard error of the mean.
[c] Coefficient of determination (r^2).

zero-order kinetics. The alginate beads with NaAlg/ibuprofen ratios of 1:1 and 1:2 showed first-order release patterns at pH 6.8. However, those with NaAlg/ibuprofen ratios of 1:6, 1:8 and 1:10 displayed zero-order release patterns. The alginate beads with an NaAlg/ibuprofen ratio of 1:4 showed a transition state from first-order to zero-order release patterns.

In conclusion, ibuprofen-loaded alginate beads could optimize the in vitro release with zero-order kinetics for a controlled release drug delivery system and the release rate of ibuprofen could be adjusted by adding the excipients or by varying the NaAlg/ibuprofen ratio. When excipients are used to obtain regular and spherical beads, their effects on drug release should be investigated.

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