DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 5, pp. 491–495, 2004

RESEARCH PAPER

# Oral Controlled Release Formulation for Highly Water-Soluble Drugs: Drug–Sodium Alginate–Xanthan Gum–Zinc Acetate Matrix

**W. M. Zeng, Ph.D.***

Research and Development, Toronto Institute of Pharmaceutical Technology, Toronto, Ontario, Canada

## ABSTRACT

An oral controlled release formulation matrix for highly water-soluble drugs was designed and developed to achieve a 24-hour release profile. Using ranitidine HCl as a model drug, sodium alginate formulation matrices containing xanthan gum or zinc acetate or both were investigated. The caplets for these formulations were prepared by direct compression and the in vitro release tests were carried out in simulated intestinal fluid (SIF, pH7.5) and simulated gastric fluid (SGF, pH1.2). The release of the drug in the sodium alginate formulation containing only xanthan gum completed within 12 hours in the SIF, while the drug release in the sodium alginate formulation containing only zinc acetate finished almost within 2 hours in the same medium. Only the sodium alginate formulation containing both xanthan gum and zinc acetate achieved a 24-hour release profile, either in the SIF or in the pH change medium. In the latter case, the caplet released in the SGF for 2 hours was immediately transferred into the SIF to continue the release test. The results showed that the presence of both xanthan gum and zinc acetate in sodium alginate matrix played a key role in controlling the drug release for 24 hours. The helical structure and high viscosity of xanthan gum might prevent zinc ions from diffusing out of the ranitidine HCl–sodium alginate–xanthan gum–zinc acetate matrix so that zinc ions could react with sodium alginate to form zinc alginate precipitate with a cross-linking structure. The cross-linking structure might control a highly water-soluble drug to release for 24 hours. Evaluation of the release data showed the release mechanism for the novel formulation might be attributed to the diffusion of the drug.

*Key Words:* Sodium alginate; Xanthan gum; Zinc acetate; Drug delivery; Highly water-soluble drug.

*Correspondence: W. M. Zeng, Ph.D., Research and Development, Toronto Institute of Pharmaceutical Technology, 55 Town Center Court—Suite 200, Toronto, Ontario, M1P 4X4, Canada; Fax: 416-296-7077; E-mail: wenming@tipt.com.



DOI: 10.1081/DDC-120037479
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

## INTRODUCTION

The development of a monolithic matrix formulation for highly water-soluble drugs has been an interesting topic of research compared to the membrane coated systems. However, problems have been encountered for matrix systems for the oral controlled release delivery of freely water-soluble drugs—dose dumping, the burst phenomenon, and difficulty in achieving 24-hour linear release profile.[1] Recently, a new approach for in situ interactions between drug and electrolyte(s) has been designed to control the release of highly water-soluble drugs from oral hydrophilic monolithic systems,[2,3] in which the model drug diltiazem hydrochloride in conjunction with sodium bicarbonate and hydroxypropylmethlcellulose (HPMC)[2] and the model drug metoprolol tartrate in combination with sodium carbonate and poly(ethylene oxide) (PEO)[3] have respectively achieved a 24-hour release profile in a zero-order manner in a different pH environment.

Sodium alginate and xanthan gum are natural polymers, both of which have been employed as matrices for prolonged drug delivery systems.[4–9] Sodium alginate is a water-soluble salt of alginic acid, a naturally occurring, nontoxic polysaccharide found in all species of brown algae. Sodium alginate contains two uronic acids, β-D-mannuronic acid (M) and α-L-guluronic acid (G), and is composed of homopolymeric blocks MM or GG, and blocks with an alternating sequence, the MG blocks. It can form hydrophilic gels by interacting with many divalent cations except magnesium. Gelation occurs by cross-linking of the uronic acid units with divalent cations.[10] Cross-linking by calcium occurs primarily with the GG blocks to form the so-called ''egg-box'' structure.[11] However, it has been suggested that cross-linking with zinc may occur in the MM and MG blocks as well.[12]

Xanthan gum is an anionic polyelectrolyte with a β-(1→4)-D-glucopyranose glucan (as cellulose) backbone with side chains of -(3→1)-α-linked D-mannopyranose-(2→1)-β-D-glucuronic acid-(4→1)-β-D-mannopyranose on alternating residues. Slightly less than half (∼40%) of the terminal mannose residues are 4,6-pyruvated and the inner mannose is mostly 6-acetylated.[13] Each molecule consists of about 7000 pentamers and the gum is less polydisperse than most hydrocolloids. Its natural state has been proposed to be bimolecular, antiparallel double helices. It may form a very stiff intramolecular (single molecule hairpin) double stranded helical conformation by the annealing of the less stiff ''natural'' denatured elongated single-stranded chains. The glucan backbone is protected by the side chains, which lie alongside, making it relatively stable to acids, alkalis, and enzymes. In solution this polymer is known to tolerate high concentration of electrolytes and its viscosity is also nearly independent of pH and temperature.[8]

To date, only the poorly water-soluble drug ketoprofen in the sodium alginate matrix combined with HPMC has been investigated for 24-hour release with zero-order release kinetics.[5] The soluble drugs chlorpheniramine maleate[7] and pentoxifylline[9] in the tablets containing xanthan gum are released in 12 hours at a constant rate. Our preliminary exploration shows that inclusion of the highly water-soluble drug ranitidine HCl in sodium alginate matrix combined with xanthan gum could result in a 12-hour release profile. However, up to now, there have not been any reports on achieving a 24-hour release profile of highly water-soluble drugs from sodium alginate–xanthan gum matrix in combination with other agents.

The objective of the present study was to develop a sodium alginate matrix combined with xanthan gum and zinc acetate using the highly water-soluble drug ranitidine HCl as the model drug to achieve a 24-hour release profile.

## EXPERIMENTAL

### Materials

Ranitidine HCl was purchased from Pharmrite, North American Corporation (Edison, NJ). Sodium alginate (Keltone HVCR) was purchased from ISP Inc. (Canada). Xanthan gum was purchased from Gum Technology Corporation (USA). Zinc acetate was purchased from Alfa Aesar company (USA). Polyvinylpolypyrrolidone k90 (PVP k90) from ISP Inc. (Canada) and magnesium stearate from Wilco Inc. (Canada) were purchased respectively. Deionized water was used throughout the experiment.

### Methods

#### Preparation of Compressed Caplets

Table 1 shows three formulations composed of various quantities of materials used, in which each caplet contains 30% of drug, corresponding to 250 mg of ranitidine HCl.

The drug and the corresponding quantities of the other components except magnesium stearate were mixed in a high shear mixer (Robot Coupe, USA) for

*Table 1.* Composition of formulation prepared by direct compression.

| Formulation | Ranitidine HCl (%) | Sodium alginate (%) | Xanthan gum (%) | Zinc acetate (%) | PVP k90 (%) | Magnesium stearate (%) |
|---|---|---|---|---|---|---|
| A | 30 | 32 | 32 | 0 | 5 | 1 |
| B | 30 | 32 | 0 | 32 | 5 | 1 |
| C | 30 | 32 | 16 | 16 | 5 | 1 |

4 minutes. Prior to compression the mixture for each formulation was mixed with 1% magnesium stearate. The total weight of the powder mixture used to prepare each batch was always 50 g. The caplets, each weighing about 833.3 mg, were prepared by direct compression using a rotary tableting press (Stokes Compacting Equipment, USA) equipped with 15-mm oblong die and punches. The caplets were compressed to a crushing strength of 7–8 kg.

### In Vitro Release Tests

The in vitro dissolution tests of ranitidine HCl from the matrix caplets were carried out using the USP 23 dissolution test apparatus II (ERWEKA DT6, Heusenstamm, Germany) at the stirring speed of 50 rpm at 37±0.5°C in 900 ml of the dissolution medium. The dissolution medium consisted of either simulated gastric fluid (SGF, pH 1.2) or simulated intestinal fluid (SIF, pH 7.5). Also, a selected formulation was tested for dissolution using a pH change method by transferring the caplets after 2 hours in SGF to SIF. Ranitidine HCl concentration was spectrophotometrically determined either at 314 nm in the SIF or at 224 nm in the SGF, respectively (Ultraspec 2000, Amersham Pharmcia Biotech, Cambridge, England, UK). All release tests were run in triplicate, and mean values were reported (SD within about 5%). Sink conditions were maintained in all experiments.

## RESULTS AND DISCUSSION

Figure 1 shows that the ranitidine HCl in formulation A with 32% sodium alginate and 32% xanthan gum completely released within 12 hours in the SIF, while 94.7% of the drug in formulation B containing 32% sodium alginate and 32% zinc acetate released within 2 hours in the same medium. Only the drug in formulation C containing 32% sodium alginate, 16% xanthan gum, and 16% zinc acetate could achieve a 24-hour release profile with 95.5% of the drug released in the SIF within 24 hours. It appears that the presence of both zinc acetate and xanthan gum was crucial in controlling the release process.

In the SGF, the drug in formulation C released 96.0% within 16 hours, as shown in Fig. 2, which is much faster than 84.7% of formulation C in the SIF at the same time. After 41.6% of the drug released in the SGF for the first 2 hours, the release rate of the drug in formulation C slowed down in the SIF for the later 22 hours, with a total of 92.0% of the drug released within 24 hours.

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

$$M_t/M_\infty = kt^n \quad (1)$$

where $M_t$ and $M_\infty$=the amounts of drug release at time t and the overall amount released, respectively, k=a release constant incorporating structural and geometric characteristics of the release device, and n=a release exponent indicative of the mechanism of release. Generally, for a nonswellable matrix, n=0.5, 0.5<n<1.0, or n=1 for a slab or n=0.45, 0.45<n<1.0, or n=1.0 for a cylinder is indicative of Fickian release, anomalous transport, or zero-order or case II release,

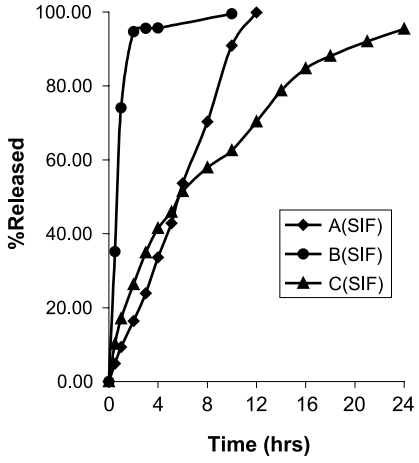


*Figure 1.* Release profiles of formulation A, B, and C in the SIF.

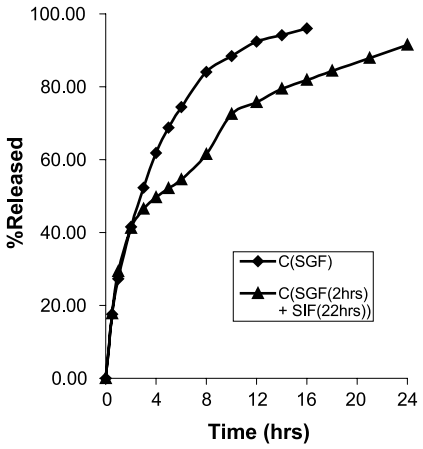


*Figure 2.* Release profiles of formulation C in the SGF and the SIF.

respectively, up to 60% of the release profile. However, for a swellable matrix, $n=0.45$, $0.45<n<0.89$, or $n=0.89$ for a cylinder is indicative of Fickian release, anomalous transport, or zero-order or case II release, respectively.

From model fitting, it was observed that the simple power law expression [Eq. (1)] provided an n value of 0.41 for formulation A, indicating a Fickian release mechanism. Furthermore, the released data of formulation A fitted very well with zero-order release kinetics from 0 to 10 hours, which may attributable to the role of xanthan gum that could control a drug release at a constant rate,[6] as the pure sodium alginate matrix with a soluble drug was completely eroded within 6 hours.[15]

Formulation B produced an n value of 1.49, almost doubling 0.89 to attainment of ideal zero-order or case II drug release. The release profile in Fig. 1 showed that zinc ions could not form a cross-linking structure with sodium alginate to prevent the drug release, whereas addition of zinc acetate in the formulation B greatly speeded up the drug release. This may be attributed to the channels formed within the matrix caused by zinc ions' leaching out of the sodium alginate–zinc acetate matrix quickly due to the high solubility of zinc acetate.

n Values of formulation C in the SIF and SGF are 0.38 and 0.42, respectively, indicating that both are a Fickian release mechanism. However, the drug release rate in the SGF is much faster than that in the SIF. This may result from the chemical conversion of sodium alginate to insoluble and nonswellable alginic acid by acidity so that the matrix appeared unswollen and porous in acid environment.[6] Formulation C released either in the first 2 hours in the SGF or in the later 22 hours in the SIF also exhibited a diffusion release mechanism with an n value of 0.40.

As discussed above, only formulation C could achieve a 24-hour release profile with a diffusion release mechanism. Sodium alginate is a water-soluble salt of alginic acid, while zinc alginate does not dissolve in water. As observed in the dissolution testing, the caplets of formulation A swelled at the beginning of the testing, then eroded, and finally disappeared gradually with time, which may result from the control of swelling and erosion of sodium alginate and xanthan gum. The caplets of formulation B quickly swelled, dissolved, and disappeared, which may be caused by zinc ions' leaching out of the drug–sodium alginate–zinc acetate matrix rapidly. The caplets of formulation C swelled, but did not disappear after finishing the dissolution testing, and the final volume of a caplet was almost three times the original caplet size. This showed that zinc ions in formulation C reacted with sodium alginate to form zinc alginate precipitate with a cross-linking structure in the presence of xanthan gum.[10] Xanthan gum is a thickening agent that could greatly increase the viscosity of the drug–sodium alginate–xanthan gum–zinc acetate matrix upon contact with water, and has a double-stranded helical conformation,[13] which might prevent zinc ions from diffusing out of the matrix, so that zinc ions would have enough time to react with sodium alginate to form zinc alginate precipitate with the cross-linking structure. The cross-linking structure might play a key role in controlling a highly water-soluble drug to release for 24 hours.

## CONCLUSION

The present research developed a novel oral controlled release formulation for highly water-soluble drugs specifically, a drug–sodium alginate–xanthan gum–zinc acetate matrix, in which for the first time for ranitidine HCl achieved a 24-hour release profile. The presence of both xanthan gum and zinc acetate in the matrix played a key role in controlling the drug release for 24 hours. The helical structure and high viscosity of xanthan gum might prevent zinc ions from diffusing out of the ranitidine HCl–sodium alginate–xanthan gum–zinc acetate matrix so that zinc ions could react with sodium alginate to form zinc alginate precipitate with a cross-linking structure. The cross-linking structure might control a highly water-soluble drug to release for 24 hours. Evaluation of the release data showed the release mechanism for the

novel formulation might be attributed to the diffusion of the drug.

## ACKNOWLEDGMENTS

I would like to thank Dr. Alexander MacGregor and Mr. Frank Martinuzzi for their valuable suggestions in the design of oral controlled release formulations and Mrs. Naglaa Fahmy for her help with choosing the dry binder during this project.

## REFERENCES

1. Nur, A.O.; Zhang, J.S. Recent progress in sustained/controlled oral delivery of captopril: an overview. Int. J. Pharm. **2000**, *194*, 139–146.
2. Pillay, V.; Fassihi, R. Electrolyte-induced compositional heterogeneity: a novel approach for rate-controlled oral drug delivery. J. Pharm. Sci. **1999**, *88* (11), 1140–1148.
3. Pillay, V.; Fassihi, R. A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system. J. Control. Release **2000**, *67*, 67–87.
4. Rubio, M.R.; Chaly, E.S. In-vitro release of acetaminophen from sodium alginate controlled release pellets. Drug Dev. Ind. Pharm. **1994**, *20* (7), 1239–1251.
5. Giunchedi, P.; Gavini, E.; Moretti, M.D.L.; Pirisino, G. Evaluation of alginate compressed matrices as prolonged drug delivery systems. Pharm. Sci. Technol. **2000**, *1* (3), 156–165.
6. Lu, M.F.; Woodward, L.; Borodkin, S. Xanthan gum and alginate based controlled release theophylline formulations. Drug. Dev. Ind. Pharm. **1991**, *17* (14), 1987–2004.
7. Dhopeshwarkar, V.; Zatz, J.L. Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Dev. Ind. Pharm. **1993**, *19* (9), 999–1017.
8. Talukdar, M.M.; Plaizier-Vercammen, J. Evaluation of xanthan gum as a hydrophilic matrix for controlled-release dosage form preparations. Drug Dev. Ind. Pharm. **1993**, *19* (9), 1037–1046.
9. EI-Gazayerly, O.N. Release of pentoxifylline from xanthan gum matrix tablets. Drug Dev. Ind. Pharm. **2003**, *29* (3), 241–246.
10. Yotsuyanagi, T.; Yoshioka, I.; Segi, N.; Ikeda, K. Acid-induced and calcium-induced gelation of alginic acid: bead formation and pH dependent swelling. Chem. Pharm. Bull. **1991**, *39*, 1072–1074.
11. Smidsrod, O.; Skjak-Braek, G. Alginate as immobilization matrix for cells. TIB. Tech. **1990**, *8*, 71–78.
12. McDowell, R.H. *Properties of Alginates*; Alginate Industries, Ltd.: London, 1978.
13. Kang, K.; Pettitt, D. *Industrial Gums: Polysaccharides and Their Derivatives*, 3rd Ed.; Whistler, R., Bemiller, J., Eds.; Academic Press, **1993**; 341–397.
14. Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release II: fickian and anomalous release from swellable devices. J. Control. Release **1987**, *5*, 37–42.
15. Efentakis, M.; Koutlis, A.; Vlachou, M. Development and evaluation of oral multiple-unit and single-unit hydrophilic controlled-release systems. Pharm. Sci. Technol. **2000**, *1* (4), 341–353.