Formation of Water-Insoluble Gel in Dry-Coated Tablets for the Controlled Release of Theophylline[1)]

Kaoru KANEKO,*[,a] Ken KANADA,[a] Masaharu MIYAGI,[a] Noriyasu SAITO,[a] Tetsuya OZEKI,[b] Hiroshi YUASA,[b] and Yoshio KANAYA[b]

Pharmaceutical Laboratories, Kissei Pharmaceutical Co., Ltd.,[a] 4365–1 Kashiwabara, Hotaka, Minamiazumi, Nagano 399–83, Japan and Laboratory of Medical & Pharmaceutical Technology, School of Pharmacy, Tokyo University of Pharmacy and Life Science,[b] 1432–1 Horinouchi, Hachioji, Tokyo 192–03, Japan.
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Sodium alginate (ALNa) of a natural polysaccharide is known to form a water-insoluble gel when combined with a bivalent metal. In this study, we prepared tablets containing ALNa and calcium gluconate (GLCa) as a bivalent metal, and studied the application of the water-insoluble gel involving the controlled release of a test drug by permeation of water. Dry-coated tablets containing theophylline (TP) as a model drug, ALNa and GLCa were prepared by the dry powder compression method.

The controlled release of TP was evaluated by the dissolution test according to JP XIII. The release rate was extremely high for the tablets which contained only TP and GLCa. A zero order or sigmoidal release profile was observed for the tablets that contained only TP and ALNa. On the other hand, the lowest dissolution rate and a sigmoidal release profile were observed for the tablet containing TP and GLCa in its core and ALNa in its outer phase. These results suggest that dry-coated tablets containing ALNa and GLCa and prepared by the direct powder compression method would be useful for the controlled release of drugs.

Key words sodium alginate; calcium gluconate; dry-coated tablet; gel; controlled release

Techniques for the controlled release of oral drugs utilizing diffusion-control, water-soluble substance, ion-exchange resins, dissociation of complexes, osmotic pump, and intragastric accumulation have been studied, and controlled release using these techniques has been realized.[2)]

Sodium alginate (ALNa) is the sodium salt of alginic acid, a natural polysaccharide extracted from marine brown algae. It has been widely used as a food additive and has the ability to form a water-insoluble gel with a bivalent metal.[3–5)] Therefore, ALNa has been studied for use as a controlled release preparation.[6–16)] However, most studies using ALNa have been limited to its form as a gel bead. Earlier, we reported that a gel formed on the surface of tablets by under-coating with calcium gluconate (GLCa) and over-coating with ALNa is useful for masking the taste of bitter drugs at the time of oral administration.[17)] In this study, we examined the controlled release of a drug substance from dry-coated tablets prepared from these gel-forming agents by the dry powder compression method.

Experimental

Materials and Measurement of the Properties of the Powders Theophylline (TP, Shiratori Pharmaceutical Co., Ltd.), a bronchodilator, was used as the model compound. ALNa (I-1, Kimitsu Chemical Industries Co., Ltd.) and GLCa (Tomita Pharmaceutical Co., Ltd.) were used as the gel-forming agents.

The density and mean particle size of each powder were measured with an air comparison pycnometer (930, Toshiba-Beckman Co., Ltd.) and a laser micron sizer (LMS-24, Seishin Enterprise Co., Ltd.), respectively. The obtained values are shown in Table 1.

Table 1. Mean Diameter and Density of Materials Used

Material	Mean diameter (μm)	Density (g/cm^3)
Theophylline (TP)	52.3±0.2	1.49
Sodium alginate (ALNa)	103.5±6.1	1.70
Calcium gluconate (GLCa)	26.7±0.7	1.69

Dry-Coated Tablet Preparation The preparation process and formulation of the dry-coated tablets containing the gel-forming agents ALNa and GLCa are shown in Fig. 1 and Table 2, respectively.

In order to make the powder mixture for tableting, TP was mixed with ALNa or GLCa for 5 min using a motor grinder (RMO, Mitamura Riken Kogyo Co., Ltd.). The powder mixture was compressed into a core tablet with a diameter of 6 mm at a compression pressure of 1000 kg/punch achieved with a rotary tableting machine (Cleanpress Correct 12HUK, Kikusui Seisakusho Co., Ltd.). After a die had been filled with about half the amount of the ingredient desired for the outer phase, the tablet core was placed on the center of the die. The residual ingredient was put into the die, and the preparation was then compressed into a dry-coated tablet with a diameter of 10 mm at a compression pressure of 1000 kg/cm^2 in a hydraulic press (Riken Seiki Co., Ltd.).

Dissolution Test Dissolution testing of the obtained dry-coated tablets was carried out according to the JP XIII paddle method at 100 rpm with the tablet in 900 ml of purified water at 37 °C. The test solution was removed at appropriate time intervals. The concentration of TP in the solution was determined by UV-spectrophotometry at 272 nm.

Results and Discussion

Figure 2 shows the release profiles of TP from the dry-coated tablets, which were prepared according to the

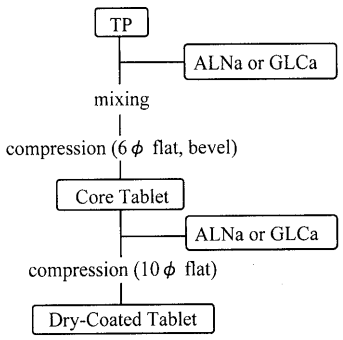

Fig. 1. Process for Preparation of Dry-Coated Tablets

* To whom correspondence should be addressed.

Table 2. Formulation of Dry-Coated Tablets Presented as Composition Ratios

		A	B	C	D	E	F
Core tablet	TP	10	10	10	10	10	10
	ALNa			45		45	
	GLCa				45		45
Outer phase	ALNa	90		45			45
	GLCa		90		45	45	

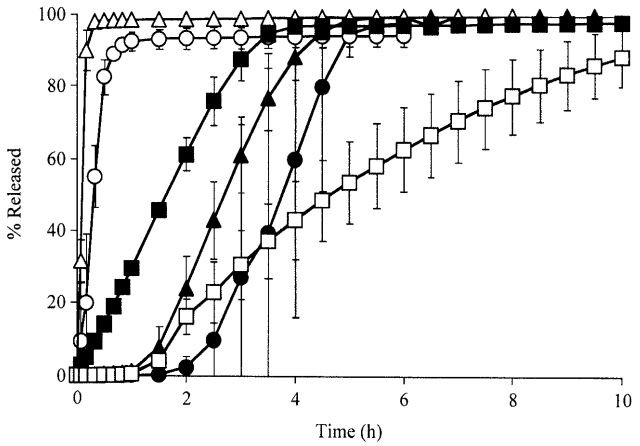

Fig. 2. Release Profiles of TP from Dry-Coated Tablets

●, A; ○, B; ▲, C; △, D; ■, E; □, F. Each point represents the mean ± S.D. ($n=3$).

formulations shown in Table 2. The highest rates of release of TP were attained with formulations B and D. The water-insoluble gel was not formed with B and D because each of these formulations consisted of TP and GLCa only. These results indicate that the release rate with GLCa is high.

In the case of tablets with formulations A and C, the release rate of TP after a lag time of about 1 to 2 h was lower than that of formulation B and D; and the release profiles showed a sigmoidal form. Although a water-insoluble gel was not formed because each formulation consisted of TP and ALNa only, these results suggest that a water-soluble hydro-gel of ALNa was formed by permeation of the dissolution fluid from the tablet surface, and that TP was released by diffusion through this hydro-gel layer. The lag time for formulation A was longer than that for formulation C. The time it took for the dissolution fluid to permeate to the TP-containing core was longer in formulation A because the amount of ALNa in its outer phase was larger than that in the outer phase of formulation C.

In the case of the tablet with formulation E, that is, in the one containing ALNa in its core and GLCa in its outer phase, TP was released immediately after the start of the dissolution test, and the release rate was almost the same as that of formulations A and C. This finding suggests that after the outer phase of GLCa was dissolved immediately, a water-soluble hydro-gel was formed with ALNa in the core.

In the case of tablets having formulation F, *i.e.*, those containing GLCa and ALNa in the core and the outer phase, respectively, TP was released at the lowest rate in this study after a lag time of about 1 h. It has been proposed that alginic acid is made up of two repeating sugar residues, α-(1→4)-L-guluronic acid (G) and β-(1→4)-D-mannuronic acid (M), a high molecular weight linear copolymer consisting of homopolymeric blocks (MM, and GG) and heteropolymeric blocks (MG),[18,19] and that gelation and crosslinking are due to the stacking of GG blocks of alginate chains with the formation of an "egg-box" junction.[20-22] In the case of formulation F, we suggest that a hydrogel of ALNa was first formed with the dissolution medium. Then, a water-insoluble gel was formed at the contact plane between the tablet core containing GLCa and the outer phase of ALNa; TP was then released through the gel. Therefore, a sustained-release profile would be observed.

In conclusion, the release rate of TP was extremely high in the case of tablets containing only TP and GLCa; in the case of those containing only TP and ALNa, the release rate was zero-ordered and sigmoidal. On the other hand, in the tablet having TP and GLCa in the core and ALNa in the outer phase, the lowest and sigmoidal release rate was observed. These results suggest that dry-coated tablets containing ALNa and GLCa prepared by the direct powder compression method would be useful for the controlled release of drugs.

References and Notes

1) A part of this work was presented at the 40th Kantoh Branch Meeting of the Pharmaceutical Society of Japan, Kanagawa, October 1996.
2) "Iyakuhin-no Kaihatsu Yakubutsu Sotatsu-hou," Vol. 13, Hirokawa-shoten, Tokyo, 1989.
3) Smidsrød O., Haug A., *Acta Chem. Scand.*, **19**, 329—340 (1965).
4) Haug A., Smidsrød O., *Acta Chem. Scand.*, **19**, 341—351 (1965).
5) Thom D., Grant G. T., Morris E. R., Rees D. A., *Carbohydr. Res.*, **100**, 29—42 (1982).
6) Kim C.-K., Lee E.-J., *Int. J. Pharm.*, **79**, 11—19 (1992).
7) Østberg T., Vesterhus L., Graffner C., *Int. J. Pharm.*, **97**, 183—193 (1993).
8) Shiraishi S., Imai T., Otagiri M., *Biol. Pharm. Bull.*, **16**, 1164—1168 (1993).
9) Tomida H., Nakamura C., Yoshitomi H., Kiryu S., *Chem. Pharm. Bull.*, **41**, 2161—2165 (1993).
10) Sugawara S., Imai T., Otagiri M., *Pharm. Res.*, **11**, 272—277 (1994).
11) Simon L. D., Ruiz-Cardona L., Topp E. M., Stella V. J., *Drug Dev. Ind. Pharm.*, **20**, 2341—2351 (1994).
12) Hodsdon A. C., Mitchell J. R., Davies M. C., Melia C. D., *J. Controlled Release*, **33**, 143—152 (1995).
13) Lee B.-J., Min G.-H., *Arch. Pharm. Res.*, **18**, 183—188 (1995).
14) Cui F., Kawashima Y., Takeuchi H., Niwa T., Hino T., *Chem. Pharm. Bull.*, **44**, 837—842 (1996).
15) Murata Y., Miyamoto E., Kawashima S., *J. Controlled Release*, **38**, 101—108 (1996).
16) Murata Y., Katayama N., Kajita T., Miyamoto E., Kawashima S., *Drug Delivery Syst.*, **12**, 49—55 (1997).
17) Kaneko K., Kanada K., Yamada T., Miyagi M., Saito N., Ozeki T., Yuasa H., Kanaya Y., *Chem. Pharm. Bull.*, **45**, 1063—1068 (1997).
18) Rees D. A., Samuel J. W. B., *J. Chem. Soc.* (*C*), 2295—2298 (1967).
19) Haug A., Larsen B., Smidsrød O., *Acta Chem. Scand.*, **21**, 691—704 (1967).
20) Katchalsky A., Cooper R. E., Upadhyay J., Wassermann A., *J. Chem. Soc.*, 5198—5204 (1961).
21) Grant G. T., Morris E. R., Rees D. A., Smith P. J. C., Thom D., *FEBS Lett.*, **32**, 195—198 (1973).
22) Bryce T. A., McKinnon A. A., Morris E. R., Rees D. A., Thom D., *Faraday Discuss. Chem. Soc.*, **57**, 221—229 (1974).