[Chem. Pharm. Bull. 33(6)2469—2474(1985)]

The Effects of Thickness and Hardness of the Coating Film on the Drug Release Rate of Theophylline Granules Coated with Chitosan–Sodium Tripolyphosphate Complex

YOSHIAKI KAWASHIMA,*,[a] TETSURO HANDA,[a] AKIHIRO KASAI,[a] HIDEO TAKENAKA[a] and SHAN YANG LIN[b]

Gifu Pharmaceutical University,[a] Mitahora, Gifu 502, Japan
Veterans General Hospital,[b] Shipai, Taipei, Taiwan 112, Republic of China

(Received September 6, 1984)

The drug release from theophylline granules coated with chitosan–sodium tripolyphosphate complex followed zero-order kinetics after an induction period, which depended on the swelling of the granules during the dissolution. The swelling was greater in the acidic medium than in the alkaline one, resulting in an increase of the drug release rate. A linear correlation between the drug release rate and the reciprocal of coating film thickness was found. By hardening the coating film with glutaraldehyde, the swelling of the granules was reduced and the drug release rate was decreased. Pre-drying of the granules prior to the hardening was fairly effective in reducing the drug release rate. It was found that the coating film became seamless after treatment with glutaraldehyde. Even when the dissolution solvent was exchanged from disintegration test solution No. 1 (pH 1.2) to No. 2 (pH 6.8), the drug release rate changed little.

Keywords——theophylline; chitosan–sodium tripolyphosphate complex coated granule; coating film thickness; coating film hardness; zero-order kinetics; swelling

Introduction

In the previous study,[1] we developed a novel technique for coating granules with a polyelectrolyte complex of chitosan and sodium tripolyphosphate for the preparation of a biodegradable controlled-release dosage form. Chitosan is now widely accepted as a potentially useful pharmaceutical material, because of its excellent biocompatibility and biodegradability.[2,3] In the present study, we investigated the drug release behavior of theophylline granules coated with chitosan–sodium polyphosphate complex, in order to develop a controlled relase dosage form of theophylline with a narrow therapeutic index. The aim of the study was to determine the relationship between the coating film thickness of the granules and the drug release rate. The effects of hardening of the coating film with glutaraldehyde on the drug release rate were clarified. Finally, the effects of the pH of the dissolution medium on the drug release rate and the swelling of the coated granules during dissolution were investigated.

Experimental

Materials Used——Chitosan (supplied by Kyowa Yushi Co., Tokyo and Katakura Chikkarin Co., Tokyo) with 89.3% degree of deacetylation was comminuted by using a cutting type mill (MX 530G mixer, Matsushita Electric Industry, Osaka) and the material screened through a 150 mesh sieve was employed. Sodium tripolyphosphate (Nakarai Chemicals, Co.) (average diameter, 63 μm) was used as a complexing agent for chitosan. Theophylline anhydrate (Wako Junyaku, Co.) (average particle diameter, 75 μm) of JP X grade was used. Glutaraldehyde (Wako Junyaku, Co.) was used as a hardening agent for the chitosan–sodium polyphosphate complex film of the coated

granules.

Preparation of Theophylline Granules Coated with Sodium Tripolyphosphate–Chitosan Complex——Theophylline granules coated with chitosan–sodium polyphosphate complex film were prepared by using the technique developed in the previous study.[1] The procedure is redescribed briefly. Firstly, granules containing theophylline and sodium tripolyphosphate (weight ratio = 10 : 7) were prepared by using the spherical agglomeration technique[4,5] in liquid. Then resultant granules sieved at 12 to 20 mesh (3 g) were dispersed in a hydrochloric acid solution of chitosan (0.3, 0.6, 0.7 or 0.9% (w/v), 500 ml) by using a propeller-type agitator with four blades at 1400 rpm. During agitation, the granules were coated with the complex film produced by the reaction of chitosan with sodium polyphosphate. After agitation for 1 h, the coated granules were separated and washed with water, then dried in a desiccator for 10 d.

Hardening the Coating Film of Chitosan–Sodium Polyphosphate Complex——The plain coated granules (without drying) were soaked in acetone (50 ml) for 30 min to dry them, and filtered off with the aid of an aspirator for 1 h. The pre-desiccated coated granules were dried further in a desiccator *in vacuo* for 0, 1, 2, 3 or 4 h. In the present study, the residual acetone concentration in the dried granules was not checked. Finally, the dried coated granules were treated in 5% glutaraldehyde solution (30 ml) at 37 °C for 0.5, 1, 2, 3 or 4 h. The coated, hardened granules were filtered off, then washed with water and dried in a desiccator for 10 d.

Measurements of the Coating Film Thickness and the Swelling Ratio of the Coated Granules——The coating film thickness was determined by directly measuring the cross section in photomicrographs of the coated granules. The swelling ratio of the coated granules was represented by the ratio of the Green diameter[6] of the swollen granules to that of the dried granules.

Determination of Residual Glutaraldehyde in the Coated Granules Hardened with Glutaraldehyde——The coated granules (100 mg) were powdered in a mortar, then glutaraldehyde contained in the granules was extracted with water or the disintegration test solution No. 1 (25 ml). The glutaraldehyde in the extract was determined by spectrophotometric assay of the 2,4-dinitrophenylhydrazone precipitated by reacting glutaraldehyde with 2,4-dinitrophenylhydrazine (at 346 nm in ethyl acetate).[7,8]

Dissolution Test——The drug release from the coated granules with or without hardening with glutaraldehyde was determined by a rotating basket method in distilled water, the disintegration test solutions No. 1 and No. 2, specified in JP X, and buffer solutions[9] with various pH values (2.1, 4.0, 6.0 and 7.9) at 37 °C. The basket was modified by attaching a turbine type propeller with 6 blades to the upper part of the basket and rotating it at 100 rpm. The sample weight was 100 or 200 mg. Theophylline in the sample (1 ml) withdrawn from the system was assayed spectrophotometrically in acidic solution (0.1 N hydrochloric acid) at 269 nm.

Results and Discussion

The Effects of Coating Film Thickness of the Granules and the pH of the Dissolution Medium on the Drug Release Rate

The drug release patterns of theophylline granules coated with chitosan–sodium tripolyphosphate complex in distilled water and the disintegration test solution No. 1 (pH 1.2) and No. 2 (pH 6.8) specified in JP X are displayed in Fig. 1. All the granules tested were sized at 12 to 20 mesh by screening so that the size effect on the drug release rate could be neglected. The drug release rates of the coated granules were significantly delayed compared with that of the reference uncoated granules. After an induction period, defined as the intercept (t_i) of the straight line extrapolated to the abscissa in Fig. 1, the drug release patterns of the coated granules obeyed zero-order kinetics. The induction period depended on the degree of swelling of the coated granules during the dissolution. Rapid swelling at the initial stage shortened the induction period. The degree of swelling was affected by the coating film thickness of the granules and the pH of the dissolution medium used, as discussed later. The drug release rate, given by the slope of the straight line, was affected by the chitosan solution concentration employed for coating the granules and the dissolution medium used, *i.e.* distilled water, or disintegration test solution No. 1 or 2.

In the previous study,[1] it was found that the coating film thickness of the granules increased with the chitosan concentration in the coating solution employed. The effect of coating film thickness of the granules on the drug release rate was investigated in distilled water with granules coated in the chitosan solution having various concentrations. The drug release rate per unit surface area of granule, J, at the steady state is represented by Eq. 1.

$$J = D^*(C_i - C)/l \quad (1)$$

where C and C_i are the drug concentrations in the dissolution medium and inside the coating film, respectively, D^* is the apparent diffusion coefficient of the drug in the coating film and l is the coating film thickness. The drug release rate per unit of the granules (mg/cm^2/h) was

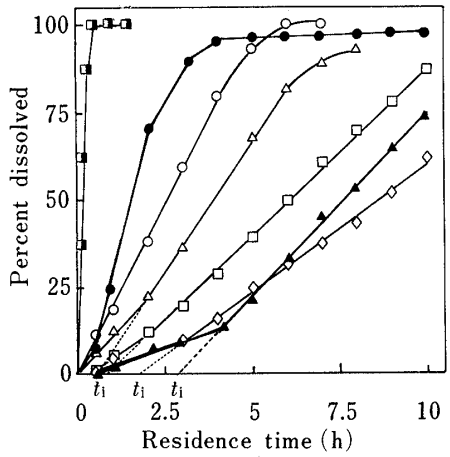

Fig. 1. Dissolution Behavior of the Coated Granules

Temperature: 37 °C. Dissolution medium: ●, disintegration test solution No. 1; ▲, disintegration test solution No. 2; □, ○, △, ◇, distilled water. Concentration of chitosan solution used for coating (%): ○, 0.3; △, 0.6; □, 0.7; ◇, ●, ▲, 0.9; ◨, uncoated granules.

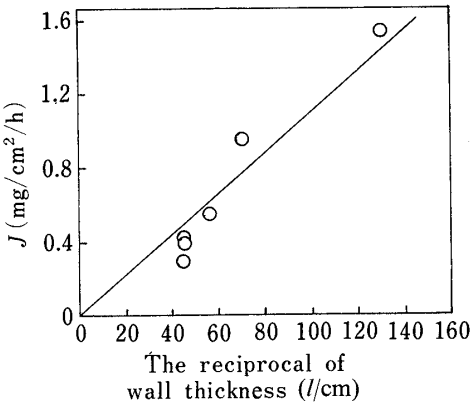

Fig. 2. Drug Release Rate as a Function of the Reciprocal of Wall Thickness

$C_s = 11.0$ (mg/ml).

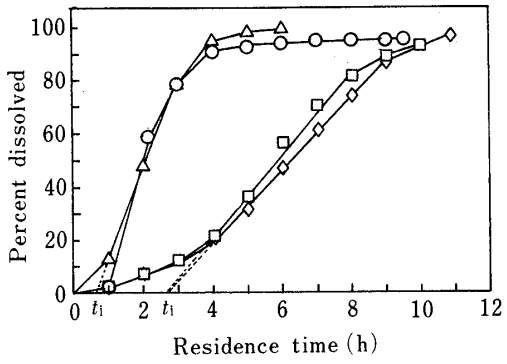

Fig. 3. The Drug Release Rate of the Coated Granules as a Function of the pH of the Dissolution Medium

Temperature: 37 °C. Concentration of chitosan solution used for coating: 0.9%. pH of the medium: ○, 2.1; △, 4.0; □, 6.0; ◇, 7.9.

TABLE I. Swelling Ratio of the Coated Granules

Media	The coated granules without GA[a] treatment	The coated granules with GA treatment (drying for 4 h and in 5% GA soln. for 2 h)
Water	1.22	1.07
pH 1.2	b)	1.17
pH 2	3.27	—
pH 4	2.42	—
pH 6	1.50	—
pH 6.8	1.55	1.11
pH 8	1.38	—

a) Glutaraldehyde. *b*) At pH 1.2, the granules swelled rapidly and finally dissolved.

calculated from the straight line in Fig. 1 and was plotted against the reciprocal of the coating film thickness. The linear relationship between J and $1/l$ (Fig. 2) suggested that sink condition ($C_i \gg C$) holds in the steady state and that the apparent diffusion coefficient of drug is independent of the coating film thickness. As the drug concentration inside the coating film was assumed to be equal to the solubility of the drug, C_s, Eq. 1 could be transformed to Eq. 2.

$$J = D^* \cdot C_s / l \tag{2}$$

The apparent diffusion coefficient of the drug through the coating film was found to be 2.76×10^{-7} (cm^2/s) from the slope of the straight line in Fig. 2.

The drug release rate also depended on the pH of the dissolution medium employed, as shown in Figs. 1 and 3. When the pH was lower than 4, the drug release rate was enhanced and the induction period was shortened as compared with that at pH ≥ 6. The findings could be interpreted in terms of the degree of swelling of coated granule defined as the swelling ratio during the dissolution. The degree of swelling depended on the pH of the medium (Table I). With decreasing pH, the degree of swelling increased, which loosened the coating film texture and increased the void volume in the texture. The increased void volume (porosity, ε) and the shortened diffusion path length in the texture, h, might enhance the apparent diffusion coefficient of the drug, as indicated by Eq. 3.

$$D^* = D \cdot \varepsilon / h \tag{3}$$

where D is the intrinsic diffusion coefficient of the drug in the medium. At low pH, it was assumed that the electrostatic attraction force between the chitosan cation and the tripolyphosphate anion is reduced due to the decreased charge on sodium tripolyphosphate. Therefore, the network of chitosan–tripolyphosphate film becomes loose. As regrards the effects of ionic strength and concentration of the buffer on the drug release, no significant effect was found in the case of aspirin granules with chitosan in the previous study.[10]

The Effect of Hardening the Coating Film with Glutaraldehyde on the Drug Release Rate

The granules treated with glutaraldehyde released the drug more slowly than the non-treated granules as shown in Figs. 4 and 5. The effect of drying time of the granules before treatment with glutaraldehyde on the drug release rates is illustrated in Fig. 4. The drug

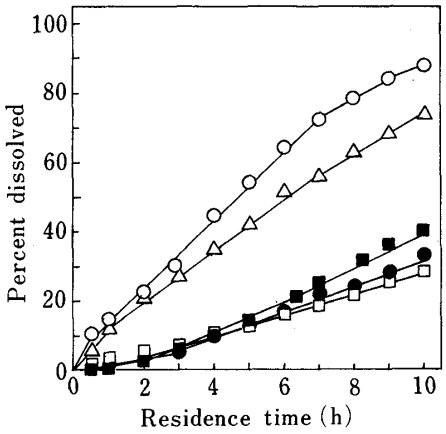

Fig. 4. Dissolution Behavior of the Coated Granules Treated with Glutaraldehyde in Disintegration Test Solution No. 1 at 37 °C

Treatment time with glutaraldehyde: 4 h. Concentration of chitosan solution used for coating: 0.9%. Drying time before treatment (h): ○, 0; △, 1; □, 2; ■, 3; ●, 4.

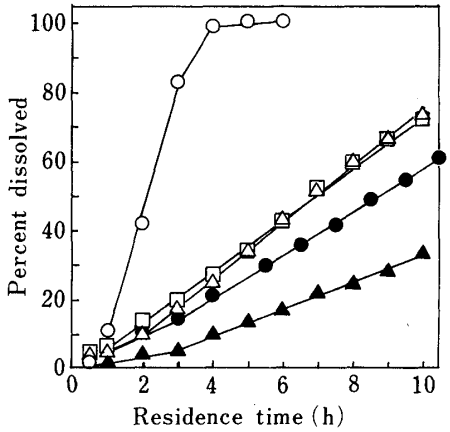

Fig. 5. Dissolution Behavior of the Coated Granules Treated with Glutaraldehyde in Disintegration Test Solution No. 1 at 37 °C

Drying time before treatment: 4 h. Treatment time with glutaraldehyde (h): ○, 0.5; △, 1; □, 2; ●, 3; ▲, 4.

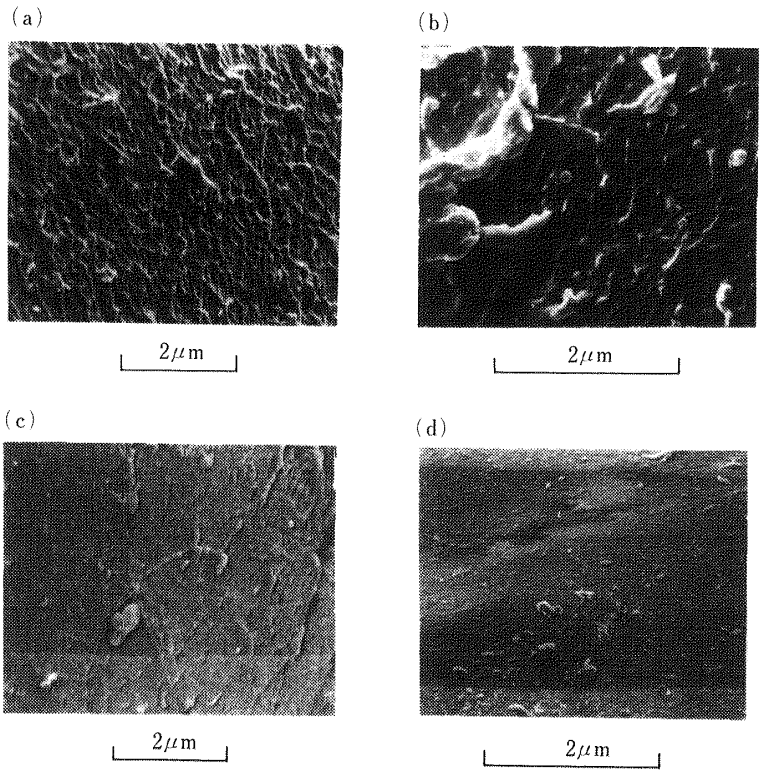

Fig. 6. Surface Topography of the Coated Granule

Concentration of chitosan solution used for coating: 0.9%. Pre-drying time and hardening time (h): (a) 0 and 0, (b) 4 and 1, (c) 0 and 4, (d) 4 and 4, respectively.

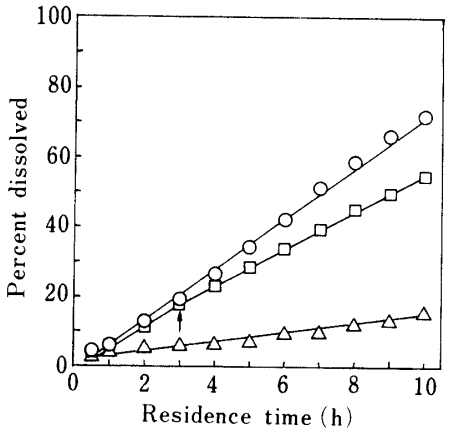

Fig. 7. Effect of Exchanging the Dissolution Medium on the Dissolution Behavior of the Coated Granules Treated with Glutaraldehyde at 37 °C

Drying time and hardening time (h): 4 and 2 h, respectively. Dissolution Medium: ○, disintegration test solution No. 1; △, disintegration test solution No. 2; □, change of the dissolution medium from disintegration test solution No. 1 to No. 2 at 3 h after the start.

release rate was significantly reduced in the granules dried for 2 h. Overdrying of the granules did not decrease the drug release rate further. The drug release rate also depended strongly on the treatment time of the granules with glutaraldehyde, as shown in Fig. 5. Longer treatment was more effective for reducing the drug release rate of the resultant granules.

The surface topography of the granules was investigated by scanning electron microscopy (Fig. 6). The surface of the non-treated granules was rough and the network of chitosan–tripolyphosphate complex on the surface was loose, as can be seen in Fig. 6(a). Drying of the granules before treatment with glutaraldehyde was effective in tightening the interstices of the network in Fig. 6(b). Even without pre-drying, the extensively treated granules with glutaraldehyde had a smooth surface coated with seamless film, as shown in Fig. 6(c). On treatment with glutaraldehyde, chitosan in the coating film formed a Schiff's base, which closely linked the chitosan chains. Due to this reaction, a seamless coating film might be

TABLE II. Amount of Glutaraldehyde Remaining in the Coated Granules

Extraction medium	a	b	c	d	e
Water (ppm)	89.7	161.7	354.6	277.7	185.8
pH 1.2 (ppm)	237.5	491.8	1243.2	816.4	874.1

Pre-drying time: 4 h. Hardening time (h): a, 0.5; b, 1; c, 2; d, 3; e, 4.

formed on the granule surface. Pre-drying prior to the treatment might be useful to tighten physically the coating film texture as indicated in Fig. 6(b) and (d). The dense texture of coating film with low porosity might reduce the apparent diffusion coefficient of the drug in the film and depress the swelling of granules, as shown in Table I, leading to decreased drug release rates as shown in Figs. 4, 5 and 7.

Figure 7 shows the drug release patterns from the granules treated with the aldehyde in disintegration test solutions No. 1 (pH 1.2) and No. 2 (pH 6.8). In disintegration test solution No. 1, the drug was released more rapidly than in disintegration test solution No. 2. This finding might be interpreted in terms of the degradation of the Schiff's base in an acidic solution,[11] resulting in the cleavage of the cross-links of chitosan chains. The resultant loose texture of the coating film might enhance the drug release rate. The degradation of the Schiff's base was confirmed by the fact that the amount of glutaraldehyde remaining in the coating film determined in the acidic solution (pH 1.2) was higher than that in distilled water as listed in Table II. The considerable amount of glutaraldehyde retained in the coated granules suggests that an effective method for its removal will be required before commercializing the present technique. When the dissolution medium was exchanged from disintegration test solution No. 1 to No. 2 at 3 h after the start, the drug release rate changed little, as shown in Fig. 7. This finding indicated that the texture, once relaxed in the acidic solution, did not recover the original tight network in the alkaline solution. The above finding is relevant to the prediction of the drug release behavior in the gastro-intestine (GI) tract from the granules prepared in the present study.

References and Notes

1) Y. Kawashima, T. Handa, A. Kasai, H. Takenaka, S. Y. Lin and Y. Ando, *J. Pharm. Sci.*, accepted.
2) S. Miyazaki, K. Ishii and T. Nadai, *Chem. Pharm. Bull.*, **29**, 3067 (1981).
3) Y. Sawayanagi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **30**, 2935, 4213, 4216 (1982).
4) Y. Kawashima and C. E. Capes, *Ind. Eng. Chem., Fundam.*, **19**, 312 (1980).
5) Y. Kawashima, H. Ohno and H. Takenaka, *J. Pharm. Sci.*, **70**, 913 (1981).
6) H. Green, *J. Franklin Inst.*, **204**, 713 (1927).
7) H. Terada, T. Hayashi, S. Kawai and T. Ohno, *J. Chromatogr.*, **130**, 281 (1977).
8) L. J. Papa and L. P. Turner, *J. Chromatogr. Sci.*, **10**, 744, 747 (1972).
9) The compositions of the buffers of pH 2, 4, 6 and 8 are (NaCl, NH_2CH_2COOH, HCl), (NaCl, CH_3COONa, CH_3COOH), (NaCl, Na_2HPO_4, NaH_2PO_4) and (Na_2HPO_4, KH_2PO_4), respectively.
10) Y. Kawashima, S. Y. Lin, A. Kasai, T. Handa and H. Takenaka, *Chem. Pharm. Bull.*, **33**, 2107 (1985).
11) S. Alman, H. J. Smith, M. Mahbouba, J. C. Evans and P. H. Morgan, *J. Pharm. Pharmacol.*, **33**, 323 (1981).