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Preparation of a Prolonged Release Tablet of Aspirin with Chitosan

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A prolonged release tablet of aspirin was prepared by compressing aspirin agglomerated by massing with an acetic acid solution of chitosan. The parameters controlling the drug release rate were the chitosan content in the tablet, the physical state of chitosan used for granulation *i.e.* liquid solution or gel, and the pH of the dissolution test solution. When the chitosan solution was used for agglomeration, the drug release rate of the resultant tablet was faster than when the gel was used. The drug release became more prolonged with increasing chitosan content in the tablet or with decreasing pH of the dissolution test solution. The drug release kinetics of the tablet after a short swelling period were represented by equation 10 in the text, which was derived by assuming that the tablet dimensions decreased isotropically during the dissolution. It was found that the decomposition rate of aspirin in the tablet stored at 37°C and at R.H. 75.1% was determined by the amount of water adsorbed by the chitosan in the tablet, leading to zero order kinetics with respect to the aspirin.

Keywords—aspirin; prolonged release tablet; chitosan; drug release rate; gel; swelling; stability

Introduction

Chitosan ((1→4)-2-amino-2-deoxy-β-D-glucan), prepared by alkaline N-deacetylation of chitin ((1→4)-2-acetamide-2-deoxy-β-D-glucan), is a potentially useful pharmaceutical material owing to its good biocompatibility and biodegradability. Miyazaki *et al.*¹⁾ prepared sustained release dosage forms of indomethacin and papaverine hydrochloride dispersed in a dried gel of chitosan. Sawayanagi *et al.*²⁾ suggested that chitosan might be suitable as a diluent for direct tableting of pharmaceuticals as well as crystalline cellulose, and prepared a sustained release tablet of a water-soluble drug by direct compression.

The aim of the present study was to prepare a prolonged release tablet of aspirin by massing with acetic acid solution or gel of chitosan. Aspirin is commonly used as an analgesic or antipyretic but it is still desirable to develop a new dosage form with prolonged releasing action. A further aim was to obtain the drug release rate equation for this tablet. Finally, the stability of aspirin in the tablet with chitosan was investigated.

Experimental

Materials Used—Chitosan (Flonac N[®] supplied by Kyowa Yushi Co., Tokyo and Katakura Chikkarin Co., Tokyo) with 89.3% degree of deacetylation was comminuted with a cutting type mill (MX 530G mixer, Matsushita Electric Industry, Osaka) and was used after passage through a 150 mesh sieve. Microcrystalline aspirin produced by pouring its propylene glycol solution into cold water with agitation was filtered off and dried, and used in the preparation of granules for tableting.

Preparation of Tablets—The dried microcrystalline aspirin (40 g) was massed with acetic acid solution of chitosan (9.8 to 42.1 g) at various concentrations (0.65 to 11.8 weight%) in a mortar (Ishikawa Seisakusho Co.,

Osaka) with an agitator. Acetic acid solution of chitosan (0.65—2.6%) was a low-viscosity fluid, while it was gel-like at concentrations higher than 8.7%. The mass was granulated in an extruder (Type KU1, Erweka GmbH, Frankfurt am Main) then the granules were dried in a fluidized bed dryer (Type TR2, Glatt Lufttechnischer Apparate, Haltingen) for 30 min at 50°C. The dried granules were screened and their average diameters were determined (Table I). The granules sized 16 to 35 mesh were compressed with a single punch tableting machine (Type EK0, Erweka GmbH, Frankfurt am Main) and the hardness of the resultant tablet was measured with a hardness tester (Type TBT, Erweka Apparatebau GmbH, Frankfurt am Main). In the preparation of the tablet for the dissolution test, the upper punch of the machine was adjusted to give a hardness of approximately 5 kg to cancel the hardness variation effect on the dissolution of the tablet. The weights and dimensions of the tablets are listed in Table I.

Dissolution Test—The dissolution tests of microcrystalline aspirin particles and their granules sized 16 to 35 mesh prepared with the formulations termed (a) to (f) in Table I were conducted by a paddle method with stirring at 150 rpm. The sample weight and the medium for the dissolution test were 500 mg and distilled water at 37°C, respectively. A 2 ml aliquot was sampled and filtered with a membrane filter (0.45 μ m). The same amount of water warmed at 37°C was added to the dissolution vessel to maintain the dissolution medium volume constant. The aspirin in the filtrate was determined by fluorometric analysis using a fluorometer (type 650-60, Hitachi Manufacturing Co., Tokyo)^{3,4)} at 298 nm (excitation) and 408 nm (emission) after decomposing it to salicylic acid in sodium hydroxide solution (0.1 N). The dissolution tests of the tablets were undertaken in the same manner as described for the granules except for a few points. The dissolution media used were distilled water, the disintegration test solutions No. 1 and No. 2 specified in JPX or buffer solutions (composition of buffer: pH 2=NaCl, NH₂CH₂COOH, HCl; pH 4=NaCl, CH₃COONa, CH₃COOH; pH 6=NaCl, Na₂HPO₄, NaH₂PO₄; pH 8=Na₂HPO₄, KH₂PO₄) with various pH values (2, 4, 6 and 8) and ionic strength values (0.1, 0.3, 0.7 and 3.0). The released drugs were assayed spectrophotometrically with a dualwavelength spectrophotometer (Type 556, Hitachi Manufacturing Co., Tokyo) at 225 and 243.2 nm for aspirin and with a double-beam spectrophotometer (Type 100-61, Hitachi Manufacturing Co., Tokyo) at 304 nm for salicylic acid in a mixture of buffer solution (pH 2.2) and ethanol (volume ratio = 1 : 1).

Stability Test of the Tablet—The tablets prepared with the formulations (c), (d) and (f) in Table I and the control tablet without chitosan were stored at 37°C and at relative humidity (R.H.) 75.1%. Salicylic acid, aspirin and water contained in the tablets after 2 to 118 d were assayed by spectrophotometry as described above and by the method of Karl Fischer, respectively.

Results and Discussion

Physical Properties of the Granules and the Tablets

The average diameters of the granules obtained are given in Table I. The average diameter increased with increasing chitosan concentration in the binder solution. The elasticity of the mass of aspirin with chitosan increased with the chitosan concentration of the binder. Consequently, the granule size of the extruded mass from the extruder (2.24 mm pore size) increased with the chitosan concentration. Further, the destruction of the extruded granules during drying was prevented by increasing their chitosan contents.

The times required for releasing 50% of the drug from the aspirin granules (T_{50}) are shown in Fig. 1. T_{50} significantly increased with the chitosan content in the granules until the content reached to 2.4%. Above this content, T_{50} did not increase any further. The granules containing more than 2.4% chitosan were prepared with gel-like chitosan as a binder, which wetted aspirin particles less effectively than low viscosity chitosan solution did on massing. Therefore the distribution of chitosan in the resultant granules was assumed to be poor. This segregated distribution of chitosan in the granule is expected to be undesirable from the viewpoint of prolonging the drug release.

The hardness of the tablet increased significantly when the granules contained more than 4.4% chitosan as shown in Fig. 2. This finding contrasted with that in Fig. 1, suggesting that the chitosan blocks in the granules enhanced the intergranular binding in the tablet.

Dissolution Behavior of the Tablet

The dissolution patterns of the aspirin with chitosan are shown in Fig. 3. All tablets containing chitosan exhibited prolonged release behavior compared with the tablet without chitosan. The dissolution rate in the disintegration test solution No. 1 was slower than that in

TABLE I. Formulation and Average Diameter of Granules (A) and Dimensions of Tablets (B)

(A)				
Granules	Concentration of chitosan soln. (w/w%)	Weight of chitosan soln. used (g)	Chitosan content in granules (%)	Average diameter of granules (μm)
a	0.65	10.0	0.16	370.4
b	1.3	9.9	0.32	379.3
c	2.6	9.8	0.65	339.6
d	9.8	10.0	2.40	403.3
e	8.7	20.9	4.40	408.3
f	11.8	42.1	11.10	419.1

(B)			
Granules used	Tablet for dissolution test		
	Weight (mg)	Diameter (mm)	Thickness (mm)
a	270.6	10.041	2.690
b	273.6	10.040	2.815
c	273.7	10.062	2.807
d	264.8	10.048	2.809
e	349.7	10.043	3.745
f	368.4	10.081	4.066
Recrystallized aspirin	327.9	10.066	3.292

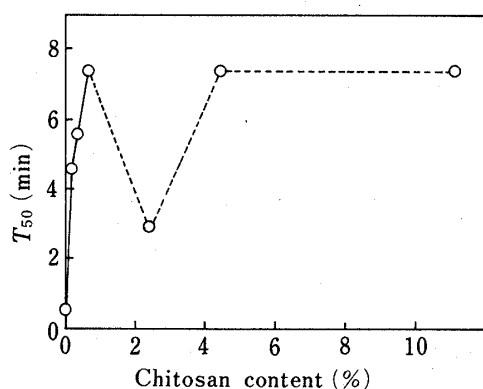


Fig. 1. Correlation between T_{50} of Granules and Chitosan Content in Granules

—, chitosan solution as a binder; ----, chitosan gel as a binder.

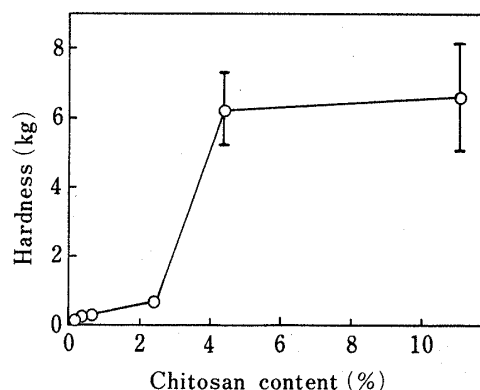


Fig. 2. Relation between Tablet Hardness and Chitosan Content in the Tablet

the No. 2 test solution. The other parameters controlling the drug release rate were the chitosan content in the granules used for tableting and the physical state of chitosan used for granulation, *i.e.* solution or gel. The drug release rate from the tablet is illustrated by plotting T_{50} of the tablet against the chitosan content in Fig. 4.

The plot of T_{50} of the tablet against the chitosan content was similar to that of the granules in Fig. 1. The finding in Fig. 4 indicates that the drug release rate of the tablet corresponds reasonably well to that of the individual granule composing the tablet, although the drug release rate of the tablet was significantly delayed. The tablet did not disintegrate

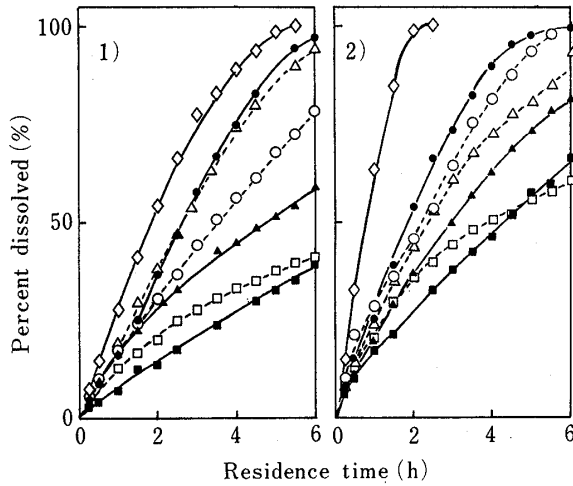


Fig. 3. Dissolution Behavior of Tablets in No. 1 and No. 2 Disintegration Test Solutions (JP X)

1) No. 1 test solution (pH 1.2). 2) No. 2 test solution (pH 6.8).
 ◇, aspirin tablet without chitosan; ○, tablet prepared from granules (a) with 0.16% chitosan; △, tablet prepared from granules (b) with 0.32% chitosan; □, tablet prepared from granules (c) with 0.65% chitosan; ●, tablet prepared from granules (d) with 2.40% chitosan; ▲, tablet prepared from granules (e) with 4.40% chitosan; ■, tablet prepared from granules (f) with 11.1% chitosan.

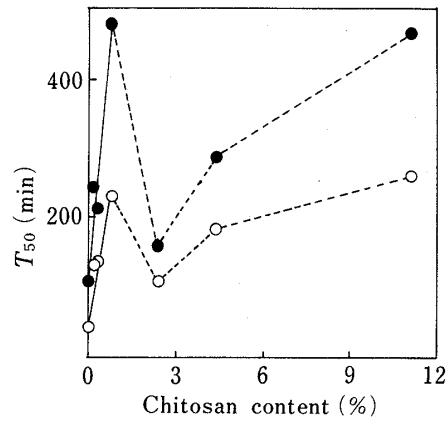


Fig. 4. Correlation between T_{50} of Tablet and Chitosan Content

●, in No. 1 disintegration test solution (JP X); ○, in No. 2 disintegration test solution (JP X). —, chitosan solution used as a binder; -----, chitosan gel used as a binder.

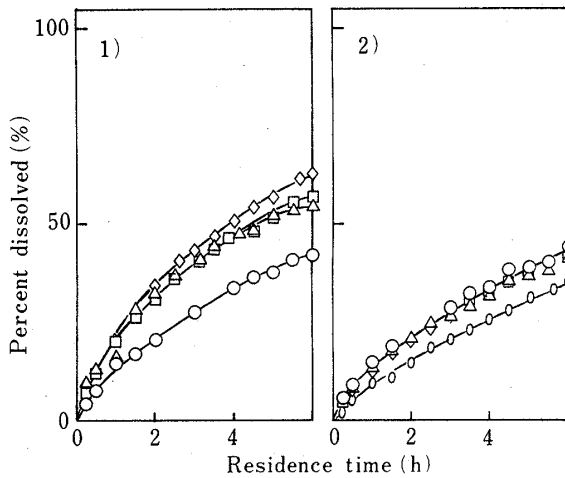


Fig. 5. Effects of pH and Ionic Strength on the Dissolution Behavior of Aspirin Tablet

1) pH; ○, 2, □, 4, △, 6, ◇, 8. 2) ionic strength (μ); ○, 0, □, 0.1, △, 0.3, ◇, 0.7, ○, 3.0 (pH=6.79).

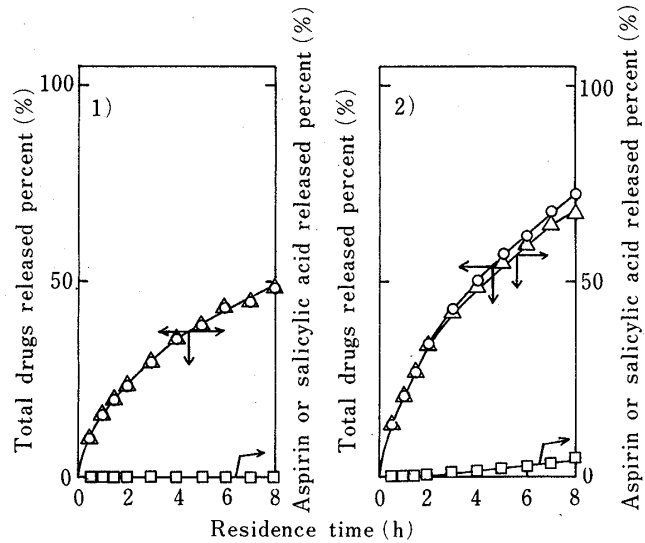


Fig. 6. Decomposition of Aspirin in Tablets during Dissolution Test

1) pH 2. 2) pH 8. ○, total drugs; △, aspirin; □, salicylic acid.

during the dissolution test, which may account for the significantly decreased release rate of the tablet. It was also found that T_{50} of the tablet in the disintegration test solution No. 1 was greater than that in the test solution No. 2 (Fig. 3). Chitosan dissolves in acidic solution more easily than in alkaline solution, whereas the solubility of aspirin in acidic solution is lower than that in alkaline solution. The above dissolution properties suggest that the rate-determining step is the dissolution of aspirin particles dispersed on the tablet surface as well as in the chitosan matrix, rather than the dissolution of the chitosan matrix of the tablet.

The effect of pH and ionic strength of the dissolution medium in the dissolution rate of

the tablet was investigated and the results are shown in Fig. 5. The dissolution of the tablet depended on the pH, but showed little dependence on the ionic strength. At ionic strength 3.0, the dissolution rate was decreased compared with the others, but this finding might be due to the decreased solubility of aspirin in the medium with higher salt concentration and a salting-out effect of sodium chloride on the dissolution of chitosan.

The amount of salicylic acid produced by decomposition of aspirin during the dissolution test was estimated based on the decomposition kinetics of aspirin in the dissolution medium. The decomposition of aspirin followed first-order kinetics and the rate constants (k) were found to be $1.10 \times 10^{-4} \text{ min}^{-1}$ and $5.44 \times 10^{-4} \text{ min}^{-1}$ at pH 2 and 8, respectively. The amount of salicylic acid produced by decomposition of aspirin in the tablet ($S_i(t_i)$) during the dissolution time, t_i , is given by Eq. 1,

$$S_i(t_i) = S(t_{i-1}) - \sum_{n=1}^i \left[\frac{A(t_n) + A(t_{n-1})}{2} (1 - \exp(-k\Delta t)) \right] \quad (1)$$

where A and S are the amounts of aspirin and salicylic acid, respectively, observed in the dissolution medium, t_i and t_{i-1} are the dissolution times and $\Delta t = t_n - t_{n-1}$. In Fig. 6, the amount of salicylic acid produced by the decomposition of aspirin and the aspirin released are plotted vs. the residence time. No decomposition of aspirin was found in the acidic solution but a little decomposition ($< 7.4\%$) was found in the alkaline solution.

Dissolution Rate Equation for the Tablet

It was found that the tablet decreased in size isotropically without disintegration after swelling at the initial stage. Therefore Eq. 2 was assumed to hold,

$$l_t = l_0 \cdot d_t/d_0 \quad (2)$$

where d_0 and d_t are the tablet diameter at time (t) = 0 and = t , respectively, l_0 and l_t are the tablet thickness at $t=0$ and = t , respectively. The drug concentration (c) in the tablet is given by Eq. 3,

$$c = W_0/V_0 = 4W_0/\pi d_0^2 l_0 \quad (3)$$

where V_0 is the initial tablet volume and W_0 is the initial drug content in the tablet. The residual drug content in the tablet (W_t) is given by Eq. 4,

$$W_t = V_t \cdot c = W_0 \cdot d_t^3/d_0^3 = W_0 - W \quad (4)$$

where V_t and W are the tablet volume and the drug amount dissolved. The tablet diameter (d_t) at time = t is described by Eq. 5.

$$d_t = d_0 (1 - W/W_0)^{1/3} \quad (5)$$

The surface area of the tablet (S_t) at time = t is given by Eq. 6.

$$S_t = 2 \cdot \pi d_t^2/4 + \pi d_t l_t = \pi d_0^2/2 \cdot (1 + 2l_0/d_0)(1 - W/W_0)^{2/3} \quad (6)$$

Under the sink condition, the dissolution rate equation of the tablet is described by the Noyes-Nernst Eq. 7,

$$dC/dt = DC_s S_t / \delta V \quad (7)$$

where C and C_s are the drug concentration in bulk and the drug solubility, respectively, D is the diffusion coefficient, V is the bulk liquid volume and δ is the diffusion layer. By substituting S_t into Eq. 7, Eq. 8 is obtained.

$$dC/dt = DC_s / \delta V \cdot \pi d_0^2/2 \cdot (1 + 2l_0/d_0)(1 - W/W_0)^{2/3} \quad (8)$$

TABLE II. Apparent Dissolution Rate Constant of Tablets Prepared from Granules (c) with 0.65% Chitosan

pH	K ($\times 10^{-6} \text{ s}^{-1}$)	C_s (mg/ml)	D/δ ($\times 10^{-4} \text{ cm/s}$)
2	4.97	5.0	2.808
4	8.29	6.8	3.469
8	10.63	8.1	3.717

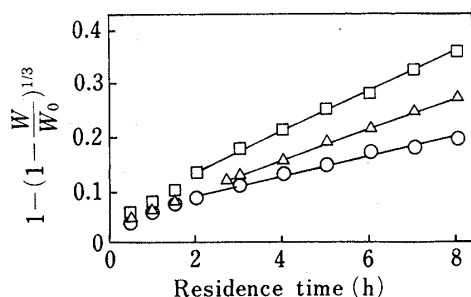


Fig. 7. Applicability of the Dissolution Rate Eq. 10 to the Dissolution Behavior of Tablets pH; \circ 2, \triangle 4, \square 8.

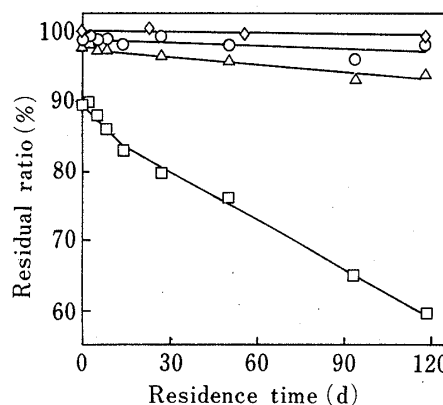


Fig. 8. Stability of Aspirin in Tablets Stored at 37°C and at R.H. 75.1% Chitosan content (%); \diamond 0, \circ 0.65, \triangle 2.4, \square 11.1.

Equation 8 can be transformed to Eq. 9.

$$dW/dt = k(1 - W/W_0)^{2/3} \quad (9)$$

$$k = \pi DC_s / 2\delta \cdot (1 + 2l_0/d_0) \cdot d_0^2$$

The integrated form of Eq. 9 is Eq. 10.

$$1 - (1 - W/W_0)^{2/3} = Kt \quad (10)$$

$$K = \pi DC_s / 6\delta W_0 \cdot (1 + 2l_0/d_0) \cdot d_0^2$$

Equation 10 was adapted to the dissolution data of the tablet as shown in Fig. 7. Except for the initial stage characterized by the swelling, all the data were fitted to straight lines as shown in Fig. 7. The apparent dissolution rate constant (D/δ) was determined from the slope of the straight line in Fig. 7, as listed in Table II. The dissolution rate constant increased with pH, suggesting that the diffusion coefficient of the drug increased, since the diffusion layer thickness is independent of pH.

Stability of Aspirin in the Tablet

The decomposition kinetics of aspirin in the tablet stored at 37°C and at R.H. 75.1% could be interpreted in terms of a zero order rate process as shown in Fig. 8. The chitosan in the tablet seemed to be responsible for accelerating the decomposition rate. At the initial stage, aspirin in the tablet with chitosan was rapidly decomposed, followed by a slow decomposition. The apparent decomposition rate constant of aspirin was determined from the slope of the straight line in Fig. 8. The rate constant was linearly correlated with both the moisture and the chitosan contents in the tablet as shown in Fig. 9. A linear relationship between the moisture and the chitosan content in the tablet also existed, as expected from Fig.

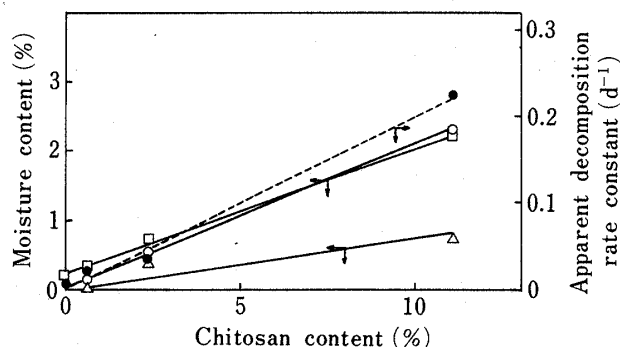


Fig. 9. Effect of Chitosan Content on the Moisture Content of Tablets and on the Apparent Decomposition Rate Constant of Aspirin

○, the moisture content before drying; △, the moisture content after drying; □, the equilibrium moisture content in 75.1% R.H. at 37°C; ●, apparent decomposition rate constant.

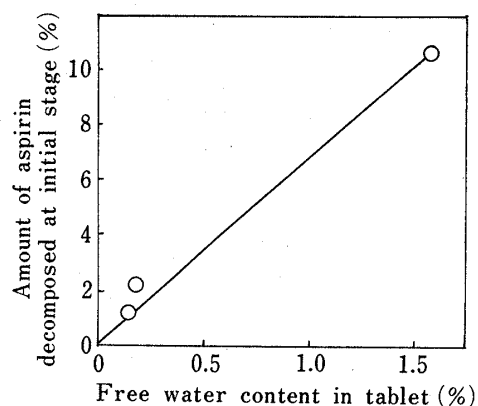


Fig. 10. Relationship between Initial Amount of Aspirin Decomposed and Amount of Free Water in the Tablets

9. It was assumed that the decomposition reaction was controlled by the water adsorbed by the chitosan, leading to zero-order kinetics with respect to the aspirin concentration. In the initial state, the free water in the chitosan matrix might react with the aspirin, resulting in rapid decomposition of aspirin. Thereafter, the water bound with chitosan molecules might react with the aspirin, resulting in the fairly slow decomposition process. The free water content was assumed to be the difference in moisture content before and after drying the tablet under a vacuum for 10 d (Fig. 9). In fact, the amount of aspirin decomposed at the initial stage was a linear function of the free water content in the tablet, as shown in Fig. 10.

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