Sustained-Release Dosage Forms Containing Chlorpheniramine Maleate with Water-Insoluble Glucan[1,2]

Ken Masumoto,[*,a] Kumiko Matsumoto,[a] Akiyoshi Yoshida,[a]
Shin'ichi Hayashi,[a] Naoki Nambu,[b]
and Tsuneji Nagai[b]

The Research and Development Department of Rohto Pharmaceutical Co., Ltd.,[a]
Tatsumi Nishi 1–8–1, Ikuno-ku, Osaka 544, Japan and Faculty of
Pharmaceutical Sciences, Hoshi University,[b] Ebara
2–4–41, Shinagawa-ku, Tokyo 142, Japan

In order to investigate the pharmaceutical availability of the water-insoluble glucan produced by Streptococcus mutans, application of the glucan as a filler for sustained-release tablets was studied. Glucan alone or the combined powder of glucan with lactose was used as a filler for these tablets and chlorpheniramine maleate (CPM), a potent antihistaminic, was used as a medicament. When the concentration of glucan was higher than 60%, directly compressed tablets were very hard and scarcely disintegrated. The release of CPM from a single face of the tablets was linear when plotted as a function of the square root of time. The release rate of CPM increased with a decrease of the concentration of glucan. The amount of CPM released increased in proportion to the initial concentration of CPM when the amount of CPM in the tablet was less than 25 mg. The effects of the tablet weight, the compressional pressure and the concentrations of glucan and CPM on the drug release rate from the whole tablets were also studied.

Further, the release profile of the tablet containing glucan was compared with that of a commercial tablet containing the same active ingredient. In the case of the tablet containing glucan, in contrast to the commercial tablet, no gap was observed in the release profile when the dissolution medium was changed from No. 1 to No. 2 disintegration media in JP X. In conclusion, these results suggest that the water-insoluble glucan may be useful as a filler for directly compressed sustained-release tablets.

Keywords——sustained-release dosage form; chlorpheniramine maleate; water-insoluble glucan; Streptococcus mutans; directly compressed tablet; filler; dissolution property

Many types of dosage form related to sustained-release type tablets have been reported,[3] but the manufacturing processes of these tablets are generally complicated. Synthetic polymers are usually used as a filler for these tablets. However, a natural, innocuous substance is desirable as a filler or an additive, and a naturally occurring polymer such as glucan may be a good candidate.

Streptococcus mutans is a major cariogenic organism. It has already been recognized that this organism produces water-soluble or insoluble polysaccharides, such as glucan and fructan, from sucrose. It has also been shown that this water-insoluble glucan consists mainly of α-(1→3) linkages.[4−7] Recently water-insoluble glucan was elucidated to play an important role in the formation of dental plaque.[8] Many biochemical studies related to glucan formation have also been reported.[9−11] However, there are few reports concerning the utilization of this glucan. The authors reported in a previous paper[12] that water-insoluble glucan can be used as a filler for directly compressed tablets.

Cellulose, a naturally occurring polymer, is a well known polysaccharide obtained from plants, and its derivatives are widely used in many fields. Application of such cellulose derivatives as hydroxypropyl cellulose (HPC),[13] hydroxypropylmethyl cellulose (HPMC),[14]

methyl cellulose (MC)[15] and microcrystalline cellulose (MCC),[16] as fillers for sustained-release tablets has also been reported. However, there have been few reports concerning the preparation of sustained-release tablets by the direct compression method.

The present study was designed to investigate the possibility of using glucan as a filler for sustained-release tablets prepared by the direct compression method. In addition, the release profiles of chlorpheniramine maleate, a potent antihistaminic, from tablets containing glucan were investigated.

Experimental

Materials——Water-insoluble glucan was obtained by the same method as described in the previous paper.[12] Commercial lactose JP X and chlorpheniramine maleate (CPM) JP X (Kongo Kagaku Co., Ltd.) were used after being passed through 100—200 mesh (149—77 μm) and 48 mesh (297 μm) sieves, respectively. The arithmetic mean particle size of the glucan determined by using an image analysis system (Hamamatsu TV Co., Ltd. HTV C1285/ C995-02) was 110.5 μm. The moisture contents of glucan and lactose determined with a microwave moisture meter (Anritsu Denki K375-A1) were 5.41 and 0.04%, respectively. CPM was used after being dried for 3 h at 105 °C. Polaramine® tablet (Schering Corp., U.S.A.) which contains 6 mg of CPM per tablet was used as a commercial sustained-release tablet.

Tablet Making by Direct Compression——Usually, flat-faced tablets (13 mm diameter, 100—300 mg) were made in an environment with a relative humidity of about 50% at room temperature, by direct static compression for 30 s under 100—400 kg/cm^2, i.e., 1.45—5.81 t/punch, using a Shimadzu evacuable die for preparing KBr tablets for infrared spectroscopy, and an oil pressure pump (Riken Kiki Co., Ltd). Tablets for dissolution testing by the rotating disk method were prepared with a hand-built apparatus, by direct static compression for 30 s under 200 kg/cm^2, i.e., 2.90 t/punch. The punch was removed after compression and the back of the tablet sealed with paraffin wax to prevent permeation of the dissolution medium.

Measurement of the Hardness and the Disintegration Time of Tablets——This was done by the same method as described in the previous paper.[12]

Dissolution Study——The dissolution study was carried out according to dissolution test method No. 1 in JP X (rotating basket method) using a dissolution tester (Toyama Sangyo NTR-VS) with 500 ml of dissolution medium at 37 °C. In the case of the rotating disk method, the basket of dissolution test method No. 1 in JP X was replaced with a disk, i.e., the die with the sample tablet. Disintegration medium No. 1 (pH 1.2) and after 120 min medium No. 2 (pH 6.8) in JP X were used as dissolution media and the rotation velocity was 100 rpm. At appropriate time intervals, 5 ml of the solution was taken out with a 5 ml transfer pipette equipped with a filter (Ishikawa Manufacturer, Fine Filter-F), then the solution was diluted with the dissolution medium to an appropriate concentration and the concentration of CPM was measured by the ultraviolet absorption method at 263 nm (No. 1 medium) or 260 nm (No. 2 medium). After each sampling, an equal volume of fresh dissolution medium was added to the test apparatus to maintain the original volume. In the case of the commercial tablet, the concentration of CPM was measured by high performance liquid chromatography (HPLC) after filtration of the solution through a membrane filter (Toyo, TM-2 0.45 μ). The apparatus and operating conditions of HPLC were as follows: pump, model 110 A (Altex Scientific Inc.); ultraviolet (UV) detector, model SPD-2A (Shimadzu Corp.) set at 262 nm; column, Nucleosil 10C18, 4 mm i.d. × 30 cm (Macherey Nagel Co.); mobile phase, 55% CH$_3$CN/45% CH$_3$COOH–(C$_2$H$_5$)$_3$N; flow rate, 1.0 ml/min; sample size, 20 μl; sensitivity, 0.01 a.u.f.s.

Measurement of the Hydrated Portion of Tablets——The hydration of tablets by penetration of dissolution media was determined as follows. Six tablets fixed in the dies were immersed in dissolution media and removed at appropriate time intervals coinciding with those used in the dissolution rate studies. The hydrated portion was removed mechanically and weighed after drying.

Results and Discussion

Physical Properties of Tablets Containing Glucan

The authors reported in a previous paper[12] the relationship between the hardness or the disintegration time of tablets and the concentration of glucan (4—50%), as well as the effect of compressional pressure on the hardness of tablets containing 10% glucan. The hardness of tablets increased proportionally with increase in the concentration of glucan. The tablets disintegrated immediately when the concentration of glucan was below 20% but showed longer disintegration times with an increase in concentration of glucan; tablets

TABLE I. Relationship between the Hardness of Tablets Compressed at Various
Pressures and the Concentration of Glucan or the Tablet Weight

Tablet weight (mg)	Concentration of glucan (%)	Hardness[a] (kg) Compressional pressure (kg/cm²)			
		100	200	300	400
100	60	6.1 ± 0.29	6.3 ± 0.89	6.2 ± 0.33	6.0 ± 0.23
	80	6.1 ± 0.18	6.2 ± 0.53	6.7 ± 0.54	6.3 ± 0.28
	100	6.9 ± 0.20	6.7 ± 0.51	6.5 ± 0.69	6.7 ± 0.42
200	60	12.5 ± 1.45	15.9 ± 0.90	17.4 ± 0.48	17.8 ± 1.62
	80	16.3 ± 0.75	21.0 ± 0.63	22.7 ± 0.76	23.2 ± 1.21
	100	23.9 ± 1.25	>30	>30	>30
300	60	21.0 ± 1.40	>30	>30	>30
	80	29.0 ± 0.89	>30	>30	>30
	100	>30	>30	>30	>30

a) Each value represents the mean ± S.D. of six determinations.

containing more than 40% glucan did not disintegrate within 60 min. Moreover, no inhibition of the dissolution of ascorbic acid (V.C.) from tablets containing glucan was observed. In conclusion, immediate disintegration of the tablet was observed with rapid dissolution of water-insoluble medicaments when the concentration of glucan was low. On the other hand, sustained release of drug was suggested from tablets containing glucan at high concentrations. Therefore, in this study, the physical properties of tablets containing high concentrations of glucan were investigated in order to design sustained-release type tablets.

The relationships between the hardness of tablets containing glucan with lactose and the concentration of glucan, the compressional pressure or the tablet weight are shown in Table I. The hardness of tablets (except for the 100 mg size) increased with increase in the concentration of glucan and the compressional pressure. No remarkable change of the hardness of 100 mg tablets was observed. The reason for this is considered to be that the 100 mg tablets are probably too thin (0.55—0.60 mm) for accurate measurement of the hardness. The disintegration times of all tablets were over 90 min in the disintegration test of JP X. Moreover, all tablets kept their original forms in the basket during the dissolution test even after 8 h. In conclusion, a concentration of glucan in tablets of over 60% might be enough to inhibit the disintegration of the tablets.

Release of Chlorpheniramine Maleate from a Single Face of a Tablet

i) **Release from Tablet Containing Glucan Alone**——The release pattern of CPM from a single face of a tablet containing 10 mg of CPM and 290 mg of glucan is shown in Fig. 1. As shown in Fig. 1, 56% of CPM was released in 8 h, and plots of percent release of CPM as a function of the square root of time showed good linearity ($r = 0.999$).

The mechanism of release from glucan tablets might be of the leaching type proposed by Higuchi.[19] The drug might be leached by the dissolution medium permeated through intergranular capillary channels of glucan. In the case of a tablet containing a large amount of drug or a drug which has low solubility, Eq. (1) can be applied:[19]

$$Q = \sqrt{\frac{D\varepsilon}{\tau}} \, (2A - \varepsilon C_s) C_s t \qquad (1)$$

where Q is the amount of drug released per unit exposed area in time t, D is the diffusion coefficient of the drug in the permeating medium, τ is the tortuosity factor of the capillary system, A is the total amount of drug per unit volume of the matrix, C_s is the solubility of the
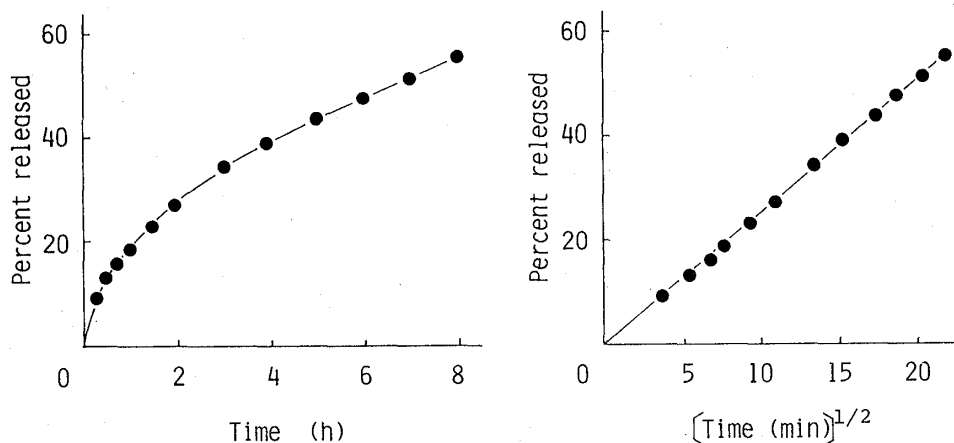
Fig. 1.   Release Pattern of Chlorpheniramine Maleate (CPM) from a Single Face of
a Tablet

Tablets containing 10 mg of CPM with 290 mg of glucan were compressed under
200 kg/cm^2.
Each point represents the mean of three determinations.

drug in the permeating medium, and ε is the porosity of the matrix. The above equation was proposed for release of drugs in a granular insoluble matrix with connecting capillaries. However, in the case of a tablet containing CPM, which has high solubility, the drug will completely dissolve when the glucan matrix is hydrated. Therefore, the assumption $A \geqq C_s$ in Eq. (1) is invalid, and the following equation (Eq. (2)) should be applied:[14,20)

$$W = 2W_0 \left(\frac{S}{V}\right) \sqrt{\frac{Dt}{\pi\tau}} \tag{2}$$

where W is the amount of drug released in time t, W_0 is the initial amount of drug in a tablet, S is the area exposed, V is the volume of the matrix and other terms are the same as in Eq. (1). Equation (2) can be simplified to Eq. (3) by using the apparent release rate constant, k:

$$P = k\sqrt{t} \tag{3}$$

where $P = W/W_0$, and $k = 2S/V(D/\tau\pi)^{1/2}$. Equation (3) means that plots of percent release of drug as a function of the square root of time should be linear. The results in Fig. 1 are in good agreement with Eq. (3).

ii) **Relation between Concentration of Glucan or the Release of Drug and the Hydration of Tablets**——The data in Fig. 1 are in good agreement with Higuchi's equation, though water penetration might be considered to be a limiting step in the drug release mechanism. Thus, the relation between the hydrated portion of the tablet and the percent release of drug at several concentrations of glucan was studied, as shown in Fig. 2. If the drug release is controlled only by the rate of penetration of dissolution media into the tablet matrix, the percent released should correspond to the hydrated portion of the tablet and a plot of one *versus* the other should be linear with unit slope and a zero point intercept.[17)] However, Fig. 2 shows that the percent released does not correspond to the hydrated portion of the tablet. Therefore, the penetration of dissolution medium is not the limiting process in the release of drug, and the release from glucan tablets might be of the leaching type, but modified by the rate of penetration of dissolution medium into the tablet matrix. Figure 2 also shows that the percent release lagged gradually behind the hydration with the passage of time when the concentration of glucan in the tablets was 85 or 96.7%. However, the lag time was small even in later time periods when the concentration of glucan in the tablets was 80%. Therefore, glucan gel formed may lose its function as a barrier for dissolution when the concentration of glucan
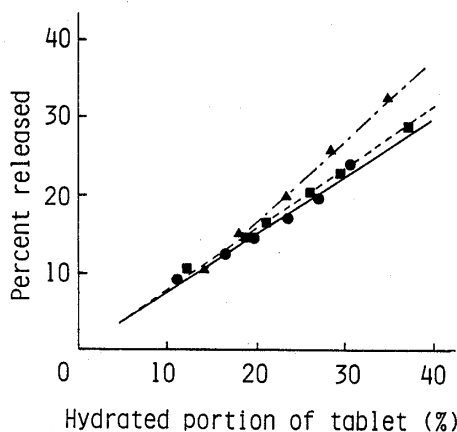
Fig. 2. Percent of Drug Released as a Function of the Amount of Hydrated Portion of a Tablet

Tablets contained 10 mg of CPM with 290 mg of glucan/lactose and were compressed under 200 kg/cm^2.

Concentrations of glucan in tablets were 80 (▲---▲), 85 (■---■) and 96.7% (●—●).

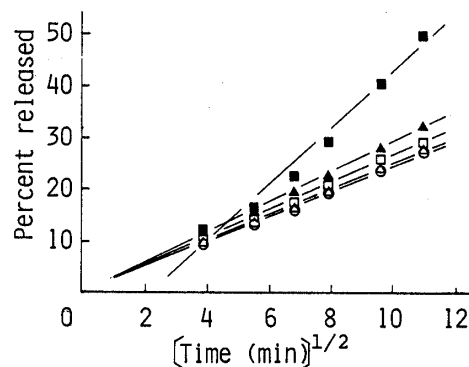Each point represents the mean of three determinations.

Fig. 3. Effect of Glucan Concentration on the Release Rate of Chlorpheniramine Maleate (CPM) from a Single Face of a Tablet

Tablets contained 10 mg of CPM with 290 mg of glucan/lactose and were compressed under 200 kg/cm^2.

Concentrations of glucan in tablets were 80 (■), 85 (▲), 90 (□), 95 (△) and 96.7% (○).

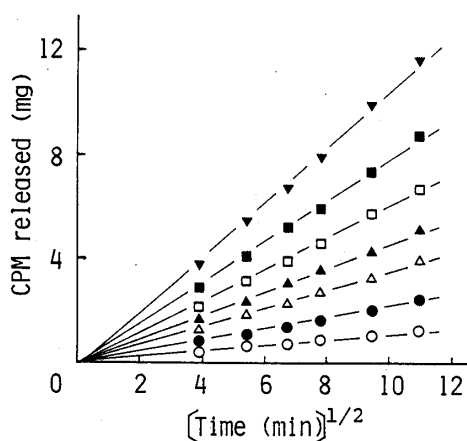Each point represents the mean of three determinations.

Fig. 4. Effect of the Initial Amount of Chlorpheniramine Maleate (CPM) on the Release Pattern of CPM from a Single Face of a Tablet

Initial amounts of CPM in 300 mg tablets compressed under 200 kg/cm^2 were 5 (○), 10 (●), 15 (△), 20 (▲), 25 (□), 30 (■) and 40 mg (▼).

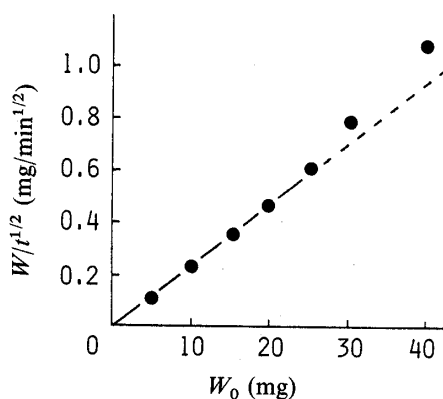Each point represents the mean of three determinations.

Fig. 5. Relationship between the Initial Amount of Chlorpheniramine Maleate (CPM) and the Amount of CPM Released per Square Root of Time

Each point represents the mean of three determinations.

in tablets is lower than 80%.

iii) **Effect of Concentration of Glucan on the Release Rate**——The effect of the concentration of glucan on the release rate of CPM from a single face of the tablets is shown in Fig. 3. The values of apparent release rate, k, calculated from Eq. (3) were 5.46×10^{-2}, 2.95×10^{-2}, 2.66×10^{-2}, 2.56×10^{-2} and 2.50×10^{-2} min$^{-1/2}$ at 80, 85, 90, 95 and 96.7% glucan, respectively. The value of k increased with decrease in the concentration of glucan (96.7—85%). However, k increased markedly when the concentration of glucan decreased to 80%, and the relationship between the percent released and the square root of time did not show either linearity or a zero point intercept. The term k is a reflection of S, V, D, τ and π,

but S, V, D and π are essentially constant in this case. Therefore, the increase of k may be explained by a decrease of the tortuosity τ of the tablet. On the other hand, the marked increase of k at 80% glucan cannot be explained only by a decrease of τ. The variation of other factors may affect the release rate at the lower concentration of glucan. For example, swelling of the glucan matrix by rapid hydration of glucan polymer may occur and the glucan gel formed may lose its function as a barrier for dissolution.

iv) Effect of Concentration of Chlorpheniramine Maleate on the Release Rate——The effect of the concentration of CPM on the release patterns of CPM from a single face of the tablets is shown in Fig. 4. Figure 5 shows the relationship between W_0 and $W/t^{1/2}$ from the results in Fig. 4. The plots of these relations were linear and passed through the zero point when the amount of CPM was lower than 25 mg. However, an upward deviation from linearity was observed when the amount of CPM was larger than 30 mg. Then, Eq. (4) is obtained by transformation of Eq. (2):

$$\frac{W}{\sqrt{t}} = 2W_0 \left(\frac{S}{V}\right) \sqrt{\frac{D}{\tau\pi}}$$ (4)

where D and π are constant. Therefore, the plot of $W/t^{1/2}$ as a function of W_0 should be linear and pass through the zero point if the terms S/V and τ are constant. In fact, however, an upward deviation from linearity at large amounts of CPM can be seen in Fig. 5. The change of the term S/V should be negligible during the early stages of release because of the very small swelling of glucan, while τ may be constant at small amounts of CPM (<25 mg) and may decrease gradually as the amount of CPM is increased above 30 mg. A similar phenomenon was reported by Lapidus *et al.*[14]

Release of Chlorpheniramine Maleate from the Whole Tablet

As mentioned above, the mechanism of release from a single face of tablets in the dissolution study was investigated, so the next step was to compare the release profiles from the single face with those from the whol tablets at several concentrations of glucan. Moreover, the effects of the compressional pressure and the tablet weight on the release from the whole tablet were studied, and the release profile of the tablet containing glucan was compared with that of the commercial tablet from the viewpoint of practical use.
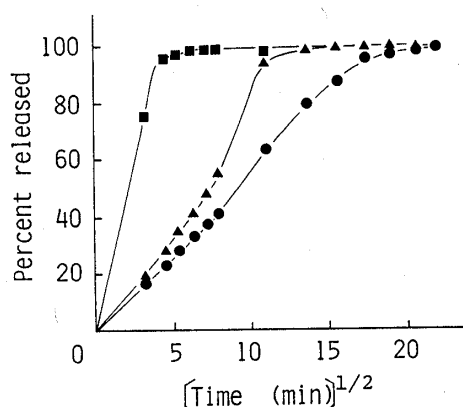

Fig. 6. Release Patterns of Chlorpheniramine Maleate (CPM) from Whole Tablets Containing 60 (■), 80 (▲) and 96.7% (●) Glucan

All tablets contained 10 mg of CPM and were compressed under 400 kg/cm².
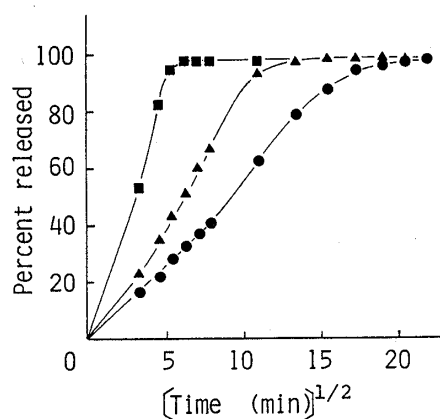Each point represents the mean of three determinations.

Fig. 7. Effect of the Tablet Weight on the Drug Release Pattern

Tablets weighing 100 (■), 200 (▲) and 300 mg (●) and containing 10 mg of chlorpheniramine maleate were compressed under 400 kg/cm².
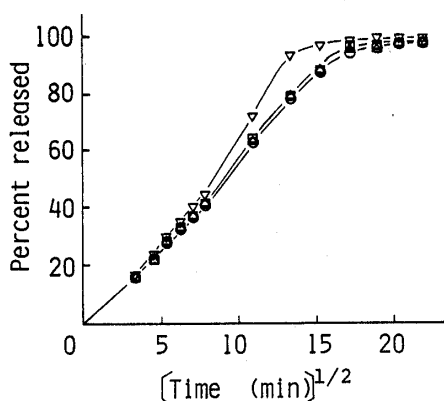Each point represents the mean of three determinations.

Fig. 8. Release Patterns of Chlorpheniramine Maleate (CPM) from Tablets Compressed under 100 (∇), 200 ($\square$), 300 ($\triangle$) and 400 kg/cm² (O)

All tablets contained 10 mg of CPM with 290 mg of glucan.
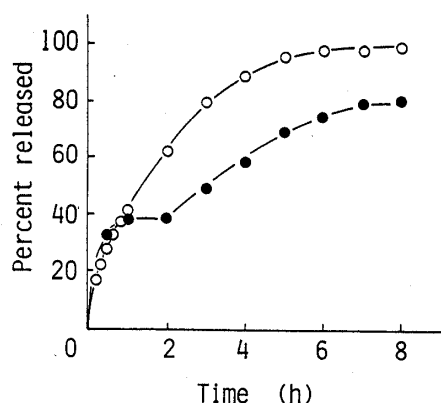
Each point represents the mean of three determinations.

Fig. 9. Comparison of the Release Patterns of the Glucan Tablet and the Commercial Tablet, Polaramine®

The glucan tablet containing 6 mg of chlorpheniramine maleate (CPM) with 294 mg of glucan was compressed under 400 kg/cm² (O). Polaramine® contains 6 mg of CPM (●).

Each point represents the mean of three determinations.

i) Effect of Concentration of Glucan on the Release Rate——Release patterns of CPM from the whole tablets for glucan concentrations of 60, 80 and 96.7% are shown in Fig. 6. Differing from the case of the single face, where the linear relationship between the percent released and the square root of time held until 8 h, a linear relationship held only until 60 min when the glucan concentration was 96.7%, and upward deviation from linearity was observed after this. Moreover, the release of the drug was almost completed within 20 min when the concentration of glucan was 60% and significantly prolonged release was not observed. In the case of the whole tablet, swelling of the glucan matrix by hydration might occur quickly and thoroughly. Consequently, the function as a physical barrier to diffusion of the drug might decrease and the release rate of the drug would increase.

ii) Effect of Tablet Weight on the Release Pattern——Release patterns of CPM from tablets of several weights containing 10 mg of CPM, and glucan alone as a filler are shown in Fig. 7. Drug release from the 300 mg tablet was maintained for more than 5 h. In contrast, the drug release from 100 and 200 mg tablets was almost completed in 40 and 120 min, respectively. Decrease of the tortuosity and increase of the amount of drug in the tablet might account for the fast release. Moreover, the fast release in the case of tablets of small weight might be due to the rapid completion of hydration of the tablet.

iii) Effect of Compressional Pressure on the Release Rate——Figure 8 shows the release patterns of the tablets compressed under 100—400 kg/cm². No remarkable change was observed in the release patterns except from tablets compressed under 100 kg/cm². It is possible that the intergranular space of glucan in the tablet compressed under 100 kg/cm² is larger. Consequently, the penetration of the medium into the tablet and the diffusion of the drug through the tablet are easier, and the release of the drug is rapid. For practical tablet manufacture, where the compressional pressure may vary slightly, it is convenient that the drug release rate does not change over a reasonable range of compressional pressure.

iv) Comparison of the Release Patterns of Glucan Tablet and a Commercial Sustained-Release Tablet, Polaramine®——In Fig. 9, the release pattern from the glucan tablet is compared with that from a commercial sustained-release tablet, Polaramine®, which contains the same active ingredient, CPM. No gap was observed in the release curve from the glucan tablet at 120 min when the dissolution medium was changed from No. 1 to No. 2 of JP X.

However, a remarkable gap was observed in the case of the Polaramine® tablet. This gap seemed to be due to a dissolution of the enteric coated layer in No. 2 medium. The pH of the gastro-intestinal fluid varies from person to person. Therefore, it is advantageous that the glucan tablet shows no gap in the release curve despite the pH change. In addition, glucan tablets can be easily prepared by direct compression of a powder mixture, and release of the drug continues for 5—6 h. Moreover, the results of dissolution studies showed good reproducibility. It is often assumed for sustained-release preparations that a 30—50% in vitro drug release in 1 h is good and that continuous drug release over 5—7 h is satisfactory.[18] Thus, it appears that the water-insoluble glucan may be a useful filler for directly compressed sustained-release tablets.

References and Notes

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