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In Vitro Dissolution Profile and *in Vivo* Absorption Study of Sustained-Release Tablets Containing Chlorpheniramine Maleate with Water-Insoluble Glucan[1)]

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In vitro dissolution profiles and *in vivo* absorption of chlorpheniramine maleate (CPM) from sustained-release tablets prepared with water-insoluble glucan produced by *Streptococcus mutans* were studied. Glucan alone or a conbination of glucan with lactose was used as a vehicle, and the tablets were made by direct compression method.

The release rate of CPM increased with decreasing concentration of glucan. The tablet containing 10 mg of CPM and 190 mg of glucan released CPM over 8 h. Plasma levels of CPM following oral administration of the sustained-release tablets were low but were well sustained as compared with the result for the immediate-release tablet.

Keywords——*in vitro* dissolution profile; *in vivo* absorption study; sustained-release tablet; chlorpheniramine maleate; water-insoluble glucan; *Streptococcus mutans*; direct compression method; plasma level; bioavailability

In previous papers we have reported on the pharmaceutical availability of the water-insoluble glucan produced by *Streptococcus mutans* as a vehicle for use in directly compressed tablets[2)] and sustained-release tablets.[3)]

Usually *in vitro* dissolution data are used to characterize drug release from dosage forms, based on the assumption that a correlation exists between *in vitro* dissolution and *in vivo* availability. However, recently, *in vivo* availability has been used more often to evaluate dosage forms and the correlation between *in vitro* dissolution and *in vivo* availability has been studied in some detail.[4,5)]

In the present study, as a part of a series of studies on pharmaceutical applications of water-insoluble glucan produced by *Streptococcus mutans*, sustained-release tablets were prepared with the glucan by the direct compression method, and the correlation between *in vitro* dissolution and *in vivo* availability was investigated. Chlorpheniramine maleate (CPM) was selected as an active ingredient. CPM is a potent antihistaminic, with a biological half-life of 12—21.6 h.[6)] CPM is usually dosed every 4 to 6 h in the case of conventional nonsustained-release dosage forms. However, in view of the burden of frequent dosing to the patient, it is desirable to develop a sustained-release dosage form.

Experimental

Materials——The same water-insoluble glucan, lactose, microcrystalline cellulose and chlorpheniramine maleate as described in the previous paper[2)] were used.

Tablet Making——Tablets, 200 mg in weight and 7.5 mm in diameter, were made by direct compression at 4 t/punch using a concave-face punch (Kikusui Seisakusho Ltd., Kyoto).

Dissolution Rate Study——The dissolution rate study was carried out according to the dissolution test method No. 1 in JP X (rotating basket method) using a dissolution tester (Toyama Sangyo NTR-VS) with 500 ml of the dissolution medium at 37 °C. The disintegration medium No. 1 (pH 1.2) and after 120 min the 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 Manufacturing, Fine Filter-F). After each sampling, an equal volume of fresh dissolution medium was added to the test apparatus to maintain the initial volume.

Quantitative Analysis for Chlorpheniramine——This was done by the same ultraviolet (UV) absorption method as described in the previous paper.[3]

Plasma Level of Chlorpheniramine in Rabbits——Male albino rabbits weighing 2.5—3.0 kg were used in this study. Each rabbit was fasted for 24 h with water *ad libitum* until administration of the tablet. The mouth of each rabbit was opened forcibly while the rabbit was under restraint in a box, and the tablet was easily passed into the esophagus by using a hand-built apparatus. The rabbits had free access to water and feed after tablet administration. Blood samples (3 ml each) were taken from the rabbits at 0, 0.5, 1, 1.5, 2, 3, 4, 6, and 12 h postadministration with a heparinized syringe. The blood samples were centrifuged at 3000 × *g* for 10 min at 4 °C, and the plasma was stored in a refrigerator until assayed.

High-Performance Liquid Chromatography (HPLC) Method for the Determination of Chlorpheniramine in Plasma Samples——The concentration of chlorpheniramine in the plasma was determined by a modification of the HPLC method described by Athanikar *et al.*[7] Plasma samples (1 ml) were supplemented with 200 μl of diphenhydramine hydrochloride (4 μg/ml), basified with 1.0 ml of 5% KOH, and extracted with 10 ml of diethyl ether by shaking for 15 min followed by centrifugation at 1000 × *g* for 20 min. The diethyl ether layer (8 ml) was transferred to a test tube and evaporated *in vacuo* using a rotary evaporator at 40 °C. HPLC carrier (200 μl) was added to the residue and a 100 μl aliquot was injected into the HPLC column. The apparatus and operating conditions were as follows: pump, model LC-5A (Shimadzu Corp.); UV detector, model SPD-2A (Shimadzu Corp.) set at 262 nm; column, Nucleosil 7C18, 4 mm i.d. × 30 cm (Macherey Nagel Co.); mobile phase, 45% CH_3OH/55%H_2O (0.005 M PIC B_6, 1% $(C_2H_5)_3N$, pH 2.6); flow rate, 1.0 ml/min; sample size, 100 μl; sensitivity, 0.005 AUFS, column temperature, 40 °C.

Results and Discussion

In Vitro Dissolution Profiles

Figure 1 shows the dissolution profiles from tablets containing 10 mg of CPM. Formulae of tablets used in this study are listed in Table I.

Tablet A prepared with only microcrystalline cellulose as a vehicle disintegrated immediately and the release of CPM from tablet A was completed in 20 min. On the other hand, in the case of tablet C prepared with only glucan as a vehicle, as has already been reported,[3] the penetration of the medium into the tablet or the leaching out of the drug from the tablet was prevented by hydration and subsequent swelling or gelation of the glucan, and consequently sustained release (over 8 h) was observed. However, when the glucan concentration was decreased to 85% (tablet B), the drug release was maintained for only 3 h.

Plasma Levels Following Oral Administration

Tablet A was administered as an immediate-release tablet. Sustained release from tablet

Table I. Formulae of Tablets Used in This Study

Formula		A	B	C
Content of ingredient (mg)	Chlorpheniramine maleate	10	10	10
	Glucan	0	170	190
	Microcrystalline cellulose	190	0	0
	Lactose	0	20	0
Dosage form		Immediate-release tablet	Sustained-release tablet	

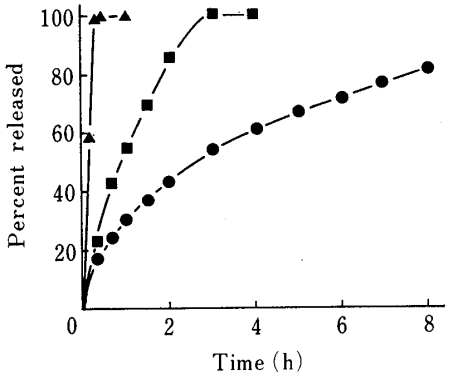

Fig. 1. *In Vitro* Dissolution Profiles of Immediate-Release Tablet A (▲) and Sustained-Release Tablets B (■) and C (●)

Each point represents the mean of three determinations.

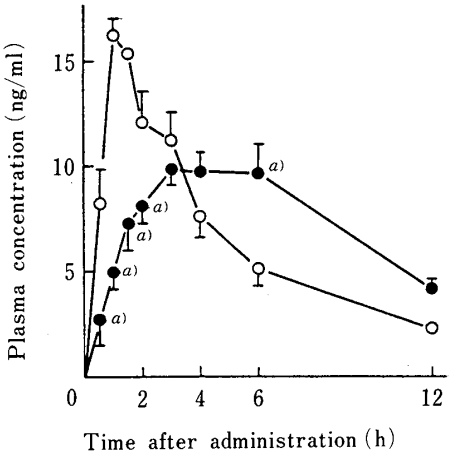

Fig. 2. Plasma Concentration Profiles of Chlorpheniramine after Administration of Immediate-Release Tablet A (○) and Sustained-Release Tablet C (●)

Each point represents the mean ± S.E. of three rabbits.
a) Statistically significant difference from tablet A at the 0.10 level by Student's *t*-test.

TABLE II. Mean Peak Plasma Concentration, Peak Time and Area under Plasma Concentration–Time Curve of Chlorpheniramine from Immediate-Release and Sustained-Release Tablets

Parameter	Immediate-release tablet	Sustained-release tablet
Peak plasma concentration (ng/ml)	14.7 ± 1.63	10.1 ± 0.78
Peak time (h)	0.8 ± 0.17	5.0 ± 1.00
AUC, 0—12 (ng·h/ml)[a)]	82.9 ± 9.05	90.1 ± 5.22[b)]

Each value represents the mean ± S.E. of three rabbits.
a) The area under the curve from 0 to 12 h after administration.
b) No statistically significant difference was found at the 0.10 level by Student's *t*-test.

B was expected to be poor, since 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.[8)] Therefore, tablet C was administered as a sustained-release tablet.

Plasma drug levels after oral administration of the two kinds of tablets are shown in Fig. 2. Moreover, the mean peak plasma concentration, peak time and area under the plasma concentration curve (*AUC*) of each type of tablet are summarized in Table II.

Plasma level after the administration of the sustained-release tablet (tablet C) was lower at the earlier stages but higher later as compared with that of the immediate-release tablet (tablet A). The lower but sustained plasma level after oral administration of tablet C reflects the comparatively slow drug release *in vitro* of tablet C as compared with tablet A, as shown in Fig. 1. The mean peak plasma concentration (C_{max}) of CPM from tablet C was about two to three times that from tablet A, and the mean peak plasma concentration times (T_{max}) of CPM from tablets A and C were 0.8 and 5.0 h, respectively. There was a significant difference ($p = 0.1$) in C_{max} and T_{max} between tablets A and C. However, there was no significant difference ($p = 0.1$) in the area under the plasma concentration–time curve from 0 to 12 h after

administration of CPM between tablets A and C, so no decrease in the extent of bioavailability due to the use of the sustained-release dosage form was apparent.

In the present study, the *in vitro* sustained-release characteristic was confirmed to be reflected in the plasma level profile after oral administration of a sustained-release tablet containing CPM with water-insoluble glucan. Thus, it appears that the water-insoluble glucan may be useful as a vehicle for directly compressed sustained-release tablets.

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References and Notes

1) This paper forms Part XLVIII of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XLVII: T. Takai, K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **32**, 1942 (1984).
2) K. Masumoto, N. Nambu, A. Yoshida, S. Hayashi, and T. Nagai, *Chem. Pharm. Bull.*, **31**, 209 (1983).
3) K. Masumoto, K. Matsumoto, A. Yoshida, S. Hayashi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **32**, 1055 (1984).
4) W. A. Cressman, C. A. Janicki, P. C. Johnson, J. T. Doluisio, and G. A. Braun, *J. Pharm. Sci.*, **58**, 1516 (1969).
5) M. Nakano, N. Ohmori, A. Ogata, K. Sugimoto, Y. Tobino, R. Iwaoku, and K. Juni, *J. Pharm. Sci.*, **72**, 378 (1983).
6) E. A. Peets, M. Jackson, and S. Symchowicz, *J. Pharmacol. Exp. Ther.*, **180**, 364 (1972); J. A. Thompson and F. H. Leffert, *J. Pharm. Sci.*, **69**, 707 (1980); A. Yacobi, R. G. Stoll, G. C. Chao, J. E. Carter, D. M. Baaske, B. L. Kamath, A. H. Amann, and C. Lai, *ibid.*, **69**, 1077 (1980).
7) N. Y. Athanikar, G. W. Peng, R. L. Nation, S. Huang, and W. L. Chiou, *J. Chromatogr.*, **162**, 367 (1979).
8) F. W. Goodhart, R. H. McCoy, and F. C. Ninger, *J. Pharm. Sci.*, **63**, 1748 (1974).