[Chem. Pharm. Bull.
30(8)2919—2925(1982)]

Interaction of Phenothiazines with Pectin in the Solid State[1,2]

YASUYUKI TAKAHASHI,[a] NAOKI NAMBU,*,[b] and TSUNEJI NAGAI[b]

Research Laboratory of Wakamoto Pharmaceutical Company,[a] Kanade-378, Oi-machi, Ashigarakami-gun, Kanagawa 258, Japan and *Hoshi Institute of Pharmaceutical Sciences,[b] Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan*

(Received December 2, 1981)

The interaction of phenothiazines with pectin in the solid state was investigated, and the formation of coprecipitates was confirmed by infrared absorption spectroscopy and powder X-ray diffractometry.

There was a positive correlation between the amount of drug in the coprecipitate and the primary binding number n_1 of phenothiazines with pectin in aqueous solution.

The initial dissolution rate of drug from the coprecipitates in purified water followed zero-order kinetics and was very small compared with that of the intact drug. The dissolution rate of diethazine/pectin coprecipitate was almost independent of the rotating speed in 0.1 N hydrochloric acid.

These results suggest that coprecipitates of drugs with pectin might be useful as sustained-release preparations.

Keywords——pectin; phenothiazines; coprecipitates; infrared absorption spectroscopy; X-ray diffraction pattern; dissolution rate; binding parameters

In a previous study,[3] the interaction between phenothiazines and pectin in aqueous solution was investigated by the equilibrium dialysis method. Hydrophobic bonding is considered to play a predominant role in the interaction of phenothiazines with petcin on the basis of the relationships between binding parameters obtained by analysis of Scatchard plots and the drug properties.[3] The relation between the formation of coprecipitates and the binding parameters, as well as the micelle formation of phenothiazines, was also discussed.[3]

In the present work, we attempted to study the interaction of phenothiazines with pectin in the solid state. Namely, with the aim of developing useful sustained-release preparations, the amounts of drug in coprecipitates of eight derivatives of phenothiazines with pectin, the binding parameters of the drugs to pectin in aqueous solution,[3] and the dissolution properties of the drugs from the coprecipitates were investigated.

Experimental

Materials——Low-methoxyl pectin (Sunkist Growers Inc.), the molecular weight of which was determined to be 120000 by gel chromatography on Sephadex G-100, was used.[4]

The eight derivatives of phenothiazines used were as follows: anergen; chlorpromazine; diethazine; methdilazine; promazine; promethazine; trifluoperazine; triflupromazine. These drugs are hydrochloride salts except for trifluoperazine (dihydrochloride salt).

Preparation of Coprecipitates of Phenothiazines and Pectin——The coprecipitates of phenothiazines with pectin were prepared according to the modified method described by Graham *et al.*[5] Ten ml of 15% aqueous solution of a phenothiazine was added to 50 ml of 2% aqueous solution of pectin in a light-resistant flask, and the solution was agitated at 37°C for 24 h. The suspension was centrifuged for 10 min at 3000 rpm at 20°C in a Hitachi 18 PR-5 centrifuge. The supernatant was removed by decantation, 30 ml of water was added to the precipitate and the suspension was centrifuged again. This procedure was repeated twice. The coprecipitate formed was dried under reduced pressure over anhydrous phosphoric acid in a desiccator at room temperature for 24 h.

Determination of Drugs in Coprecipitates——Drugs in the coprecipitates were determined according to the method described in the previous paper.[4]

Infrared (IR) Absorption Spectroscopy——IR absorption spectra were measured with a Shimadzu IR-400 infrared spectrophotometer by the KBr disk method.

X-Ray Diffraction Studies——Powder X-ray diffractometry was carried out with a Rigaku Denki Geigerflex Model D-2 diffractometer using Ni-filtered Cu-K_α radiation.

Determination of Drug Dissolution Rates from Coprecipitates——The dissolution rate was determined by a stationary disk method, using the apparatus described in a previous paper.[6] Experiments were carried out under the following conditions: 200 ml of purified water as the dissolution medium (ececpt that 1/30 N and 1/10 N hydrochloric acid were used for the dissolution studies of diethazine/pectin coprecipitate); at 37°C; 300 rpm rotating speed (except that 50, 100 and 600 rpm were used for diethazine/pectin coprecipitate); and 1.3 cm diameter of the drug compressed disk (200 kg/cm^2 for 3 min).

Results and Discussion

IR Absorption Spectroscopy and Powder X-Ray Diffractometry of Phenothiazines/Pectin Coprecipitates

It was previously reported that, during an experiment on drug interactions in aqueous solution, white precipitates which were believed to be the coprecipitates of various drugs with pectin were observed, though isothipendyl (ITP) and chlorpromazine-sulfoxide (CPZ-O)[3] did not give coprecipitates.

In the present study, coprecipitates with pectin were prepared according to the above method for the following eight phenothiazines: anergen, chlorpromazine, diethazine, methdilazine, promazine, promethazine, trifluoperazine and triflupromazine.

Figure 1 shows IR absorption spectra of the coprecipitate of promazine with pectin in comparison with those of the physical mixture. Absorption bands at 2240 and 2280 cm^{-1}, which are considered to be due to the hydrochloride of the tertiary amines in the side chain of promazine and which are observed for the physical mixture, disappeared in the coprecipitate. A similar phenomenon was observed for benzydamine hydrochloride.[4] Furthermore, the absorption bands at 1040, 1120 and 1240 cm^{-1}, which are also considered to be due to the tertiary amine moiety, disappeared in the coprecipitate. The results suggest that the tertiary amine moiety binds strongly to carboxyl residues of galacturonic acid moieties in the pectin molecule. The carboxylate antisymmetric stretching band at 1607 cm^{-1} and the ester-carbonyl stretching band at 1740 cm^{-1}, both of which are observed in the pectin molecule,[7] were observed in the coprepitate, but disappeared in the physical mixture. The intensities of the absorption bands at 1607 and 1740 cm^{-1} were enhanced in the coprecipitate, suggesting an

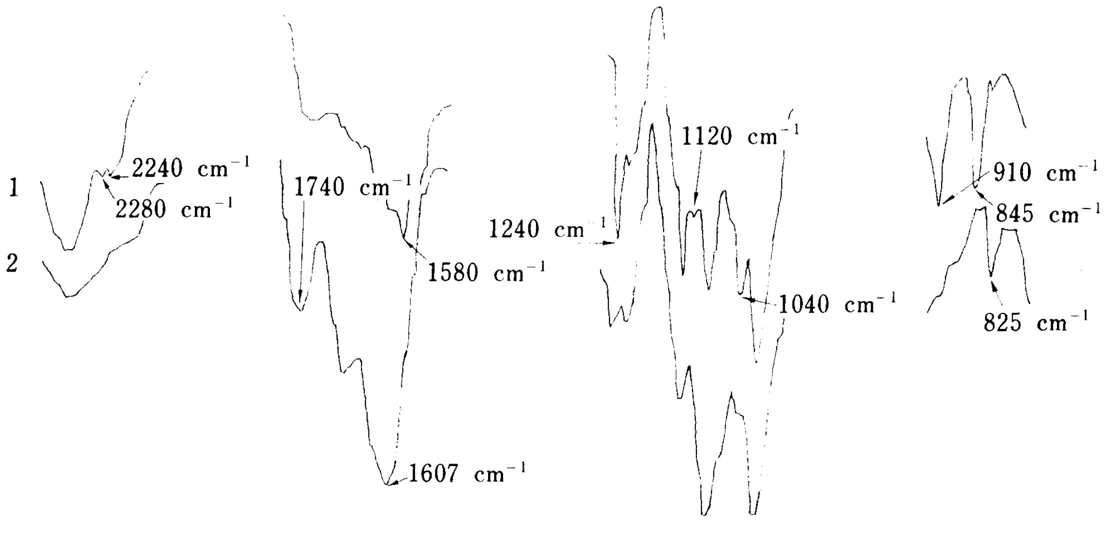

Fig. 1. IR Absorption Spectra of the Promazine-Pectin System (KBr Disk Method)

(1): physical mixture of promazine and pectin.
(2): coprecipitate of promazine and pectin (content of promazine, 23.6%).

interaction of promazine and pectin. A characteristic absorption band of glucopyranose in the pectin molecule at 910 cm^{-1}, which is known to be due to the vibration of a dioxane-like ring,[8] disappeared in the coprecipitate. This suggested that the vibration of the galacturonic ring in pectin might be suppressed by coprecipitate formation. An absorption band at 845 cm^{-1} is considered to be due to the deformation vibration of C_1–H of the galacturonic moiety in pectin.[8] In the galacturonic monomer, C_1 differs from C_2–C_6 in that C_1 is adjacent to two oxygen atoms. Therefore, it may be considered that coprecipitate formation affected the deformation vibration including these oxygen atoms.

A similar phenomenon was also observed in the chlorpromazine/, trifluoperazine/and triflupromazine/pectin systems, except that the band at 1607 cm^{-1} was not observed in the trifluoperazine/pectin coprecipitate.

Figure 2 shows the powder X-ray diffraction patterns of intact diethazine and chlorpromazine, and of the coprecipitates of the drugs with pectin. Both of the coprecipitates showed no peak and were found to be amorphous. It has been reported that a similar change in the powder X-ray diffraction patterns upon formation of a coprecipitate is observed in the benzydamine hydrochloride/pectin system,[4] and sulfamethizole/polyvinylpyrrolidone system.[9]

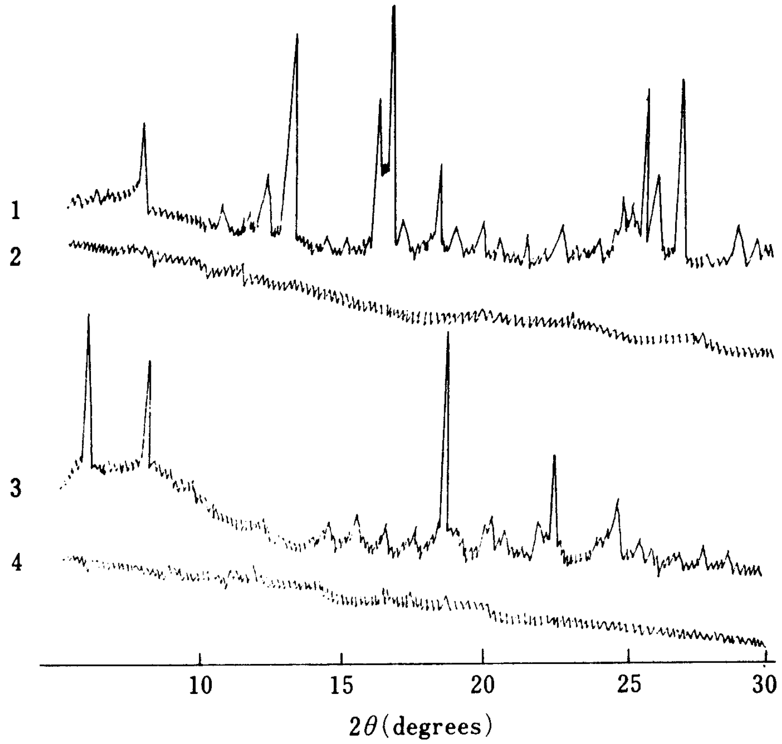

Fig. 2. Powder X-Ray Diffraction Patterns of Drug/Pectin Systems (Cu-$K\alpha$ Radiation)

(1): intact diethazine.
(2): diethazine/pectin coprecipitate (content of diethazine, 53.8%).
(3): intact chlorpromazine.
(4): chlorpromazine/pectin coprecipitate (content of chlorpromazine, 49.8%).

The IR absorption spectra and the powder X-ray diffraction patterns of the drug-pectin coprecipitates clearly differ from those of physical mixtures of the phenothiazines with pectin.

Relation between Amount of Drug in the Coprecipitates and Binding Parameters obtained in Aqueous Solution

The amounts of drug in the coprecipitates, the binding parameters of drugs with pectin in aqueous solution obtained by the equilibrium dialysis method[3] and the initial dissolution

Table I. Binding Parameters, Amount of Drugs in Coprecipitates and Initial Dissolution Rate of Phenothiazines in Coprecipitates

Drug	Binding parameters			Amount of drug in coprecipitate ($\times 10^4$ M)	Initial dissolution rate (k')	
	K_1(M^{-1})	n_1	K_1n_1(M^{-1})		k' ($\times 10^6$ M/min)	Ratio
Trifluoperazine	6250	34.5	216000	8.5	0.483	0.167
Promazine	5280	33.3	176000	9.6	2.89	1.00
Promethazine	1760	54.6	96100	22.8	4.27	1.48
Anergen	1430	66.7	95400	15.6	4.35	1.51
Triflupromazine	1042	31.2	32500	13.1	2.40	0.830
Diethazine	740	108	79900	34.8	5.94	2.06
Chlorpromazine	597	164	97900	27.9		
Methdilazine	211	168	35400	22.3	3.09	1.07

K_1: primary binding constant.
n: primary maximum binding number.

rates of drugs from the coprecipitate are summarized in Table I.

The n value, the maximum binding number of pectin to the drug in aqueous solution obtained by the equilibrium dialysis method, was plotted against the amount of drug in the coprecipitate (Fig. 3), and a correlation coefficient of 0.818 was obtained between the logarithmic value of the primary binding number n_1 and the amouht of drug in the coprecipitate; this is significant at the 5% level in the t-test.

As shown in Table I, The amount of drug in the coprecipitate tends to decrease with increase of K_1n_1, though some drugs are exceptional. In the previous study of the interaction of various drug and pectin in aqueous solution, a negative relation between K_1n_1 and the hydrophobicity of drugs was observed.[3] Ionic bonding was also involved in the interaction at higher concentrations of drugs.[3] Thus, the amount of drug in the coprecipitate may be related to the strength of ionic bonding, because very high concentrations of drugs were used in preparing the coprecipitates.

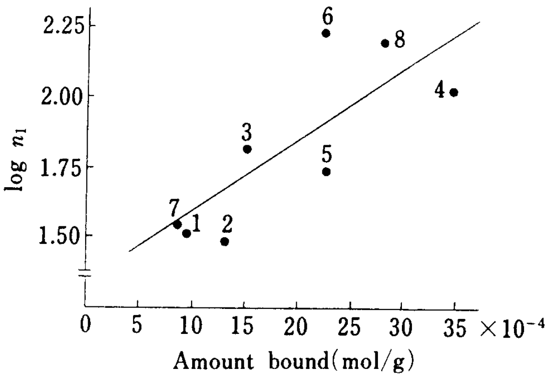

Fig. 3. Relation between Primary Binding Number (n_1) and Amount of Drug Bound to Pectin in Coprecipitates

1: promazine, 2: triflupromazine, 3: anergen, 4: diethazine, 5: promethazine, 6: methdilazine, 7: trifluoperazine, 8: chlorpromazine.

Dissolution Rates of Phenothiazines/Pectin Coprecipitates

The dissolution of drugs from coprecipitates was linear with respect to time, except for chlorpromazine/pectin coprecipitate. The dissolution rate of phenothiazine/pectin copreci-

Table II. Initial Dissolution Rate k' of Intact Drug and of Drug/Pectin Coprecipitate at 37°C in Purified Water

Drug	k' of intact drug ($\times 10^4$ M/min) (A)	k' of coprecipitate ($\times 10^6$ M/min) (B)	Ratio (A/B)
Triflupromazine	5.66	2.40	236
Diethazine	9.45	5.94	159
Anergen	3.44	4.35	79.1
Promethazine	9.84	4.27	230
Trifluoperazine	9.95	0.483	2060
Promazine	10.1	2.89	349

pitate was very small compared with the intact drug, as shown in Table II. The dissolution rate of the coprecipitate of benzydamine hydrochloride, a cationic drug, with pectin was also reported to be very small compared with that of the intact drug.[4]

These results indicate that the dissolution rates of the complexes, that is, salts formed between cationic drugs and a polyanionic electrolyte, pectin, are very small, suggesting the pectin complexes of cationic drugs might be practically useful as sustained-release preparations.

The dissolution rates for diethazine/pectin coprecipitate were plotted according to the Cooper–Kingery equation.[10] The relation between the square root of rotating speed and the initial dissolution rate was linear, as shown in Fig. 4. The reason why the straight line did not pass through the origin was considered to be due to a suppression of the dissolution of the drug by gel-formation of pectin in water.[11]

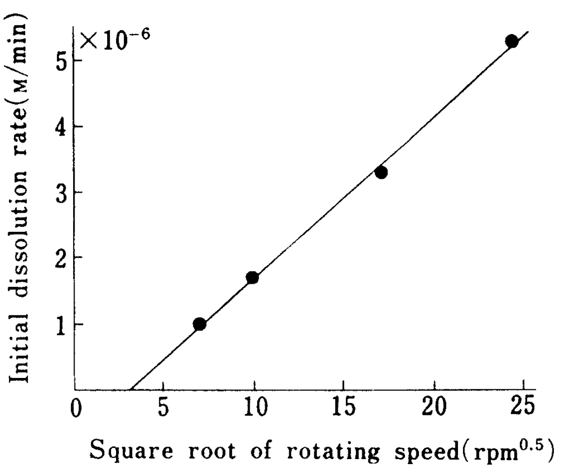

Fig. 4. Relationship between Square Root of Rotating Speed and Initial Dissolution Rate of Diethazine/Pectin Coprecipitate at 37°C in Purified Water (Stationary Disk Method)

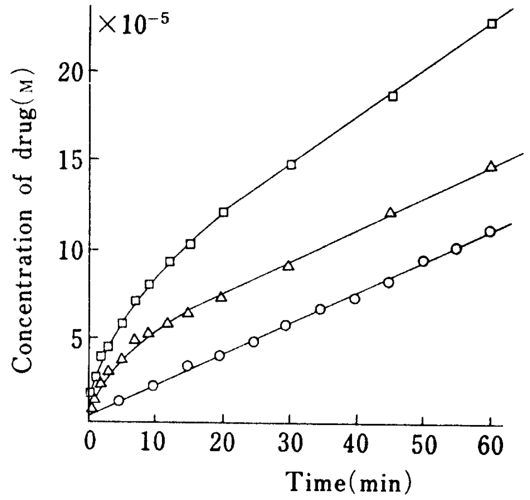

Fig. 5. Dissolution Curves of Diethazine/Pectin Coprecipitate at 100 rpm at 37°C (Stationary Disk Method)

○: in purified water.
△: in 1/30 N HCl.
□: in 1/10 N HCl.

As shown in Fig. 5, the dissolution of diethazine/pectin coprecipitate in purified water was linear, whereas in 1/30 N and 1/10 N hydrochloric acid the plot was initially curved but became linear. The dissolution rate of the coprecipitate up to 20min in 1/10 N hydrochloric acid was almost independent of the rotating speed, as shown in Fig. 6.

Therefore, the dissolution of diethazine from the coprecipitate in 1/10 N hydrochloric acid was not considered to follow the diffusion-controlled mechanism.[12] The following processes might be considered to account for the initial dissolution curves observed in 1/10 N and 1/30 N hydrochloric acid.

(A) It is generally known that polyuronides such as pectin and alginate are efficient natural ion exchangers.[13–15] In the present study, the proton of hydrochloric acid might be enhanced by the drug cation in the coprecipitate, and the drug would be released from the coprecipitate faster in diluted hydrochloric acid than in purified water. Also the initial dissolution rate of the drug in 1/10 N hydrochloric acid was larger than that in 1/30 N hydrochloric acid. In other words, since the coprecipitates seem to be a salt formed between the cationic drugs and polyanionic electrolyte, pectin, the solubility of the coprecipitates might be pH-dependent and the dissolution rate might be larger in an acidic medium.

(B) It has been reported that the amounts of drug released from tablets containing alginate, an anionic pectin-like polysaccharide, became smaller with increasing amounts of alginate due to gel-formation by alginate in water.[16] Therefore, it was considered that the release of the drug from diethazine/pectin coprecipitate might be influenced by gel-formation of pectin in water. The gel-forming ability of pectin in dilute hydrochloric acid is smaller than in purified water, because pectin is an anionic polyelectrolyte. Thus, the initial dissolution rate of the drug would be faster in dilute hydrochloric acid than in purified water.

The initial dissolution rate of diethazine/pectin coprecipitate was larger in an acidic medium than in purified water, as shown in Fig. 5. The dissolution rate of the coprecipitate in acidic medium was, however, significantly smaller than that of the intact drug in purified water (Table II). Furthermore, the dissolution rate in 1/10 N hydrochloric acid was almost independent of the rotating speed, as shown in Fig. 6. These results indicated that the coprecipitate might be suitable for use as a sustained-release preparation for oral administration.

Relation between the Dissolution Rate of Coprecipitate and Binding Parameters obtained in Aqueous Solution

Next we will discuss the relation between the dissolution rate of drugs from the coprecipitates and the binding parameters obtained in aqueous solution. The maximum binding number n and binding constant K are the parameters under equilibrium conditions in a liquid phase. On the other hand, the dissolution rate of the drug from the coprecipitate may be regarded as a parameter of the solid state. Therefore, in order to relate the various binding parameters, the following equations are introduced. n and K in equation 1 are constant.

$$nD + P \underset{K}{\rightleftarrows} DnP \underset{C_s}{\rightleftarrows} (DnP)_{\text{solid}} \qquad (1)$$

$$K \cong K'SC_s \qquad (2)$$

D and P are the equilibrium concentrations of drug and of pectin, respectively, C_s is the rate constant for transfer from the liquid phase to the solid drug/pectin coprecipitate, k and K' are the apparent dissolution rate of the drug from the coprecipitate and the dissolution rate constant of the drug itself, respectively, and S is the surface area of the coprecipitate. K' may have a positive relation to a reciprocal of the binding constant K, that is, the dissociation constant K^{-1}, in the solid state. Furthermore,

$$K' \propto aK^{-1} \quad (a \text{ is constant}) \qquad (3)$$

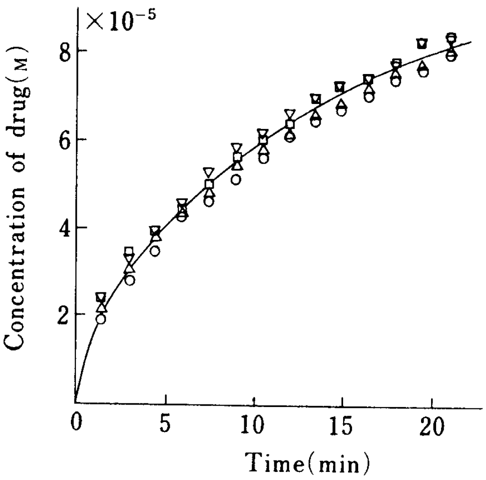

Fig. 6. Dissolution Curves of Diethazine/Pectin Coprecipitate in 1/10 N HCl at Various Rotating Speed at 37°C (Stationary Disk Method)

○: 50 rpm, □: 300 rpm, △: 100 rpm, ▽: 600 rpm.

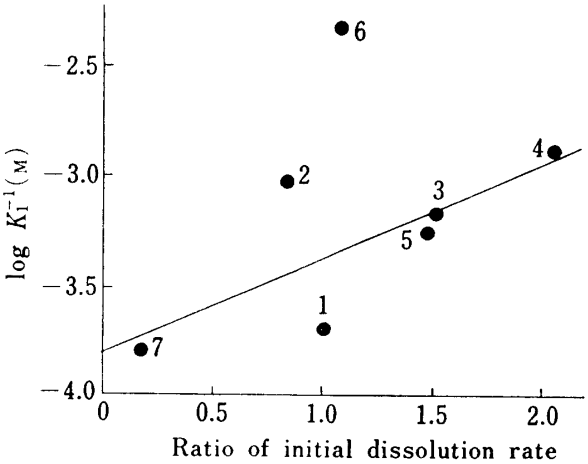

Fig. 7. Relation between Ratio of Initial Dissolution Rate and Reciprocal of Primary Binding Constant (K_1^{-1}) of Drug to Pectin in Coprecipitates

1: promazine, 2: trifupromazine, 3: anergen, 4: diethazine, 5: promethazine, 6: methdilazine, 7: trifluoperazine.

$$k \cong K^{-1} SC_s \qquad (4)$$

the free energy of dissolution may be expressed by equation. 5.

$$-\Delta G = RT \ln K^{-1} \qquad (5)$$

Thus, it was considered that the dissolution rate of drug from the coprecipitate should be proportional to a logarithmic value of the reciprocal of the binding constant obtained in aqueous solution.

The result, as expected, showed that the dissolution rate tended to increase with log K_1^{-1} values eucept for methdilazine/pectin coprecipitate, with a correlation coefficient of 0.735, as shown in Fig. 7.

Thus, there seems to be a relation between the binding parameters of phenothiazines with pectin in aqueous solution and both the amount of drug in the coprecipitates of phenothiazines with pectin, and the initial dissolution rate of the drug from the coprecipitate.

The initial dissolution rate of drug from the coprecipitate followed zero-order kinetics and was very small compared with that of the intact drug. The dissolution rate of diethazine/pectin coprecipitate was almost independent of the rotating speed in 1/10 N hydrochloric acid. From a pharmaceutical point of view, coprecipitates of drugs with pectin are potentially useful as sustained-release preparations.

Acknowledgement The authors are grateful to Messrs Toshio Kuroda and Yoshiaki Saito of Wakamoto Pharmaceutical Company for their support in this work. Thanks are also due to Misses Tomoko Ando and Michiyo Honda for their assistance in the experimental work.

References and Notes

1) This paper forms Part XXVI of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XXV: M. Ishida, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 980 (1982).
2) A part of this work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1980, and at the 2nd International Conference on Pharmaceutical Technology, Paris, June, 1980.
3) Y. Takahashi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **29**, 828 (1981).
4) Y. Takahashi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **26**, 3836 (1978).
5) H.D. Graham, Y.M. Baker, and A.N. Njoku-Obi, *J. Pharm. Sci.*, **52**, 192 (1963).
6) Y. Hamada, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **23**, 1205 (1975).
7) S.M. Bociek, and Welti, *Carbohydrate Research*, **42**, 217 (1975).
8) K. Nakanishi, "Sekigaisen Kyushu Supekutoru-Teisei to Enshu," Nankodo, Tokyo, 1960.
9) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **27**, 1223 (1979).
10) A.R. Cooper, and W.D. Kingery, *J. Phys. Chem.*, **43**, 1460 (1951).
11) D.A. Rees, *Advance Carbohydrate Chem. Biochem.*, **24**, 267 (1969).
12) W. Nernst, *Z. Phys. Chem.*, **47**, 52 (1904).
13) O. Smidsrφd, and A. Haug, *Acta Chem. Scand.*, **22**, 1989 (1968).
14) D. Cozzi, P. G. Desideri, L. Lepri, and G. Ciantelli, *J. Chromatogr.*, **35**, 396 (1968).
15) R. Kohn, *Pure and Appl. Chem.*, **22**, 371 (1975).
16) M. Bamba, F. Puisieux, J. P. Marty, and J. T. Carstensen, *Int. J. Pharm.*, **2**, 307 (1979).