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## Dissolution of Diethazine Hydrochloride from the Coprecipitate with Pectin<sup>1,2)</sup>

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The physical mixture and the coprecipitate of diethazine hydrochloride (DZ), a cationic drug used as a model water-soluble drug, with pectin were studied to determine their dissolution properties in purified water by means of the modified USP dissolution method and the stationary disk method.

The release curve of the drug from the physical mixture of DZ and pectin followed the equation already reported by Bamba *et al.* for the release of a drug from preparations containing a gel-forming excipient. The equation was applicable to the release of the drug from tablets containing up to at least 10% pectin. The apparent dissolution rate from the physical mixture with lactose was significantly larger than that with pectin.

The dissolution rate of the physical mixture of DZ and sodium pectate was determined to assess the interference of ionic ( $\text{Na}^+$ ) interaction with the release of the drug from DZ/pectin coprecipitate. The initial dissolution rate from the physical mixture with sodium pectate was larger than that from the physical mixture with pectin or from the coprecipitate, but was very small compared with that of the intact drug, suggesting that the interference of  $\text{Na}^+$  with the dissolution is small.

The initial apparent dissolution rate from the physical mixture with pectin, at a short time after initiation, was almost the same as that from the coprecipitate (complex).

These results suggest that cationic water-soluble drugs may be formulated as sustained-release preparations by adding a small amount of pectin, owing to the gel-forming ability of pectin and the complex formation between the drug and pectin in aqueous solution.

**Keywords**—pectin; diethazine hydrochloride; coprecipitate; dissolution rate; gel-formation; sustained-release preparations; binding parameter

In a previous paper,<sup>4)</sup> it was shown that coprecipitates (complexes) were formed between pectin and such water-soluble micelle-forming drug as anergen hydrochloride, chlorpromazine hydrochloride, diethazine hydrochloride (DZ), promazine hydrochloride, trifluoperazine dimaleate, and so on. It was also reported that these complexes were water-insoluble, and that the apparent drug dissolution rate from the complexes was almost independent of the stirring speed of the sample in 0.1 N hydrochloric acid, suggesting that such complexes of drugs with pectin might be useful as sustained-release preparations.<sup>5)</sup> Various attempts to prepare sustained-release dosage forms by retarding the dissolution rate of water-soluble drugs have been reported.<sup>6-11)</sup>

In the present study, the coprecipitate and the physical mixture of DZ, a cationic drug used as a model water-soluble drug, with pectin were studied to determine the drug dissolution behavior in purified water, with a view to the development of sustained-release preparations using pectin. The release mechanisms of the drug from the preparations is discussed.

### Experimental

**Materials**—Low methoxyl pectin (pectin; Sunkist Growers Inc.), the molecular weight of which was determined to be 120000 by gel chromatography on Sephadex G-100, was used.<sup>12)</sup> Very pure diethazine hydrochloride (DZ), mp 184–186°C, was used, and lactose was of J.P.X grade. Sodium pectate was obtained in the following manner. The neutralization point preliminarily determined from the titration curve of 0.1 N NaOH against 1% pectin in purified water was pH 6.58. One-tenth normal sodium hydroxide was

added dropwise to 1% pectin in purified water up to the neutralization point, then the solution was evaporated to dryness under reduced pressure. Sodium pectate thus obtained was dried under reduced pressure over phosphorus pentoxide in a desiccator at room temperature for 24 h.

**Preparation of Coprecipitate**—The coprecipitate of DZ with pectin was prepared according to the method described in a previous paper.<sup>4)</sup>

**Determination of DZ**—DZ was determined by measurement of ultraviolet absorption using a Hitachi 124 spectrophotometer. DZ in the coprecipitate was determined according to the method described in a previous paper.<sup>12)</sup>

**Determination of Dissolution Rate**—a) By Modified USP Dissolution Methods: Tablets (300 mg) were compressed in a cylindrical die of 13 mm diameter with Shimadzu hydraulic press for KBr tablets for infrared spectroscopy. The powder sample passing through a 100 mesh sieve was used. Tablets were all prepared at a compression force of 200 kg/cm<sup>2</sup> for 3 min. The dissolution apparatus used in this study is illustrated in Fig. 1; a cylindrical stainless-steel basket (13 mm height, 25 mm diameter), to the bottom of which the sample tablet was fixed with a small portion of purified water, was quickly forced to the bottom of the vessel by hand. Immediately, the paddle was immersed into the vessel so as to make a distance of 10 mm between the paddle and the bottom of the basket, as shown in Fig. 1, and rotation of the paddle was started. Every experiment was carried out under the following conditions: 900 ml of purified water as the dissolution medium; at 37°C; 100 rpm paddle velocity. One ml of the solution was sampled at appropriate time intervals, and the volume was kept constant by adding the same volume of dissolution medium at the same temperature.

b) By a Stationary Disk Method: The same apparatus as described in the previous paper<sup>13)</sup> was used in this method. Every experiment was carried out under the following conditions: 300 ml of purified water as the dissolution medium; at 37°C; 100 and 300 rpm stirrer velocity; and 1.3 cm diameter disk of the powder sample compressed under 200 kg/cm<sup>2</sup> for 3 min.

**Equilibrium Dialysis Method for Determination of Amount of DZ Bound to Pectin and to Sodium Pectate**—Amounts of DZ bound to pectin and to sodium pectate were determined according to the equilibrium dialysis methods described in a previous paper.<sup>4)</sup>

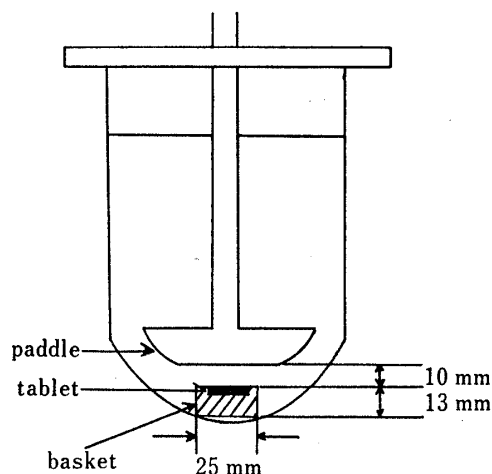


Fig. 1. Modified USP Dissolution Apparatus used in This Study

## Results and Discussion

### Dissolution Pattern of DZ from the Physical Mixture with Pectin owing to the Gel-forming Ability of Pectin

It is known that polysaccharides such as pectin, sodium alginate and carrageenan form gels in water.<sup>14)</sup> Bamba *et al.* suggested that the rate-limiting processes in the release of the drug from preparations containing a gel-forming excipient was the permeation of water into the preparations and the diffusion rate of the drug in the gel.<sup>7)</sup> They reported that equation 3 gave a significantly better fit than equations 1 and 2 in the release of quinidine sulfate from alginate formulae.<sup>7)</sup> In these equations,  $m$  is percent of drug undissolved,  $K$  is a cube root dissolution rate constant (mass/time<sup>1/3</sup>),

$$\sqrt[3]{100-m} - \sqrt[3]{m} = Kt \quad (1)$$

$$100-m = Q\sqrt{t} \quad (2)$$

$$\ln m = -bt + a \quad (3)$$

$t$  is time,  $Q$  (percent per square root of time) is Higuchi's constant, and  $a$  (time<sup>-1</sup>) and  $b$  are the intercept and slope of the log-linear plot in equation 3.

Dissolution data of DZ from tablets of physical mixture of DZ-pectin (42.9–57.1%) in purified water at 37°C were obtained with the modified USP dissolution apparatus, as shown in Fig. 2, and analyzed by means of these three equations. The agreement of experimental

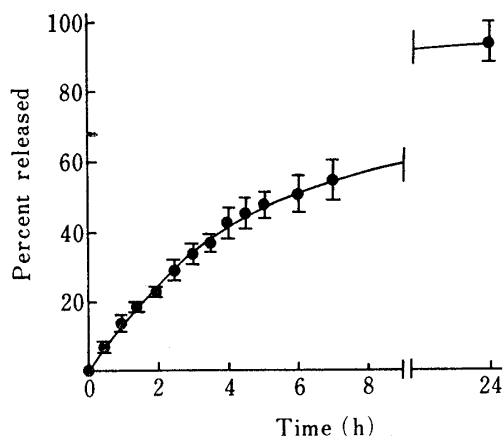


Fig. 2. Release Curve of DZ from Tablet of Physical Mixture of DZ-Pectin (42.9–57.1%) in Purified Water at 37°C in the USP Dissolution Apparatus

Each point is the mean of three determinations.

┘ shows standard deviation.

and theoretical values was evaluated by means of the  $F$ -test and Friedman rank test.<sup>7,15)</sup> The  $F$ -test indicated significant agreement at 0.0, 0.5, 1.0, 1.5, 4.0 and 5.0 h between the actual values and the calculated values according to equations 1A, 2A and 3A (recast from equations 1, 2 and 3), as shown in Table I. When the population means of the actual values and the calculated values were estimated according to the usual equation,  $[\bar{x} \pm t(\phi, \alpha)\sigma_e]/\sqrt{n}$ , the values derived from Eq. 3A were statistically equal to the actual values over the whole time. Analysis of the dissolution data according to the Friedman rank test (Table II) showed that Eq. 3A gave a significantly better fit than Eq. 1A or 2A. The coefficients of correlation with equations 1, 2 and 3 were 0.985, 0.988 and 0.999, respectively.

The finding that the release curve of the drug from the physical mixture can be described by equation 3 indicates that the two processes of “penetration of water into the tablet” and “diffusion of dissolved drug through the gelled layer formed by pectin” are the rate-limiting processes. In a previous paper,<sup>5)</sup> it was reported that the initial dissolution rate for DZ/pectin coprecipitate plotted according to the Cooper-Kingery equation apparently became extremely small at rotating velocities below 50 rpm. This phenomenon was considered to be due to suppression of the dissolution of the drug by gel-formation of pectin. The dissolution pattern of DZ in this study was in accordance with that of quinidine sulfate from the formulae containing carrageenan, a polysaccharide which forms a gel in water.<sup>7)</sup>

TABLE I. Comparison of Observed Data with Values predicted by Three Equations for the Release of DZ from Tablets of Physical Mixture of DZ-Pectin (42.9–57.1%) using the Method of Analysis of Variance and Estimation of Population Mean

Time (h)	Actual value	1A <sup>a)</sup>	2A <sup>b)</sup>	3A <sup>c)</sup>
0.0**	100.0 ± 3.4 <sup>d)</sup>	86.9 ± 3.4	102.5 ± 3.4	96.4 ± 3.4
0.5**	90.5 ± 2.5	83.8 ± 2.5	87.9 ± 2.5	90.6 ± 2.5
1.0*	86.1 ± 2.5	80.6 ± 2.5	82.0 ± 2.5	85.4 ± 2.5
1.5*	81.7 ± 2.0	77.5 ± 2.0	77.3 ± 2.0	80.6 ± 2.0
2.0	76.8 ± 2.3	74.5 ± 2.3	73.4 ± 2.3	76.1 ± 2.3
2.5	67.5 ± 3.3	71.6 ± 3.3	70.0 ± 3.3	71.9 ± 3.3
3.0	66.6 ± 3.8	68.7 ± 3.8	66.9 ± 3.8	67.8 ± 3.8
3.5	62.4 ± 4.4	65.9 ± 4.4	64.1 ± 4.4	64.1 ± 4.4
4.0*	57.5 ± 3.6	63.3 ± 3.6	61.4 ± 3.6	60.5 ± 3.6
4.5	54.2 ± 5.6	60.6 ± 5.6	58.9 ± 5.6	57.2 ± 5.6
5.0*	52.6 ± 4.0	58.1 ± 4.0	56.6 ± 4.0	54.0 ± 4.0
6.0	49.4 ± 7.3	53.2 ± 7.3	52.2 ± 7.3	48.2 ± 7.3
7.0	45.3 ± 7.8	48.6 ± 7.8	48.2 ± 7.8	43.1 ± 7.8
24.0	7.3 ± 7.8	6.1 ± 7.8	1.9 ± 7.8	7.1 ± 7.8

a) Value calculated according to Eq. 1A,  $m = [\sqrt[3]{100 - kt}]^3$ .

b) Value calculated according to Eq. 2A,  $m = 100 - Q\sqrt[3]{t}$ .

c) Value calculated according to Eq. 3A,  $m = e^{a-bt}$ .

d) Value of percent not released, with 95% confidence limits calculated according to the equation  $[xt \pm (\phi, \alpha)\sigma_e]/\sqrt{n}$ .

\*, \*\*:  $p < 0.05$  (\*) and  $p < 0.01$  (\*\*) according to the method of analysis of variance among the experimental data and the values calculated with the three equations (1A, 2A and 3A).

TABLE II. Comparison of Three Equations Describing the Release of DZ from Tablets of Physical Mixture of DZ-Pectin (42.9–57.1%) using the Least-Squares Method

Time (h)	Actual value	1A <sup>a)</sup>	$\Delta 1A^b)$	2A <sup>a)</sup>	$\Delta 2A^b)$	3A <sup>a)</sup>	$\Delta 3A^b)$
0.0	100.0 <sup>c)</sup>	86.9	-13.1	102.5	2.5	96.4	-3.6
0.5	92.5	83.8	-8.7	87.9	-4.6	90.6	-1.9
1.0	86.1	80.6	-5.5	82.0	-4.4	85.4	-0.7
1.5	81.7	77.5	-4.2	77.3	-4.1	80.6	-1.1
2.0	76.8	74.5	-2.3	73.4	-3.4	76.1	-0.7
2.5	67.5	71.6	4.1	70.0	2.5	71.9	4.4
3.0	66.6	68.7	2.1	66.9	-0.3	67.8	1.2
3.5	62.4	65.9	3.5	64.1	1.7	64.1	1.7
4.0	57.5	63.3	5.8	61.4	3.9	60.5	3.0
4.5	54.2	60.6	6.4	58.9	4.7	57.2	3.0
5.0	52.6	58.1	5.5	56.6	4.0	54.0	1.4
6.0	49.4	53.2	3.8	52.2	2.8	48.2	-1.2
7.0	45.3	48.6	3.3	48.2	2.9	43.1	2.2
24.0	7.3	6.1	-1.2	1.9	-5.4	7.1	-0.2
$\sum \Delta^2/12$			38.8		15.3		5.7
$F_{1A-3A} = 38.8/5.7 = 6.8 > 4.3 = F(12, 12; 0.01)$							
$F_{2A-3A} = 15.3/5.7 = 2.7 = 2.7 = F(12, 12; 0.05)$							

a) Equations 1A, 2A and 3A are shown in the legend to Table I.

b) The values are the differences between calculated values according to equations 1A, 2A and 3A and the actual values.

c) The results are all expressed as amount not released (%).

### Release of DZ from Practical Formulae containing Lactose and Pectin

When the amount of DZ dissolved from the tablets containing 40% DZ and various amounts of lactose and pectin using the modified USP dissolution apparatus were plotted according to equation 3, the plot was not linear for the formulae containing lactose alone, while it was linear for that containing lactose and pectin, as shown in Fig. 3. Equation 3 could thus describe the release of the drug from the tablets containing 10% pectin, at least. The dissolution rate decreased with increase of the concentration of pectin, suggesting the possibility of control of the dissolution rate of water-soluble drugs by changing the concentration of pectin in the formula. The initial dissolution rate of the drug from DZ/pectin coprecipitate, in which the amount of DZ bound was  $3.48 \times 10^{-3}$  mol per 1 g of the coprecipitate, in purified water using the stationary disk method was 1/160 as compared with that of the intact drug.<sup>5)</sup>

### Interference of Ionic Interaction with the Dissolution of the Drug observed by the Use of Sodium Pectate

The presence of inorganic cations such as  $\text{Li}^+$ ,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$  could influence the interaction of cationic drugs with pectin, because pectin is an anionic polyelectrolyte.<sup>12,16)</sup> In this study, the dissolution rate of DZ from the physical mixture with sodium pectate was determined by using the stationary disk method.

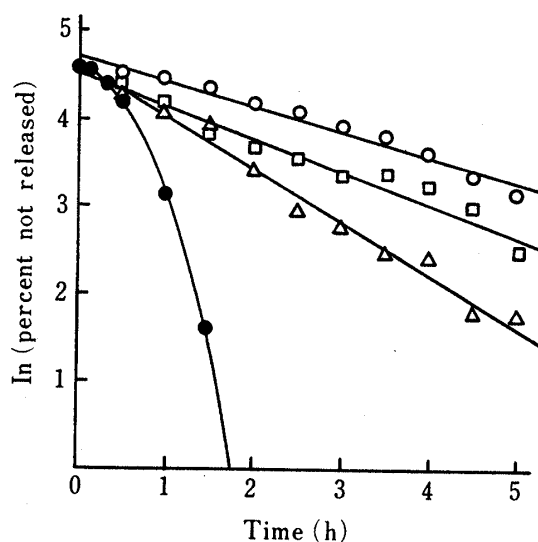


Fig. 3. Release of DZ from Tablets containing Pectin and Lactose plotted according to Equation 3

Percent of pectin in the formulae:  
○, 60%; □, 30%; △, 10%; ●, 0%.

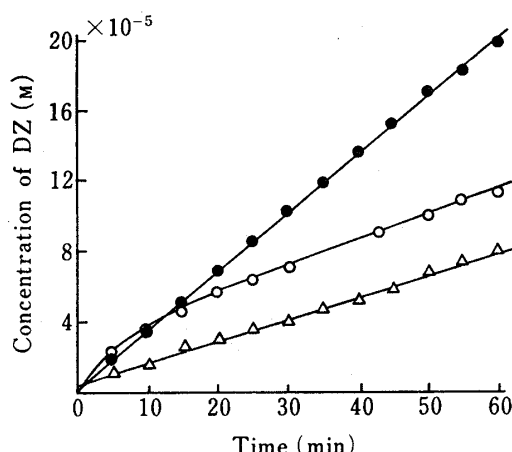


Fig. 4. Dissolution Curves of DZ-Pectin (39.2–60.8 %) System in Purified Water at 100 rpm at 37°C obtained by the Stationary Disk Method

●: physical mixture of DZ and sodium pectate.  
○: physical mixture of DZ and pectin.  
△: coprecipitate of DZ and pectin.

Figure 4 shows the dissolution curves of DZ from the physical mixture with sodium pectate, the physical mixture with pectin and the coprecipitate with pectin. Dissolution from the physical mixture with sodium pectate and from the coprecipitate was linear, while that from the physical mixture with pectin was not linear at the initial stage but subsequently became linear. The slope after 20 min for the physical mixture with pectin was almost the same as that for the coprecipitate, indicating rapid formation of an insoluble complex between DZ and pectin. A similar dissolution pattern was observed with the pectin-benzylamine hydrochloride system, although the plot of the amount dissolved from the physical mixture was linear and passed through the origin.<sup>12)</sup>

Since the dissolution rate from the physical mixture with sodium pectate was larger than that from the coprecipitate, an inhibitory effect of  $\text{Na}^+$  on the dissolution rate of the drug from the pectin-DZ system, was assumed to occur, as shown in Table III. The initial dissolution rate from the physical mixture with sodium pectate was, however, very small compared with that of intact DZ,  $9.45 \times 10^{-4} \text{ M/min}$ ,<sup>5)</sup> suggesting that the interference of  $\text{Na}^+$  with the dissolution is small.

TABLE III. Apparent Dissolution Rate of DZ-Pectin (39.2–60.8%) System in purified Water at 37°C as determined by the Stationary Disk Method

Preparation	Apparent dissolution rate ( $k'$ )			
	100 rpm		300 rpm	
	$k' \times 10^6 \text{ M/min}$	Ratio	$k' \times 10^6 \text{ M/min}$	Ratio
Coprecipitate	1.26	1.00	2.32	1.00
Physical mixture with pectin <sup>a)</sup>	1.45	1.15	2.51	1.08
Physical mixture with sodium pectate	3.35	2.66	4.17	1.80

a) Values were calculated from the linear region of dissolution plots after 20 min.

The equilibrium dialysis method was applied in order to observe whether or not sodium pectate interacts with DZ in aqueous solution similarly to pectin. The data were plotted according to Scatchard, as shown in Fig. 5. It seemed that an equal or rather larger extent of binding occurred between the drug and sodium pectate as compared with the interaction with pectin. The binding parameters showed a larger value of  $K_2$  (secondary binding constant) but a smaller value of  $n_2$  (secondary maximum binding number) in the sodium pectate system,

TABLE IV. Binding Parameters for DZ to Pectin and to Sodium Pectate at 37°C as determined by the Equilibrium Dialysis Method

System	$K_1 (\text{M}^{-1})$	$K_2 (\text{M}^{-1})$	$n_1$	$n_2$	$K_1 n_1 (\text{M}^{-1})$	$K_2 n_2 (\text{M}^{-1})$
Pectin/DZ	495	21.2	110	900	54500	19100
Sodium pectate/DZ	506	124	101	343	51100	42500

as shown in Table IV. The relation between the binding parameters and the dissolution rate is now under detailed investigation.

It is generally known that polyuronides as pectin and alginate are highly effective natural ion exchangers.<sup>17-19)</sup> The dissolution of the drug from the physical mixture with sodium pectate might be rationalized as follows: i) as soon as the disk containing the mixture of sodium pectate and DZ is submerged into the water, sodium pectate and DZ dissociate into  $\text{Na}^+$ -pectin<sup>-</sup> and DZ cation, respectively, in the saturated layer on the disk surface; ii) ion exchange reaction occurs between  $\text{Na}^+$  and DZ cation, and immediately a coprecipitate of DZ with pectin is formed; iii) the drug is released from the coprecipitate.

The following conclusions were reached.

A) The initial dissolution rate of DZ from the physical mixture with pectin calculated from the slope of the straight line after 20 min was almost the same as that from the coprecipitate, as shown in Fig. 4 and Table III. B) The dissolution pattern of the drug from the physical mixture with pectin using the modified USP dissolution apparatus followed the equation already reported for the release of drugs from preparations containing gel-forming excipients. C) The equation was applicable to the release of the drug from tablets containing up to at least 10% pectin.

These results suggest that it may be possible to formulate cationic water-soluble drugs as sustained-release preparations by adding a small amount of pectin, owing to the gel-forming ability of pectin and coprecipitate (complex) formation between the drug and pectin in aqueous solution.

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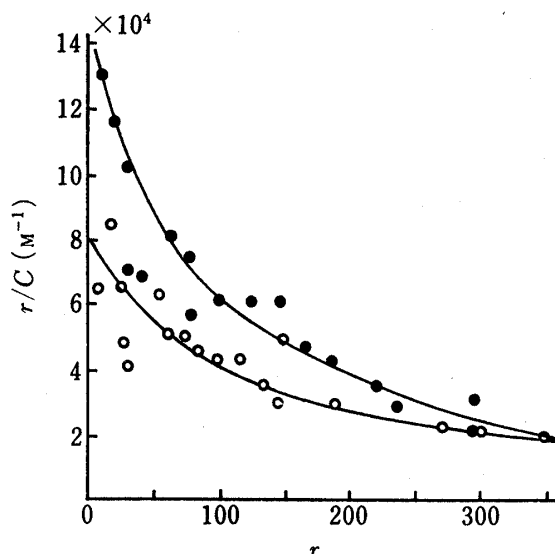


Fig. 5. Scatchard Plot for Binding of DZ to Pectin and to Sodium Pectate in Purified Water at 37°C as determined by the Equilibrium Dialysis Method

○: binding to pectin.  
●: binding to sodium pectate.  
r: mol of drug bound per mol of pectin.  
C: equilibrium concentration (M).

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