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Dissolution of Thioridazine Hydrochloride from the Coprecipitate with Pectin[1)]

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The coprecipitate of thioridazine hydrochloride, a cationic drug used as a model of water-soluble drug, with pectin was studied to determine the drug dissolution properties in purified water and in hydrochloric acid (pH 1) by means of the modified JP dissolution method.

The dissolution pattern of the drug from the coprecipitate in water was shown to fit best with the equation reported by Higuchi, based on the porous penetration hypothesis. The apparent dissolution rate of thioridazine from the coprecipitate in water derived from Higuchi's equation was as follows: coprecipitate < physical mixture with pectin < physical mixture with lactose. A similar result was obtained for these preparations in hydrochloric acid (pH 1). The results suggest that the coprecipitates of cationic water-soluble drugs with pectin may be applicable to sustained-release preparations.

Keywords——pectin; thioridazine hydrochloride; coprecipitate; dissolution rate; Higuchi equation; sustained-release preparations

In a previous paper,[2)] it was reported that the release curve of the drug from a physical mixture of diethazine hydrochloride and pectin followed the eqution reported by Bamba *et al.*[3)] for the release of a drug from preparations containing a gel-forming excipient. It was also suggested that it may be possible to formulate cationic water-soluble drugs as a sustained-release preparations by adding a small amount of pectin, owing to the gel-forming ability of pectin and the formation of a coprecipitate between the drug and pectin in aqueous solution.[2)]

The present work was carried out to determine the drug dissolution behavior in purified water and hydrochloric acid (pH 1). Thioridazine hydrochloride, which is a phenothiazine-type drug, was used as a model drug.

Experimental

Materials——Low methoxyl pectin (pectin; Sunkist Growers Inc.), the average molecular weight of which was determined to be 120000 by gel chromatogaphy on Sephadex G-100, was used.[4)] Pure thioridazine hydrochloride (TRZ), mp 158—160 °C, was used, and lactose was of JP X grade.

Preparation of Coprecipitate——The coprecipitate of TRZ with pectin was prepared according to the method described in a previous paper.[5)]

Determination of TRZ——TRZ was determined by measurement of ultraviolet absorption using Hitachi 124 spectrophotometer. TRZ in the coprecipitate was determined according to the method described in a previous paper.[4)]

Determination of Dissolution Rate——Tablets (300 mg) were prepared according to the method described in a previous paper.[2)] A modified JP dissolution apparatus, as illustrated in Fig. 1, was used in this study. A tablet was held by two cylindrical stainless-steel baskets (13 mm height, 25 mm diameter) as shown in Fig. 1: the tablet was placed on the bottom of one basket, which was covered with another basket, and the two baskets were fixed together

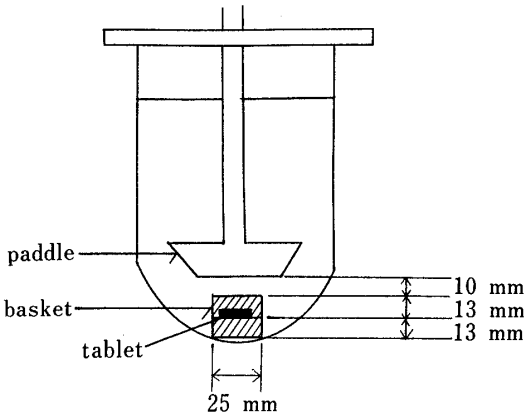

Fig. 1. Modified JP Dissolution Apparatus Used in This Study

by tying with a fine thread. The basket was quickly immersed into the vessel so as to make a distance of 10 mm between the paddle and the basket, and rotation of the paddle was started. Every experiment was carried out under the following conditions: 900 ml of purified water or hydrochloric acid (pH 1) as the dissolution medium; at 37 °C; 100 rpm paddle velocity. Since the presence of inorganic cations such as Li^+, K^+, Na^+ and Ca^{2+} could influence the interaction of cationic drug with pectin,[4,6] purified water was used. One ml of the solution was sampled at appropriate time intervals, and the volume was kept constant by adding the same volume of fresh dissolution medium at the same temperature.

Results and Discussion

Dissolution Patterns of TRZ from the Coprecipitate

Bamba *et al.* investigated the processes involved in the release of quinidine sulfate from preparations containing a gel-forming excipient, carrageenan, using the three equations given in Table I.[3] They reported that Eq. 3 gave a significantly better fit than Eqs. 1 and 2, and suggested that the rate-limiting process was the permeation of water into the preparations or the diffusion rate of the drug in the gel.[3] The release curve of the drug from a physical mixture of diethazine hydrochloride and pectin also followed Eq. 3.[2]

In the present study, the drug release characteristics from the coprecipitates of TRZ, a cationic water-soluble drug, as well as diethazine hydrochloride, with pectin were observed. Dissolution data on TRZ from tablets of coprecipitate and from a physical mixture of TRZ–pectin (61%–39%) in purified water or in hydrochloric acid (pH 1) at 37 °C were obtained with the modified JP dissolution apparatus, as shown in Fig. 2, and analyzed by means of the above three equations. The data up to 4 h were used for analysis of the physical mixture in hydrochloric acid (pH 1), because the dissolution of the drug from this system was completed within 4 h. The agreement of experimental and theoretical values was evaluated by means of the *F*-test and Friedman rank test.[3,7] Only the system of coprecipitate in purified water gave significant agreement. The *F*-test of the system of coprecipitate in purified water indicated significant agreement at 0.00, 0.08, 0.17, 1.0 and 3.0 h between the actual values and values calculated according to Eqs. 1A, 2A and 3A (recast from Eqs. 1, 2 and 3), as shown in Table II. When the population means of the actual values were estimated according to the usual equation, $[\bar{x} \pm t(\phi, \alpha)\sigma_e]/\sqrt{n}$, the values derived from Eq. 2A were statistically equal to the actual values over the whole time. Analysis of the dissolution data for the system of coprecipitate in purified water according to the Friedman rank test (Table III) showed that Eq. 2A gave a significantly better fit than Eq. 1A or 3A. The coefficients of correlation with Eqs. 1, 2 and 3 were, however, almost equal, as shown in Table I.

The finding that the release curve of the drug from the coprecipitate in purified water can be described by Eq. 2 indicates that the release of the drug from the tablet depends mainly on the penetration rate of the drug from "pores" which are presumably present in the solid matrix

TABLE I. Coefficients of Correlation with the Three Equations in the Dissolution Study of TRZ–Pectin (61.0%–39.0%)

System	Eq. 1	Eq. 2	Eq. 3
Coprecipitate in water[a]	0.980	0.978	−0.982
in HCl[b]	0.968	0.984	−0.982
Physical mixture in water	0.968	0.990	−0.974
in HCl	0.995	0.986	−0.995

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

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

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

m: percent of drug undissolved.
k: cube root of the dissolution rate constant (mass/time$^{1/3}$).
t: time.
Q: percent per square root of time (Higuchi's constant).
a: (time^{-1}), intercept of log-linear plot in Eq. 3.
b: slope of log-linear plot in Eq. 3.
a) Purified water. *b*) pH 1.

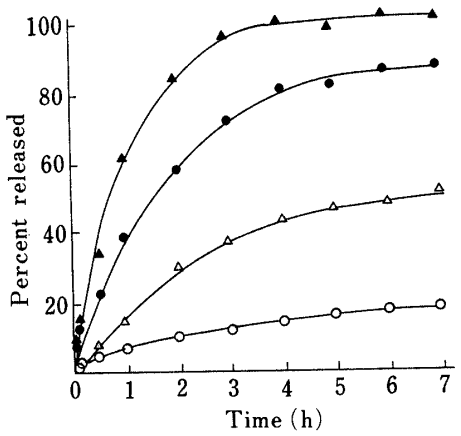

Fig. 2. Release Curves of TRZ from Tablets of Coprecipitates and Physical Mixtures of Drug–Pectin (61%–39%) in Purified Water and in HCl (pH 1) at 37 °C in the Modified JP Dissolution Apparatus

○, coprecipitate in water; ●, coprecipitate in HCl; △, physical mixture in water; ▲, physical mixture in HCl.
Each point is the mean of two determinations.

TABLE II. Comparison of Observed Data with Values Predicted by the Three Equations for the Release of TRZ from Tablets of Coprecipitate of TRZ–Pectin (61.0%–39.0%) in Water Using the Method of Analysis of Variance and Estimation of Population Mean

Time (h)	Actual value	1A[a]	2A[b]	3A[c]
0.0[e]	100.0±0.6[d]	97.8±0.6	101.3±0.6	97.8±0.6
0.08[e]	99.0±0.6	97.6±0.6	99.4±0.6	97.6±0.6
0.17[f]	98.6±0.7	97.4±0.7	98.6±0.7	97.4±0.7
0.5	96.9±0.4	96.6±0.4	96.6±0.4	96.6±0.4
1.0[f]	94.6±0.3	95.5±0.3	94.6±0.3	95.5±0.3
2.0	91.9±1.5	93.2±1.5	91.9±1.5	93.2±1.5
3.0[f]	90.3±0.5	91.0±0.5	89.8±0.5	90.9±0.5
4.0	88.0±0.8	88.8±0.8	88.0±0.8	88.8±0.8
5.0	86.0±1.1	86.7±1.1	86.5±1.1	86.7±1.1
6.0	84.4±1.5	84.6±1.5	85.1±1.5	84.6±1.5
7.0	84.3±1.5	82.5±1.5	83.8±1.5	82.5±1.5

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 $[\bar{x}\pm t(\phi,\alpha)\sigma_e]/\sqrt{n}$. *e*) $p<0.01$ and *f*) $p<0.05$, 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 III. Comparison of the Three Equations Describing the Release of TRZ from Coprecipitates of TRZ–Pectin (61.0%–39.0%) in Water Using the Least-Squares Method

Time (h)	Actual value	1A[a]	Δ1A[b]	2A[a]	Δ2A[b]	3A[a]	Δ3A[b]
0.0	100.0	97.8	−2.2	101.3	1.3	97.8	−2.2
0.08	99.0	97.6	−1.4	99.4	0.4	97.6	−1.4
0.17	98.6	97.4	−1.2	98.6	0.0	97.4	−1.2
0.5	96.9	96.6	−0.3	96.6	−0.3	96.6	−0.3
1.0	94.6	95.5	0.9	94.6	0.0	95.5	0.9
2.0	91.9	93.2	1.3	91.9	0.0	93.2	1.3
3.0	90.3	91.0	0.7	89.8	−0.5	90.9	0.7
4.0	88.0	88.8	0.8	88.0	0.0	88.8	0.8
5.0	86.0	86.7	0.7	86.5	0.5	86.7	0.7
6.0	84.4	84.6	0.2	85.1	0.7	84.6	0.2
7.0	84.3	82.5	−1.8	83.8	−0.5	82.5	−1.8
$\sum \Delta^2/9$			1.748		0.353		1.748
		$F_{1A-2A} = 1.748/0.353 = 4.95 > 3.18 = F(9, 9; 0.05)$					
		$F_{3A-2A} = 1.748/0.353 = 4.95 > 3.18 = F(9, 9; 0.05)$					
		$F_{1A-3A} = 1.748/1.748 = 1.00 < 3.18 = F(9, 9; 0.05)$					

a) Eqs. 1A, 2A and 3A are given in the legend to Table II. *b*) The values are the differences between calculated values according to Eqs. 1A, 2A and 3A and the actual values. *c*) The results are all expressed as amount not released (%).

construction of the coprecipitate.[8] There was no significant agreement concerning drug release in the other system with any of the three equations. If the dissolution pattern of TRZ from the tablet is dictated by the actual dissolution of the drug then Eq. 1 should hold, while if it is dictated by porous penetration then Eq. 2 should hold, and if it depends on the gel-forming ability of the excipient contained in the tablet then Eq. 3 should hold.[3] These three factors might be involved in a complex manner in the dissolution of TRZ in hydrochloric acid (pH 1) and in the case of the physical mixtures.

The dissolution pattern of the drug from the tablet of physical mixture of diethazine hydrochloride and pectin in purified water followed Eq. 3,[2] but that of TRZ (a cationic water-soluble drug like diethazine hydrochloride) and pectin did not fit Eq. 3 better than Eq. 1 or 2 in the present study. Although the reason is not clear, it might be considered that the amount of pectin in the system of diethazine hydrochloride–pectin (42.9%–57.1%)[2] is larger than that of TRZ–pectin (69%–31%), and since the gel-forming ability of pectin in water becomes progressively larger as the amount of pectin increases, the dissolution pattern of the drug in such a system should be better fitted by Eq. 3.

Comparison of Apparent Dissolution Rates of TRZ Observed in Several Systems

As shown in Fig. 2, the apparent dissolution rates of TRZ from several systems were as follows: coprecipitate in purified water < physical mixture in purified water < coprecipitate in hydrochloric acid (pH 1) < physical mixture in hydrochloric acid (pH 1). The dissolution rate was larger in hydrochloric acid. This phenomenon might be similar to the drug dissolution from diethazine hydrochloride–pectin coprecipitate up to 60 min using the stationary disk method.[9] The drug cation in the coprecipitate might be substituted by the proton of hydrochloric acid, and thus the drug would be released faster in diluted hydrochloric acid than in purified water, since it is generally known that polyuronides such as pectin and alginate are efficient natural ion exchangers.[10–12] Furthermore, the effect of the gel-forming ability of pectin on the release of the drug must also be considered. The gel-forming ability of pectin in diluted hydrochloric acid is smaller than in purified water, because pectin is an

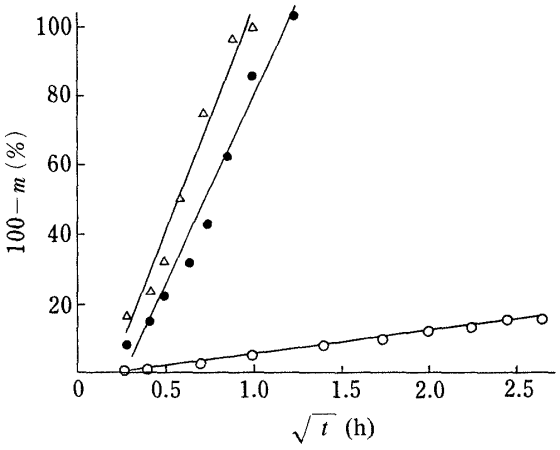

Fig. 3. Dissolution Curves of TRZ from Tablets of TRZ–Pectin and TRZ–Lactose at 37 °C in the Modified JP Dissolution Apparatus as Calculated by Eq. 2

○, TRZ–pectin coprecipitate (content of TRZ, 61%) in purified water; ●, physical mixture of TRZ and lactose (content of TRZ, 61%) in purified water; △, physical mixture of TRZ and lactose (content of TRZ, 61%) in HCl (pH 1). Each point is the mean of two determinations.

TABLE IV. Higuchi's Constants of TRZ–Pectin (61%–39%) and TRZ–Lactose (61%–39%) in Purified Water and HCl (pH 1) at 37 °C as Determined in the Modified JP Dissolution Apparatus

System	Higuchi's constant ($\%/\sqrt{t}$)	Ratio
Coprecipitate in water	6.61	1.00
in HCl	36.2	5.48
Physical mixture with pectin in water	22.2	3.36
in HCl	56.7	8.58
Physical mixture with lactose in water	108	16.3
in HCl	134	20.3

anionic polyelectrolyte. The reason why the dissolution rate from the physical mixture in purified water is slower on the next to that from the coprecipitate in purified water may be interpreted as follows: the coprecipitate might be formed on the face of the tablet during the experiment, so that the release of the drug would for the most part correspond to release from the coprecipitate.

The control experiments were performed by using lactose instead of pectin to compare the dissolution rate. The dissolution rate from the coprecipitate in purified water (according to Eq. 2) was much smaller than that from the physical mixture of the drug and lactose in purified water and in hydrochloric acid (pH 1), as shown in Fig. 3. As compared with the apparent dissolution rate obtained from Eq. 2 (Higuchi's constant), the apparent dissolution rate from the coprecipitate was much smaller, as follows: coprecipitate < physical mixture with pectin < physical mixture with lactose (Table IV). The phenomena were observed in both purified water and hydrochloric acid (pH 1), as shown in Table IV. These results suggest that the coprecipitates of cationic water-soluble drugs with pectin may be applicable as sustained-release preparations.

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References and Notes

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