Release of a Water-Soluble Drug from a Wax Matrix Timed-Release Tablet

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Abstract □ The purpose of this work was to characterize the release of drug from a wax matrix tablet under relatively mild agitation conditions. It was found that phenylpropanolamine hydrochloride was released from a typical wax matrix by a diffusion mechanism. After an initial rapid release of drug from the tablet, the amount dissolved was proportional to the square root of time. The advance of the solvent front into the tablet matrix was also proportional to the square root of time. Compression force was not a major factor affecting drug release. Data on drug release from a single tablet face compared to release from a totally exposed tablet indicated that drug release is proportional to the total surface area.

Keyphrases □ Timed-release tablets, wax matrix—water-soluble drug release (phenylpropanolamine hydrochloride), mild agitation conditions, mechanisms □ Phenylpropanolamine hydrochloride—release rate from wax matrix timed-release tablet, mechanisms □ Drug release—phenylpropanolamine hydrochloride release rate from wax matrix timed-release tablet □ Wax matrix (timed-release tablet)—release rate of phenylpropanolamine hydrochloride, mechanisms

Numerous compositions have been suggested for sustaining drug release over a long period (1, 2). However, the fabrication of such compositions has been largely empirical and little work has been carried out to explain the mechanism involved. Usually some *in vitro* procedure is used to characterize drug release from the dosage form. It is often assumed that a 30–50% *in vitro* drug release in 1 hr is good and that a continuous drug release over 5–7 hr is satisfactory, but only recently has any correlation between *in vitro* drug release and *in vivo* performance been reported (3).

Ideally, a sustained-release preparation should provide part of the drug at the absorption site quickly to achieve sufficient absorption to produce a rapid therapeutic response. The balance of the drug should be provided at a sufficient rate to maintain pharmacological activity. In the most simple case, *i.e.*, a one-compartment open model with essentially 100% drug absorption and total urinary excretion *via* first-order kinetics, the drug should be provided to the blood at a rate equal to the rate loss from that compartment (4). Examples of the effect of zero- and first-order drug dissolution on resulting blood levels (one-compartment model) were well described (4) using analog computational methods, and some shortcomings of certain drug release patterns were pointed out.

A timed-release tablet granulation may typically contain 20–30% of a mixture of wax and fatty acid. The balance of the formulation is drug and various diluents. The usual practice for formulating a sustained-action tablet is to layer an immediate-release dose with the slow releasing wax matrix or to place the wax matrix as a core in a press-coated tablet. These methods should then provide an immediate drug blood level that is maintained by the balance of the drug being released over some prolonged period.

The *in vitro* drug release characteristics of timed-release tablets may be determined by various methods which can generally be classified as high agitation or low agitation. With high agitation, the total amount of drug released is a function of the amount released by diffusion plus the amount eroded away. This type of release is obtained from the rotating-bottle method (5) or the basket-rack assembly (6). *In vitro* release by these methods causes tablets to be gradually worn away until the entire mass is broken into small particles, at which time the drug is considered to be 100% released. More gentle methods, such as circulating fluid over a tablet contained in a well, do not cause tablet erosion; drug is released entirely by a diffusional process, typically over 8 or 10 hr for a water-soluble material. Above a certain stirring speed, the drug release rate should be independent of revolutions per minute if it is diffusion controlled.

An inherent problem in timed-release medication is to obtain maximum drug availability. Analysis of some data where sustained-action and immediate-release forms of drug were compared indicates that part of the dose is unavailable; the drug release might be too slow and the full dose is not being utilized. One objective of the present study was to obtain *in vitro* dissolution characteristics that might logically lead to the use of a satisfactory input function for *in vivo* evaluation and correlation. Another objective was to develop a method for logical characterization of the release properties of various tablet formulations. Because of the need for more knowledge of the formulation of timed-release dosage forms, the following work was carried out using phenylpropanolamine hydrochloride in a wax matrix tablet as a typical system.

EXPERIMENTAL

Preparation of Phenylpropanolamine Hydrochloride Tablets—A timed-release granulation was prepared according to the formula shown in Table I. Single-layer tablets weighing 1.080 g, representing 150 mg of phenylpropanolamine hydrochloride, were compressed[1] using 15.9-mm (0.63-in.), flat-faced, beveled edge punches and dies. Tablets were made using compression forces of 226.8, 453.6, 544.3, and 907.2 kg. Measurements of tablet breaking strength and thickness resulted in the values shown in Table II.

***In Vitro* Release Procedure**—Dissolution of tablets subjected to various compression forces was studied. Special attention was directed toward tablets compressed at 544.3 kg, since they met the requirements of a proposed formulation with respect to hardness. A tablet and capsule dissolution apparatus (7) was employed using a platform with a center well. Four hundred milliliters of 0.1 *N* HCl was placed in the jacketed beaker maintained at 37.5 ± 0.5°.

[1] Carver press.

Table I—Formula for Preparation of Phenylpropanolamine Hydrochloride Timed-Release Tablets

Ingredients	Per 1000 Tablets, g
Phenylpropanolamine hydrochloride NF	150.0
Wax–fat mixture	202.5
Diluent	721.5
Calcium stearate NF	4.5
Colloidal silicon dioxide NF	1.5
	1080.0

When the solution reached equilibrium temperature, a tablet was introduced into the center well of the platform. Dissolution was initiated using a constant stirring rate of 75 rpm. One-milliliter samples were removed *via* pipet in the outlet port. One milliliter of fresh 0.1 *N* HCl was added to maintain constant volume. Samples were collected throughout the dissolution study at various time intervals and assayed. Phenylpropanolamine hydrochloride was analyzed using the periodate oxidation procedure and read spectrophotometrically as benzaldehyde in heptane (8).

A dissolution study of a tablet-in-the-die (compression force of 544.3 kg) was made for comparison of drug release from a fixed surface area. The penetration rate of the dissolution media into the tablets compressed using 544.3 kg of force was determined. Seven tablets were placed on a dissolution platform containing seven wells and placed into the dissolution apparatus. Tablets were removed at intervals coinciding with the dissolution rate studies. Excess water on the surface of the tablet was absorbed with absorbent paper. The tablet thickness was carefully measured so as not to compress the hydrated layer. The hydrated layer was removed from both sides of the tablet with a scalpel, and the thickness of the dry part of the tablet was measured.

RESULTS AND DISCUSSION

The cumulative amount of drug released for tablets made using 226.8 kg of compression force is given in Table III, together with the tablet position during dissolution. The dissolution data for tablets made at various compression forces are shown in Fig. 1. A comparison of the data of the various compression forces tested showed little difference; however, the tablets did not vary greatly in thickness. All tablets showed a relatively fast initial drug release (33–40%) during the 1st hr followed by a slower release. About 80% drug was released in 6–7 hr.

The mechanism of drug release from a wax matrix was discussed in detail previously (9). In the treatment of those data, it was assumed that drug release was either first order or a diffusion-controlled process. One indication of the mechanism can be obtained using a plot of the logarithm of the percent remaining in the matrix against time. A first-order release would be linear, while the diffusion-controlled process would generate an S-shaped curve (9).

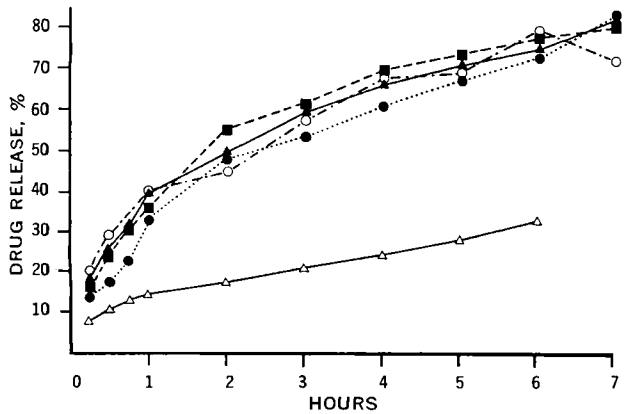

Figure 1—*Effect of compression force on release profiles of phenylpropanolamine from wax matrix tablets. Compression force was:* ●, *226.8 kg;* ○, *453.6 kg;* ▲, *544.3 kg;* ■, *907.2 kg; and* △, *544.3 kg (tablet-in-die).*

Table II—Compression Conditions and Physical Properties of Timed-Release Phenylpropanolamine Hydrochloride Tablets

Compression Force, kg	Breaking Strength[a], kg/in.^{2}	Thickness, mm
226.8	9.6	4.88
453.6	16.5	4.62
544.3	19.0	4.39
907.2	25.5	4.27

[a] Measured on modified Strong-Cobb tablet hardness tester.

Extended studies up to 10 hr were performed on the tablets compressed at 544.3 kg, and the data obtained were used to explain the mechanism of drug release.

The logarithm of the percent of drug remaining in the matrix was plotted against time (Fig. 2) and produced an S-shaped curve, indicating a lack of conformance to first-order kinetics. Therefore, an attempt was made to determine whether the drug release could be described by a diffusion equation proposed by Higuchi (10):

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug released per unit area of the tablet exposed to the solvent, D is the diffusion coefficient of the drug in the permeating fluid, ϵ is the porosity of the matrix, τ is the tortuosity of the matrix, A is the concentration of solid drug in the matrix, C_s is the solubility of drug in the dissolution medium, and t is time. In this work, $2A$ exceeded ϵC_s by a factor of at least three, thereby justifying the use of this particular diffusion equation. This includes porosity due to air and water-soluble ingredients including the drug. If:

$$K = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 2)}$$

then:

$$Q = Kt^{1/2} \qquad \text{(Eq. 3)}$$

For a diffusion-controlled mechanism as postulated here, a plot of the amount of drug release *versus* the square root of time should be linear as predicted by Eq. 3. The data were graphed in this manner (Fig. 3) for tablets made at various compression forces, and a linear plot of percent drug release was obtained for times greater than 1 hr. It is evident that the differences in tablet thickness and hardness resulting from different compression conditions employed did not cause more than 10% variation in the release of phenylpropanolamine hydrochloride at any particular time interval. Therefore, under the mild agitation conditions of testing, drug

Table III—Release of Phenylpropanolamine Hydrochloride from Wax Matrix Tablets[a]

Hours	Tablet Position	Cumulative Amount Released		
		Percent	Q', mg	Q, mg/cm^2
0.25	Stationary	13.5	20.2	3.29
0.50	Stationary	17.6	26.4	4.29
0.75	Stationary	22.8	34.2	5.56
1.0	Sliding[b]	33.0	49.5	8.05
2.0	Sliding[b]	48.4	72.6	11.81
3.0	Slight elevation	53.8	80.7	13.12
4.0	Slight elevation	61.3	92.0	14.96
5.0	Rotation	68.0	102.0	16.59
6.0	Floating below propeller	74.0	111.0	18.05
7.0	Broken by propeller	84.0	126.0	20.49

[a] Compression force of 226.8 kg; data from two trials. [b] Density of tablet begins to approach density of the dissolution medium.

Table IV—Comparison of Dissolution Rate per Area with Compression Force for Free Tablets and Tablet-in-a-Die

Hours	Compression Force, kg	Release Rate, mg/hr cm²	Percent Release	Tablet Position
0–1	226.8	8.05	33.0	Sliding
0–1	453.6	9.76	40.0	Stationary
0–1	544.3	9.64	39.5	Stationary
0–1	907.2	10.41	36.0	Stationary
0–1	544.3 (tablet-in-die)	10.75	14.4	Stationary
2–4	226.8	2.28	48.4–61.3	Slight elevating
2–4	453.6	2.27	45.3–68.2	Sliding
2–4	544.3	2.19	49.3–66.7	Sliding
2–4	907.2	2.74	54.9–69.8	Sliding
2–4	544.3 (tablet-in-die)	2.78	17.8–24.5	Stationary

release does not appear to be affected by compression force over the ranges studied.

Evaluation of the slope, K in Fig. 3, with the aid of Eq. 3 gave a value of 6.35 mg/cm² $hr^{1/2}$, equivalent to 26.6% $hr^{1/2}$ for the composite results of all runs. The factors comprising K are given by Eq. 2; these are diffusion coefficient, porosity, tortuosity, concentration of drug in the matrix, and solubility of drug in the dissolution medium. Drug solubility is a constant in any particular dissolution fluid. Therefore, drug release from a wax matrix can be altered by altering the factors comprising K. Generally, K is modified by a change in formulation such as increased or decreased wax content or a change in diluent. For instance, compressional force might be expected to change the porosity, ϵ, and hence K; however, in this work, K was not significantly affected by change in compressional force. Further characterization of K for various systems would allow some general conclusions to be made regarding drug release as a function of formulation variables.

Another equation may be used to calculate the value of K. By multiplying both sides of Eq. 3 by the surface area, S, of the tablet from which drug is released:

$$QS = KSt^{1/2} \qquad \text{(Eq. 4)}$$

or:

$$Q' = KSt^{1/2} \qquad \text{(Eq. 5)}$$

where Q' is the amount of drug released.

Differentiation of Eq. 5 with respect to time gives (9):

$$\frac{dQ'}{dt} = \frac{KS}{2t^{1/2}} \qquad \text{(Eq. 6)}$$

Substitution of Q'/KS for $t^{1/2}$ results in:

$$\frac{dQ'}{dt} = \frac{K^2S^2}{2Q'} \qquad \text{(Eq. 7)}$$

Equation 7 states that, for a diffusion-controlled process, the rate of drug release is linearly related to $1/Q'$, the reciprocal of the amount of drug release. Release rates that expressed milligrams of drug release as a function of time were calculated at the various time intervals. A plot of these release rates, dQ'/dt *versus* $1/Q'$, gives a slope of $K^2S^2/2$. The constant, K, was calculated from the slope and found to be 8.83. This value does not compare exactly with the K of 6.35 calculated according to Eq. 4. However, the lack of smoothness of the graph of amount released *versus* time probably accounts for the discrepancy.

Tablets undergoing dissolution were generally stationary in the well for the first few hours. Some movement then occurred because of the loss of drug and diluent. At the end of 6–7 hr, tablets began to rotate in the well as the tablet density began to approach the density of the dissolution medium. Tablets throughout the experiments maintained their original shape; no erosion of any kind occurred.

Drug Release from a Fixed Surface Area—The dissolution of a tablet-in-a-die, compressed at 544.3 kg, was required for a strict evaluation of dissolution rates per unit area. The area available for release from the total single tablet surface and from a single face of the tablet was 6.35 and 1.98 cm², respectively. Dissolution rates of phenylpropanolamine hydrochloride from a tablet-in-a-die was determined by the same method as described for free tablets. The die containing the tablet was lowered into the dissolution medium in an upright position, creating an air space between

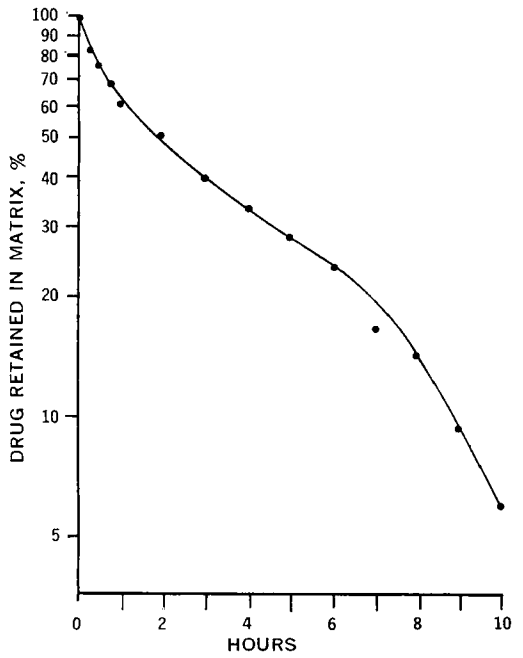

Figure 2—*Release of phenylpropanolamine hydrochloride from a wax matrix tablet. Compression force was 544.3 kg.*

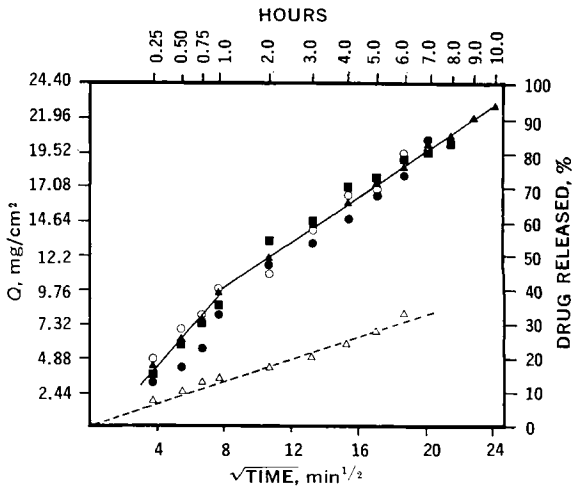

Figure 3—*Amount of drug release* versus *the square root of time using phenylpropanolamine hydrochloride 150-mg wax matrix tablet. Compression force was:* ●, *226.8 kg;* ○, *453.6 kg;* ▲, *544.3 kg;* ■, *907.2 kg; and* △, *544.3 kg (tablet-in-die).*

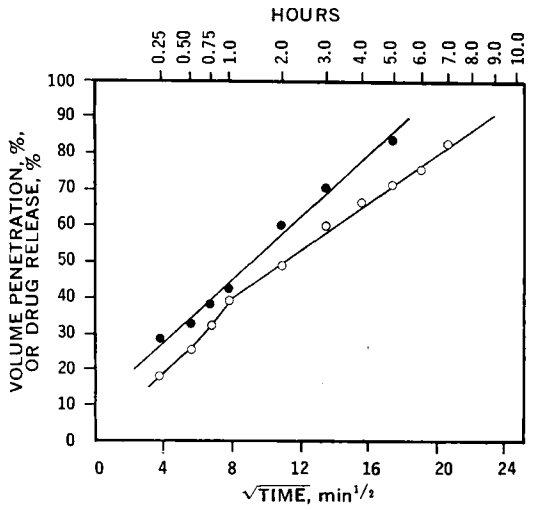

Figure 4—*Comparison of fluid penetration and percent drug release from a phenylpropanolamine hydrochloride 150-mg wax matrix tablet. Compression force was 544.3 kg. Key: ●, percent volume penetration of dissolution fluid; and ○, percent drug release.*

the lower tablet surface and the medium. This procedure assured that the upper surface was the only releasing surface. Adjustment of stirring height was made to provide the same tablet to propeller distance as used for the free tablet.

The pattern of drug release for the tablet-in-a-die was linear with the square root of time throughout the entire period (Fig. 3). A comparison of dissolution rates (Q *versus* t) was made for free tablets and the tablet-in-a-die compressed at 544.3 kg (Table IV). Comparisons in rates were made for the 1-hr time period and the average 2–4-hr time period. These rates for all conditions, various compressional forces, and various surface areas compare favorably, indicating that diffusion in free tablets is occurring through both top and bottom surfaces and the sides. Therefore, the dissolution apparatus does not restrict diffusion from any part of the tablet surface.

Penetration of Dissolution Media into Tablets—Wax matrix tablets are slowly permeated by the dissolution media as a function of time. The percent of volume penetration and percent drug release as a function of $t^{1/2}$ is shown in Fig. 4. It can be seen that some correlation exists between drug release and fluid penetration and that volume penetrated is proportional to the $t^{1/2}$. In the earlier time period, drug release lags about 1 hr behind fluid penetration. In later time periods, the lag time increases. An extrapolation of penetration and drug release curves results in a time period of about 7 hr for complete penetration and about 11.5 hr for complete drug release.

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GLC Determination of γ-Hydroxyphenylbutazone in Plasma

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Abstract □ A recently described GLC method for the determination of phenylbutazone and its major metabolite, oxyphenbutazone [1-phenyl-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butylpyrazolidine], in plasma was extended to the estimation of the second major metabolite, γ-hydroxyphenylbutazone [1,2-diphenyl-3,5-dioxo-4-(3-hydroxybutyl)pyrazolidine]. The method is sensitive to 1.0 μg/ml.

Keyphrases □ γ-Hydroxyphenylbutazone—GLC determination in plasma □ Phenylbutazone metabolites—GLC determination of γ-hydroxyphenylbutazone in plasma □ GLC—analysis, γ-hydroxyphenylbutazone in plasma

Since the classic work of Burns *et al.* (1) on the metabolism of the antiarthritic phenylbutazone, a number of methods for the determination of the drug and its major metabolite oxyphenbutazone have been published (2, 3). These workers also described the isolation of a second metabolite, γ-hydroxyphenylbutazone, from urine following repeated high doses but no assay of this metabolite apparently has been described. GLC procedures have been reported for the determination of phenylbutazone (3) and oxyphenbutazone (2), required for pharmacokinetic studies in these laboratories (4, 5). The method for oxyphenbutazone (2) has now been extended to allow simultaneous determination of γ-hydroxyphenylbutazone in human plasma following single and multiple doses of phenylbutazone.

EXPERIMENTAL

Reagents—All reagents and chemicals used were described previously (2). Complimentary samples of phenylbutazone[1], oxyphen-

[1] Ciba-Geigy, Canada.