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Influence of Shape Factors on Kinetics of Drug Release from Matrix Tablets II: Experimental

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Abstract □ Tablets were prepared from two slow-release formulations, both containing stearyl alcohol as a homogeneous insoluble matrix. The release of salicylic acid and of ephedrine was measured *in vitro*. It was found that the release profiles could be described by a nonlinear expression for both cylindrical and biconvex tablets. Even though the rate of drug release varied noticeably with tablet shape, regression analysis of the release data indicated that the rate constants included in the expression did not vary significantly ($p = 0.05$) with shape for tablets of the same overall composition.

Keyphrases □ Tablets, slow release—release of salicylic acid and ephedrine from homogeneous insoluble matrix (stearyl alcohol), experimental relationship between release and tablet shape □ Drug release from matrix tablets—experimental relationship between release and tablet shape, salicylic acid and ephedrine from stearyl alcohol □ Timed-release tablets—slow release of salicylic acid and ephedrine from homogeneous insoluble matrix (stearyl alcohol), effect of tablet shape

In a previous report (1), an expression, having a cubic form, was presented describing the dissolution kinetics of a drug from a slow-release matrix tablet:

$$f_t = G_1K_rt^{1/2} - G_2(K_rt^{1/2})^2 + G_3(K_rt^{1/2})^3 \qquad \text{(Eq. 1)}$$

where f_t is the fraction of drug released to time t, K_r is the release rate constant having the dimension of the reciprocal of the square root of time, and G_1–G_3 are shape factors. The values of G_1–G_3 are dependent on the shape of the tablet under study; values for three tablet shapes—spherical, cylindrical, and biconvex—are shown in Table I. For the first two shapes, the shape factors are constants and may be obtained from measurements of the initial dimensions of the tablet. However, for a biconvex tablet, the values of the shape factors vary with time and may be obtained partially from the initial dimensions of the tablet and partially in the course of the kinetic considerations of the release process.

A plot of the fraction of drug released, f_t, against the square root of time, $t^{1/2}$, will give a nonlinear curve, the exact profile depending on the tablet shape. One purpose of this study was to determine if the proposed equation describes experimental release data for cylindrical and biconvex tablets. Values for the release rate constants, K_r, may then be obtained for both tablet shapes by nonlinear regression analysis of the curves.

The value of the release rate constant varies inversely with the initial tablet radius, r_0, as shown previously (1):

$$K_r = \frac{K_b}{r_0} \qquad \text{(Eq. 2)}$$

where K_b is a proportionality constant, termed the boundary retreat rate constant, having the dimensions of length per unit square root of time. The boundary retreat rate constant is a measure of the rate at which dissolution fluid is able to penetrate into the insoluble tablet matrix to effect drug dissolution and release; it may be expressed (1) in terms of the same fundamental parameters described by

Table I—Values of Shape Factors for Three Shapes of Slow-Release Tablets[a]

Shape Factor	Tablet Shape		
	Spherical	Cylindrical	Biconvex
G_1	3	$q + 2$	$\frac{3p}{C_3}\left\{C_4 + C_6\left(\frac{Z_t}{K_r}\right)\right\}$
G_2	3	$2q + 1$	$\frac{3p^2}{C_3}\left\{C_5 + C_7\left(\frac{Z_t}{K_r}\right) + q\left(\frac{Z_t^2}{K_r^2}\right)\right\}$
G_3	1	q	$\frac{p^3q}{C_3}\left\{4 + 3\left(\frac{Z_t^2}{K_r^2}\right) - \frac{Z_t^3}{K_r^3}\right\}$

[a] Measurable parameters: r_0 = initial tablet radius, h_0 = half the initial tablet height, R_0 = initial radius of the spherical segment of the tablet, and HD_0 = initial height of the spherical segment of the tablet. Ratio constants: $a = R_0/r_0$, $q = r_0/h_0$, and $p = r_0/HD_0$. Simplifying factor (time dependent): $Z_t = 1/t^{1/2}\,[(C_1)^{1/2} - (C_1 - K_r t^{1/2} C_2)^{1/2}]$. Simplifying constants: $C_1 = a^2 - 1$, $C_2 = 2(a - 1)$, $C_3 = 6p^3 - 3p^2q + q$, $C_4 = 4p^2 + p^2q - 2pq + q$, $C_5 = 2p(1 + q)$, $C_6 = q(p^2 - 1)$, and $C_7 = 2q(p - 1)$.

Higuchi (2) in his derivation of the release of drugs from granular matrixes:

$$K_b = \frac{1}{A}\sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 3)}$$

where A is the weight of drug per unit tablet (unreleased) volume, D is the diffusion coefficient of the drug in the dissolution fluid, ϵ is the porosity of the matrix, τ is the tortuosity factor of the matrix, and C_s is the equilibrium solubility of the drug in the dissolution fluid. As noted by Higuchi (2), such an equation is essentially valid only if A exceeds ϵC_s by a factor of three or four.

Hence, it may be seen that the value of the boundary retreat rate constant depends only on the physicochemical properties of the tablet constituents and the degree of compression and, therefore, is independent of both the initial tablet radius, which partly governs the size of a tablet, and the tablet shape.

Substituting from Eq. 3 into Eq. 2 and rearranging give:

$$K_r = \frac{1}{Ar_0}\sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s} \qquad \text{(Eq. 4)}$$

While the value of the release rate constant, like that of the boundary retreat rate constant, is independent of tablet shape, it does depend on the initial tablet radius. Hence, if a pair of tablets of the same formulation (D and C_s constant), having an equal overall weight and compressed to the same degree (ϵ, τ, and A constant) is considered, the release rate constants, K_r, should not differ, providing the initial radii are equal and the test conditions are identical. Because such a pair of tablets need not be of the same shape, a second purpose of this study was to determine if the release rate constants for cylindrical and biconvex tablets having the same initial radius differ.

EXPERIMENTAL

Dissolution Fluids—Three dissolution fluids were prepared: *(a)* 0.1 *M* hydrochloric acid having a pH[1] of 1.10 ± 0.02 (mean ± *SD* of three batches), *(b)* glass-distilled water having a pH of 5.79 ± 0.09 (eight batches) after standing for at least 48 hr, and *(c)* phosphate buffer (3) having a pH of 7.52 ± 0.09 (three batches). The fluids will be referred to as the pH 1.1 fluid, the pH 5.8 fluid, and the pH 7.5 fluid, respectively.

[1] Model NX pH meter, Sargent-Welch Scientific Co., Skokie, Ill.

Table II—Formulations of Salicylic Acid Tablets (*A*) and Ephedrine Tablets (*B*) and Densities (ρ) of the Ingredients.

Ingredient	Formulations, mg/Tablet		ρ, g/ml
	A	*B*	
Salicylic acid[a] USP (drug)	90.0	—	1.70
Ephedrine[b] (BPC 1968) (drug)	—	75.0	1.42
Lactose[c] (BP 1968) (diluent)	15.0	30.0	1.45
Stearyl alcohol[d] (matrix)	37.5	37.5	0.94
Polyvinylpyrrolidone[e] (binder)	7.5	7.5	0.87

[a] Lot 721654, Fisher Scientific Co., Montreal, Quebec, Canada. [b] Lot 36410, British Drug Houses (Canada), Toronto, Ontario, Canada. [c] Lot 38450, British Drug Houses (Canada), Toronto, Ontario, Canada. [d] Lot 37434, British Drug Houses (Canada), Toronto, Ontario, Canada. [e] Plasdone C, Lot G-90509A-69, General Aniline and Film Corp., New York, N.Y.

Manufacture of Tablets—All ingredients used were of the purity supplied by the manufacturer, and solids were passed through 0.25-mm (60-mesh) stainless steel sieves prior to use. Two model formulations were prepared, one containing salicylic acid and the other ephedrine (Table II). The drug and lactose were mixed together and incorporated into a hot 50% (w/w) solution of stearyl alcohol in methylene chloride[2]. By maintaining mixing during cooling, an ointment-like mass was obtained. It was then spread thinly on paper-covered trays and allowed to solidify at room temperature. Once hardened, the mass was forced through a 0.42-mm (40-mesh) stainless steel sieve to obtain a powder.

After mixing the powder with polyvinylpyrrolidone, a quantity of distilled water equal to approximately twice the weight of the polyvinylpyrrolidone was incorporated. A wet mass was produced and granules were prepared by forcing the mass through a 1.00-mm (18-mesh) stainless steel screen. The granules were dried at room temperature, and a sample of 0.42–0.84-mm (20–40 mesh) size range was taken. Aliquots of the sample were added to each dissolution fluid and the resulting solutions, after filtration, were assayed spectrophotometrically for drug content.

If the sized granules could be compressed satisfactorily on a rotary tablet press[3], batches of tablets for experimental use were prepared using a laboratory press[4] adapted to incorporate assumed 3.175-mm (0.125-in.) radius tablet punches. For each formulation, two batches of tablets were prepared at 1600 psig. The first was compressed using flat-faced punches to give cylindrical tablets, and the second was compressed using concave punches[5] to give biconvex tablets. The weight and height of each tablet were measured before it was sealed in a No. 00 gelatin capsule and stored in a closed amber glass bottle.

Assay—Standard Beer's law curves were prepared for both drugs in each dissolution fluid. The wavelengths of measurement[6] were 294 nm (301 nm in the pH 1.1 fluid) for salicylic acid and 256 nm for ephedrine. The absorptivities of the drugs corresponded to literature values (5, 6) and remained unchanged with time and in the presence of the soluble tablet excipients.

Dissolution Test—*Apparatus*—A modified Baun and Walker (7) apparatus (Fig. 1) was used. The dissolution cell (A) consists of a glass tube (19 mm o.d. and 1 mm thick) having a screen (B) at each end. Because acidic dissolution fluids can deteriorate stainless steel (8), the screens are cut from the porous area of a polypropylene büchner funnel[7] and have a pore diameter of ap-

[2] USP reagent, Lot 707202, Fisher Scientific Co., Montreal, Quebec, Canada.

[3] Manesty Drycota (type DC500), Manesty Machines, Liverpool, England.

[4] Carver laboratory press (model B), Fred S. Carver Inc., Summit, N.J.

[5] These were Stokes "extra deep" concave punches (4) for which a = 1.500. It may be calculated that, for punches having r_0 = 3.175 mm, p = 2.618.

[6] Model DU 2400 spectrophotometer, Beckman Instruments Inc., Fullerton, Calif.

[7] Kimble Products Co., Toledo, Ohio.

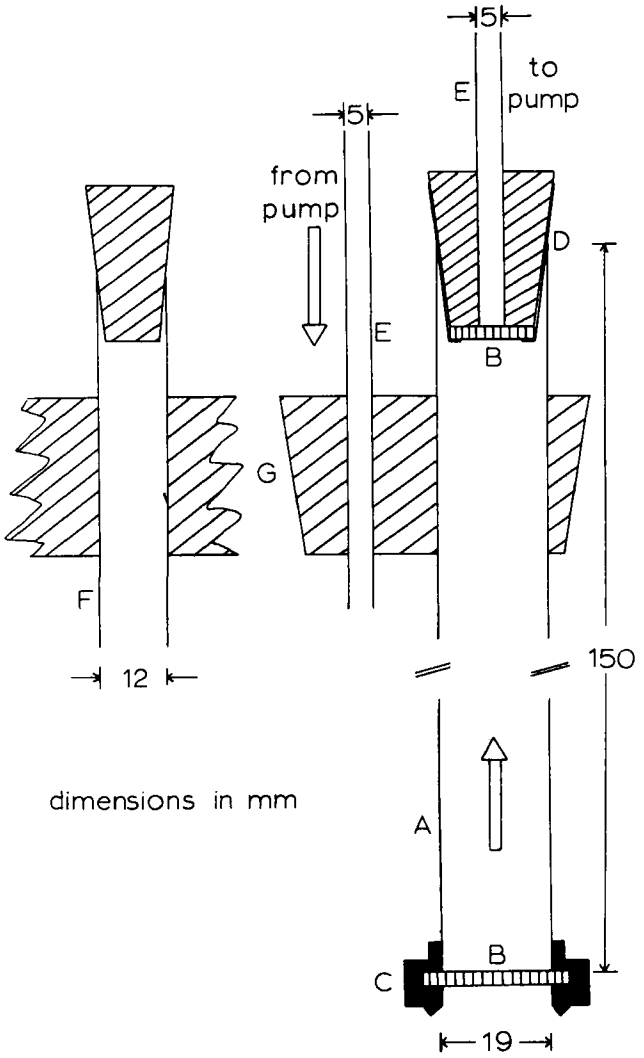

Figure 1—*The dissolution apparatus. Key: A, dissolution cell; B, screens; C, lower screen assembly; D, upper screen assembly; E, flow tubes; F, sample port; and G, reservoir stopper. (The numbers represent outside diameter in millimeters, with 1-mm thick tubes).*

proximately 0.75 mm. A lower screen assembly (C), which fits tightly onto the dissolution tube and can be removed easily, may be produced by boring a 19-mm diameter hole through both portions of a polyethylene snap cap[8] and holding the screen between them. An upper screen assembly (D) may be produced by holding the screen between a rubber stopper and a hollow polyethylene stopper[9] having a 10-mm diameter hole bored through its base. The flow of dissolution fluid is through glass tubes (E) (5 mm o.d. and 1 mm thick) and Tygon tubing[10]. A port (F), consisting of a stoppered glass tube (12 mm o.d. and 1 mm thick), is available for withdrawing samples of the dissolution fluid by pipet. The cell (A), the inlet tube (E), and the port (F) are all held in a neoprene stopper (G), which seals the reservoir containing the dissolution fluid; neither the inlet tube nor the port dips below the fluid level. The reservoir, an amber glass bottle, is suspended in a thermostatically controlled water bath.

Test Procedure—For 60 min prior to a test, the required volume of dissolution fluid, maintained at 37 ± 0.1°, was circulated through the apparatus at 50 ± 2 ml/min. This rate gave only a very slight agitation to the tablet which rested on the lower screen assembly. The pump[11] was then stopped, the upper screen assembly was removed, and the tablet was dropped into the dissolution cell. The assembly was immediately replaced and pumping was recommenced. At suitable time intervals[12], samples of the dissolution fluid were withdrawn through the port by pipet and replaced with an equal volume of the dissolution fluid. The samples were assayed spectrophotometrically to determine drug release.

Each ephedrine tablet floated, touching the upper screen assembly, before release was complete, an indication that the release of drug without any compensating reduction in overall tablet volume had lowered its density. Because fissures were noticeable in many tablets at the time of flotation (which was recorded), beyond this time all ephedrine tablets were assumed not to present an unbroken surface to the dissolution fluid as required by the theory (1).

Immediately after the conclusion of the test, the tablet was carefully removed and the final sample of the dissolution fluid was taken. The tablet was then slowly dried, weighed, and powdered, and an aliquot of the powder was dissolved in dissolution fluid. After filtration to remove insoluble particles, this solution

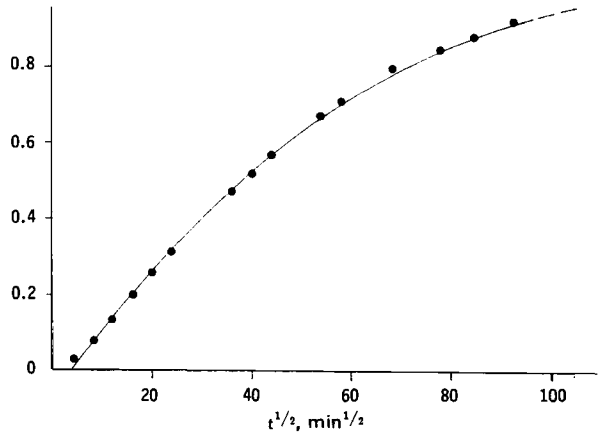

Figure 2—*Experimentally determined (●) fractions of drug released, f_t, at the sample times, t, and the optimum release curve for a cylindrical salicylic acid tablet (No. '13) in pH 1.1 fluid. Parameter values ± SE are: K_r = 0.00491 ± 0.00007 $min^{-1/2}$, and $t_0^{1/2}$ = 3.71 ± 0.38 $min^{1/2}$.*

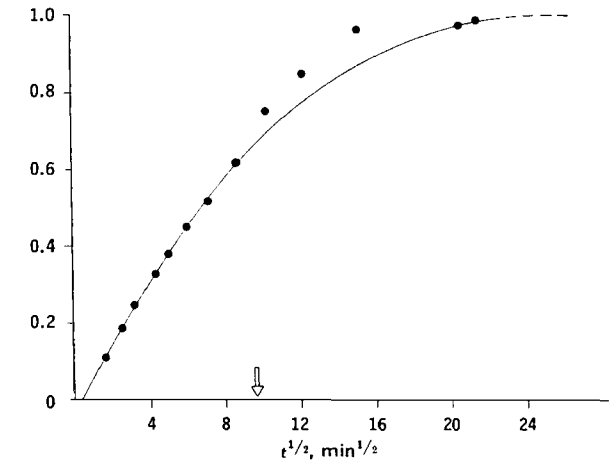

Figure 3—*Experimentally determined (●) fraction of drug released, f_t, at the sample times, t, and the optimum release curve for a cylindrical ephedrine tablet (No. 14) in pH 1.1 fluid. Parameter values ± SE are: K_r = 0.0277 ± 0.0004 $min^{-1/2}$, and $t_0^{1/2}$ = 0.422 ± 0.061 $min^{1/2}$. The arrow denotes time of tablet flotation.*

[8] Snap cap No. 3, Kimble Products Co., Toledo, Ohio.
[9] Stopper No. 1, Nalge Co., Rochester, N.Y.
[10] Tygon type R3603, Fisher Scientific Co., Montreal, Quebec, Canada.
[11] "Miniature Flow Inducer" MHRE/200, Mk. 3, Watson-Marlowe Ltd., Marlowe, England.

[12] The sampling times were arranged so that the drug released in any one time interval would be approximately equal to that in any other interval. Such a procedure precludes bias by ensuring that the release results are approximately equally spaced in the range $f_t = 0$ to $f_t = 1$.

Table III—Tablet Parameters

Parameter	Salicylic Acid Tablets		Ephedrine Tablets[b]	
	Cylindrical[a]	Biconvex[b]	Cylindrical	Biconvex
Weight, mg	150.1 ± 0.4	149.9 ± 0.3	150.0 ± 0.7	149.4 ± 0.9
Radius, r_0, mm	3.175	3.175	3.175	3.175
Height, $2h_0$, mm	3.752 ± 0.008	4.827 ± 0.011	4.108 ± 0.015	5.278 ± 0.039
$q = r_0/h_0$	1.693 ± 0.003	1.315 ± 0.003	1.546 ± 0.006	1.203 ± 0.009
Radius of spherical segment, R_0, mm	—	4.763	—	4.763
$a = R_0/r_0$	—	1.5	—	1.5
Height of spherical segment, HD_0, mm	—	1.213	—	1.213
$p = r_0/HD_0$	—	2.618	—	2.618
Volume, V_0, ml	0.1188 ± 0.0002	0.1163 ± 0.0003	0.1301 ± 0.0005	0.1306 ± 0.0012

[a] Mean ± *SD* of 11 tablets. [b] Mean ± *SD* of 12 tablets.

was assayed spectrophotometrically to determine the residual drug content of the tablet.

Evaluation Procedure—The cumulative drug released was computed[13] from the sample assays using a modified Wurster and Taylor (9) equation. The total drug content of each tablet was calculated by adding the residual drug content to the cumulative drug released at the time of the final sample. Then, knowing the total drug content, the fraction of drug released at each sample time, f_t, was computed.

In practice, Eq. 1 must be modified to account for a lag time before drug is first released or detected:

$$f_t = G_1K_r\{t^{1/2} - t_0^{1/2}\} - G_2(K_r\{t^{1/2} - t_0^{1/2}\})^2 + G_3(K_r\{t^{1/2} - t_0^{1/2}\})^3 \quad \text{(Eq. 5)}$$

where $t_0^{1/2}$ is the root lag time. If there is no lag time, $t_0^{1/2} = 0$, then Eq. 5 reduces to Eq. 1.

The experimental results were analyzed using a nonlinear regression computer program[14]. Optimum values of the release rate constant, K_r, and the root lag time, $t_0^{1/2}$, to three significant figures were found together with estimates of their standard errors.

Measurement of Some Fundamental Parameters—The density of each tablet ingredient was found using standard pycnometer techniques. The equilibrium solubility of each drug at 37°, C_s, was found by a method essentially similar to that reported by Desai *et al.* (10).

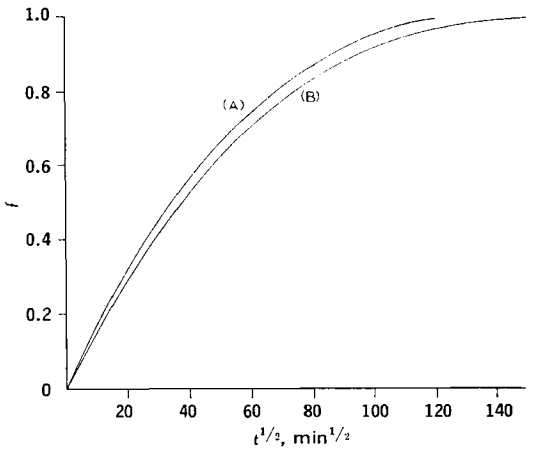

Figure 4—*Effect of shape on fraction of drug released,* f_t, *with time,* t; *mean profiles of salicylic acid tablets in pH 1.1 fluid. Key: (A), cylindrical,* $K_r = 0.00493\ min^{-1/2}$; *and (B), biconvex,* $K_r = 0.00497\ min^{-1/2}$. *For comparative purposes, the lag times are ignored.*

[13] Model 9100A calculator, Hewlett-Packard Co., Loveland, Colo.

[14] University of Toronto Computer Centre, IBM System 370-165. The program contained an iterative subroutine, GAUSHS (similar to the IBM FORTRAN IV Contributed Program 360D-13.6.007), and a model subroutine containing the appropriate release expression (Eq. 5).

RESULTS AND DISCUSSION

The drug content of the granules was found to be 91.2 ± 0.4 mg (mean ± *SD* of three results) for salicylic acid tablets and 74.0 ± 1.7 mg (14 results) for ephedrine tablets, expressed per 150.0 mg of granules. The parameters of the tablets (Table III) indicated that the salicylic acid granules were more compressible at 1600 psig than was an equal weight of ephedrine granules. However, the mean weight and volume of cylindrical and biconvex tablets containing the same drug were essentially equal. Hence the parameters ϵ, τ, and A described in Eqs. 3 and 4 could be considered constant between the two tablet shapes, a requirement for determining whether the release rate constant is a function of tablet shape.

Fitting Experimental Data to Proposed Equation—Example data of the fraction of drug released, f_t, from a tablet at various sample times, t, are shown in Table IV. Where tablet flotation was noted (ephedrine tablets), only values of f_t prior to flotation were used in computing the release rate constant, K_r, and root lag time, $t_0^{1/2}$. Figures 2 and 3 show example release profiles for single tablets, calculated from the optimum parameter values. The fit of the release curves to the experimental data points is good, deviation occurring only with ephedrine tablets after flotation. The deviation is due to fissures forming in the tablets, a factor probably resulting from an inadequate tablet formulation (possibly, in this case, too little matrix substance). The fissures permitted the dissolution fluid to flow virtually unimpeded to and from the remaining undissolved drug near the tablet center; normally the fluid would diffuse more slowly through the "ghost" region.

Further indications of the goodness of fit of each optimum curve to its corresponding experimental data may be obtained from the computed standard errors of the parameters. The standard error was 2.12 ± 0.96% (mean ± *SD* of 23 experiments) of

Table IV—Fractions of Drug Released from a Biconvex Salicylic Acid Tablet (No. 6) in pH 5.8 Fluid[a]

Minutes[b]	Fraction Released[c], f_t
24	0.042
48	0.069
92	0.116
150	0.152
243	0.209
390	0.258
610	0.335
1250	0.471
1485	0.515
1749	0.552
2155	0.591
2677	0.647
3085	0.680
4457	0.786
5589	0.851
6025	0.887

[a] Computed parameter values ± *SE* are: $K_r = 0.00562 \pm 0.00009\ min^{-1/2}$, and $t_0^{1/2} = 3.51 \pm 0.43\ min^{1/2}$. [b] Each experiment was conducted using slightly different sample times, so average values of f_t cannot be shown. [c] Based on assayed drug content.

Table V—Mean Values of Release Rate Constant, K_r, and Root Lag Time, $t_0^{1/2}$

Fluid	Cylindrical Tablets		Biconvex Tablets	
	K_r, $min^{-1/2}$	$t_0^{1/2}$, $min^{1/2}$	K_r, $min^{-1/2}$	$t_0^{1/2}$, $min^{1/2}$
	Salicylic Acid Tablets[a]			
pH 1.1	0.00493 ± 0.00007[b]	3.63 ± 0.29[b]	0.00497 ± 0.00009[c]	3.32 ± 0.06
pH 5.8	0.00530 ± 0.00012	3.93 ± 0.39	0.00550 ± 0.00009[d]	3.37 ± 0.31
pH 7.5	0.00828 ± 0.00032	2.52 ± 0.31	0.00846 ± 0.00027[c]	2.29 ± 0.09
	Ephedrine Tablets[a]			
pH 1.1	0.0275 ± 0.0012	0.61 ± 0.16	0.0292 ± 0.0016[c]	0.41 ± 0.18
pH 5.8	0.0232 ± 0.0004	1.39 ± 0.16	0.0267 ± 0.0009[d]	1.06 ± 0.16
pH 7.5	0.0224 ± 0.0006	0.98 ± 0.26	0.0225 ± 0.0004[c]	0.99 ± 0.14

[a] Mean ± *SD* of four experiments. [b] Mean ± *SD* of three experiments. [c] No significant difference ($p = 0.05$) between the mean K_r values obtained from tablets differing only in shape. [d] Significant difference ($p = 0.05$) between the mean K_r values obtained from tablets differing only in shape.

Table VI—Mean Boundary Retreat Rate Constants, K_b, of Tablets and Equilibrium Solubilities of Drugs at 37°, C_s

Fluid	K_b[a], mm × 10^2 $min^{-1/2}$		C_s[c], mg/ml	
	Salicylic Acid Tablets	Ephedrine Tablets	Salicylic Acid	Ephedrine
pH 1.1	1.58 ± 0.03[b]	9.00 ± 0.50	2.64 ± 0.02	90.6 ± 0.5
pH 5.8	1.71 ± 0.05	7.93 ± 0.63	3.64 ± 0.05	66.6 ± 0.4
pH 7.5	2.66 ± 0.09	7.14 ± 0.23	9.54 ± 0.33	60.1 ± 0.9

[a] Mean ± *SD* of eight experiments (both cylindrical and biconvex tablets). [b] Mean ± *SD* of seven experiments (both cylindrical and biconvex tablets). [c] Mean ± *SD* of three experiments.

the optimum value of the release rate constant for salicylic acid tablets and 2.79 ± 1.33% (24 experiments) for ephedrine tablets; the standard error was 12.4 ± 2.0% and 12.9 ± 6.8% of the optimum value of the root lag time, respectively. Both the statistical data and the visual curve fitting indicate that the experimental results can be closely described by the proposed expression (Eq. 5).

Values of Rate Constants K_r and K_b—The mean values of the release rate constant, K_r, and the root lag time, $t_0^{1/2}$, are shown in Table V. The K_r values obtained under identical conditions from tablets differing only in shape were not significantly different ($p = 0.05$) when an unpaired t test was applied, except for experiments conducted in the pH 5.8 fluid. Because the initial radii of both the cylindrical and biconvex tablets were identical (Table III), mean values of the boundary retreat rate constant, K_b, would also lead to the same statistical conclusions (Eq. 2).

Since Eq. 3 indicates that the boundary retreat rate constant should not vary with tablet size or shape, an explanation of the discrepancies should be sought. A possible explanation may lie with the lack of buffering capacity in the pH 5.8 fluid, which was distilled water, resulting in a measurable pH change within the fluid as released drug accumulated. In the case of salicylic acid tablets, the pH fell to 3.39 ± 0.01 (mean ± *SD* of four experiments); in the case of ephedrine tablets, the pH rose to 9.53 ± 0.19 (four experiments). Hence, the equilibrium solubility, C_s, of the drug in the fluid gradually fell during a test procedure, giving, as a consequence of Eq. 3, a gradually decreasing boundary retreat rate constant. Conceivably, this time-dependent variability of the boundary retreat rate constant may partly explain the discrepancies seen. The pH of the other dissolution fluids had not changed measurably at the conclusion of an experiment.

For experiments conducted at a constant pH, the results indicate that there is no significant difference ($p = 0.05$) between the rate constants (both K_r and K_b) obtained from tablets of different shapes. However, the actual rate of drug release varies noticeably between tablet shapes, with the biconvex tablet giving the slower release (Figs. 4 and 5). The effect of tablet shape on the release rate is thus distinguished from its lack of effect on the rate constants.

Fundamental Parameters—According to Eq. 3, the value of the boundary retreat rate constant depends on certain fundamental parameters related to the tablet composition. As defined (2), the values of the equilibrium solubility, C_s, the diffusion coeffi-

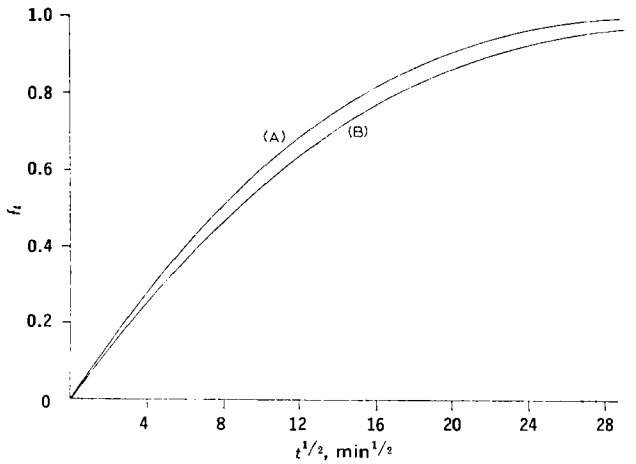

Figure 5—*Effect of shape on fraction of drug released, f_t, with time, t; mean profiles of ephedrine tablets in pH 7.5 fluid. Key: (A), cylindrical, $K_r = 0.0224\ min^{-1/2}$; and (B), biconvex, $K_r = 0.0225\ min^{-1/2}$. For comparative purposes, the lag times are ignored.*

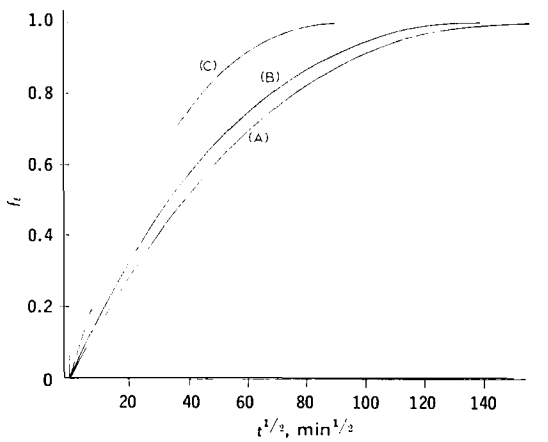

Figure 6—*Effect of fluid pH on fraction of drug released, f_t, with time, t; mean profiles of biconvex salicylic acid tablets. Key: (A), pH 1.1, $K_r = 0.00497\ min^{-1/2}$; (B), pH 5.8, $K_r = 0.00550\ min^{-1/2}$; and (C), pH 7.5, $K_r = 0.00846\ min^{-1/2}$. For comparative purposes, the lag times are ignored.*

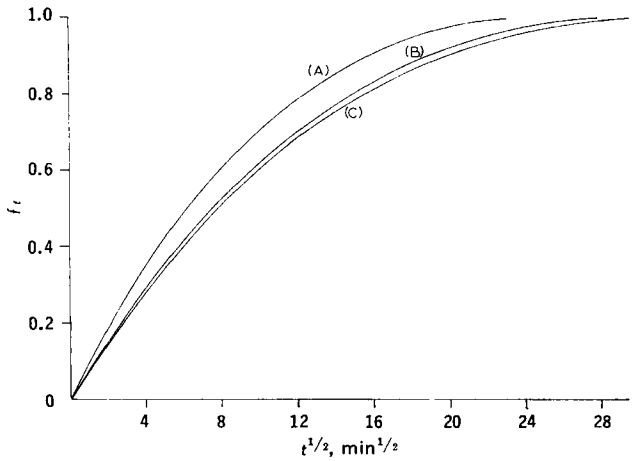

Figure 7—*Effect of fluid pH on fraction of drug released,* f_t, *with time,* t; *mean profiles of cylindrical ephedrine tablets. Key: (A), pH 1.1,* $K_r = 0.0275\ min^{-1/2}$; *(B), pH 5.8,* $K_r = 0.0232\ min^{-1/2}$; *and (C), pH 7.5,* $K_r = 0.0224\ min^{-1/2}$. *For comparative purposes, the lag times are ignored.*

cient, D, and the weight per unit tablet volume, A, apply exclusively to the drug when it is the only soluble solid distributed throughout the insoluble matrix. However, when formulating slow-release tablets, it is often necessary to include additional soluble solids as excipients, in which case the three parameters become composite values related to all soluble components. The use of lactose and polyvinylpyrrolidone, both of which are soluble in the dissolution fluids, in the formulations of the tablets used in this study was deliberate, in that it was hoped to approximate formulations applicable to large-scale manufacture. Hence, while the boundary retreat rate constant increases with the equilibrium solubility of the drug (Table VI), the dependence should be classified as a rank-order relationship in the absence of the required composite solubility data for all soluble components. The effect of changing pH on the release profiles is shown in Figs. 6 and 7.

Because Eqs. 3 and 4 are only essentially valid if A exceeds ϵC_s by a factor of three or four (2), it was felt worthwhile to ascertain whether the fissuring in the ephedrine tablets could be the physical result of a nonadherence to this requirement. By using the densities of the tablet ingredients (Table II) and employing the calculation method of Desai *et al.* (10), the mean porosity of the matrix of the salicylic acid tablets and the ephedrine tablets was 0.661 and 0.694, respectively; the mean values for A were 957 and 863 mg/ml, respectively. While the values for these two parameters (ϵ and A) have regard for all of the soluble solids in the tablets, the equilibrium solubility, C_s, values refer only to the drugs (Table VI). Hence, the calculated $A:\epsilon C_s$ ratios are only approximate, their values being 500 and 14 for salicylic acid and ephedrine tablets, respectively. Even so, the tablets used in this study apparently comply with the theoretical requirement (2), suggesting that the fissuring imperfection seen with ephedrine tablets is probably due to inadequate formulation.

In view of the complexity of the formulations, the tablets used in this study could not be suitable tools with which to predict rate constants from the direct measurement of fundamental parameters, as Eqs. 3 and 4 might suggest. Indeed, Hersey (11) suggested that predictions of the dissolution rates of drugs from fundamental parameters are hazardous, particularly given the relative ease with which direct measurements of rate constants may be made. Thus, when determining release rates of drugs from such complex dosage forms as slow-release tablets, direct experimental measurement is probably the preferred procedure.

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