Table III—Mouse L-1210 Antitumor Evaluation

Compound[a]	%T/C (Dose)[b]	T − C[c]	NSC Number
III	108 (200)[d]	−1.1	237649
IV	105 (200)[d]	0.5	235817
V	120 (200)[e]	−0.3	235818
VI	110 (400)	−1.5	235821
VII	126 (200)[d,e]	0.3	235819
VIII	103 (400)	1.2	235820
IX	98 (400)	0.0	237651
X	100 (400)	−0.5	264080
XI	101 (400)	0.1	249986
XII	97 (400)	−1.0	249988
XIV	95 (400)	0.5	264081
XV	95 (400)	−1.1	264082
XVI	91 (200)[d]	−3.0	266768
XVII	112 (200)[d]	−4.4	266767
XVIII	101 (100)[f]	0.1	266769
XIX	101 (400)	−0.9	267970
XX	98 (400)	−0.8	267971
XXI	104 (400)	−0.8	267972

[a] Test compounds were administered intraperitoneally on Days 1, 5, and 9 following intraperitoneal tumor implantation. [b] The tabulated dose (milligrams per kilogram) was the highest dose given producing the indicated %T/C in a dose–response assay. [c] The difference of the average body weight change in grams of the test group (T) and the control group (C) measured on Day 5. [d] Toxic at 400 mg/kg. [e] Activity could not be reproduced. [f] Toxic at 200 mg/kg.

methylethyl)pentanamide (XXI): General Preparation for XIX and XX—A mixture of XVIII (0.77 g, 2.96 mmoles) as the crude dihydrochloride salt (use of the oxalate salt gave similar results) and phthalic anhydride (0.48 g, 3.26 mmoles) was combined with 50 ml of triethylamine and refluxed with stirring for 4 hr. Most of the triethylamine was removed by flash distillation (bath 45°), and the residue was partitioned between 50 ml of 10% hydrochloric acid and 100 ml of chloroform and separated. The aqueous layer was extracted twice with chloroform; the organic layers were combined, dried, and evaporated, yielding 0.69 g of a yellow syrup, which crystallized. The crystals in 5 ml of chloroform were chromatographed on 37 g of alumina. Elution with 200 ml of chloroform gave 290 mg of white crystals of XXI after recrystallization.

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Formulation Factors Affecting Strength and Dissolution of Uncoated Oxytetracycline Tablets

S. ESEZOBO and N. PILPEL [x]

Abstract □ The effect of various formulation and processing factors on the properties of 300-mg oxytetracycline tablets was studied. At a constant moisture level and packing fraction, an increase in gelatin concentration resulted in increased tensile strength, increased disintegration and dissolution times, and reduced capping tendency. The Wagner theory of dissolution applied satisfactorily to tablets containing up to 5% (w/w) gelatin but was less applicable at higher gelatin levels. Dissolution rate constants were calculated, and their values depended on the gelatin content and packing fraction of the tablets.

Keyphrases □ Oxytetracycline tablets—tensile strength and dissolution, effect of various formulation and processing factors □ Tablets, oxytetracycline—tensile strength and dissolution, effect of various formulation and processing factors □ Tensile strength—oxytetracycline tablets, effect of various formulation and processing factors □ Dissolution—oxytetracycline tablets, effect of various formulation and processing factors □ Dosage forms—oxytetracycline tablets, tensile strength and dissolution, effect of various formulation and processing factors

Recently, various investigators (1, 2) reported that commercial oxytetracycline hydrochloride capsules, nominally containing the same dose but produced by different manufacturers, are not biologically equivalent. Brice and Hammer (1) performed disintegration and dissolution tests and found that, in general, batches that gave poor

Table I—Values of Tensile Strength for the Oxytetracycline Flat-Faced Tablets[a] Prepared with a Single-Punch Machine at a Packing Fraction of 0.85–0.87

Gelatin Concentration, % (w/w)	Log Tensile Strength, MNm^{-2}	Tensile Strength, MNm^{-2}
0	0.15	1.41
2.50	0.25	1.77
3.75	0.33	2.17
5.00	0.41	2.57
6.25	0.43	2.72
7.50	0.51	3.20

[a] Tablets weighed 325 mg and had a moisture content range of 2.4–3.2% (w/w).

serum levels also had slower *in vitro* dissolution rates.

Further investigations (3, 4) on several samples of commercial 250-mg oxytetracycline dihydrate tablets BP showed that the dissolution rate profiles varied between generic brands obtained from different manufacturers and also between and within batches from one source. More recently, Chalmers and Elworthy (5) conducted studies on a particular oxytetracycline formulation (similar in some respects to the one used in the present investigations but with povidone as the binding agent). Their work was concerned primarily with the effects of particle size, binder concentration, binder volume, and massing time on the tensile strength and disintegration and dissolution times of the resulting granules and tablets.

Preliminary work was reported (6) on the effects of moisture, gelatin binding agent, and packing fraction on the properties of certain oxytetracycline tablets prepared with a hand press. It was considered necessary to extend the work along two lines: (*a*) to see whether any correlation existed between the properties of tablets made in a hand press and in high speed tableting machines, and (*b*) to analyze in detail the dissolution results obtained on all of the tablets to arrive at a better understanding of the mechanisms of dissolution in typical oxytetracycline tablet formulations.

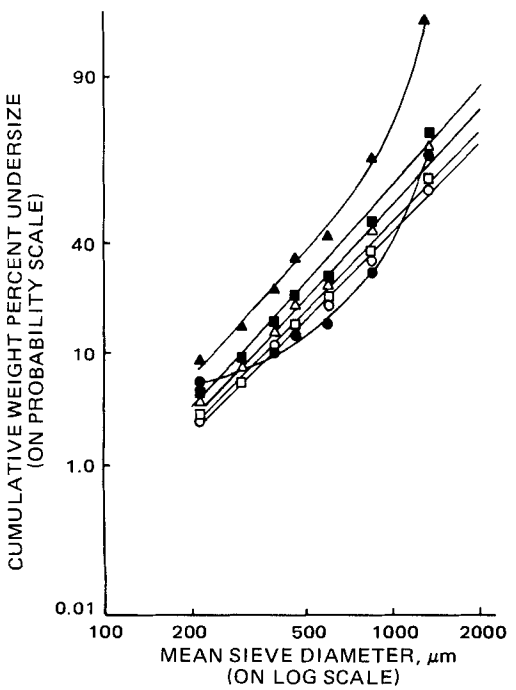

Figure 1—*Sieve analysis of granules on a log probability plot. Key (% w/w gelatin): ●, 0; ▲, 2.50; ■, 3.75; △, 5.00; □, 6.25; and ○, 7.50.*

Table II—Effect of Gelatin Concentration on the Capping Pressure of 300-mg Deep Biconvex Tablets Using a Hand-Operated Hydraulic Press

Gelatin Concentration, % (w/w)	Capping Pressure, MNm^{-2}	Packing Fraction (ρ_f)
0	29.8	0.74
2.50	59.5	0.81
3.75	89.3	0.83
5.00	119.1	0.85
6.25	119.1	0.87
7.50	148.9	0.88

Two methods of analysis were employed. The first involved using the equation of Wagner (7):

$$\text{\% dissolved by time } t = \frac{W}{W^\infty} \times 100 = \frac{\int_0^t s(t)\,dt}{\int_0^\infty s(t)\,dt}$$

$$\times 100 = \text{\% surface area generated by time } t \text{ of total surface generated} \quad \text{(Eq. 1)}$$

in which it is assumed that the surface area of the drug available for dissolution is initially zero, then increases to a maximum as disintegration occurs, and then falls off progressively to zero when dissolution is complete. The W and W^∞ are the amounts of drug dissolved at time t and at infinite time, respectively; the integrals represent the cumulative surface areas, S, that have been made available for dissolution from time zero to the particular time t and infinity, respectively.

The applicability of Eq. 1 can be tested by plotting values of cumulative percent drug dissolved on a probability scale (ordinate) *versus* the corresponding time values on a logarithmic scale (abscissa) and seeing whether straight-line graphs are obtained.

The second method of analysis was the equation proposed by Kitazawa *et al.* (8):

$$\ln \frac{C_s}{C_s - C} = kt \quad \text{(Eq. 2)}$$

where k is the dissolution rate constant, C_s is the concentration of the solute at saturation, and C is the actual solute concentration in solution at time t. Equation 2 was derived from a study of the dissolution of uncoated caffeine tablets and showed that a change in the dissolution rate at a cer-

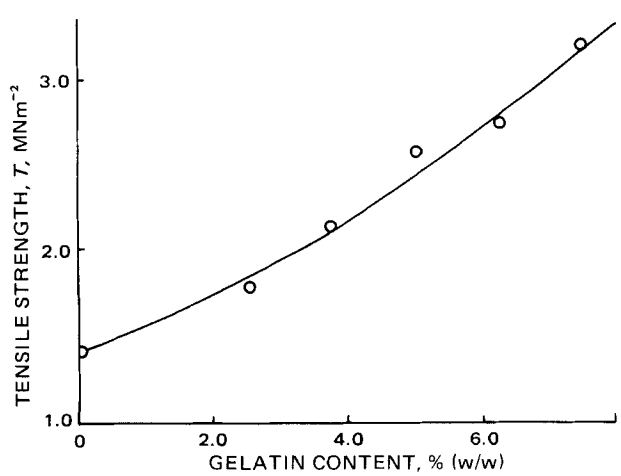

Figure 2—*Tensile strength* versus *gelatin content of flat-faced tablets prepared with a single-punch machine. The range of ρ_f was 0.85–0.87, and the range of moisture content was 2.4–3.2% (w/w).*

Table III—Influence of Gelatin Content on the Dissolution and Disintegration of Biconvex Tablets at $\rho_f \simeq 0.80$

Gelatin Concentration, % (w/w)	Moisture Content, % (w/w)	Mean Packing Fraction (ρ_f)	Dissolution Time, min[a]			Disintegration Time, min[b]	
			$t_{25\%}$	$t_{50\%}$	$t_{75\%}$	Mean Packing Fraction (ρ_f)	Mean Disintegration Time, min
		Tablets Prepared with Single-Punch Machine					
0	2.70	0.79	1.88	3.13	4.50	0.79	1.54
2.50	2.40	0.80	2.25	3.25	5.25	0.79	1.62
3.75	2.70	0.80	3.75	5.75	8.75	0.79	2.79
5.00	3.60	0.80	15.50	25.00	35.50	0.78	6.46
6.25	3.20	0.80	50.00	101.00	141.00	0.80	31.38
		Tablets Prepared with Multipunch Machine					
0	2.70	0.79	2.00	3.38	6.00	0.79	1.05
2.50	2.40	0.79	2.13	3.25	5.25	0.78	1.48
3.75	2.70	0.80	3.50	5.38	8.75	0.78	2.75
5.00	3.60	0.78	10.00	17.50	30.50	0.77	7.07
6.25	3.20	0.79	62.00	144.00	—[c]	0.79	30.74

[a] Mean of four tablets. [b] Mean of 20 tablets. [c] Sixty-one percent released after 180 min.

tain time, t, represented a change in the surface area of the tablet due to it breaking into small particles.

EXPERIMENTAL

Materials—The basic formulation employed was 90.2% (w/w) oxytetracycline dihydrate[1] EP, 7.2% (w/w) microcrystalline cellulose BPC[2], and 3.6% (w/w) alginic acid HED[3] BPC.

Granule Preparation—Granules were prepared using gelatin[4] as previously reported (6).

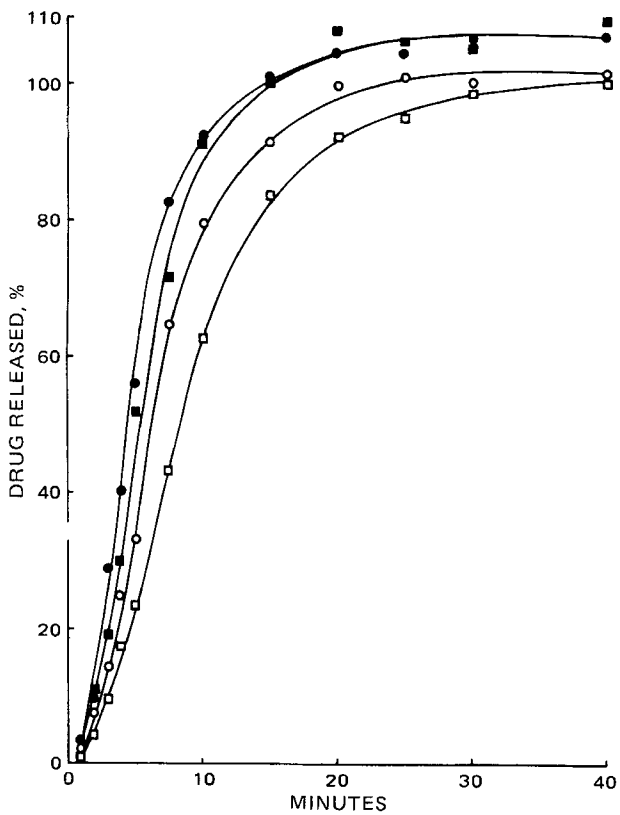

Figure 3—*Drug release* versus *time for tablets containing 3.75% (w/w) gelatin prepared with a single-punch machine of a constant pressure setting. Key (packing fraction, ρ_f): ●, 0.79; ■, 0.80; ○, 0.81; and □, 0.82.*

Tableting Procedure—A hand-operated hydraulic press[5] (6) and single-punch[6] and rotary-punch[7] tableting machines equipped with flat-faced or deep concave punches, 1.03 cm in diameter, were used to compress the granules. The granules had been lubricated with 1% (w/w) magnesium stearate. The compression speed of the single-punch machine was adjusted to 70 strokes/min. The multipunch machine was modified by blocking off 14 stations so that only two compression stations, fitted with deep concave punches on opposite sides of the revolving turret, were used. It was operated at 30 rpm.

The setting on each machine was adjusted to produce tablets (about 400–500) from each batch of granules with predetermined weights and packing fractions. The following tablets were prepared (all contained approximately 250 mg of oxytetracycline):

type of machine	shape	total weight, mg	tablets packing fraction (ρ_f)
hand press	deep biconvex	300 ± 10	0.69–0.90
single punch	flat faced	325 ± 10	0.85 ± 0.05
	deep biconvex	300 ± 10	0.80 ± 0.05
rotary punch	deep biconvex	300 ± 10	0.80 ± 0.05

Tests on Tablets—*Tensile Strength*—The tensile strengths of 325-mg flat-faced tablets were determined using the diametral compression test (6, 9, 10) on 20 tablets of each batch, and the means were calculated. The measurements were made in a room having a relative humidity of 50%.

Capping Pressure—Capping pressure was determined by subjecting the 300-mg biconvex tablets, which had been compressed to different packing fractions with the hand press, to the diametral test. The packing fraction at which each batch of tablets capped was noted, and the corresponding pressure employed to achieve tablets of this packing fraction was regarded as the capping pressure. The determination was made on at least 20 tablets per packing fraction in each batch, and capping was said to occur at a particular packing fraction when at least 50% of tablets tested capped.

Disintegration—The disintegration times of the 300-mg deep biconvex tablets were measured individually on 20 tablets by the BP method in a disintegration apparatus[8], and a mean time was calculated. Distilled water was used as the disintegration fluid (6).

Dissolution—The dissolution times of the 300-mg deep biconvex tablets were measured in an apparatus similar in principle to the "beaker method" of Levy and Hayes (6, 11). Individual tablets were placed in a pH 2 dissolution buffer solution and stirred at 100 rpm. Samples were removed at known time intervals and assayed in a spectrophotometer[9] for oxytetracycline content. The mean of four tablets was calculated at each gelatin concentration and packing fraction.

RESULTS

The size distributions of the granules used for preparing the tablets are shown in Fig. 1 as a log-probability plot.

[1] ICI Ltd., Pharmaceuticals Division, Macclesfield, Cheshire, United Kingdom.
[2] Avicel PH101, Honeywell and Stein Ltd., London, United Kingdom.
[3] Alginate Industries Ltd., London, United Kingdom.
[4] Bloom No. 300, acid-treated hide, Richard Hodgson and Sons Ltd., Beverley, Yorkshire, United Kingdom.
[5] Research and Industrial Instrument Co., Ltd., London, United Kingdom.
[6] Model F3, Manesty Machines Ltd., Liverpool, United Kingdom.
[7] Model D3B, Manesty Machines Ltd., Liverpool, United Kingdom.
[8] Manesty disintegration tester, Manesty Machines Ltd., Liverpool, United Kingdom.
[9] CE202, Cecil Instruments Ltd., Cambridge, United Kingdom.

Table IV—Combined Effects of Gelatin Content and Packing Fraction on the Dissolution Rates of Biconvex Tablets at $\rho_f \simeq 0.80$ Using Eq. 2

Gelatin Content, % (w/w)	Packing Fraction (ρ_f)	t_1, min	k_1, min^{-1}	k_2, min^{-1}
0	0.73	5.0	0.280	0.152
	0.81	—[a]	0.320	—[a]
	0.86	—[a]	0.490	—[a]
	0.87	—[a]	0.358	—[a]
	0.92	5.0	0.180	0.139
2.50	0.72	—[a]	0.253	—[a]
	0.80	—[a]	0.270	—[a]
	0.81	—[a]	0.313	—[a]
	0.85	—[a]	0.256	—[a]
	0.88	10.4	0.160	0.132
3.75	0.69	42.5	0.047	0.018
	0.78	30.0	0.109	0.200
	0.84	36.0	0.065	0.040
	0.86	17.0	0.024	0.078
	0.90	30.5	0.022	0.040
5.00	0.70	25.0	0.031	0.018
	0.79	49.0	0.035	0.017
	0.83	82.0	0.007	0.019
	0.86	113.0	0.007	0.019
6.25	0.69	124.0	0.017	0.028
	0.78	85.0	0.013	0.023
	0.83	145.0	0.009	0.021

[a] A single straight regression line with slope = k was obtained.

The calculated values of the tensile strengths in Table I are for the 325-mg flat-faced tablets, prepared at packing fractions between 0.85 and 0.87 and containing moisture levels between 2.4 and 3.2% (w/w) with the single-punch tableting machine. The tensile strength is plotted *versus* percent (w/w) of gelatin in Fig. 2.

The information on the effects of gelatin concentration on the capping tendency of the 300-mg biconvex tablets is presented in Table II.

Table III lists the mean dissolution times for 25, 50, and 75% of drug released from the tablets (having packing fractions of approximately 0.80) prepared with both single-punch and multipunch machines. Table III also includes the mean disintegration times for these tablets.

Figure 3 shows a representative graph of the variation in dissolution profiles for tablets containing 3.75% (w/w) gelatin prepared with the single-punch machine at the same pressure settings. Similar variations were also obtained for tablets prepared with the multipunch machine at a fixed pressure setting.

The marked effect of gelatin concentration on the dissolution profiles of the tablets prepared with the single-punch machine at a packing fraction of approximately 0.80 is illustrated in Fig. 4. To test whether the data given in Table III and plotted in Fig. 4 were amenable to the Wagner (7) type of analysis, the values of percentage drug dissolved were plotted against time on a log–probability graph (Fig. 5). In general, straight lines could be drawn through the points for the tablets containing 0, 2.5, and 3.75% (w/w) gelatin. For tablets made with 5.0 and 6.25% (w/w) gelatin, curved lines were obtained.

The apparent pseudo-first-order plots corresponding to curves A and B in Fig. 5, together with similar curves obtained for tablets prepared (at the same packing fraction) with a hand-operated press and multipunch machine, are shown in Fig. 6. The Kitazawa *et al.* (8) types of plot of $\ln [C_s/(C_s - C)]$ *versus* time are shown in Figs. 7 and 8 for tablets compressed with the hand-operated press to different packing fractions and containing 0 and 5% (w/w) gelatin, respectively. Similar plots were obtained for tablets made (at approximately the 0.80 packing fraction) with the single-punch machine (Fig. 9). Depending on the packing fraction and gelatin content, either a single straight line or two intersecting straight lines were obtained for each formulation. For those with two straight lines, the time at which the lines intersect is termed t_1, the slope of the first is designated k_1, and the slope of the second is designated k_2. Additional relevant data showing the effects of both packing fraction and gelatin content on these values are listed in Tables IV and V.

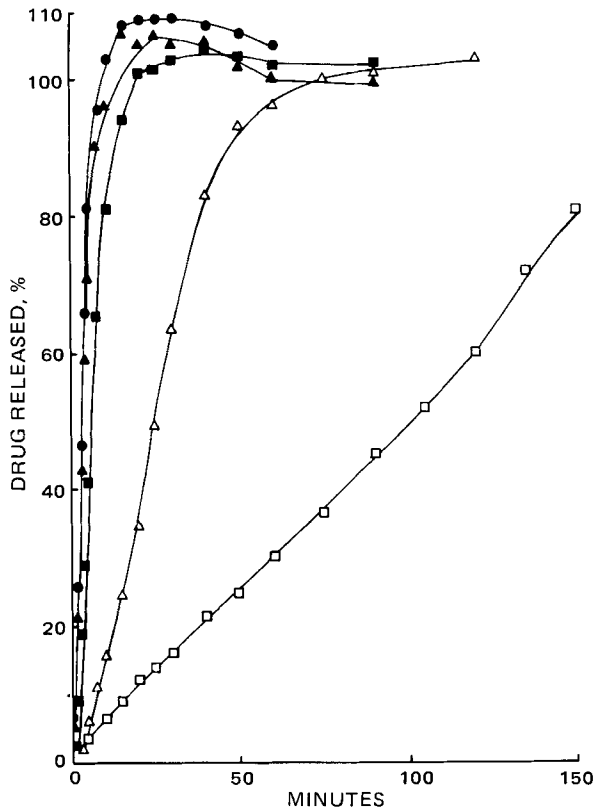

Figure 4—*Effect of gelatin content on the dissolution of tablets prepared with a single-punch machine at $\rho_f \simeq 0.80$. Key: ●, 0% (w/w) gelatin and 0.79 mean ρ_f; ▲, 2.50% (w/w) gelatin and 0.80 mean ρ_f; ■, 3.75% (w/w) gelatin and 0.80 mean ρ_f; △, 5.00% (w/w) gelatin and 0.80 mean ρ_f; and □, 6.25% (w/w) gelatin and 0.80 mean ρ_f.*

DISCUSSION

With some formulations, variations in granule size (Fig. 1) may cause significant changes in the disintegration and dissolution rates of the tablets (12, 13). However, these changes were small for two oxytetracycline formulations, one containing gelatin (14) and the other povidone (5) as the binding agent.

Increasing the gelatin concentration increased the tensile strengths of the tablets (Fig. 2). Therefore, the result was similar to that obtained on loosely packed beds (15) on tablets prepared with a hand-operated press (6) and when povidone was used as the binding agent (5). This result could be attributed to the considerable amount of heat generated during the tableting of powders or granules, producing overall temperature rises of about 5–30° and still higher rises of the contact points between the asperities on the particles (16, 17). This temperature increase could cause

Table V—Effects of Gelatin Content on the Dissolution Rates of Biconvex Tablets at $\rho_f \simeq 0.80$ Using Eq. 2

Gelatin Content, % w/w	Tablets Prepared with Single-Punch Machine, ρ_f Range = 0.79–0.80			Tablets Prepared with Multipunch Machine, ρ_f Range = 0.78–0.80		
	t_1, min	k_1, min^{-1}	k_2, min^{-1}	t_1, min	k_1, min^{-1}	k_2, min^{-1}
0	—[a]	0.271	—[a]	—[a]	0.274	—[a]
2.50	—[a]	0.217	—[a]	—[a]	0.250	—[a]
3.75	—[a]	0.150	—[a]	—[a]	0.150	—[a]
5.00	20	0.020	0.056	36	0.042	0.076
6.25	115	0.008	0.033	114	0.008	0.025

[a] A single straight regression line with slope = k was obtained.

melting of asperities and, in the present systems, of the gelatin binding agent; on cooling, they would solidify to form strong bonds between the particles (18). The amount of bonding that would take place and, therefore, the strength of the tablet would be expected to depend *in part* on the amount of gelatin present.

As observed previously (6), the 300-mg deep biconvex tablets spontaneously capped when subjected to the diametral compression test, presumably because of their very thin edges. These tablets are known to be subject to capping in production. However, the higher the gelatin concentration in the formulations, the higher was the packing fraction to which the tablets could be compressed before capping occurred (Table II). Therefore, to overcome the tendency of the 300-mg biconvex oxytetracycline tablets to cap during production, a reasonably high concentration of gelatin should be incorporated into the formulation.

Small changes in the packing fraction of oxytetracycline tablets containing the same gelatin concentration and prepared at the same nominal pressure setting of the machine produced wide variations in their dissolution profiles (Fig. 3). This effect could also account for the reported variations in the dissolution rates of oxytetracycline tablets from different manufacturers and between or within batches obtained from one manufacturer (3, 4).

Besides bond formation, another mechanism that might contribute to the observed increases in both the disintegration and dissolution times of the tablets with an increase in gelatin content (Table III and Fig. 4) might be the formation of a thin film of gelatin around the powder particles or granules; its thickness would depend on the quantity of gelatin employed. This thin film could subsequently be converted into a mucilaginous viscous barrier when the tablets and breakup fragments contacted the test media (19), which would increase their disintegration and dissolution times. The greater rate of disintegration than of dissolution (Table III) was as expected, since the disintegration tests only measured the time for the tablets to break into granules or particles that could pass through a No. 10 mesh screen while dissolution tests measured the time for the oxytetracycline particles to dissolve from the intact tablets, fragments, granules, or aggregates.

Analysis of the dissolution results showed that the oxytetracycline tablets containing less than 5% (w/w) gelatin conformed satisfactorily to Wagner's (7) concept of a log-normal distribution plot, since linear graphs were obtained for these samples (Fig. 5). [Wagner (7) obtained linear plots on results obtained by various other workers using, for example, tablets of buffered aspirin, griseofulvin, and potassium chloride.] When more than 5% (w/w) gelatin was present, the graphs became curved and exhibited kinks when linearized by the first-order method of plotting (Fig. 6).

The value of a Wagner plot (Fig. 5) (7) is that it enables a dissolution rate to be described in terms of two parameters: the medium $t_{50\%}$ and the standard deviation. One can also obtain values of $t_{20\%}$, $t_{90\%}$, *etc.*, from these plots. Under theoretically ideal circumstances, when a tablet disintegrates and liberates the primary particles of drug, the dissolution rate is limited by the effective surface area of the particles. On this basis, Wagner (7) suggested that both the $t_{50\%}$ and standard deviation values might provide information on the likely behavior of tablets in *in vivo* tests, but this suggestion has not yet been confirmed.

Analysis by the Kitazawa *et al.* (8) method showed that tablets compressed to a packing fraction of approximately 0.80 and containing less than 5% (w/w) gelatin yielded straight lines, with one dissolution rate constant, k, in each case (Fig. 9). These tablets broke up rapidly into small particles as soon as they were in contact with the dissolution medium, resulting in a sudden increase in surface area and a subsequent constant decrease as the granules dissolved.

However, for tablets containing 5 and 6.25% (w/w) gelatin, the dissolution rate constants changed from k_1 to k_2 at certain times, t_1, at all packing fractions (Figs. 8 and 9). Similar observations were obtained with tablets containing less than 5% (w/w) gelatin when their packing fractions were either below 0.75 or above 0.85 (Fig. 7). This change in the dissolution rate constant is ascribed to an increase in surface area due to break-up of the tablets into large and small fragments at time t_1. The changes in the dissolution rate profile with packing fraction (Fig. 7 and Table IV) showed that the dissolution rate was a maximum (6) at packing

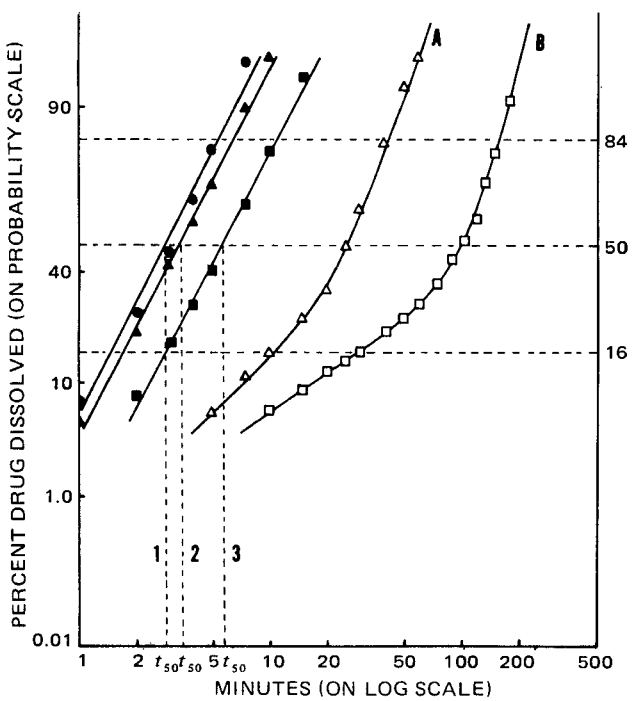

Figure 5—*Wagner plot of dissolution results on tablets ($\rho_f \doteq 0.80$) prepared with a single-punch machine.*

key	gelatin content, % (w/w)	mean (ρ_f)	t_{50}, min	σ
●	0	0.79	2.8	1.93
▲	2.50	0.80	3.3	1.94
■	3.75	0.80	5.6	1.93
△	5.00	0.80	—	—
□	6.25	0.80	—	—

1, σ = 1.93; 2, σ = 1.94; 3, σ = 1.93

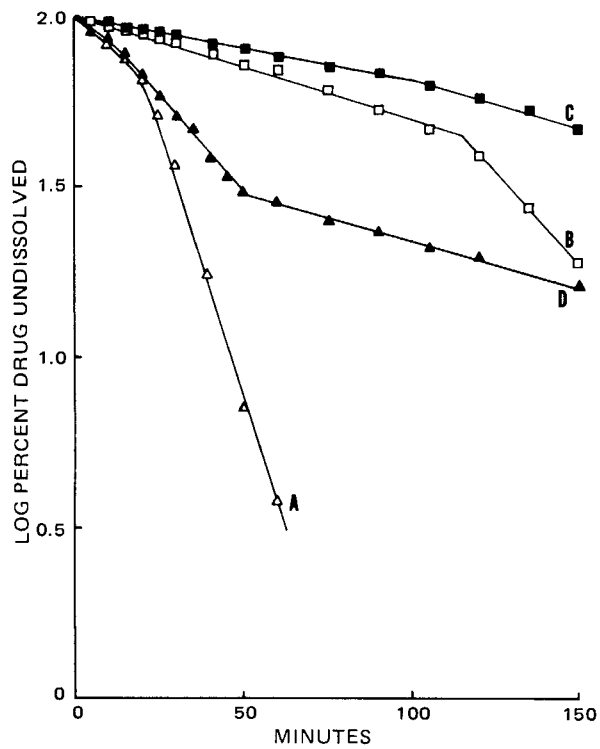

Figure 6—*Apparent pseudo-first-order plot for tablets that did not conform to the Wagner plot.*

key	machine used for preparing tablets	gelatin content, % (w/w)	k value of first section, min^{-1}	k value of second section, min^{-1}
A	single punch	5.00	0.069	—
B	single punch	6.25	0.007	0.025
C	multipunch	6.25	0.004	0.007
D	hydraulic press	5.00	0.026	0.006

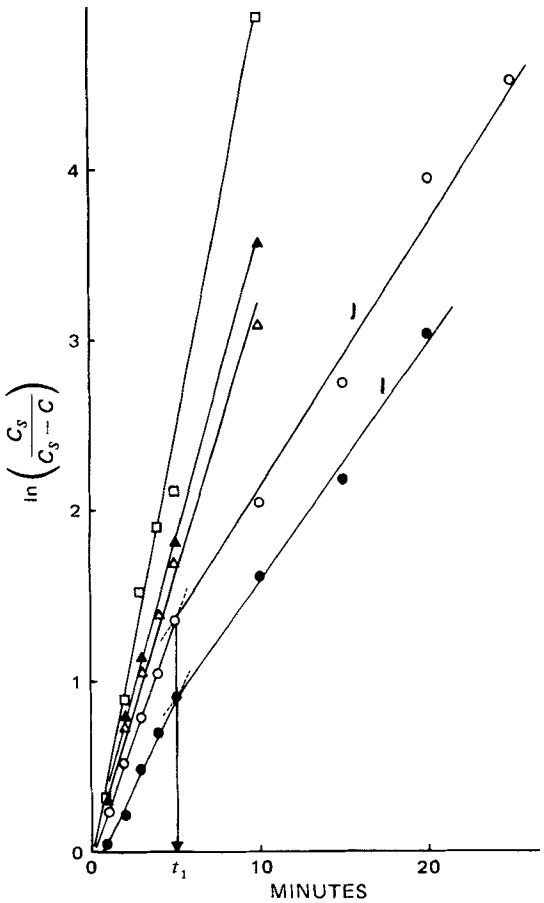

Figure 7—*Determination of dissolution rate constants of oxytetracycline tablets using Eq. 2. The tablets had 0% (w/w) gelatin and were prepared at different packing fractions with the hydraulic press. Key (packing fraction, ρ_f): ○, 0.73; △, 0.81; □, 0.86; ▲, 0.87; and ●, 0.92.*

fractions between 0.75 and 0.85. This maximum was not observed for the formulation containing povidone as the binding agent (5), illustrating the need for a detailed reinvestigation each time a tablet formulation is

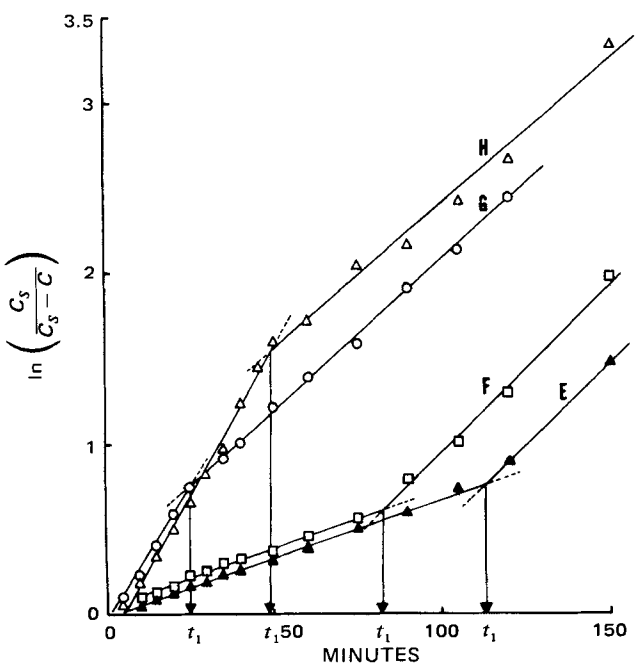

Figure 8—*Determination of dissolution rate constants of oxytetracycline tablets using Eq. 2. The tablets had 5% (w/w) gelatin and were prepared at different packing fractions with the hydraulic press. Key (packing fraction, ρ_f): ○, 0.70; △, 0.79; □, 0.83; and ▲, 0.86.*

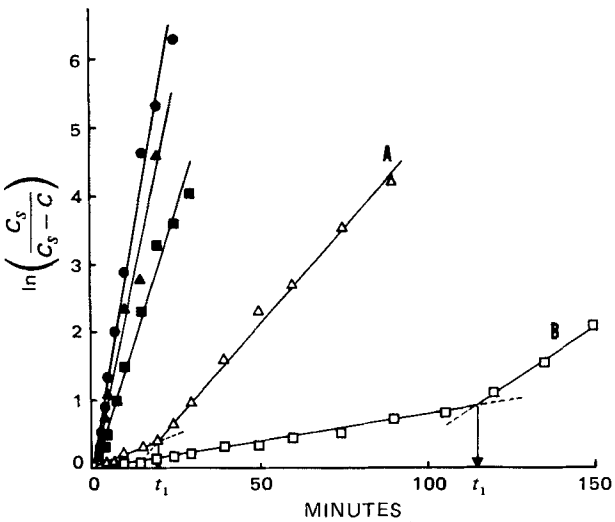

Figure 9—*Effect of gelatin content on the determination of dissolution rate constants using Eq. 2 for oxytetracycline tablets prepared with a single-punch machine at ρ_f 0.80. Key: ●, 0% (w/w) gelatin and 0.79 mean ρ_f; ▲, 2.50% (w/w) gelatin and 0.80 mean ρ_f; ■, 3.75% (w/w) gelatin and 0.80 mean ρ_f; △, 5.00% (w/w) gelatin and 0.80 mean ρ_f; and □, 6.25% (w/w) gelatin and 0.80 mean ρ_f.*

altered. The times corresponding to the kinks in Fig. 6 were identical with the t_1 values obtained from Figs. 8 and 9 because Eqs. 1 and 2 were both derived from the same basic equation of Noyes and Whitney (20):

$$\frac{dC}{dt} = k(C_s - C) \qquad \text{(Eq. 3)}$$

where the symbols are as defined for Eq. 2.

Visual observations during the tests confirmed that in the first sections (*i.e.*, up to times t_1) in graphs A–C in Figs. 6 and 9 and in graphs E and F in Fig. 8, dissolution was occurring from intact tablets; the second sections (*i.e.*, after times t_1) represented dissolution from broken fragments of the tablets. The tablets whose results are shown in graph D of Fig. 6 and in graphs G–J of Figs. 7 and 8 initially broke up quite rapidly into fairly large fragments, and these fragments then broke up into smaller fragments very slowly. Similar conclusions were reached by Kitazawa *et al.* (8).

In contrast to their results (8) on caffeine tablets, no good correlation was obtained between the values of t_1 and disintegration time or between k_1 and k_2 for the oxytetracycline tablets investigated. The disintegration times of these tablets were less than the t_1 values, possibly because in the present work [in contrast to that of Kitazawa *et al.* (8)] more vigorous agitation was employed in the disintegration test than in the dissolution test.

Irrespective of the tableting equipment employed, the values of k for

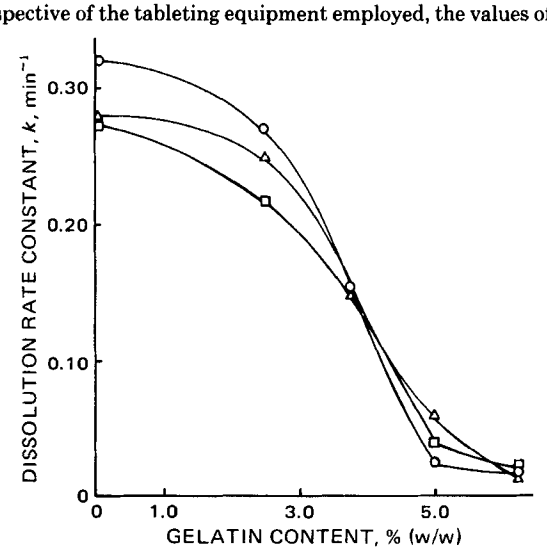

Figure 10—*Effect of gelatin content on the k values calculated using Eq. 2 for tablets prepared with the three types of machines at $\rho_f \simeq 0.80$. Key: ○, hydraulic press; □, single punch; and △, multipunch.*

all tablets decreased with their binding agent content (Fig. 10). Although this finding is similar to a previous one where povidone was substituted for gelatin (5), it is also clear that the nature of the binding agent has a profound effect on the dissolution characteristics of a formulation.

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Micellar Distribution Equilibria: Ultracentrifugal Study of Apparent Partition Coefficients

JUNG Y. PARK * and EDWARD G. RIPPIE *

Abstract □ Ultracentrifugation was used for the partial isolation of polysorbate 80 micelles in aqueous media to determine the apparent partition coefficients of various drug species between water and the micellar pseudophase. The ratio of solute concentration in the micelles to that in water was measured for procaine, salicylic acid, sulfapyridine, sulfisoxazole, and sodium 2-naphthalenesulfonate over ranges of pH, surfactant concentration, drug concentration, and micelle sedimentation. Apparent partition coefficients for the systems investigated were independent of both drug concentration and surfactant concentration, indicating that the mode(s) of surfactant–drug interaction are essentially invariant over the ranges of systematic variables studied. The method provides a relatively simple and rapid means of quantitatively evaluating drug–surfactant interactions above the CMC, when surfactant and solute can be assayed in mixtures without interference.

Keyphrases □ Micellar distribution—ultracentrifugal study of apparent partition coefficients of various drugs between water and micellar pseudophase □ Partition coefficients, apparent—various drugs between water and micellar pseudophase, ultracentrifugal study □ Ultracentrifugation—determination of apparent partition coefficients of various drugs between water and micellar pseudophase □ Solute–micelle interactions—ultracentrifugal study of apparent partition coefficients of various drugs between water and micellar pseudophase

Much experimental evidence relating to the mechanisms of interactions between secondary solutes and surfactant micelles is obtained from measurements of the magnitude of solute–micelle interactions and their dependence on variables such as concentration, ionic strength, temperature, and pH. Experimental techniques often introduce inherent systematic errors. Methods such as dialysis, gel filtration, and ultrafiltration, which are based on the mechanical or physicochemical isolation of the micellar pseudophase from the aqueous phase (1, 2), require the use of semipermeable membranes, selectively permeable gels, or other materials that may interact with various components and perturb the system beyond the desired separation.

The micellar isolation or separation process also may result in the destruction of the micellar structure of the surfactant system by concentrating the surfactant until it separates as a true second phase. Solute–micelle interactions also were studied extensively through the solubilization resulting from such interactions (3–6). While this latter method overcomes the problems previously mentioned, it is limited to a single thermodynamic activity for a given solute.

The analytical ultracentrifuge was used to determine the molecular weight, size, and molecular interactions of micelles (7, 8) and to determine the partition coefficients of drugs between liquid and liquid crystalline phases (9) that have been caused to separate. Ultracentrifugation offers the capability of either complete or partial micellar isolation without membranes or other added components within a reasonably short experiment time. The present paper investigates the feasibility of determining solute–micelle interactions, over a range of both solute and surfactant concentrations, using a moderate partial micelle separation by ultracentrifugation. Previously studied systems of aqueous polysorbate 80 solutions containing