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DISSOLUTION OF HARD GELATIN CAPSULES I. SIMPLE METHOD FOR CALCULATING THE RATE CONSTANT

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SUMMARY

This paper describes a simple method for calculating the dissolution rate constant from cumulative per cent dissolved–time data. The method is based on a semi-logarithmic plot of the successive increments in the cumulative per cent dissolved during equal sampling intervals (ΔA) against $t_{mid} - t_0$ (time taken at mid-interval – time at which ΔA reaches maximum and begins decreasing with time). The applicability of such a method for the determination of dissolution rate constant is tested against 7 capsule and one tablet formulations. The advantage of this method lies in the fact that the cumulative per cent dissolved at time = ∞ (A_∞) need not be known.

INTRODUCTION

The most commonly employed techniques for the determination of the dissolution rate constant for tablets and capsules are the methods for Wagner (1969) and Gibaldi and Feldman (1967). For both of these methods, the amount of drug dissolved at time = ∞ (A_∞) must be known. However, in a number of cases, dissolution tests are not carried out long enough to obtain a good estimate for A_∞, or one may desire, for practical reasons, to stop the test before completion. In such instances, non-linear regression analysis of the cumulative amount dissolved–time data can be applied using an appropriate computer program (El-Yazigi, 1978). However, such a program may not be available at hand, and the determination of the dissolution rate constant therefore may not be possible. This report describes a simple technique for the determination of the dissolution rate constant for capsules without the use of a computer program and in which A_∞ need not be known.

THEORETICAL

Under sink conditions, the rate of dissolution dA/dt may be expressed as

$$dA/dt = K \cdot S \cdot C_s \quad (1)$$

where K is a constant, S is the surface area of contact between the dissolving solid and the solvent, and C_s is the solubility of the solid in the solvent. For capsules, at time, t = 0, the drug is completely enclosed in the capsule shell, hence S = 0. As the gelatin shell begins to dissolve, S commences to increase until it reaches a maximum and begins decreasing with time at $t = t_0$. At $t \geqslant t_0$, the effective surface area begins to decrease and may be assumed proportional to the amount remaining to be dissolved $[(A_\infty - A_0) - A]$, or

$$S = k[(A_\infty - A_0) - A] \text{ for } t \geqslant t_0 \tag{2}$$

where A_∞, A_0, and A are the amounts of drug dissolved at $t = \infty$, $t = t_0$ and t = t, respectively, and k is a proportionality constant. Substituting for S in Eqn. 1 yields:

$$dA/dt = k_s[(A_\infty - A_0) - A] \text{ for } t \geqslant t_0 \tag{3}$$

where k_s is a constant equal to $(k \cdot K \cdot C_s)$ and has dimensions of reciprocal time. Solving Eqn. 3 by integrating between the limits $t = t_0$ and t = t and re-arranging yields:

$$\ln [(A_\infty - A_0) - A] = \ln (A_\infty - A_0) - k_s(t - t_0) \text{ for } t \geqslant t_0 \tag{4}$$

If one takes two successive readings at time = t and time = t + Δt and transforms Eqn. 4 into exponential form, one obtains:

$$(A_\infty - A_0) - A_t = (A_\infty - A_0)\, e^{-k_s(t-t_0)} \tag{5}$$

and

$$(A_\infty - A_0) - A_{t+\Delta t} = (A_\infty - A_0)\, e^{-k_s(t+\Delta t-t_0)} \tag{6}$$

Subtracting Eqn. 6 from Eqn. 5 yields:

$$A_{t+\Delta t} - A_t = \Delta A = (A_\infty - A_0)\,(1 - e^{-k_s\Delta t})\, e^{-k_s(t-t_0)} \tag{7}$$

Taking the logarithm of both sides of Eqn. 7 yields:

$$\ln \Delta A = \ln \{[A_\infty - A_0]\,[1 - e^{-k_s\Delta t}]\} - k_s(t - t_0) \tag{8}$$

If Δt is constant for any run, then $\{[A_\infty - A_0][1 - e^{-k_s\Delta t}]\}$ is constant, and a plot of ln ΔA against $t_{mid} - t_0$, where t_{mid} is the time at mid-interval, should yield straight line with slope equal to $-k_s$ and intercept equal to ln $\{[A_\infty - A_0]$ $[1 - e^{-k_s\Delta t}]\}$. It should be noted that Eqn. 8 is a first-order rate equation, and somewhat analogous to the equation used in Guggenheim's method for the determination of the first-order rate constant for chemical reactions (Bell, 1967).

MATERIALS AND METHODS

Seven capsule and one tablet formulations were utilized in the dissolution tests. A list of these formulations appears in Table 1. Capsules containing aspirin (150 mg), quinidine

TABLE 1

LIST OF FORMULATIONS TESTED

Formulation	Drug	Dosage form	Strength (mg)	Manufacturer
I	Chloramphenicol	Capsule	250	Park-Davis
II	Ampicillin trihydrate	Capsule	250	Bristol Italiana
III	Tetracycline · HCl	Capsule	250	Lagap
IV	Tetracycline–PO_4 complex	Capsule	250	Bristol Italiana
V	Isoniazid	Tablet	50	Roche
VI	Aspirin	Capsule	150	*
VII	Quinine-SO_4	Capsule	125	*
VIII	Quinidine-SO_4	Capsule	100	*

* Prepared manually.

sulphate (100 mg), and quinine sulphate (125 mg) were prepared manually using the appropriate capsule shell size and without the addition of any excipients. Chloramphenicol (B.D.H., U.K.), tetracycline · HCl (Sigma, U.S.A.), ampicillin anhydrous (Upjohn, U.S.A.), isoniazid (B.D.H., U.K.), quinine sulphate (B.D.H., U.K.), quinidine sulphate (Merck, W. Germany), and aspirin (Merck, W. Germany) were used as obtained. The commercial products studied were purchased from local pharmacies.

Dissolution test

Dissolution tests were carried out using the U.S.P. XIX dissolution apparatus at various stirring rates, viz. 25, 50, or 100 rpm. Distilled water maintained at 37 ± 0.1°C was used as dissolution medium. Samples were taken at 5-min intervals and analyzed spectrophotometrically at the wavelength of maximum absorption for each drug, after suitable dilution.

RESULTS AND DISCUSSION

The mean cumulative per cent of labelled content dissolved–time obtained for the formulations studied are given in Fig. 1.

The successive increments in the cumulative per cent dissolved during 5-min intervals (ΔA) were calculated from the cumulative per cent of the labelled content dissolved–time data, and plotted semi-logarithmically against $t_{mid} - t_0$ (time at mid-interval – time at which ΔA reached a maximum) using least-square regression analysis. The slope of the resulting straight line is equal to $-k_s$. Table 2 lists the values of the dissolution rate (k_s) for all the formulations used as an average of 6 determinations. For most experiments, t_0 was 5 min, and in no case did it exceed 10 min. In the few experiments in which t_0 reached 10 min, slow dissolution of the capsule shell was observed.

As can be seen in Fig. 2 which shows a representative semi-logarithmic plot of ΔA vs $t_{mid} - t_0$, the dissolution data were adequately described by Eqn. 8. It should be noted,

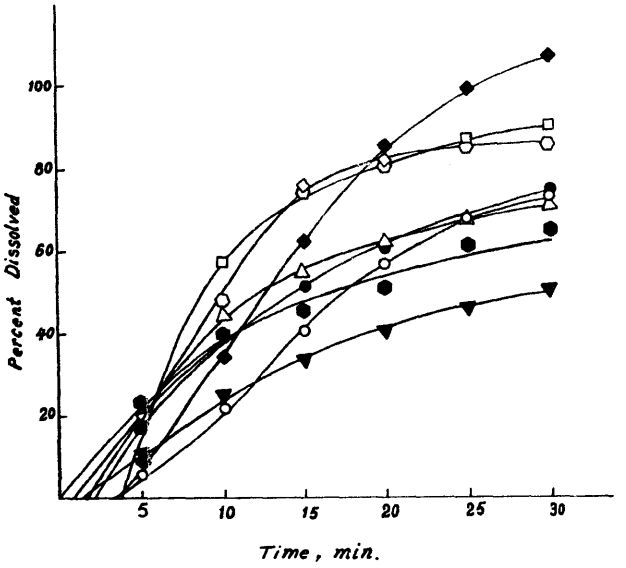

Fig. 1. Mean cumulative per cent of labelled content dissolved–time profiles for the formulations studied; n = 6. Key: I (●), II (▼), III (●), IV (♦), V (○), VI (○), VII (△), VIII (□).

however, that the k_s values presented in Table 2 reflect mainly the dissolution rate of the capsule content since the first data point(s) which is primarily a function of the dissolution rate of the capsule shell was not included in the plot. This is also the case with Wagner's approach for the determination of k_s where only the terminal points are included in the $\log(A_\infty - A)$ vs t plot (Wagner, 1969).

In comparing this to Wagner's approach, the data of one randomly selected unit (capsule or tablet) from each formulation studied were subjected to both treatments, and the dissolution rate constant was calculated and presented in Table 3. When Wagner's

TABLE 2

DISSOLUTION RATE CONSTANTS FOR THE FORMULATIONS TESTED CALCULATED ACCORDING TO EQN. 8

Formulation	Dissolution rate constant (k_s) (min^{-1})	S.D.
I	0.0743 [a]	0.0210
II	0.0966	0.0416
III	0.0664	0.0250
IV	0.0744	0.0249
V	0.140	0.033
VI	0.0850	0.0351
VII	0.101	0.014
VIII	0.151	0.024

[a] Mean of 6 determinations.

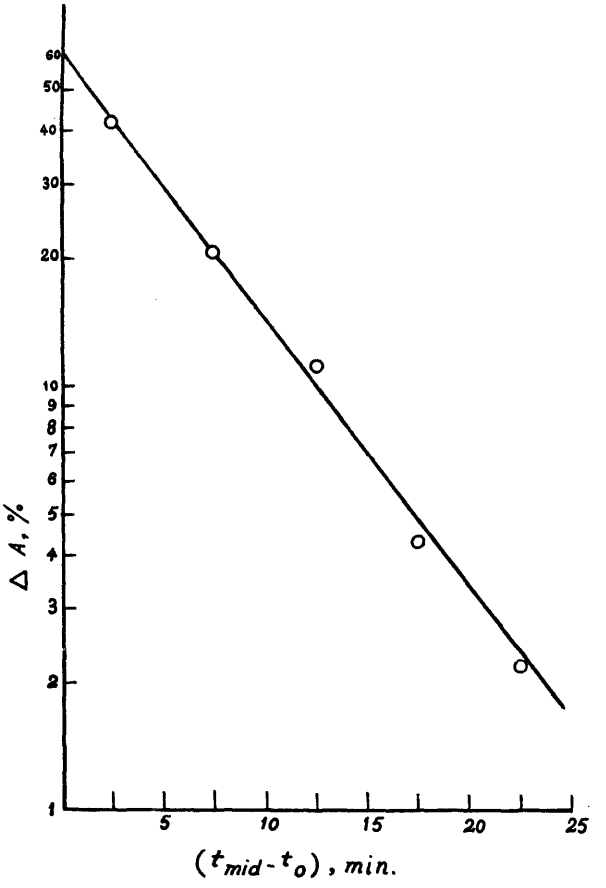

Fig. 2. Representative semi-logarithmic plot of the successive measurements in per cent dissolved in 5 min (ΔA) vs time taken at mid-interval-time needed for ΔA to begin decreasing with time ($t - t_0$) obtained for a randomly selected capsule of formulation VIII.

method was used, ln ($A_\infty - A$) was plotted against ($t - t_0'$) using least-square linear regression, and the slope of the resulting line is equal to $-k_s$ according to the following equation:

$$\ln (A_\infty - A) = \log M - k_s(t - t_0') \text{ for } t \geqslant t_0' \tag{9}$$

where M is a constant and t_0' is the time at which the apparent first-order dissolution phase commences. The calculation and plotting was first carried out by giving A_∞ the value of 100 and later by giving it the value of the last data point obtained. The value of t_0' was either 0 or 5 min.

As can be seen in Table 3 which lists the values of the dissolution rate constant (k_s) as obtained by these two approaches, the values obtained by the approach described here are somewhat greater than the values obtained by Wagner's approach when A_∞ was given the value of 100 and generally similar but occasionally smaller than the values obtained

TABLE 3

DISSOLUTION RATE CONSTANTS FOR A RANDOMLY SELECTED UNIT OF EACH FORMULATION TESTED CALCULATED ACCORDING TO EQNS. 8 AND 9

Formulation	k_s (calculated according to Eqn. 8 [a]) (min^{-1})	k_s (calculated according to Eqn. 9 [b])	
		(min^{-1}) [c]	(min^{-1}) [d]
I	0.0567	0.0754	0.0559
II	0.129	0.130	0.0264
III	0.0820	0.0799	0.0292
IV	0.0661	0.0795	0.0827
V	0.103	0.135	0.0981
VI	0.100	0.117	0.0720
VII	0.0908	0.116	0.0886
VIII	0.121	0.148	0.109

[a] The equation developed here.
[b] Wagner equation (1969)
[c] Values of k_s calculated according to Eqn. 9 assuming A_∞ is equal to the value of A of the last data point obtained.
[d] Values of k_s calculated according to Eqn. 9 assuming $A_\infty = 100$.

when A_∞ took the value of the last data point obtained. It is apparent therefore, that if one were to determine k_s accurately according to Eqn. 9, a good estimate for A_∞ must be known, a requirement that can be eliminated if the approach described here is employed.

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