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PHYSICAL MODEL FOR RELEASE OF DRUG FROM GELFORMING SUSTAINED RELEASE PREPARATIONS

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SUMMARY

Certain sustained release preparations contain a substance which, when exposed to an aqueous medium, forms a gel. Liquid will continue to penetrate the gel layer with time (θ) and the release of drug is both a function of liquid penetration rates (α) and diffusion of drug through the gelled layer (with a permeation coefficient of Π). The thickness of the layer will be a function of time, because as liquid penetrates, more gel is formed. Development of this model leads to a third-power equation for the amount of drug released (m) as a function of time: $m = a\theta^3 + b\theta^2 + c\theta$; the coefficients a, b and c contain an integral: $\int_0^1 \exp[(-\pi/\alpha)(1/u)du$ which is evaluated graphically and found equal to $0.93 \exp[-2.6\pi/\alpha]$. The data by Bamba et al. (1979) were used to demonstrate that the fit of experimental data to the third-power equation is a good as or superior to conventional plotting techniques.

INTRODUCTION

The release of drug from a matrix which contains gelforming substances has been investigated experimentally by Bamba et al. (1979). When wetted the water will penetrate the tablet, and a gelation will occur in the wetted layer. These authors showed that when quinine sulfate is the drug in the preparation, then the gelation and dissolution kinetics are not rate-limiting, but both the diffusion of water into the tablet, and the diffusion of the dissolved drug substance out of the wetted portion are rate-limiting. This gives rise to the interesting situation where the release is a function of *two* different processes, *both* through a film of time-dependent thickness. It is the intent of this note to propose the appropriate model and data treatment for this situation.

THE PHYSICAL MODEL

A tablet containing M grams of drug per cm^3 of tablet is considered. The tablet is exposed to the dissolving liquid at time zero. As shown in Fig. 1A, the depth of penetra-

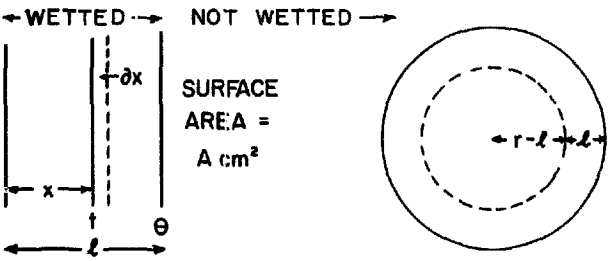

FIG 1A FIG 1B

Fig. 1. Schematic for water penetration (A) in a plane and (B) in a sphere.

tion at time t is x and at time θ is ℓ. The radius of the tablet is L cm, so that the radius of unwetted tablet at time θ is $L - \ell$.

THE MATHEMATICAL MODEL

The situation at time θ is depicted in Fig. 1. The level x will have been reached at time t, and hence drug dissolved at this point will have diffused for a period of $(\theta - t)$ s, hence the concentration, C(x) (provided there is no volume change) is given by

$$C(x) = M \exp[-\zeta(\theta - t)] \tag{1}$$

where the term ζ is a diffusion constant. This is inversely proportional to the thickness of the wetted gelled film through which the diffusion takes place, i.e.

$$\zeta = \Pi/x \tag{2}$$

where Π is a permeation constant. The described model considers each segment dx independent of the others, i.e. it assumes that Π is concentration independent. The amount of drug, dQ, at time θ is the volume element at $\{x | x + dx\}$ of cross-section A cm^2 can be derived from Eqns. 1 and 2 and is:

$$dQ = A\,dx\,M \exp[-(\Pi/x)(\theta - t)] \tag{3}$$

The amount remaining in the wetted layer (which at time θ is ℓ cm thick) is then given by:

$$Q = M\int_0^{\ell} A \exp[-(\Pi/x)(\theta - t)]\,dx \tag{4}$$

Bamba et al. (1979) have shown that the amount of the unwetted portion can be approximated by either a σ^--function or a cube root function. In the latter case (Carstensen and Musa, 1972) the 'radius' of the tablet decreases linearly with time, i.e.

$$\theta = \ell/\alpha \tag{5a}$$
$$t = x/\alpha \tag{5b}$$
$$\text{and } A = (L - \ell)^2 4\pi \tag{5c}$$

where L is the 'radius' of the tablet, and where α is a constant (cm/s). Introducing Eqn. 5 into the integrand gives it the form:

$$\exp[-(\Pi/x)(\theta - t)] = \exp[-\Pi/x)\theta] \exp[(\Pi/x)t] = \exp[-(\Pi/x)(\ell/\alpha)] \exp(\Pi/\alpha) \quad (6)$$

Eqns. 5 and 6 are introduced into Eqn. 4 and it is noted that this *applies to time* θ, i.e. as far as Eqn. 4 is concerned at this point, ℓ is a defined and constant quantity which does not come into the integration:

$$Q = M\, 4\pi(L - \ell)^2\, e^{\Pi/\alpha} \int_0^{\ell} \exp[-(\Pi/\alpha)(1/\{x/\ell\})]\, dx \quad (7)$$

The substitution $u = x/\ell$ is now made. It follows that the upper limit is at $u = 1$ and that $dx = (1/\ell)du$, so that Eqn. 7 becomes

$$Q = M\, 4\pi(L - \ell)^2\, e^{\Pi/\alpha}\, \ell \int_0^{1} \exp[-(\Pi/\alpha)(1/u)\, du \quad (8)$$

The integral in Eqn. 8 is not readily solved in closed form. Plots of the integrand:

$$F(u) = e^{-(\Pi/\alpha)(1/u)}$$

as a function of u are shown in Fig. 2 for various values of Π/α. It is noted that at the lower limit ($u = 0$) $e^{-\infty} = 0$, so that the curves all are (a) positive and (b) intersect at zero. For $u = 1$, the value is $e^{-\Pi/\alpha}$ and the function has no extrema in the interval $0 < u \leqslant 1$, so

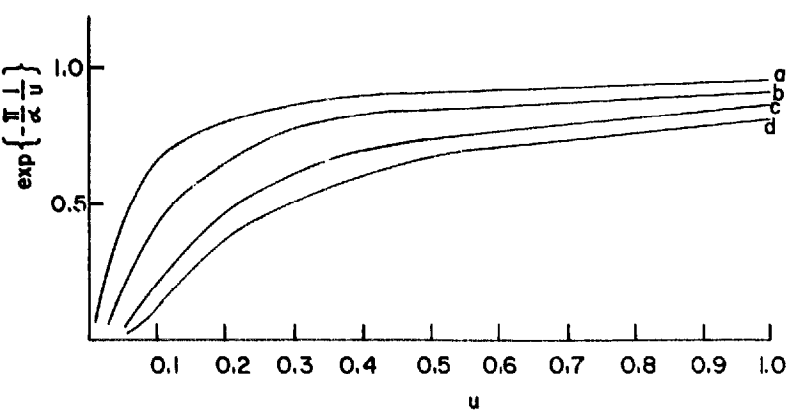

Fig. 2. Examples of the function $\exp(-\Pi/\alpha)(1/u)$ versus u, for selected values of (Π/α). a: $(\Pi/\alpha) = 0.04$; b: $(\Pi/\alpha) = 0.08$; c: $(\Pi/\alpha) = 0.15$; and d: $(\Pi/\alpha) = 0.2$. For graphical clarity, oniy 4 of the 8 values shown in Fig. 3 are shown in Fig. 2.

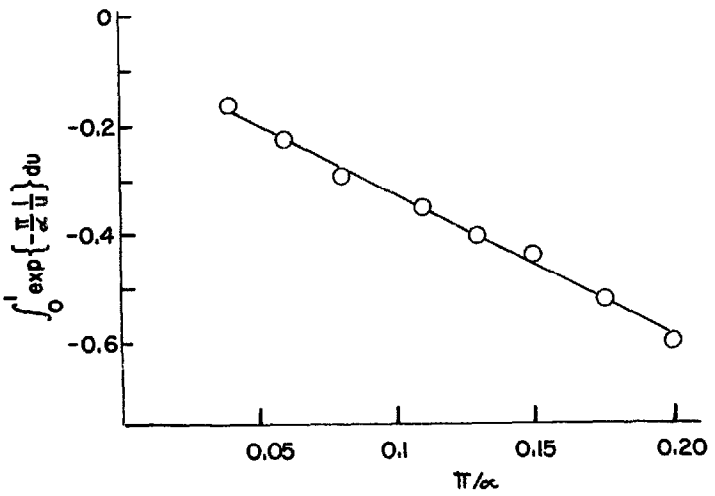

Fig. 3. Areas underneath the curves in Fig. 2 shown in logarithmic form as a function of Π/α.

that the area under the curve $f\{\Pi/\alpha\}$ in the interval stated is

$$0 < f\{\Pi/\alpha\} = \int_0^1 F(u)\,du < e^{-\Pi/\alpha}$$

The areas in Fig. 2 have been estimated graphically and are plotted in Fig. 3 and (in the ranges of Π/α values used) follow the relation:

$$f\{\Pi/\alpha\} = \int_0^1 F(u)\,du = 0.934\, e^{-2.592(\Pi/\alpha)}$$

The correlation coefficient for the logarithmic form of this equation (8 points as shown in Fig. 3) is 0.994.

The important point is that the integrals have a finite positive value which is a function of π/α. This is denoted $f\{\pi/\alpha\}$ in the following, the letter 'f' denoting 'function'. Eqn. 8 can now be written:

$$Q = M\,4\,\pi(L-\ell)^2\, e^{\Pi/\alpha\ell}\, f\{\Pi/\alpha\} \tag{9}$$

The amount of drug released at time θ is the amount originally present in the wetted layer (Q_0) less that present at time θ. Q_0 is given by:

$$Q_0 = (4/3)\pi M\,[L^3 - (L-\ell)^3] \tag{10}$$

Combining Eqns. 9 and 10 gives:

$$Q_0 - Q = 4\pi M e^{\Pi/\alpha} f\{\Pi/\alpha\}[-\ell L^2 + 2\ell^2 L - \ell^3] + (4/3)\pi M[3L^2\ell - 3L\ell^2 + \ell^3] \tag{11}$$

Introducing Eqn. 5a into this then gives the expression for m, the percent released as being cubic in time:

$$m = a\theta^3 + b\theta^2 + c\theta \tag{12}$$

where

$$a = 4\pi M\alpha^3[1 - 3e^{\Pi/\alpha}f\{\pi/\alpha\}]/(0.03Q_0) \tag{13a}$$
$$b = \alpha^2 4\pi M[e^{\Pi/\alpha}f\{\Pi/\alpha\} - 4L]/(0.03Q_0) \tag{13b}$$
$$c = 4\pi M\alpha[L^2 - e^{\Pi/\alpha}f\{\Pi/\alpha\}]/(0.03Q_0) \tag{13c}$$

RESULTS AND DISCUSSION

Data reported by Bamba et al. (1979) are shown in Fig. 4. These are fitted by multiple regression, and the least squares fit values for a, b and c are shown in Table 1. Comparison of goodness of fit is made with the least squares fit parameters obtained from the equation:

$$m = 100 - \exp[d - et] \tag{14}$$

which was the *conventional* equation found by Bamba et al. (1979) to fit the data best. The goodness of fits are compared by the sums of squares of the deviations, $\Sigma(m - \tilde{m})^2$.

TABLE 1

LEAST SQUARES PARAMETERS a, b AND c FROM EQN. 12 AND d AND e FROM EQN. 14 AND s^2 AND s^{*2} (VARIANCE ESTIMATES) FOR THE FORMULAE REPORTED BY BAMBA ET AL. (1979).

Formula	%	a	b	c	s^2	d	e	s^{*2}
Alginate	10	0.187	−2.832	21.74	3.16	−0.20	4.60	5.00
	15	−0.0038	−0.754	15.23	0.61	−0.17	4.60	1.04
	20	−0.26	−0.291	11.82	0.85	−0.13	4.60	1.38
	25	−0.0049	−0.28	9.58	1.52	−0.10	4.60	1.66
	30	−0.085	0.63	5.67	0.59	−0.079	4.60	1.20
	50	−0.19	1.53	2.72	1.49	−0.050	4.60	9.32
	60	−0.044	0.43	2.37	0.06	−0.037	4.61	0.18
Carragheenan	10	0.262	−4.709	32.40	3.03	−0.28	4.55	4.47
	30	0.251	−3.038	15.49	2.96	−0.08	4.56	4.15
	50	−0.065	0.319	4.19	1.31	−0.04	4.59	0.93
Gum Guar	10	0.212	−2.969	19.68	3.53	−0.12	4.57	3.64
	30	0.081	−0.786	6.944	1.83	−0.06	4.60	3.95
	50	0.0000645	−0.273	5.024	0.22	−0.03	4.58	2.02
Carob Gum	50	0.551	−7.565	37.08	13.15	−0.20	4.47	46.0
	60	0.032	−1.215	17.11	0.36	−0.17	4.60	0.59

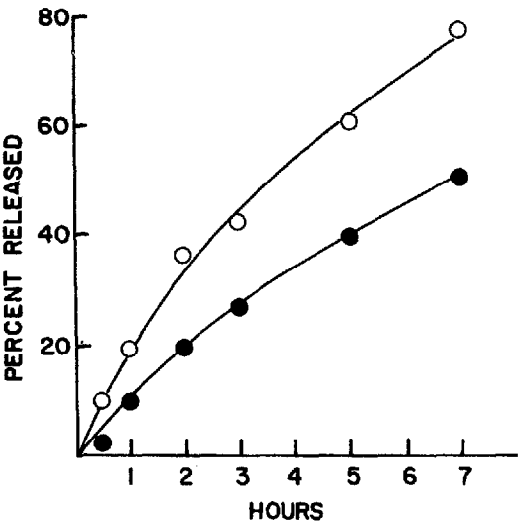

Fig. 4. Release curves of data reported by Bamba et al. (1979) for alginate 10% (○) and for alginate 25% (●). The points are experimental points and the curves the least squares fit curves according to Eqn. 12.

m is here the observed, and $\tilde{m}$ the least squares fit value of the percent of drug released. For the comparisons the sums have been converted into variance estimates by dividing by the number of degrees of freedom, i.e. (s^2) for Eqn. 12 by dividing by $n - 3$ and (s^{*2}) for Eqn. 14 by dividing by $n - 2$. It is noted that the form of Eqns. 12 and 14 are in the same units allowing direct comparison.

It is seen that in general $s^2 < s^{*2}$ so that the fits according to Eqn. 12 are no worse, and probably better than those of Eqn. 14. This superiority is, however, not statistically significant as shown by F-ratios (s^2/s^{*2}) and the conclusion is limited to stating that Eqn. 12 and Eqn. 14 provide fits where one is not preferential over the other. Eqn. 12 however, has a well-defined physical basis, whereas, as found by Bamba et al. (1979), Eqn. 14 simply suggested that two rate processes might be limiting. The adequacy of the fits according to Eqn. 12 are hence taken to support the suggested model.

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