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RELEASE MECHANISMS IN GELFORMING SUSTAINED RELEASE PREPARATIONS

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SUMMARY

A system consisting of quinidine sulfate, excipient and gum (in various concentrations) was tested in tablet form. The insensitivity of this system to (a) the nature of the excipient and (b) the pH of the dissolution liquid is noted. The release mechanism is established as being limited by the rate of water penetration and back diffusion of the dissolved substance, whereas gelation rates and actual dissolution rate of the drug are not rate determining.

INTRODUCTION

A fair amount of attention has been given in the literature to release of medicaments from insoluble matrices (Higuchi, 1963; Cobby et al., 1974a, b; Fessi et al., 1978) as well as to release through fixed membranes (Carstensen, 1973). In some systems (Huber et al., 1966, 1968) the use of a hydrophilic polymer is made. In these cases solvent will penetrate and gel the matrix, the active substance will dissolve and diffuse out through the gel in front of it.

In essense several hyoptheses could be visualized for this; one of the following process could be rate determining: (a) the permeation of water, (b) the gelation rate, (c) the dissolution rate of the drug in the penetrating water, (d) the diffusion rate of the drug in the gel and (e) the Higuchi porous penetration (1963).

It is the aim of this article to present data and interpretations of four such systems, using quinidine sulfate as a model drug.

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TABLE 1

FORMULAE USED

The compression weight is 512 mg and the quinidine sulfate content is 200 mg per tablet. Any of the listed combinations have been made, and are referred to in the following by denoting it with the polymer and the percentage of the polymer.

		Figures are in percent weight by weight						
Drug =	Quinidine sulfate	39	39	39	39	39	39	39
Polymer	Carragheenan [a] Alginate [a] Guar [a] Carob gum [a]	10	15	20	25	30	50	60
Excipient	StaRx 1500 Spraydried lactose	50	45	40	35	30	10	0
Lubricant:	Magnesium stearate	1	1	1	1	1	1	1

[a] Gums obtained from CECA, 11 rue Morane, Saulnier, 78140 Velizy, France.

TABLE 2

PHYSICAL CHARACTERISTICS OF THE TABLETS USED (LACTOSE DILUENT)

Formula	e (Porosity in %)	Friability (in %)	Hardness (in kg force)
Alginate			
10%	24.10	0.90	7.5
15%	23.22	0.85	8.5
20%	22.10	0.95	8.5
25%	21	0.90	9
30%	20.31	0.80	9.5
50%	19.70	0.75	10.5
60%	18.90	0.85	12
Carragheenate			
10%	20.92	0.90	7
15%	17.74	0.80	7.5
20%	17.07	0.95	7.5
25%	15.43	0.95	8
30%	12.30	0.80	8
50%	12.03	1.20	9
60%	11.13	1.20	9.5
Guar			
10%	22.54	0.90	7.5
15%	19.90	0.80	8
20%	19.70	0.80	8.5
25%	15.90	0.90	9
30%	15.30	0.95	9
50%	14.40	0.80	9
60%	13.37	0.90	10
Caroube			
10%	17.63	0.90	9
30%	14.75	0.75	10
50%	13.32	0.85	10
60%	12.03	0.90	10

TABLE 3

COMPARISON OF DISSOLUTION CURVES BY DIFFERENT pH CONDITIONS

The fit used is Eqn. 2, i.e. $\ln[100 - m] = bt + a$. r^2 is the correlation coefficient squared, s^2 is $s_{yx}{}^2$. b is in units of reciprocal hours, a is in units of ln[percent]

Formula	1/2-change				pH 1.2				pH 5.5				pH 7.5			
	–b	a	r^2	$10^4 s^2$	–b	a	r^2	$10^4 s^2$	–b	a	r^2	$10^4 s^2$	–b	a	r^2	$10^4 s^2$
Carragheenan																
10%	0.28	4.55	0.99	36.2	0.28	4.59	0.99	8.9	0.28	4.59	0.99	10.1	0.28	4.59	0.99	12.9
30%	0.08	4.56	0.98	10.5	0.10	4.60	0.99	0.9	0.10	4.60	0.99	1.3	0.10	4.59	0.99	1.04
50%	0.04	4.59	0.97	5.2	0.04	4.60	0.99	1.2	0.05	4.59	0.97	5.2	0.05	4.59	0.97	5.0
Alginate																
10%	0.20	4.60	0.99	27.5	0.13	4.53	0.97	56.6	0.16	4.66	0.96	92.5	0.18	4.68	0.95	217
30%	0.08	4.61	0.99	5.9	0.07	4.59	0.99	2.3	0.06	4.58	0.98	4.5	0.06	4.58	0.98	5.2
50%	0.05	4.60	0.97	13.3	0.04	4.59	0.94	9.7	0.04	4.60	0.95	8.1	0.04	4.60	0.97	4.6
Gum guar																
10%	0.12	4.57	0.99	12.0	0.15	4.59	0.99	4.1	0.15	4.59	0.99	3.9	0.16	4.59	0.99	5.0
30%	0.06	4.60	0.98	5.9	0.06	4.61	0.99	0.9	0.06	4.61	0.99	1.6	0.06	4.61	0.99	0.6
50%	0.03	4.58	0.98	2.0	0.03	4.61	0.95	7.4	0.04	4.61	0.95	9.3	0.04	4.61	0.90	16.8
Carob gum																
50%	0.20	4.47	0.97	155	0.23	4.53	0.96	117	0.24	4.54	0.98	115	0.24	4.53	0.96	132
60%	0.17	4.60	0.99	1.0	0.18	4.61	0.99	1.7	0.19	4.63	0.99	9.8	0.20	4.63	0.99	18.7

EXPERIMENTAL

Tablets were made with the formulations shown in Table 1.
The tablets were directly compressed on a single punch machine at 512 mg using a 12 mm diameter flat faced punch. The machine was instrumented and the tablets were all produced at a compression force of 4 tons. The hardness of the tablets (Table 2) was in the range 7–12 kg (measured on a Heberlein [1] hardness tester). The friabilities were all below 1.5% and did not differ significantly from formula to formula. The porosities (Table 2) were measured with a mercury porosimeter.

Dissolution studies were made in a continuous flow apparatus [2] with a Dessaga cell and the 1/2-change method (Carstensen, 1977) was used. In a separate experiment (Table 3) dissolution was carried out using the same method but at the constant pH values shown. The assay method using was a UV-spectrophotometric method employing the quinidine absorption peak (in 0.1 N H_2SO_4) at 255 nm.

To evaluate the penetration of liquid, separate experiments were run where tablets were exposed to dissolution for a certain length of time (t' hours) and then removed. The gelatinized part was removed mechanically (with a spatula) and the remaining *dry* portion weighed and analyzed.

DISCUSSION

The practical aim of this study was to evaluate various gums for sustained release purposes in a directly compressed tablet. The purpose of this *writing*, however, is to elucidate which of the five mechanisms (a)–(e) in the Introduction apply to the systems studied.

The first point to be made is that the gums are macromolecular acids and are good buffers and, hence, that the liquid penetrating the tablet on forming a gel will attain a fairly constant pH in the gel, regardless of its original pH. It is therefore not surprising that the release rates of the different formulae are independent (or fairly independent) of the dissolution medium used (Table 3). A slight exception for the alginate must be stated. Dissolution data quoted in the following will always refer to the half-change method. Typical release curves are shown in Fig. 1.

The second point to be made is that there is no significant difference between the tablets made with soluble diluent (spraydried lactose [3]) and those made with insoluble diluent (StaRx 1500 [4]). The evaluation was made by comparing the release figures after 3 h and after 7 h, both via a Friedman rank test (Bennett and Franklin, 1954) and a paired *t*-test. In neither case could, in the assembly of all the formulae produced, a significant difference be demonstrated. From a formulation point of view this is very important, since this fair independence of excipients and of dissolution medium is a sign of a reproducible production item. The formulae reported in the following are solely the lactose formulae.

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[1] Heberlein, Ed. Frogerais, 15 rue de L'yser, Vitry sur Seine, France.
[2] Cellule Dessaga obtained from Roucaire, 20 Avenue Europe, 75140 Velizy, France.
[3] Spraydried Lactose obtained from Seppic, 70 Champs-Elysees, Paris, France.
[4] StaRx 1500 obtained from Expandia, 13 Avenue de l'Opera, 75, Paris, France.

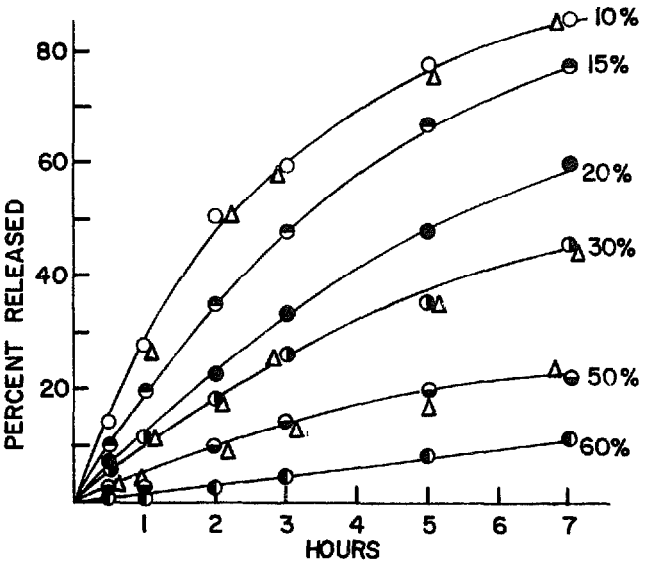

Fig. 1. Release curves of quinidine sulfate from formulae containing carrageenan in various percentages and lactose (circles) and StaRx (triangles). The percentages of carrageenan are indicated by the following symbols: ○ = 10%; ⊖ = 15%; ● = 25%; ◍ = 30%; ⊜ = 50% and ◐ = 60%.

If the dissolution pattern of the drug from the formula is dictated by the actual dissolution of the drug (case c) then a cube root relationship should hold (Eqn. 1 below), if it is dictated by porous penetration then Eqn. 2 below should hold whereas in the other three cases one might expect an equation of the type 3. m in these equations signifies % of drug undissolved, t is time (usually in hours), K designates a cube root dissolution rate constant (mass/time$^{1/3}$), a (time^{-1}) and b are slopes and intercepts of log–linear plots of the type in Eqn. 3, and Q (% per square root of time) is a Higuchi constant.

$$\sqrt[3]{100} - \sqrt[3]{m} = Kt \tag{1}$$

$$100 - m = Q\sqrt{t} \tag{2}$$

$$\ln m = -bt + a \tag{3}$$

To compare the data statistically, the dependent parameter must be in the same form (linear, logarithmic, etc.), and the equations have therefore been recast in the form shown below, for comparison purposes:

$$m = [\sqrt[3]{100} - kt]^3 \tag{1A}$$

$$m = 100 - Q\sqrt{t} \tag{2A}$$

$$m = e^a e^{-bt} \tag{3A}$$

The goodness of fit is evaluated by the residuals s_{yx} (Bennett and Franklin, 1954) and

TABLE 4

COMPARISON OF FITS OF DATA USING THE LEAST SQUARES EQUATIONS (CAROBA GUM 60%):

Eqn. 1A: $\sqrt[3]{100} - \sqrt[3]{m} = 0.227\ t + 0.034$ ($r^2 = 0.997$)
Eqn. 2A: $100 - m = 28.631\ t - 7.55\ s$ ($r^2 = 0.9698$)
Eqn. 3A: $\ln m = -0.1791\ t + 4.6092$ ($r^2 = 0.9996$)

Time (h)	C_{1A} [a]	$\tilde{C}_{1A}$	Δ_{1A}	$\tilde{C}_{2A}$	Δ_{2A}	$\tilde{C}_{3A}$	Δ_{3A}	
0	0	2.2	2.2	−7.6	−7.6	0	0	
0.5	8.2	9.2	1.0	12.8	4.6	8.2	0	
1	16.9	15.9	1.0	28.6	12.3	4.3	0.8	
2	29.2	22.4	0.8	32.8	3.6	29.8	0.6	
3	40.9	39.5	1.4	42.0	1.1	41.3	0.4	
5	59.6	58.2	1.4	56.6	3.0	59.0	0.6	
7	71.2	72.5	1.3	68.3	2.9	71.3	0.1	
$\Sigma\Delta^2/5$			2.618		52.2		0.306	$F_{1-3} = 2.6/0.3 = 8.6 > 5.1 = F_{crit}$ (5%) $F_{2-3} = 52/0.3 = 170 > 11 = F_{crit}$ (1%)

[a] The results are all expressed as amount released (%) and compared with the least squared fits values designated with an over-wiggle and an index corresponding to the equation in the title. The Δ values are the differences between curve and actual points.

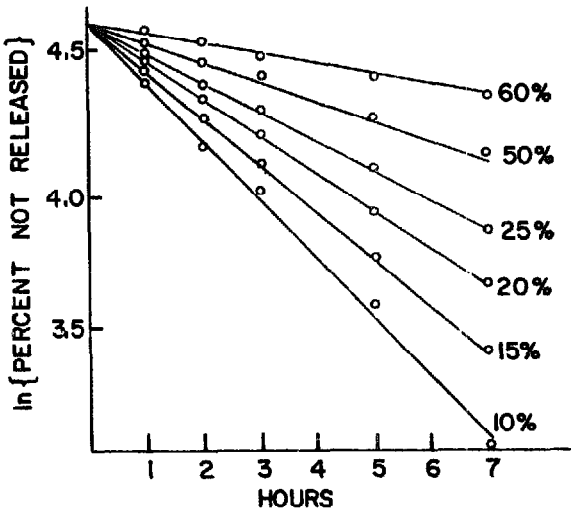

Fig. 2. Release of quinidine sulfate from alginate formulae, plotted according to Eqn. 3. The half-hour points are omitted for graphical clarity. The percent of alginate in the formula is indicated at each line.

are exemplified in Table 4. Eqn. 3A is shown to be significantly better fitting than Eqns. 1A and 2A by *F*-test. It should be pointed out that in no case of the formulae tested did e^a differ significantly from 100. The data for the alginate formula are shown in Fig. 2. The analysis so far rules out dissolution and porous penetration as being the limiting steps in the drug release mechanism. The problem remaining, then is to attempt to evaluate whether it is the water penetration rate, the gelation rate or the drug diffusion rate through the gel which is rate determining.

If *only* water penetration is the explanation, then the amount unwetted (M) should correspond to the amount of drug not released (divided by 0.39) and a plot of one versus the other should be linear with unit slope (provided units are consistent) and zero intercept. The data are plotted in this fashion for three of the formulae in Fig. 3, and it is seen that either linearity or zero intercept is lacking. However, it is still possible to distin-

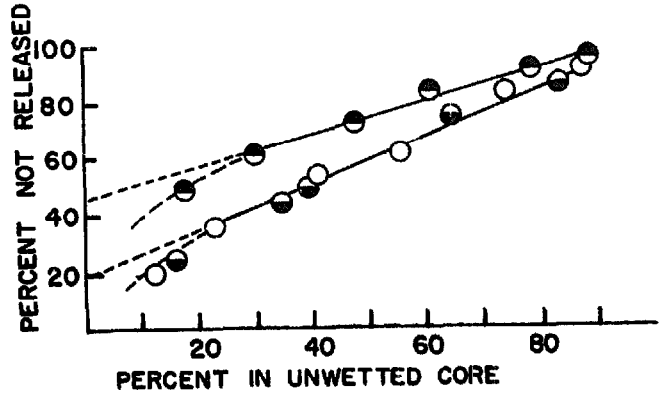

Fig. 3. Percent of drug not released as a function of the amount of unwetted core. Symbols are: ● = gum Guar, ● = alginate and ○ = carragheenan.

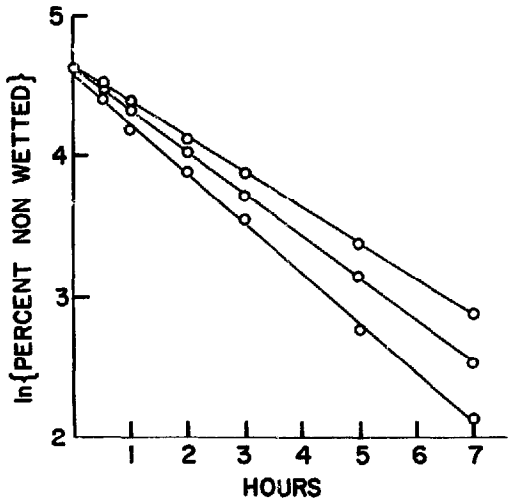

Fig. 4. The logarithm of the amount not wetted as a function of time for the following three formulae: Top = Guar 10%, middle = alginate 10% and bottom = carragheenan 10%.

guish between whether the penetration is diffusion or gelatin controlled. If it is strictly diffusion controlled, then the diffusion equation for the penetration is as given by Jost (1952) and as shown in Eqn. 4 below. r_0 is here the radius of a sphere, and the assumption made at this point is that the tablet can be approximated by a sphere (which of course is a large assumption). D is the diffusion coefficient of water *in the gel.*

$$m'/100 = (\pi/6) \sum_{\nu=1}^{\infty} (1/\nu^2) \exp[-\pi Dt/(\nu^2 r_0^2)] \tag{4}$$

Neglecting experimental higher order terms (Pitkin and Carstensen, 1975) reduces Eqn. 4 to Eqn. 5 below:

$$\ln(m'/100) = -(\pi D/r_0^2)\, t + \ln[(\pi/6) \sum_{\nu=1}^{\infty} (1/\nu^2)] = -(D\pi/r_0^2)\, t \tag{5}$$

Hence the unwetted weight should be log–linear in time and the slope should be given by Eqn. 5. The plots are linear as shown in Fig. 4 [5]. It is now possible to calculate the diffusion coefficient knowing the value of the initial 'radius'. To obtain an estimator for r_0, the radius of the sphere with the same volume as the cylinder has been calculated. It should be noted that a complication exists in that the tablet swells (and the form becomes more spherical) and the volume used has been the average of the volumes at time zero and at 7 h. The diffusion coefficients obtained in this fashion are shown in Table 5 and are of the order $1.5–2.5 \cdot 10^{-6}$ cm^2/s.

[5] It should be noted that in this case the fit of the experimental data to a cube root equation was also fairly good.

TABLE 5

WATER PENETRATION DATA AND CALCULATED DIFFUSION COEFFICIENTS

	Carragheenan 10%	Alginate 10%	Gum guar 10%
Equivalent radius, r_0 cm	0.565	0.585	0.560
Least squares intercept, a	4.576	4.608	4.600
Least squares slope, b	−0.349	−0.295	−0.246
Diffusion coefficient, D cm^2/s	$2.5 \cdot 10^{-6}$	$2.4 \cdot 10^{-6}$	$1.5 \cdot 10^{-6}$

Due to the assumptions made (sphericity) too much emphasis should not be put on the absolute value of these figures, but the fact that they are in the range of usual diffusion coefficients lends credence to the views stated. The interpretation has therefore been reduced to the point where one can state that the two processes (a) and (d), i.e. the diffusion of water into the tablet and diffusion of dissolved drug out or through the gelled layer, are the two processes which together are the limiting processes in the liberation of the drug from the tablet.

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