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DRUG RELEASE FROM POLYMERIC, MULTI-PERFORATED, LAMINATED MATRICES.

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ABSTRACT

The release of drug from a planar matrix through multiple holes in a superimposed impermeable laminate has been predicted by a relationship derived from first principles[1]. In this work, drug release from a laminated matrix has been investigated and fitted to the model. Although zero-order release kinetics are not predicted by the model, zero-order release was observed possibly due to depletion of the drug from the matrix being compensated for by the modification of an essentially planar geometry.

INTRODUCTION

A disadvantage of diffusion controlled matrices is their inability to achieve the ideal of zero-order drug release kinetics[2,3]. A theoretical rationale has been proposed for obtaining zero-order drug release kinetics from a perforated, laminated, non-permeable membrane[4]. However, the required device geometry may not be achievable in practice. A model has now been derived which describes drug release from a planar matrix

which can be fabricated and releases drug through multiple holes in an impermeable laminate (equation 1)[1]:

$$Q = \pi a_i^2 (2DC_s)^{\frac{1}{2}} \rho^{\frac{1}{2}} t^{\frac{1}{2}} + \pi a_i (2DC_s) t + 2/3\pi (2DC_s)^{3/2} \rho^{-\frac{1}{2}} t^{3/2} \qquad \text{equation 1}$$

where Q is the amount of drug released at time, t, D is the diffusion coefficient of the drug in the matrix, a_i is the radius of the hole, C_s is the solubility of the drug in the matrix and ρ is the weight of drug per unit volume of matrix.

In this work we have measured the release of benzoic acid from polyHEMA matrices prepared by γ-irradiation and by photoinitiation. The release occurred from planar matrices exposed through single and multiple holes in an impermeable laminate. Release rates have been analysed by non-linear regression analysis using PharmG[5]. In addition, a visual determination of the development of the diffusion pattern was carried out and the data analysed by non-linear regression analysis.

MATERIALS AND METHODS

MATERIALS

(a) Gel materials

2-hydroxyethylmethacrylate (HEMA), N,N-dimethylethanolamine (99%) (Fluka), (dl)-camphoroquinone (Aldrich) and glycerol B.P. (McCarthys) were used as received. Water was distilled once from an all glass still.

(b) Additional materials

Benzoic acid (Analytical Grade), Fisons. Non-permeable, perforated membranes, Johnson and Johnson.

Non-permeable, perforated, Perspex membranes (of known hole diameter and separation).

METHODS

(a) Method of gel preparation:

(i) Photoinitiated polymerization system for polyHEMA-glycerol hydrogels:

Monomer solutions were prepared containing HEMA monomer, in the concentration range 35-50% $^{w}/w$, glycerol (to 100% $^{w}/w$) and the photoinitiator system of (dl)-camphoroquinone (0.06% $^{w}/w$) and N,N-dimethylethanolamine (1% $^{w}/w$).

The monomer solutions were degassed for 15 minutes, followed by flushing with 'white spot' nitrogen (BOC) for 15 minutes as standard procedure. The solutions were poured into sealed Perspex moulds and placed 30cm from a light source (visible light : 240v, 150w). The polymerization procedure was carried out at ambient temperature for 6 hours.

(ii) γ-irradiated polymerization system for polyHEMA-water hydrogels:

Monomer solutions were prepared containing HEMA monomer, in the concentration range 60-80% $^{w}/w$, and water to 100% $^{w}/w$. Benzoic acid was added, at a concentration of 1% $^{w}/w$ prior to polymerization and the solution deaerated. The monomer solutions were poured

into sealed moulds and irradiated at ambient temperature with a dose of 450 kRad using a 2000 Ci ^{60}Co source.

(iii) Visual representation of the diffusion pattern:

PolyHEMA-glycerol gels of known monomer-solvent composition were prepared in the absence of solute as described above. The gels were placed in a dissolution cell[6] and a Perspex disc, with a 4 mm diameter hole cut into its centre, secured on top. The gels were exposed to dissolution medium for different time intervals. Cross-sections through each gel were taken and photographed.

(iv) Method of *in vitro* release testing:

The *in vitro* drug release characteristics of benzoic acid from polyHEMA gels laminated with non-permeable, perforated membranes were determined using an *in vitro* release test[6]. The polyHEMA gels were placed in the central cavity of the base of a Perspex dissolution cell[1]. Perspex discs, thickness 1 mm, with single holes of known diameter, or with multiple holes of known diameter and specific separation cut into the centre, were placed over the gel disc as laminates, secured and made watertight. Drug release was allowed to occur through the hole from the exposed surface of the polymer for periods of time ranging from 0 to 110 hours. Non-permeable, perforated membranes (Johnson and Johnson) were also used as laminates.

RESULTS AND DISCUSSION

(a) Visual representation of the diffusion pattern:

Transparent polyHEMA-glycerol gels generally become opaque on exposure to aqueous media as a result of solvent-water exchange[7].

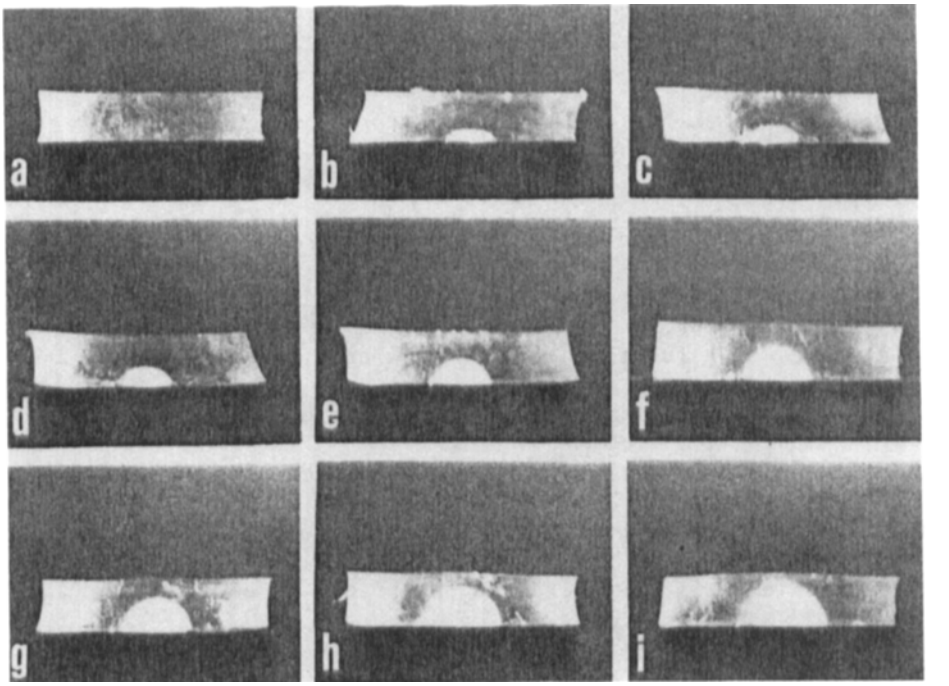

FIGURE 1
The diffusion pattern in polyHEMA-glycerol gels following dissolution from a single hole (diameter 4 mm) at (a) time = 0, (b) 0.5 hours, (c) 1 hour, (d) 2 hours, (e) 5 hours, (f) 10 hours, (g) 15 hours, (h) 20 hours and (i) 40 hours.

Therefore, the "front of water penetration or drug dissolution" can be visualised by the opaque gel/transparent gel boundary.

Photographs of gel cross-sections taken at time intervals show the diffusion pattern from a single planar hole (Figure 1) illustrating the development of a series of sphere segments as predicted[1]. Measurements of segment height (H) and chord length (a) were taken from each photograph enabling a calculation to be made of sphere radius, r, and the surface area of each sphere

segment calculated from equation 2[1]:

$$A = 2\pi \left[\tfrac{1}{2} a_i^2 + a_i \left(\frac{2DC_s t}{\rho} \right)^{\frac{1}{2}} + \left(\frac{2DC_s t}{\rho} \right) \right] \qquad \text{equation 2}$$

Figure 2 shows the relationship between sphere segment surface area and segment height, H. Figure 3 is a plot of sphere segment surface area as a function of time showing a non-linear increase in surface area with time. Ideally, for zero-order control of drug release, the area from which release occurs should increase as a function of the square-root of time. Non-linear regression analysis of experimental data and the predicted equation for the surface area of the releasing face (equation 2) was performed on a Sirius microcomputer using PharmG[5]. Estimates of the parameters and the standard error associated with each parameter suggested that the second parameter in equation 2 (associated with time, t) did not differ significantly from zero and could, therefore, be omitted from the model. The computer generated line of best fit is shown in Figure 4. The intercept on the ordinate axis represents the surface area from which release can occur at t=o and which enables a calculation to be made of hole radius.

(b) *In vitro* drug release test:

Figure 5 shows a typical plot of the cumulative amount of benzoic acid released, Q ($mg.cm^{-2}$), from polyHEMA-glycerol gels as a function of time from both a single hole and from multiple holes. The release profile is characterized by an initial burst, followed by apparent constant drug release. However, a plot of Q as a

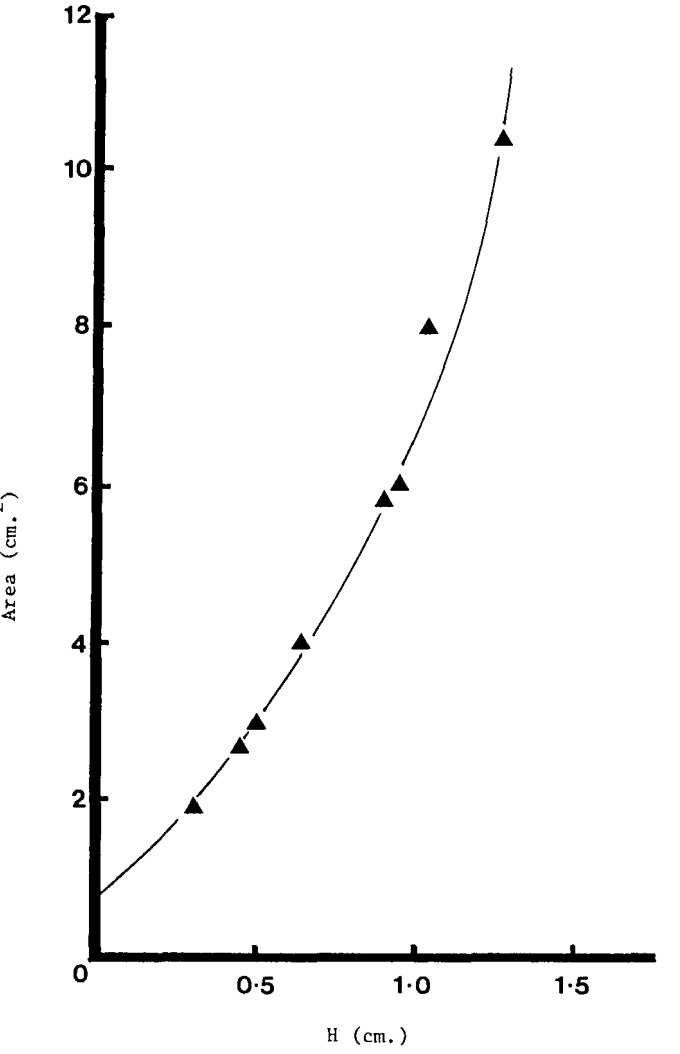

FIGURE 2
Sphere segment surface area as a function of segment height, H.

function of $t^{\frac{1}{2}}$ (for square-root of time dependent kinetics) shows good linear correlation suggesting that the observed increase in releasing surface area does not compensate for drug depletion to the extent of providing for zero-order drug release.

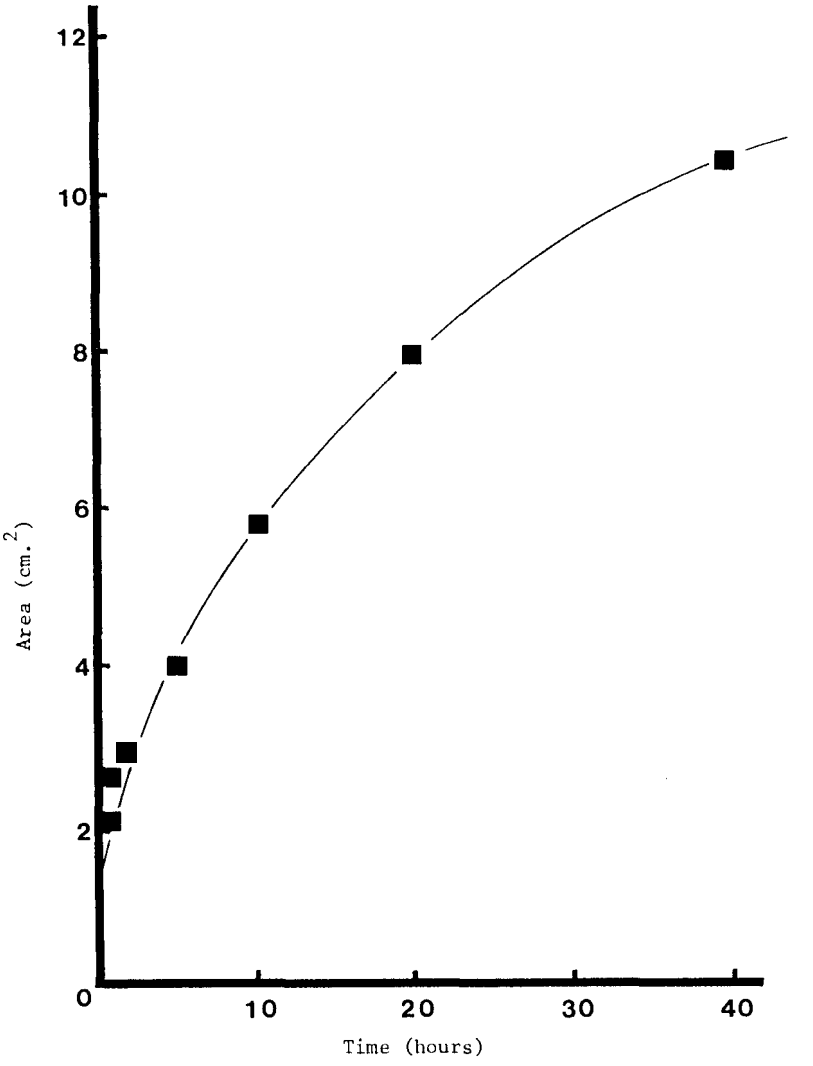

FIGURE 3

Sphere segment surface area as a function of time.

Figure 6 shows a typical plot of cumulative amount of benzoic acid released as a function of time from a multiple, perforated laminate (Johnson and Johnson). The release profile is similar to that of Figure 5 although a plot of Q *versus* $t^{\frac{1}{2}}$ does not show good linear correlation. The kinetics of drug release and the goodness

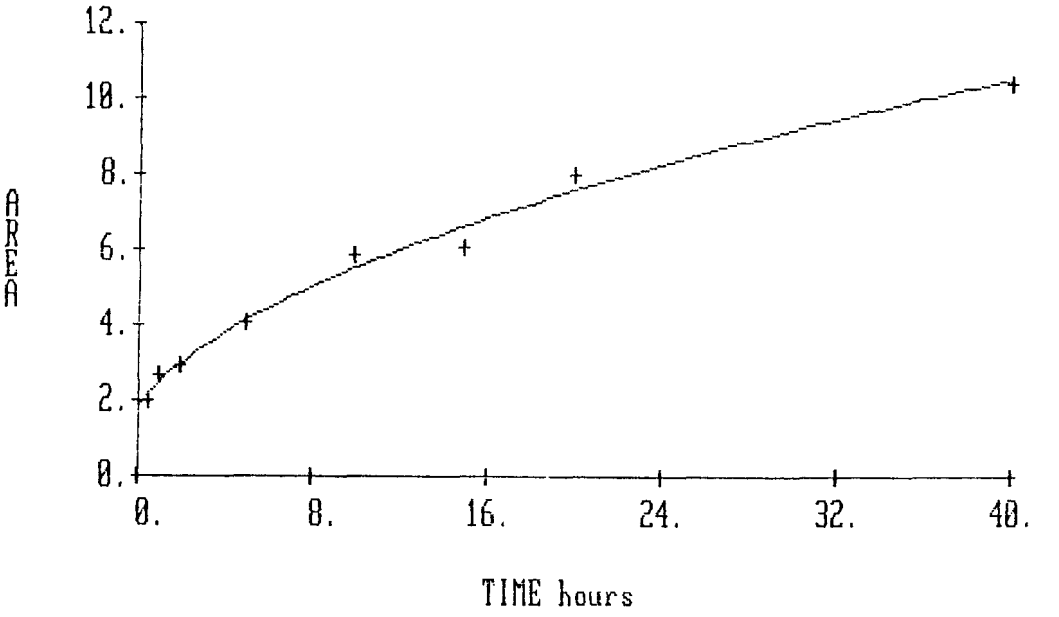

FIGURE 4
Sphere segment surface area as a function of time.

of fit of the predicted model with experimental data was calculated.

Equation 1 is a three parameter model, the three parameters being referred to as P_1, P_2 and P_3 where:

$$P_1 = \pi N a_i^2 (2DC_s)^{\frac{1}{2}} \rho^{\frac{1}{2}}$$

$$P_2 = \pi N a_i (2DC_s)$$

$$P_3 = {}^2/_3 \pi N (2DC_s)^{3/2} \rho^{-\frac{1}{2}}$$

Estimates of these parameters were made on the assumption that P_1, P_2 and P_3 had positive values. Non-linear regression analysis predicts the line of best fit, shown in Figures 7 and 8, for the release of benzoic acid from (i) a single hole and (ii) multiple holes respectively. Estimates of the parameters and the standard

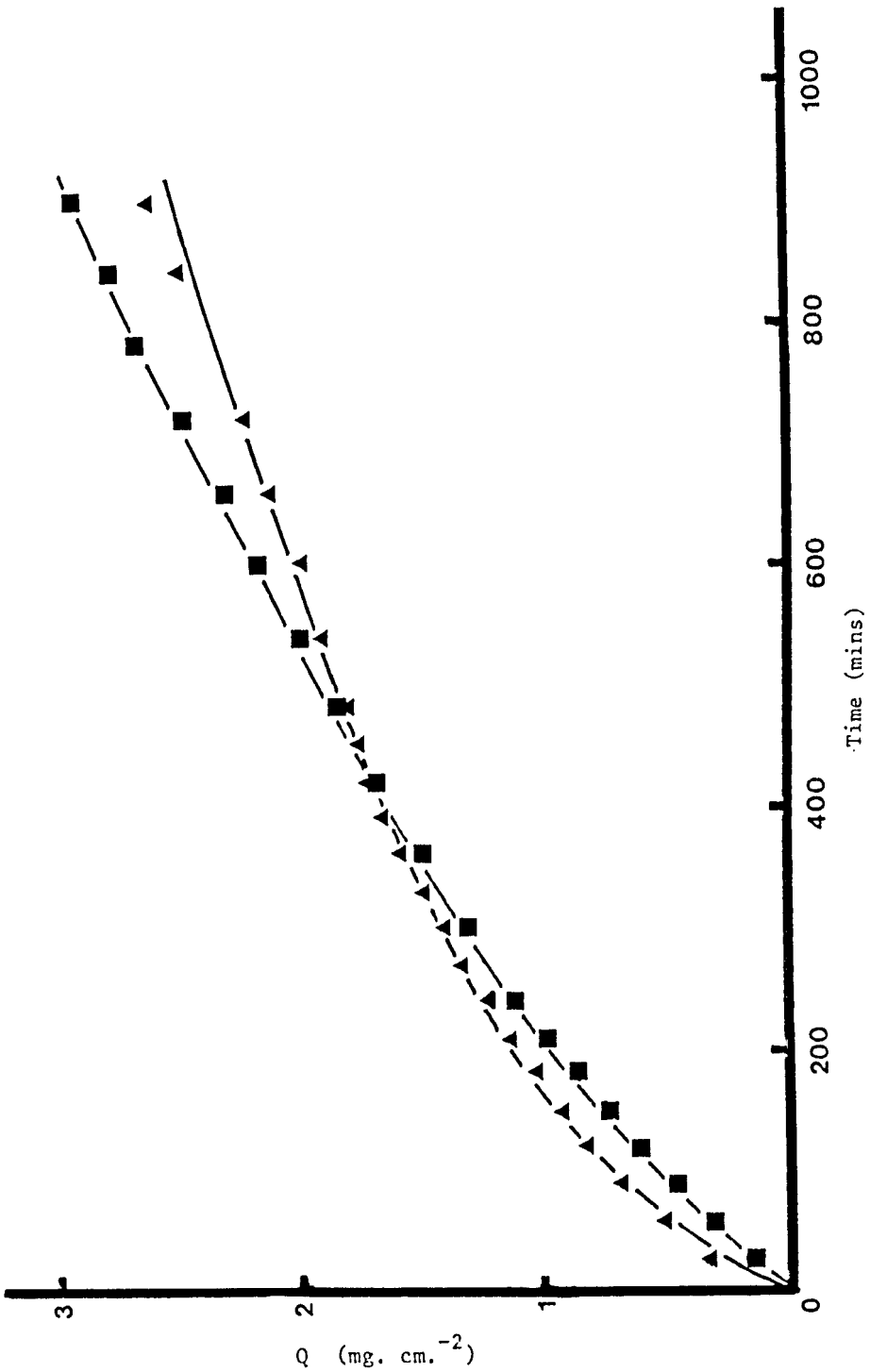

FIGURE 5

Cumulative amount of benzoic acid released from polyHEMA-glycerol gels as a function of time from a single hole (diameter 4 mm) (▲) and from multiple holes (diameter 2 mm, hole separation 8 mm) (■).

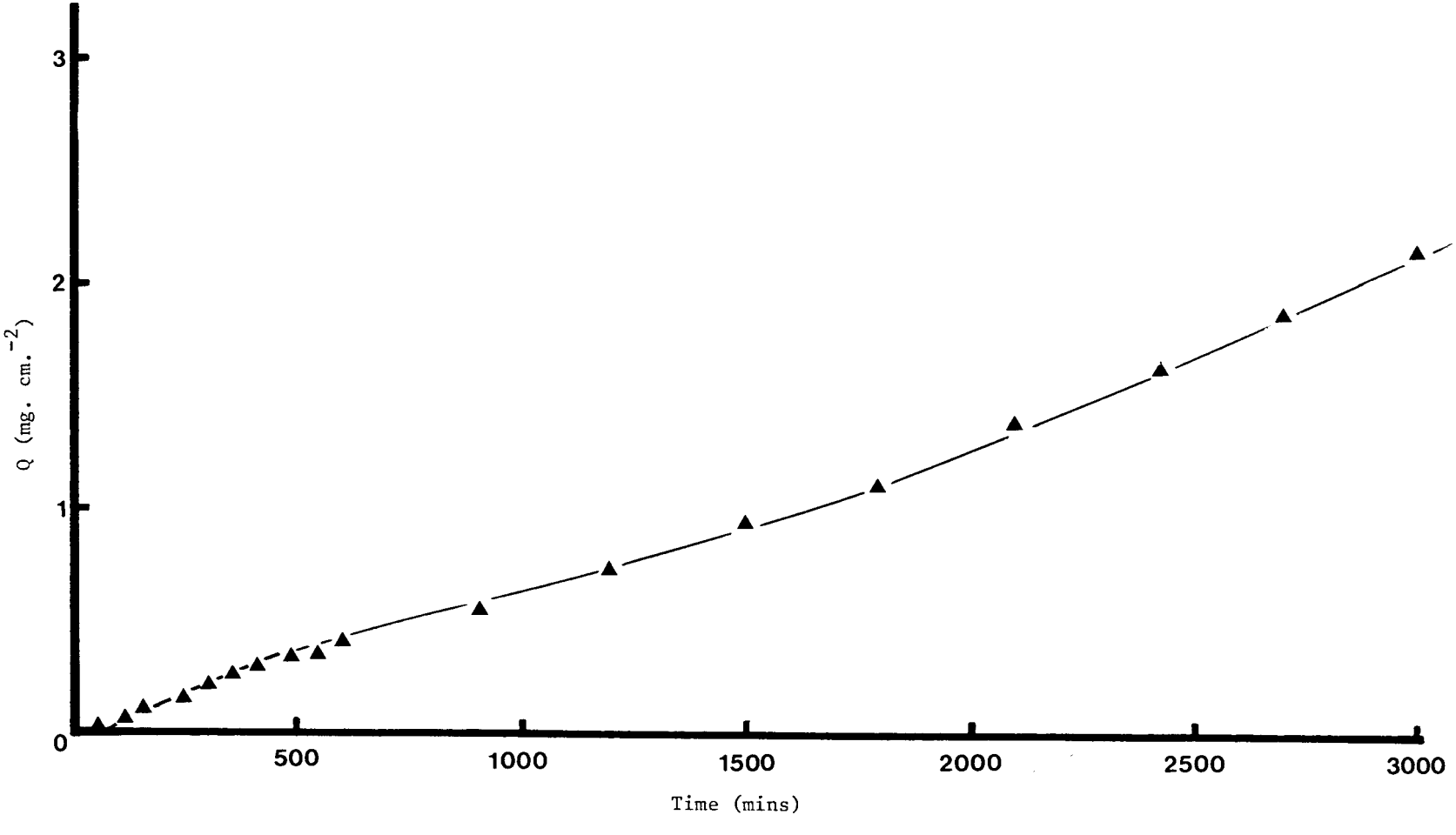

FIGURE 6
Cumulative amount of benzoic acid released from polyHEMA-glycerol gels as a function of time from a proprietary, perforated, medical tape (Johnson and Johnson).

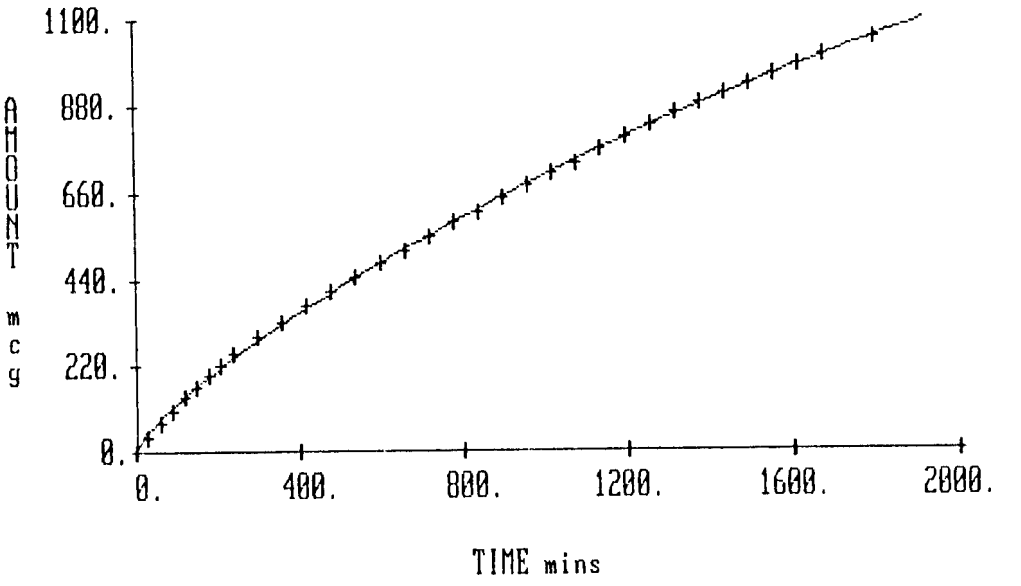

FIGURE 7
Cumulative amount of benzoic acid released from polyHEMA-glycerol gels as a function of time from a single hole (diameter 4 mm).

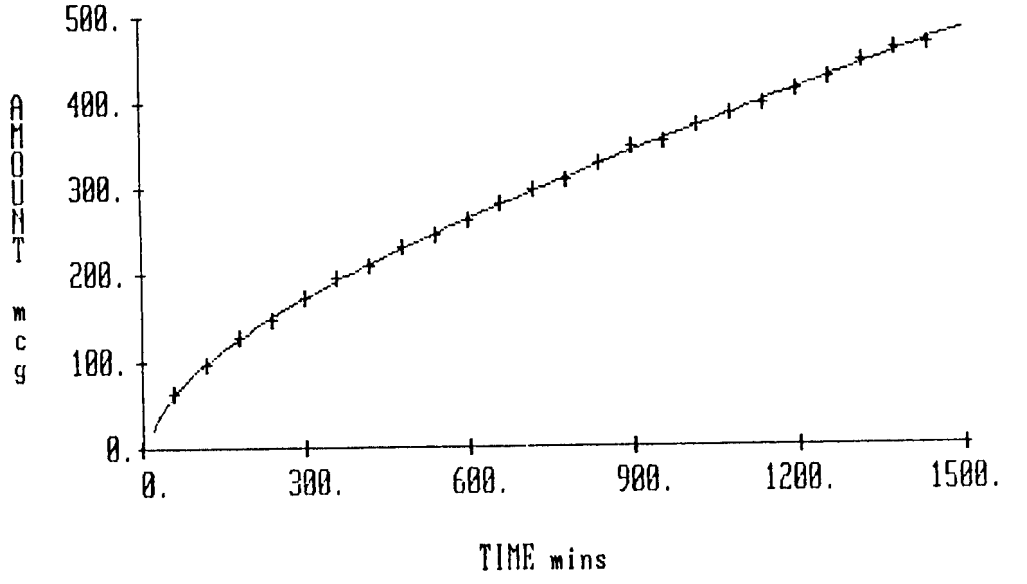

FIGURE 8
Cumulative amount of benzoic acid released from polyHEMA-glycerol gels as a function of time from multiple holes (diameter 2 mm, hole separation 8 mm).

TABLE 1

Parameter estimates and associated values of standard error, coefficient of variation and t for the release of benzoic acid through a single hole (diameter 12 mm) for models 1 and 2.

MODEL 1				MODEL 2			
PARAMETER	S.E.	C.V.%	t	PARAMETER	S.E.	C.V.%	t
P_1 105.478	6.189	5.868	17.04	P_1 105.475	2.002	1.898	52.68
P_2 0.928	0.598	64.420	1.55	P_2 0.928	0.085	9.133	10.95
P_3 0.000	0.014	1.38×10^6	0.000				

F ratio = 0.000 ($p<0.001$)
degrees of freedom: 21 (Model 2), 20 (Model 1).

error associated with each parameter were generated. From these estimates, t values were calculated which indicates when a parameter estimate does not differ significantly from zero and, therefore, when such a parameter may be omitted from the model. The value of t obtained for parameter P_3 indicated that the value of this parameter did not differ significantly from zero ($p<0.001$). Therefore, the original three parameter model could be reduced by one parameter. The F-ratio test performed on the predicted data points generated for the original three parameter model (Model 1) and the reduced, two parameter model (Model 2) assesses whether the reduced model differs statistically from the original.

For the *in vitro* release of benzoic acid from polyHEMA-glycerol gels through a single hole (diameter 12mm) values for P_1, P_2 and P_3 are given in Table 1 together with values of the standard error, coefficient of variation and t for both models.

TABLE 2

Parameter estimates and associated values of standard error, coefficient of variation and t for the release of benzoic acid from a single hole (diameter 12 mm) incorporating the parameter P_4

MODEL 1				MODEL 2			
PARAMETER	S.E.	C.V.%	t	PARAMETER	S.E.	C.V.%	t
P_1 114.829	5.205	4.533	22.06	P_1 114.818	1.433	1.248	80.14
P_2 0.621	0.436	70.218	1.42	P_2 0.622	0.054	8.641	11.58
P_3 0.000	0.009	9.6×10^6	0.00				
P_4 11.968	2.180	18.219	5.49	P_4 11.961	1.482	12.386	8.07

F-ratio = 0.000 ($p<0.001$)
degrees of freedom: 20 (Model 2), 19 (Model 1)

A comparison of t values for P_1 and P_2 between Model 1 and Model 2, and the value of the F-ratio test show that the two models do not differ significantly when P_3 is assigned a value of zero ($p<0.001$).

The data point at t=o was omitted from the analysis giving a better fit of the data as the computer generated line of best fit was not forced through zero. In omitting the t=o data point, a positive intercept on the time axis was generated suggesting that an additional parameter be included such that Model 1 becomes:

$$Q = P_1 t^{\frac{1}{2}} + P_2 t + P_2 t^{3/2} + P4 \text{ and}$$

Model 2 becomes:

$$Q = P_1 t^{\frac{1}{2}} + P_2 t + P_4$$

The additional parameter may be accounted for in terms of the lag time for diffusion of the drug from the gel matrix[8]. Values of parameter estimates, standard error, coefficient of variation

TABLE 3

Parameter estimates and associated values of standard error, coefficient of variation and t for the release of benzoic acid from a single hole (diameter 12 mm) with negative parameter limits.

MODEL 1				MODEL 2			
PARAMETER	S.E.	C.V.%	t	PARAMETER	S.E.	C.V.%	t
P_1 98.163	4.277	4.357	22.95	P_1 114.819	1.438	1.253	79.80
P_2 2.042	0.342	16.749	5.97	P_2 0.621	0.054	8.675	11.53
P_3 -0.030	0.007	23.321	4.28				
P_4 6.373	2.040	32.005	3.13	P_4 11.963	1.484	12.405	8.06

F-ratio = 20.18 ($p<0.001$).
degrees of freedom: 20 (Model 2), 19 (Model 1).

and t for the release of benzoic acid from a single hole for Model 1 and Model 2 incorporating the parameter P_4 are given in Table 2 showing that the inclusion of parameter P_4 enhances the goodness of fit.

Initially, all parameter estimates were assumed to have positive values (equation 1). Setting the parameter estimates with negative limits is shown to improve the fit of the data (Table 3).

From Table 3 it is evident that, when assigned a negative value, parameter P_3 (Model 1) differs significantly from zero ($P<0.001$) and should be included in the model such that:

$$Q = P_1 t^{\frac{1}{2}} + P_2 t - P_3 t^{3/2} + P_4$$

The reason for the negative value of parameter P_3 is unclear although it may be associated with the influx of water into the hydrogel, affecting gel structure and, therefore, drug diffusion.

TABLE 4

Parameter estimates and values of P for the release of benzoic acid (a) from polyHEMA-glycerol gels and (b) from polyHEMA-water gels through holes of different diameter.

	HOLE DIAMETER (cm)	P_1	P_2	P_3	P_4	P
(a)	1.2	98.1627	2.0421	-0.0304	6.3730	-1.397
		110.8417	2.0107	-0.0297	10.5752	-1.228
	0.8	22.9775	0.3907	-0.0066	7.5013	-1.007
		12.4451	1.1299	-0.0206	1.8834	-4.980
	0.4	10.0743	0.0211	0.0001	13.3286	+0.442
		16.6994	-0.3663	0.0101	10.0000	-0.796
	0.2	4.2570	0.0200	0.0010	19.6607	+0.0940
(b)	1.2	98.3406	0.0534	-0.0039	4.7735	-0.0074
	0.8	45.3709	-0.3862	0.0074	-10.8088	-0.4440
	0.4	8.7887	0.0590	0.0010	15.3481	+0.3960
	0.2	6.1008	-0.0495	0.0003	9.5426	-1.3390

However, Model 2 still describes the data better (Table 3) implying, once again, that parameter P_3 should be omitted from the model.

INFLUENCE OF HOLE DIAMETER

For the *in vitro* release of benzoic acid from polyHEMA-glycerol gels and from polyHEMA-water gels through a series of holes of different diameter, experimental data was fitted to the four parameter model (where P_3 is assigned a negative value). Table 4 gives the values of P_1, P_2, P_3 and P_4 together with the values obtained for the ratio P, where:

$$P = \left[(P_2/P_3)/(P_1/P_2)\right]$$

and which should have a value of -1.5.

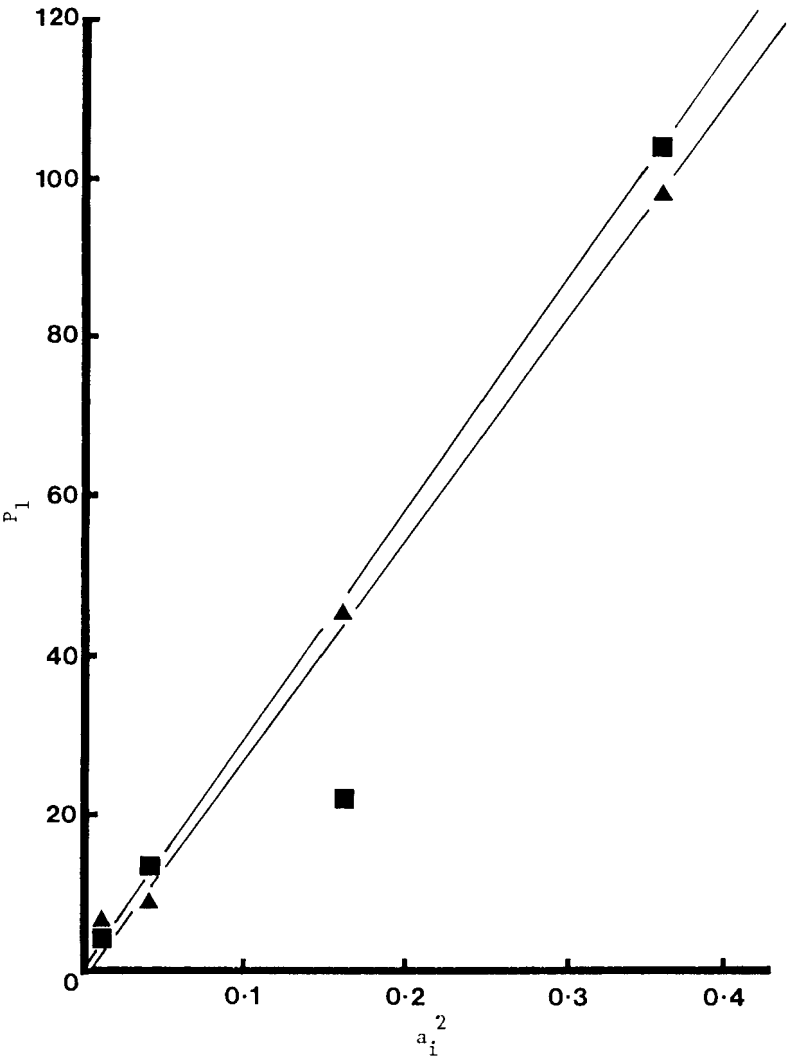

FIGURE 9
Influence of hole radius, a_i, on the value of parameter, P_1, plotted as P_1 *versus* a_i^2 for polyHEMA-glycerol gels (■) and polyHEMA-water gels (▲).

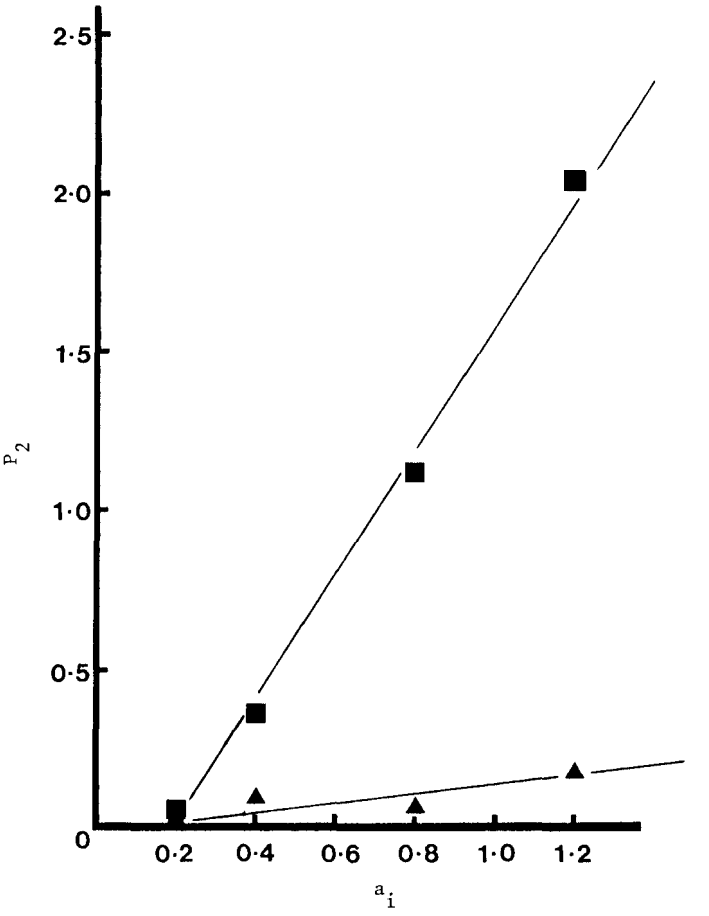

FIGURE 10
Influence of hole radius, a_i on the value of parameter, P_2 for polyHEMA-glycerol gels (■) and polyHEMA-water gels (▲).

Figure 9 shows the relationship between parameter, P_1 and hole radius, a_i. A linear relationship is observed for P_1 as a function of a_i^2 for both polyHEMA-glycerol and polyHEMA-water gels. Figure 10 shows the relationship between parameter P_2 and hole radius, a_i for polyHEMA-glycerol and polyHEMA-water gels. The value of P_2 is shown to be directly proportional to the hole

TABLE 5

Estimates of parameter P_3 for the release of benzoic acid from polyHEMA-glycerol and polyHEMA-water gels through a series of holes of different diameter.

DIAMETER (cm)	P_3 polyHEMA-glycerol	P_3 polyHEMA-water
1.2	-0.0304	-0.0039
	-0.0297	
0.8	-0.0066	0.0074
	-0.0206	
0.4	0.0001	0.0010
	0.0101	
0.2	0.0010	0.0003

radius. The observed relationships between hole radius and parameters P_1 and P_2 correlate well with the predicted models. For P_3, which is predicted to be independent of hole size, constant values would be expected for the case where D, C_s and ρ (equation 1) are kept constant (i.e., where polymer composition is not changed). Values of P_3, for the release of benzoic acid through a series of holes of different diameter are given in Table 5. However, values of P_3 do not appear to remain constant with changing hole radius implying that this parameter should be omitted from the model.

CONCLUSION

The release of drug from a planar matrix surface exposed through single or multiple holes in an impermeable laminate can be predicted. The model (equation 1) proposes that drug release

increases as a function of $t^{\frac{1}{2}} + t + t^{3/2}$. The values of the parameters obtained and the subsequent statistical analysis of the data showed that the original model (Model 1) did not accurately describe the release of drug. The modified release equation (Model 2), however, fitted the data. Although zero-order release kinetics are not predicted by the model, depletion of drug from a matrix was found to be compensated for, to an extent, by the modification of an essentially planar geometry by laminating an impermeable perforated membrane to the planar releasing face of a matrix.

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