Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices III

Quantitative Studies Involving the Polyethylene Plastic Matrix

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The procedure described in the previous paper has been applied to a number of cases. Release of sulfanilamide, caffeine, and potassium acid phthalate from polyethylene matrix disks into aqueous media were studied. The results show that in these cases the absolute tortuosity values are relatively small when all pores are accessible to the solvent. This situation is achieved, for example, when there is surfactant in the solution permitting adequate wetting of the channels. A direct correlation between surfactant activity and the rate of release has been found. Even when there was a relatively small amount of inaccessible pores, the tortuosities in these cases were found to be considerably greater. The results were obtained when surfactant was not incorporated in the release medium. It is proposed that these findings are consistent with an "encapsulated" drug particle model.

A PREVIOUS INVESTIGATION (1) showed that the Higuchi equation can be utilized to describe drug release from polyethylene matrices. The results of experiments which investigated the effects of drug type, concentration of drug in tablet, solvent media, etc., indicated that the above factors not only altered release rates directly as predicted by theory, but also indirectly by altering other parameters. Before a quantitative evaluation of the polyethylene system could be made, it was therefore necessary to establish experimental procedures to determine independently all parameters for the conditions of each study. In this way the interdependence of all parameters can be eliminated.

Experimental procedures to determine the diffusion coefficient, drug solubility, and matrix porosity were reported in a previous communication (2). These parameters can then be used in the equations which describe the release rates from matrices containing solid medicament and from matrices saturated with a solution of drug.

The release rate of drug imbedded in an insoluble matrix obeys the following equation:

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 1)}$$

where

D = diffusion coefficient of the drug in the permeating fluid,
ϵ = the porosity of the matrix,
τ = tortuosity of the matrix,
A = the total amount of drug present in the matrix per unit volume,
C_s = the solubility of the drug in the release medium,
Q = grams of drug released per unit area of surface.

If the same matrix is saturated with a solution, the release rates would obey the following relationship:

$$Q = 2\,C_0\epsilon\left(\frac{Dt}{\tau\pi}\right)^{1/2} \qquad \text{(Eq. 2)}$$

where C_0 = concentration of the solution in the matrix. The other terms have the same meaning as in Eq. 1.

Once the parameters of the matrix have been established, one can use Eq. 1 to determine the remaining parameter, tortuosity, from release data obtained using the matrix containing the solid drug. Equation 2 can also be used to calculate the tortuosity of the same matrix, but the release data obtained from the resaturated matrix must be used. If the tortuosities independently calculated by these methods agree well with each other, this would provide strong evidence that this method of attack can be used to quantitatively study the effect of experimental conditions on the release rates of drugs from inert matrices. Using this approach, this paper reports the effect of drug concentration, drug solubility, and other factors upon the parameters—tortuosity, porosity, and diffusion coefficient.

EXPERIMENTAL

The release rates from polyethylene matrices containing solid drug as well as solutions were studied using the techniques described previously (1). The parameters were evaluated as described in the subsequent paper (2).

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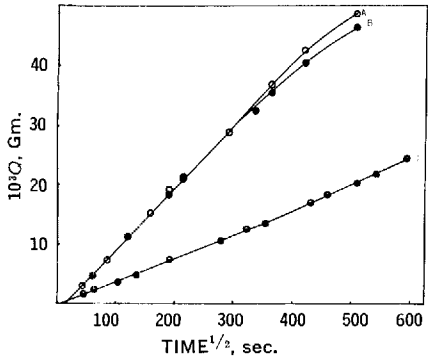

Fig. 1.—Release of potassium acid phthalate from polyethylene plastic matrices containing 20% potassium acid phthalate in various media. Key: A, 0.10% polysorbate 80 as the release medium; B, 0.10% HTAB; C, water.

RESULTS AND DISCUSSION

If a given matrix is studied by both the solid and saturated solution methods, it must be established that all parameters remain constant during the experiments. Since the addition of surfactant to the aqueous solvent media greatly increases the rate of drug release from polyethylene matrices, it had been postulated that all of the maximum possible matrix porosity is made available by the surfactant. This was verified by the fact that the porosity determined by the liquid leaching method (2) was equal to the combined porosity of drug and air. The latter was calculated by the physical measurement method (2). This was not true in nonsurfactant experiments. It was, therefore, decided to use surfactant solutions as the release medium to establish the quantitative applicability of the theory.

Quantitative Application of Theory.—Polyethylene matrices containing 20% sulfanilamide, caffeine, and potassium acid phthalate were studied. Both the solid and liquid leaching experiments were performed utilizing surfactant solutions. It should be pointed out that the compounds were selected on the basis of their suitability for establishing basic physicochemical points rather than their therapeutic value; similarly, the surfactants used were selected on the basis of their surfactant activity and system compatibility. All surfactant solutions used were above their critical micelle concentration to provide maximum surfactant activity.

The surfactant solution used in the sulfanilamide and caffeine studies was 0.1% dioctyl sodium sulfosuccinate[1] (AOT) but 0.1% hexadecyl trimethylammonium bromide solution (HTAB) was used with the potassium acid phthalate studies since the latter was not compatible with AOT.

The solid release curves of these systems are shown in Figs. 1, 2, and 3. Solid leaching curves in water are also included to show the magnitude of the surfactant effect which will be discussed later. Liquid leaching curves of the same matrices are shown in Figs. 4 and 5. To demonstrate the applicability of the solid and liquid leaching concepts, calculations of τ values using Eqs. 1 and 2, respectively, will be shown and compared.

[1] Marketed as Aerosol OT by the American Cyanamid Co., Wayne, N. J.

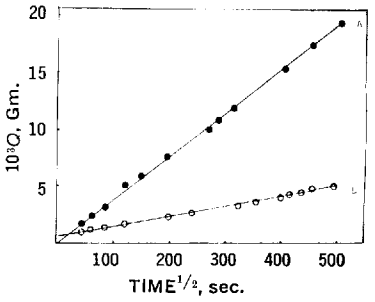

Fig. 2.—Release of caffeine from polyethylene matrices containing 20% drug into 0.10% AOT (A) and into water (B).

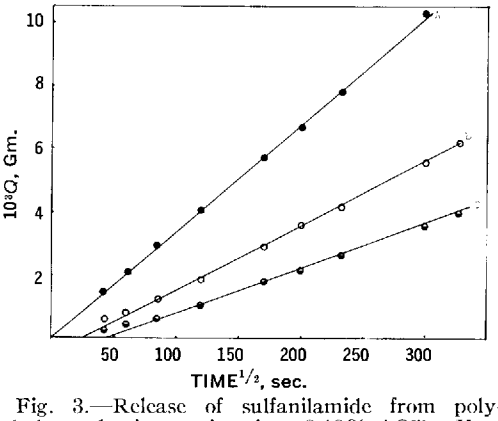

Fig. 3.—Release of sulfanilamide from polyethylene plastic matrices into 0.10% AOT. Key: A, 20% drug in matrix; B, 10% drug; C, 5% drug.

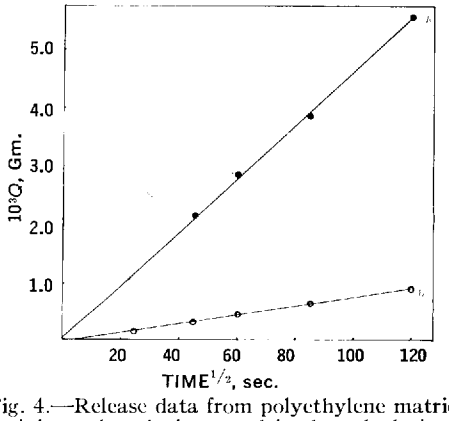

Fig. 4.—Release data from polyethylene matrices containing only solutions used in the calculation of tortuosity. Key: A, tablets originally contained 20% solid potassium acid phthalate which was released completely in 0.10% HTAB, was then equilibrated with a saturated potassium acid phthalate solution, and then released in 0.10% HTAB; B, same as A, except caffeine was used instead of potassium acid phthalate and 0.10% AOT was used instead of HTAB.

The following calculations using the data of a polyethylene matrix containing 20% sulfanilamide

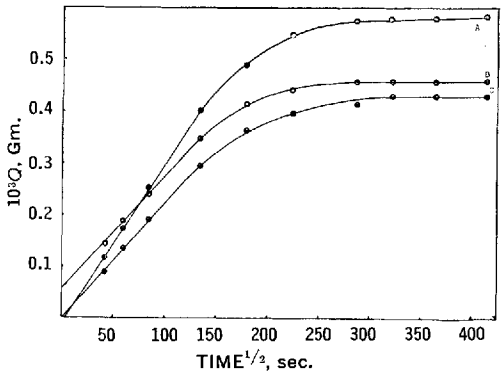

Fig. 5.—Solute release data from polyethylene plastic matrices used in the calculations of porosity and tortuosity. Key: A, tablets originally contained 20% sulfanilamide which was released completely in 0.10% AOT, was then equilibrated with a saturated sulfanilamide solution, and then released in 0.10% AOT; B, same as A, except tablets contained 10% drug; C, same as A, except tablets contained 5% drug.

in a surfactant medium will serve as an illustrative example.

weight of the tablet = 0.300 Gm.

volume of tablet = $\pi r^2 h$ = 0.328 ml.

$C_s = 1.08 \times 10^{-2}$ Gm./ml.

$C_0 = 0.95 \times 10^{-2}$ Gm./ml.

$$A = \frac{\text{wt. of drug}}{\text{vol. of tablet}} = \frac{0.060 \text{ Gm.}}{0.328 \text{ ml.}} = 0.182 \text{ Gm./ml.}$$

$D = 12.9 \times 10^{-6}$ cm.^{2}/sec.

$$\text{volume of plastic} = \frac{0.240}{0.960} = 0.250 \text{ ml.}$$

$$\text{volume of drug} = \frac{0.06}{1.500} = 0.040$$

volume of air = 0.328 − 0.290 = 0.038 ml.

$$\epsilon = \frac{0.038 + 0.04}{0.328} = 0.237$$

$Q/t^{1/2}$ = slope of solid leaching (Fig. 3) = 3.30×10^{-5} Gm./sec.$^{1/2}$

$Q/t^{1/2}$ = slope of liquid leaching (Fig. 5) = 0.303×10^{-5} Gm./sec.$^{1/2}$

Solving Eq. 1 for the value of τ and substituting the values of above parameters one obtains the following

$$\tau = \frac{D\epsilon(2A - \epsilon C_s)C_s}{(\text{slope})^2}$$

$$= \frac{(12.9 \times 10^{-6}) \times (0.237)\,(2 \times 0.182 - 0.237 \times 1.08 \times 10^{-2})(1.08 \times 10^{-2})}{(3.30 \times 10^{-5})^2}$$

$$= 10.7$$

and similarly Eq. 2 yields

$$\tau = \frac{4C_0^2\epsilon^2 D}{\pi\,(\text{slope})^2}$$

$$= \frac{4 \times (0.95 \times 10^{-2})^2 \times (0.237)^2 \times 12.9 \times 10^{-6}}{3.142 \times (0.303 \times 10^{-5})^2}$$

$$= 9.1$$

Comparison of the above values of τ shows excellent agreement and thereby indicates that the theory and the parameters employed are valid. Similar agreement was obtained with caffeine. A similar study with potassium acid phthalate showed a reasonably good agreement; the relatively higher τ value obtained for potassium acid phthalate by the solid leaching experiment may be due to the poorer wetting properties of HTAB compared to AOT. These results are summarized in Table I.

Examination of the ϵ due to air in Table I shows that it does not remain constant, although the same concentration of different drugs is used. This may be a reflection of the relative flow properties of the drug and plastic when under compression.

The above approach was also used to study polyethylene matrices containing 5 and 10% sulfanilamide. The curves are shown in Figs. 3 and 5, and the calculated parameters are listed in Table II.

Examination of Table II clearly shows that the ϵ of the matrix is not a direct function of the drug percentage. Although the porosity contribution from the drug increases with increasing concentration of drug, the porosity contribution from air is decreasing. In addition, there seems to be a slight increase in τ. Again, it should be noted that excellent agreement was shown between the tortuosities calculated from the solid leaching and solution leaching data.

These results explain why the release rates in an earlier study (1) did not follow the predicted rates assuming all parameters were constant and confirm the hypothesis that the porosity was not proportional to A.

Mechanism of Surfactant Action.—The surfactant seems to be instrumental in making available the maximum possible porosity. It was felt, therefore, that the effect should be investigated further. To eliminate the possibility that surfactant may

Table I.—Calculation of Tortuosity of Potassium Acid Phthalate, Sulfanilamide, and Caffeine in Polyethylene Matrices

Tablet Compn.	D 10^6 cm.^{2} sec.$^{-1}$	C_s 10^2 Gm. ml.$^{-1}$	Vol. of Tablet, ml.	ϵ Due to Air	ϵ Due to Air and Drug	A Gm. ml.$^{-1}$	C_0 10^2 Gm. ml.$^{-1}$	10^5Q Solid Leaching	10^5 Q Liquid Leaching	τ by Eq. 1	τ by Eq. 2
20% Potassium acid phthalate	18.2	11.60	0.331	0.165	0.276	0.181	9.30	10.2	4.36	18.5	8.0
20% Caffeine	6.3	2.50	0.264	0.128	0.254	0.179	2.50	3.8	0.71	8.2	6.4
20% Sulfanilamide	12.9	1.08	0.328	0.115	0.237	0.182	0.95	3.3	0.30	10.7	9.1

TABLE II.—POROSITY AND TORTUOSITY OF 5, 10, AND 20% SULFANILAMIDE IN POLYETHYLENE MATRICES USING SURFACTANT SOLUTION AS RELEASE MEDIUM

Tablet Compn.	ϵ Due to Air	ϵ Air Plus Drug	τ by Eq. 1	τ by Eq. 2
5% Sulfanilamide	0.125	0.154	8.5	6.7
10% Sulfanilamide	0.103	0.162	9.6	8.5
20% Sulfanilamide	0.115	0.237	10.7	9.1

solubilize some component of the plastic material, the polyethylene powder was shaken in the presence of excess of surfactant solution overnight. This slurry was then filtered and the polyethylene was washed with hot and cold water. Twenty per cent potassium acid phthalate tablets were made using this washed and then dried polyethylene powder. The release rates in water and surfactant were then studied; results were identical with the unwashed plastic indicating that the surfactant does not solubilize any of the plastic component.

The increase in release rates of drugs from a polyethylene matrix by surfactants seems to be a general effect. It has been shown that not only is this effect present with all the compounds studied but also that it is independent of the chemical nature of the surfactant. This is demonstrated by the identical release behavior of 20% potassium acid phthalate in polysorbate and HTAB solutions (Fig. 1).

The release rates of 20% sulfanilamide tablets were studied in several solution concentrations of AOT. The results obtained are presented in Fig. 6. In order to compare these results with the surfactant property of these solutions, plots of both the release rate and surface tension *versus* the surfactant concentration are shown together in Fig. 7. The data reveal an excellent correlation between the release rates and the surface tension of the release media. It was expected that the release rates would increase with increasing concentration of surfactant because of increased wetting power of surfactants with increased concentration in regions below the critical micelle concentration (CMC). It is interesting that the reported (3) CMC for AOT is 0.08% which is near the point in Fig. 7 where the plateau of the release rate curve begins.

If the above-proposed mechanism of surfactant action is true, then the presence of surfactant either within the tablet matrix or in the release medium could give essentially the same results. On the basis of the same principle, a drug with inherent surfactant activity may yield identical release rates in the presence and in the absence of a surfactant in the release medium.

Release rates of 20% potassium acid phthalate tablets containing 2% HTAB were studied in water. These results are plotted in Fig. 8 along with the results of 20% potassium acid phthalate determined in a solution of 0.1% HTAB. As expected, the release rates were about the same. The slightly higher release rate observed with the former case might be accounted for by small porosity differences due to the incorporation of the surfactant.

To study the second premise, hexadecylpyridinium

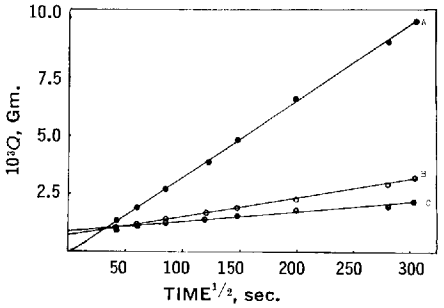

Fig. 6.—The effect of surfactant concentration of the release rate of sulfanilamide from a polyethylene plastic matrix containing 20% sulfanilamide. Key: A, 0.10, 0.50, and 1.0% AOT solutions; B, 0.05% AOT; C, 0.01% AOT.

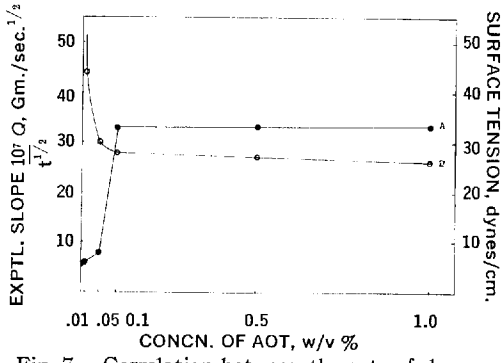

Fig. 7.—Correlation between the rate of drug release from matrix and the surface activity of the release medium. Key: A corresponds to experimental slope of the Q *vs.* $t^{1/2}$ plots (Fig. 6) for drug release from 20% sulfanilamide–polyethylene matrices at different surfactant (AOT) concentrations; B gives surface tension lowering as a function of the surfactant concentration.

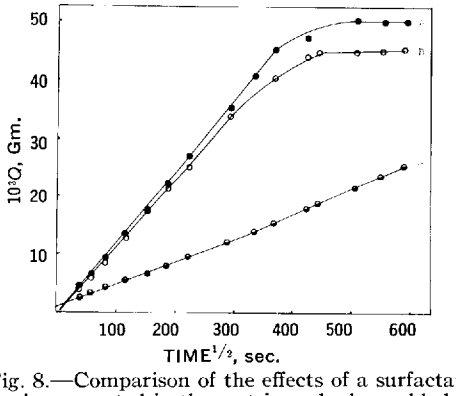

Fig. 8.—Comparison of the effects of a surfactant when incorporated in the matrix and when added in the release medium upon the release rate of potassium acid phthalate from polyethylene plastic matrices containing 20% potassium acid phthalate. Key: A, 20% potassium acid phthalate and 2% hexadecyltrimethylammonium bromide in the matrix with water as the release medium; B, only 20% potassium acid phthalate in the matrix and 0.10% surfactant in the release medium; C, same as B, except water is the release medium.

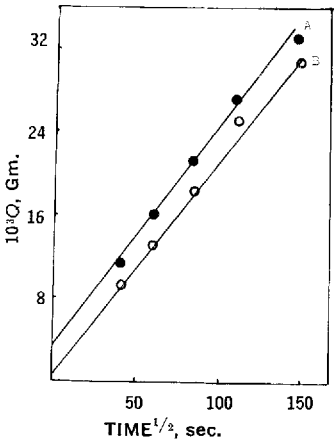

Fig. 9.—Release of hexadecylpyridinium chloride from polyethylene plastic matrices containing 20% hexadecylpyridinium chloride. Key: A, release medium contained 0.10% hexadecyltrimethylammonium bromide; B, water.

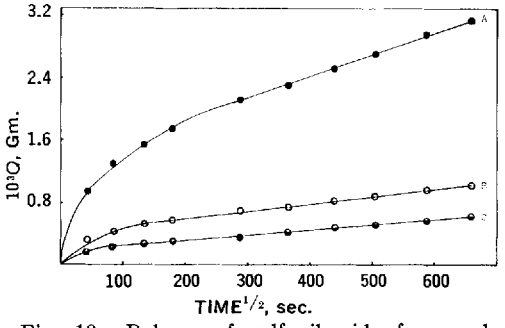

Fig. 10.—Release of sulfanilamide from polyethylene plastic matrices into water. Key: A, 20% drug in matrix; B, 10% drug; C, 5% drug.

TABLE III.—TORTUOSITY OF 5, 10, AND 20% SULFANILAMIDE IN POLYETHYLENE MATRICES USING SOLID RELEASE RATES IN WATER

Tablet Compn.	τ Using ϵ of Drug and Air	τ Using ϵ of Drug Only
5% Sulfanilamide	44,700	12,790
10% Sulfanilamide	4,700	1,700
20% Sulfanilamide	1,500	740

chloride was selected as the drug with inherent surfactant properties. Release rates were obtained in water and in 0.1% HTAB solution. The results are shown in Fig. 9. The release rates in both experiments were essentially the same as indicated by their slopes. The intercept in the data for the release in surfactant is probably due to the better initial wetting of the tablet surface when the surfactant was used in the release medium.

Nonsurfactant Release Rates.—As previously noted and illustrated in Figs. 1 and 2, the release rates in water are considerably slower than those obtained in surfactant solutions. Analysis of the parameters and the release rates strongly suggest that the wetting of all pores and the release of air from them are not achieved in nonsurfactant solutions. To further complicate matters, it appears that removal of air is slowly but continuously occurring as indicated by the slight curvature of several release rates observed in nonsurfactant solutions.

Attempts to apply Eq. 1 to both initial and limiting slopes of these curves yielded a very high value for the apparent tortuosity. Calculations were made assuming the two limiting cases—all air removed or no air removed. This seems to indicate that the air remaining in the tablets blocks pathways leading to drug particles and in this way effectively encapsulates them.

To further study this effect, the release rates of matrices containing 5, 10, and 20% sulfanilamide were studied in water. The results are shown in Fig. 10. The slopes in all these cases initially decreased with time and then exhibited a constant value. It is believed that the initially greater rate is due to the surface drug that is readily accessible to the solvent. The magnitudes observed are consistent with this assumption.

Using Eq. 1 and applying it to the constant slope portions of these curves, tortuosities were calculated using the two porosity values. The results of these calculations are shown in Table III.

The apparent tortuosities calculated in this manner are extremely high. These results suggest that drug is indeed effectively encapsulated by the polyethylene plastic. The increase in the calculated τ values with decreasing A is consistent with this type of model because the more dilute the internal (drug) phase the greater the likelihood of isolation of a drug particle in a sea of plastic. Then, if the wetting of the channels in the plastic itself is insufficient, the permeability of the media is largely determined by the low permeability of the plastic itself and not by a simple average of the void space and the plastic permeabilities.

It is believed that situations such as these may be best defined physically by the use of concepts other than the "average porosity" and the "average tortuosity" as are implied by Eq. 1. Preliminary theoretical studies based on the use of mixture relationship such as the Clausius-Mosotti and the Bruggeman equations (4) have yielded effective τ values of the order of magnitudes given in Table III when reasonable assumptions were made. A future communication will describe in detail comparisons of data with these theories for encapsulation.

SUMMARY

The interpretation of data based upon the quantitative determination of the parameters, ϵ, τ, and D, and their use in Eqs. 1 and 2 was shown to be valid for studies in which the porosity was known throughout the experiment. The results were excellent and showed that these methods can be quantitatively used to study the effect of various variables on the release rates of drugs from inert matrices.

REFERENCES

(1) Desai, S. J., Simonelli, A. P., and Higuchi, W. I., *J. Pharm. Sci.*, **54**, 1459(1965).
(2) Desai, S. J., Singh, P., Simonelli, A. P., and Higuchi, W. I., *ibid.*, **55**, 1224(1966).
(3) "Aerosol Surface Active Agents," American Cyanamid Co., Wayne, N. J.
(4) Higuchi, W. I., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 598(1960).