Drug Release from Methyl Acrylate–Methyl Methacrylate Copolymer Matrix I: Kinetics of Release

B. FARHADIEH, S. BORODKIN, and J. D. BUDDENHAGEN

Abstract □ The release rates of four commonly used drugs incorporated into a methyl acrylate–methyl methacrylate copolymer matrix were studied. The quantity released per unit surface area in single-surface release experiments was found to be proportional to the square root of time. The hardness of the tablet had little effect on the release-rate constant, although some tablets swelled and broke open before complete elution. Heating the tablets at 70° or exposing them to acetone vapor prevented the breaking and increased the release-rate constant. The effects of drug, drug concentration, compressional force, heating, and exposure to acetone vapor on the drug release-rate constant were analyzed in terms of matrix porosity and tortuosity. Drug release from tablets in which the total surface was exposed showed little deviation from linearity during the first 75% of the release when plotted against the square root of time.

Keyphrases □ Drug release—methyl acrylate–methyl methacrylate matrix □ Kinetics, drug release—copolymer matrix □ Release rate, drug–copolymer matrix—factors affecting □ Linearity—drug release from matrix *versus* square root of time

Higuchi (1) suggested that the release of drug from a planar system having an insoluble granular matrix should follow the equation:

$$Q = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_S)C_S t\right]^{1/2} \qquad \text{(Eq. 1)}$$

where Q = the amount of drug released after time t per unit exposed area, D = the diffusivity of the drug in the permeating fluid, τ = the tortuosity, A = the amount of drug present in the matrix per unit volume, C_S = the solubility of the drug in the permeating fluid, and ϵ = porosity of the matrix.

Desai *et al.* (2–5) studied this relationship extensively, using polyvinyl chloride and polyethylene as the insoluble matrixes. Drug release from tablets compressed using the latter plastic was found to be linear with the square root of time, as predicted by Eq. 1. Singh *et al.* (6, 7) extended the study to solid drug mixtures using the same two plastics.

The purpose of this investigation was to examine drug release from a methyl acrylate–methyl methacrylate copolymer matrix. The use of this plastic as the matrix substance in tablets suitable for oral administration has been described (8, 9). Four commonly used drugs were employed in this evaluation. Release rates from one surface were obtained to determine whether the described relationship is applicable. Release rates from tablets in which all surfaces were exposed to the release medium were obtained for comparison.

EXPERIMENTAL

Chemicals—The plastic used for all tablets was a powdered methyl acrylate–methyl methacrylate copolymer.[1] This plastic is insoluble and inert in aqueous media at all pH values. The drugs used were either USP or NF grade.

[1] Rohm & Haas Co., Philadelphia, Pa.

Table I—Physical Constants of Drugs Used

Drug	$\lambda_{max.}$, nm.	ρ, g. cm.$^{-3}$	Solubility at 37°, g./ml.	$D \times 10^6$, cm.^{2}-sec.$^{-1}$	Predominant Particle-Size Range, μ[a]
Sodium pentobarbital	240[b]	1.342	0.750[c]	18.5	149
Methapyrilene HCl	312[d]	1.295	0.676[d]	19.2	149
Ephedrine HCl	257[d]	1.203	0.325[d]	21.9	177–420
Dextromethorphan HBr	278[d]	1.368	0.036[d]	18.3	149

[a] Range containing greater than 75% by weight of the drug. [b] In 0.1 *N* NH_4OH. [c] In water. [d] In 0.1 *N* HCl.

Determination of Physical Constants of Drugs—The particle-size ranges were determined using U.S. Standard sieves with a Ro-Tap mechanical shaker. Solubilities were obtained by adding an excess of drug to the solvent, shaking the mixture in a 37° water bath for 24 hr. with a Burrell wrist-action shaker, filtering, and assaying by UV spectrophotometry. Densities were determined with a Beckman air compression pycnometer, model 930. Diffusion coefficients were obtained using the procedure described by Desai *et al.* (3). This method involves measurement of the solute transfer rate through a sintered-glass disk located between two conical flasks. The cell constant, using a saturated sodium salicylate solution at 30°, was found to be 0.380 cm. For the drugs used in this study, the diffusion coefficients were measured at 37° using saturated solutions. In all cases the diffusion of drug across the sintered glass was linear with time after 1 hr.

The physical constants determined for the drugs used are listed in Table I.

Tablet Compression—All tablets were compressed on a Manesty layer press using 1.03-cm. ($^{13}/_{32}$-in.) flat-face punches and dies. Uniform mixtures of drug and plastic were used. For each drug–plastic mixture, tablets were compressed at several different hardnesses ranging from 12 to 27 Strong-Cobb hardness units. In all cases, tablets weighing approximately 242 mg. were made. Exact thickness and weight measurements were then obtained on 20 tablets to establish the averages for each lot. All individual values were within 3% of the mean.

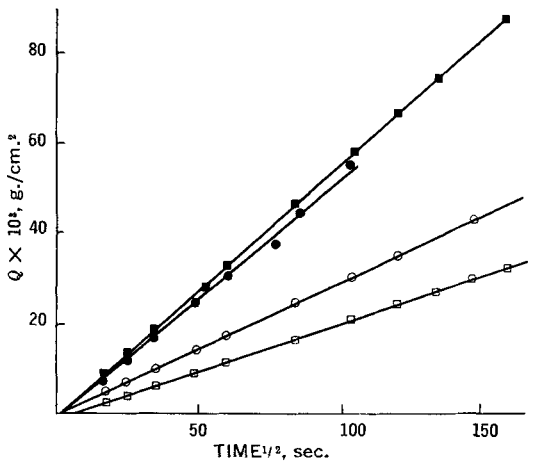

Figure 1—*Single-surface release from tablets containing 100 mg. of drug. Key:* ●, *sodium pentobarbital;* ■, *methapyrilene HCl;* ○, *ephedrine HCl; and* □, *dextromethorphan HBr.*

Table II—Release-Rate Constants and Fractional Release Times from Single-Surface Leach Tests on Tablets

Drug	Concentration, mg./Tablet	$k \times 10^4$, g. cm.$^{-2}$ sec.$^{-1}$	Time (hr.) Required for Release of 25%	50%	75%
Sodium pentobarbital	50	2.25	1.21	4.83	10.86
	100	5.38	0.84	3.38	7.60
Methapyrilene HCl	50	2.05	1.45	5.81	13.08
	100	5.48	0.81	3.25	7.32
Ephedrine HCl	50	1.46	2.87	11.46	25.79
	100	2.94	2.83	11.31	25.44
Dextromethorphan HBr	30	0.606	5.99	23.95	53.88
	100	2.14	5.33	21.34	48.01

Release-Rate Determinations—Release rates from a single tablet surface were determined using a resin-kettle flask with four ground-glass openings in the cover. The flask contained 600 ml. of solvent maintained at 37° in a constant-temperature water bath. Water was used in the sodium pentobarbital leaches, while 0.1 *N* HCl was used for methapyrilene hydrochloride, ephedrine hydrochloride, and dextromethorphan hydrobromide. Tubes containing one tablet each, imbedded in wax with only one flat face exposed, were inserted into three of the openings, so that the tablets were 2.54 cm. (1 in.) below the solvent surface. The fourth opening was equipped with a motor-driven stainless steel stirrer run at 100 r.p.m. Results from experiments using 200 and 400 r.p.m. indicated that the stirring rate was not critical.

Release rates from the total tablet surface were determined by putting three tablets into a basket of 40-mesh screen attached to a stirring rod. The chamber was then inserted into a resin-kettle flask containing 600 ml. of solvent at 37° and rotated at 100 r.p.m.

In both test methods, samples were withdrawn periodically through a small drilled hole which was otherwise closed with a stopper. The samples were assayed spectrophotometrically after the required dilutions.

RESULTS AND DISCUSSION

For a particular drug with solubility C_S, diffusivity D, and a given drug matrix concentration A, if τ and ϵ remain constant, drug release from a single surface should follow the relationship

$$Q = kt^{1/2} \qquad \text{(Eq. 2)}$$

where k is the release-rate constant and

$$k = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_S)C_S\right]^{1/2} \qquad \text{(Eq. 3)}$$

All tablets formulated with methyl acrylate–methyl methacrylate copolymer were found to follow the time dependency predicted by Eq. 2. Linearity was obtained when Q was plotted *versus* $t^{1/2}$ in single-surface release experiments from tablets compressed at maximum hardnesses (Figs. 1 and 2). Table II shows the release-rate constants obtained from these tablets. The table also includes the time required for 25, 50, and 75% drug release which is calculated from the following expression:

$$t_F = \left(\frac{Q_\infty F}{k}\right)^2 = \left(\frac{IF}{kS}\right)^2 \qquad \text{(Eq. 4)}$$

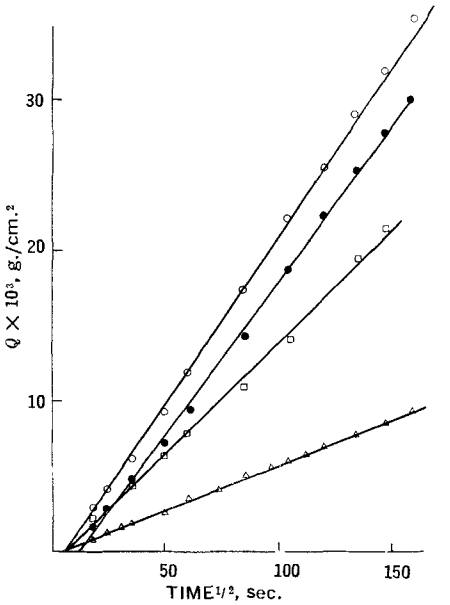

Figure 2—*Single-surface drug release from tablets. Key:* ○, *sodium pentobarbital, 50 mg.;* ●, *methapyrilene HCl, 50 mg.;* □, *ephedrine HCl, 50 mg.; and* △, *dextromethorphan HBr, 30 mg.*

where t_F is the time required to release F fraction of the total amount of drug I in the tablet through surface area S.

The differences in release-rate constants obtained for the four drugs at the same concentration can be attributed to the parameters appearing in Eq. 3. However, because of the physicochemical characteristics of the drugs, these are dependent variables and therefore difficult to study individually. Thus, in a comparison of different drugs there would be not only changes in solubility and diffusivity, but differences in the tortuosity and porosity of the matrix would result. This is exemplified by the solubility effect on the release-rate constant obtained from 100-mg. tablets. Although the release-rate constant increased with greater drug solubility, the increases were not quantitatively identical to those predicted if solubility was the predominant effect. Keeping all variables except solubility constant, the calculated release-rate constants for ephedrine hydrochloride, methapyrilene hydrochloride, and sodium pentobarbital were 2.77, 3.56, and 3.64 times that of dextromethorphan hydrobromide. However, the experimental rate constants obtained for these three drugs were 1.37, 2.56, and 2.51 times dextromethorphan hydrobromide.

The effect of the diffusion coefficient on the release-rate constant appears to be minimal. This is due both to the small differences observed in the values of D for the four drugs and their square root relationship to k. A 12.5% change in the diffusion coefficient (maximum difference observed between the experimental and average values) would change the release-rate constant by only 5.7%.

The effect of drug concentration A on the release-rate constant was tested by studying two different concentrations of each of the four drugs. In comparing the release-rate constants for different concentrations of a single drug, the solubility and diffusion coefficient remain constant. Furthermore, the expression proposed by Higuchi (1)

$$\epsilon = \epsilon_0 + kA \qquad \text{(Eq. 5}$$

Table III—Evaluation of Porosity and Tortuosity Factors

Drug	Concentration, mg./Tablet	Average Weight, g.	Average Thickness, cm.	A, g. cm.$^{-3}$	ϵ_0	ϵ	τ
Sodium pentobarbital	50	0.243	0.294	0.202	0.238	0.389	12.0
	100	0.240	0.264	0.450	0.169	0.505	12.6
Methapyrilene HCl	50	0.243	0.286	0.208	0.210	0.370	18.8
	100	0.248	0.257	0.462	0.109	0.466	12.2
Ephedrine HCl	50	0.244	0.274	0.216	0.164	0.343	36.5
	100	0.240	0.250	0.475	0.084	0.478	31.3
Dextromethorphan HBr	30	0.245	0.280	0.127	0.193	0.286	12.5
	100	0.243	0.251	0.473	0.127	0.472	6.3

Table IV—Effect of Tablet Hardness on Release Rate of 100-mg. Sodium Pentobarbital Tablets

Hardness, Strong-Cobb Units	$k \times 10^4$, g. cm.$^{-2}$ sec.$^{-1/2}$	ϵ_0	ϵ	τ
13.1	5.21	0.254	0.554	11.1
16.7	5.57	0.235	0.541	10.2
20.0	5.56	0.219	0.536	10.8
23.2	5.30	0.188	0.515	12.6
26.2	5.38	0.169	0.505	12.7

Table V—Effect of 70° Heating and Acetone Vapor Exposure on the Release Rate

Tablet	Treatment	$k \times 10^4$, g. cm.$^{-2}$ sec.$^{-1/2}$	ϵ	τ
Sodium pentobarbital, 100 mg. (hardness = 13.1)	None	5.21	0.554	11.1
	70°	5.87	0.554	8.77
	Acetone	5.50	0.557	10.2
Methapyrilene HCl, 100 mg. (hardness = 14.4)	None	5.10	0.502	13.3
	70°	5.95	0.524	9.29
	Acetone	5.57	0.499	11.1

where ϵ_0 is the initial porosity and k is the specific volume of the drug, indicates that porosity is proportional to the drug concentration A when ϵ_0 is negligible. Assuming this along with relative constancy in the tortuosity, Eq. 2 indicates that k would be proportional to A. Calculations show that increasing the amount of drug per tablet from 50 to 100 mg. with sodium pentobarbital, methapyrilene hydrochloride, and ephedrine hydrochloride and from 30 to 100 mg. in the case of dextromethorphan hydrobromide should increase the k by factors of 2.23, 2.22, 2.20, and 3.72, respectively. The increases obtained experimentally were 2.39, 2.67, 2.01, and 3.53, respectively. The small differences between the calculated and observed values can be attributed to a significant ϵ_0 and tortuosity changes accompanying changes in drug concentrations.

The porosities and tortuosities for these tablets are shown in Table III. The porosity values were calculated from Eq. 5. For these tablets, ϵ_0 was obtained by dividing the calculated volume of air by the tablet volume. The tablet volume was calculated from its dimension, while the air volume was obtained by subtracting the calculated volumes of drug and plastic (density = 1.275 g./ml.) from the volume of the tablet.

The tortuosity values were calculated from Eq. 3. Generally, the tortuosity was found to decrease with increasing concentration of drug in the tablet. This decrease, however, varied from practically zero in the case of sodium pentobarbital to a factor of 2 when dextromethorphan hydrobromide concentration was increased 3.33 times. The higher tortuosities obtained with ephedrine hydrochloride *versus* the other drugs may be attributed to its larger particle-size distribution (177–420 μ *versus* less than 149 μ). Desai *et al.* (2) observed that larger particle sizes of solute exhibit considerably higher tortuosities than smaller particle sizes.

The hardness of the tablet was found to have little effect on the leach rate. When a sodium pentobarbital–plastic blend was compressed to five different hardnesses, from 13 to 26 Strong-Cobb units, the release-rate constants varied randomly from 5.21 to 5.57 $\times$ 10^{-4} g. cm.$^{-2}$ sec.$^{-1/2}$. The results are shown in Table IV. Similar results were obtained in a study using methapyrilene hydrochloride tablets with varying hardnesses. Although a lower compression force increases the tablet porosity, it also decreases the tortuosity. Thus, it appears that the changes in the release-rate constant caused by these two parameters are compensating to some extent.

During release-rate testing, tablet breakage occurred with all 100-mg. sodium pentobarbital tablets before completion of drug release. This resulted in positive deviation from Eq. 2. This breakage came after 50% release at the higher hardnesses and 25% release at hardness 13. No such problem was encountered with the other three drugs, where tablets with hardnesses as low as 14.4 remained intact throughout the leach.

Heating the tablets at 70° for 24 hr. was found to overcome the rapid sodium pentobarbital tablet breakage observed in the softest tablet. However, such treatment increased the release-rate constant substantially. Likewise, this heating condition increased the methapyrilene hydrochloride release-rate constant from the softest tablet to the same extent. These results are given in Table V. It appears that the rate increase caused by heating can be attributed to a marked decrease in tortuosity.

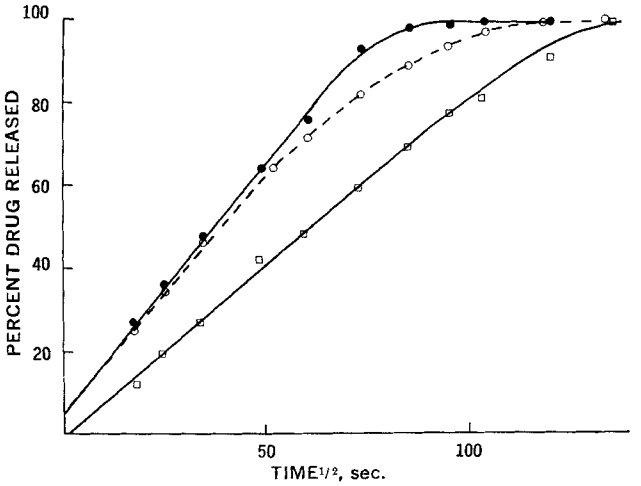

Figure 3—*Drug release from tablets in which all surfaces are exposed. Key:* ●, *sodium pentobarbital, 100 mg.;* ○, *methapyrilene HCl, 100 mg.; and* □, *ephedrine HCl, 50 mg.*

Exposure of sodium pentobarbital tablets to acetone vapor (9) was also found to overcome the tablet breakage problem. In this treatment the tablets were kept in a desiccator under 200 mm. Hg acetone vapor for 2 hr. at 33°. The residual acetone was then eliminated from the tablets at 50°. The results of such treatment are given in Table V. As in the case of the 70° heating, the tortuosity decreased and the release-rate constant increased, but to a lesser extent.

The leach rate of drug from the total tablet surface was also studied. Higuchi's evaluation (1) of drug release from a spherical pellet would indicate that initial release should follow the square root of time relationship, but that significant deviation would occur toward the end of the leach. Figure 3 shows the results obtained from three tablets when the percent of drug released was plotted against the square root of time. In all cases there appeared to be little deviation from linearity during the release of the first 75% of the drug. Apparently, the flat cylindrical shape of the tablet gives more prolonged linearity than a sphere.

SUMMARY AND CONCLUSIONS

The results of this study show that drug release from tablets compressed directly from mixtures of drug and methyl acrylate–methyl methacrylate copolymer follow the time dependency suggested by Higuchi's theoretical relationship (1). This was observed to be the case with all four drugs tested. The release rate for any given tablet may be expressed by a constant k, equal to the slope of the Q *versus* $t^{1/2}$ plot, or by a fractional life term. The magnitude of this release-rate constant is dependent on the matrix porosity and tortuosity as well as the solubility, diffusivity, and concentration of the drug.

Deviation from linearity occurs only when tablets break open before completion of drug release. This breakage may be prevented by heat or exposure to acetone vapor.

Tablet hardness appears to have little effect on the release-rate constant. This can be attributed to compensating effects from tortuosity and porosity.

Drug release from tablets in which all surfaces are exposed shows little deviation from the Q *versus* $t^{1/2}$ linearity during the first 75% of the release. Greater deviations in the later stages can be attributed to geometric effects.

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Drug Release from Methyl Acrylate–Methyl Methacrylate Copolymer Matrix II: Control of Release Rate by Exposure to Acetone Vapor

B. FARHADIEH, S. BORODKIN, and J. D. BUDDENHAGEN

Abstract □ The rate of drug release from tablets made with a methyl acrylate–methyl methacrylate copolymer matrix containing dispersed solid drug can be decreased by exposure to acetone vapor. As in the case of untreated tablets, the quantity of drug released per unit surface area is proportional to the square root of time. An apparatus was developed to study the treatment variables. The extent of reduction in release rate is dependent on the amount of acetone absorbed. This reduction is primarily due to an increase in the tortuosity of the matrix. Generally, the release-rate constant is lowered by decreasing the temperature or increasing the acetone vapor pressure. Thus, exposure of tablets to acetone vapor under controlled conditions is an added means for regulating the drug-release rate.

Keyphrases □ Drug release—methyl acrylate–methyl methacrylate matrix □ Acetone vapor effect—drug release rates, copolymer matrix □ Temperature, pressure effects—acetone absorption, copolymer matrix □ Tortuosity, copolymer matrix—drug release-rate relationship

In the first paper of this series (1), it was shown that the release of drug from a methyl acrylate–methyl methacrylate copolymer matrix follows the relationship proposed by Higuchi (2), in which the amount of drug released per unit surface area is linear with the square root of time. Desai *et al.* (3–6) studied this theoretical relationship extensively, using polyethylene and polyvinyl chloride as plastic matrixes. Endicott (7) demonstrated that the release of drug from tablets compressed with methyl acrylate–methyl methacrylate copolymer can be prolonged by exposure to acetone vapor.

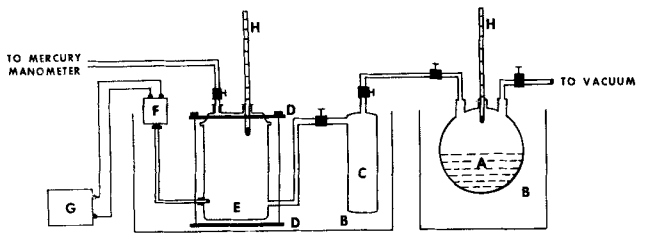

Figure 1—*Acetone vapor treatment apparatus. Key: A, acetone reservoir; B, constant-temperature water bath; C, acetone vapor trap; D, holder plastic plate; E, acetone treatment chamber; F, pressure sensor; G, amplifier and recorder; and H, thermometer.*

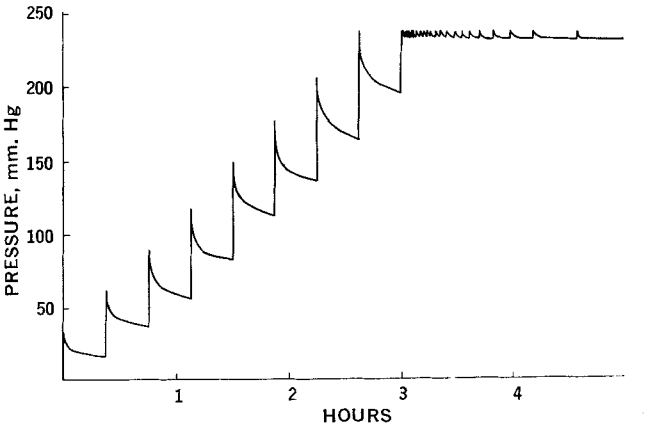

Figure 2—*Recorder tracing of acetone vapor pressure* versus *time at 29°.*

The purposes of this study were: (*a*) to determine whether drug release from tablets treated with acetone vapor would continue to follow the square root of time relationship, and (*b*) to use this relationship to evaluate the effect of different exposure conditions. The tablets used were primarily those made with sodium pentobarbital, although other drugs were examined. The principal acetone exposure variables were temperature and acetone vapor pressure.

EXPERIMENTAL

Chemicals—The plastic used in all tablets was a powdered methyl acrylate–methyl methacrylate copolymer (8).[1] This polymer is insoluble and inert in aqueous media at all pH values. The acetone was reagent grade. All drugs were USP or NF. The densities, diffusion constants, solubilities, and particle-size ranges of these drugs were determined previously (1).

Tablet Compression—All tablets were compressed on a Manesty

[1] Rohm & Haas Co., Philadelphia, Pa.