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Drug Release from Methyl Acrylate–Methyl Methacrylate Copolymer Matrix III: Simultaneous Release of Noninteracting Drug–Excipient Mixtures

B. FARHADIEH

Abstract □ The simultaneous release of mixtures of noninteracting chemicals incorporated in a methyl acrylate–methyl methacrylate copolymer was studied. Different mixtures of dextrose–methapyrilene hydrochloride and sodium chloride–methapyrilene hydrochloride in the plastic were compressed into tablets, and single-surface release was obtained in 0.1 *N* HCl at 37°. The amounts of both drug and excipients released per unit surface area were linearly dependent on the square root of time. The release rate constants were analyzed in terms of the solubility, diffusion coefficient, concentration of each chemical, and porosity and tortuosity of the tablets. It was concluded that for each tablet system the individual solid–liquid boundaries of the incorporated chemicals had merged together, and the release could be explained by Higuchi's square root of time relationship.

Keyphrases □ Methyl acrylate–methyl methacrylate copolymer—tablets, simultaneous release of noninteracting drug–excipient mixtures □ Copolymers—methyl acrylate–methyl methacrylate copolymer tablets, simultaneous release of noninteracting drug–excipient mixtures □ Drug release—from methyl acrylate–methyl methacrylate copolymer tablets, effect of water-soluble excipients □ Tablets—water-soluble drug in methyl acrylate–methyl methacrylate copolymer tablets, effect of water-soluble excipients □ Methapyrilene hydrochloride—release from methyl acrylate–methyl methacrylate copolymer tablets, effect of water-soluble excipients

It was shown previously (1) that drug release from tablets compressed directly from mixtures of a single drug and a methyl acrylate–methyl methacrylate copolymer follows the time dependency suggested by Higuchi's (2) theoretical relationship. The magnitude of the release rate constant was dependent on the solubility, diffusivity, and concentration of the drug as well as the matrix porosity and tortuosity.

BACKGROUND

Singh *et al.* (3) considered the simultaneous release of a mixture of two noninteracting drugs dispersed in an inert insoluble matrix composed of a polyethylene–polyvinyl chloride mixture. The developed relationships expressed the diffusion-controlled rate of release of both drugs as functions of solubilities, diffusivities, and concentrations of each drug in the matrix and the porosities and tortuosities of the matrix. Thus, the release of drug a, which had the slower moving solid–liquid boundary, was described by (2):

$$\frac{dQ_a}{d(t^{1/2})} = \left[D_a \frac{\epsilon_1}{\tau_1} (2A_a - \epsilon_1 C_a{}^s) C_a{}^s \right]^{1/2} \qquad \text{(Eq. 1)}$$

where subscript 1 refers to that region of the tablet matrix bounded on one side by the solvent front and on the other side by the solid–liquid boundary of drug a. This part of the tablet will be described as region 1 in subsequent discussions. The release of drug b, with the faster moving solid–liquid boundary, was described by the following, more complex, expression:

$$\frac{dQ_b}{d(t^{1/2})} = \frac{2D_b\epsilon_1}{\tau_1 \dfrac{k_a}{A_a}} \left[\frac{\dfrac{\epsilon_2}{\tau_2} C_b{}^s}{\dfrac{\epsilon_2}{\tau_2} + \dfrac{\epsilon_1}{\tau_1} \left[\dfrac{\dfrac{k_b}{A_b} - \dfrac{k_a}{A_a}}{\dfrac{k_a}{A_a}} \right]} \right] \qquad \text{(Eq. 2)}$$

where subscript 1 is the same as in Eq. 1, and subscript 2 refers to region 2 in the tablet bounded on one side by the solid–liquid boundary for drug a and on the other side by the solid–liquid boundary for drug b. Other symbols used in Eqs. 1 and 2 are defined as follows:

- Q_i = grams of drug i released per unit area of exposed tablet surface at time t
- D_i = diffusion coefficient of drug i in the release medium
- A_i = concentration of drug i in the tablet
- $C_i{}^s$ = solubility of drug i in the release medium
- ϵ_j = porosity of region j of the tablet
- τ_j = tortuosity of region j of the tablet
- k_i = slope of Q_i *versus* $t^{1/2}$ plot for release of drug i from the tablet

The methyl acrylate–methyl methacrylate copolymer has been used to control and regulate the release of highly water-soluble drugs. The purpose of this investigation was to investigate the effect of two common, highly water-soluble excipients on the release of a model of a highly water-soluble drug from matrixes of this copolymer. Methapyrilene hydrochloride was selected as the model drug. It was also proposed to determine whether the mathematical model developed by Singh *et al.* (3) and tested with salicylic and benzoic acid combinations was valid for simultaneous release of highly water-soluble noninteracting chemicals.

EXPERIMENTAL

Chemicals—The plastic used in all tablets was a powdered methyl acrylate–methyl methacrylate copolymer[1]. This polymer is insoluble and inert in aqueous media at all pH values. The drug employed was methapyrilene hydrochloride NF. Anhydrous dextrose USP and

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

Table I—Physical Constants of Chemicals Used

Chemical	Wavelength of Maximum Absorption, nm	Density, g/cm³	Solubility at 37°, g/ml	Diffusion Coefficient, $D \times 10^6$ cm²/sec
Plastic[a]	—	1.275	—	—
Methapyrilene hydrochloride	312[b]	1.295	0.676	19.2
Dextrose	425	1.513	0.766	9.22
Sodium chloride	589[c]	2.164	0.317	21.04

[a] Methyl acrylate–methyl methacrylate copolymer. [b] In 0.1 *N* HCl. [c] Atomic absorption method.

200-mesh sodium chloride powder (CP) were used as the other noninteracting soluble constituents of the tablets.

Physical Constants (Table I)—The pertinent physical constants of methapyrilene hydrochloride and the plastic were determined previously (1). The solubility of sodium chloride in water at 37° was determined by phase solubility analysis (4). Saturated aqueous solutions of dextrose, prepared at 37°, were assayed to obtain dextrose solubility. Densities of sodium chloride and dextrose were measured by the method described previously (1). The procedure described by Desai *et al.* (5) was used to obtain the diffusion coefficient of sodium chloride. The diffusion coefficient of dextrose at 37° was estimated by the method of Wilke (6).

The following complexation–solubility studies were carried out to see whether the drug–excipient mixtures were noninteracting. An excess of methapyrilene hydrochloride (8.0 g) was weighed into several 50-ml glass-stoppered erlenmeyer flasks, and 2 ml of 0.1 *N* hydrochloric acid solution was added to each. Known, but varying, quantities of either sodium chloride or dextrose were then added to these flasks. The stoppered flasks were equilibrated for 24 hr in a 25° constant-temperature shaking water bath. The content of each flask was centrifuged and an aliquot of the clear supernatant liquid was taken, diluted with 0.1 *N* hydrochloric acid solution, and assayed for the methapyrilene content.

Tablet Compression and Treatment—All tablets were compressed on a modified laboratory press[2], using 1.03-cm ($^{13}/_{32}$-in.) flat-faced punches and die. Different weight-to-weight ratios of sodium chloride and methapyrilene hydrochloride or dextrose and methapyrilene hydrochloride were homogeneously dispersed in the plastic and compressed. The total weight of the drug and inert chemical was maintained at 56.6% of tablet weight. For each mixture, compressional force was adjusted to yield tablets with hardnesses ranging from 12 to 14 Strong-Cobb hardness units[3].

In all cases, tablets weighing approximately 300 mg were made. Exact thickness and weight measurements were obtained on 10 tablets to establish the average for each lot. All individual values were within 1.0% of the mean. To prevent possible tablet breakage during release rate studies, all tablets were heat treated at 60° for 24 hr.

Release Rate Determinations—The apparatus and procedure used in the determination of release rates from a single tablet surface were described previously (1). Release data are based on a single experiment with three tablets used in each experiment. The solvent was 0.1 *N* HCl; it was kept at a constant temperature of 37° and agitated constantly at 100 rpm. Samples were withdrawn periodically and assayed for methapyrilene hydrochloride, sodium chloride, or dextrose.

Due to the high solubilities of methapyrilene hydrochloride and the two inert chemicals used, release studies were limited to tablets in which the ratios of inert soluble chemical to methapyrilene were 2:1, 1:1, and 1:2. At extreme ratios ($\geq$3:1 or $\leq$1:3), $\epsilon_1 C_s > 2A$ and Eq. 1 cannot be applied.

Assay Procedures—Methapyrilene hydrochloride was assayed by UV spectrophotometry at 312 nm. An atomic absorption spectrophotometer[4] was used for the determination of sodium chloride. In this method, samples diluted with 0.1 *N* hydrochloric acid were atomized into an air–acetylene flame and the sodium content was measured at 589 nm. Dextrose was assayed colorimetrically at 425 nm using the method of Keston (7) and Teller (8). The accuracy of the individual assay methods was better than 1.0%.

RESULTS AND DISCUSSION

The results of complexation–solubility experiments show that the drug excipients used in this study can be considered noninteracting in the sense that they do not interact to produce a new species with completely different physicochemical properties. Due to its high solubility, the saturated solution of methapyrilene hydrochloride could be considered nonideal. Addition of other soluble chemicals to such a system could cause a drop in the saturation solubility of the drug through salting out or the common ion effect. Thus, in solutions

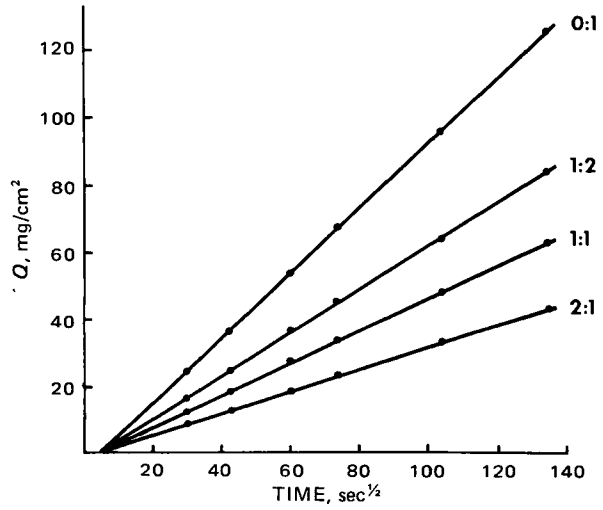

Figure 1—*Release of methapyrilene hydrochloride from tablets containing different ratios of dextrose to methapyrilene hydrochloride.*

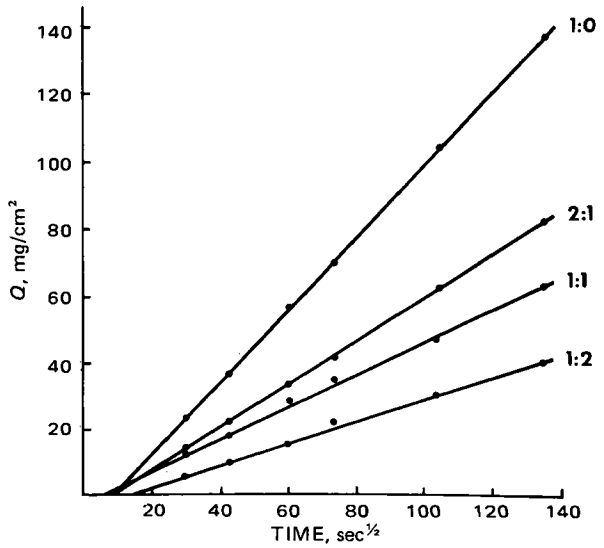

Figure 2—*Release of dextrose from tablets containing different ratios of dextrose to methapyrilene hydrochloride.*

[2] Model B, Carver laboratory press, Fred S. Carver, Inc., Menomonee Falls, WI 53051

[3] Abbott modified Strong-Cobb hardness unit.

[4] Model 303, Perkin-Elmer Corp., Norwalk, Conn.

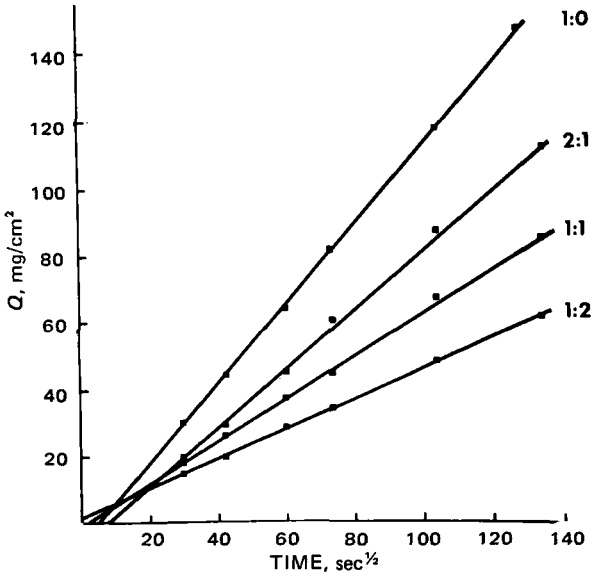

Figure 3—*Release of sodium chloride from tablets containing different ratios of sodium chloride to methapyrilene hydrochloride.*

containing 0.3 and 0.6 *M* sodium chloride, the methapyrilene solubility decreased by 6 and 19%, respectively. Similarly, in solutions containing 0.1 and 0.5 *M* dextrose, the solubility decreased by 7 and 11%, respectively.

The individual release profiles of methapyrilene hydrochloride and dextrose for tablets containing various ratios of these two chemicals are presented in Figs. 1 and 2, respectively. Similarly, Figs. 3 and 4 summarize the results of release studies for tablets containing different ratios of sodium chloride and methapyrilene hydrochloride. In each release study, dissolution was followed until at least 80% of each soluble component of the tablets had been released.

The total amounts released from dextrose–methapyrilene hydrochloride tablets and from sodium chloride–methapyrilene hydrochloride tablets are displayed in Figs. 5 and 6, respectively. These curves were prepared by the method of least squares (9). The good linearity of these lines, as evidenced by their statistically high correlation coefficient (Tables II and III), indicates that the amount released per unit tablet surface area is a linear function of the square root of time for both the total and the individual soluble components of the tablets studied. These linear fits also confirm that release of the soluble components of the tablets is diffusion controlled and adheres to either Eq. 1 or 2, depending on the magnitude of the inert soluble chemical to methapyrilene hydrochloride ratio.

The longest lag time observed (Figs. 1–6) was about 1.5 min (9.5

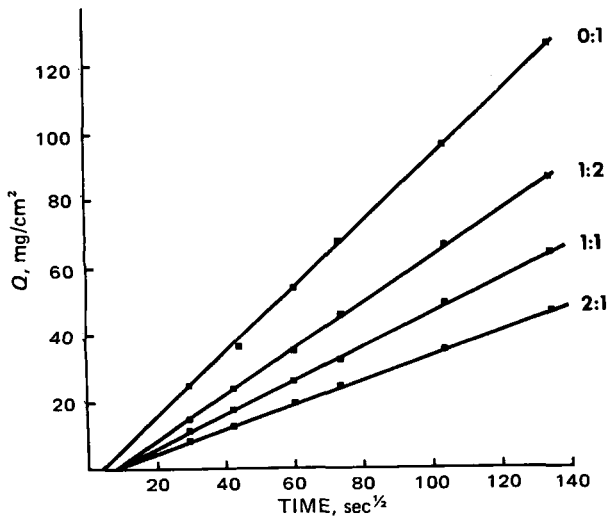

Figure 4—*Release of methapyrilene hydrochloride from tablets containing different ratios of sodium chloride to methapyrilene hydrochloride.*

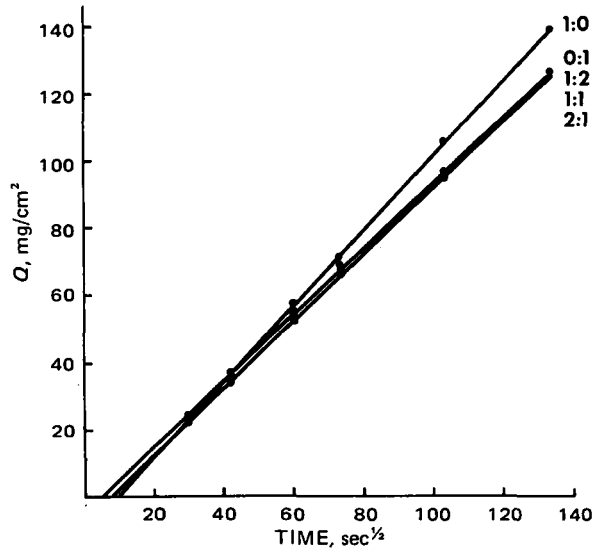

Figure 5—*Sum of methapyrilene hydrochloride and dextrose release in the same experiments as in Figs. 1 and 2.*

sec$^{1/2}$) and was probably due to initial wetting of the tablet surface and establishment of the pseudo-steady-state condition required by the model (2, 3). The observed lag time, however, was very short in comparison to the total depletion time (approximately 5 hr) and can, therefore, be ignored (10). For the same reason, its inclusion or exclusion in computation of the release rate constant should have an insignificant effect on the magnitude of the rate constant.

The release rate constants for tablets containing dextrose and methapyrilene hydrochloride are given in Table II. Similar data for tablets containing sodium chloride and methapyrilene hydrochloride are given in Table III. The condition of an equal boundary movement rate for dextrose–methapyrilene hydrochloride is satisfied when the ratio of their respective concentrations in the tablet matrix (A_{dex}/A_{meth}) equals 1:1.95. For tablets containing sodium chloride–methapyrilene hydrochloride, that condition exists when (A_{NaCl}/A_{meth}) equals 1:1.80.

According to Singh *et al.* (3), Eq. 1 is valid for release of the chemical whose boundary is moving at a lower rate. Thus, for dextrose–methapyrilene hydrochloride tablets, this equation can be used to describe methapyrilene hydrochloride release at ratios lower than 1:1.95 and dextrose release at higher ratios. Similarly, for sodium

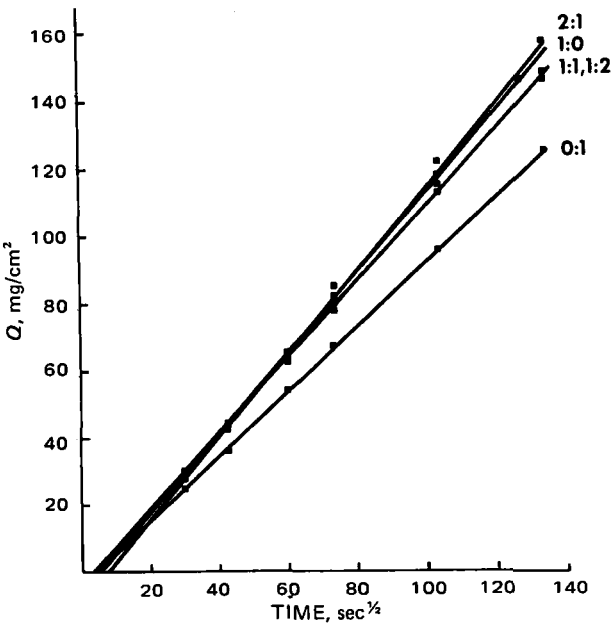

Figure 6—*Sum of sodium chloride and methapyrilene hydrochloride release in the same experiments as in Figs. 3 and 4.*

Table II—Release Rate Constants for Dextrose–Methapyrilene Hydrochloride Tablets

A_{dex}/A_{meth} Ratio	A_{dex}, g/cm³	A_{meth}, g/cm³	$k_{dex} \times 10^4$[a], g/cm² sec½	$k_{meth} \times 10^4$[a], g/cm² sec½
1:0	0.699	—	10.9 (0.996)	—
2:1	0.461	0.230	6.6 (0.999)	3.3 (0.999)
1:1	0.339	0.339	4.9 (0.999)	4.7 (0.999)
1:2	0.222	0.445	3.3 (0.999)	6.4 (0.999)
0:1	—	0.607	—	9.6 (0.999)

[a] Values in parentheses are the correlation coefficients for plot of amount released per unit tablet surface area *versus* square root of time.

Table III—Release Rate Constants for Sodium Chloride–Methapyrilene Hydrochloride Tablets

A_{NaCl}/A_{meth} Ratio	A_{NaCl}, g/cm³	A_{meth}, g/cm³	$k_{NaCl} \times 10^4$[a], g/cm² sec½	$k_{meth} \times 10^4$[a], g/cm² sec½
1:0	0.739	—	11.9 (0.999)	—
2:1	0.458	0.228	8.6 (0.998)	3.5 (0.999)
1:1	0.339	0.339	6.5 (0.999)	5.0 (0.999)
1:2	0.207	0.416	4.47 (0.999)	6.7 (0.999)
0:1	—	0.607	—	9.6 (0.999)

[a] Values in parentheses are the correlation coefficients for plot of amount released per unit tablet surface area *versus* square root of time.

chloride–methapyrilene hydrochloride tablets, sodium chloride release can be explained by Eq. 1 when the ratio is higher than 1:1.80, and it can be used for methapyrilene hydrochloride release at lower ratios.

The total porosity of the matrix, the diffusion coefficient, the solubility, and the concentration in the matrix of the predicted slower moving component of each tablet studied were substituted in Eq. 1, and the apparent tortuosity values, τ_1, for region 1 were calculated (Tables IV and V). The values listed in parentheses in Tables IV and V were obtained by using the parameters of the faster moving chemicals in these calculations. Although these values are incorrect (3), they are listed for comparison purposes.

The tortuosity values for each component of the two tablet systems studied are practically the same and are not greatly affected by the ratios of soluble excipient to drug. An explanation for these results would be to assume that region 2 has practically disappeared in each tablet system and that the boundaries of both soluble components of each tablet have merged to a single boundary moving at a fixed rate.

According to the theory (3) for the simultaneous release of a mixture of two noninteracting drugs dispersed in an inert plastic matrix, the position of the solid–liquid boundary, s_i, for drug i at time t is given by:

$$s_i = (k_i/A_i)t^{1/2} \qquad \text{(Eq. 3)}$$

where k_i and A_i are as defined previously. The s values for both soluble components of dextrose–methapyrilene hydrochloride tablets were calculated at the time period when 50% of each soluble component of the tablets was released (Table VI). The time required for 50% release was determined by the method discussed previously (1).

Table IV—Tortuosity of Region 1 for Tablets Containing Dextrose and Methapyrilene Hydrochloride

A_{dex}/A_{meth} Ratio	ϵ[a] Total	τ_1 Dextrose	τ_1 Methapyrilene
1:0	0.580	3.30	—
2:1	0.585	4.48	(4.56)[b]
1:1	0.596	3.97	(9.47)[b]
1:2	0.598	—[c]	9.10
0:1	0.634	—	7.10

[a] $\epsilon_{total} = \epsilon_{dex} + \epsilon_{meth} + \epsilon_{air}$; Ref. 1. [b] Incorrect value, included for comparison purposes. [c] The value of $(2A - \epsilon_1 C_s)$ is negative.

Table V—Tortuosity of Region 1 for Tablets Containing Sodium Chloride and Methapyrilene Hydrochloride

A_{NaCl}/A_{meth} Ratio	ϵ[a] Total	τ_1 Sodium Chloride	τ_1 Methapyrilene
1:0	0.552	3.33	—
2:1	0.589	3.86	(3.54)[b]
1:1	0.594	4.62	(8.44)[b]
1:2	0.626	(4.51)[b]	7.29
0:1	0.636	—	7.10

[a] $\epsilon_{total} = \epsilon_{NaCl} + \epsilon_{meth} + \epsilon_{air}$. [b] Incorrect value, included for comparison purposes.

Table VI—Solid–Liquid Boundary Position(s) at $t_{50\%}$ Release for Tablets Containing Dextrose–Methapyrilene Hydrochloride

A_{dex}/A_{meth} Ratio	$t_{50\%}$ Release, hr, for Dextrose	$t_{50\%}$ Release, hr, for Methapyrilene Hydrochloride	$s \times 10^2$, cm, at $t_{50\%}$ Release for Dextrose	$s \times 10^2$, cm, at $t_{50\%}$ Release for Methapyrilene Hydrochloride
2:1	2.88	2.91	14.5	14.6
1:1	3.01	3.15	14.9	14.9
1:2	2.88	3.04	15.2	15.1

Table VII—Solid–Liquid Boundary Position(s) at $t_{50\%}$ Release for Tablets Containing Sodium Chloride–Methapyrilene Hydrochloride

A_{NaCl}/A_{meth} Ratio	$t_{50\%}$ Release, hr, for Sodium Chloride	$t_{50\%}$ Release, hr, for Methapyrilene Hydrochloride	$s \times 10^2$, cm, at $t_{50\%}$ Release for Sodium Chloride	$s \times 10^2$, cm, at $t_{50\%}$ Release for Methapyrilene Hydrochloride
2:1	1.73	2.53	14.8	14.7
1:1	1.68	2.81	14.9	14.9
1:2	1.57	2.78	16.1	16.2

The $\dot{s}$ values for both soluble components of sodium chloride–methapyrilene hydrochloride tablets are summarized in Table VII. These data are in accord with the assumption made and again indicate that region 2 apparently did not exist in each tablet system for the ratios studied. The merger of boundaries at these ratios could be expected. The high solubilities of soluble components of each tablet system, plus the restriction imposed by Eq. 1 where $2A > \epsilon C_s$, necessitate the use of A values that are not greatly different from those calculated for the equal boundary movement condition (Tables II and III). Differences of these magnitudes in A values of the soluble components of the tablets investigated apparently are not enough to cause a separation of boundaries of the respective chemicals.

The methyl acrylate–methyl methacrylate copolymer sample used in this study contained octylphenoxyethanol[5], a nonionic surfactant. The concentration of this surfactant in the copolymer was 0.82% (w/w), as measured by the spectrophotometric determination of a 2% (w/v) solution of the copolymer in acetonitrile at 276 nm.

It has been shown (3, 5, 11) that incorporation of the surfactant in the tablet matrix or the release medium increased the release rates of the incorporated drugs and greatly reduced the dependence of the matrix tortuosities on the ratios of the drug mixtures. These effects have been attributed to the enhanced penetration of the release medium into the tablet matrix and elimination of air pockets through the surface tension-lowering effect of the surfactant.

The critical micelle concentration (CMC) of octylphenoxyethanol in water at 25°, as measured by the surface tension method, was 0.016

[5] Triton X-405, Rohm and Haas Co., Philadelphia, Pa.

g/100 ml. Separate solubility studies at concentrations above the surfactant's CMC did not reveal any change in the solubility of soluble chemicals used in this investigation. The concentration of the surfactant in the tablets probably was enough to cause an increase in their porosities and, consequently, to minimize the dependence of tablet tortuosities on the ratios of the soluble components of the tablets.

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Binding of Spirolactones to Human Plasma Proteins

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Abstract □ The lipophilicity and plasma binding of 16 spirolactones and 4 hydroxy acid analogs were determined. Mathematical expressions were derived to correlate quantitatively the extent of plasma binding to the lipophilicity of the drugs. The nonspecific binding of these spirolactones and their hydroxy acid analogs was also analyzed using purified serum albumin. A computer program was developed to examine the mechanism of drug–serum protein interactions. One class of binding sites was observed for the range of concentrations used. The number of binding sites and the equilibrium binding constant were computed and were sensitive to substitution at the C-6 and C-7 positions. Hydrolysis of the C-17 lactone ring in spirolactones to form hydroxy acid analogs resulted in a decrease in the lipophilicity and, hence, the equilibrium constant for binding.

Keyphrases □ Spirolactones—lipophilicity and plasma protein binding determined and correlated quantitatively □ Lipophilicity—spirolactones, correlated quantitatively with plasma protein binding □ Plasma protein binding—spirolactones, quantitatively correlated with lipophilicity □ Binding, plasma protein—spirolactones, quantitatively correlated with lipophilicity

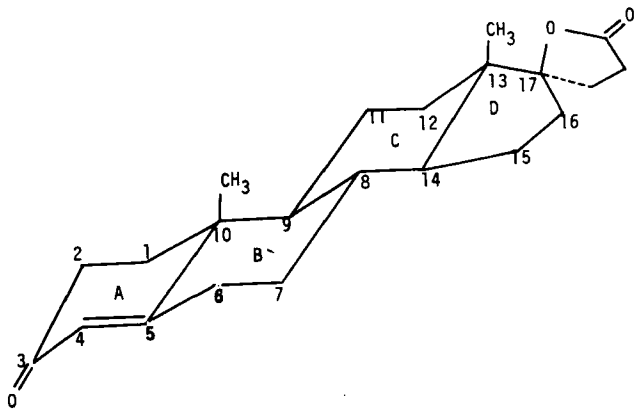
Spironolactone[1] has been used clinically to manage refractory edema and found to have the greatest selectivity of the competitive antagonists of aldosterone (1, 2).

The interaction of organic molecules with plasma proteins has been recognized for many years as an important parameter of tissue permeation and clinical efficacy of a drug (3, 4). Recently, this laboratory demonstrated that modifying the molecular structure of disopyramide significantly influenced both the antiarrhythmic activity (5) and the extent of plasma protein–drug interactions (6). Quantitative correlation was observed between the extent of drug–plasma protein interactions and the physicochemical parameters of disopyramide derivatives (6–8). Furthermore, a linear correlation was established between the extent of plasma protein binding and the frontier electron density, estimated by molecular orbital calculations, on the alkyl side chain of trichomonicidal metronidazole[2] derivatives (9).

Biopharmaceutical studies of spironolactone and its derivatives revealed that they were extensively bound to human plasma and that the strength of the plasma binding was sensitive to structural variation. The results are reported and analyzed in this paper.

EXPERIMENTAL

The procedure for measuring the lipophilicity and the membrane ultrafiltration technique for determining the binding of spirolactones to plasma protein and serum albumin[3] (1.4056×10^{-4} *M*) are essen-



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[1] Searle Laboratories, Division of G.D. Searle & Co., Chicago, IL 60680

[2] Flagyl, Searle Laboratories, Division of G.D. Searle & Co., Chicago, IL 60680

[3] Fraction V, fatty acid poor, Nutritional Biochemical Corp., Cleveland, Ohio.