Drug Release from Compressed Hydrophilic Matrices

By H. LAPIDUS* and N. G. LORDI

This study is concerned with the release of drugs from the planar surface and the whole surface of a hydrophilic polymer tablet matrix. The sustained drug-release characteristics of hydroxypropyl methylcellulose 15,000 cps. previously described was found to be the result of a hydration layer being formed at the tablet surface. As long as the integrity of the hydrated polymer was maintained, the release of drug was diffusion controlled. Environmental conditions have been investigated. Diffusion coefficients for the drugs used were calculated by means of the model equations predicting drug release from inert matrices and ointment bases. Comparison of the rates of drug release from the planar surface of a compressed polymer matrix with theoretically predicted values was made.

A PHYSICAL BARRIER is used in the majority of prolonged-action dosage forms to decrease the rate of drug release to the absorption site. One type of prolonged action tablet can be prepared by compressing a mixture of a hydrophilic polymer and drug (1). In contact with moisture, the tablet swells, effecting delayed release of drug. Huber, Dale, and Christenson (2) proposed that drug release was controlled both by drug diffusion through and attrition of the gel sheath formed around the tablet. However, their data precluded quantitative interpretation of the exact mechanism of release.

Recently, the authors reported data characterizing the release of chlorpheniramine maleate from a hydroxypropyl methylcellulose ether matrix (3). Release patterns measured from one face of flat-surfaced tablets could be linearized when plotted as a function of the square root of time. This suggested to us that equations derived by Higuchi (4) and Higuchi (5) for drug release from insoluble matrices and from homogeneous ointments were applicable to this system. A question was also raised concerning the significance of the rate of water penetration through the hydrated matrix as a factor in controlling drug release.

Further data are presented here to establish the extent of application of the Higuchi equations to the availability of both water-soluble and insoluble drugs from hydratable matrices. In addition, the effect of temperature, added diluent, and polymer type on release patterns measured from plane surfaces and whole tablets is reported. Whole-tablet release data were utilized to estimate the relative contributions of attrition and diffusion to drug availability from this type of dosage form. A technique for measurement of drug release from the fully hydrated polymer was also developed in order to ascertain the relative importance of the rate of water penetration and drug diffusion in the gel matrix.

EXPERIMENTAL

Materials—A hydroxypropyl methylcellulose ether 90 HG,[1] 15,000 cps. was selected for detailed study as a base material because of its demonstrated effectiveness in retarding drug release from tablets (2). The other polymers employed as base materials were hydroxypropyl methylcellulose 90 HG, 25 cps., methylcellulose MC, 4,000 cps., sodium carboxymethylcellulose (Hercules Company, Wilmington, Del.), carpolene,[2] and polyvinylpyrrolidone K30 (General Aniline and Film Corp., New York, N. Y.).

Table I lists the drugs employed in this study. Included are the solubilities measured at 37°, the wavelengths used for their spectrophotometric assay, and the moles of drug required to produce an absorbance value of 1.00 in 1 ml. of water. Beer's law was followed in all instances. Chlorpheniramine maleate (CPM) and sodium salicylate were included as examples of water-soluble drugs; benzoic acid and benzocaine were representative of water-insoluble drugs.

Lactose (USP) and tricalcium phosphate (NF) were added as diluents. Neither the diluents nor gums, with the exception of carpolene, interfered with the spectrophotometric analysis. An absorbing species was extracted from carpolene matrices necessitating blank corrections.

Drug Release from Tablets—Tableting granulations were prepared by mixing the drug with the base material and granulating with USP ethanol, except for tablets where polyvinylpyrrolidone and carpolene were used as bases. In these cases, the powders were blended and compressed directly.

Received February 16, 1968, from the College of Pharmacy, Rutgers—The State University, Newark, NJ 07104
Accepted for publication May 3, 1968.
* Present address: Bristol-Myers Co., Products, Hillside, N. J.

[1] Methocel 90 HG, Dow Chemical Co., Midland, Mich.
[2] Carbopol 934, B. F. Goodrich Chemical Co., Akron, Ohio. Carpolene is the title under which this article was provisionally admitted to National Formulary XIII.

TABLE I—SOLUBILITIES AND ABSORBANCE OF DRUGS USED IN THIS STUDY

Drug	Solubility (37°) g./ml.	Wavelength of Maximum Absorbance, mμ	Moles/ml. × 10^7 to Obtain Absorbance of 1.0000
Chlorpheniramine maleate[a]	0.6100	262	1.72
Sodium salicylate[b]	0.6850	294	2.84
Benzocaine[c]	0.0012	282	0.58
Benzoic acid[d]	0.0042	274	13.60

[a] Roselle Labs—USP. [b] Merck Co.—reagent. [c] Merck Co.—NF. [d] New York Quinine Co.—USP.

In some experiments with hydroxypropyl methylcellulose 90 HG, 15,000 cps. hydroalcoholic solutions were used to granulate in order to assess the effect of initial water content on drug-release patterns. Water was added to the USP ethanol in varying concentrations (10 and 20%), and all of the solution was used for the granulation. Increased water concentration in the granulation did not provide any observable effect in drug release from the tablet matrix.

Details of the tableting procedures were previously reported (3). Compression forces of both 3,000 and 10,000 lb. were utilized. However, no significant difference in drug-release patterns was observed from tablets of differing density. This observation has been confirmed by Huber and Christenson (6).

The techniques, equipment, and composition of the solvents used to measure drug release from both the single face of a tablet and whole tablets were previously described (3). Flat-faced tablets of 1.11 cm. ($^7/_{16}$ in.) diameter, weighing 300 mg., were used in all experiments. In cases where the drug concentration was altered or where diluents were added, the polymer concentrations were increased or decreased to produce a 300-mg. tablet.

Two-layer tablets were prepared for some experiments in which the inner layer contained drug and the outer layer was a placebo. This was accomplished by lightly pretamping the drug layer initially placed in the die, adding the placebo granulation, and then compressing the combined granulations.

Drug Release from Gels—Predetermined amounts of drug, diluent, and hydroxypropyl methylcellulose 90 HG, 15,000 or 25 cps. were added to a tared beaker. Approximately 10 ml. of boiling water was added with careful stirring, ensuring complete dispersion of the gum and either dispersion or solution of the drug and diluents. Care was taken to ensure that the stirring did not introduce air into the system. The beaker was then covered with plastic wrap and placed in the freezer compartment of a refrigerator for 15 min., after which time the plastic wrap was removed and the total weight of the beaker and contents recorded. From these values an accurate calculation of total water content was made, thereby determining the exact gel concentration. At this time the gel was completely transparent and contained no air bubbles.

The density of the gel was measured by weighing a quantity of hydroxypropyl methylcellulose 90 HG, 15,000 cps. into a tared graduate having a ground-glass stopper. Approximately 10 ml. of boiling water was then added to the graduate and the contents stirred gently and cooled. From the final weight and volume of the gel, the density was calculated. This figure was used to determine the w/v % drug in the gel.

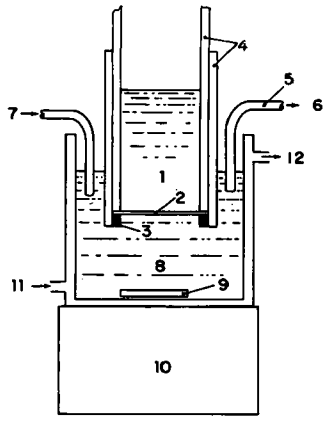

Fig. 1—Sketch of the diffusion cell used to measure drug-release rates from a fully hydrated polymer matrix. Key: 1, hydrated gel; 2, Gelman membrane; 3, Kel-F gasket; 4, Kel-F tubing; 5, Tygon tubing; 6, to Beckman flow cell; 7, from Beckman flow cell; 8, solvent; 9, stirring rod; 10, magnetic stirrer; 11, inlet for water jacket; 12, outlet for water jacket.

The gel was forced into the internal cylinder of the diffusion cell, a sketch of which is shown in Fig. 1, and cut so that it was flush with the bottom of the tube. A precut Gelman Acropor membrane, type AN-3000, pore size 3.0 μ, and 85% porosity (7) was placed over the exposed gel and kept firmly in place by an 0.31-cm. ($^1/_8$-in.) gasket composed of the same Kel-F material. A thin film of silicone grease was applied to the external walls of the inner tube and the tube and gasket forced (telescoped) into the outer sleeve of polymer material. The cylinders were designed to ensure a tight fit in order to prevent any water seepage between the walls. The inner tube was then corked to prevent any water evaporation and the entire cell secured in a jacketed beaker containing 125 or 300 ml. of water maintained at 37°. The volume of solvent was varied, depending on the concentration and absorbancy of the drug being studied. The water level was maintained just above that of the gel plug. The beaker rested on a magnetic stirrer, and a stirring bar was rotated in the beaker at a rapid rate in order to ensure adequate mixing. The release medium was cycled through the flow cell of the spectrophotometer and a continuous recording of the drug release obtained.

Analysis of Results—In applying the Higuchi model to release of drug from a compressed hydrophilic matrix, water penetration is visualized as a front moving into the tablet, hydrating the polymer, and dissolving the active material, which then diffuses out through the swollen matrix. If the drug has limited water solubility such that it has not completely dissolved when the polymer is hydrated, then diffusion will commence from a saturated solution. The expression describing drug release from the single face of a tablet would be (4)

$$\frac{W_r}{t^{1/2}} = S\left[D'\epsilon C_s\left(\frac{2W_0}{V} - \epsilon C_s\right)\right]^{1/2} \quad \text{(Eq. 1)}$$

where W_r is the amount of drug released in time t, W_0 is the dose of the drug, S is the effective diffusional area, V is the effective volume of the hydrated matrix, C_s is the solubility of the drug in the release medium, ϵ is the porosity of the hydrated matrix, and D' is the apparent diffusion coefficient of drug in the hydrated matrix. The following expression relates D' to the actual diffusion coefficient, D, of the drug in the release medium: $D' = D/\tau$ where τ is the tortuosity of the hydrated matrix.

If the drug has completely dissolved when the matrix is hydrated, then the following expression should apply (5):

$$\frac{W_r}{t^{1/2}} = 2W_0\left(\frac{S}{V}\right)\left(\frac{D'}{\pi}\right)^{1/2} \qquad \text{(Eq. 2)}$$

If the assumptions made in the derivation of Eqs. 1 and 2 hold for measurements of drug release from compressed hydrophilic matrices, the right-hand side of these expressions should be constant. The experimental conditions were established so that drug release was measured in a near-perfect sink, since the concentration in the release medium was insignificant compared to that in the tablet. In addition, the percent drug released was significantly less than 30% of the initial dose, conforming to the restrictions placed on Eq. 2 by Higuchi (5). However, the S and V terms are larger than the corresponding surface area and volume of tablet prior to immersion in the solvent, owing to swelling of the matrix when hydrated.

Experimental data in the form of absorbance readings were fitted to a linear function of $t^{1/2}$ using the least mean squares criterion. Absorbance readings at 34 time intervals were obtained over a period of 115 min. for this purpose. The slopes computed in absorbance units were converted to moles/min.$^{1/2}$ using appropriate conversion factors. The variance observed for the slopes in all cases analyzed never exceeded 2% and generally were less than 1% of the slope values, indicating excellent linearity.

Although Eqs. 1 and 2 predict a zero intercept, small negative intercepts were observed in all cases, including both measurements of release from the tablets and gels. This was attributed largely to failure of the systems to immediately attain the state of diffusion described by Eqs. 1 and 2.

RESULTS AND DISCUSSION

Effect of Drug Concentration—Figure 2 shows square root of time plots for representative runs of sodium salicylate, benzocaine, and benzoic acid used as the drug contained within the hydroxypropyl methylcellulose 90 HG, 15,000 cps. polymer matrix. Although the solubilities of all the drugs tested vary, their rates of release were apparently linear with the square root of time.

In the previous publication (3) it was noted that a plot of the slopes of the lines obtained as a function of the dose of chlorpheniramine maleate in the tablet was linear up to a 25% concentration of the drug. This is reproduced in Fig. 3 along with sodium salicylate data. The conclusions drawn in that publication suggesting that Eq. 1 applies to this system were in error. Equation 1 was derived assuming $(W_0/V) \gg C_s$. In the case of chlorpheniramine and sodium salicylate, however, C_s is greater than W_0/V.

Further investigation showed that a portion of the standard tablet containing 14.4% of the tablet mass swelled to a volume of 4.34 times that of its original volume. The estimated value of $2W_0/V$ in Eq. 1, considering the swelling of the hydrated portion of the tablet, is 0.074 g./ml. in a 16.6% chlorpheniramine maleate tablet. This is much smaller than C_s (0.615 g./ml.), therefore, invalidating the application of Eq. 1 for the more water-soluble drugs.

If Eq. 2 applies in this situation, one would also expect a linear relationship as the concentration of drug is increased, all other parameters remaining constant. However, the $S/V(D')^{1/2}$ term is subject to variation as the drug-to-polymer ratio is increased. The surface-to-volume ratio would be a function of the extent to which the polymer swells on hydration and its resistance to attrition. That the hydroxypropyl methylcellulose 90 HG, 15,000 cps. resists attrition under the conditions of measurement is indicated by the linear $t^{1/2}$ relation observed at even 5:1 drug-to-polymer ratios. No significant difference in the surface-to-volume ratio was observed at the different polymer levels studied. The diffusion coefficient, being a function of the drug concentra-

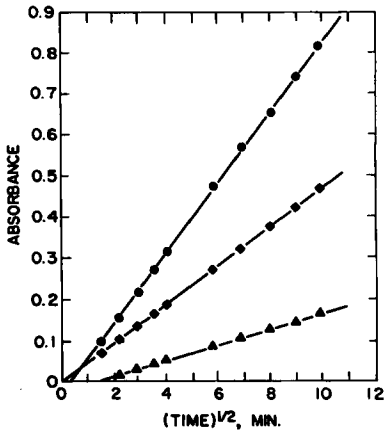

Fig. 2—Drug release as a function of the square root of time from a hydroxypropyl methylcellulose 90 HG, 15,000 cps. tablet matrix. Key: ●, benzocaine 25% w/w; ■, sodium salicylate 8.3% w/w; ▲, benzoic acid 33% w/w.

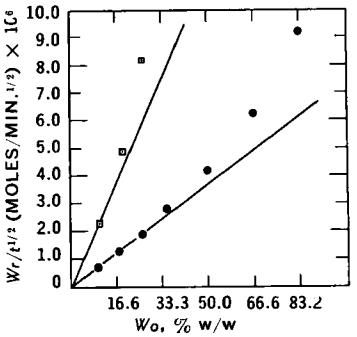

Fig. 3—Rates of drug release in water as a function of drug concentration in a hydroxypropyl methylcellulose 90 Hg, 15,000 cps. tablet matrix. Key: ⊡, sodium salicylate; ●, CPM.

tion, decreases as the concentration is increased (8). Therefore, the positive deviation in linearity shown in Fig. 3 must be the result of a change in tortuosity of the hydrated polymer. The tortuosity of a gel is an inverse function of polymer concentration (9); therefore, as the drug is increased beyond the 25% level, one could expect τ to decrease significantly. At the lower drug concentrations, τ remains essentially constant. Hence, linearity is apparently maintained, and the results conform with those predicted from Eq. 2.

The plot of $W_r/t^{1/2}$ *versus* W_0 for sodium salicylate, Fig. 3, shows a similar relationship to that for chlorpheniramine maleate except that deviation appears to occur at lower drug content. The greater apparent effect of sodium salicylate in decreasing the tortuosity of the gel may be due to the greater ability of sodium ion, compared to the chlorpheniramine ion, to dehydrate the polymer.

The effect of concentration of benzocaine and benzoic acid can be seen in Fig. 4. This result is predicted by Eq. 1. Since the C_s term is very small, *i.e.*, 1.2×10^{-3} g./ml. at 37° in the case of benzocaine, Eq. 1 reduces to:

$$\frac{W_r}{t^{1/2}} = S\left[\frac{2D'\epsilon C_s W_0}{V}\right]^{1/2} \qquad \text{(Eq. 3)}$$

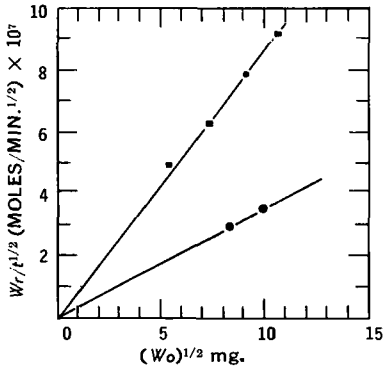

Fig. 4—Rates of drug release from 0.3-g. tablets as a function of the square root of W_0 *assuming the effective volume of the matrix is constant. Key:* ■, *benzocaine;* ●, *benzoic acid.*

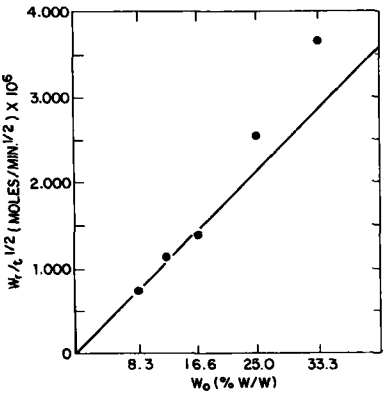

Fig. 5—Rates of drug release as a function of chlorpheniramine concentration in a hydroxypropyl methylcellulose 90 HG, 15,000 cps. tablet matrix at pH 1.5.

A linear relationship should be observed if drug-release rate ($W_r/t^{1/2}$) is plotted *versus* $(W_0)^{1/2}$ assuming that $S/V^{1/2}$ is constant. This is apparently a correct assumption since Fig. 4 shows such linearity.

Limited data were obtained in the case of benzoic acid due to the low degree of sensitivity found in the assay for benzoic acid. The concentrations of the solutions obtained from tablets containing less than 25% by weight of benzoic acid were not high enough to give acceptable absorbance readings.

A plot of drug-release rates for tablets with varying concentrations of chlorpheniramine maleate in a pH 1.5 medium is shown in Fig. 5. Comparison of these results with those shown in Fig. 3, where water was the solvent, showed a deviation from linearity at a lower drug level. Deviation occurred after 16.6% w/w of drug in 0.1 *N* HCl in comparison to 25% w/w of drug in water. These results are understandable if, in addition to the decrease in tortuosity due to the dissolution of drug in tablets with high drug levels, consideration is given to the additive effect of lowered viscosity introduced by protonation (3). In the acid medium the tortuosity has been lowered by both the decreased viscosity of the gel due to less tightly bound water molecules and the effect of drug dissolution.

Effect of Diluents—The effects of the addition of the water-soluble diluent lactose, and the water-insoluble diluent tribasic calcium phosphate, to 16.6% by weight chlorpheniramine maleate in a hydroxypropyl methylcellulose 90 HG, 15,000 cps. matrix (to be referred to as the standard tablet) can be seen in Fig. 6. The increase in specific release rates was similar for both diluents up to the addition of 33% by weight of diluent. At a dilution level of 50%, however, a marked divergence occurred which was accentuated at the 66.6% level.

The observed divergence can be explained by the difference in solubility of the diluents and their subsequent effects on the tortuosity factor. As the water-soluble diluent dissolved, it diffused outward and decreased the tortuosity of the diffusion path of the drug. On the other hand, the tricalcium phosphate did not diffuse outward, but rather became entrapped within the matrix and effected an increase in release

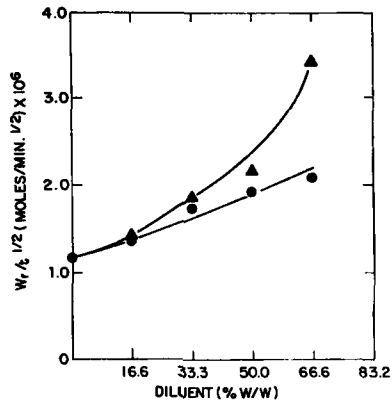

Fig. 6—Effects of addition of tablet diluents on the rate of chlorpheniramine maleate release from a hydroxypropyl methylcellulose 90 HG, 15,000 cps. tablet matrix. Key: ▲, *lactose;* ●, *tricalcium phosphate.*

TABLE II—DRUG RELEASE FROM HYDROXYPROPYL METHYLCELLULOSE HG 15,000 cps. TABLET MATRICES FROM VARIOUS SOLVENTS AND TEMPERATURES

Drug	% Drug (w/w)	Solvent	$W_r/t^{1/2}$ (Moles/Min.$^{1/2}$) × 10^6 25°	37°	50°
CPM	16.6	Water	1.05	1.16	1.24
CPM	16.6[a]	Water	1.48	1.83	2.22
Benzocaine	8.3	Water	0.43	0.47	
CPM	16.6	0.15 *M* Na_2SO_4	0.93	0.95	∞
CPM	16.6	0.20 *M* Na_2SO_4	1.06	∞	
CPM	16.6	0.1 *N* HCl	1.38	1.40	1.66

[a] The tablet base had 33.3% w/w lactose in addition to the polymer.

of drug only by the fact that its presence necessarily decreased the gum concentration.

Further evidence for these conclusions was obtained when the hydrated portions of the following three tablets mentioned were removed from the tablet after 2 hr. of exposure to the solvent, weighed, dried, and the residue reweighed. Measurements were made in triplicate. The results for the standard tablet were 11.8 ± 0.4% residue, 8.0 ± 0.8% residue, for the tablet containing an added 16.6% lactose and for the tablet with 16.6% tricalcium phosphate 9.5 ± 0.7% residue. These results were consistent with the fact that a lower concentration of polymer produced faster drug release, and the addition of a soluble diluent acted to further increase release due to its dissolution and, therefore, complete elimination from the matrix.

Effect of Temperature—The experimental results summarized in Table II show the expected increase in release rate of all drugs tested as the temperature was increased.

For systems governed by Eq. 2, only the diffusion coefficient and the tortuosity term should be affected by an increase in temperature. Furthermore, if the work by Longsworth (10) on the temperature dependence of diffusion coefficients in aqueous solutions is considered, the diffusion coefficient for molecules of somewhat similar properties to those of the drugs used here appears to increase by about 33% when the temperature is raised from 25 to 37°. Since $W_r/t^{1/2}$ is proportional to $D^{1/2}$, a 15% increase in slope measured at 37° over that measured at 25° would result. A less than 33% increase in the diffusion coefficient would be expected when the temperature is raised from 37 to 50° since an Arrhenius-type relationship with temperature should be observed. A 10% increase in slope is observed from 25 to 37° and a 7% increase from 37 to 50° for the standard tablet. The apparent diffusion coefficient would appear to have a smaller temperature dependence than the bulk diffusion coefficient. However, an increase of over 20% in the slopes is observed when lactose is substituted for polymer. This must be attributed to a significant temperature-induced decrease in tortuosity.

In the case of an insoluble drug in suspension which would be characterized by Eq. 2 in addition to the diffusion and tortuosity terms, the solubility term (C_s) is also increased. Although the relative increase in release rate observed for benzocaine is very similar to that observed for chlorpheniramine maleate, this does not seem contradictory if consideration is given to the fact that C_s is very small. The solubility of benzocaine is 9×10^{-4} g./ml. at 25° and 1.2×10^{-3} g./ml. at 37°, both values being negligible in comparison to $2W_0/V$ (0.37 g./ml.).

It is of interest to note the effect of increased temperature on release of chlorpheniramine maleate from hydroxypropyl methylcellulose 90 HG, 15,000 cps. tablets into 0.1 *N* HCl (Table II). In relation to this experiment, it has been shown that as the gel point is approached, small increments of temperature produced greater changes in viscosity than at lower temperatures (11). Therefore, since the gel at 25° has already been disoriented, as indicated by the 30% increase in release rates over that for water, an increase in temperature to 37° showed a small effect. On the other hand, the change from 37 to 50° brought the matrix much closer to its gel point at which temperature-induced discontinuities and diminished tortuosities became exaggerated. These results illustrate the similarity between temperature, salt, and pH effects on the hydroxypropyl methylcellulose 90 HG, 15,000 cps. matrix.

Extremely rapid release of chlorpheniramine maleate was observed within minutes after the standard tablet was placed in 0.2 *M* solutions of either sodium or magnesium sulfate at 37° (Table II). As was reported previously (3), a noticeable elongation of the tablet was observed, similar in appearance to a "gum drop." This same effect was duplicated by immersing a similar tablet into water held at a temperature (95°) above the gelation point of hydroxypropyl methylcellulose 90 HG, 15,000 cps. which was reported to be 85° (12). As the gel point for a polymer of this type is reached, the bound water molecules are removed from the hydration shell.

When the concentrations of both salts reached 0.2 *M*, hydration of the polymer along with almost instantaneous dehydration of the formed gel produced a solid aggregation of polymer particles with massive discontinuities and no inhibition for outward diffusion. The effect is similar to that of decreasing the gel point of the polymer to 37° by aiding the withdrawal of water from the gelled matrix with the use of dissolved electrolytes. Proof of this conclusion was shown by running an experiment in 0.2 *M* Na_2SO_4 at 25° and obtaining a normal release pattern with no gum drop effect. As can also be seen in Table II, a similar effect was observed in 0.15 *M* Na_2SO_4 solution. Whereas 37° was a sufficient temperature to reach the gelation point in 0.2 *M* salt solutions, 50° was necessary in 0.15 *M* solutions.

Effect of Polymer Type—Hydroxypropyl methylcellulose 90 HG, 25 cps. was chosen for investigation in order to determine the effect of polymer molecular weight on drug release. Initially, this tablet was positioned so that its surface was set flush with the edge of the Kel-F holder. A plot of absorbance *versus* the square root of time for a 16.6% by weight chlorpheniramine tablet showed linearity for ap-

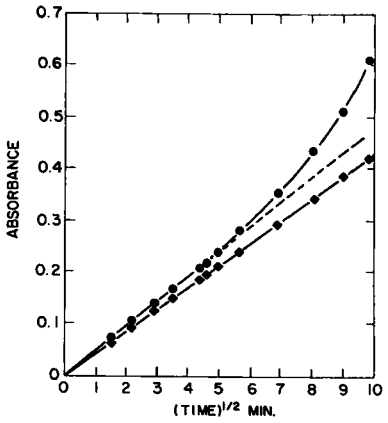

Fig. 7—Release of chlorpheniramine maleate from a hydroxypropyl methylcellulose 90 HG, 25 cps. tablet matrix. Key: ●, planar tablet surface placed flush in holder; ■, planar tablet surface recessed in holder.

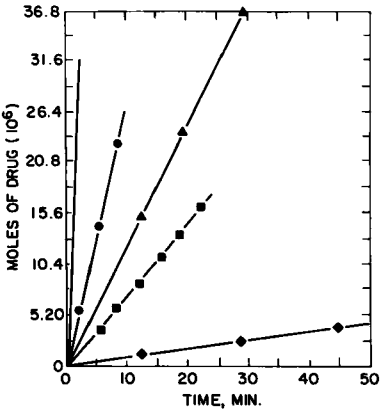

Fig. 8—Drug release from various compressed polymer matrices. Key: ●, CPM from polyvinylpyrrolidone; ▲, sodium salicylate from sodium carboxymethylcellulose; ■, CPM from methylcellulose MC, 4,000 cps.; ◆, CPM from sodium carboxymethylcellulose; ———, CPM from lactose.

proximately 25 min. An upward deviation from linearity was observed at later times as can be seen in Fig. 7. When this same tablet was recessed in the Kel-F holder and the assay procedure repeated, the drug release pattern was shown to remain linear with the square root of time for the entire 115-min. time period.

In the former case, hydration of the lower molecular weight polymer occurred rapidly, and the gum resisted attrition for the first 25 min. After this period, significant erosion of the surface due to the convective movement of the solvent past the tablet was observed. The eroded particles exposed greater surface area for drug release, resulting in a progressive increase in release rate. When the tablet was recessed 0.15 cm. in the holder, convection maintained the hydrated layer within the boundary of the holder.

Figure 8 shows the release of chlorpheniramine maleate from a tablet where lactose, polyvinylpyrrolidone, methylcellulose MC, 4,000 cps., and sodium carboxymethylcellulose had been used as the tablet matrix. The tablets contained 16.6% by weight of drug in all cases, and the release of drug maintained linearity when plotted against time at 37°.

Lactose served as a base line for a matrix which undergoes simple dissolution. The very water-soluble polyvinylpyrrolidone forms a hydrated layer that is very susceptible to attrition. The drug-release rate from this tablet was slightly less than that of lactose but by such a small degree as to indicate the formation of a hydration layer of minor significance.

The release of chlorpheniramine maleate from a methylcellulose MC, 4,000 cps. matrix was slower than that from the polyvinylpyrrolidone matrix but still maintained a straight-line relationship with time. The retarding action can be directly attributed to the formation of a hydration layer by this polymer. This hydration layer, however, did not resist attrition and remain intact. The MC variety of polymer is less hydrostable than the hydroxypropyl derivative. Consequently, attrition becomes more important than diffusion; the hydrated layer dissolved away almost as rapidly as it formed. Recessing this tablet did not alter its linear release pattern but merely reduced the slope slightly.

When the sodium carboxymethylcellulose tablet was removed from the flow cell, it was found to be misshapen and had the distinctive gum drop appearance. The outer area of the hydrated portion was clear and showed greater continuity than had been found in the previous two cases. When a tablet containing 16.6% by weight of sodium salicylate was analyzed, the same linear relationship with time was observed, although a more rapid release was apparent (Fig. 8). The significantly higher release rate of sodium salicylate as compared to chlorpheniramine maleate from the carboxymethylcellulose matrix shown in Fig. 8 indicated that the latter drug interacted with the polymer. Since sodium salicylate was an anionic drug, interaction with sodium carboxymethylcellulose was not likely, while complexation of chlorpheniramine maleate could be expected with the polymer on the basis of the work performed by Kennon and Higuchi (13).

It appears that the polymer which forms the hydration layer least susceptible to erosion and dissolution will show the greatest retarding action on drug release. If the hydrated layer remains intact, the drug diffuses through that layer, and the release pattern is linear with the square root of time. If the hydrated layer does not maintain its integrity, the release of drug will be linear in relation to time as is expected from a system of constant surface area subject to dissolution in a perfect sink.

Another polymer material used as a tablet matrix was carpolene. The advantage of this acidic polymer, as stated by Mayron (14), was that the polymer did not dissolve or hydrate in gastric juice but was neutralized and became water dispersible in the intestinal tract. The result of the neutralization was proported to increase the rate of release of the drug. In this study of carpolene rapid and continued release of chlorpheniramine maleate was obtained in 0.1 *N* HCl throughout the 115-min. period of analysis (Fig. 9). The decreased release rate observed in pH 7.5 buffer could be attributed to the increased gelation of the polymer in an alkaline media and interaction of the cationic chlorpheniramine with the polymer. The pKa of carpolene is 6.6 (15);

therefore, the polymer is almost completely dissociated at pH 7.5.

The rapid release of sodium salicylate in contrast to the slow release of chlorpheniramine maleate observed in water (pH ≈ 5.5) indicated that the latter reacted with the polymer. Precipitation of a carpolene complex with chlorpheniramine was observed when the polymer was added to an aqueous solution of the drug.

Barrier-Layer Effect on Drug Release—Figure 10 shows the release of chlorpheniramine maleate from a standard tablet and a standard tablet with a 25- or 50-mg. barrier layer of compressed hydroxypropyl methylcellulose 90 HG, 15,000 cps. on its surface. The quantity of drug released after 115 min. for the tablet with the 25-mg. barrier layer was 18% of that which was observed with the standard tablet. In addition, a time lag of 2.2 min. was noted before drug appeared in the solvent. The release curve was linear with time rather than with the square root of time. The tablet with a 50-mg. barrier layer showed slower drug release than the tablet with the smaller barrier layer. The time lag was approximately 5 min. for this tablet. The delay in the observance of drug release is clearly due to the time required for the water to pass through the barrier layer and then for the dissolved drug to pass back through this partially hydrated layer. This delay also accounts for the apparent zero-order release rate. The drug is not depleted very rapidly from the barrier layer; therefore, this layer acts as a "buffer" zone of constant concentration and area. Since this is the case, the concentration gradient does not change, and a zero-order release rate is observed. Deviation from zero-order release should be subsequently observed. The rate will ultimately decrease as drug is depleted from the core.

The 2-min. delay before drug release is observed as an indication of the time required for the water to penetrate the additional thickness provided by the barrier layer. A thickness of the standard tablet equivalent to the barrier layer contained about 4 mg. of chlorpheniramine maleate. Since only 4.7 mg. of drug is released from this tablet after 115 min. under standard conditions, it appears that the penetration of water into the tablet is not the rate-determining step for drug release.

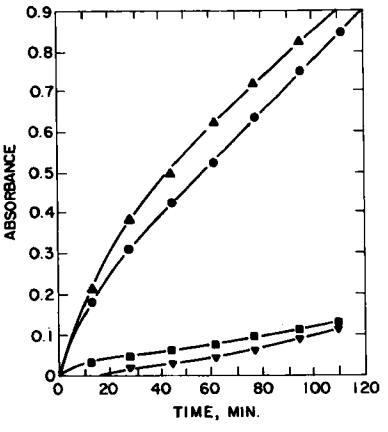

Fig. 9—Drug release from a carpolene compressed tablet matrix in various solvent media. Key: ▲, CPM, in pH 1.5 solution; ●, sodium salicylate in water; ■, CPM in pH 7.5 buffer; ▼, CPM in water.

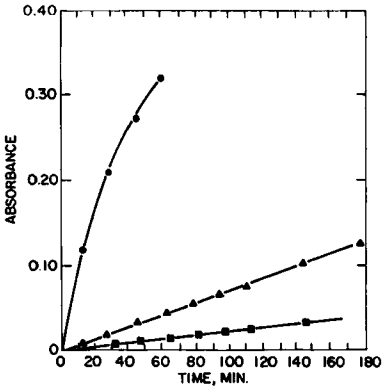

Fig. 10—Effect of a barrier layer on chlorpheniramine maleate release from the planar surface of a standard tablet. Key: ●, standard tablet; ▲, 25-mg. barrier layer; ■, 50-mg. barrier layer.

Another indication that water penetrability is not the rate-determining step is shown by Higdon and Robinson (16) whose calculation of the diffusion coefficient for water through an 8% sodium carboxymethylcellulose gel was 2.06×10^{-5} cm.²/sec. A value for the diffusion coefficient of benzoic acid was given by Higuchi *et al.* (17) as 1.1×10^{-5} cm.²/sec. Therefore, the diffusion coefficient of water in the polymer is about twice the value of a typical drug investigated in this study.

Diffusion Measurements from a Hydrated Polymer—The objective in making diffusion measurements in a fully hydrated hydroxypropyl methylcellulose 90 HG, 15,000 cps. polymer gel was to establish that diffusion was the controlling mechanism in drug release from the tablet. If the diffusion coefficients of the drugs used in this study could be obtained, then by substitution into Eqs. 1 and 2, it would be possible to confirm the application of these equations to drug released from the plane surface of a tablet matrix without attrition.

The data obtained are summarized in Table III. Drug-release rates from a fully hydrated polymer gel were evaluated for all the drugs used in the tablet study. The relative effects were similar to those observed with tablets.

Since $W_r/t^{1/2}$ equals the slope obtained from this particular system, the following equation may be used to calculate the apparent diffusion coefficient of water-soluble drugs in the gel.

$$D' = \frac{\pi}{60}\left(\frac{\text{slope}}{2S \cdot C_0}\right)^2 \qquad \text{(Eq. 4)}$$

where C_0 is the initial concentration of drug in the gel in moles/ml. The cross-sectional area of the diffusion cell was 0.094 cm.². The Gelman membrane had a porosity of 85%; hence, the actual diffusional area (S) was 0.59 cm.².

Extrapolation of a plot of D' as a function of polymer concentration indicated an approximate diffusion coefficient for chlorpheniramine maleate of 8×10^{-6} cm.² sec.$^{-1}$, which seemed reasonable for a molecule of its molecular weight. Approximate diffusion coefficients and tortuosities were calculated using this value and are listed in Table III.

The relative values of the experimentally observed release rates for the soluble drug are understandable in terms of τ values obtained for each diffusion

TABLE III—DRUG RELEASED FROM A FULLY HYDRATED HYDROXYPROPYL METHYLCELLULOSE 90 HG MATRIX IN WATER AT 37°

Drug	Polymer	% Drug (w/w)	% Polymer	$W_r/t^{1/2}\ S$ (moles min.$^{-1/2}$ cm.$^{-2}$)	D' (cm.^{2} sec.$^{-1}$ × 10^6)	τ	D (cm.^{2} sec.$^{-1}$ × 10^6)
CPM	Viscosity grade, cps.						
	15,000	5.27	2.6	3.26	5.37	1.49	8.0
CPM	15,000	5.35	5.4	2.65	3.45	2.32	8.0
CPM	15,000	5.34	8.0	2.34	2.69	2.97	8.0
CPM	15,000	5.28	10.6	2.02	2.04	3.92	8.0
CPM	15,000	5.34	15.7	1.68	1.40	5.70	8.0
CPM	15,000	2.73	10.9	1.13	2.55	3.92	10.0
CPM	15,000	4.08	10.9	1.55	2.07	3.92	8.1
CPM	15,000	5.28	10.6	2.02	2.04	3.92	8.0
CPM	15,000	6.47	10.3	2.43	1.94	3.92	7.6
CPM	15,000	7.99	10.7	2.95	1.89	3.92	7.4
Sodium salicylate	15,000	5.35	10.7	7.54	4.68	3.92	18.3
Benzoic acid	15,000	5.20	10.4	5.37	14.66	3.92	57.5
Benzocaine	15,000	5.20	10.4	5.48	0.94	—	—
CPM	25	5.23	10.5	2.24	2.53	3.16	8.0
CPM	25	5.22	15.7	1.73	1.50	5.33	8.0
CPM	25	5.37	21.4	1.62	1.29	6.2	8.0

measurement. An increase in the polymer concentration showed a corresponding increase in tortuosity for the same concentration of drug. If the τ value is assumed to be independent of drug concentration, the data indicate an overall decrease in diffusion coefficient of about 25% as the chlorpheniramine maleate concentration is increased from 2.7 to 8%. In addition, the lower expected tortuosity of the 25 cps., as compared to the 15,000 cps. hydroxypropyl methylcellulose 90 HG, was confirmed.

An approximate diffusion coefficient of 18.3 × 10^{-6} cm.^{2} sec.$^{-1}$ at 37° was indicated for a 5.35% sodium salicylate solution. This value compares favorably with the value reported by Desai *et al.* (18) which was 10 × 10^{-6} cm.^{2} sec. at 30° for a 6.8% solution.

The following form of Eq. 1 was used to calculate the apparent diffusion coefficients of the insoluble drugs in the gel.

$$D' = \frac{1}{120 \times C_s \times C_0}\left(\frac{\text{slope}}{S}\right)^2 \text{cm.}^2 \text{ sec.}^{-1}$$

The diffusion coefficient of benzoic acid, estimated using the τ value which characterized a 10–11% gel, is too large. Higuchi *et al.* (17) report a value of 11.1 × 10^{-6} at 30°. This suggested that the τ values characterizing release of benzoic acid and benzocaine from the gel were close to unity. This did not seem unreasonable when the length of the diffusional path was considered. A greater amount of drug is concentrated in the surface layer of the gel in the suspension case. In the same 2-hr. period, molecules diffusing from a suspended solid phase had a much shorter distance to travel and, therefore, a less tortuous path than molecules diffusing from a solution. It is also reasonable to assume that as the concentration of the solid phase is increased, the tortuosity value should be progressively lowered.

The estimated diffusion coefficient of benzocaine, 9.4 × 10^{-7}, is too low and cannot be considered the true diffusivity for this drug. Since benzocaine is very insoluble, solution of the drug at the gel interface becomes the rate-determining step rather than diffusion of the drug through the gel matrix. Therefore, the apparent diffusion coefficient is in error.

Correlation of Diffusion Data with Drug Release from a Tablet—Apparent diffusion coefficients derived from gel-diffusion measurements were substituted in Eqs. 1 and 2 and theoretical drug-release rates from hydroxypropyl methylcellulose 90 HG, 15,000 cps. compressed matrices calculated. The dry-tablet volume was 0.311 ml. for the standard tablets. Analysis of the swollen portion of a tablet showed that the polymer matrix swelled 4.3 times its original volume during the 2-hr. test period. The surface-to-volume ratio of the hydrated tablet was assumed constant during the course of the experiment and the lateral swelling of the tablet was ignored. The S term, or the effective diffusional area calculated on a dry basis of flat face, was 0.98 cm.^{2}. A standard tablet recessed 0.15 cm. in the holder so as to prevent lateral swelling, yielded a 10% lower slope than a tablet that was not recessed. The apparent diffusion coefficients estimated in 10.4–10.7% polymer gels were substituted in Eqs. 1 and 2. An average value of 11.8 ± 0.6% polymer was obtained when the hydrated portion of a stan-

TABLE IV—COMPARISON OF THE RATES OF DRUG RELEASE FROM THE PLANAR SURFACE OF A COMPRESSED HYDROXYPROPYL METHYLCELLULOSE 90 HG 15,000 cps. MATRIX WITH THE THEORETICALLY PREDICTED VALUES

Drug	% Drug in Tablet (w/w)	D' × 10^6	Theoretical Release ($W_r/t^{1/2}$) moles/min.$^{1/2}$ × 10^6	Actual Release ($W_r/t^{1/2}$) moles/min.$^{1/2}$ × 10^6	% Theory
CPM	16.6	2.04	1.13	1.16	103
Sodium salicylate	16.6	4.68	4.44	4.85	109
Benzoic acid	33.0	14.66	6.06	4.38	72
Benzocaine	16.6	0.94	0.42	0.47	112

dard tablet after a 2-hr. assay was removed, dried, and weighed. This polymer concentration will vary, however, depending on the drug or diluent content. Some actual and theoretical release rates are summarized in Table IV.

The actual drug-release rates obtained from the tablet containing 16.6% chlorpheniramine maleate and sodium salicylate came within 3 and 9% of theory, respectively, as calculated by Eq. 2. The theoretical value for benzocaine was 12% of the experimental value, while in the case of benzoic acid, a 28% faster release rate was predicted than was observed. This deviation reflects the high D' value calculated for benzoic acid. The agreement between actual drug-release rates and theoretical values appears to confirm the fact that diffusion is the major factor in determining drug release from a planar surface of a tablet prepared from a hydroxypropyl methylcellulose 90 HG, 15,000 cps. matrix.

Although the theoretical values predicted by Eq. 1 for insoluble drug systems are in good agreement with the actual values obtained, the error encountered in determining diffusivity must limit any conclusions that might be drawn.

Drug Release from Whole Tablets—The results obtained when drug release from a plane surface of a standard tablet was analyzed for 5 hr. showed linearity for the entire run (Fig. 11) when percent total drug released was plotted *versus* the square root of time. This established that an intact hydrated layer was maintained over this period of time; therefore, diffusion was the most important factor contributing to the rate of drug release in this system. However, when release from a whole tablet was analyzed rather than from a plane surface, linearity was not maintained, since other factors influenced the drug-release rate.

In Fig. 11 plots of percent of total drug released *versus* the square root of time show the release of chlorpheniramine maleate from the whole standard tablet. The release pattern in 0.1 *N* HCl is also shown together with drug release from a similar tablet containing 33% by weight lactose as a diluent in addition to the drug. It can be seen that the standard tablet showed a linear relationship for approximately 100 min., after which time there was a positive deviation. If diffusion were the only factor involved in drug release from the tablet, linearity would have been maintained as in the release from the plane surface.[3]

Attrition of the tablet surface accounts for the positive deviation. If attrition is considered to be the wearing away of the external surface of the hydration layer, the eroded material will go into solution quickly and provide drug in addition to that already available from diffusion.

When the standard tablet was exposed to 0.1 *N* HCl, the drug-release rate was faster than that observed in water. The tablet containing lactose showed release of drug to be somewhere in between that for the water and acid. These results are similar to those obtained in the flow cell. A whole tablet containing tricalcium phosphate was also

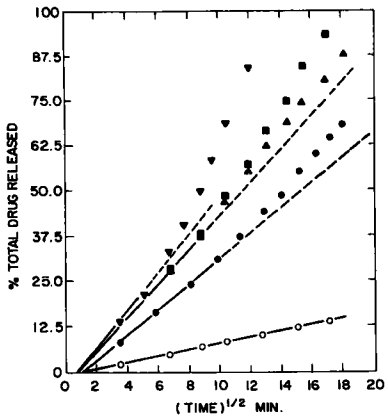

Fig. 11—Chlorpheniramine maleate release from a whole tablet. Key: ▼, hydroxypropyl methylcellulose 90 HG, 25 cps.; ■, standard tablet in pH 1.5 solution; ▲, 33.3% w/w of polymer replaced with lactose in the standard tablet; ●, standard tablet in water; ○, planar surface of a standard tablet.

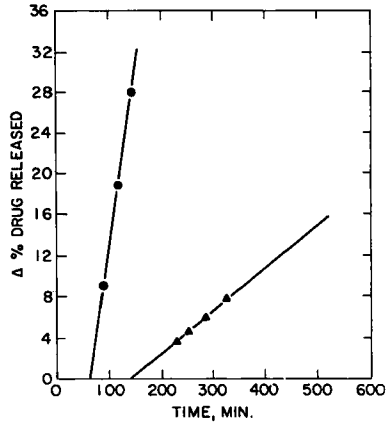

Fig. 12—Difference between the linear extension of the drug plot versus $t^{1/2}$ *and the actual drug release from a whole tablet. Key: ●, hydroxypropyl methylcellulose 90 HG, 25 cps.; ▲, hydroxypropyl methylcellulose 90 HG, 15,000 cps.*

evaluated in this manner but is not graphically illustrated. The release of drug was faster in this tablet than the standard, but this could not be numerically evaluated due to the diluent producing opacity in the circulating media. This was not encountered in measurements from plane surfaces. Therefore, the fact that attrition of the hydrated layer is important in determining release from the whole tablet was confirmed.

The difference between the linear extension of the drug release plot *versus* $t^{1/2}$ and the actual drug-release data on Fig. 11 was plotted for hydroxypropyl methylcellulose 90 HG, 25 cps. and hydroxypropyl methylcellulose 90 HG, 15,000 cps. matrices. A straight line is obtained in both cases (Fig. 12). Assuming that the deviation in drug release from linearity is considered the result of attrition, it is not possible to determine the relative contribution made by this factor drug release. By extrapolating the data in Fig. 11, it was determined that the

[3] Higuchi (4) has described a theoretical treatment of drug release from a spherical pellet of a homogeneous matrix. He concluded that for the first 50% of release there should be no deviation between a sphere and a plane of the same area. Thereafter, the rate of release would be less from a sphere. The swollen standard tablet maintained essentially cylindrical geometry under the conditions of measurement.

hydroxypropyl methylcellulose 90 HG, 15,000 cps. matrix would release 82% of drug through diffusion in approximately 9.5 hr. Attrition, based on the slope obtained in Fig. 12, would contribute 18% drug at 9.5 hr. Similarly, the hydroxypropyl methylcellulose 90 HG, 25 cps. matrix would be totally depleted of drug after 2.8 hr. Attrition accounts for 36% of drug release in this case while diffusion contributes the remainder. It appears from these data that the lower molecular weight polymer is approximately two times more susceptible to attrition than the higher molecular weight species.

The area of the planar surface of the tablet is 0.98 cm.^{2}. The area for the standard whole tablet is 3.06 cm.^{2}. The ratio of experimental drug-release rates between the whole tablet and the planar surface was 4:1, while the ratio for the dry, unhydrated surfaces was 3:1. These results are not unexpected if the hydrated surface is considered in both cases. Hydration of the planar surface results in essentially a projection of the same area. Hydration of the whole tablet, however, changes the tablet diameter resulting in an increase in the area of the planar surface in proportion to the square of the radius. In addition, the increase in the circumference provides more area to the rim of the tablet in proportion to the radius. The added diffusional area resulting from hydration would account for the increased drug release observed over that expected from the unhydrated surface.

Chlorpheniramine maleate release patterns obtained from methylcellulose MC, 4000 cps. tablets appear to be completely dependent on attrition since a straight-line relationship holds when drug release is plotted against time.

It would appear that since the surface of the tablet was diminishing, a nonlinear release rate would be expected. However, erosion was not uniform, and fragmented particles continued to add to the drug concentration.

REFERENCES

(1) Christenson, G. L., and Dale, L. B., U. S. pat. 3,065,143 (1960).
(2) Huber, H. E., Dale, L. B., and Christenson, G. L., *J. Pharm. Sci.*, **55**, 974(1966).
(3) Lapidus, H., and Lordi, N. G., *ibid.*, **55**, 840(1966).
(4) Higuchi, T., *ibid.*, **52**, 1145(1963).
(5) Higuchi, W. I., *ibid.*, **51**, 802(1962).
(6) Huber, H. E., and Christenson, G. L., *ibid.*, **57**, 164 (1968).
(7) Filter Process Report, Gelman Instrument Co., Ann Arbor, Mich., December 1965.
(8) Hober, R., "Physical Chemistry of Cells and Tissues," Blakiston Co., Philadelphia, Pa., 1945.
(9) Higuchi, W. I., *J. Pharm. Sci.*, **56**, 315(1967).
(10) Longsworth, L. G., *J. Phys. Chem.*, **58**, 770(1954).
(11) Ott, E., "Cellulose and Cellulose Derivatives," part II, Interscience Publishers, New York, N. Y., 1955, p. 908.
(12) "Methocel," Dow Chemical Co., **64**, 1563(1960).
(13) Kennon, L., and Higuchi, T., *J. Pharm. Sci.*, **45**, 157 (1956).
(14) Mayron, D., U. S. pat. 3,074,852(1963).
(15) Johnson, C., personal communication, B. F. Goodrich Co.
(16) Higdon, W. T., and Robinson, J. D., *J. Chem. Phys.*, **37**, 1161(1962).
(17) Higuchi, W. I., Parrott, E. L., Wurster, D. E., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 376(1958).
(18) Desai, S. J., Singh, P., Simonelli, A. P., and Higuchi, W. I., *J. Pharm. Sci.*, **55**, 1224(1966).

Keyphrases

Matrices—compressed, hydrophilic
Polymers—compressed, hydrophilic matrices
Release rates—compressed hydrophilic matrices
Diffusion—drug from matrices
Diluent effect—drug release rates, matrices
Temperature effect—drug release rates, matrices
UV spectrophotometry—analysis
Hydroxypropyl methylcellulose tablets—hydration layer

Renal Metabolizing Activity Studied in Dog and Monkey by the Isolated Perfused Kidney *In Situ*

By G. BENZI, F. BERTÉ, A. CREMA, and E. ARRIGONI

The drug metabolizing power of the renal tissues in an isolated *in situ* kidney preparation has been evaluated in the dog and monkey. Under these experimental conditions, the kidney remained connected to the other parts of the living animal, except for blood circulation which was supplied by a pump-oxygenator system. The disappearance of the tested substances (oxazepam and aminopyrine) from extracorporeal blood was partially replaced by their metabolites. In fact, both the drugs and the metabolites were present at different concentrations in the excreted urine and in the cortical and medullar renal tissues.

IN PREVIOUS PAPERS (1–3) the techniques were described for the perfusion of isolated areas of the body (liver, brain, uterine–fetal complex) to study some of their drug-metabolizing activities, such as demethylation, acetylation, and glucuronide conjugation.

In a systematic investigation (4, 5) on drug

Received March 18, 1968, from the Departments of Pharmacology, Pavia and Pisa Universities, Italy.
Accepted for publication May 2, 1968.
The authors are grateful to P. Mascherpa, Department of Pharmacy, University of Pania, under whose direction the program of the present research was developed.