Some Factors Affecting the Release of a Water-Soluble Drug from a Compressed Hydrophilic Matrix

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A number of factors controlling the rate of drug release from a hydrophilic matrix were investigated. The release of chlorpheniramine maleate from a hydrated methylcellulose matrix was found to be controlled largely by drug diffusivity rather than dissolution of polymer and water penetrability. The release pattern obtained appears to follow the theoretical relationships previously proposed for solid drugs dispersed in solid matrices.

THIS STUDY has been undertaken in an effort to quantitatively describe the mechanism of drug release from a prolonged action tablet previously patented (1), more recently described in the literature (2), and currently providing the basis for several pharmaceuticals. This tablet utilizes a hydrophilic polymer as a matrix in order to inhibit the release of water-soluble and slightly water-soluble active ingredients so as to afford continuous release of said medication.

The release pattern obtained from such a tablet, when measured under idealized conditions, appears to follow the theoretical relationships proposed by Higuchi in his equation dealing with the rate of release of solid drugs suspended in ointment bases (3) and subsequently applied to solid drugs dispersed in solid matrices (4). The equation describing drug release from the single face of a tablet is

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

where Q is the amount of drug released per unit surface after time, t, D is the diffusion coefficient of the drug in the release medium, ϵ is the porosity of the tablet, τ is the tortuosity of the tablet, C_s is the solubility of the drug in the release medium, and A is the concentration of the drug in the tablet.

Desai *et al.* (5) have recently reported an experimental study of factors influencing drug release from tableted insoluble plastic matrices to which Eq. 1 was applied. This report deals with release from a matrix that reacts with the release medium, a case which was excluded in the derivation of Eq. 1.

EXPERIMENTAL

The tablets used in this study were prepared by mixing chlorpheniramine maleate U.S.P. with a hydroxypropyl methylcellulose ether[1] and granulating with U.S.P. ethanol. The granulation was dried and screened through a 20 mesh sieve. A 7/16 in. flat face tablet was made from this granulation using a Carver press at a force of 3000 lb. Each granulation was assayed by dispersing it in water to effect solution of the drug and measuring the absorbance of the resulting solution at 262 mμ.

Chlorpheniramine maleate was selected as an example of a soluble drug whose ultraviolet absorption characteristics enabled its measurement without interference from other components of the tablet. The methylcellulose was selected as an example of a polymer whose effectiveness in delaying drug release had been demonstrated both *in vivo* and *in vitro* (1). It rapidly hydrated on contact with water, yet was not readily water dispersible.

The tablet was forced into a cylindrical tube composed of a fluorocarbon polymer[2] which had been machined so that a precise fit was obtained. Consequently, drug release could be measured from a single face of the tablet. No water was observed to penetrate between the tablet and the walls of the cylinder, thus eliminating the need to embed the tablet in wax as has previously been required with glass (5).

In order to obtain an accurate picture of the initial stages of drug release, a modification of the continuous flow technique described by Sjogren and Ervik (6) was utilized. A sketch of the apparatus is shown in Fig. 1.

The tablet in its holder was placed into a specially designed flow cell so that a constant flow of solvent could be maintained past the tablet face with no undue turbulence. The total volume of fluid circulating through the apparatus was 155 ml. The entire flow cell was immersed in a water bath so as to maintain the temperature at 37°. The flow of solvent through the cell was accomplished by means of a model T-8 Sigma-Motor pump set at a speed of 75 ml./min. A continuous flow cell, Beckman No. 92522, was positioned in a Beckman DK-2 recording spectrophotometer. The instrument was operated at the required fixed wavelength (262 mμ for all release media studied) and absorbance recorded as a function of time, usually for a period of 115 min. An absorbance value of 1.00 measured under these conditions was equivalent to the release of 10.3 mg. of drug in pure water.

Figure 2 shows the absorbance-time curve characterizing the release of chlorpheniramine maleate in pure water using a 300-mg. tablet containing 50 mg. of drug. This result was duplicated on numerous occasions to within ±1% deviation. The lag time in the apparatus at 75 ml./min. was 1.1 min. At lower flow rates an oscillation in the absorbance curve (the dotted line in Fig. 2), whose amplitude increased with diminishing flow rate, was observed during the first 15 min. of the experiment. The oscillation was effectively eliminated at 75 ml./min. flow rate.

In some experiments drug release from the whole tablet was measured, using the U.S.P. disintegration test apparatus (7) and a large beaker in place of the specially designed flow cell. A single tablet was confined in one of the tubes of the apparatus by a coarse wire mesh screen so that the tablet would not float to the surface. The release pattern was found to be independent of the rate of flow of solvent main-

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[1] Marketed as Methocel 90 HG 15,000 by Dow Chemical Co., Midland, Mich.
[2] Marketed as Kel-F by the M. W. Kellog Co., Jersey City, N. J.

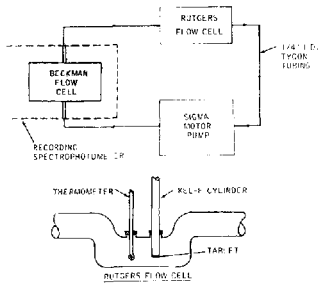

Fig. 1.—Apparatus used to study release rates.

tained through the spectrophotometer. The total volume of solvent was 1 L.

RESULTS AND DISCUSSION

Figure 3 shows plots of amount of drug released as a function of $\sqrt{t}$ demonstrating the apparent application of Eq. 1, which predicts a linear relationship, to this system. These data refer to 300-mg. tablets containing between 25 and 150 mg. of chlorpheniramine maleate, the remainder of the tablet being polymer. Furthermore, Fig. 4 indicates that a plot of the slopes of these lines (determined by a least mean squares fitting of the data) as a function of the dose of drug in the tablet is also linear up to 100 mg.

This is in agreement with a further extension of Higuchi's theory (4) which considers the effect the dissolution of the active material may have on the release rate. In this case the leaching type of release mechanism depends not only on diffusion outward but also on the change in porosity due to the elimination of this material from the tablet matrix. Equation 1 can be modified by introducing a linear relation between drug concentration and porosity, assuming that the initial porosity of the matrix is negligible. Therefore,

$$\frac{Wr}{t^{1/2}} = W_0\left(\frac{S}{V}\right)\sqrt{\frac{DKC_s}{\tau}(2 - KC_s)} \quad \text{(Eq. 2)}$$

should quantitatively describe Fig. 4. Here Wr is the amount of drug released in time, t, W_0 is the dose, S is the effective diffusional area, V is the effective volume of the matrix, and K is introduced to convert A ($= W_0/V$) to its corresponding volume fraction.

If one visualized water penetration as a front moving into the tablet, hydrating the polymer matrix, and dissolving the active material, which then diffuses out through this hydrated matrix, the application of Eq. 1 to this system would appear to be valid. Since the polymer swells on hydration, V in Eq. 2 is considerably greater than the volume of the tablet. Furthermore, it was noted that the face of the hydrated polymer film formed at the surface of the tablet was not planar but slightly convex. A slight lateral extension of the film was also observed, making S in Eq. 2 greater than the area of the tablet face. However, no significant change in diffusional area was evident once the film formed. Generally, this required less than 3 min. In an experiment in which the tablet (containing 50 mg. of drug) was depressed 0.15 mm. in its holder, $Wr/\sqrt{t}$ was found to be 12% less than the value observed when the tablet was flush with the surface of the holder. This indicated the magnitude of the area change owing to lateral extension, although a change in the effective diffusional path length may also be involved.

If Eq. 2 was applied to an insoluble matrix, K would be the specific volume of the drug. However, K must be interpreted as the fraction of hydrated polymer volume replaced by a unit weight of drug. Thus, K equals the product of the specific volume of the drug and the ratio of the volume of the hydrated to unhydrated matrix. Consequently, the replacement of polymer by an insoluble as well as a soluble diluent should result in an increase in the rate of drug release (contrary to the case of an inert matrix). The $Wr/\sqrt{t}$ values observed for 300-mg. tablets containing 50 mg. of chlorpheniramine maleate and 75 mg. of diluent were 33.2 and 24.6% greater than that observed in the absence of the diluent for lactose and tricalcium phosphate, respectively.

The tortuosity must also be a function of the extent of hydration and type of gel structure formed as water penetrates the matrix. This factor would also be influenced by air entrapped in the matrix as well as the presence of diluent. The deviation from linearity observed in Fig. 4 at high drug doses (>100 mg.) could be explained by an effective decrease in tortuosity resulting in increased drug release.

Equation 1 was derived assuming that $A \gg \epsilon C_s$. In the case of chlorpheniramine maleate, $C_s > A$. In order for Eq. 2 to apply, ϵ must be $\lesssim 0.1$. This requires that the free volume of solvent (that available to dissolve drug) be less than 10% of the volume of the hydrated matrix. If $\epsilon C_s \gtrsim A$, then the following equation would apply (4):

$$\frac{Wr}{t^{1/2}} = 2W_0\left(\frac{S}{V}\right)\sqrt{\frac{D}{\tau}} \quad \text{(Eq. 3)}$$

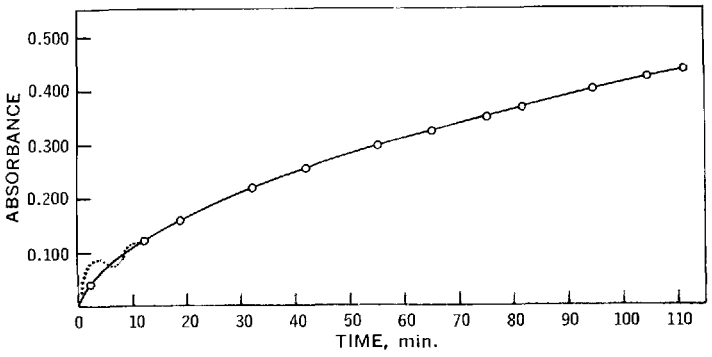

Fig. 2.—Absorbance *vs.* time curve characterizing the release of chlorpheniramine maleate and the effect of flow rates on the actual spectrophotometric recording. Key: ——, 75 ml./min.; . . . . ., 18 ml./min.

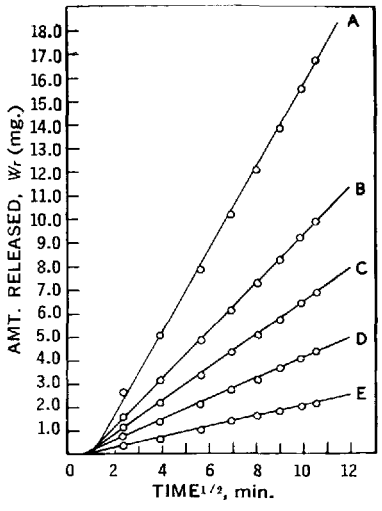

Fig. 3.—Drug release as a function of the square root of time for tablets with varying concentrations of chlorpheniramine maleate. Key: A, 150 mg. per tablet; B, 100 mg. per tablet; C, 75 mg. per tablet; D, 50 mg. per tablet; E, 25 mg. per tablet.

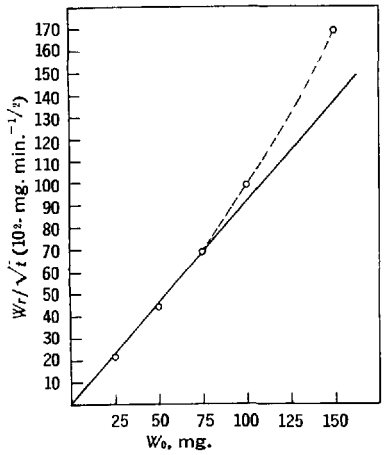

Fig. 4.—Plot of the slopes of the lines represented in Fig. 3 as a function of the dose of drug in the tablet.

In this case, the solvent penetrating the matrix is assumed to completely dissolve the drug on contact. This does not appear to be the case in the specific system reported here.

The term $S/V\tau^{1/2}$ in Eqs. 2 and 3 should measure the effect of the polymer and that of any other parameter which alters the hydration of the polymer in controlling drug release from tablets consisting of only drug and polymer. This presumes no significant complexation between the drug and polymer. The effect of changes in the ionic composition of the solvent should be largely reflected in this term.

Table I lists $Wr/\sqrt{t}$ values obtained in experiments in which the pH or salt content of the solution was varied. In all cases listed, excellent linearity of $Wr/\sqrt{t}$ plots was observed. A specific proton effect was noted. The results indicate that release rates in gastric and intestinal juices will be significantly different if pH is the only factor influencing release. This is consistent with the observed reduction in viscosity of methylcellulose solutions at pH values < 3 (8). This can be attributed to a reduction in hydration owing to protonation of ether linkages. In effect, the tortuosity of the hydrated film is decreased. The decrease in slope observed at pH 7.5 is probably the result of a decrease in the effective solubility of chlorpheniramine maleate owing to a decrease in dissociation.

On the other hand, electrolytes apparently increase the tortuosity of the hydrated film. Since ions reduce the activity of water, hydration of the matrix should be reduced, resulting in a decreased drug release rate. However, when the concentration of sodium sulfate and magnesium sulfate was raised to 0.2 *M*, a very sharp rise in drug release was encountered. This apparent inconsistency may be explained by considering that when the salt content is increased beyond a certain point, the activity of the water becomes so greatly reduced as to prevent uniform hydration of the gum. This then results in a massive discontinuity in the gel structure. In fact, upon removal of the tablet holder from the solvent, a noticeable elongation of the tablet was observed at the 0.2 *M* concentration. It no longer had a flat surface exposed but looked like an inverted "gum drop" with a greatly enlarged surface. Another factor that may be important is that the gel point of the methylcellulose is reduced to less than 37° in these solutions. The effect was not observed when release was measured at 25°.

Table I.—Effect of pH and Salt Concentration on $Wr/\sqrt{t}$ Values Obtained for Tablets Containing 50 mg. Chlorpheniramine Maleate

Solvent	Ionic Strength	pH	$Wr/\sqrt{t}$ 10^2 mg. min.$^{-1/2}$
0.15 *M* sodium acetate			
0.015 *M* boric acid	0.15	7.5	38.6
Water	0	≈5.5	45.5
0.015 *M* sodium acetate			
0.06 *M* acetic acid	0.015	5.2	45.1
0.001 *N* hydrochloric acid	0.001	3.0	47.6
0.1 *N* hydrochloric acid	0.1	1.5	54.7
0.30 *M* sodium chloride	0.30	...	38.6
0.60 *M* sodium chloride	0.60	...	36.0
0.10 *M* sodium sulfate	0.30	...	40.9
0.15 *M* sodium sulfate	0.45	...	37.5
0.175 *M* sodium sulfate	0.525	...	41.6
0.10 *M* magnesium sulfate	0.40	...	44.4
0.15 *M* magnesium sulfate	0.60	...	41.0

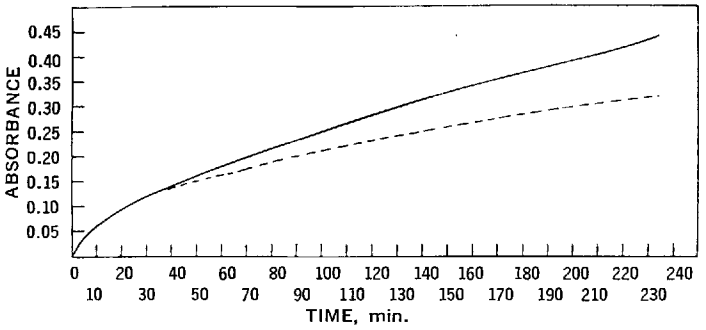

Fig. 5.—Absorbance *vs.* time curve showing release of chlorpheniramine maleate from a whole tablet. The dotted line represents the release pattern that would be necessary in order to maintain linearity if plotted against the square root of time.

Besides diffusion through a hydrated matrix, two other processes could be rate determining in affecting drug release from a compressed hydrophilic matrix. These are the rate of penetration of water through the hydrated layer and convective transport of hydrated polymer away from the tablet. Christenson and Dale (1) have suggested that hydration of the surface of the tablet results in a relatively water impermeable barrier. Drug release is achieved as the barrier is worn away. Fresh surface of the tablet is subsequently exposed, and the barrier is renewed. The tablet is described as having slowly disintegrated rather than dissolved.

Fatt and Goldstick (9) have recently presented a theoretical treatment of water transport in swelling membranes which should apply to a hydrophilic polymer matrix. They have shown that the mass of water absorbed by a thick slab of material should be a function of $\sqrt{t}$, assuming an average transport coefficient. The relative hydration and, consequently, the effective volume of the hydrated film diminish with increasing depth of penetration of the water front. If water penetration was the rate-determining step, then the transport coefficient characterizing the water-matrix system rather than the diffusivity of the drug would be the crucial parameter. The effect of electrolytes, pH, and diluents would be explainable in terms of alteration in the permeability of the swollen matrix to water.

The derivation of Eq. 1 presumes a uniform matrix through which diffusion takes place. If the rate of hydration of the matrix is slow compared to the dissolution of solid drug embedded in the matrix, then drug release would involve a leaching mechanism described by Eq. 1. If the rate of hydration is rapid, as was the case for the hydroxypropyl methylcellulose ether, then dissolution would only occur in a matrix in which hydration was effectively complete. Although the hydrated portion of the matrix through which the drug is diffusing may not be completely uniform, the results enable us to assume uniformity, at least for the time during which release was measured. This was nominally 2 hr. When release rates were observed for a period of 5 hr., the linear relationship described by Eq. 1 continued to apply. An estimate was obtained of the mass of the unhydrated tablet involved in the diffusional process. In the case of a 300-mg. tablet containing 50 mg. of chlorpheniramine maleate, 4.7 mg. of drug was released in water in 115 min. At that time, the tablet was removed from the solution and the hydrated matrix scraped from the face of the holder and assayed for drug which amounted to 2.6 mg. The total, 7.2 mg., indicated that 7.2/50 or about 14.4% of the mass of the tablet had been involved at this point. At the end of 5 hr. only 7.0 mg. of drug had been released.

That convective transport was not the rate-controlling step was confirmed by measurements of release patterns from whole tablets as shown in Fig. 5. Examination of the tablet at the end of a run in which 86% of the dose had been released showed a thick hydrated layer surrounding a small unswollen core. The figure shows that $Wr/\sqrt{t}$ was only constant during the early stages of release. Since Eq. 2 only applies to release from a plane surface, it is difficult to assess the actual factors contributing to the release in this case. Convective transport may still play a role as it must when the concentration of polymer in the tablet is significantly lowered by the addition of diluents. However, the existence of an intact hydrated layer establishes that diffusion is the most important factor contributing to the rate in this system.

The relative contribution of convective transport, water penetrability, and drug diffusivity to drug release from a hydrophilic matrix can only be assessed by independent measurement of the permeability of the hydrated polymer to water and drug in conjunction with a study of release patterns measured under the conditions described in this report. The experimental techniques, while not accurately reflecting *in vivo* conditions, do provide a reproducible means of evaluating different polymer–drug combinations. It should be anticipated that different systems in which the water solubility of the polymer or the drug may be altered would provide additional information to further clarify the mechanism of drug release.

The data reported here are only preliminary. Results of experiments in progress will be reported later.

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