nonlinear trend in the male excretion data was apparent, reflected in the RMS deviation (1.162 mg of α-hydroxytriazolam/kg·day) which was nearly four times greater than that for the female data. A plausible nonlinear model of the male excretion data is one in which the quantity of α-hydroxytriazolam excreted approaches an asymptotic value with increasing doses of triazolam. An exponential function of the dose was adopted, $E = A[1 - e^{-B \cdot (\text{dose})}]$, where A and B are adjustable parameters. The best fit parameters for the male excretion data, estimated using NONLIN (6), were $A = 4.02 \pm 0.40$ mg of α-hydroxytriazolam/kg·day and $B = 0.038 \pm 0.010$ kg·day/mg; the associated RMS deviation was 0.70 mg of α-hydroxytriazolam/kg·day, a significantly better fit of the experimental data than that afforded by the one-parameter linear model ($F_{\text{statistic}} = 34.6$; $n = 22$).

In conclusion, triazolam absorption, as reflected by α-hydroxytriazolam urinary excretion data for female and male mice, increased with triazolam dose. The quantity of α-hydroxytriazolam excreted by female mice was proportional to the triazolam dose, while the male excretion data were adequately represented by a model which predicts that the quantity of α-hydroxytriazolam excreted approaches an asymptotic value with increasing doses of triazolam.

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Mechanisms of Potassium Chloride Release from Compressed, Hydrophilic, Polymeric Matrices: Effect of Entrapped Air

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Abstract □ The release of potassium chloride from hydroxypropyl methylcellulose matrices was investigated for tablets prepared with several different compression forces. It was determined that the release kinetics for these systems deviates significantly from the classical $t^{1/2}$ dependence. This behavior was attributed to air entrapped in the matrix during preparation. Removal of the air prior to release restored the traditional $t^{1/2}$ behavior.

Keyphrases □ Potassium chloride—release from hydroxypropyl methylcellulose matrices, effect of entrapped air, kinetics □ Matrices, hydroxypropyl methylcellulose—release of potassium chloride, effect of entrapped air, kinetics □ Kinetics—release of potassium chloride from hydroxypropyl methylcellulose matrices, effects of entrapped air

Compressed, hydrophilic, polymeric matrices provide a convenient method for achieving sustained release of highly water-soluble drugs (1, 2). Release profiles are usually analyzed using equations derived by T. Higuchi (3) and W. Higuchi (4) and adapted by Lapidus and Lordi (5, 6). However, such systems often exhibit complex kinetics (7, 8) that are poorly explained by these traditional models of drug release. Modeling efforts in this area may be assisted by better understanding of the physical factors that contribute to (*a*) the swelling of the polymeric matrix due to transport of the penetrating species into the porous system and (*b*) the initial dissolution and release of the incorporated drug.

The goal of this work was to investigate some of the factors affecting the overall release behavior, especially the importance of entrapped air in the porous structure. The model system chosen consisted of potassium chloride as the water-soluble drug and hydroxypropyl methylcellulose as the hydrophilic polymer. Some of the technological factors influencing the overall potassium chloride release profile in this system have been analyzed by Salomon *et al.* (9–11). Their studies revealed that the release deviates significantly from the traditional $t^{1/2}$ dependence called for by the Higuchi and Lapidus–Lordi models during the early stages of the experiments. Even improved mathematical models especially developed for this system (12) could not fully describe the release behavior. To investigate this physical phenomenon more thoroughly, the experimental procedure of Salomon *et al.* (9–11) was followed with improved time resolution.

EXPERIMENTAL

Materials—The materials used were potassium chloride[1] (water solubility, 332 mg/cm³ at 37°) and hydroxypropyl methylcellulose[2]. This polymer had the following characteristics according to the manufacturer:

[1] Ph. Helv./Ph. Eur. grade; Siegfried, Zofingen, Switzerland.
[2] Methocel K 15M Premium; Dow Chemical Co., Midland, MI 48640.

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Table I—Physical Characteristics of Investigated Tablets [a]

Compression Force, kN	Pressure, MPa	Thickness, mm	Apparent Density, g/cm³	Void Fraction	Mean Pore Diameter, μm
5	28	2.75 ± 0.09	1.025 ± 0.043	0.385 ± 0.026	6.25 ± 1.30
10	56	2.37 ± 0.04	1.208 ± 0.004	0.275 ± 0.003	2.22 ± 0.14
27	150	2.10 ± 0.04	1.370 ± 0.008	0.178 ± 0.005	0.36 ± 0.04
50	280	2.05 ± 0.02	1.390 ± 0.019	0.166 ± 0.011	0.25 ± 0.12

[a] Average of three experiments (± *SD*).

number average molecular weight $\overline{M}_n$ = 120,000, intrinsic viscosity [η] = 11.0 dl/g, number average degree of polymerization $\overline{DP}_n$ = 650, viscosity of a 2% solution at 20° η = 150 poises, and degree of substitution 19–24% methoxy and 4–12% hydroxypropoxy (based on total weight of polymer). In addition, this resin is completely amorphous and remained so during these experiments, as verified by X-ray diffraction.

Diffusion Experiments—Equal amounts by weight of potassium chloride and hydroxypropyl methylcellulose of particle size 63–100 μm were combined using a tridimensional mixer[3]. A 500-mg portion of the resulting mixture was compressed with the desired force (5,10, 27, or 50 kN corresponding to pressure of 28, 56, 150, and 280 MPa, respectively) in a 15-mm acrylic die on a hydraulic press[4] equipped with flat-faced punches. The tablet was left within the die and one face was sealed with a plastic stopper. The assembly was then placed in 500 ml of distilled water at 37° as described previously (9, 11). The release of potassium chloride was followed by continuous monitoring of the conductivity[5] of the release medium. Tablets prepared in the same manner as those used in the release experiments were characterized using the method of Gupte (13) (see Table I).

Samples were also prepared at 28 and 280 MPa using the same procedure as before but removing the air entrapped in the tablets by a modification of the technique developed by Desai *et al.* (14). The tablet holder was placed in a filter flask which was sealed, placed in a 37° water bath, and evacuated to a pressure of 0.03–0.06 mm Hg. Distilled water (500 cm³) was aspired into the flask, stirring begun, and the contents circulated through the conductivity cell as above.

RESULTS AND DISCUSSION

The results of the release experiments are summarized in graphical form in Fig. 1, which represents the fractional release, M_t/M_∞, as a function of time. The most striking feature is the increase in release rate after 1.4–4.0 hr (depending on the pressure used). In addition, the release from tablets compressed at 280 MPa is significantly faster than the others, in the range of $M_t/M_\infty < 0.2$. For $M_t/M_\infty > 0.2$, the release rate from all tablets except those compressed at 28 MPa is quite similar.

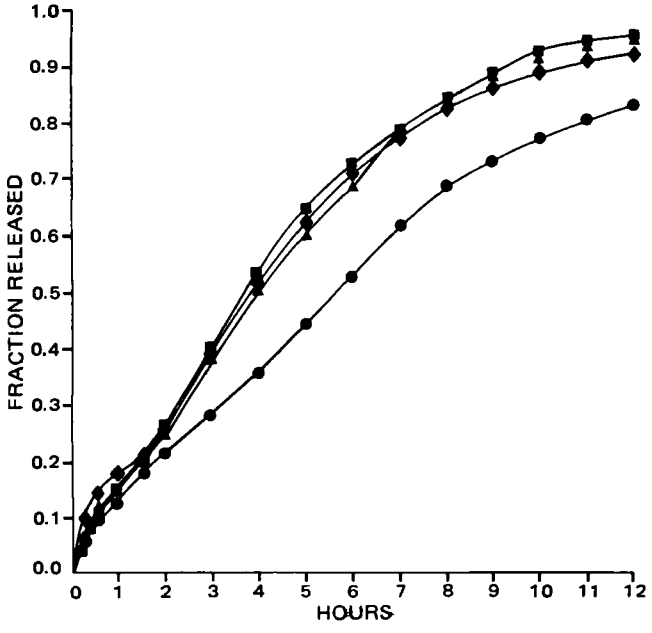

Figure 1—*Potassium chloride release profiles from tablets prepared at different pressures. Key: (●) 28 MPa; (■) 56 MPa; (▲) 150 MPa; (◆) 280 MPa.*

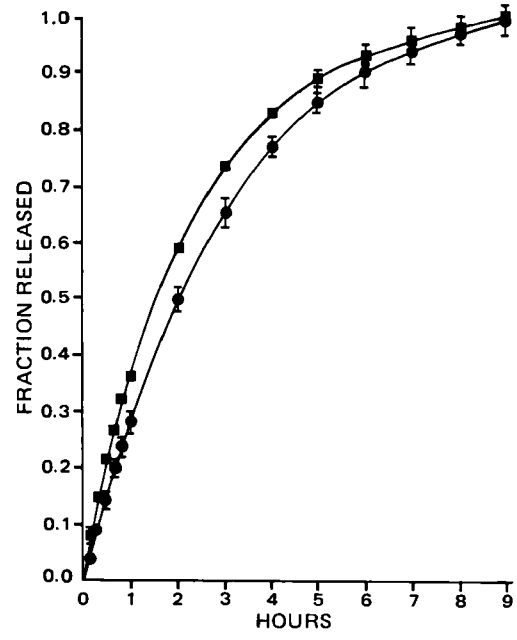

Figure 2—*Potassium chloride release profiles from evacuated tablets prepared at 28 MPa (●) and 280 MPa (■).*

In the systems studied, the release rate was found to vary inversely with tablet porosity and mean pore diameter. Since the opposite effect is normally expected, one must infer that release is not governed by the traditional porous-diffusion mechanism. One possible explanation is that air trapped within the tablets acts as a transport barrier. Consequently, as the initial porosity of the tablets increases, the initial air content increases leading to slower release of the drug.

To test this assumption, a new series of experiments using tablets prepared at the two extreme pressures was undertaken utilizing the modification of the technique developed by Desai *et al.* for polyethylene matrices (14) (Fig. 2). This technique effectively eliminated all observed anomalies in the release rate. Moreover, only a small difference was observed between the tablets prepared at 28 MPa and those prepared at 280 MPa. The release behavior could be fitted well to the equation:

$$\frac{M_t}{M_\infty} = a + bt^{1/2} \qquad \text{(Eq. 1)}$$

for values of $M_t/M_\infty \leq 0.6$.

When the experimental data were fitted to Eq. 1, the average values obtained for the coefficients *a* and *b* and the corresponding lag times were as shown in Table II. The fact that the values of the intercept, *a*, are not equal to zero could reasonably be attributed to the time lag associated with tablet swelling, although the physical manipulation of the equipment at the beginning of each experiment introduces uncertainty at these very short times.

Table II—Fitting of Release Data from Fig. 2 to a Square-Root of Time Release Behavior

Pressure, MPa	Intercept (*a*)	Slope (*b*), $hr^{-1/2}$	Time lag, hr	*r*
28	−0.181 ± 0.0009	0.476 ± 0.032	0.145	0.996–0.998
280	−0.127 ± 0.017	0.502 ± 0.014	0.064	0.998–0.999

[3] Turbula mixer model T2A; Bachofen, Basle, Switzerland.
[4] Specac, Sidcup, England.
[5] E518 conductivity meter; Metrohm, Herisau, Switzerland.

Table III—Characteristic Time of Increase in Release Rate Due to Entrapped Air as a Function of Void Fraction of the Tablets

Pressure, MPa	Void Fraction	Characteristic Time, hr
28	0.385	3.5–4.0
56	0.275	1.9–2.5
150	0.178	1.7–1.8
280	0.166	1.4–1.5

Even though the values of the volume and porosity of these tablets are continuously changing during swelling and release, owing to the short time-scale of the experiment, the changes are not large and therefore one may obtain an approximate value for the effective solute diffusivity D' by use of an equation adapted by Lapidus and Lordi (6):

$$\frac{M_t}{M_\infty} = \frac{S}{M_\infty}\left[D'\epsilon C_s\left(\frac{2M_\infty}{V} - \epsilon C_s\right)\right]^{1/2} t^{1/2} \qquad \text{(Eq. 2)}$$

where S is the surface area available for release (1.767 cm^2), V is the volume of the tablet (0.477 cm^3 at 28 MPa and 0.362 cm^3 at 280 MPa), C_s is the solubility of the active agent (332 mg/cm^3), ϵ is the tablet porosity (0.17 at 280 MPa and 0.38 at 28 MPa), and D' is expressed as D/τ, where τ is the tortuosity of the matrix and D is the effective diffusivity of the drug. Using these values, D' could be calculated from the slope of the plot of M_t/M_∞ *versus* $t^{1/2}$ yielding $D' = 1.04 \times 10^{-5}$ cm^2/sec for systems prepared at 28 MPa and $D' = 1.83 \times 10^{-5}$ cm^2/sec for systems prepared at 280 MPa.

The unusual release behavior of compressed hydroxypropyl methylcellulose tablets is attributed to the entrapped air. The characteristic time at which the increase in release rate is observed can be roughly correlated with the initial tablet porosity (Table III), although the observed increase was sharp only for systems prepared at 150 and 280 MPa. The correlation of this characteristic time with tablet void volume may be interpreted as representing pore filling with gradual displacement of entrained air (see Fig. 3). It is observed that air continues to escape from the tablet throughout most of the drug release. After ~2 hr a nonflat moving front has been formed at the polymer–water interface (Fig. 3c). On complete release of the drug (Fig. 3d), the tablet is not at mechanical equilibrium, although swollen. The outermost portion of the tablet is transparent, but a large amount of air remains entrapped.

Consequently, the inflection in the release curves does not represent the point at which all the air has been displaced, but probably a point at which the pressure of the entrained air (which is compressed as water enters the tablet) equals the pressure of the incoming water. The air then escapes gradually through the pores of the tablet, aided by the softening of the polymer as it absorbs water.

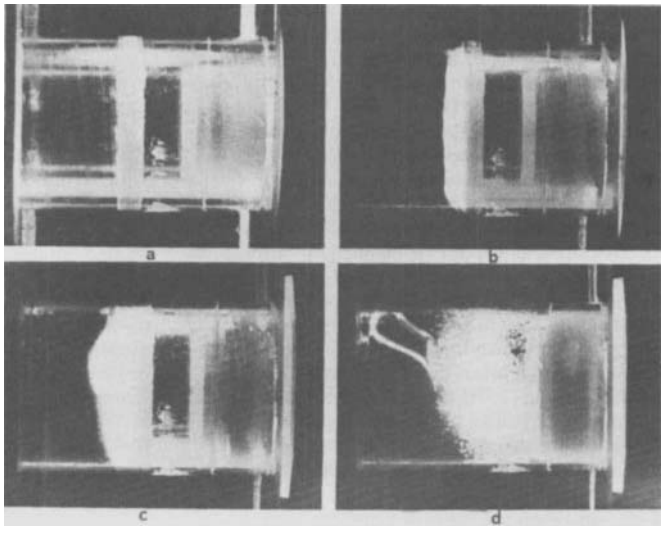

Figure 3—*Sequential swelling of potassium chloride–hydroxypropyl methylcellulose systems at* t = *0 (a),* t = *0.17 hr (b)* t = *2.50 hr (c), and* t = *24 hr [complete potassium chloride release (d)].*

Table IV—Fitting of Release Data from Fig. 1 to Eq. 3 for $M_t/M_\infty \leq 0.7$

Pressure, MPa	Intercept (a)	Slope (b), hr^{-1}	r
28	0.034	0.083	0.998
56	0.019	0.125	0.999
150	0.030	0.113	0.997
280	0.045	0.118	0.994

In contrast, when the tablets are evacuated prior to the introduction of water, the water is forced into the pores rather quickly by atmospheric pressure, as calculated by standard equations for flow in porous media (15). This results in the introduction of a saturated aqueous phase throughout the tablet at the beginning of the experiment. Release then proceeds by a purely diffusive mechanism. An additional simplification effected by this treatment in the case of hydroxypropyl methylcellulose is that potassium chloride release occurs quickly relative to the swelling so that volume changes of the tablet are less important.

It is interesting to observe that the effect of the entrained air is to improve the release profile as compared with traditional $t^{1/2}$ release. For example, although the release profiles are obviously not truly linear with time, the release curve may be fitted to:

$$\frac{M_t}{M_\infty} = a + bt \qquad \text{(Eq. 3)}$$

with $r > 0.99$ up to $M_t/M_\infty = 0.7$, as shown in Table IV. These systems therefore represent an approximation to zero-order release kinetics, although no physical significance should be given at this point to the values of the intercept and the slope reported.

We can conclude that air entrapped during preparation can have a significant effect on the release of drugs from hydrophilic matrices such as hydroxypropyl methylcellulose. This factor is therefore an important consideration in the design of *in vitro* release experiments.

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