Progestin Permeation through Polymer Membranes V: Progesterone Release from Monolithic Hydrogel Devices

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Abstract □ Progesterone release from monolithic devices prepared from various copolymers of poly(hydroxyethyl methacrylate) and poly(methoxyethoxyethyl methacrylate) or poly(methoxyethyl methacrylate) was examined. In general, plots of the fraction of drug released *versus* (time)$^{1/2}$ were linear during the early stages of drug release. This behavior is similar to that found for drugs released from hydrophobic polymers such as polydimethyl siloxane. However, for some release curves using the hydrogels, a breakpoint appeared during the early stages of drug release. These breakpoints were due to the effects of water absorption by these polymers. From analyses of permeability coefficients, it was demonstrated that release rates also were dependent on the initial drug load and the equilibrium water content of the polymer. These conclusions were verified from cross-membrane diffusion studies on films depleted of their initial drug load. In conjunction with this work, the aqueous solubility of progesterone was determined by several methods; an average value of 38 μg/ml at 23° was obtained.

Keyphrases □ Hydrogels—progesterone permeation, release from monolithic devices of various comonomer compositions evaluated □ Progesterone—permeation through hydrogel membranes □ Delivery devices, controlled—hydrogel membranes, progesterone permeation

Poly(hydroxyethyl methacrylate), a synthetic hydrogel, was first synthesized by Wichterle and Lim in 1960 (1). This polymer and many of its derivatives have been investigated extensively for possible biomedical applications (2). Among these uses are controlled-release drug delivery (3–7). Toward this end, this laboratory has been involved with studies on the mechanisms of solute transport through hydrogels (8–10). These studies have demonstrated that hydrogels are permeable to solutes that are only slightly soluble in water (*e.g.*, steroids) and to water-soluble solutes including both electrolytes and nonelectrolytes. It was shown that the transport mechanisms depend on solute size, the aqueous solubility of the solute, polymer hydration, and the nature and concentration of the cross-linking agent.

Recently, attention has been devoted to the role of polymerization conditions on the transport mechanisms and rate (11). Hydrogel films may be prepared under various conditions of temperature, initiator concentration, additive concentration, and solvent concentration and type. A study in this laboratory (11) demonstrated that permeability and partition coefficients for progesterone in poly(hydroxyethyl methacrylate) were independent of the nature and concentration of the solvents employed (*e.g.*, water, ethanol, and *tert*-butanol).

In this study, progesterone release from monolithic hydrogel devices was examined as a function of polymer composition, initial drug load, and initiator concentration. Planar and rod-shaped hydrogel devices were prepared from poly(hydroxyethyl methacrylate) and some of its derivatives. Progesterone was added to the monomer solution prior to polymerization. In all cases, polymerizations were carried out in the absence of a solvent, and the concentration of progesterone exceeded its saturation solubility when these devices were fully hydrated. Analyses of data obtained from the release of progesterone from rod-shaped monolithic devices and from transport studies on drug-depleted films revealed that: (*a*) permeability coefficients were dependent on the initial drug load, (*b*) initial release rates were dependent on the rate of water uptake by the devices, and (*c*) steady-state release rates were dependent on polymer hydration.

EXPERIMENTAL

Materials—Hydroxyethyl methacrylate[1] was a highly purified sample (9) and was used as received. Methoxyethyl methacrylate and methoxyethoxyethyl methacrylate were synthesized from methyl methacrylate[2] by transesterification with the appropriate alcohol. Azobis(methylisobutyrate) was synthesized by the method of Mortimer (12).

Progesterone[3] and [1,2-^{3}H]progesterone[4] were used as received. TLC analyses, with 20% (v/v) ethyl acetate in toluene as the developing reagent, indicated that the progesterone was pure. Only one spot was detectable under UV light. Radiolabeled progesterone had the same R_f value as the unlabeled material with >95% of the detectable activity associated with the primary spot. The remaining radioactivity was distributed uniformly on the plate.

Methods—Rod-shaped monolithic hydrogel devices were prepared in a polyethylene mold by polymerization at 60° for 24 hr. Azobis(methylisobutyrate), at a concentration of 7.84 mmoles/liter of the monomer, was used as the initiator. Prior to polymerization, a mixture of labeled and unlabeled progesterone was dissolved in the monomer to obtain a homogeneous solution. The maximum concentration utilized approximated the saturation solubility of a drug in the monomer. The dimensions of the dried devices used in the experiments were ~4 (height) × ~0.5 (diameter) cm.

Planar monolithic hydrogel devices were prepared using similar techniques, except only unlabeled drug was utilized. The thickness of the dried samples was ~0.03 cm.

Progesterone release studies on the rod-shaped devices were conducted at room temperature (23 ± 1.0°) in a 1-liter beaker containing 900 ml of deionized water. All release experiments were performed in duplicate. To reduce boundary layer effects, the aqueous phase was stirred continuously at 1600 rpm by externally mounted, constant-speed synchronous motors. The devices were supported in the cell *via* metallic holders made from nickel–chrome wire. At selected intervals, usually every hour in root time, the medium was replaced with fresh deionized water. Under these conditions, the progesterone concentration in the aqueous phase was far below saturation (<10% of the saturation solubility) so that sink conditions were maintained. The amount of progesterone released was determined by withdrawing ~0.5 ml of sample in triplicate. These samples were weighed in tared vials, 10 ml of scintillation fluid[5] was added, and the concentration was determined using a scintillation counter[6].

Water influx experiments were performed on rod-shaped monolithic devices prepared in a fashion analogous to that described, except that the labeled drug was omitted. At selected intervals, the devices were re-

[1] Courtesy of Hydron Laboratories, New Brunswick, N.J.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] Steraloids Inc., Pauling, N.Y.
[4] New England Nuclear, Boston, Mass.
[5] Formula 950A, New England Nuclear, Boston, Mass.
[6] Model 3385, Packer Instrument Co., Downers Grove, Ill.

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moved from the water bath and weighed. Surface water was removed with tissue paper prior to weighing.

Permeability coefficients were determined on the planar devices in an all-glass diffusion cell at room temperature (23 ± 1°) (8, 9). Prior to these permeation experiments, the films were depleted of the initial drug load by placing them in a large volume of water. The aqueous phase was stirred continuously and exchanged at regular intervals. Drug release was followed by UV spectroscopic measurements. Film thicknesses were determined with a lightwave micrometer[7]. The water content of the hydrated films was determined as described previously (8).

Partition coefficients, K_d, defined as the ratio of the drug concentration in the film and in the bulk aqueous phase, were determined by a solution depletion technique (8) in which 20 ml of progesterone was allowed to equilibrate with a known volume of polymer. The aqueous phase contained both labeled and unlabeled drug. Adsorption of the drug onto glass and the initial aqueous phase concentration of the drug did not affect the values obtained.

Three methods were utilized to determine the aqueous solubility of progesterone. In the first method, a rod-shaped hydrogel matrix device containing labeled and unlabeled drug was placed in an aqueous solution in a covered beaker. The aqueous phase was stirred continuously, and the concentration was checked repeatedly until a constant value was reached.

The second method was similar to the first, except that several rod-shaped hydrogel devices containing both labeled and unlabeled drug were placed in an open beaker. The aqueous phase was stirred continuously. The volume of the aqueous phase decreased over time. The aqueous phase concentration was monitored until a steady-state value was reached. At this time, the aqueous phase was passed through a glass membrane filter until successive portions produced the same value.

In the third method, excess solid progesterone was added to a beaker containing ~1 liter of water. This solution was sonified for ~6 hr. The solution was allowed to cool and then was left undisturbed for 2 days. The resulting supernate was filtered through a glass filter, and the concentration was determined by UV spectroscopy.

RESULTS AND DISCUSSION

Progesterone Release from Monolithic Hydrogel Devices—The release of medicaments from monolithic devices has been investigated extensively (4, 13–16). Equations that describe the release rate based on Fick's laws have been developed for several common shapes (13, 16). For rod-shaped monolithic devices prepared from polydimethyl siloxane, Roseman (14) showed that time release profiles could be described by the following equation:

$$(1 - F) \ln (1 - F) + F = Kt \qquad \text{(Eq. 1)}$$

where:

$$K = \frac{4C_s D}{C_0 r_0^2} \qquad \text{(Eq. 2)}$$

and:

F = fraction released at time t (seconds) = M_t/M_∞
M_t = amount of drug released (milligrams) at time t
M_∞ = total amount of drug released (milligrams) at infinite time
C_s = saturation solubility of drug in polymer (milligrams per cubic centimeter)
C_0 = initial drug concentration in matrix (milligrams per cubic centimeter)
r_0 = radius of the cylinder (centimeters)
D = diffusion coefficient (square centimeters per second)

When F is plotted *versus* the square root of time using Eq. 1, a nonlinear relationship results such that increasing negative deviations from linearity occur over time (14). At early times, Eq. 1 can be simplified to (14):

$$F = \frac{M_t}{M_\infty} = \left(\frac{8C_s Dt}{C_0 r_0^2}\right)^{1/2} \qquad \text{(Eq. 3)}$$

From Eq. 3, it is apparent that a plot of F *versus* $t^{1/2}$ should be linear during the early stages of drug release and that the release rate should be dependent on the saturation solubility of the drug in the polymer, its diffusion coefficient in the polymer, and the radius of the device. These conclusions were verified experimentally for such hydrophobic polymers as polydimethyl siloxane (13, 14).

[7] Van Kueren Co., Watertown, Mass.

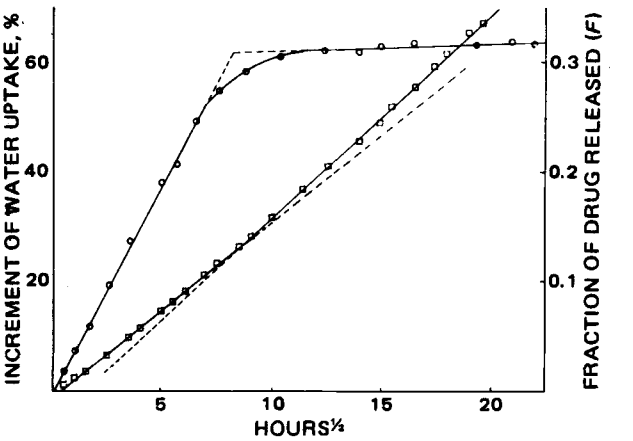

Figure 1—*Plots of water uptake (○) and fraction of drug released (□) versus $t^{1/2}$ for poly(hydroxyethyl methacrylate) with an initial drug load of 16% (w/w).*

Figures 1 and 2 are plots of F *versus* $t^{1/2}$ for progesterone release from rod-shaped hydrogel devices. A breakpoint in these release curves is clearly evident during the early stages. The existence of these breakpoints was confirmed from plots of $\Delta M_t/\Delta t$ *versus* t. This function is constant in each case until ~8 hr in root time. At longer times, $\Delta M_t/\Delta t$ again is constant but its value is somewhat greater.

Also given in Figs. 1 and 2 are plots of the water uptake of these devices (defined as the increased weight of hydrated polymer per initial weight of the nonhydrated device) *versus* the square root of time. The breakpoints in these curves correspond with those in the drug release curve. Based on this finding, it may be inferred that the influx of water affects the initial release rate of the drug. From the observed smaller slope in the drug release curve prior to the breakpoint, it may be concluded that drug release is slower during the early stages of release.

Since hydration of these devices occurs simultaneously with drug release, it is difficult to define precisely the reasons for this initial decreased release rate. The situation is complicated further by the fact that the existence of these breakpoints in the drug release profiles was not observed universally. In other systems examined (Table I), which differed in the initial drug load or in the monomer composition, breakpoints in the drug release profiles were not found. Of particular interest was the fact that a breakpoint was not observed in the system prepared with methoxyethoxyethyl methacrylate. This device has the highest equilibrium water content; therefore, it was expected that release from this device would be most affected by water uptake.

Some insight into the events that control release was obtained from visual inspection of the devices during hydration. As noted, these monolithic devices were prepared by dissolving progesterone in the monomer and then polymerizing. Subsequent to polymerization, the devices are

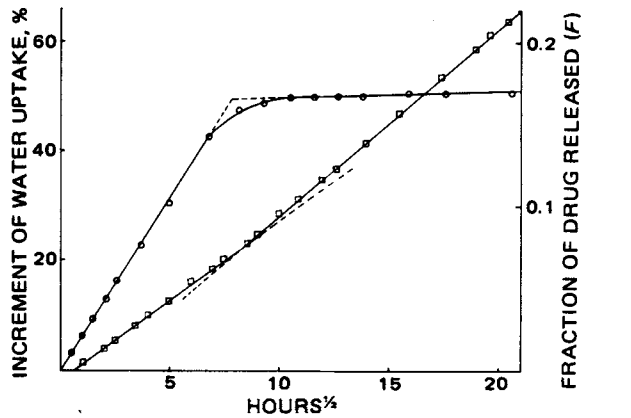

Figure 2—*Plots of water uptake (○) and fraction of drug released (□) versus $t^{1/2}$ for a copolymer of methoxyethoxyethyl methacrylate and hydroxyethyl methacrylate (monomer mole ratio of 2:1). The initial progesterone load was 9.1% (w/w).*

Table I—Release Characteristics for Progesterone from Monolithic Hydrogel Devices

System	Monomers[a]	Initial Drug Load, % (w/w)	Permeability $\times 10^6$, cm²/sec	Slope of Water Influx Plot, $hr^{-1/2}$	Water Saturation Time, $hr^{1/2}$	$Q \times 10^5$, cm/sec	Appearance of Breakpoint
1	M	7.8	3.64	0.44	14	3.91	No
2	67% M, 33% H	9.1	2.01	0.78	8.2	5.56	Yes
3	H	16.7	1.55	0.60	8	5.09	Yes
4	H	13.0	1.22	0.63	9.5	4.18	No
5	H	9.1	1.05	0.65	7.5	3.35	No
6	H	4.8	0.88	0.67	7.5	2.30	No
7	80% H, 20% O	9.1	0.61	0.34	8.0	1.34	No
8	67% H, 33% O	9.1	0.44	0.46	8.5	1.53	No

[a] M is methoxyethoxyethyl methacrylate, H is hydroxyethyl methacrylate, and O is methoxyethyl methacrylate.

Table II—Comparison of Permeation Parameters from Monolithic Devices and Drug-Depleted Films

Monomers[a]	Initial Drug Load, % (w/w)	$P \times 10^6$ (from Matrix)	$P \times 10^6$ (from Cross-Membrane)	W_f (with Drug)	W_f (after Drug Depletion)	K_d	$D^b \times 10^8$, cm²/sec	$D^c \times 10^8$, cm²/sec
M	7.8	3.64	—	0.38	—	130[d]	2.80	—
67% M, 33% H	9.1	2.01	1.84	0.36	0.54	141	1.43	1.30
H	16.7	1.55	1.50	0.34	0.43	130	1.19	1.15
H	13.0	1.22	—	0.35	—	129[d]	0.95	—
H	9.1	1.05	1.05	0.35	0.43	143	0.73	0.73
H	4.8	0.88	0.88	0.35	0.43	127	0.69	0.69
80% H, 20% O	9.1	0.61	0.57	0.24	0.37	212	0.29	0.27
67% H, 33% O	9.1	0.44	—	0.25	—	192[d]	0.23	—

[a] M is methoxyethoxyethyl methacrylate, H is hydroxyethyl methacrylate, and O is methoxyethyl methacrylate. [b] From matrix release studies. [c] From cross-membrane studies. [d] For polymer with 0% initial drug load.

clear, which suggests that progesterone is dispersed molecularly in the polymer matrix. Upon contact with water, progesterone located at the outer portion of the device precipitates. This zone of precipitation proceeds inwardly with time. More importantly, the time required for completion of this process appears to coincide with the breakpoints in the water uptake curves. This finding implies that the outer regions, where progesterone precipitation has occurred, must be fully hydrated, or nearly so, at very early times. This result is significant since drug release occurs from this region during the early stages.

The following information may be concluded concerning drug release during the early stages: (*a*) solute release occurs only from the outermost regions of the devices, (*b*) the parameters that normally affect release (*e.g.*, solubility of drug in the matrix, partitioning, and hydration) are probably constant, and (*c*) water influx occurs *via* diffusion through this outer hydrated region. Previous work (9, 10) demonstrated that both water transport and the permeation of steroids occur predominately within the water-filled channels or pores of the hydrogels. This observation suggests that during the early stages of release, a counterflow of solute and solvent must occur in these water-filled channels. This counterflow could affect the release rate by providing an additional resistance to flow. The magnitude of this effect should be dependent on the relative rates of drug efflux and water influx.

An empirical parameter, Q, will be developed to serve as a semiquantitative measure of the magnitudes of these crossflows. The magnitude of Q will be compared with the experimental results obtained from the drug release curves.

The rate of drug efflux from monolithic devices during the early stages of release is given by Eq. 3. The amount of drug released at infinite time, M_∞, is given by $\pi r_0^2 h C_0$. Substitution of this value for M_∞ in Eq. 3 gives:

$$M_t = (8\pi^2 h^2 D C_0 C_s r_0^2 t)^{1/2} \quad \text{(Eq. 4)}$$

or by substitution of the permeability coefficient, P, for DK_d:

$$M_t = (8\pi^2 h^2 r_0^2 C_0 C_w P t)^{1/2} \quad \text{(Eq. 5)}$$

Differentiation of Eq. 5 gives the release rate:

$$\frac{dM_t}{dt} = (2\pi^2 h^2 r_0^2 C_0 C_w P) t^{-1/2} \quad \text{(Eq. 6)}$$

For the various devices investigated, the values of h, r_0, and C_w are constant. Therefore, the relative drug release rate can be expressed by $(dM_t/dt) \alpha \sqrt{C_0 P}$. The permeability coefficients were obtained *via* Eqs. 1 and 2. For systems that produced a breakpoint, P was obtained from the slope of the line above the breakpoint. The values of P are listed in Table I.

The relative rate of drug efflux from the various devices should be dependent on C_0 and P $[(dM_t/dt) \alpha \sqrt{C_0 P}]$. This relative release rate also should be dependent on the relative rate of water uptake by the devices. Equations that quantitatively state the water influx rate by devices with cylindrical geometry have not been developed. However, it is apparent that the relative rates must be proportional to the slope, β, of a water uptake *versus* $t^{1/2}$ plot.

It was hypothesized that drug release should be affected by the relative rates of solute and solvent crossflows in the water-filled channels or pores of the device. The magnitude of these crossflows should be proportional to the product of the relative rates of drug efflux and water influx. Therefore, the empirical parameter, Q, is defined as the product of these relative rates:

$$Q = \beta \sqrt{P C_0} \quad \text{(Eq. 7)}$$

where β is a measure of the relative rate of water influx. This semiempirical parameter should provide a relative measure of the effects of water uptake on the release of solutes from hydrogel devices.

The Q values (Table I) range from 1.33×10^{-5} to 5.56×10^{-5} cm/sec. However, a breakpoint in the drug release curve arises only when Q is $> \sim 5 \times 10^{-6}$ cm/sec. Thus, as the magnitude of the solute and solvent crossflows increases (as measured by Q), breakpoints occur in the drug release curve. This situation can also explain the lack of a breakpoint in the drug release curve for methoxyethoxyethyl methacrylate since the water uptake rate by this device is relatively slow (Table I). The magnitude of the counterflow of solute and solvent is small; thus, a breakpoint in the drug release profile is not observed.

Progesterone Transport in Drug-Depleted Films—In the development of the permeability coefficients listed in Table I, the aqueous solubility of the solute, progesterone, in water must be known. For the present study, a value of 38 μg/ml was utilized based on the average value obtained from the three techniques described for the measurement of the aqueous solubility. This value is substantially higher than that of 12.6 μg/ml given by Roseman (14) and that of 27 μg/ml given by Sundarum and Kincl (17). Both of these values were obtained at 37°, whereas the value used in this study was obtained at 23°.

This uncertainty in the value for the aqueous solubility of progesterone

leads to a considerable uncertainty in the P values listed in Table I. Thus, a second method was developed to determine progesterone permeability in the monolithic devices. When permeability is assessed from studies of the transfer rate of solute across a thin film, the P values can be obtained directly from plots of a concentration variable *versus* time. It was shown previously (9) that when the solute has a high film–water partition coefficient, the following equation can be utilized to obtain the permeability coefficient:

$$\ln\left(\frac{C_3 - C_4}{C_1 - C_2}\right) = \frac{-2AP}{Vl}(t_{ss} - t_{oss}) \qquad \text{(Eq. 8)}$$

where:

V = compartment volumes (176 ml)
C_1 = concentration in Compartment I at onset of steady state (t_{oss})
C_2 = concentration in Compartment II at onset of steady state
C_3 = concentration in Compartment I at t_{ss} (anytime during steady state)
C_4 = concentration in Compartment II at t_{ss}
A = membrane area (14.2 cm^2)
l = wet membrane thickness

Table II is a summary of the values of P, D, and K_d obtained from measurements on hydrogel films. These films were prepared with the initial drug loadings listed in Table II and then subsequently were depleted of drug prior to the permeation experiments. The P values obtained *via* this method are in excellent agreement with those obtained from the progesterone release studies with rod-shaped devices.

This agreement between the P values obtained from the release studies and the transport studies provides further evidence that the aqueous solubility of progesterone is close to 38 μg/ml. In fact, this combined method for the determination of the permeability may be excellent for the determination of the solubility of slightly soluble solutes in aqueous solution.

Sufficient data are available in the paper by Roseman (14) to estimate the aqueous solubility of progesterone at 37° using this technique. Roseman reported diffusion coefficients in polydimethyl siloxane of 16.5×10^{-7} cm^2/sec (estimated from matrix release studies) and 4.50×10^{-7} cm^2/sec (obtained from membrane transport studies). With these values and 0.572 mg/ml for C_s and 50.2 for K_d, the aqueous solubility of progesterone is 42 μg/ml *via* Eq. 5. This result is in good agreement with that obtained in the present study.

The permeation parameters shown in Tables I and II may be utilized to understand the various factors that control the release of solutes from monolithic hydrogel devices.

From a comparison of the P values with the equilibrium water contents, W_f, it is apparent that permeability increases as the equilibrium water content of the polymer increases. This conclusion is consistent with previous results (8, 9). The K_d values shown in Table I obtained on the depleted films are also consistent with the previous work, suggesting that the incorporation of drug into the device with its subsequent precipitation does not affect the equilibrium solubility of progesterone in the polymer matrix.

However, drug incorporation is not without effect on the transport properties of the matrix. This effect is demonstrated by the comparison of P values obtained from transport studies (with no added drug) with those obtained in the presence of drug. In each case, the permeability of the drug-filled polymers is greater. This effect is proportional to the initial drug load, as demonstrated by studies with devices prepared from hydroxyethyl methacrylate. As the initial drug load decreases, the permeability decreases and approaches the value obtained from films prepared without drug. This result may indicate that the ultimate precipitation of progesterone in the matrix devices affects the average pore size of the matrix phase. Previous work (8, 9) demonstrated that the pore mechanism dominates progesterone permeation in hydrogels of the type utilized in the present study. It is expected that the presence of solid drug particles would affect the formation of these pores and, therefore, lead to the observed increases in permeability.

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