For clinical studies, especially bioavailability or bioequivalency studies, collection and analysis of urine samples rather than plasma samples may be preferable (6). The distribution of chlorthalidone between plasma and erythrocytes is not instantaneous, so it is difficult to obtain a blood sample and to prepare the plasma quickly enough so that the determined chlorthalidone concentration is the same as the plasma concentration *in vivo* (7). The analysis of urinary samples can be accomplished rapidly with the fully automated system.

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ACKNOWLEDGMENTS

Presented in part at the 7th Technicon International Congress, December 1976, and at the APhA Academy of Pharmaceutical Sciences, Phoenix meeting, November 1977.

The authors thank Mr. M. Patel for excellent technical assistance.

Progestin Permeation through Polymer Membranes IV: Mechanism of Steroid Permeation and Functional Group Contributions to Diffusion through Hydrogel Films

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Abstract □ Hydrogel films were prepared from hydroxyethyl methacrylate, both with (Film II) and without (Film I) 5.25 mole % of ethylene glycol dimethacrylate. Permeation, diffusion, and partition coefficients for progesterone, testosterone, nandrolone, norethindrone, 17α-hydroxyprogesterone, estradiol, and hydrocortisone were determined. A solute permeation model was proposed based on the separation of a domain (B) composed of "bulk-like" water and a domain (A) composed of polymer, interfacial water, and bound water present in the films. The separate contributions from the "pore" and "solution–diffusion" mechanisms to the total permeability were calculated from the model. Steroid permeabilities through Films I and II were analyzed in accordance with this model. Permeation of Film II occurred *via* the solution–diffusion mechanism. Permeation of Film I occurred predominately by the pore mechanism with a small contribution (~20%) from the solution–diffusion mechanism. The latter contribution was dependent on the solubility of the solute within the A domains of the hydrogel film. Functional group contributions to permeation of Film II were ascribed to either steric or hydrogen bonding effects.

Keyphrases □ Progesterone—permeation through hydrogel films, models, structure–activity relationships, steroids □ Hydrogel films—progesterone permeation, structure–activity relationships, steroids, models □ Structure–activity relationships—steroid permeation through hydrogel films □ Models—steroid permeation through hydrogel films

In previous reports from this laboratory (1, 2), the permeation mechanisms of a model hydrophobic drug, progesterone, through poly(hydroxyalkyl methacrylate) films were examined. The importance of film hydration was emphasized. Similar conclusions were drawn by others (3–5) for hydrophilic solute permeation through hydrogel films. Several investigators (2, 4, 5) indicated that, depending on the hydrogel composition, either a "pore" or a "solution–diffusion" mechanism may dominate permeation. For polymers prepared from various comonomers or from hydroxyethyl methacrylate without added cross-linking agents, the pore mechanism dominates. At high concentrations of the cross-linking agent, ethylene glycol dimethacrylate and possibly tetraethylene glycol dimethacrylate, the solution–diffusion mechanism appears to dominate permeation. These results were found for both hydrophobic (2) and hydrophilic (4, 5) solutes.

These conclusions are tenuous without further investigation. One problem is the partition coefficient reported for the hydrophobic solute progesterone (2). This value, which is >100, appears to be inconsistent with a pore mechanism in which transport presumably occurs within water-filled pores or microchannels present in the film. For permeation within these channels, partition coefficients close to one are expected. Hydrophilic solutes in hydrogels generally exhibit partition coefficients close to this value (6).

For this reason, the permeation mechanism of hydrophobic solutes through hydrogel films was examined in greater detail. The permeation characteristics for several steroids that have systematic structural differences were determined in films prepared from hydroxyethyl methacrylate, both with and without 5.25 mole % of ethylene glycol dimethacrylate as a cross-linking agent. The results substantiate previous conclusions concerning the two mechanisms for solute permeation in hydrogel films, provide an explanation for the proposed pore-type permeation mechanism for solutes having high hydrogel–water partition coefficients, and demonstrate the effects of steroid structural differences on permeation rates through hydrogel films.

0022-3549/79/0800-0970$01.00/0

EXPERIMENTAL

Materials—Hydroxyethyl methacrylate[1] was a highly purified sample containing the following levels of impurities[1]: methacrylic acid, 0.06%; ethylene glycol dimethacrylate, 0.024%; and diethylene glycol methacrylate, 0.24%. Ethylene glycol dimethacrylate[2] was purified by base extraction and distillation. Azobis(methylisobutyrate) was prepared by the method of Mortimer (7).

Hydrocortisone[3], 17α-hydroxyprogesterone[3], progesterone[3], testosterone[3], nandrolone[3], estradiol[3], norethindrone[4], 6,7-^{3}H-estradiol[5], and 1,2-^{3}H-progesterone[6] were used as received. TLC analysis, with 20% (v/v) ethyl acetate in toluene and 5% (v/v) methanol in chloroform as developing reagents, indicated that all steroids were pure. In all cases, a single UV-detectable spot was observed. Radiolabeled steroids had the same R_f values as the unlabeled counterparts, with >95% of the detectable activity associated with the primary spot. The remaining radioactivity was distributed evenly throughout the remainder of the plate.

Methods—Hydrogel films were prepared by polymerization between sealed polyethylene plates at 60° for 24 hr. Azobis(methylisobutyrate) (7.84 mmoles/liter of monomer) was the initiator.

Film I was prepared from a mixture of hydroxyethyl methacrylate and 40% (v/v) deionized water. Film II was prepared from a mixture of hydroxyethyl methacrylate with 5.25 mole % ethylene glycol dimethacrylate as the cross-linking agent and 40% (v/v) ethanol as the solvent. These mixtures were homogeneous before and after polymerization. Subsequent to polymerization, the films were soaked in water (changed repeatedly) for 3–4 weeks prior to use.

The diffusion experiments were performed at room temperature (24 ± 1°) in an all-glass cell described previously (1). An aqueous solution of 17α-hydroxyprogesterone, progesterone, testosterone, nandrolone, norethindrone, estradiol (~5 μg/ml), or hydrocortisone (~250 μg/ml) was placed into one chamber. The second chamber was filled with deionized water. The concentration increase was followed in the initially steroid-free chamber by UV spectrophotometry[7] or by liquid scintillation counting of the radiolabeled compounds using scintillation fluid[8] and a scintillation counter[9].

Partition coefficients, defined as the ratio of the concentrations in the film and in the bulk aqueous phase, were determined by a solution depletion technique (1) in which 50 ml of a steroid solution was allowed to equilibrate with a known volume of polymer. Adsorption of the steroids onto glass was checked and was not a problem. The steroid equilibrium concentration in the bulk aqueous solutions was obtained as described previously.

Film thicknesses (~0.03 cm) were measured on the water-swollen films using a lightwave micrometer[10].

RESULTS AND DISCUSSION

Permeability and diffusion coefficients for steroids in hydrogel films were calculated using:

$$\ln\left\{\frac{C_0V - (2V + K_dV_m)C_4}{C_0V - (2V + K_dV_m)C_2}\right\} = -\frac{2AU}{Vl}(t_{ss} - t_{oss}) \qquad \text{(Eq. 1)}$$

where:

C_0 = initial drug concentration in Compartment I
V = compartment volumes (176 ml)
K_d = partition coefficient
V_m = membrane volume
C_2 = concentration in Compartment II at the onset of steady state (t_{oss})
C_4 = concentration in Compartment II at the time t_{ss}
A = membrane area (14.2 cm^2)
l = wet membrane thickness
$U = DK_d$
D = diffusion coefficient
t_{ss} = any time during steady state

[1] Courtesy of Hydron Laboratories, New Brunswick, N.J.
[2] Monomer Polymer Laboratories, Philadelphia, Pa.
[3] Steraloids Inc., Pauling, N.Y.
[4] Sigma Chemical Co., St. Louis, Mo.
[5] Amersham Corp., Arlington Heights, Ill.
[6] New England Nuclear, Boston, Mass.
[7] Cary model 15, Varian Instruments, Palo Alto, Calif.
[8] Formula 950-A, New England Nuclear, Boston, Mass.
[9] Model 3385, Packard Instrument Co., Downers Grove, Ill.
[10] Van Kueren Co., Watertown, Mass.

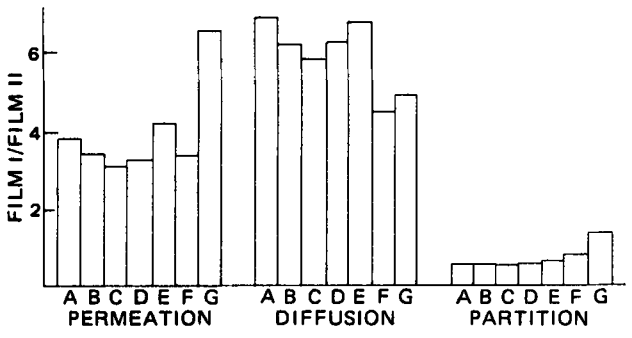


Figure 1—*Relative comparison of steroid permeation, diffusion, and partition coefficients in Films I and II. Key: A, testosterone; B, norethindrone; C, nandrolone; D, progesterone; E, 17α-hydroxyprogesterone; F, estradiol; and G, hydrocortisone.*

The values of U, D, and K_d for the various steroids in Films I and II are given in Table I. The relative values for each steroid in these films are shown in Fig. 1. Except for hydrocortisone and possibly estradiol, the relative permeation factors for all steroids were the same. This finding suggests that similar mechanisms control the permeation of these solutes.

Equation 1 differs somewhat from that used previously (Eq. A15, *Appendix*) (1, 2, 8). An assumption implicit in the previous work is that the amount of drug within the polymer film during steady-state diffusion is small (9). However, the K_d values in Tables I and II suggest that, during steady-state diffusion, a significant portion of the initial drug load added to Compartment I of the diffusion cell will be associated with the polymer film. In effect, this association of drug with the film reduces the concentration gradient between the aqueous compartments and results in permeability coefficients that are too low if the amount of drug in the film is assumed to be small. The magnitude of the effect depends on K_d. For example, with progesterone, which has a K_d of 129, Eq. 1 yields a value of 8.44×10^{-7} cm^2/sec for the permeability in polyhydroxyethyl methacrylate, whereas the equation used in previous work (Eq. A15, *Appendix*) provides a value of 5.62×10^{-7} cm^2/sec for progesterone in the same film. The difference in the calculated permeability coefficients for hydrocortisone, $K_d = 27$, is much less for the same film, *i.e.*, 2.39×10^{-7} cm^2/sec *versus* 2.32×10^{-7} cm^2/sec.

Equation 1 is derived on the assumptions that the drug partitions into the film in accordance with its equilibrium partition coefficient and that the partition coefficient is concentration independent. Experiments with several steroids over a wide concentration range suggest that this assumption is valid for the hydrogels. The derivation of Eq. 1 from Fick's first law is given in the *Appendix*.

These results raise questions with respect to the validity of conclusions reached in previous work (1, 2, 8) on the effects of various factors on the permeability of hydrogel films to progesterone. The conclusions reached depended primarily on relative changes in permeability and/or diffusion coefficients. All previously reported values of U and D were recalculated according to the methods outlined in the present paper. The new values are consistent with the conclusions stated in those papers.

Steroid Permeation through Hydrogel Films—Solute permeation through polymeric films is normally described in terms of either a "pore" or a "solution-diffusion" mechanism. In the pore mechanism, transport occurs *via* diffusion through solvent present within microchannels or pores. The K_d values are usually less than one and reflect solute distribution between the membrane solvent and bulk solvent. Solution-diffusion transport occurs *via* dissolution and diffusion of the solute within the segments making up the polymer matrix. The K_d values for this mechanism vary widely but usually are much greater than one.

For progesterone diffusion through hydrogel films, previous work (2) indicated that the solution-diffusion mechanism dominates in Film II whereas the pore mechanism dominates in Film I. These conclusions are based on an analysis of permeation data according to methods outlined by other investigators (4, 5).

The data in Table I indicate that the K_d values for both Films I and II are much greater than one. These high K_d values for Film I appear to be inconsistent with the pore mechanism for solute transport. The possibility remains, however, that K_d is dominated by the high solute solubility within the hydrophobic regions of the hydrogel (10) whereas permeation is dominated by diffusion within "fluctuating pores" (11) or microchannels within this film.

Separation of pore and solution-diffusion contributions to total per-

Table I—Permeation Parameters for Steroids in Hydrogel Films

Steroid	Film I			Film II			K_d^I/K_d^{II}
	Permeability Coefficients, $U \times 10^7$ cm²/sec	Diffusion Coefficients, $D \times 10^9$ cm²/sec	Partition Coefficients, K_d	Permeability Coefficients, $U \times 10^7$ cm²/sec	Diffusion Coefficients, $D \times 10^9$ cm²/sec	Partition Coefficients, K_d	
Testosterone	9.05	18.8	48	2.40	2.70	89	0.54
Norethindrone	9.47	13.5	70	2.83	2.16	131	0.54
Nandrolone	7.56	20.4	37	2.45	3.45	71	0.52
Progesterone	8.44	7.04	129	2.61	1.12	232	0.56
17α-Hydroxyprogesterone	8.78	10.6	83	2.02	1.53	132	0.63
Estradiol	9.69	5.48	177	2.85	1.21	235	0.75
Hydrocortisone	2.39	8.86	27	0.36	1.78	20	1.35

meation is necessary to determine the dominant mechanism in Film I. The following discussion concerns the development of a model for diffusion within hydrogels that will provide for the calculation of these separate contributions from the data in Table I. This model is based on the physical–chemical properties of hydrogels and, in particular, on the water distribution within these films.

Macroscopically, hydrogel films are homogeneous single-phase systems having water and polymer as components. Microscopically, the polymer and water can be visualized as separate dispersed phases.

Jhon and Andrade (12) hypothesized that water can exist in at least three different environments within synthetic hydrogel films in a fashion analogous to that proposed (13) for biological membranes. These environments include hydration or bound water, interfacial water, and normal or "bulk-like" water. The bound water is strongly associated with the polymer, probably as water hydrating the hydrophilic polymer groups. Interfacial water is not well defined but may be associated with hydrophobic interactions between the polymer segments. Bulk-like water is similar to bulk water in aqueous solutions.

Sung (14) defined the concentrations of these various water types within poly(hydroxyethyl methacrylate) films, prepared with and without 1 mole % of ethylene glycol dimethacrylate. The amount of bulk-like water is highly dependent on the total hydrogel water content. Films cross-linked with ethylene glycol dimethacrylate have a lower percentage of bulk-like water than hydrogels prepared without cross-linker at equal total water contents. Interpolation of Sung's data is possible with the assumption that the distribution of water into bound, interfacial, and bulk-like fractions is similar in a 1-mole % ethylene glycol dimethacrylate cross-linked gel containing the same weight fraction of total water (nonequilibrium value) as a 5.25-mole % cross-linked gel that is equilibrated with water.

The equilibrium weight fraction of water in Film II is 0.35. A 1-mole % cross-linked gel contains less than 5 volume % of bulk-like water at this weight fraction. From this value, it may be inferred that the volume percent of bulk-like water in Film II approaches zero. A value of 22.8 volume % of bulk-like water is obtained for hydrogel films prepared without cross-linker having a total water weight fraction of 0.43 (Film I).

These results, together with other data (2–6) on solute permeation through hydrogel films, provide the basis for the model of solute permeation through these films.

In this model, the hydrogel films prepared without cross-linker are composed of two domains, A and B. Domain A is composed of polymer segments that associate by hydrophobic interactions and are surrounded by bound and interfacial water. Domain B is bulk-like water and forms the fluctuating pores described previously (11). Increasing the mole percent of cross-linker increases the amount of A and reduces the amount of B. A hydrogel such as Film II, having no bulk-like water, is assumed to be composed entirely of A-type domains. Although the relative amounts of Domains A and B change as the mole percent of cross-linker is changed, the inherent permeabilities of the domains are assumed to remain constant. Therefore, the total permeability of a hydrogel film is a summation of the individual permeabilities of Domains A and B and varies in accordance with the volume percent of bulk-like water present.

Transport in the hydrogel A domains occurs through the bound and interfacial water, through the hydrophobic regions, or through some combination of these. Irrespective of the specific transport region, permeation in the A regions occurs by the solution–diffusion mechanism as previously defined. The K_d values for transport in the A regions vary widely, depending on the solute solubility characteristics.

Transport in the B domains occurs by simple diffusion in bulk-like water. The K_d values must be precisely one since the solute is simply partitioning from bulk water into hydrogel domains of bulk-like water.

Film II, having no bulk-like water, is a diffusion barrier composed exclusively of A-type domains. As postulated in the model, solute transport occurs only by the solution–diffusion mechanism in such a film.

Several lines of evidence support this contention and are consistent for both hydrophobic and hydrophilic solutes:

1. It is supported by the cited data, which indicate that films containing high cross-linker concentrations have little or no bulk-like water.

2. Past work has shown that both hydrophobic (2) and hydrophilic (4, 5) solutes exhibit limiting values for the diffusion coefficient as the cross-linking agent concentration increases. This result is inconsistent with a pore mechanism since, if this mechanism is operative, the diffusion

Table II—Model Analysis of Steroid Permeation Data

Steroid	Partial Molar Volume[a], cm³/mole	Diffusion Coefficient in Water, $D_0 \times 10^6$ cm²/sec	Diffusion Coefficient in Bulk-Like Water of Film I, $D_B \times 10^7$ cm²/sec	ln (D_B/D_0)	D_B/P_T
Testosterone	237.4	6.04	7.20	−2.13	0.80
Norethindrone	252.0	5.83	7.29	−2.08	0.77
Nandrolone	218.1	6.35	5.67	−2.42	0.75
Progesterone	269.8	5.59	6.43	−2.16	0.76
17α-Hydroxyprogesterone	272.1	5.56	7.22	−2.04	0.82
Estradiol	214.9	6.41	7.49	−2.15	0.77
Hydrocortisone	273.6	5.55	2.11	−3.27	0.88

[a] Calculated from group contributions, Ref. 24.

coefficients must decrease with increasing cross-linker content due to a reduction in the average pore size as a consequence of reduced polymer chain mobility.

3. Film II was nearly impermeable to hydrophilic solutes such as inositol and sucrose (6). Since sucrose is of approximately the same molecular weight as the steroids used in the present study, its diffusion coefficient should be similar to the steroids if the pore mechanism is operative in Film II.

4. The conclusion that transport occurs by the solution-diffusion mechanism in Film II is consistent with the high partition coefficients obtained for the steroids used in the present study.

5. The disproportionately large decrease in the permeability coefficient of hydrocortisone, a relatively water-soluble steroid, in Film II compared with Film I, coupled with a lower partition coefficient in Film II than in Film I, suggests a dependence on bulk water not seen with the more hydrophobic steroids yet consistent with the pattern exhibited by the sugars.

Film I contains 22.8% of bulk-like water making up the B domains; the remainder is designated as A-type domains. Based on the proposed model and using the data in Table I, it is possible to estimate the contribution of each domain to the total permeability. Total Film I permeability can be represented as a summation of the individual domain contributions:

$$P_T = P_A + P_B \qquad \text{(Eq. 2)}$$

where:

P_T = total permeability in Film I
P_A = permeability coefficient in the A domains
P_B = permeability coefficient in the B domains

The P_A value is obtained from the relation $P_A = (\phi_A)P_T^{II}$, where P_T^{II} is the permeability coefficient of the solute in Film II and ϕ_A is the volume fraction of A-type domains in Film I. The ϕ_A value is given by $\phi_A = 1 - \phi_B$, where ϕ_B is the volume fraction of bulk-like water present in Film I (0.228).

Equation 2 may be rewritten as:

$$P_T - (\phi_A)P_T^{II} = P_B \qquad \text{(Eq. 3)}$$

The calculated P_B values represent the total permeability attributable to the pore mechanism in Film I. By definition, the partition coefficient in the B domains equals one. Therefore, P_B quantitatively equals the diffusion coefficient, D_B, using $P_B = K_d D_B$. These values are given in Table II along with the ratio D_B/P_T, which is the percent pore-type permeation in Film I. This ratio is approximately 0.77 for all of the steroids investigated except hydrocortisone, which is 0.88. This finding indicates that the pore contribution to transport in Film I is similar for the more hydrophobic steroids, with the relatively water-soluble steroid hydrocortisone permeating *via* pores to a greater extent. This result is consistent with the proposed model. The relatively high values of D_B/P_T for all steroids suggest that permeation through Film I is dominated by the pore mechanism, a result consistent with previous work (2).

The high K_d values with Film I are consistent with the model. Although permeation is dominated by the pore mechanism, Film I is composed primarily of A-type domains, which dominate the partitioning of hydrophobic solutes but make little contribution to permeability.

An implicit assumption of the model is that the A domains are similar in Films I and II. Were this strictly true, the partition coefficients, which are dominated by A-type domains, in Film I should be related to those in Film II according to the volume fraction of A-type domains present in Film I (0.772). These values are given in Table I as the ratio K_d^I/K_d^{II}. The estradiol value is in close agreement with the predicted value. However, for the other steroids, except hydrocortisone, this ratio is approximately 0.54. Thus, qualitative agreement with the predicted value is found, but the quantitative agreement is not good. This finding implies that differences exist between the A domains of Films I and II. This conclusion is expected based on the high cross-linker content in Film II. The corrections that must be made to overcome this deficiency in the model are not readily apparent.

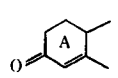
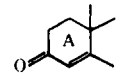
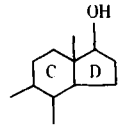
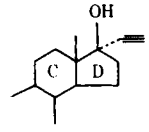
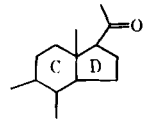
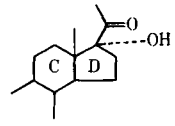
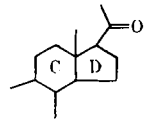
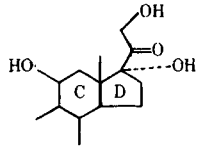
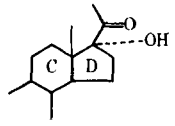
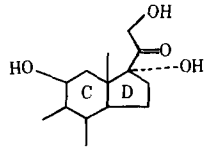
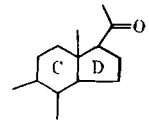
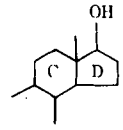
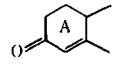
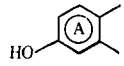
Sufficient data were available from previous work (2) to test the model in predicting progesterone permeation in gels containing intermediate concentrations of the cross-linking agent ethylene glycol dimethacrylate. From the data of Sung (14), the volume percent of bulk-like water in a film prepared from 0.75 mole % of cross-linker is approximately 0.15. Based on this value, the permeability coefficient for progesterone in this cross-linked gel can be calculated from Eq. 3 by assuming that the total permeation arising from transport in the B regions is given by $P_B = \beta D_B$; β is defined by the ratio ϕ_B^I/ϕ_B, where ϕ_B^I is the volume fraction of bulk-like water in the cross-linked film. By using the values found in Tables I and II for P_T^{II} and D_B, 0.15 for ϕ_B^I, 0.228 for ϕ_B, and 0.85 for ϕ_A, the total permeability for a film containing 0.75 mole % cross-linker is calculated to be 6.45×10^{-7} cm²/sec. This value is in good agreement with the experimental value of 5.64×10^{-7} cm²/sec (2).

A theoretical treatment of solute permeability in hydrated polymer films was developed by Yasuda *et al.* (15). This treatment examines solute diffusion as a function of the free volume of the water–polymer system and predicts a linear correlation for plots of ln (D/D_0) *versus* the square of the cross-sectional solute radius; D is the diffusion coefficient in the polymer film and D_0 is the diffusion coefficient in bulk water. All solutes should correlate with a single straight line for a given polymer film provided the free volumes accessible to the various solutes are equal or can be resolved into equivalent contributions.

Wisniewski and Kim (6) examined the permeabilities of ions and various other hydrophilic solutes in Film I-type hydrogels. A plot of ln (D/D_0) *versus* the square of the cross-sectional radius was linear, with partition coefficients approximately equivalent to the volume fraction of bulk-like water in the film. This information suggested (6) that these solutes are restricted to permeation through the free volume of bulk-like water that is located in the B-type domains proposed in the present study. The D_B values obtained in the present study represent the diffusion coefficients of hydrophobic steroids in the bulk-like water and, therefore, should correlate with the previous data (6). The values of ln (D_B/D_0) are given in Table II. The D_0 values were calculated by a literature method (16).

Lacey and Cowsar (17) showed that the minimal cross-sectional area for steroids of the type investigated in the present study is about 36 Å². When using this value to determine the minimal cross-sectional radius, a value of −2.7 for ln (D_B/D_0) is required for an exact correlation with the data of Wisniewski and Kim (6). The data given in Table II are, in general, somewhat more positive than this value. Thus, as with the comparison with the K_d values in Films I and II discussed previously, the model presented here fits the expected value qualitatively but not quantitatively. The somewhat larger values of ln (D_B/D_0) compared to the predicted value arise from D_B values that are too large. This result indicates that the model predicts a contribution from pore-type permeation that is too large. This discrepancy probably arises from the assumption that A-type domains have similar permeation characteristics in Films I and II. The A domains are probably more permeable in Film I due to a lower cross-link density, leading to increased values for $\phi_A P_T^{II}$. Therefore, the observed deviations are in the right direction.

Table III—Functional Group Contributions to Diffusivity

Pair	Functional Group Changes		Relative Molecular Volume	Relative Diffusivity Factor
1	 Nandrolone	 Testosterone	1.09	0.78
2	 Nandrolone	 Norethindrone	1.16	0.63
3	 Progesterone	 17α-Hydroxyprogesterone	1.01	1.37
4	 Progesterone	 Hydrocortisone	1.01	1.59
5	 17α-Hydroxyprogesterone	 Hydrocortisone	1.01	1.16
6	 Progesterone	 Testosterone	0.88	2.41
7	 Nandrolone	 Estradiol	0.99	0.35

Effect of Steroid Structure on Permeation through Hydrogel Films—Previous work (1, 2, 18–23) demonstrated that hydrogels are excellent candidates for use in controlled-release drug delivery systems. The major advantages of these polymers for this purpose are biocompatibility (24, 25) and the potential for controlling permeation characteristics through modifications in the hydrogel composition. Several studies using hydrophobic (2) and hydrophilic (4, 5, 20, 21) solutes indicated that permeability coefficients can be varied by more than an order of magnitude by changing either the cross-link density or the monomer composition.

Several studies (6, 26) demonstrated effects of molecular structure on solute permeation in films prepared without added cross-linker. The importance of the solute molecular volume on the permeation characteristics has been demonstrated. However, no studies have considered the effects of molecular structure on permeability in films containing high cross-linker concentrations. Studies on the permeation characteristics of these films are of interest since intermolecular interactions between the solute and polymer segments are expected to increase and should dominate the overall permeability of these films.

For poly(dimethyl siloxane), a film in which solutes permeate by the solution-diffusion mechanism, small changes in steroidal structure can lead to variations in the diffusion coefficients of more than two orders of magnitude (17). These dramatic changes in the diffusion coefficients in the solution-diffusion-type poly(dimethyl siloxane) films are not observed with Film II, a solution-diffusion-type hydrogel. Changes in permeability coefficients are even less, indicating the importance of solute partitioning in the overall film permeation characteristics. Specific effects of solute structure on the diffusion coefficients in Film II are demonstrated more clearly by the comparisons made in Table III. In this table, relative diffusivity factors, defined as the ratio of diffusion coefficients for steroids that differ by one structural feature, have been calculated. From the results in this table, the following conclusions were obtained:

1. The addition of a C-19 angular methyl group decreases diffusivity by a small factor (0.78) due to steric hindrance (relative K_d values are independent of cross-linker content).
2. The same effect is seen on the addition of a C-17 ethynyl group, where diffusivity decreases by a factor of 0.63.
3. The addition of hydroxyl groups increases diffusivity by rather substantial factors, as seen from Comparisons 3–6 in Table III. However, the effect of the first hydroxyl group is proportionately greater than the second and third hydroxyl groups (Table III, Comparisons 3 and 5).
4. Changing the A ring of the steroid nucleus from an alicyclic (nandrolone) to an aromatic (estradiol) ring produces a decrease in diffusivity by a factor of 0.35. This decrease occurs in spite of the change from a keto to a hydroxy function at the 3-position of the steroid nucleus, which should increase diffusivity (Table III, Comparison 6).

The outlined group contributions to diffusivity should be valuable in predicting approximate diffusion coefficients for other steroids. For example, the diffusion coefficient of testosterone may be approximated as follows. Beginning with progesterone, the effect of removing the side chain at C-17 may be approximated by a factor of 1/0.63 (*i.e.*, the inverse of the effect noted for the addition of a C-17 ethynyl group to nandrolone) times a factor of 1.37 (the effect of the addition of a C-17 hydroxyl group to progesterone). The result of this calculation gives 2.42×10^{-9} cm^2/sec for the diffusion coefficient of testosterone in Film II, a result that compares favorably with the experimental value of 2.70×10^{-9} cm^2/sec.

CONCLUSIONS

Steroid permeation in poly(hydroxyethyl methacrylate) films is complex. However, to a first approximation, the total observed permeability can be separated into pore and solution-diffusion components by applying a model describing the polymer films in terms of domains. Such an analysis supports the contentions of Film I being a pore-type and Film II being a solution-diffusion-type barrier for both hydrophilic and hydrophobic solutes.

As expected from the inherent nature of solution-diffusion permeation, structural alterations in steroidal solutes affect diffusion. Decreases in molecular volume and increases in hydrogen bonding capacity increase diffusivity. By quantifying these effects for specific functional groups, it is possible to predict diffusion coefficients.

APPENDIX

When a linear concentration gradient exists within a barrier film, the instantaneous concentration gradient within the film may be expressed as:

$$-\frac{dC}{dl} = \frac{C_I' - C_{II}'}{l} \qquad \text{(Eq. A1)}$$

where C_I' and C_{II}' represent the surface concentrations of the diffusant in the membrane at the donor (I) and receptor (II) sides of the film and l represents the thickness of the film. Provided that the partition coefficient, K_d, is independent of the solute concentration, this equation may be rewritten as:

$$-\frac{dC}{dl} = \frac{K_d(C_I - C_{II})}{l} \qquad \text{(Eq. A2)}$$

where C_I and C_{II} are the donor and receptor phase concentrations, respectively. The flux of solute within the film can be described by Fick's first law as:

$$J = -D\frac{dC}{dl} = -D\frac{(C_I' - C_{II}')}{l} \qquad \text{(Eq. A3)}$$

which can be rewritten as:

$$J = \frac{DK_d}{l}(C_I - C_{II}) = \frac{U}{l}(C_I - C_{II}) \qquad \text{(Eq. A4)}$$

where the permeability $U = DK_d$.

During steady state, the flux out of Compartment I equals the flux into Compartment II, which also equals the flux within the film barrier. This may be expressed as:

$$-J = \frac{V}{A}\frac{dC_I}{dt} \qquad \text{(Eq. A5)}$$

and:

$$J = \frac{V}{A}\frac{dC_{II}}{dt} \qquad \text{(Eq. A6)}$$

where V is the compartment volume and A is the film area. Subtracting Eq. A6 from Eq. A5 and equating to Eq. A4 give:

$$\frac{d(C_I - C_{II})}{dt} = -\frac{2UA}{lV}(C_I - C_{II}) \qquad \text{(Eq. A7)}$$

Equation A7 is valid only during steady-state flux. Under these conditions, the concentrations of solute in Compartments I and II are C_1 and C_2 at t_{oss} (onset of steady state) and C_3 and C_4 at t_{ss} (any time during steady state). When using these concentrations and times for the limits of integration, Eq. A7 gives:

$$\ln\left\{\frac{C_3 - C_4}{C_1 - C_2}\right\} = \frac{-2UA}{lV}(t_{ss} - t_{oss}) \qquad \text{(Eq. A8)}$$

Steady-state mass balance gives:

$$C_0V = C_1V + C_2V + C_mV_m \qquad \text{(Eq. A9)}$$

$$C_0V = C_3V + C_4V + C_mV_m \qquad \text{(Eq. A10)}$$

where C_0 is the initial concentration in the donor phase, C_m is the solute concentration within the film, and V_m is the film volume. The film concentration may be defined as:

$$C_m = K_d\frac{(C_1 + C_2)}{2} = K_d\frac{(C_3 + C_4)}{2} \qquad \text{(Eq. A11)}$$

Substitution of Eq. A11 into Eqs. A9 and A10 and rearranging give:

$$C_1 = \frac{2}{2V + K_dV_m}\left(C_0V - C_2V - \frac{K_dC_2V_m}{2}\right) \qquad \text{(Eq. A12)}$$

and:

$$C_3 = \frac{2}{2V + K_dV_m}\left(C_0V - C_4V - \frac{K_dC_4V_m}{2}\right) \qquad \text{(Eq. A13)}$$

Substituting Eqs. A12 and A13 into Eq. A8 and rearranging give:

$$\ln\left\{\frac{C_0V - (2V + K_dV_m)C_4}{C_0V - (2V + K_dV_m)C_2}\right\} = -\frac{2UA}{lV}(t_{ss} - t_{oss}) \qquad \text{(Eq. A14)}$$

In the limit where K_d is small and t_{oss} approaches zero, C_2 also approaches zero and Eq. A14 may be written as:

$$\ln\left\{1 - \frac{2C_4}{C_0}\right\} = -\frac{2UAt}{lV} \qquad \text{(Eq. A15)}$$

Equation A15 was developed (9) for the case of quasi-steady-state diffusion in a film, assuming that the amount of solute in the film is negligible.

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ACKNOWLEDGMENTS

Presented in part at the APhA Academy of Pharmaceutical Sciences, Hollywood, Fla., meeting, November 1978.

Supported by NIH Grant HD-09791-03.

The authors thank Dr. S. W. Kim, Dr. D. E. Gregonis, and Dr. J. D. Andrade for their contributions to this work.