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Progestin Permeation through Polymer Membranes I: Diffusion Studies on Plasma-Soaked Membranes

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Abstract □ The potential of several commercially available polymeric materials for use in controlled-release drug delivery devices was investigated. Progesterone was used as a model hydrophobic drug. The progesterone permeation rates through polydimethylsiloxane, two polyether urethanes, a hydroxyethyl methacrylate, a polyether urethane–polydimethylsiloxane blend, and a cellulosic membrane were determined. The permeabilities were obtained on nonsoaked membranes and on membranes soaked in plasma for varying times. The purpose of the plasma soaks was to examine the effects of lipid absorption and degradative processes within the membrane on progesterone permeability. This study identified several polymers that show potential for use in controlled-release drug delivery devices. The plasma treatment studies showed that several polymers may not be acceptable. The plasma soak studies were interpreted in terms of the mechanisms of drug permeation through the membranes.

Keyphrases □ Polymer membrane, various—permeabilities to progesterone, effect of soaking in plasma, potential for use in controlled-release drug delivery devices □ Progesterone—permeability through various polymer membranes, effect of soaking in plasma □ Delivery devices, controlled release—various polymer membranes evaluated, permeability to progesterone, effect of soaking in plasma □ Diffusion—progesterone through various polymer membranes, effect of soaking in plasma □ Dosage forms—controlled-release delivery devices, various polymer membranes evaluated, permeability to progesterone, effect of soaking in plasma

Recently, attention has been directed toward the use of polymeric materials to control the release of drugs for extended periods *in vivo*. Some applications of these materials have been the controlled release of contraceptive steroids (1–3), anti-inflammatory agents (4), antihistamines (5), narcotic antagonists (6), inorganic fluorides (7, 8), and antitumor agents (9).

Much of the previous work on controlled-release drug delivery devices utilized polydimethylsiloxane (silicone rubber) because of its biocompatibility and its high permeability to hydrophobic drugs (10, 11). However, this polymer has several disadvantages for certain applications. It is weakly permeable to hydrophilic drugs, especially charged species (12), and tends to absorb large quantities of lipids from biological fluids (13–15). Lipid absorption may cause a decrease in the release rate of drugs as a function of time when controlled-release devices are implanted in body tissues (16, 17).

Other polymers that can be utilized in controlled-release drug delivery devices have been evaluated. The class of polymers known as the hydrogels has shown promise. These polymers can be utilized to control the release of both hydrophobic and hydrophilic drugs, and the release rates can be varied over a wide range by changes in the monomer composition and cross-linker percent (4, 5, 7, 9, 18).

In the present study, the potential use of several commercially available polymeric materials in controlled-release drug delivery devices was investigated. Progesterone was used as a model hydrophobic drug. The rate of permeation of progesterone through several polymeric films was determined on both water-swollen membranes and water-swollen membranes pretreated by soaking in plasma for varying periods. The purpose of the plasma soaks was to examine the effects of lipid absorption and/or any other effects of these biological fluids on the permeability of drug molecules. The results were interpreted in terms of the mechanisms of drug permeation through the films.

EXPERIMENTAL

Materials—Progesterone[1] and 1,2-^{3}H-progesterone[2] were used as received. The polymer films investigated were polydimethylsiloxane[3] (silicone rubber), two polyether urethanes (polyurethane I[4] and polyurethane II[5]), a polyether urethane–polydimethylsiloxane polymer blend[6], a regenerated cellulosic material[7], and a hydroxyethyl methacrylate[8] (hydrogel).

[1] Steraloids Inc., Wilton, N.H.
[2] New England Nuclear, Boston, Mass.
[3] Dow Corning Co., Midland, Mich.
[4] Biomer, Ethicon Co., Somerville, N.J.
[5] Pellethane, The Upjohn Co., Stanford, Conn.
[6] Avcothane, AVCO Everett Research Laboratories, Everett, Mass.
[7] Cuprophan, Vital Assists Inc., Littleton, Colo.
[8] Courtesy of Hydron Laboratories, New Brunswick, N.J.

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The cellulosic, polydimethylsiloxane, and polyurethane II films were obtained from the manufacturer. The polyurethane I and the polyether urethane–polydimethylsiloxane blended films were prepared by solvent casting using dimethylacetamide and tetrahydrofuran, respectively, with vacuum drying. Polyhydroxyethyl methacrylate films were prepared by a free radical polymerization using 7.84 mmoles of azobis(methylisobutyrate)/liter of monomer as the initiator. The initiator was prepared by the method of Mortimer (19). The polymerizations were carried out between glass plates at 60° for 24 hr. The monomer solutions were mixed with 40% (v/v) water prior to polymerization. Cross-linked hydrogels, containing 0.75 and 3.75 mole % ethylene glycol dimethacrylate[9] as the cross-linker, were prepared similarly, except that the initial monomer solution contained 40% (v/v) ethylene glycol.

Plasma was prepared by centrifugation of a 9:1 mixture of bovine blood with 3.8% sodium citrate and was stored in glass containers at −15°.

Methods—All polymer films, except the hydrogels, were wiped with methanol–water (50:50) to remove surface contaminants. The films then were immersed immediately in a large volume of deionized water to equilibrate for 24 hr at room temperature (24 ± 1°). The hydrogels were transferred directly from the polymerization mold into a large volume of deionized water, which was changed twice daily. The gels were equilibrated at room temperature until the weight fraction of water was constant.

Films receiving plasma treatment were transferred from the water equilibration baths into 20 ml of plasma at room temperature. The plasma was changed daily to minimize bacterial contamination. The polymer films were rinsed with deionized water at the same time the plasma was changed to reduce bacterial problems. After the plasma soaks, the polymer films were rinsed and reequilibrated with deionized water at room temperature for 24 hr.

The diffusion coefficients of progesterone in the polymer films were determined in a glass diffusion cell with two compartments of equal volume (176 ml). The membrane was clamped between the compartments and was not supported. Each compartment was stirred continuously at 1600 rpm by externally mounted constant-speed synchronous motors. A ±10% change in the stirring speed did not affect the observed permeabilities. Initially, one chamber was filled with deionized water. The second chamber was filled with an aqueous solution containing 11.2 μg of unlabeled progesterone/ml together with an appropriate amount of the labeled steroid.

Progesterone permeation through the membranes was followed by determining the increase in radioactivity in the initially progesterone-free compartment. Samples of approximately 0.1 ml were withdrawn and weighed in tared vials. Scintillation fluid[10], 10 ml, was added to each vial, and the concentration was determined using a liquid scintillation spectrometer[11].

The partition coefficients were measured by a solution depletion technique. For several membranes, the partition coefficients were dependent on the solute concentration in the aqueous phase. For this reason, the partition coefficients were measured under conditions such that the ratios of the volume of membrane to the volume of solution and the initial bulk concentration of progesterone were similar to those used in the diffusion experiments. The bulk solutions were allowed to equilibrate with the membrane until a constant concentration was obtained. The equilibrium concentrations were obtained from measurements of the radioactivity in the aqueous phase by scintillation counting as already described.

The approximate thicknesses of the films were: polyhydroxyethyl methacrylate, 0.07 cm; polyurethane I, 0.025 cm; polyurethane II, 0.013 cm; polydimethylsiloxane, 0.016 cm; polyether urethane–polydimethylsiloxane, 0.016 cm; and the cellulosic membrane, 0.0029 cm. The accurate thickness of the wet membranes used in the calculation of the diffusion coefficient was determined by direct measurement using a light wave micrometer[12] accurate to 2.5×10^{-5} cm at the minimum allowable pressure (60 g). Because of the low pressures involved in these measurements, film deformation should be minimal.

RESULTS AND DISCUSSION

The membranes were chosen because of their potential for use in drug delivery systems. Polyurethanes I and II are commercially available copolymers of urethane and ethylene glycol. These membranes have been considered for use in artificial hearts and other implant devices. The hydrogels have shown potential for use as controlled-release drug delivery devices (4, 5, 7, 9). These membranes are biocompatible, and the permeability of solutes can be varied over a wide range by changes in the monomer composition and percent cross-linker (18).

Polydimethylsiloxane was utilized in previous studies on controlled-release drug delivery systems for steroids (1–3). The polymer blend of polydimethylsiloxane and polyurethane may offer some advantages not shared by the individual polymers. The cellulosic film was included as a model membrane because solutes permeate this membrane by diffusion through pores in the polymer network.

The diffusion coefficients for progesterone in the various membranes were calculated by means of the following relationship, which was derived elsewhere (20):

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = -\left(\frac{1}{V_1} + \frac{1}{V_2}\right)\frac{AUt}{l} \qquad \text{(Eq. 1)}$$

where C_t is the concentration of progesterone at time t, C_0 is the initial concentration of progesterone, V_1 and V_2 are the compartment volumes (176 ml), A is the membrane area (14.2 cm²), l is the wet membrane thickness, and U is the permeability, which is defined as:

$$U = DK_d \qquad \text{(Eq. 2)}$$

Table I—Diffusion Coefficients, Partition Coefficients, and Permeabilities for Progesterone in Polydimethylsiloxane, Polyurethane I, and Polyurethane II at 25°

Membrane	Plasma Soaking Time	D, cm²/sec	K_d	$U \times 10^7$, cm²/sec
Polydimethylsiloxane	0	$2.15 \times 10^{1-8}$	180[a]	38.5
	1 hr[b]	2.30×10^{-8}		41.5
	24 hr[b]	2.10×10^{-8}		37.7
	3 days[b]	2.41×10^{-8}		43.5
	7 days[b]	2.30×10^{-8}		41.4
	9 days	2.79×10^{-8}		50.2
Polyurethane I	0	4.75×10^{-10}	2110[a]	10.0
	24 hr	4.35×10^{-10}		9.18
	4 days	3.95×10^{-10}		8.33
	7 days	2.82×10^{-10}		5.95
	16 days	6.17×10^{-10}		13.0
	1 hr[b]	4.40×10^{-10}		9.28
	14 days[b]	4.50×10^{-10}		9.50
Polyurethane II	0	6.5×10^{-12}	5000[a]	0.33
	0	5.0×10^{-12}		0.25
	1 hr	4.2×10^{-12}		0.21
	24 hr	4.2×10^{-12}		0.21
	24 hr	5.1×10^{-12}		0.26
	3 days	9.4×10^{-12}		0.47
	7 days	11.3×10^{-12}		0.57

[a] Average values. [b] At 5°.

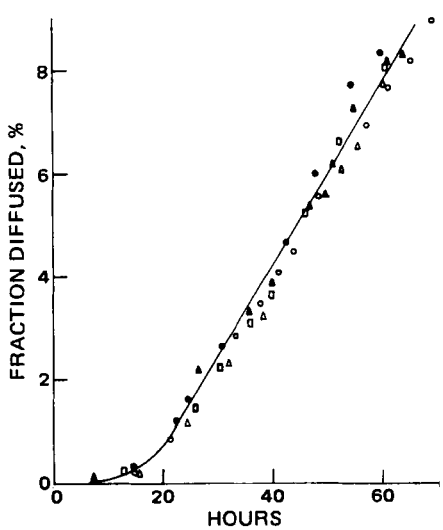

Figure 1—*Fraction of drug diffused* versus *time for progesterone permeation through hydroxyethyl methacrylate without cross-linker. Key (plasma soak times): △, no soak; ○, 1 day; □, 3 days; ●, 7 days; and ▲, 14 days.*

[9] Monomer Polymer Laboratories, Philadelphia, Pa.
[10] Aquasol, New England Nuclear, Boston, Mass.
[11] Model 3390, Packard Instrument Co., Downers Grove, Ill.
[12] Van Keuren Co., Watertown, Mass.

Table II—Diffusion Coefficients, Partition Coefficients, and Permeabilities for Progesterone in Hydrogels at 25°

Membrane	Plasma Soaking Time, days	$D \times 10^9$	K_d	$U \times 10^7$, cm²/sec
Hydroxyethyl methacrylate	0	4.38[a]	120	5.59
	1	3.95	133	5.07
	3	4.60	124	5.91
	7	4.41	134	5.67
	14	4.57	131	5.87
Hydroxyethyl methacrylate plus 0.75% ethylene glycol dimethacrylate	0	3.82[b]	134	5.19
	1	3.50	135	4.76
	3	3.76	139	5.13
	7	3.92	139	5.33
	14	3.34	133	4.54
Hydroxyethyl methacrylate plus 3.75% ethylene glycol dimethacrylate	0	0.34[c]	211	0.71
	1	0.43	161	0.76
	3	0.43	174	0.77
	7	0.40	186	0.71
	14	0.42	155	0.74

[a] Calculated with an average K_d of 128. [b] Calculated with an average K_d of 136. [c] Calculated with an average K_d of 177.

where D is the diffusion coefficient, and K_d is the partition coefficient. The values of U, K_d, and D for the various polymer membranes are shown in Tables I–III. Figures 1–3 are plots of the fraction of drug diffused against time for progesterone permeation through the membranes polyhydroxylethyl methacrylate, polyurethane I, and polyurethane II, respectively.

The permeabilities of the nonsoaked membranes varied from about 40×10^{-7} cm²/sec for silicone rubber to about 0.2×10^{-7} cm²/sec for polyurethane II. The membrane diffusion coefficients varied over a much wider range, from about 2×10^{-8} cm²/sec for silicone rubber to about 4×10^{-12} cm²/sec for polyurethane II. For all membranes, the diffusion coefficients were calculated on the basis of the average value of K_d obtained from all experiments with that polymer. In all cases except polyurethane II, the values of K_d were in good agreement for any given membrane irrespective of the prior treatment of the membrane. With polyurethane II, the values of K_d tended to vary over a wide range and were independent of the prior treatment of the membrane. The value of K_d obtained for polydimethylsiloxane was higher by a factor of about three compared to values reported previously (3, 11).

As mentioned under *Experimental*, the values of K_d were dependent on the concentration of progesterone in the bulk solution; K_d tended to increase as the bulk concentration decreased. This result may have been due to adsorption of the solute at the membrane surface. Previous K_d values (3, 11) were obtained from saturation solubilities whereas the present values were obtained at bulk concentrations considerably below saturation and are not directly comparable with those obtained previously.

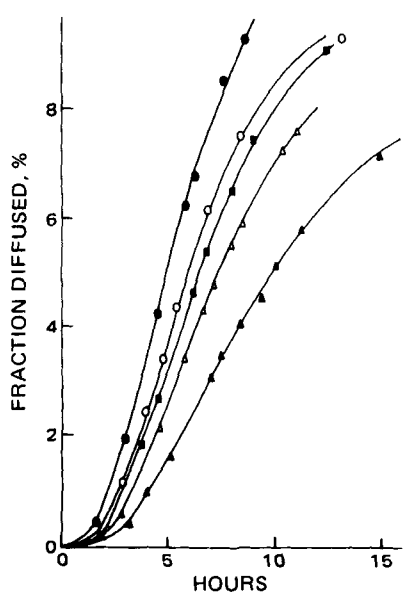

Figure 2—*Fraction of drug diffused* versus *time for progesterone permeation through polyurethane I. Key (plasma soak times): ○, no soak; ■, 1 day; △, 3 days; ▲, 7 days; and ●, 16 days.*

Table III—Plasma Soaking Times and Permeation Coefficients for Progesterone in the Polyether Urethane–Polydimethylsiloxane Blend and Regenerated Cellulose at 25°

Membrane	Plasma Soaking Time	$U \times 10^7$, cm²/sec
Polyether urethane–polydimethylsiloxane blend	0	2.00
	4 days	1.83
	7 days	1.88
Regenerated cellulose	0	3.61
	1 hr	3.98
	24 hr	3.67
	3 days	3.79
	6.3 days	4.17

The value obtained for progesterone permeability in polydimethylsiloxane was intermediate to values obtained previously (3, 11, 12, 21). Literature values varied from 6×10^{-7} cm²/sec (12) to 390×10^{-7} cm²/sec (11). These differences could arise from differences in the membranes, diffusion layer effects, or temperature. The values in the present study were obtained at 25°; previous work was at 37°.

The polydimethylsiloxane used contained a filler of unknown concentration. The presence of a filler can have dramatic effects on drug permeability in this membrane (22, 23). Drug permeability varies with both the concentration of the filler and the concentration of drug in the donor medium (23). Therefore, it is difficult to compare the values of the permeability obtained in the present study with those in previous reports. Nevertheless, progesterone permeability in polydimethylsiloxane apparently decreases in the presence of filler (3, 11, 12, 21).

Diffusion layer effects also are important in the characterization of membrane permeability (24). Although no attempt was made to characterize the thickness of the aqueous diffusion layers, the effects arising from these layers are expected to be minimal for all membranes except polydimethylsiloxane and cellulose. For this reason, the membrane permeabilities given in Tables I–III must be considered as apparent values, which include effects that arise predominantly from the membrane but may have some contribution from the aqueous diffusion layers. This conclusion is based on reasonable estimates of diffusion layer thicknesses obtained previously (25, 26) using diffusion cells similar to those used in this study. Furthermore, diffusion layer effects should not dramatically alter conclusions reached in the present study regarding the effects of plasma soaking on membrane permeability, which are of primary interest.

To investigate the potential of these polymers for use in drug delivery devices in greater detail, the effects of plasma soaking on the membrane permeabilities were investigated. The plasma soaking studies simulate two possible effects of long-term use *in vivo*: the effects of lipid absorption by the membrane and the effects arising from degradative processes within the membrane.

Molecules permeate the cellulosic membrane *via* microscopic channels

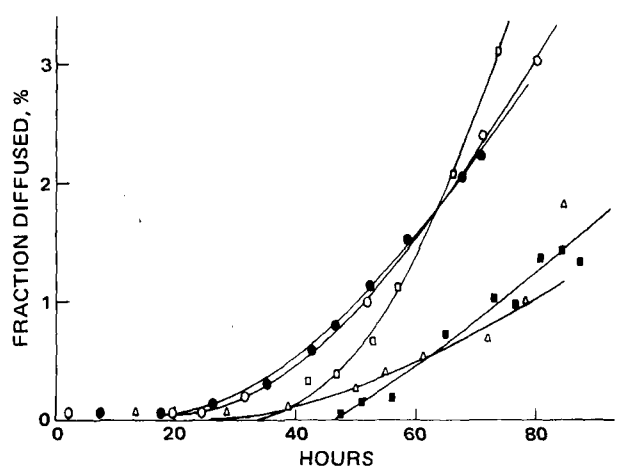

Figure 3—*Fraction of drug diffused* versus *time for progesterone permeation through polyurethane II. Key (plasma soak times): ●, no soak; ○, 5 hr; △, 1 day; □, 3 days; and ■, 7 days.*

(pores) throughout the polymer network (27). The permeation rate is governed primarily by the molecular weight of the solute (28). For a molecule with the molecular weight of progesterone, a diffusion coefficient of approximately 6×10^{-7} cm^2/sec is predicted (29). Although several attempts were made to obtain the partition coefficient of progesterone in the membrane, reproducible values could not be obtained. The trend of the values suggested, however, that K_d was less than one. This value is consistent with the arguments of Ginsburg and Katchalsky (25), who suggested that K_d values for highly water-swollen membranes of the cellulosic type may be equated to the volume fraction of water in the membrane. For the cellulosic membranes used in the present study, this value is approximately 0.67 (30). The K_d values for hydrophilic solutes such as urea and sucrose were quite close to this value (30, 31).

If it is assumed that the approximation suggested by Ginsburg and Katchalsky (25) also holds for hydrophobic solutes such as progesterone, then the value of D calculated from the average of the permeability values shown in Table III is 5.7×10^{-7} cm^2/sec. This value is in agreement with that calculated above for the diffusion coefficient of progesterone assuming that the solute permeates the cellulosic membrane *via* the pore mechanism. As seen from the values shown in Table III, the plasma soaks had no detectable effect on the measured progesterone permeability through this membrane. These results suggest that any absorbed or adsorbed species arising from the plasma treatments do not block the pores or markedly alter the effective pore size of this membrane.

The mechanism of progesterone permeation through hydrogel membranes depends on the equilibrium water content and the nature and chain length of the cross-linker. Progesterone permeation through hydroxyethyl methacrylate without cross-linker occurs predominantly *via* the pore mechanism (18). In the hydroxyethyl methacrylate membranes cross-linked with a high concentration of ethylene glycol dimethacrylate, progesterone permeation appears to occur by a process in which solution and diffusion of the progesterone in the polymer network control the permeation (18). As seen from Table II and Fig. 1, plasma soaking had little or no effect on the observed permeabilities of either the polymer without cross-linker or the membrane containing a high concentration of the cross-linker, ethylene glycol dimethacrylate. The concentration of ethylene glycol dimethacrylate was in the region where the solution and diffusion mechanism is operative.

An attempt was made to determine if the hydrogel membranes absorb lipoidal species. Measurements of the increase in weight of the polymer subsequent to the plasma soaks were taken. This technique previously was used to determine the uptake of lipids by various polymers (32). For the hydrogel membranes, the weight of the wet membrane decreased subsequent to the plasma soakings. However, the weight of these membranes returned to their initial values (prior to the plasma soaks) following a 24-hr soak in deionized water. These results suggest that the hydrogels absorbed little or no lipoidal species during the 2-week interval of plasma treatment, probably because of the low interfacial energy of these polymers (33). Since the permeabilities remained unchanged over this time, these results also suggest that no hydrolytic degradation occurred that affected the permeability of these membranes to progesterone. Finally, the results obtained with the hydrogels without cross-linker are consistent with the results of the studies on the cellulosic membranes in that the permeability of a pore-type polymer was not affected by plasma soaking.

Solute permeation through polydimethylsiloxane occurs by the solution and diffusion mechanism. The permeation rate is strongly related to the partition coefficient of the solute in the membrane (34). Lacey and Cowsar (11) demonstrated this effect for the permeation of steroids through polydimethylsiloxane. Moreover, the polymer chains of this membrane show high flexibility, as reflected in the high permeabilities of gases through this polymer (34).

Several investigators (13–15) measured the uptake of lipids by polydimethylsiloxane and showed that implants took up appreciable quantities, 0.1–16% (w/w), of lipoidal substances. The amounts absorbed seemed to be independent of time. Lipid uptake did not appreciably affect the permeability of polydimethylsiloxane (Table I). This result is in agreement with those of several previous investigators (13, 14) who showed that lipid uptake by polydimethylsiloxane did not appreciably affect the physical properties of this polymer. Based on these results, it appears that the slowly decreasing *in vivo* release rates of progestins (16, 17) from polydimethylsiloxane implants *in vivo* are not related to the lipid uptake by the membrane.

Previous studies (35, 36) established that solutes permeate polyurethanes by solution and diffusion in the polymer network. However, unlike polydimethylsiloxane or the hydrogels, which have uniform properties throughout, polyurethane membranes consist of regions of varying hydrophobicity and hydrophilicity. Presumably, this variation arises from the organization of the urethane segments and the polyethylene glycol segments of the copolymer, respectively. The polyurethanes strongly absorb lipoidal species from biological fluids. For example, polyurethanes absorbed large quantities of lipid from micellar solutions and the percent uptake was highest when the volume percent of hydrophilic groupings was near 50% (37). In another study (32), polyurethane I absorbed large quantities of lipid both *in vivo* and from simulated biological fluids *in vitro*. In addition, the mechanical properties of this polymer are affected by long-term soaking in either water or the simulated biological fluid.

The results in Table I and Fig. 2 indicate that long-term plasma soakings altered the permeability of polyurethane I. The progesterone permeability of this polymer decreased continuously for plasma soaking times up to 1 week. This decrease in permeability may have resulted from lipid uptake by the hydrophobic regions of the copolymer. This lipid probably decreased the free volume of the polymer available for progesterone permeation. Lipid uptake seemed to affect only the diffusion coefficient while K_d was relatively constant. This finding suggests that lipid uptake may not affect the overall hydrophobicity of the polymer but may affect the segmental motion of the polymer chains in the hydrophobic regions. For periods of plasma soaking greater than about 1 week, the permeability of polyurethane I to progesterone increased to values greater than those found in the non-plasma-treated membrane. This increase in diffusivity of the progesterone is believed to be related to the hydrolytic breakdown of the polymer and is consistent with the loss in the mechanical properties of this polymer as discussed by Andrade *et al.* (32).

Support for this interpretation of the effects of lipid absorption on progesterone permeation through polyurethane I can be inferred from studies performed using membranes soaked at 5°. Under these conditions, the plasma soakings had no effect on the progesterone permeation rate for soaking periods of up to 2 weeks. Polyurethanes soaked in water, lactated Ringers solution, and plasma for approximately 2 weeks at 5° gained the same amount of weight irrespective of the liquid (38). This result suggests that lipoidal species are not strongly absorbed at this temperature.

The results of the studies on the effects of plasma soaking on the permeation of progesterone through polyurethane II (Table I and Figs. 2 and 3) present a very different pattern from polyurethane I. The diffusion coefficients varied widely and seemed to be independent of plasma soaking time. These variations are believed to arise from the method of casting this polymer. Polyurethane II is a thermal-casted polymer whereas polyurethane I is solvent cast. As a result of the thermal-casting procedure, it is believed that large inhomogeneities arise during the cooling of the polymer. These inhomogeneities may account for the large variations in D and K_d obtained, even though all membranes were cut from the same polymer films.

Although systematic studies on the mechanism of solute permeation through the polyether urethane–polydimethylsiloxane blend are not available, it is anticipated that solutes permeate by solution and diffusion in the polymer network. Lipid absorption by this membrane is known to occur; however, the amounts and composition of the lipids absorbed differ from those absorbed by polyurethane I (32). The polymer blend absorbs primarily cholesterol esters whereas polyurethane I absorbs primarily free cholesterol.

The effects of plasma soaking on progesterone permeation through the polymer blend are shown in Table III. Plasma soaking times of up to 1 week had no effect on the membrane permeability.

Although studies on the effects of lipid absorption on the mechanical properties of this membrane are not available, it might be anticipated, based on the polyurethane I studies, that long-term exposure of the blended polymer to plasma may increase the permeability of the membrane due to the hydrolytic breakdown of the polyurethane component.

CONCLUSIONS

All of the polymers studied are apparently sufficiently permeable to be of use in controlled-release drug delivery systems. The permeation rates of the model hydrophobic drug, progesterone, through these membranes vary by about two orders of magnitude and, thus, allow great latitude in the release rate of a hydrophobic drug for a given application. However, based on the plasma soaking studies, the polyurethanes and, possibly, the polyether urethane–polydimethylsiloxane blend appear to yield varying release rates, depending on the length of the plasma soaks. The varying release rates arise from the effects of lipid uptake by the membrane and from degradative processes within the membrane. These

results suggest that these polymers may be of questionable value for use in controlled-release drug delivery systems. For the membrane polyurethane I, this conclusion is expected to be valid for hydrophobic molecules in general; however, this conclusion may not be valid for uncharged water-soluble molecules, which probably permeate the membrane through the more hydrophilic regions of the polymer. These regions may not be as greatly affected by lipid absorption; therefore, polyurethane I may be suitable for short-term delivery (less than 2 weeks) of uncharged water-soluble drugs.

From the analysis of the studies of the effects of plasma soaking of the membranes in terms of mechanisms of solute permeation, the following generalizations were reached:

1. For membranes that are porous in nature, lipid absorption should not alter membrane permeability drastically, provided that the solute is small relative to the average pore size of the membrane.
2. When solutes permeate the membrane by solution and diffusion and the membrane is homogeneous, lipid absorption should not alter the membrane permeability drastically.
3. Lipid absorption may lead to significant alteration in membrane permeability for copolymers having regions or domains that differ in their degree of hydrophobicity.
4. Polymers subject to hydrolytic degradation appear to be poor candidates for use in controlled-release drug delivery systems.

Finally, it can be concluded that polydimethylsiloxane, cellulosic membranes, and the hydrogels offer strong potential for use in controlled-release drug delivery systems *in vivo*. The permeation rate of hydrophobic solutes through polydimethylsiloxane and the cellulosic membrane is relatively high. The permeability of the uncross-linked hydrogels is somewhat less; the permeation rate can be varied over approximately an order of magnitude, depending on the nature and concentration of the cross-linking agent.

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