Although the terminal half-life may be reduced by biliary dysfunction or reabsorption enhancement (when $k_{20} < k_{10}$), CXT_{iv}, CXT_{oral}, and A_{ss} will always be increased by these changes. Since drug effectiveness and toxicity are closely related to CXT values after intravenous or oral dosing and to A_{ss}, the steady-state drug level, after infusion, they will increase for patients with biliary dysfunction or enhanced reabsorption. To avoid toxicity, the drug dosage may have to be reduced accordingly.

APPENDIX

From Eq. 3, partial differentiation of β with respect to k_{12} yields:

$$\frac{\partial\beta}{\partial k_{12}} = \frac{1}{2\nabla}[\nabla - (k_{21} + k_{12} + k_{10} - k_{20})] \quad \text{(Eq. A1)}$$

Since ∇ is always positive, if $k_{20} \geq k_{21} + k_{12} + k_{10}$, then $\partial\beta/\partial k_{12}$ will be positive. If $k_{21} + k_{12} + k_{10} > k_{20}$, $\partial\beta/\partial k_{12}$ has the same sign as $\nabla^2 - (k_{21} + k_{12} + k_{10} - k_{20})^2$. Thus:

$$\nabla^2 - (k_{21} + k_{12} + k_{10} - k_{20})^2 = 4k_{21}(k_{20} - k_{10}) \quad \text{(Eq. A2)}$$

and, therefore:

$$\frac{\partial\beta}{\partial k_{12}} > 0 \quad \text{if } k_{20} > k_{10} \quad \text{(Eq. A3)}$$

$$\frac{\partial\beta}{\partial k_{12}} = 0 \quad \text{if } k_{20} = k_{10} \quad \text{(Eq. A4)}$$

$$\frac{\partial\beta}{\partial k_{12}} < 0 \quad \text{if } k_{20} < k_{10} \quad \text{(Eq. A5)}$$

Similarly, partial differentiation of β with respect to k_{21} gives:

$$\frac{\partial\beta}{\partial k_{21}} = \frac{1}{2\nabla}[\nabla - (k_{21} + k_{12} + k_{20} - k_{10})] \quad \text{(Eq. A6)}$$

which is similar to Eq. A1 except that the order of k_{20} and k_{10} is reversed. Therefore:

$$\frac{\partial\beta}{\partial k_{21}} < 0 \quad \text{if } k_{20} > k_{10} \quad \text{(Eq. A7)}$$

$$\frac{\partial\beta}{\partial k_{21}} = 0 \quad \text{if } k_{20} = k_{10} \quad \text{(Eq. A8)}$$

$$\frac{\partial\beta}{\partial k_{21}} > 0 \quad \text{if } k_{20} < k_{10} \quad \text{(Eq. A9)}$$

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Progestin Permeation through Polymer Membranes III: Polymerization Solvent Effect on Progesterone Permeation through Hydrogel Membranes

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Abstract □ Hydrogels prepared from poly(hydroxyethyl methacrylate) are biocompatible and highly permeable to low molecular weight solutes. Permeation rates can be varied by altering the cross-linker concentration or using copolymers; the latter are chosen to alter the hydrogel equilibrium hydration. These factors suggest that hydrogels are good candidates for controlled-release drug delivery devices. Hydrogels may be synthesized using various temperatures, initiators (nature and concentration), and solvents (nature and concentration). This study demonstrated that progesterone permeation through poly(hydroxyethyl methacrylate) films is independent of polymerization solvent (nature and concentration) for the solvents, water, ethanol, and *tert*-butyl alcohol. The importance of hydrogel equilibrium hydration in progesterone permeation is emphasized.

Keyphrases □ Hydrogels, poly(hydroxyethyl methacrylate)—progesterone permeation, effect of various nonaqueous polymerization solvents □ Hydroxyethyl methacrylate—hydrogel films, progesterone permeation, effect of various nonaqueous polymerization solvents □ Progesterone—permeation through hydrogel membranes, effect of various nonaqueous polymerization solvents □ Delivery devices, controlled—hydrogel membranes, progesterone permeation, effect of various nonaqueous polymerization solvents

Hydrogels are biocompatible (1) and potentially useful for controlled-release drug delivery systems (2–9). Monomer composition and cross-linker type and composition determine hydrogel drug release rates.

The physical–chemical properties of hydrogels depend on polymerization conditions (10). In poly(hydroxyalkyl methacrylate) synthesis, polymerization at the gel equilibrium water content is convenient. However, varying the initial solvent composition is often advantageous in fabricating controlled-release drug delivery devices. Certain fabrication problems may be overcome through nonaqueous polymerization (4, 7). However, polymer chain organization, degree of cross-linking, and other properties may be altered, resulting in a different polymer when water is omitted. These changes could affect the permeability of these films relative to those polymerized in the presence of water.

For these reasons, a systematic study of polymerization solvent effects on progesterone permeability through films polymerized from hydroxyethyl methacrylate was undertaken. Films prepared without cross-linker were chosen because the permeabilities of these films are highly sensitive to small changes in cross-link density (9, 11, 12).

Also included in the present study are the effects of the solvents ethanol and *tert*-butyl alcohol. Based on thermodynamic (13) and swelling arguments (14), ethanol and, to a greater extent, *tert*-butyl alcohol are better solvents for poly(hydroxyethyl methacrylate) than is water. These solvents are expected to offer certain advantages in the polymerization of films containing high concentrations of cross-linking agents and aid in dissolving drugs that nor-

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Table I—Progesterone Permeation Parameters in Poly(hydroxyethyl methacrylate) Films as a Function of Polymerization Solvent Type and Concentration

Concentration, % v/v	$D \times 10^9$, cm²/sec	K_d	$U \times 10^7$, cm²/sec	H
		Water		
0	5.54	102	5.65	0.47
	4.96	109	5.41	0.46
	5.89	100	5.89	0.47
5	5.05	85	4.29	0.45
	4.99	99	4.94	0.46
10	5.08	104	5.28	0.46
	4.79	107	5.13	0.45
20	6.02	92	5.54	0.46
	5.29	107	5.66	0.51
40	6.85	103	7.06	0.47
	4.66	120	5.59	0.52
	3.81	133	5.07	0.52
	4.77	124	5.91	0.53
	4.23	134	5.67	0.50
	4.48	131	5.87	0.48
		Ethanol		
20	4.34	101	4.38	0.45
	4.77	111	5.30	0.46
	4.55	114	5.19	0.51
40	5.50	107	5.89	0.48
	4.81	96	4.62	0.50
		tert-Butyl Alcohol		
20	5.46	110	6.01	0.48
40	4.64	107	4.96	0.53
	6.84	103	7.04	0.45
Average ± *SD*	5.10 ± 0.76	109 ± 13	5.49 ± 0.69	0.48 ± 0.03

mally are not soluble in hydroxyethyl methacrylate–water solutions during polymerization. When water is used as the polymerization solvent, phase separation tends to occur during polymerization, a problem that is overcome through the use of ethanol or *tert*-butyl alcohol.

EXPERIMENTAL

Hydrogel films were prepared by free radical polymerization using azobis(methyl isobutyrate) (15) (7.84 mmoles/liter of monomer) as the initiator. Hydroxyethyl methacrylate[1] was used as received and contained the major impurities methacrylic acid (0.06%), ethylene glycol dimethacrylate (0.024%), and diethylene glycol methacrylate (0.29%).

Hydroxyethyl methacrylate mixtures with 0, 5, 10, 20, and 40% (v/v) deionized water, 20 and 40% (v/v) ethanol[2], and 20 and 40% (v/v) *tert*-butyl alcohol[3] were polymerized between sealed polyethylene plates at 60° for 24 hr. All films were transparent and homogeneous after polymerization. Subsequent to polymerization, all films were equilibrated in water (changed repeatedly) for 3–4 weeks prior to the permeation studies.

Unlabeled progesterone[4] and 1,2-^{3}H-progesterone[5] were used as received to prepare aqueous 11.2-μg of progesterone/ml solutions for the permeation and partition experiments.

Diffusion and partition experiments were conducted as described previously (8, 9). Film thicknesses, ~0.07 cm, were measured on the water-swollen hydrogels using a lightwave micrometer[6].

Hydration values were obtained as described previously (11).

RESULTS AND DISCUSSION

Progesterone diffusion coefficients in the hydrogel films were calculated using (16):

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

where C_t is the progesterone concentration at time t, C_0 is the initial progesterone concentration, A is the polymer film area (14.9 cm²), l is the film thickness, V_1 and V_2 are the compartment volumes (176 ml), and U is the permeation coefficient defined as:

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

where D is the diffusion coefficient and K_d is the partition coefficient.

Values for U, D, K_d, and H [the membrane hydration, defined as (film water concentration/bulk water concentration)] are given in Table I, as are the average values and standard deviations for each parameter. The values in each row represent results from a single polymer film.

Progesterone permeability, diffusivity, and partitioning in poly(hydroxyethyl methacrylate) films did not change when: (*a*) the initial polymerization mixture water content was varied from 0 to 40% (v/v), (*b*) the polymerization solvent was changed from water to ethanol or *tert*-butyl alcohol, and (*c*) the alcohol concentration was changed from 20 to 40% (Table I). The equilibrium hydration of the poly(hydroxyethyl methacrylate) films in water was independent of the polymerization conditions.

It was demonstrated previously (14) that the equilibrium water swelling of hydrogels polymerized in different solvents was independent of the solvent type and was dependent only on the monomer volume fraction present in the polymerization medium. This conclusion is consistent with the present study, which demonstrates that polymer hydration is independent of both solvent type and concentration, regardless of the dimensional changes that occur with water equilibration.

Hydration and permeability of hydrogel films have been theoretically related (17) and experimentally verified (9). Mechanistic interpretations of poly(hydroxyethyl methacrylate) film permeation suggest a "pore-flow" mechanism for progesterone (9). This information and the present data indicate that equally hydrated gels display an "effective porosity" independent of the polymerization solvent. Hydration is an inherent property of the gel network formed under conditions of fixed monomer type, temperature, and initiator type and concentration. Furthermore, it appears that any differences in the gel network organization that arise from polymerization solvent changes are secondary to hydration in determining progesterone permeability in hydrogel films.

[1] Courtesy of Hydron Laboratories, New Brunswick, N.J. Impurities in the sample were determined by Hydron Laboratories.
[2] IMC Chemical Group, Agnew, Calif.
[3] J. T. Baker Chemical Co., Phillipsburg, N.J.
[4] Steraloids Inc., Pauling, N.Y.
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