Mass Transport Properties of Co(polyether)polyurethane Membranes I: Preparation and Characterization

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Abstract □ A series of polyurethane copolymers containing polyethylene glycol 600, 1000, or 1540 was synthesized, purified by reprecipitation, and cast into clear, tough, flexible membranes using the solution method. The weight average molecular weight of each polymer was estimated by gel permeation chromatography. The ability of the various polymers to absorb water was measured and increased with the increasing molecular weight of the polyethylene glycol. The ability of the copolymer membranes to hold a pH gradient decreased with increasing polyethylene glycol molecular weight.

Keyphrases □ Model membrane systems—polyurethane copolymers, synthesis and analysis, mass transport properties □ Copolymers, polyurethane—model membrane systems, synthesis and analysis, mass transport properties □ Permeability—polyurethane copolymers, model membrane system, synthesis and analysis

Much attention has been focused on the use of polymeric materials as drug delivery (1, 2) and model membrane (3–5) systems. Most early work utilized polydimethylsiloxane which, while highly permeable to lipophilic drugs (6, 7), is only weakly permeable to hydrophilic, charged species (8). More recently, polymers known as hydrogels have been shown to control release of hydrophobic and hydrophilic agents. Variation in release rates can be controlled by changes in both monomer composition and the amount of cross-linking agent present (9–13).

BACKGROUND

A promising approach for the development of new model membranes is to modify systematically the polymer structure to alter its diffusion characteristics. It was suggested (14) that the hydrophilic–hydrophobic character of a membrane may be controlled by the choice of suitable structural modifications. Membranes that combine the seemingly opposite properties of mechanical strength and the ability to swell in water have been prepared by simultaneous polymerization (copolymerization) of hydrophilic and hydrophobic reactants (15–17). The membranes formed from these copolymers permitted the transport of permeants at rates comparable to porous dialysis membranes but with the apparent selectivity of partitioning-type membranes (18).

Therefore, a series of copolymers composed of hydrophilic polyethylene glycol blocks and hydrophobic urethane segments was chosen for study. Since these polymers were not readily available commercially, it was necessary to synthesize them and to characterize some of their properties prior to diffusion work. These properties included the abilities of the membranes to hydrate and to maintain a pH gradient. A molecular weight distribution and weight average molecular weight of each polymer system also were determined.

EXPERIMENTAL

Materials—Polystyrene standards[1] were used as received. Isopropylacetone[2] was purified by collecting the fraction boiling at 114–115° at atmospheric pressure, and methylenebis(4-phenyl isocyanate)[3] was distilled at 0.1–0.17 mm Hg. The colorless, clear fraction boiling at 147–151° was collected and stored in a freezer. 1,5-Pentanediol[2] was purified by distillation at 0.2–0.45 mm Hg, and the fraction boiling at 96–99° was collected. All distillates were stored in glass under dry nitrogen. Polyethylene glycols[4] 1540, 1000, and 600 were dried by the application of vacuum and heat for 4 hr. The flask then was flushed with dry nitrogen.

Methods—The average molecular weights of the polyethylene glycols were determined by end-group titration (19).

The synthetic procedures used to prepare the co(polyether)polyurethane polymers were similar to those outlined previously (16). Polyethylene glycol (0.012 mole) was dried in a 200-ml, three-necked, round-bottom flask equipped with a sealed polytef stirrer[5], a gas inlet valve, and a 200-mm West condenser fitted with a drying tube. The flask was heated to 110 ± 3°, and a suspension of 0.024 mole of methylenebis(4-phenyl isocyanate) in 25 ml of methyl sulfoxide and 25 ml of isopropylacetone was added to the polyethylene glycol with stirring. The flask was maintained at 110° for 1 hr while stirring continuously.

To the resulting clear, yellowish solution, 0.024 mole of 1,5-pentanediol and 0.016 mole of methylenebis(4-phenyl isocyanate) were added. An additional 2 hr of heating produced a viscous, yellowish solution. The polymer was isolated by pouring the solution into ~500 ml of distilled water, which produced a tough, rubbery, white precipitate. After washing with several volumes of distilled water, the polymer was dried in a heated vacuum desiccator[6] at 50°.

Individual polymer batches were blended and purified by precipitation in distilled water from a 5% (w/v) polymer solution in *N,N*-dimethylformamide. The reprecipitated polymer was washed with five 2000-ml portions of distilled water and placed in a vacuum oven for 48 hr. This procedure was carried out twice for each polymer synthesized.

The membranes were solution cast on plate glass sheets from a filtered 15% (w/v) polymer solution in *N,N*-dimethylformamide. The solution was filtered through a 0.5-μm filter[5] in a pressure filtration apparatus[7] using a 25–50-psi pressure head of dry nitrogen. The solution was spread on the glass plates with the aid of an adjustable doctor knife. The plates then were transferred quickly to an oven and dried at 50° overnight. The membrane was left on the glass plates, stored in a desiccator, and protected from light until used.

To test the effects of reprecipitating the polymer, pieces of membrane prepared from the polyethylene glycol 600 copolymer, either as originally obtained or reprecipitated (once or twice), were soaked in 30 ml of distilled water for 8 hr at 37°. An aliquot of each solution was filtered and then scanned from 240 to 350 nm.

Membranes were removed from the glass plates after hydration with 0.05 *M* phosphate buffer and were soaked for at least 20 min before use in buffer.

The thickness and diameter of both wet and dry membranes were measured by a method similar to that of Garrett and Chemburkar (20) at seven equally spaced points. The percent of water sorbed was determined by weight, and the percent swelling in thickness and diameter was determined by the difference between wet and dry measurements.

The weight average molecular weight of each synthesized polymer was estimated by gel permeation chromatography (21) using a series of gel permeation columns[8] (10^5, 10^4, 10^3, and 500 Å) with UV grade, nitrogen-blanketed tetrahydrofuran as the mobile phase.

Solutions of polystyrene (0.1–0.5%) calibration standards and polymer (0.5%) samples were prepared and chromatographed using a flow rate of 2.0 ml/min, a chart speed of 2.5 cm/min, and detector sensitivity at 0.5–1.0 aufs.

The intrinsic viscosity of the polystyrene standards in tetrahydrofuran at 25° was estimated using an empirical relationship (22), while the intrinsic viscosity of the polymer samples was measured using a capillary viscometer (23). Intrinsic viscosity was calculated as described previously (24, 25).

[1] Waters Associates, Millford, MA 01757.
[2] Aldrich Chemical Co., Milwaukee, WI 53222.
[3] Pfaltz and Bauer, Stamford, CT 06902.
[4] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[5] Teflon.
[6] Precision Scientific Co., Chicago, IL 60647.
[7] Millipore Corp., Bedford, MA 01730.
[8] μStyragel, Waters Associates, Milford, MA 01757.

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Table I—Effect of Polyethylene Glycol Content on Various Physical Parameters of the Co(polyether)polyurethane Membranes [a]

Polymer Membrane	Polyethylene Glycol Content, %	Water Content in Hydrated Membrane, %	Swelling in Hydrated Membrane (Diameter), %	Swelling in Hydrated Membrane (Thickness), %	Apparent Wet Density, g/cm^3	Apparent Dry Density, g/cm^3
600	37	9	3	1	1.26	1.24
1000	49	26	8	11	1.22	1.25
1540	56	49	14	28	1.12	1.24

[a] Average of three membranes.

The surface and cross section of each type of dried polymer membrane were examined using a scanning electron microscope[9]. The conditions used to visualize the sample were varied to optimize the resolution, while the magnification ranged from 100 to 40,000×.

A diffusion cell similar to that described by Flynn and Smith (26) was utilized.

To determine the ability of hydrogen ion to cross the membrane, the donor side of the diffusion cell was connected by tubing[8] from its sampling ports to a two-channel tubing pump[10] and an open donor solution reservoir. The receiving side of the diffusion cell was connected similarly in a closed loop to a glass-jacketed constant-temperature reservoir. A three-hole stopper sealed the reservoir and accommodated the receiving side tubing, a nitrogen inlet, and a pH electrode.

The pH-holding experiment was initiated by thoroughly flushing the receiving side reservoir with dry nitrogen. Exactly 50 ml of preheated 0.001 *M* NaCl was introduced into the nitrogen-blanketed receiving reservoir. The pH of this solution was taken as the zero-time pH reading. The experiment was begun by injecting ~15 ml of preheated 0.001 *M* HCl into the donor side connected to a 100-ml reservoir maintained at 37°. At the specified times, the tubing pump was stopped, and the solution in the receiving side reservoir was allowed to equilibrate for 1 min before the pH reading was taken. The two-channel tubing pump was set to deliver ~18 ml/min. The exact flow rate was determined prior to an experiment by measuring the amount of solution delivered in 3 min.

RESULTS AND DISCUSSION

Batches of a co(polyether)polyurethane after blending, but prior to casting, were purified by reprecipitation. The efficiency of the procedure in the removal of UV-absorbing impurities from the polymeric material was demonstrated easily by the drop in absorbance at 240 nm from 0.65 prior to reprecipitation to zero after the second reprecipitation. No attempt was made to identify the impurities.

The molecular weight distribution for each polymer demonstrated a large, sharp spike of high molecular weight material followed by the lower molecular weight materials. The weight average molecular weights were 71,000, 28,000, and 34,000 for the 1540, 1000, and 600 copolymers, respectively. The actual values of the average molecular weight calculated for a given polymer are probably less important than the fact that large differences in molecular weight and molecular weight distribution among the polymers were not observed.

Physical measurements were made on the membranes in both the hydrated and dry state. The water content of the swollen membranes was directly proportional to the amount of glycol in the polymer (Table I). This finding is in agreement with the idea that the polyethylene glycol molecules serve as hydrophilic blocks that allow the membrane to swell in aqueous solution (18). The hydrophobic urethane linkages have been considered to act as cross-links between the polymer chains and to anchor the hydrated glycol segments (27).

Examinations of the surfaces and cross sections of each polymer membrane by scanning electron microscopy (resolution limit ~0.05 μm) showed uniform homogeneous structures with no unusual morphology and no apparent pore structure. From these results, it can be concluded that a porous structure, if it exists, would probably be <500 Å in diameter.

The ability of the membranes to maintain a pH gradient was studied since it may be an indication of the permeability of the membranes to ions (Fig. 1). The 600 copolymer membrane successfully maintained the pH gradient throughout the experiment (~1 hr), while the apparent diffusion coefficient for the 1000 and 1540 copolymer membranes were 6.9×10^{-9} and 7.0×10^{-8} cm^2/sec, respectively. The amount of glycol in the polymer molecules and, consequently, the amount of water sorbed do influence the capacity of the membrane to hold a pH gradient.

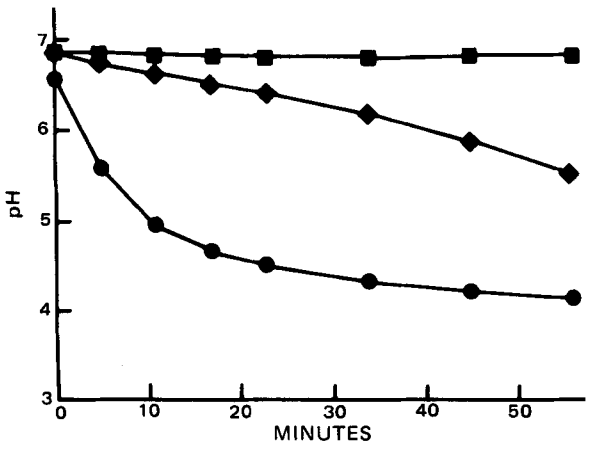

Figure 1—*Results of pH gradient-holding experiments for 600 copolymer (■), 1000 copolymer (♦), and 1540 copolymer (●).*

[9] Model JSM-35C, JEOL USA, Medford, MA 02155.

[10] Master-flex pump drive (5–100 rpm) with pump head No. 7016 and add-on pump head No. 7016, Cole-Parmer Instrument Co., Chicago, IL 60648.

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Mass Fragmentographic Determination of Timolol in Human Plasma and Urine

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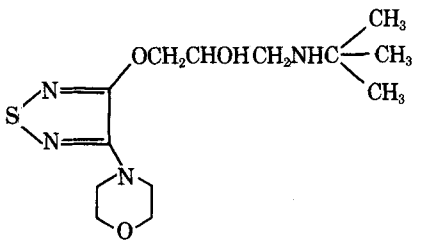
Abstract □ A mass fragmentographic procedure was developed for measuring quantities of <1.0 ng of timolol/ml of plasma or urine. The lower limit of sensitivity was 0.5 ng of timolol maleate/ml of plasma. The unchanged drug was extracted into heptane–4% isopentyl alcohol from alkalinized plasma or urine, together with propranolol hydrochloride as the internal standard. The compounds were subsequently back-extracted into 0.1 *N* HCl and then into chloroform following adjustment of the acidic phase to an alkaline pH. The chloroform layer was evaporated to dryness, and the compounds were derivatized with *N*-methyl-*N*-trimethylsilyltrifluoroacetamide–acetonitrile to form the trimethylsilyl derivatives; these derivatives were quantitated by mass fragmentography. Recovery of timolol added to normal plasma and urine was quantitative and reproducible, and no interfering substances were observed in normal biological samples. After a 20-mg oral dose of timolol maleate, plasma levels of ~3.0 ng/ml were observed at 12 hr.

Keyphrases □ Timolol—extraction, derivatization, mass fragmentographic determination, plasma and urine □ β-Adrenergic blocking agents—timolol, extraction, derivatization, mass fragmentographic determination, plasma and urine □ Mass fragmentography—determination, timolol, plasma and urine

Timolol maleate, (−)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate, is a β-adrenergic receptor blocking agent with a high β-adrenergic inhibitor capacity. Due to the intensity of its effect, it is administered orally in small doses, varying between 10 and 20 mg, depending on the treatment needs. In addition, its high extravascular diffusion rate gives it an average apparent volume of distribution of 3.64 liters/kg. A low administered dose and a high apparent volume of distribution contribute to low plasma concentrations. For a proper pharmacokinetic study, assay techniques must be capable of measuring plasma levels as low as 0.5 ng of timolol/ml.

An electron-capture GLC determination of timolol in human plasma and urine was described by Tocco *et al.* (1). The lower limit of sensitivity was 2.0 ng/ml.

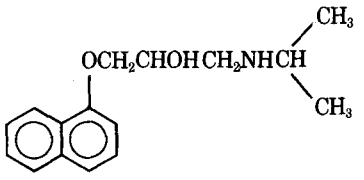
This report describes a mass fragmentographic procedure whose sensitivity threshold of 0.5 ng of timolol/ml of plasma enables plasma concentrations to be monitored for over 12 hr after oral administration of a 20-mg single dose of timolol maleate in a healthy adult.



I

EXPERIMENTAL

Reagents—Timolol (I) was used as the maleate salt[1], and propranolol (II) hydrochloride[2] served as the internal standard. All concentrations were expressed in terms of the base salt. Pesticide quality *n*-heptane[3], isopentyl alcohol[3], methylene chloride[4], ethyl acetate[5], and acetonitrile[6] nanograde reagent were used without further purification. Hydrochloric acid, sodium hydroxide, and double-distilled water were used in the preparation of 0.1 *N* HCl and 1.0 and 2.0 *N* NaOH. *N*-Methyl-*N*-trimethylsilyltrifluoroacetamide[7] served as the reagent for preparing the trimethylsilyl derivatives of timolol and propranolol.



II

[1] Merck Sharp & Dohme, Chibret, Paris, France.
[2] I.C.I., Enghien Les Bains, France.
[3] Prolabo R.P., Paris, France.
[4] Merck, Interchim, Montluçon, France.
[5] Fluka A.G., Interchim, Montluçon, France.
[6] Mallinckrodt, Interchim, Montluçon, France.
[7] Pierce Chemical Co., Interchim, Montluçon, France.

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