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Separation of chiral molecules using polypeptide-modified poly(vinylidene fluoride) membranes

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Abstract

A membrane-based chiral separation system was developed by the modification of poly(vinylidene fluoride) (PVDF) ultrafiltration membranes with polyglutamate derivatives. Both physisorbed and chemisorbed poly(γ-benzyl-L-glutamates) (PBLG) were vapor-deposited on the membranes, and the resulting poly(amino acids) were modified through debenzylation or ester exchange reaction to produce poly(L-glutamic acid) (PLGA) and polyglutamates with triethylene glycol monomethyl ether side chains (PLTEG). The enantioselectivities for chiral α-amino acids (tryptophan (Trp), phenylalanine (Phe), and tyrosine (Tyr)) and chiral drugs (propranolol, atenolol, and ibuprofen) were determined by performing permeation cell experiments, with enantioselectivities ranging from 1.04 to 1.47. The selectivity of PLGA increased as its helical content increased, which occurred at high ethanol concentrations and at low pH. In addition, an increase in enantioselectivity was observed for chemically grafted polymers compared to physisorbed polypeptides. This may be attributed to an increase in molecular weight (MW) and density of the polymer chains, which may enhance the interaction between the chiral compounds and the surface-bound polypeptides. © 2002 Published by Elsevier Science Ltd.

Keywords: Poly(vinylidene fluoride) membranes; Peptides; Chiral separation

1. Introduction

Chirality plays an important role in the function of biological processes. The macromolecules in our body, such as proteins and enzymes, are able to discriminate between the two enantiomers, interacting favorably with one isomer while producing potentially adverse effects with the other isomer. To isolate only the desired enantiomer, various methods have been developed, which include high performance liquid chromatography and capillary electrophoresis. With these methods, only a small amount of sample can be analyzed per run, and scale-up can be expensive. On the other hand, a membrane-based system is a cost-efficient method that can be operated continuously at ambient conditions [1].

For membrane separations, the chiral selector, which is a molecule that preferentially interacts with one of the isomers, is usually integrated within the membrane. The selector can be an amino acid, polymer, polypeptide, or protein, and it may be incorporated into the membrane through molecular imprinting of the selector [2], forming a solid membrane from the selector [3–9], or by covalently grafting the selector to the membrane [10,11]. Grafting of the selector can be accomplished by treating the surface, either chemically or by radiation, to produce the necessary functional groups for coupling the desired compound.

Polypeptides, which are chiral selectors for molecules with polar functional groups [12], have been grafted onto various types of membranes. For example, Papra and coworkers [13] were able to couple amino acids and presynthesized polymers to poly(ethylene terephthalate) particle-track membranes, which had been modified through hydrolysis, oxidation, and reaction with amines. In addition, Ito et al. [14] first formed amino groups on a poly(tetrafluoroethylene) membrane by glow discharge; the amino groups then initiated the *N*-carboxy anhydride (NCA) polymerization to form PBLG. In a separate study, we synthesized PBLG, poly(L-tryptophan), and poly(L-phenylalanine) by NCA polymerization on Anodisc aluminum oxide membranes, which had been modified with amino end groups [15].

The main goals of this study were to develop a novel way of grafting polypeptides onto porous PVDF membranes

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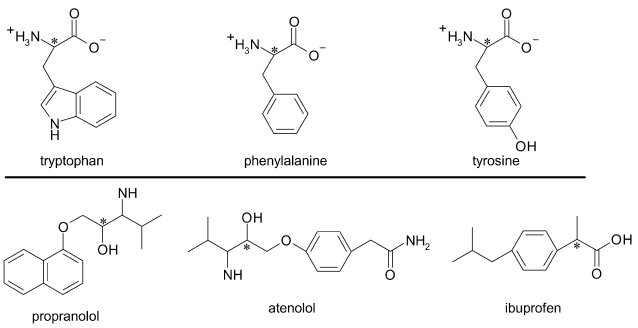

Fig. 1. Chemical structure of chiral amino acids and drugs.

using vapor deposition and to determine whether chiral separation or selectivity can be achieved using these membranes. In the vapor deposition method, developed by Chang and Frank [16], an NCA monomer of an amino acid reacts in the vapor phase with a silicon substrate modified with amino end groups to form a polymer film. Both physisorbed and chemisorbed poly(amino acids) were formed on the substrate. We use this method to understand the effect of both physisorbed and chemisorbed polyglutamates on the enantioselectivity of chiral amino acids of Trp, Phe, and Tyr. In addition, the selectivity for propranolol, atenolol, and ibuprofen was determined for the chemically modified membranes.

2. Experimental

2.1. Materials

The amino acids and drugs were purchased from Sigma-Aldrich and Fluka; their structures are shown in Fig. 1. Tetrahydrofuran (THF) and hexane were distilled over sodium, and 200-proof ethanol and distilled water were used in making the chiral solutions.

The membrane used in the modification and the permeation experiments was Hydrophilic Durapore PVDF membrane from Millipore (diameter 25 mm, thickness 125 μm, pore size 0.1 μm, porosity 70%). The membrane ($-CHR-CF_2-$) was manufactured with functional groups to make the surface hydrophilic.

2.2. Synthesis and membrane preparation

2.2.1. Monomer synthesis

The NCA monomer was synthesized according to the method outlined by Daly and Poche [17] and purified by rephosgenation [18]. The melting point range of the γ-benzyl-L-glutamate NCA was 91–93 °C.

2.2.2. Ammination

The membrane was chemically modified with amino groups using Brennan and McCarthy's three-step procedure (dehydrofluorination, bromination, and ammination) for PVDF films [19].

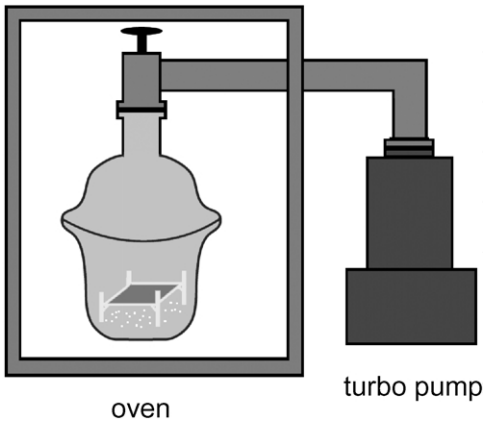

Fig. 2. Vapor deposition setup. The monomer is spread at the bottom of the glass reactor, and the membrane, which is supported on a glass holder, is placed over the monomer. The reactor is evacuated and heated to allow the NCA monomers to vaporize and polymerize on the substrate.

2.2.3. Vapor deposition

The vapor deposition setup is shown in Fig. 2. In this reaction, the NCA monomer of γ-benzyl-L-glutamate undergoes a ring-opening polymerization in the presence of amino groups to form the polymer chain, as depicted in Fig. 3. The membrane, supported on a glass holder, was placed 1.5 cm above the monomer (0.01 g), which was spread at the bottom of a glass reactor. A rough pump was used to evacuate the chamber, and the reactor was back-filled with nitrogen for two cycles. Afterwards, the system was heated to 105 °C for 2 h. During the course of the polymerization, the chamber was continuously evacuated (5×10^{-5} mbar) using a turbo pump to remove carbon dioxide that evolved from the polymerization, thus driving the reaction. The membrane was placed overnight in chloroform and then rinsed with chloroform and dried over nitrogen.

2.2.4. PLGA synthesis

The surface synthesis of PLGA, shown in Fig. 3, was adopted from the method of Idelson and Blout [20]. The membrane modified with PBLG was placed in a Schlenk tube with 15 ml of benzene. Hydrogen bromide gas was bubbled into the tube for 1 h. After 3 days, the membrane was removed and rinsed with acetone. It was placed in acetone for 2 h and then in distilled water for 2 h.

2.2.5. PLTEG synthesis

The ester exchange reaction, also shown in Fig. 3, was adopted from Chen and Yu [21], Maruyama et al. [7], and Inoue et al. [22]. A PBLG-modified membrane was added to a Schlenk tube with 20 ml of dichloroethane, 10 ml of triethylene glycol monomethyl ether (TEG), and 0.1 g of *p*-toluenesulfonic acid. After heating the system at 70 °C for

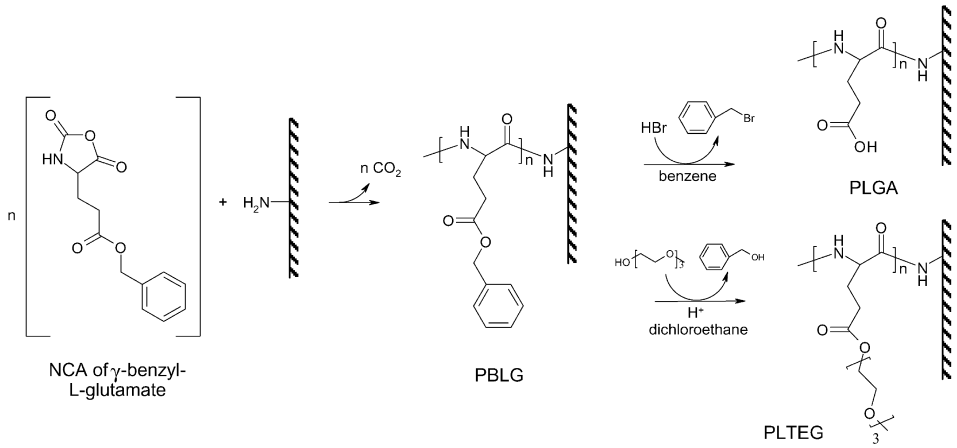

Fig. 3. Surface synthesis reaction of the chemisorbed PBLG by NCA polymerization. The monomer undergoes a ring-opening polymerization, initiated by primary amines on the membrane. PLGA is formed by cleaving the aromatic side group of PBLG and PLTEG by an ester exchange reaction.

5 days, the membrane was removed and washed with methanol.

2.3. Permeation cell experiment

In the permeation cell setup, shown in Fig. 4, two membranes were placed in the center of the cell with O-rings on either side of the membranes, and the assembly was held in place with a pinch clamp. The chiral solution (80 ml) was placed in one chamber of the cell and solvent (80 ml of aqueous ethanol) in the other. For all compounds except for propranolol (1 mM) and Tyr (0.33 mM), the concentration of the solution was 5 mM. Measurements were carried out by removing 1 ml sample from the downstream chamber twice a day for 3 days and replacing it with 1 ml of solvent.

2.4. Characterization

2.4.1. UV–visible spectroscopy (UV–vis)

The concentration of the chiral solution was determined using a Hewlett Packard B452A Diode Array UV–visible spectrophotometer. The relationship between concentration and absorbance was calibrated by taking the spectra of known concentrations; the value of the maximum absorbance was used in the calibrations. The wavelength of maximum absorbance determined for each compound was as follows: 280 nm for Trp, 258 nm for Phe, 276 nm for Tyr, 290 nm for propranolol, 274 nm for atenolol, and 264 nm for ibuprofen.

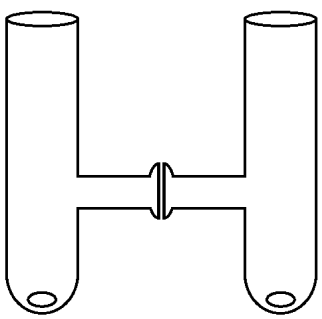

Fig. 4. Schematic of the permeation cell. Two membranes are placed in the center of the cell and held in place using a clamp. The chiral solution is charged in one compartment and solvent in the other compartment.

2.4.2. Circular dichroism (CD)

A model 62A DS circular dichroism spectrometer from Aviv Instruments, Inc. was used to determine the percentage of each enantiomer and the conformation of PLGA in solution. The right and left circularly polarized light was produced by a photoelastic modulator, and the scans were taken for wavelengths of 185–320 nm using a Hellma quartz cell with a path length of 1 cm. The enantiomer compositions were determined by first calibrating the spectra with known concentrations of each isomer. To determine the conformation of PLGA (MW = 5000), the polymer (5 mg/l) was dissolved in solvents with varying concentration of ethanol (20–80%) and pH (3–9), which was obtained by changing the hydrochloric acid/sodium hydroxide concentrations. The amount of helical content was estimated according to the method by Greenfield and Fasman [23].

2.4.3. X-ray photoelectron spectroscopy (XPS)

An SSI S-Probe monochromatized XPS spectrometer was used to detect the elemental composition of the modified membranes. The radiation source was Al Kα (1486 eV), and the membrane area analyzed was 250 × 1000 μm.

2.4.4. Fourier transform infrared spectroscopy (FTIR)

A Bio-Rad FTS-60A FTIR was used to determine the poly(amino acid) conformation on the PVDF membrane. The spectrum was taken in transmission mode using a deuterated triglycine sulfate (DTGS) detector. For each sample, 64 scans were taken at a resolution of 4 cm^{-1}.

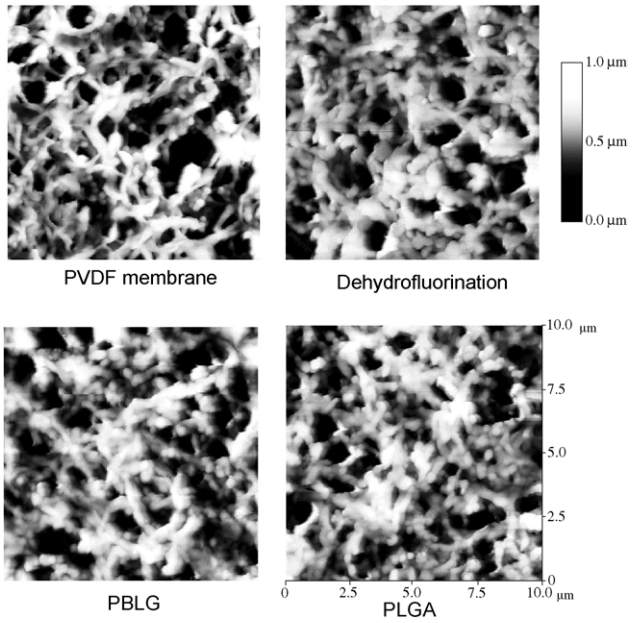

Fig. 5. Tapping mode AFM image (height mode) of 0.1 μm PVDF membrane. The pore structures of the membrane remained unchanged during the ammination process. The scan size was 10 × 10 μm with a height range of 1 μm.

2.4.5. Atomic force microscopy (AFM)

The morphology of the PVDF membrane was probed using a NanoScope IIIa MultiMode AFM from Digital Instruments. The scans were performed in the TappingMode using a silicon cantilever, and the images were captured with an E scanner at a frequency of 1 Hz.

3. Results

3.1. PVDF membrane characterization

The AFM image of the PVDF membrane is presented in Fig. 5. The membrane consisted of an open pore structure formed from PVDF fibers. The surface of the membrane was relatively rough, with a root-mean-square roughness of approximately 0.2 μm. XPS analysis indicated that the membrane was composed of carbon, oxygen, and fluorine in 3:1:2 ratios, with the oxygen-containing functional groups likely to include alcohols, acids, ketones, and aldehydes. The first part of the study focused on physisorbed polymers; the membrane was then chemically modified with amino groups to produce chemisorbed polypeptides.

3.2. FTIR

The FTIR spectra of PBLG, PLGA, and PLTEG on PVDF membranes are shown in Fig. 6. Although the spectra were for chemisorbed poly(amino acids), physisorbed polymers gave similar results. The spectra contain peaks at 1700–1750, 1652, and 1550 cm^{-1}. The peaks in the

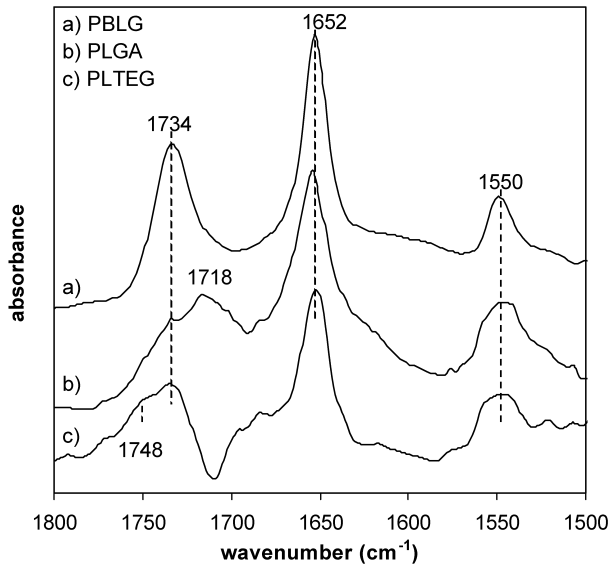

Fig. 6. FTIR spectra of chemisorbed (a) PBLG, (b) PLGA, and (c) PLTEG on PVDF membrane modified by ammination.

region of 1700–1750 cm^{-1} are from the C=O stretch of the acid or ester side chain [24]. The conformation of the helix can be determined from the location of the amide I peak (backbone C=O stretch). The amide I band for a right-handed α-helix occurs at 1650–1652 cm^{-1}, anti-parallel β-sheet at 1630 cm^{-1}, and random coil at 1658 cm^{-1}; the amide II (C–N stretch and N–H deformation) occurs at 1546–1550 cm^{-1} [24,25]. The presence of the amide I peak at 1652 cm^{-1} in Fig. 6 indicates that the conformation of the polypeptides on the membrane in the dry state was α-helical.

3.3. Permeation cell

A typical result from the permeation cell experiment is

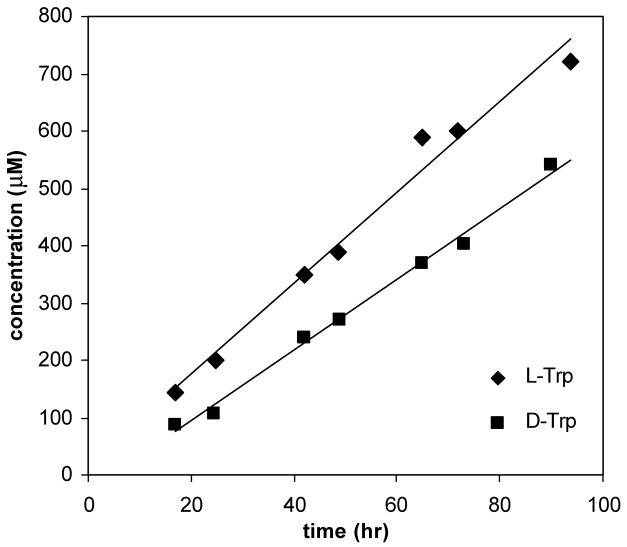

Fig. 7. Concentration of L- and D-Trp in the permeation cell as a function of time for physisorbed PLGA membrane. The solvent was 80% ethanol–20% water.

Table 1
Summary of the permeation cell experiments

Membrane	Chiral compound	P_L or P_S (cm^2/s)	P_D or P_R (cm^2/s)	Ratio	Enantioselectivity	Solvent
Physisorbed PLGA	Trp	1.75×10^{-7}	1.68×10^{-7}	P_L/P_D	1.04	20% ethanol
	Trp	1.76×10^{-7}	1.63×10^{-7}	P_L/P_D	1.08	40% ethanol
	Trp	1.54×10^{-7}	1.26×10^{-7}	P_L/P_D	0.22	50% ethanol
	Trp	2.21×10^{-7}	1.74×10^{-7}	P_L/P_D	1.27	60% ethanol
	Trp	1.67×10^{-7}	1.30×10^{-7}	P_L/P_D	1.28	80% ethanol
	Phe	1.58×10^{-7}	1.53×10^{-7}	P_L/P_D	1.03	80% ethanol
	Tyr	1.35×10^{-7}	1.38×10^{-7}	P_D/P_L	1.03	80% ethanol
	Trp	1.78×10^{-8}	1.38×10^{-8}	P_L/P_D	1.29	3.3 pH
Chemisorbed PLGA	Trp	2.08×10^{-7}	1.41×10^{-7}	P_L/P_D	1.47	60% ethanol
	Trp	2.85×10^{-7}	1.95×10^{-7}	P_L/P_D	1.46	80% ethanol
	Phe	1.71×10^{-7}	1.35×10^{-7}	P_L/P_D	1.26	80% ethanol
	Tyr	1.76×10^{-7}	1.90×10^{-7}	P_D/P_L	1.08	80% ethanol
	propranolol	2.15×10^{-7}	1.87×10^{-7}	P_S/P_R	1.16	80% ethanol
	atenolol	1.45×10^{-7}	1.56×10^{-7}	P_R/P_S	1.08	80% ethanol
	ibuprofen	1.99×10^{-7}	2.39×10^{-7}	P_R/P_S	1.20	80% ethanol
Chemisorbed PLTEG	Trp	1.58×10^{-7}	2.04×10^{-7}	P_D/P_L	1.29	80% ethanol
Physisorbed PBLG	Trp	1.42×10^{-7}	1.42×10^{-7}	P_L/P_D	1.00	60% ethanol

shown in Fig. 7. The concentration of the isomer in the solvent chamber increased linearly as a function time, and the rate of permeation through the membrane was different for each isomer. The flux J ($mol/cm^2\,h$) through the membrane can be calculated from the slope using the following equation [26]

$$J = \frac{\Delta C V}{\Delta t A} \tag{1}$$

where ΔC is the change in concentration, Δt is the permeation time, V is the downstream volume, and A is the effective membrane area (2.69 cm^2). The permeability coefficient P (cm^2/s) is given by

$$P = \frac{Jd}{C_u - C_d} \tag{2}$$

where d is the membrane thickness and $C_u - C_d$ is the concentration difference between upstream and downstream compartments [26]. The enantioselectivity is the ratio of the permeability coefficients (P_L/P_D) for the two isomers.

A summary of the resulting permeability coefficients and enantioselectivities for the different solvents and membranes is given in Table 1. PBLG-modified membranes did not show chiral selectivity for Trp isomers. For physisorbed PLGA, the enantioselectivity as a function of ethanol concentration for Trp is presented in Fig. 8. As ethanol concentration increased to 80%, the enantioselectivity (P_L/P_D) increased from 1.04 to 1.28. An enantioselectivity of 1.29 was obtained when the pH of the solvent was 3.3. Within the Trp, Phe, and Tyr amino acids, PLGA showed the largest selectivity for Trp, and very little separation was obtained for either Phe or Tyr isomers.

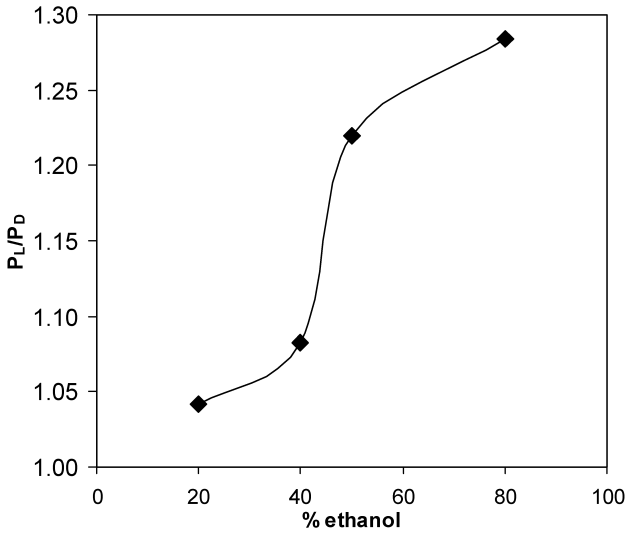

Fig. 8. Enantioselectivity of Trp as a function of ethanol concentration for PLGA physisorbed on the membrane.

3.4. Helix content

As noted previously, PLGA existed in the α-helix conformation as a dry film on the PVDF membrane. The helix content of PLGA, determined by circular dichroism as a function of ethanol concentration and pH, is shown in Fig. 9. The helix content of PLGA increased as the concentration of ethanol increased and as pH decreased. The change in conformation depending on solvent was due to the ionizable COOH groups ($pK_a = 4.32–4.45$) on the PLGA side chain [27,28]. PLGA can exist as a helix when the acid side group is not ionized, which occurs at low pH or at high ethanol concentrations. When ionized, however, the electrostatic repulsion among the side chains prevents the helix

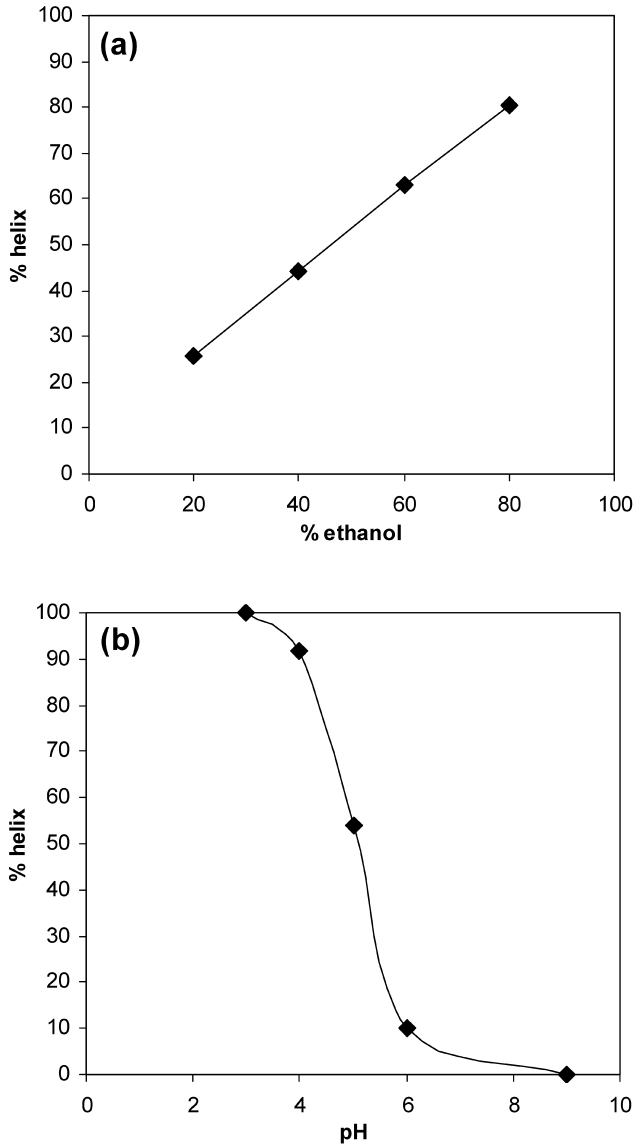

Fig. 9. Percentage of helical conformation of PLGA as a function of ethanol concentration (a) and pH (b).

formation, and only random structures are possible [14,24,26,29–31].

3.5. Chemisorbed polypeptides

Amino groups were chemically grafted unto PVDF membranes by a three-step procedure consisting of dehydrofluorination, bromination, and ammination. Dias and McCarthy [32] found that pitting in the PVDF film occurred during the dehydrofluorination step, but the AFM images in Fig. 5 showed that the membrane structure was not altered by this modification process. The percentage of nitrogen on the surface after the modification process was approximately 2%, which was determined by XPS. After performing vapor deposition, we deposited both covalently bonded and physisorbed polymers on the membrane. For this paper, we will use the term *chemisorbed* to describe the amine-modified membranes and the term *physisorbed* for membranes containing only physisorbed polymers.

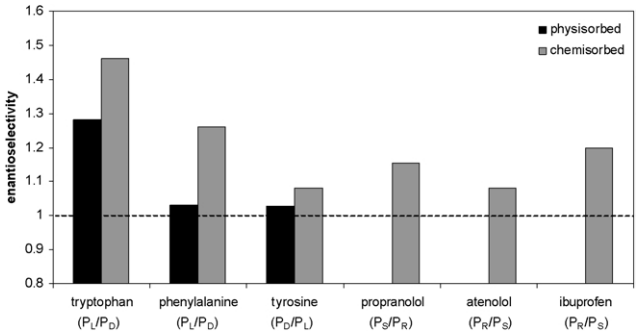

Fig. 10. Enantioselectivity of chiral amino acids by physisorbed and chemisorbed PLGA-modified membranes. The results for the separation of chiral drugs using chemisorbed PLGA are also given.

A comparison of enantioselectivity for physisorbed and chemisorbed PLGA is shown in Fig. 10. The selectivity was significantly higher for chemisorbed PLGA than for PLGA physisorbed to the membranes; for Trp and Phe molecules, a 20% increase in enantioselectivity was observed. The enantioselectivity of the chiral drugs, propranolol, atenolol, and ibuprofen, for chemisorbed PLGA is also provided in Fig. 10. PLGA did show slight enantioselectivity for propranolol and ibuprofen, with values of 1.16 and 1.20, respectively. The membrane grafted with PLTEG showed an enantioselectivity of 1.29 for Trp in 80% ethanol solution.

The enantioselectivities for the amino acids and drugs (1.04–1.47) are somewhat comparable to solid PLGA membrane systems, which range from 1.03 to 2.6 depending on the crosslinking agent and solvent [6,26]. We obtained permeability coefficients ranging from 1×10^{-7} to 2×10^{-7} cm^2/s, and these values were also consistent with those observed for solid PLGA membranes [26].

4. Discussion

4.1. Distribution of polypeptides

The polymers were incorporated into the membranes using vapor deposition, and they are believed to be distributed throughout the entire membrane. For poly(amino acid) synthesis on solid substrates, deposition occurred on both the side facing toward and the side facing away from the monomer [33]. This indicates that the NCA monomers in the vapor phase are quite mobile and are able to diffuse throughout the reactor chamber and the membrane. From the AFM images, no change in the surface morphology due to the membrane modification process was observed.

4.2. Physisorbed vs. chemisorbed polypeptides

The separation of chiral amino acids by chemically

grafted PLGA was greater than for membranes with only physisorbed PLGA. The physisorbed poly(amino acids) are synthesized from the thermal polymerization of the NCA monomers; polymers with relatively low MW are associated with this polymerization compared to the initiation by amino end groups [34]. Even after soaking the PBLG-modified membrane in chloroform, reacting it with HBr, and flowing solvent through the pores, the poly(amino acids) did not desorb from the membrane, as was confirmed by FTIR.

For a vapor polymerization of the NCA monomer without any initiator (105 °C, 5×10^{-5} mbar, 3 h), the MW of PBLG determined from viscometry was approximately 2000. However, the MW of chemisorbed PBLG, estimated from the vapor polymerization on silicon wafers silanized with (γ-aminopropyl) triethoxysilane, was 150,000 [33]. For the amine-modified membranes, both grafted and physisorbed poly(amino acids) were present on the membranes; therefore, the polymer surface density for this membrane may be larger than for the membrane containing only physisorbed polymers. The increase in the MW of the chemically grafted polymers and the increase in polymer density may have contributed to the higher enantioselectivity; the longer PLGA chains and the increase in the number of chains may increase the total interaction of the poly(amino acids) with the chiral molecules, thereby enhancing the chiral separation.

4.3. PLGA

PLGA showed modest selectivity for a wide range of chiral amino acids and drugs. In the case of Trp, the permeability coefficient of the L-isomer was larger than the D isomer. The use of PLGA incorporated into membranes has been studied by several researchers. Ogata [8] doped PLGA into poly(pyrrole) membranes and found preferential permeation of L-Trp. Crosslinked PLGA membranes were also studied for the selective transport of Trp and Phe across the membrane [27,35]. The chiral selectivity of PLGA for α-amino acids was examined in a series of experiments by Higashi and Niwa [36–39]. They found that the PLGA monolayer formed by Langmuir–Blodgett deposition was able to enantioselectively adsorb D-Trp; the amount that was adsorbed was six times larger than for L-Trp. The ratio of adsorbed D-isomer to L-isomer for Phe and Tyr amino acids was 8 and 3, respectively [37]. The enantiomeric binding of Trp by PLGA monolayers increased as the helix content, controlled by pH or surface pressure, and as the lateral density of PLGA were increased [38,39]. The chiral selectivity that we observe for PLGA may be due to this binding phenomenon. D-Trp binds and interacts more favorably with PLGA; as a result, the L-Trp molecules can permeate faster through the membrane. Furthermore, the increase in permselectivity with chemisorbed polymers may also be due to the increase in the density of PLGA in the membrane.

4.4. PLTEG

An ester exchange reaction with the TEG group was performed on PBLG to produce PLTEG. The enantioselectivity of Trp was 1.29, with the membrane preferentially passing the D-isomer. A similar result was found by Inoue et al. [22] in which a solid membrane was formed from a hexa-arm PLTEG radiating from a core. This membrane was able to completely resolve Trp, with the D-isomer permeating at a faster rate through the membrane. However, when the membrane was formed from linear PLGA, no selectivity was found. In our case, grafted linear PLTEG showed preferential permeation for D-Trp, like the hexa-arm membrane.

4.5. Helical conformation

For solid membranes composed of polymers with a glutamate backbone, the helical structure was necessary for the discrimination of chiral compounds [6,7,22,40], and the α-helical conformation was also required for the enantiomeric binding of Trp using PLGA monolayers [38]. In our study, the enantioselectivity of Trp increased from 1.04 to 1.28 as the concentration of ethanol in the solvent increased, and enantioselectivity of 1.29 was obtained at a pH of 3.3. Consequently, PLGA converts from a random coil to an α-helix as the concentration of ethanol increased and as pH decreased. Therefore, we conclude that the helical conformation of PLGA was important in the separation of chiral compounds.

4.6. Nature of the chiral interaction

The exact nature of the interaction of the polypeptide with the chiral molecules has not been determined. However, several generalizations can be made. The chiral selectivity is dependent on the interaction with the helix and the nature of the polymer side chain. As previously mentioned, the selectivity for Trp increased with the helicity of PLGA. However, helicity in itself was not enough to produce chiral discrimination. For example, poly(γ-methyl-L-glutamate) with a glutamate backbone and α-helical conformation did not exhibit enantioselective behavior; only after the side chain was modified with Igepal and Brij®30 was enantioselectivity displayed [40]. Likewise, we observed that PBLG-modified membranes showed no selectivity for Trp. Therefore, the nature of the side group is crucial for selectivity. Hydrogen bonding between the permeates and the carboxyl groups of PLGA may be important as well as the hydrophobic interaction between the chiral molecules and the PLGA side chain [26,38]. In all the compounds that we studied, the chiral molecules had the ability to form hydrogen bonds with the poly(amino acid), and the presence of aromatic groups may enable hydrophobic interactions to take place. In addition, the array of helices may create an environment where a large amount of

interaction can occur between the polypeptide and the chiral molecule. The increase in polymer chain length and density may also contribute to the increased interaction.

5. Conclusions

A novel method of grafting polypeptides to porous membranes by vapor deposition was developed. Using this method, we synthesized PLGA and PLTEG on PVDF membranes by debenzylation or esterification of the PBLG side group. In permeation cell experiments, the chemically grafted poly(amino acids) showed enhanced selectivity of 5–23% compared to the physisorbed polymers within the membrane, which may be due to the increased interaction between the polypeptide and the chiral molecule. The enantioselectivity was also dependent on the conformation of PLGA, and an increase in selectivity was observed as the helical content of the polymer increased. The chemically grafted PLGA showed discrimination for chiral α-amino acids (Trp, Phe, and Tyr) and drugs (propranolol, atenolol, and ibuprofen).

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