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Uniform-sized molecularly imprinted polymer material for (*S*)-propranolol

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Abstract

A uniform-sized molecularly imprinted polymer for (*S*)-propranolol has been prepared by a multi-step swelling and thermal polymerization method using methacrylic acid (MAA) and ethylene glycol dimethacrylate (EDMA) as a host functional monomer and cross-linker, respectively. The obtained (*S*)-propranolol imprinted MAA-EDMA materials were evaluated using aqueous-rich eluents by HPLC. The (*S*)-propranolol imprinted MAA-EDMA materials had specific recognition for (*S*)-propranolol and moderate recognition for some structurally related β-adrenergic antagonists (especially, pindolol and alprenolol), but had no recognition for other basic compounds, and neutral and acidic compounds. Enantioseparations of propranolol and some structurally related β-adrenergic antagonists were attained with the imprinted MAA-EDMA materials. Hydrophobic interaction of the naphthyloxy and isopropyl groups of propranolol, and ionic interaction of the isopropylamino group of propranolol with the (*S*)-propranolol imprinted MAA-EDMA materials could play an important role in enantioselective recognition of propranolol.

Keywords: Molecularly imprinted polymer; Chiral resolution; Propranolol; β-Adrenergic antagonist

1. Introduction

Molecularly imprinted polymer materials can be utilized for specific recognition of the target molecule as a chromatographic medium, sensor and artificial antibody [1–3]. Usually, non-aqueous bulk polymerization techniques [4] are used to obtain molecularly imprinted polymers. However, the obtained block polymers should be smashed, sieved and classified for their use as the chromatographic medium, sensor and artificial antibody. Recently, we prepared uniform-sized molecularly imprinted polymer materials for (*S*)-naproxen [5,6], where a typical multi-step swelling and polymerization method [7] with water as the suspension medium was used. They can be used with simple washing as a chromatographic medium. Moreover, the prepared imprinted polymer materials showed an equivalent molecular

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recognition ability to those prepared by non-aqueous bulk polymerization techniques [8].

Molecularly imprinted polymers for propranolol, which is one of β-adrenergic antagonists (β-blockers), were prepared through a bulk polymerization method [9–16], and used for chiral stationary phases in HPLC [9], antibody mimics in radioligand binding assay [10–12], solid phase extraction [13] and chiral selectors in capillary electrophoresis or electrochromatography [14–16]. In a previous communication [17], we reported preparation of uniform-sized molecularly imprinted polymer materials for racemic propranolol and (*S*)-propranolol using methacrylic acid (MAA) and ethylene glycol dimethacrylate (EDMA) as a functional monomer and cross-linker, respectively, by a multi-step swelling and thermal polymerization method. Further, we evaluated selectivity of the obtained imprinted MAA-EDMA materials for propranolol and its metabolites by using aqueous-rich eluents. The results indicated that the imprinted MAA-EDMA materials showed high selectivity for propranolol and moderate selectivity for propranolol metabolites. In this study, we evaluated the enantioselectivity of the (*S*)-propranolol imprinted MAA-EDMA materials for propranolol and other β-blockers, and selectivity for other basic

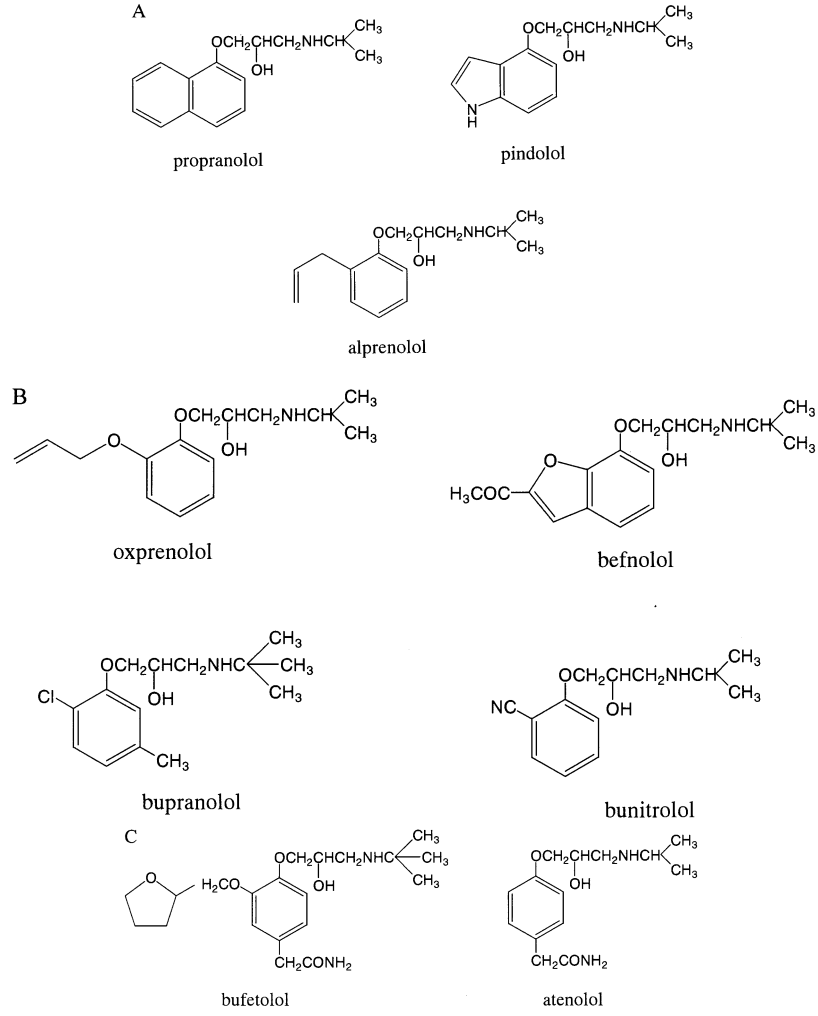
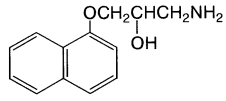
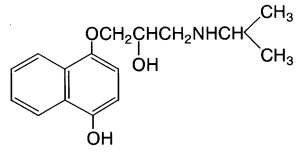


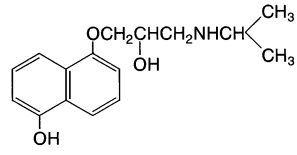
Fig. 1. Structures of propranolol and other β-blockers used in this study.



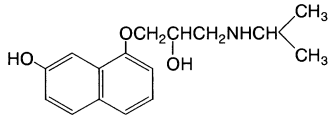
N-desisopropylpropranolol



4-hydroxypropranolol



5-hydroxypropranolol



7-hydroxypropranolol

Fig. 2. Structures of propranolol metabolites.

compounds, and neutral and acidic compounds by using aqueous-rich eluents. Further, the enantioselective mechanism of propranolol on the (*S*)-propranolol imprinted MAA-EDMA materials is discussed.

2. Experimental

2.1. Materials

EDMA and 2-(trifluoromethyl)acrylic acid (TFMA) were purchased from Tokyo Chemical Industry (Tokyo, Japan). Acrylic acid (AA) and MAA were purchased from Wako Pure Chemical Industry (Osaka, Japan). These monomers were purified by general distillation techniques in vacuo to remove the polymerization inhibitor. 2,2′-Azobis(2,4-dimethylvaleronitrile) (V-65) was purchased from Wako Pure Chemical Industry (Tokyo, Japan), and used without further purification. (*S*)-(−)-Propranolol hydrochloride, racemic propranolol hydrochloride, (*S*)-(−)-alprenolol *d*-tartrate, racemic alprenolol hydrochloride, racemic atenolol and racemic oxprenolol hydrochloride were purchased from Sigma–Aldrich Japan (Tokyo, Japan). Racemic befnolol and bupranolol hydrochlorides, and racemic ibuprofen were donated from Kaken Pharmaceutical (Tokyo, Japan). Racemic bunitrolol and bufetolol hydrochlorides were donated from Tanabe Pharmaceutical (Osaka, Japan) and Yoshitomi Pharmaceutical (Tokyo, Japan), respectively. (*S*)-(−)-Pindolol and racemic pindolol were donated from Daiso (Osaka, Japan). Racemic chlorpheiramine maleate and benzoin were purchased from Nacalai Tesque (Kyoto, Japan). Racemic tolperisone hydrochloride and hexobarbital were donated from Eisai (Tokyo, Japan) and Teikoku Chemical Industry (Osaka, Japan), respectively. The structures of propranolol and other β-block-

Table 1
Retention factor, enantioseparation factor and resolution of propranolol on the various (*S*)-propranolol imprinted polymer materials[a]

Material	Propranolol				Eluent[b]
	k_1	k_2	α	Rs	
EDMA	0.57		1.00	–[c]	1
EDMA	17.5		1.00	–	2
AA-EDMA	21.4		1.00	–	3
TFMA-EDMA	58.5	79.1	1.35	0.30	4
MAA-EDMA	16.9	35.9	2.12	0.69	4

[a] HPLC conditions: column size, 4.6 mm i.d. × 100 mm; column temperature, 25°C; flow rate, 1.0 ml min^{-1}; detection, 210 nm; loaded amount, 1000 ng.

[b] Eluent: eluent 1, 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (50:50, v/v); eluent 2, 20 mM disodium hydrogen phosphate–trisodium phosphate (pH 10.5)/acetonitrile (70:30, v/v); eluent 3, 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (50:50, v/v); eluent 4, 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (30:70, v/v).

[c] Not calculated.

Table 2
Effect of eluent pH on retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials[a]

Buffer pH	(*S*)-Propranolol imprinted			Non-imprinted			Selectivity factor
	k_2	α	Rs	k	α	Rs	
3.2	0.83	1.00	–[b]	0.51	1.00	–	1.63
4.0	5.59	1.67	0.26	1.68	1.00	–	3.33
5.1	35.9	2.12	0.69	8.52	1.00	–	4.21
6.0	94.7	2.02	0.95	24.6	1.00	–	3.85

[a] HPLC conditions as in Table 1 except that the eluent used is 20 mM phosphoric acid–sodium dihydrogen phosphate or sodium dihydrogen phosphate–disodium hydrogen phosphate/acetonitrile (30:70, v/v).
[b] Not calculated.

Table 3
Effect of buffer concentration on retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials[a]

Buffer concentration (mM)	(*S*)-Propranolol imprinted			Non-imprinted			Selectivity factor
	k_2	α	Rs	k	α	Rs	
20	35.9	2.12	0.69	8.52	1.00	–[b]	4.21
50	17.0	2.02	0.60	3.79	1.00	–	4.49
100	9.43	1.97	0.45	2.21	1.00	–	4.27

[a] HPLC conditions as in Table 1 except that the eluent used is sodium dihydrogen phosphate–disodium hydrogen phosphate/acetonitrile (30:70, v/v).
[b] Not calculated.

Table 4
Effect of acetonitrile content on retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials[a]

Acetonitrile content (%)	(*S*)-Propranolol imprinted			Non-imprinted			Selectivity factor
	k_2	α	Rs	k	α	Rs	
40	61.0	1.95	–[b]	14.7	1.00	–	4.15
50	39.7	2.00	0.48	9.08	1.00	–	4.21
70	35.9	2.12	0.69	8.37	1.00	–	4.29

[a] HPLC conditions as in Table 1 except that the eluent used is a mixture of 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1) and acetonitrile.
[b] Not calculated.

ers used in this study are illustrated in Fig. 1. The structures of propranolol metabolites, which are prepared as described previously [17], are illustrated in Fig. 2. Other reagents and solvents were used without further purification.

Water purified with a Nanopure II unit (Barnstead, Boston, MA) was used for the preparation of the eluent and the sample solution.

2.2. Multi-step swelling and polymerization method

Preparation of uniform-sized, macroporous, molecularly imprinted polymer materials for (*S*)-propranolol as well as non-imprinted polymer materials by a multi-step swelling and polymerization method was carried out as reported previously [17]. Briefly, a water dispersion of the uniformly sized, polystyrene seed particles (0.17 ml, 0.497 g ml^{-1}) was admixed with a micro-emulsion prepared from 0.48 ml of dibutyl phthalate as an activating solvent [18], 0.02 g of sodium dodecyl sulfate and 5 ml of distilled water by sonication. This first-step swelling was carried out at room temperature for 15 h with stirring at 125 rev. min^{-1} until micro oil droplets had completely disappeared. To the swollen particles, a micro-emulsion prepared from 0.375 g of 2,2′-azobis(2,4-dimethylvaleronitrile), 5 ml of toluene, 12.5 ml of water and 10 ml of 4.8% polyvinylalcohol (dp = 500, saponification value = 86.5–89 mol%) solution was added. This second-step swelling was carried out at room temperature for 2 h with stirring at 125 rev. min^{-1}. To the dispersion of swollen particles, a dispersion of 5 ml of EDMA, 7.0 mmol (ca. 0.60 g) of methacrylic acid, 0.02 g of sodium dodecyl sulfate, 12.5 ml of water and 10 ml of 4.8% polyvinylalcohol solution was added. This third-step swelling was carried out at room temperature for 2 h with stirring at 125 rev. min^{-1}. When the

Table 5
Retention factor, enantioseparation factor, resolution and selectivity factor of propranolol and other β-blockers on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials[a]

β-Blockers	(*S*)-Propranolol imprinted			Non-imprinted			Selectivity factor
	k_2	α	Rs	k	α	Rs	
Propranolol	35.9	2.12	0.69	8.52	1.00	–	4.21
Pindolol	13.0	1.48	0.30	5.51	1.00	–	2.36
Alprenolol	14.0	1.41	0.30	6.32	1.00	–	2.22
Oxprenolol	7.60	1.19	–[b]	4.60	1.00	–	1.65
Befnolol	7.41	1.19	–	4.52	1.00	–	1.64
Bupranolol	10.8	1.17	–	6.76	1.00	–	1.60
Bunitrolol	6.40	1.09	–	4.90	1.00	–	1.31
Bufetolol	5.69	1.00	–	4.49	1.00	–	1.27
Atenolol	5.42	1.00	–	4.59	1.00	–	1.18

[a] HPLC conditions as in Table 1 except that the eluent used is 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (30:70, v/v).
[b] Not calculated.

Table 6
Retention factor, enantioseparation factor and selectivity factor of other basic compounds, and neutral and acidic compounds on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials[a]

Other solutes	(*S*)-Propranolol imprinted		Non-imprinted		Selectivity factor
	k	α	k	α	
Tolperisone	6.9	1.00	5.53	1.00	1.25
Chlorpheniramine	11.8	1.00	9.74	1.00	1.21
Benzoin	0.5	1.00	0.48	1.00	1.06
Hexobarbital	0.3	1.00	0.25	1.00	1.16
Ibuprofen	0.15	1.00	0.11	1.00	1.36

[a] HPLC conditions as in Table 5.

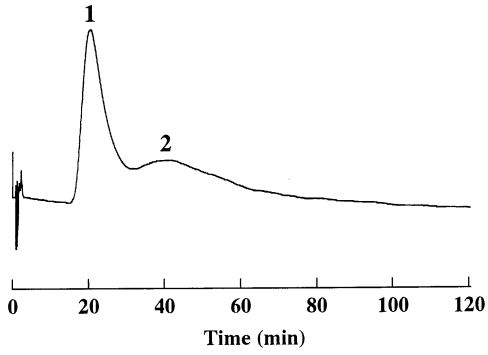


Fig. 3. Separation of propranolol enantiomers on the (*S*)-propranolol imprinted MAA-EDMA materials. Peak assignments: 1, (*R*)-propranolol; 2, (*S*)-propranolol. HPLC conditions: column size, 4.6 mm i.d. × 100 mm; eluent, 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (30:70, v/v); flow rate, 1.0 ml min^{-1}; column temperature, 25°C; detection, 210 nm; loaded amount, 1000 ng.

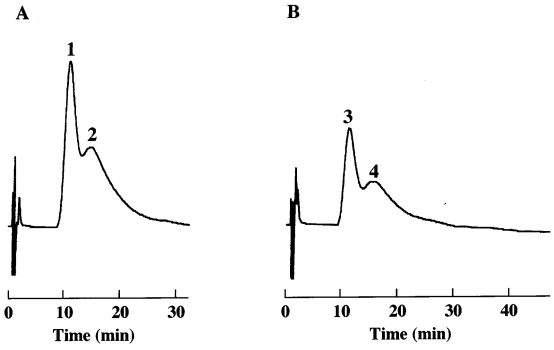


Fig. 4. Separation of pindolol (A) and alprenolol (B) enantiomers on the (*S*)-propranolol imprinted MAA-EDMA materials. Peak assignments: 1, (*R*)-pindolol; 2, (*S*)-pindolol; 3, (*R*)-alprenolol; 4, (*S*)-alprenolol. HPLC conditions as in Fig. 3.

template molecule was added, 2.0 mmol (0.59 g) of (*S*)-(−)-propranolol hydrochloride together with 0.25 ml of 0.1 M NaOH solution was admixed with the monomers utilized to prepare the dispersion for the third-step swelling. After the third-step swelling was completed, the polymerization procedure was started at 50°C under argon atmosphere with slow stirring for 24 h. The dispersion of polymerized materials was poured into 250 ml of water to remove the suspension stabilizer (polyvinylalcohol), and the supernatant was discarded after sedimentation of the materials. The polymer materials were redispersed into methanol, and the supernatant was again discarded after sedimentation. This procedure was repeated three times in methanol and twice in tetrahydrofuran (THF), then the polymer materials were filtered on a membrane filter and washed with THF and acetone followed by drying at room temperature. The chemical yields of all particles were higher than 90%.

The prepared materials were packed into a stainless-steel column (4.6 mm i.d. × 100 mm) by a slurry packing technique using methanol as the slurry and packing solvents to evaluate their chromatographic characteristics.

2.3. Chromatography

The HPLC system used was composed of an LC-9A pump, an SPD-6A spectrophotometer, a Rheodyne 7125 injector with a 20-μl loop, and a C-R6A integrator (all from Shimadzu, Kyoto, Japan). The flow-rate was maintained at 1.0 ml min^{-1}. Detection was performed at 210 nm. All separations were carried out at 25°C using a water bath (Thermo Minder Lt-100, Taitec, Saitama, Japan). The eluents are prepared by using phosphoric acid, sodium dihydrogen phosphate, disodium hydrogen phosphate and acetonitrile. The eluents used were specified in the legends of tables and figures.

The retention factor was calculated from the equation $k = (t_R - t_0)/t_0$, where t_R and t_0 are the retention times of retained and unretained solutes, respectively. The retention time of unretained solute, t_0, was measured by injecting the solution whose organic modifier content was slightly different from that of the eluent. The enantioseparation factor is calculated from the equation $\alpha = k_2/k_1$, where k_1 and k_2 are the retention factors of the first and second eluted enantiomers, respectively. Resolution is calculated from the equation $Rs = 2(t_{R2} - t_{R1})/(w_1 + w_2)$, where t_{R1} and t_{R2} are the retention times of the first and second eluted enantiomers, respectively, and w_1 and w_2 are the baseline peak widths of the first and second eluted enantiomers, respectively. Selectivity factor was calculated from the equation $S = k_{imprinted}/$

$k_{\text{non-imprinted}}$, where $k_{\text{imprinted}}$ and $k_{\text{non-imprinted}}$ are the retention factors of a solute on the molecularly imprinted and non-imprinted polymer materials, respectively.

3. Results and discussion

3.1. Selection of a functional monomer

The molecularly imprinted polymer materials for (*S*)-propranolol were prepared using a functional monomer and EDMA as a cross-linker by a multi-step swelling and thermal polymerization technique with water as a suspension medium. The materials prepared were the (*S*)-propranolol imprinted EDMA, AA-EDMA, TFMA-EDMA and MAA-EDMA materials, and were evaluated by using an aqueous-rich eluent to examine the effect of a functional monomer on the retentivity and enantioselectivity of propranolol. Table 1 shows the retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on various (*S*)-propranolol imprinted polymer materials. The EDMA and AA-EDMA materials had no chiral recognition ability. Without a functional monomer, neither propranolol was retained so much, nor enantioseparated. No chiral recognition ability of the AA-EDMA materials might be due to less hydrophobicity of AA, compared with TFMA and MAA. On the other hand, the TFMA-EDMA and MAA-EDMA materials had chiral recognition ability for propranolol. The TFMA-EDMA materials gave longer retentions for propranolol than the MAA-EDMA materials. This could be due to the fact that TFMA is more acidic than MAA. With regard to the enantioseparation factor and resolution, the MAA-EDMA materials gave higher enantioselectivity than the TFMA-EDMA materials. In the following studies, we used MAA as a functional monomer.

3.2. Effects of buffer pH and concentration, and acetonitrile content on retentivity and enantioselectivity of propranolol on the (S)-propranolol imprinted MAA-EDMA materials

Table 2 shows the effect of eluent pH on the retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted MAA-EDMA materials, where the selectivity factor is represented by the ratio of the retention factors of (*S*)-propranolol on molecularly imprinted and non-imprinted polymer materials, $k_{\text{imprinted}}/k_{\text{non-imprinted}}$. With an increase in buffer pH, the retention factor and resolution were increased, while the enantioseparation factor and selectivity factor gave a maximum at buffer pH 5.1. Table 3 shows the effect of buffer concentration on the retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted MAA-EDMA materials. The phosphate buffer concentration was varied from 20 to 100 mM. With an increase in buffer concentration, the retention factor, enantioseparation factor and resolution was decreased, while there is not so much difference in the selectivity factor. Table 4 shows the effect of acetonitrile content on the retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted MAA-EDMA materials. With an increase in acetonitrile content, the enantioseparation factor and resolution were increased, while there is not so much difference in the selectivity factor. In the following studies, we used 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (30:70, v/v) as an eluent.

With regard to the retentivity and enantioselectivity of propranolol on the (*S*)-propranolol imprinted MAA-EDMA materials, it is important to consider the apparent pK_a values of propranolol and MAA-EDMA materials. Since the pK_a value of propranolol was 9.5 [19], it seemed that propranolol was protonated among the eluent pH tested. Sellergren and Shea titrated the L-phenylalanine anilide- and benzylamine-imprinted, and non-imprinted MAA-EDMA materials with sodium hydroxide, and evaluated the degree of ionization of their materials [20]. Although the apparent average pK_a values of those MAA-EDMA materials were 8–9, the MAA-EDMA materials were partially charged even at low apparent pH such as 4. Since at eluent pH of 3, the MAA-EDMA materials were not charged,

cationic propranolol was not retained or enantioseparated on the (*S*)-propranolol imprinted materials. The effect of buffer concentration could be interpreted as a decreased ionic adsorption at high ionic strength. With an increase in buffer pH, propranolol was retained and enantioseparated because of the ionic and hydrophobic interactions with the MAA-EDMA materials. The retentive and enantioselective data described above support the view that ionic and hydrophobic interactions should play an important role in the retention and enantioseparation of propranolol.

3.3. Selectivity of the (S)-propranolol imprinted MAA-EDMA materials for various compounds

Selectivity of the (*S*)-propranolol imprinted MAA-EDMA materials for propranolol and other β-blockers, and neutral and acidic compounds were examined. Table 5 shows the retention factor, enantioseparation factor, resolution and selectivity factor of propranolol on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials. Propranolol gave the highest enantioseparation factor and selectivity factor, while pindolol and alprenolol whose structures are shown in Fig. 1, part A gave higher enantioseparation factors and selectivity factors than other β-blockers shown in Fig. 1, parts B and C. The (*S*)-propranolol imprinted MAA-EDMA materials showed moderate enantioselectivity for the β-blockers (oxprenolol, befnolol, bupranolol and bunitrolol) shown in Fig. 1, part B. On the other hand, chiral resolution of bufetolol and atenolol shown in Fig. 1, part C was not obtained. It is interesting to compare the relationship of the structures of β-blockers and the selectivity on the imprinted polymer materials. The structures of pindolol and alprenolol were very similar to that of propranolol. Pindolol and alprenolol have indolyloxy and allylphenoxy groups, respectively, and both have an isopropylamino group, while propranolol has a naphthyloxy and isopropylamino group. The structures of oxprenolol, befnolol, bupranolol and bunitrolol, which showed moderate selectivity, were similar to that of propranolol, while the structures of bufetolol and atenolol, which had a *p*-substituted acetamide group, were different from that of propranolol. The results obtained agreed well with the view that recognition of the shape and functionality of a template molecule is important in molecular imprinting [1].

With regard to enantioseparation of propranolol metabolites, we reported that enantioseparation of *N*-desisopropylpropranolol (Fig. 2) was not attained, but that enantioseparations of 4-, 5- and 7-hydroxypropranolols were attained [17]. These results suggest that the hydrophobic interaction of the naphthyloxy and isopropyl groups of propranolol and ionic interaction of the isopropylamino group of propranolol with the (*S*)-propranolol imprinted MAA-EDMA could play an important role in recognition of propranolol. Moreover, hydroxypropranolols and some β-blockers (especially, pindolol and alprenolol), which structurally resemble propranolol, could be recognized on the (*S*)-propranolol imprinted MAA-EDMA materials with the same interactions as described above.

Table 6 shows retention factors, enantioseparation factors and selectivity factors of other basic compounds, and neutral and acidic compounds on the (*S*)-propranolol imprinted and non-imprinted MAA-EDMA materials. With regard to selectivity of the imprinted polymers for other basic compounds, tolperisone and chlorpheniramine, selectivity factors were 1.25 and 1.21, respectively. Neutral compounds, benzoin and hexobarbital, and an acidic compound, ibuprofen, were not retained on the (*S*)-propranolol imprinted and non-imprinted materials. These results revealed that the (*S*)-propranolol imprinted MAA-EDMA materials had specific recognition for (*S*)-propranolol and moderate recognition for some structurally related β-blockers, but had no recognition for other basic compounds, and neutral and acidic compounds.

3.4. Separation of enantiomers and propranolol, pindolol and alprenolol on the (S)-propranolol imprinted MAA-EDMA materials

Fig. 3 shows the separation of propranolol enantiomers on the (*S*)-propranolol imprinted

MAA-EDMA materials, where the eluent used is 20 mM sodium dihydrogen phosphate–disodium hydrogen phosphate (pH 5.1)/acetonitrile (30:70, v/v). Fig. 4, parts A and B, shows the separation of enantiomers of pindolol and alprenolol, respectively, on the (*S*)-propranolol imprinted MAA-EDMA materials, where the (*S*)-enantiomers are more retarded than the corresponding (*R*)-enantiomers. As described above, the (*S*)-propranolol imprinted materials gave the highest enantioselectivity for propranolol among the β-blockers tested, and moderate enantioselectivity for pindolol and alprenolol.

4. Conclusion

We prepared uniform-sized, (*S*)-propranolol imprinted polymer materials using MAA and EDMA as a functional monomer and cross-linker, respectively. The (*S*)-propranolol imprinted MAA-EDMA materials had specific recognition for (*S*)-propranolol and moderate recognition for some structurally related β-blockers, but had no recognition for other basic compounds, and neutral and acidic compounds. Enantioseparations of propranolol and some structurally related β-blockers were attained with the imprinted MAA-EDMA materials. When a mixture of phosphate buffer solution and acetonitrile was used as the eluent, the hydrophobic interaction of the naphthyloxy and isopropyl groups and ionic interaction of the isopropyl-amino group of propranolol with the (*S*)-propranolol imprinted MAA-EDMA could play an important role in enantioselective recognition of propranolol.

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References

[1] G. Wulff, Angew. Chem. Int. Ed. Engl. 34 (1995) 1812.
[2] B. Sellergren, Trends Anal. Chem. 16 (1997) 310.
[3] A.G. Mayes, K. Mosbach, Trends Anal. Chem. 16 (1997) 321.
[4] G. Wulff, A. Sarhan, K. Zabrocki, Tetrahedron Lett. 14 (1973) 4329.
[5] J. Haginaka, H. Takehira, K. Hosoya, N. Tanaka, Chem. Lett. (1997) 555.
[6] J. Haginaka, H. Takehira, K. Hosoya, N. Tanaka, J. Chromatogr. A 816 (1998) 113.
[7] K. Hosoya, J.M.J. Fréchet, J. Polym. Sci. Part A Polym. Chem. 31 (1993) 2129.
[8] M. Kempe, K. Mosbach, J. Chromatogr. A 664 (1994) 276.
[9] L. Fisher, R. Müller, B. Ekberg, K. Mosbach, J. Am. Chem. Soc. 113 (1991) 9358.
[10] L.I. Andersson, Anal. Chem. 68 (1996) 111.
[11] H. Bengtsson, U. Roos, L.I. Andersson, Anal. Commun. 34 (1997) 233.
[12] R.J. Ansell, K. Mosbach, Analyst 123 (1998) 1611.
[13] P. Martin, I.D. Wilson, D.E. Morgan, G.R. Jones, K. Jones, Anal. Commun. 34 (1998) 45.
[14] M. Walshe, E. Garcia, J. Howarth, M.R. Smyth, M.T. Kelly, Anal. Commun. 34 (1997) 119.
[15] L. Schweitz, L.I. Andersson, S. Nilsson, Anal. Chem. 69 (1997) 1179.
[16] S. Nilsson, L. Schweitz, M. Petersson, Electrophoresis 18 (1997) 884.
[17] J. Haginaka, Y. Sakai, S. Narimatsu, Anal. Sci. 14 (1998) 829.
[18] J. Ugelstad, K.H. Kaggerud, F.K. Hansen, A. Berge, Makromol. Chem. 180 (1979) 737.
[19] A. Albert, E.P. Serjeant, The Determination of Ionization Constants. A Laboratory Manual, 3rd edn, Chapman and Hall, London, 1984, pp. 136–175.
[20] B. Sellergren, K.J. Shea, J. Chromatogr. A 654 (1993) 17.