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Note

Optical resolution of dihydropyridine enantiomers by high-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase

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Chiral dihydropyridines such as nilvadipine and nicardipine have been attracting much attention as potent calcium antagonists. Although these dihydropyridines exhibit different pharmacological effects between enantiomers[1], racemic mixtures have been used mainly because of difficulties in obtaining optical isomers in pure form and determining their optical purity in plasma. Therefore, high-performance liquid chromatographic (HPLC) separation of optical isomers of dihydropyridines is expected to be beneficial in solving these problems.

Recently, the successful chromatographic resolution of a dihydropyridine, nilvadipine, was achieved with optically active (+)-poly(triphenylmethyl methacrylate) (Chiralpak OT)[2]. It has also been reported that a stationary phase composing of α_1-acid glycoprotein is able to separate a series of dihydropyridine enantiomers using buffers[3]. We reported that optical resolution of nicardipine was possible on HPLC columns packed with xylan bis(3,5-dichlorophenylcarbamate)[4] and cellulose tris(4-*tert.*-butylphenylcarbamate)[5].

In this study, we examined the optical resolution of six dihydropyridines, nimodipine, nilvadipine, benidipine, nitrendipine, isradipine and nicardipine, on phenylcarbamate derivatives of cellulose, amylose and xylan using organic eluents.

EXPERIMENTAL

Polysaccharide phenylcarbamates and chiral stationary phases for HPLC were prepared as reported previously[6]. The stationary phases were packed manually in HPLC columns (25 × 0.46 cm I.D.). The theoretical plate numbers of the columns for benzene were 2800–3700.

Optical resolution was performed on a Jasco Trirotar-II chromatograph equipped with UV (254 nm, Jasco Uvidec 100-III) and polarimetric detectors (435 nm,

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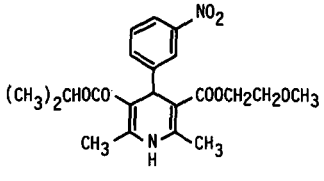
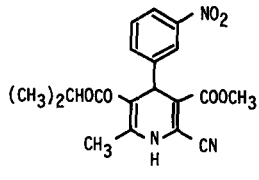
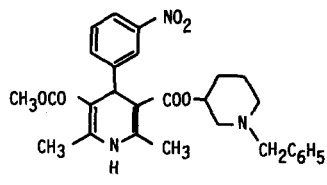


Nimodipine

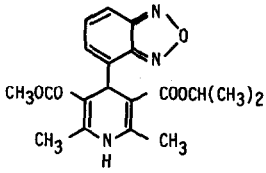


Nilvadipine

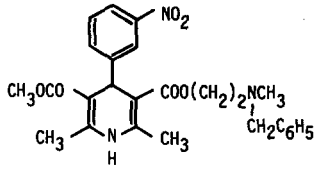


Benidipine

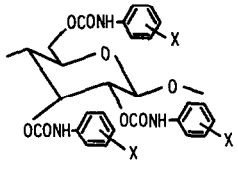
Nitrendipine



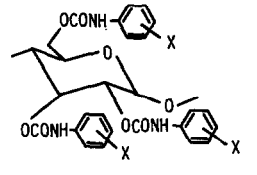
Isradipine



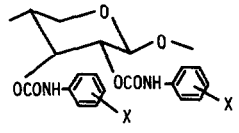
Nicardipine



Cellulose Derivatives
(X = 3,5-$(CH_3)_2$, 4-$(CH_3)_3C$)



Amylose Derivatives
(X = 3,5-$(CH_3)_2$, 4-$(CH_3)_3C$)



Xylan Derivatives
(X = 3,5-$(CH_3)_2$, 3,5-Cl_2)

Jasco DIP-181C). The elution time of 1,3,5-tri-*tert.*-butylbenzene was used as the dead time (t_0).

Nimodipine (Bayer Yakuhin), nilvadipine (Fujisawa Pharmaceutical), benidipine (Kyowa Hakko Kogyo), nitrendipine (Sigma), isradipine (Sandoz Pharmaceuticals) and nicardipine (Sigma) were used as analytes without purification.

RESULTS

Fig. 1 shows the optical resolution of nimodipine, nilvadipine and benidipine on xylan bis(3,5-dichlorophenylcarbamate), which showed an effective chiral recognition ability for nicardipine[4]. Although nilvadipine was not completely resolved, nimodipine and benidipine were completely resolved.

Isradipine and nitrendipine were more effectively resolved on cellulose 4-*tert.*-butylphenylcarbamate. The resolution of israpidine, nitrendipine and nicardipine was examined in more detail with four chiral columns and the results are summarized in Table I. Cellulose tris(3,5-dimethylphenylcarbamate), which shows high optical resolving abilities for many racemates[7–9], showed no separation of three dihydropyridines. However, cellulose 4-*tert.*-butylphenylcarbamate resolved the three compounds. Amylose tris(3,5-dimethylphenylcarbamate) showed a more effective chiral recognition ability for isradipine (Fig. 2). Although nicardipine was almost completely resolved on cellulose tris(4-*tert.*-butylphenylcarbamate) and xylan bis(3,5-dichlorophenylcarbamate) using hexane–2-propanol (90:10), the elution time was long[4,5].

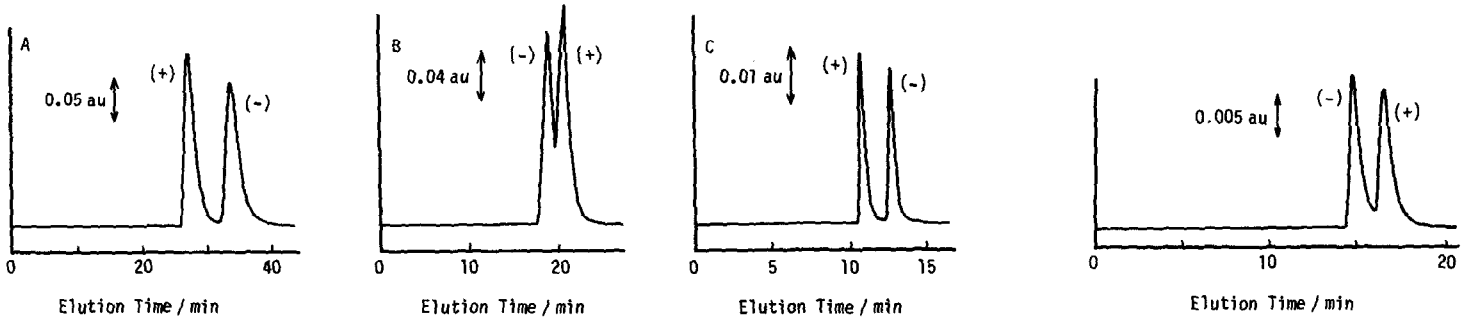


Fig. 1. Chromatographic resolution of dihydropyridine derivatives on xylan bis(3,5-dichlorophenylcarbamate). (A) Nimodipine; (B) nilvadipine; (C) benidipine. Eluent: A and B, hexane–2-propanol–diethylamine (85:15:0.1), 0.5 ml/min; C, hexane–2-propanol–diethylamine (80:20:0.1), 0.5 ml/min.

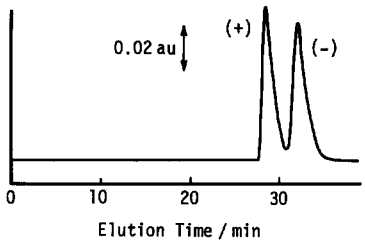
Fig. 2. Optical resolution of isradipine on amylose tris(3,5-dimethylphenylcarbamate). Eluent: hexane–2-propanol (90:10), 0.5 ml/min.

TABLE I

OPTICAL RESOLUTION OF NITRENDIPINE, ISRADIPINE AND NICARDIPINE ON PHENYLCARBAMATE DERIVATIVES OF POLYSACCHARIDES

Eluent: hexane–2-propanol (90:10).

Polysaccharide	*X*	*Nitrendipine*			*Isradipine*			*Nicardipine*		
		k'_1	α	R_s	k'_1	α	R_s	k'_1	α	R_s
Cellulose	3,5-$(CH_3)_2$	2.22	1.00		1.58	1.00		~1		
Cellulose	4-*tert.*-$(CH_3)_3C$	1.45(+)	1.27	2.14	0.98(−)	1.11	0.77	8.05(−)	1.21	1.29
Amylose	3,5-$(CH_3)_2$	1.78(+)	1.07		1.49(−)	1.19	1.35	5.5	1.00	
Amylose	4-*tert.*-$(CH_3)_3C$	2.72(−)	1.13	0.66	1.82	1.00		3.19	1.00	



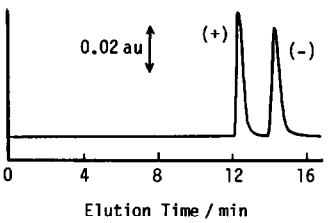


Fig. 3. Enantiomeric resolution of nicardipine on xylan bis(3,5-dimethylphenylcarbamate). Eluent: hexane–2-propanol (90:10), 0.5 ml/min.

Fig. 4. Enantiomeric resolution of nitrendipine on cellulose tris(4-*tert.*-butylphenylcarbamate). Eluent: hexane–2-propanol–chloroform (85:10:5), 0.5 ml/min.

However, as shown in Fig. 3, a more expeditious separation was attained on xylan bis(3,5-dimethylphenylcarbamate) using the same eluent.

The influence of the elution system on the chiral recognition abilities was investigated by adding 5% of chloroform to hexane–2-propanol (90:10). For instance, nitrendipine was better resolved with a small capacity factor ($k'_1 = 0.99$) and a larger separation factor ($\alpha = 1.32$) on cellulose tris(4-*tert.*-butylphenylcarbamate) (Fig. 4). The resolution factor ($R_s = 2.67$) was also larger than those (1.22 and 1.81) on EnantioPac and Chiral-AGP columns, respectively[3]. In contrast, isradipine was less efficiently resolved by adding 5% of chloroform to the eluent with amylose tris(3,5-dimethylphenylcarbamate), giving an α value of 1.10.

The possibility of preparative separation was examined with nitrendipine. About 0.5 mg of the sample was injected in one dose onto the cellulose tris(4-*tert.*-butylphenylcarbamate) column with hexane–2-propanol–chloroform (85:10:5) as the eluent and was almost completely separated into two peaks with an R_s value of 0.97. This suggests that preparative separations will be possible with a larger column.

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