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Preparative Method of *R*-(−)-Ibuprofen by Diastereomer Crystallization

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The economic and effective method for preparation of *R*-(-)-ibuprofen by diastereomer crystallization was developed. *R*-(-)-ibuprofen was resolved from racemic ibuprofen by forming *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine diastereomeric salt with *R*-(+)-α-methylbenzylamine and crystallization. The purity of *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine diastereomeric salt was tested and confirmed using HPLC and ^{1}H-NMR method. The pure diastereomeric salt collected from repeated recrystallization was further fractionated by liquid-liquid extraction to the pure enantiomer without racemization. R-(-)-ibuprofen was recovered producing overall yield of 2.4% with the purity more than 99.97%.

Key words: R-(-)-Ibuprofen, Resolution, Crystallization, α-Methylbenzylamine

INTRODUCTION

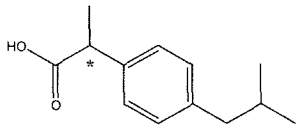
Ibuprofen, 2-(4-isobutyl phenyl)propionic acid, **1**, is an effetive non aspirin based analgesic/anti-inflammatory agent. It belongs to a large class of chemotherapeutics that are 2-aryl propionic acids, including such drugs as naproxen, fenoprofen, and flurbiprofen (Stephanie *et al.*, 1996). It is used extensively in the treatment of acute and chronic pain, steoarthritis, rheumatoid arthritis and related conditions. *S*-(+)- ibuprofen is therapeutically important, 28 times more physiologically potent than *R*-(-)-ibuprofen (Ducret *et al.*, 1997). It is usually marketed as a racemic mixture even if it is known that the pharmacological activity is due almost exclusively to the *S*-(+) enantiomer (eutomer)(Canarapo *et al.*, 1999).

There are many reports published on determination of ibuprofen as well as its enantiomres in pharmaceutical formulations and biological matrix (plasma, serum and urine) by different techniques such as capillary zone electrophoresis (Wei *et al.*, 2004; Makino *et al.*, 2003; Abushoffa *et al.*, 2003) and liquid chromatography using different chiral stationary phases (CPAs) (Johannsen, 2001; Bonato *et al.*, 2003; Van Overbeke, 1994).

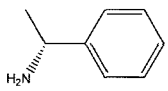
Because of the widespread usage of ibuprofen, it is necessary to develope methods for resolving enantiomers of ibuprofen serving for researching their biological activities and quality control of the drug.

There is no report on preparative resolution of *R*-(-)-Ibuprofen by diastereomer crystallization using *R*-(+)-α-methylbenzylamine as chiral solvating agent. Although most research efforts these days are focused on applying new asymmetric organic synthesis and enzymatic methodologies to commercial applications, classical resolution stillremains a widely used technique for industrial scale separation of enantiomers. Issues associated with resolution of enantiomers include selection and recovery of the resolving agent (if required), racemization of the undesired isomer, and choice of bicatalysis or chemocatalysis (if applicable).

In this work, we developed an economic and effective



Ibuprofen, 1



R-(+)-alpha-methylbenzylamine, **2**

Fig. 1. Structure of ibuprofen (**1**) and *R*-(+)-α-methylbenzylamine (**2**) *Chiral center.

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method for preparation of *R*-(-)-ibuprofen in laboratory scale by preferential crystallization using *R*-(+)-α-methylbenzylamine, **2**, as chiral solvating agent.

MATERIALS AND METHODS

Chemicals

R-(+)-α-methylbenzylamine, Triflouroacetic acid, Magnesium sulfate and Chloroform-d were purchased from Aldric Chemical Co., U.S.A. Ethanol, *n*-hexane, isopropanol (HPLC grade), ethyl ether (GR) were purchased from Duksan pure chemical company Co. Ltd., Korea. Ibuprofen was acquired from ILDONG pharmaceutical Co., Ltd. (Ansung Korea).

Instrument

The HPLC system included isocratic LC-10ADvp pump, SPD-10Avp UV detector and C-R4A chromatopac were purchsed from Shimazdu Co., Ltd. with Chiralcel OD-H column were puchased from Daicel chemical industries, Ltd., Japan. Brucker DDX-400 NMR instrument were from Brucker company, Germany. VV2011 vacuum rotaty evaporator system was purchased from Heidolph Company, Germany.

Formation of *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine diastereomeric salt and preferential crystallization

To a solution of racemic ibuprofen (4 g, 19.2 mmole) in absolute ethanol (48 mL) was added *R*-(+)-α-methylbenzylamine (2.5 mL, 19.2 mmole) at 60°C. After 15 min of refluxed stirring, the mixture clear. Then solution was cooled down slowly and allowed to stand at room temperature for 10 h. The crystals formed were filtered, dried in drying oven at 45°C for 1.5 h, cooled down to room temperature in dessicator, weighed using analytical balance.

Purity test of the formed diastereomeric salt

2 mg of formed diastereomeric salt crystals dissolved in 4 mL of 1N HCl solution were added with 2 mL of ethyl ether, then votex mixed for 2 min and centrifuged for 10 min. The ethyl ether layer containing *R*-(-)-ibuprofen was evaporated under nitrogen stream until dryness. The residue after the evaporation subsequently was recontituted in 1 mL of *n*-hexane: isopropanol: triflouroacetic acid (100:1:0.1, v/v/v). 10 mL of the solution were injected to the Shimadzu HPLC system at wavelength of 225 nm and flowrate at 1 mL/min using Chiralcel OD-H column (150 mm × 4.6 I.D).

After checking the purity, the crystals were repeatedly recrystallized in absolute ethanol until the pure diastereomeric salt was obtained as white needle crystals. The ^{1}H-NMR spectrum were recorded on on Brucker DDX-400 NMR instrument ($CDCl_3$) δ 7.3242 (m, 4H) δ 7.2373 (d, J = 3.867 Hz, 2H), δ 7.0954 (d, J=8.015, 2H), δ 4.1222 (q, J= 6.638 Hz, 1H), δ 2.4425 (d, J = 7.178 Hz, 2H), δ 1.8407 (m, 1H), δ 1.4918 (d, J = 7.133 Hz, 3H), δ 1.3985 (d, J = 6.64 Hz, 3H), δ 0.8933 (d, J = 6.583, 6H).

Extraction of *R*-(-)-ibuprofen from *R*-(-)-ibuprofen-*R*-(+)-methylbenzylamine diastereomeric salt

To 250 mL separating funnel contained 1N HCl solution was added the resolved *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine diastereomeric salt and vigrously shaken. Then, five times extractions with ethyl ether were carried

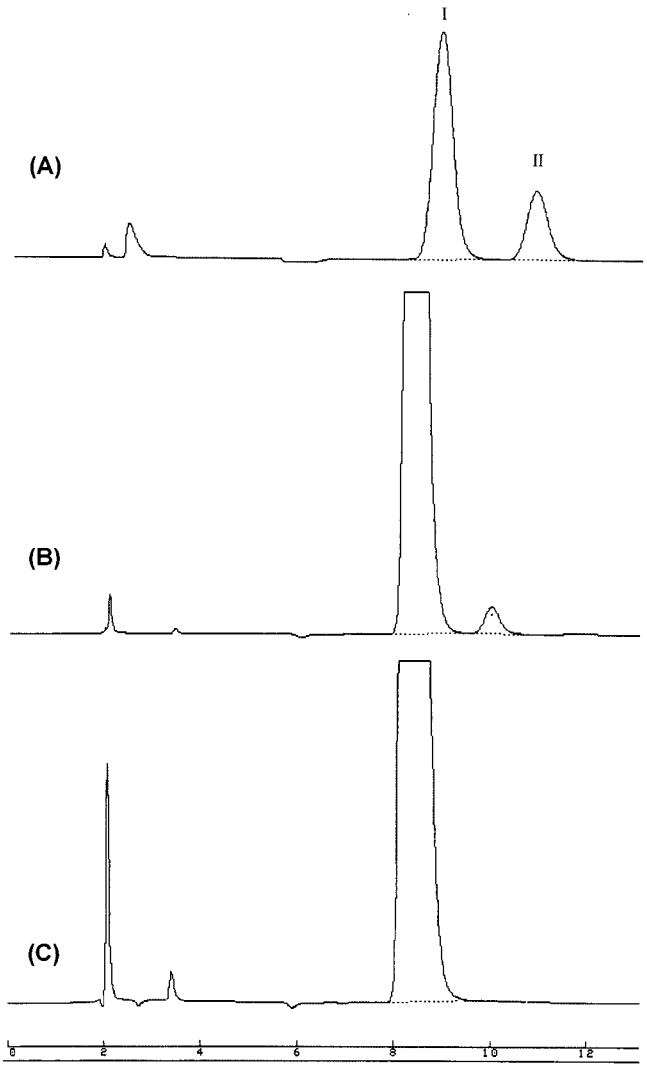


Fig. 2. Chromatograms of *R*-(-)-ibuprofen-*R*-(+)-α-methyl benzylamine diastereomeric salts. ***A***: *R*-(-)-ibuprofen-*R*-(+)-α-methyl benzylamine after first crystallization; **B**: *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine after the third recrystallization; **C**: *R*-(-)-ibuprofen-*R*-(+)-α-methyl benzylamine after the eighth recrystallization. (I): *R*-(-)-ibuprofen; (II): *S*-(-)-ibuprofen. Column: Chiralcel OD-H (5 μm, 150 × 4.6 mm I.D.), mobile phase: n-hexane:-isopropanol-trifluoroacetic acid (100:1:0.1, v/v/v); UV detector: 225 nm.

out. Combined organic extracts were dried by stirring with $MgSO_4$ for 1 h, filterd and evaporated to dryness and then weighed to determine the yield.

Purity test of the recovered *R*-(-)-ibuprofen

1 mg of the recovered *R*-(-)-ibuprofen dissolved in 1 mL of *n*-hexane: isopropanol: triflouroacetic acid (100:1:0.1, v/v/v) as a mobile phase. 10 mL of the solution were injected to the Shimadzu HPLC system at wavelength of 225 nm and flowrate at 1 mL/min using Chiralcel OD-H column (150 mm × 4.6 I.D).

RESULTS AND DISCUSSION

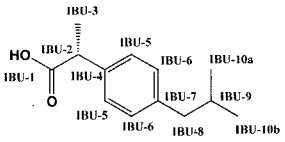
Formation of *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine diastereomeric salt and preferential crystallization and purity test of the formed diastereomeric salt

The result of *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine diastereomeric salt purities were showed in Fig. 2. After first and third recrystallizations, the diastereomeric salt collected had yield of 56% and 11% and chromatographic purities of 72% and 98.75% respectively. The diastereomeric salt collected had yield of 5% with chromatographic purity over 99.97% after the eighth recrystallization.

Extraction of *R*-(-)-ibuprofen from *R*-(-)-ibuprofen-*R*-(-)-ibuprofen-*R*-(+)-methylbenzylamine diastereomeric salt and purity test of the recovered *R*-(-)-ibuprofen

Fig. 3 showed the pure *R*-(-)-ibuprofen collected after

Table I. ^{1}H-NMR chemical shift of racemic ibuprofen, *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine (400 MHz, $CDCl_3$).



Assignment	Integration	Chemical shift (ppm) Racemic ibuprofen δ 1 (ppm)	*R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine δ 2 (ppm)	Chemical shift difference (ppm) δ 2 - δ 1
IBU-10	6H	0.9014 0.8848	0.9045 0.8880	0.0031 0.0032
IBU-3	3H	1.5101 1.4921	1.5175 1.4996	0.0074 0.0075
IBU-9	1H	1.8743 1.8575 1.8405 1.8237 1.8068 1.7901		
IBU-8	2H	2.4520 2.4341	2.4568 2.4389	0.0048 0.0048
IBU-2	1H	3.7386 3.7209 3.7030 3.6852	3.7485 3.7307 3.7128 3.6949	0.0099 0.0098 0.0098 0.0097
IBU-6	2H	7.1091 7.0890	7.1160 7.0960	0.0069 0.0070
IBU-5	2H	7.2072 7.1868	7.2376 7.2172	0.0304 0.0303

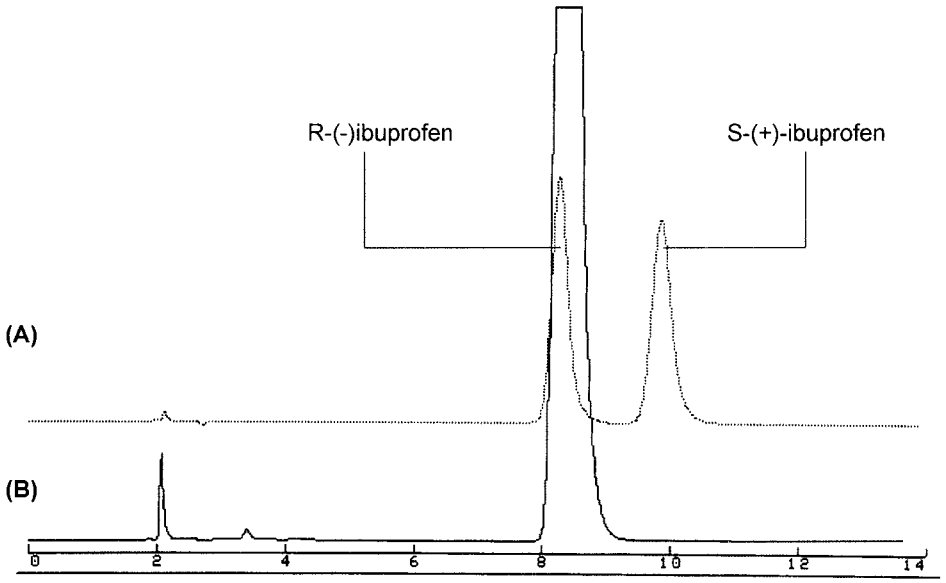


Fig. 3. Chromatogram of (B) after the fractionation from *R*-(-)-ibuprofen-*R*-(+)-α-methylbenzylamine and racemic ibuprofen (A). A: racemic ibuprofen; B: *R*-(-)-ibuprofen. Column :Chiralcel OD-H (5 μm, 150 × 4.6 mm I.D.), mobile phase: n-hexane:-isopropanol-trifluoroacetic acid (100: 1:0.1, v/v/v); UV detector: 225 nm.

TableII. Results of the preparation of *R*-(-)-ibuprofen by diastereomer crystallization using *R*-(+)-α-methylbenzylamine as a chiral solvating agent.

Racemic ibuprofen/ *R*-(+)-α-methylbenzylamine (Molar ratio)	After first crystallization		After 8TH recrystallization*		After fractionation**		Overall yield (%) [2]
	Yield (%) [1]	Purity[3] (%)	Yield (%) [1]	Purity (%)[3]	Yield (%) [2]	Purity[3] (%)	
19.2mmole : 19.2 mmole	56	72	5	99.97	2.4	99.97	2.4

*The yield and purity of diastereomeric salt after 8TH recrytallization

**The yield and purity of diastereomeric salt after liquid-liquid extraction to collect the pure *R*-(-)-ibuprofen.

[1]The yield of diastereomeric salt calculated

= (weight of diastereomeric salt collected/ total weight of initial racemic ibuprofen and *R*-(+)-α-methylbenzylamine)× 100%

[2]The yield of *R*-(-)-ibuprofen enantiomer calculated

= (weight ofrecovered *R*-(-)-ibuprofen/ weight of *R*-(-)-ibuprofen contained in the initial racemic ibuprofen)× 100%

[3]Chromatographic purity = peak area of *R*-(-)-ibuprofen/(peak area of *R*-(-)-ibuprofen + peak area of *S*-(-)-ibuprofen) × 100%

the liquid-liquid extraction. In this described experimental conditions, *R*-(-)-ibuprofen is eluted first with retention time in 8.5 min. (Romas and Lana, 1997). The *R*-(-)-ibuprofen was recovered with the yield of 2.4% calculated versus the amount of the enantiomer containing in the initial racemic ibuprofen.

Table II shows the result of the overall process of the preparation of *R*-(-)-ibuprofen. The chromatographic purity was more than 99.97%.

CONCLUSIONS

It is recognized that *R*-(-)-ibuprofen enantiomer was relatively selectively resolved by *R*-(+)-α-methyl benzylamine as a chiral solvating agent with the produced yield was 2.4% and the high purity without racemization. The method procedure is simple and not required complex apparatus and restrict conditions which is suitable for the academic laboratories as well as small scale research laloratories.

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