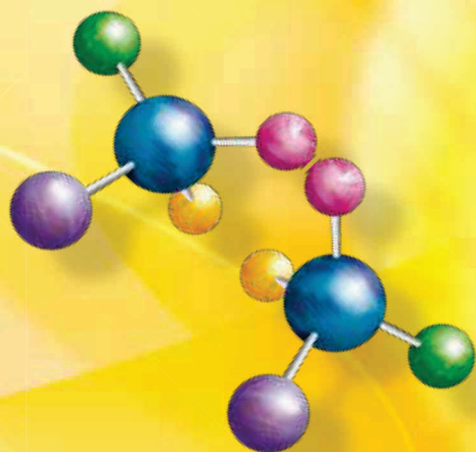


From Analysis to Plant-Scale Purification

Chiral Separation



Chiral Technology offered by YMC

Chromatography using chiral stationary phase (packing material) is an effective and popular method for optical isomer separation. However, cost for purification can be an issue because of expensive packing materials when a large scale purification is required. YMC has developed various products for chromatography for a wide range of scale from microanalysis to plant-scale preparation. Based on our experience and achievement, we reduce the cost of chiral separation by using optimized products or/and high efficiency separation methods and by providing contract purification service.

HPLC and SFC columns/packing materials P.2-7

CHIRAL ART, HPLC columns/packing materials with polysaccharide derivatives chiral selector for chiral separation offer outstanding stability and high resolution by utilizing high-strength super wide pore silica and optimal packing technology. Alcyon SFC CSP, columns for supercritical fluid chromatography, are useful for improving efficiency of analysis and purification by reducing separation time and solvent consumption.



Preparative LC systems and columns P.8

YMC has a great selection of preparative LC systems and columns which are effective for separation of chiral compounds. Our preparative systems with a recycle function improve efficiency of preparative separation and reduce solvent consumption. We provide the best solution from dynamic axial compression columns (DAC), preparative systems, and packing materials depending on the scale from a laboratory-scale to a pilot-scale and to a plant-scale.



Contract purification P.9, 10

YMC offers contract purification service for isolating optical isomers using various chromatography techniques such as HPLC, SFC, and SMB. We provide services using in-house manufactured packing materials and preparative systems for chiral separation to accommodate a wide scale of purification from milligram to kilogram that are compliant with GMP. We propose high efficiency and cost effective methods by selecting the optimal products based on our expertise.



HPLC Columns/Packing Materials

CHIRAL ART

SFC Columns

Alcyon SFC CSP

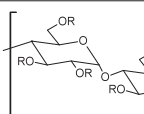
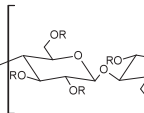
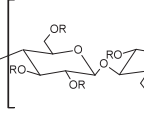
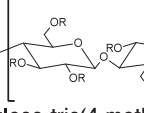
Features

- Columns for chiral separation with polysaccharide derivatives
- Applicable to various chiral compounds
- Applicable from LC/MS microanalysis to large-scale preparative purification
- Enhanced resolution and durability



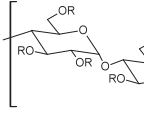
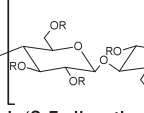
Immobilized type

Columns/packing materials useful for both normal-phase and reversed-phase chromatography

Column/ Packing material	Particle size (μm)	Chiral selector	USP Classification
Amylose-SA	3 5 10 20	 Amylose tris(3,5-dimethylphenylcarbamate)	L99
Cellulose-SB		 Cellulose tris(3,5-dimethylphenylcarbamate)	—
Cellulose-SC		 Cellulose tris(3,5-dichlorophenylcarbamate)	—
Cellulose-SJ		 Cellulose tris(4-methylbenzoate)	—

Coated type

Columns/packing materials with high resolution for various compounds

Column/ Packing material	Particle size (μm)	Chiral selector	USP Classification
Amylose-C Amylose-C Neo	3 5 10 20	 Amylose tris(3,5-dimethylphenylcarbamate)	L51
Cellulose-C		 Cellulose tris(3,5-dimethylphenylcarbamate)	L40

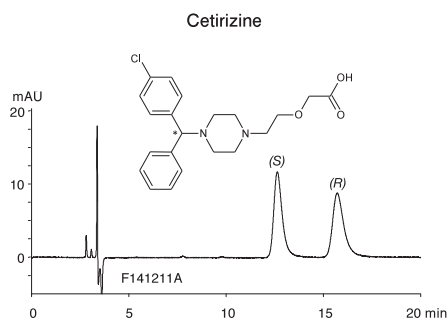
*Please see `Care and Use Instruction` of CHIRAL ART columns on our web site for usable solvents

*Amylose-C Neo columns/packing materials are upgraded products of Amylose-C

HPLC Columns/Packing Materials

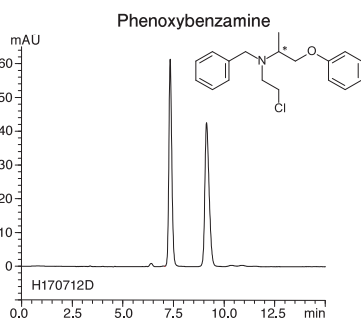
CHIRAL ART

Useful for Separation of a Wide Range of Chiral Compounds

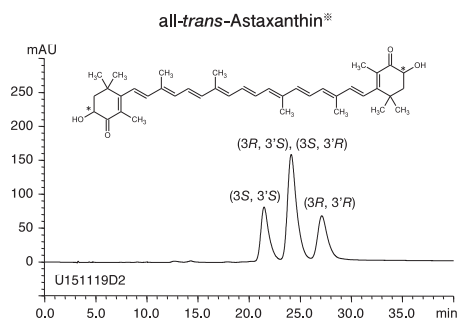


Column : CHIRAL ART Cellulose-C
5 μ m, 250 X 4.6 mm.I.D.
Eluent : *n*-hexane/2-propanol/formic acid/DEA*
(70/30/0.1/0.1)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 230 nm
Injection : 2 μ L (0.2 mg/mL)

*diethylamine



Column : CHIRAL ART Cellulose-SJ
5 μ m, 250 X 4.6 mm.I.D.
Eluent : *n*-hexane/ethanol/diethylamine
(95/5/0.1)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 270 nm
Injection : 5 μ L (1 mg/mL)

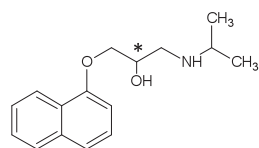


Column : CHIRAL ART Cellulose-SC
5 μ m, 250 X 4.6 mm.I.D.
Eluent : *n*-hexane/THF (80/20)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : VIS at 476 nm
Injection : 5 μ L (0.5 mg/mL)

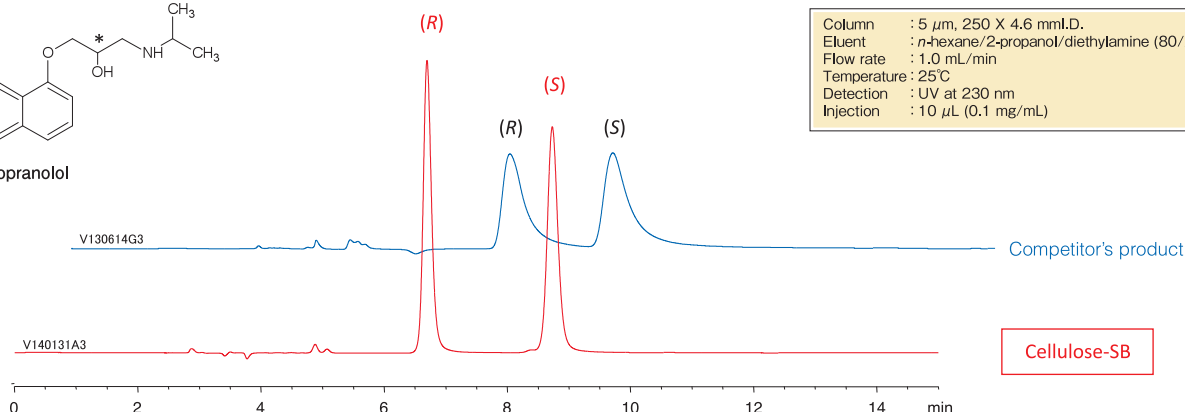
*Courtesy of Fuji Chemical Industry Co., Ltd.

CHIRAL ART are suitable for separation of a wide range of compounds.

Excellent Peak Shape



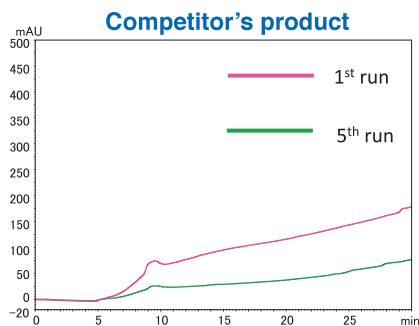
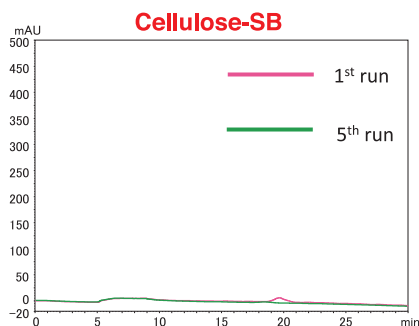
Propranolol



Column : 5 μ m, 250 X 4.6 mm.I.D.
Eluent : *n*-hexane/2-propanol/diethylamine (80/20/0.1)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 230 nm
Injection : 10 μ L (0.1 mg/mL)

CHIRAL ART provide good peak shapes on ionic and metal coordination compounds.

Low Column Bleeding (Immobilized Type)

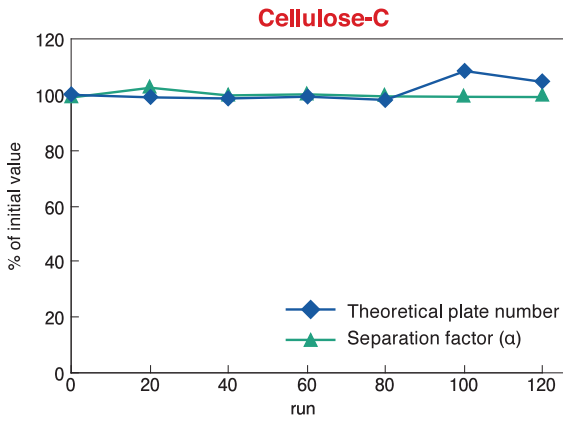


Gradient test

Column : 5 μ m, 250 X 4.6 mm.I.D.
Eluent : A) *n*-hexane
B) ethanol
2-80%B (0-30 min)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 230 nm

CHIRAL ART immobilized type show remarkably reduced background signal under the typical gradient conditions. CHIRAL ART immobilized type offer excellent robustness on gradient analysis and highly sensitive analysis on LC/MS due to the very low ion suppression as well as a stable baseline.

Extended Packing Durability



Sequential gradient test

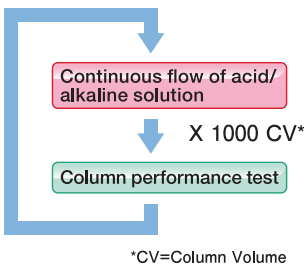
Column : 5 μ m, 250 X 4.6 mmI.D.
 Eluent : A) *n*-hexane, B) ethanol
 0-100%B (0-15 min)
 Flow rate : 3.0 mL/min
 Pressure : 10-30 MPa/run
 Temperature : 37°C

Column performance test

Column : 5 μ m, 250 X 4.6 mmI.D.
 Eluent : *n*-hexane/ethanol (90/10)
 Flow rate : 1.0 mL/min
 Temperature : 37°C
 Detection : UV at 230 nm
 Sample : *trans*-Stilbene oxide

CHIRAL ART have outstanding packed bed stability provided by using high-strength super wide pore silica and innovative packing technology. The column efficiency and selectivity are maintained even after the sequential gradient tests at a high flow rate (three times higher than normal flow rate) and under high pressure (rapid pressure change). CHIRAL ART are useful for shortening analysis time, (re-)equilibration time, or/and column cleaning time by increasing the flow rate. CHIRAL ART are also effective when using highly viscous solvents as a mobile phase on immobilized type columns.

Wide Usable pH Range (Immobilized Type)



Continuous flow of acid/alkaline solution

Column : 5 μ m, 50 X 4.6 mmI.D.
 Eluent : Buffer/methanol (90/10)
 Flow rate : 1.0 mL/min

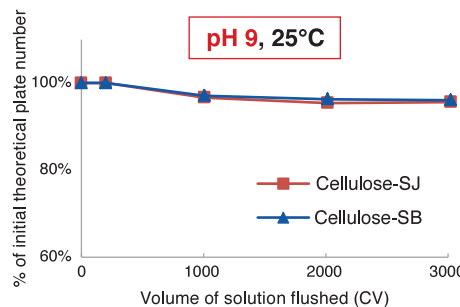
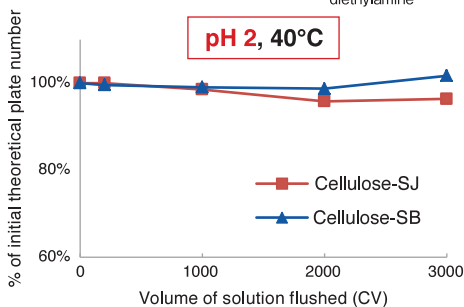
[Acidic condition]
 Buffer : 0.1% H₃PO₄ (pH 2)
 Temperature : 40°C

[Basic condition]
 Buffer : 20 mM NH₄HCO₃-DEA* (pH 9)
 Temperature : 25°C

Column performance test

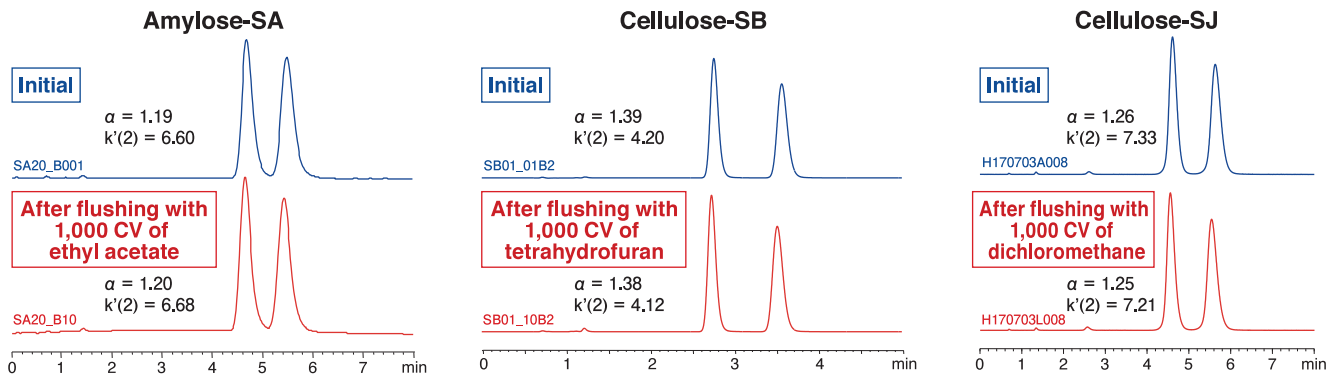
Column : 5 μ m, 50 X 4.6 mmI.D.
 Eluent : methanol/water (70/30) for Cellulose-SJ
 acetonitrile/water (30/70) for Cellulose-SB

Flow rate : 1.0 mL/min
 Temperature : 25°C
 Detection : UV at 254 nm
 Sample : 1-(1-Naphthyl)ethanol for Cellulose-SJ
 Benzoin for Cellulose-SB



CHIRAL ART Immobilized type have excellent chemical stability and can be used across a wide pH range. CHIRAL ART also enable the robust analysis of ionic compounds requiring pH control of mobile phase in reversed-phase conditions.

High Solvent Versatility (Immobilized Type)



Retention rate of initial column performance (After flushing with 1,000 CV of each solvent at 40°C) *CV=Column Volume

	Amylose-SA		Cellulose-SB		Cellulose-SJ	
	α	$k'(2)$	α	$k'(2)$	α	$k'(2)$
Ethyl acetate	100.3%	101.2%	100.0%	99.1%	99.3%	99.0%
Tetrahydrofuran	100.0%	100.0%	99.3%	98.0%	99.2%	99.7%
Dichloromethane	100.3%	100.6%	101.3%	99.6%	99.6%	98.4%

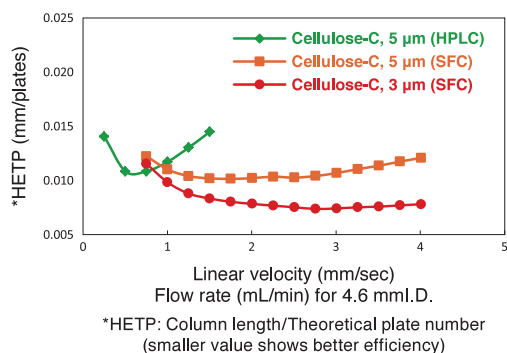
CHIRAL ART immobilized type have high solvent versatility. After flushing with various solvents, the losses of initial column performances were less than 2%.

SFC Columns

Alcyon SFC CSP

Faster Separation Than Conventional HPLC

Correlation between linear velocity and column efficiency



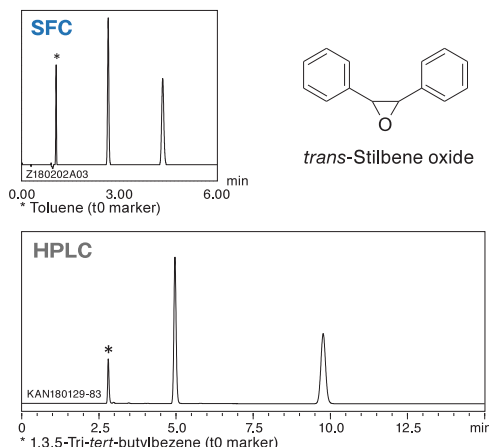
SFC

Column : Alcyon SFC CSP Cellulose-C
3 μm , 150 X 4.6 mm I.D.
5 μm , 250 X 4.6 mm I.D.
Eluent : CO₂/methanol (80/20)
Flow rate : 0.75-4.00 mL/min
Temperature : 35°C
Detection : UV at 220 nm
Back pressure : 13.8 MPa (2000 psi)
Sample : *trans*-Stilbene oxide

HPLC

Column : CHIRAL ART Cellulose-C
5 μm , 250 X 4.6 mm I.D.
Eluent : *n*-hexane/2-propanol (90/10)
Flow rate : 0.25-1.50 mL/min
Temperature : 25°C
Detection : UV at 230 nm
Sample : *trans*-Stilbene oxide

Example of fast separation with high resolution



SFC

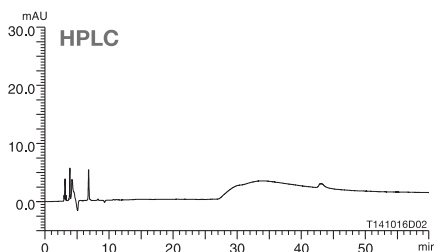
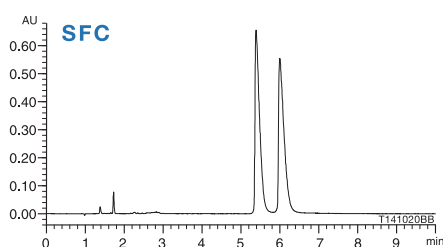
Column : Alcyon SFC CSP Amylose-C Neo
5 μm , 250 X 4.6 mm I.D.
Eluent : CO₂/methanol (80/20)
Flow rate : 3.0 mL/min
Temperature : 40°C
Detection : UV 220 nm
Back pressure : 13.8 MPa (2000 psi)

HPLC

Column : CHIRAL ART Amylose-C Neo
5 μm , 250 X 4.6 mm I.D.
Eluent : *n*-hexane/2-propanol (90/10)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV 230 nm

Faster chiral separation is achieved on supercritical fluid chromatography (SFC) compared to HPLC separation due to lower viscosity and larger diffusion coefficient of supercritical fluid.

Excellent Peak Shapes

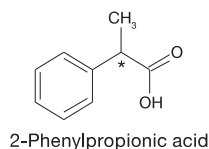


SFC

Column : Alcyon SFC CSP Cellulose-C
5 μm , 250 X 4.6 mm I.D.
Eluent : CO₂/methanol (98/2)
Flow rate : 3.0 mL/min
Temperature : 35°C
Detection : UV at 220 nm
Back pressure : 13.8 MPa (2000 psi)

HPLC

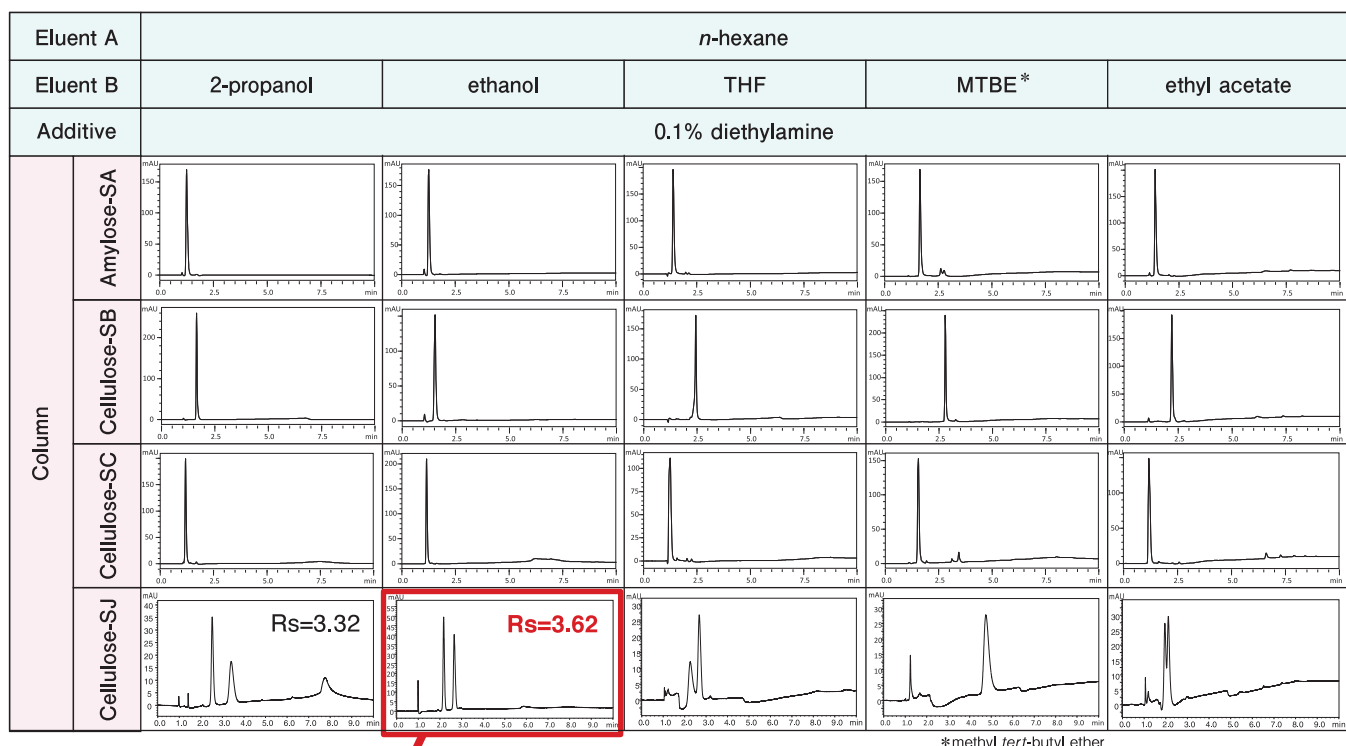
Column : CHIRAL ART Cellulose-C
5 μm , 250 X 4.6 mm I.D.
Eluent : *n*-hexane/2-propanol (99/1)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 220 nm



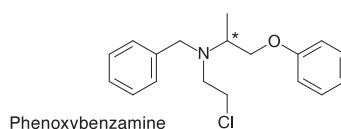
Excellent peak shape of 2-phenylpropionic acid is obtained on SFC chiral separation. In HPLC, a mobile phase without acidic additives gave very broad peak shapes of acidic compounds. On the other hand, both peak shape and resolution are very good under SFC conditions even without adding any acid. It is considered that supercritical carbon dioxide acts as weak acid.

Example of Method Scouting

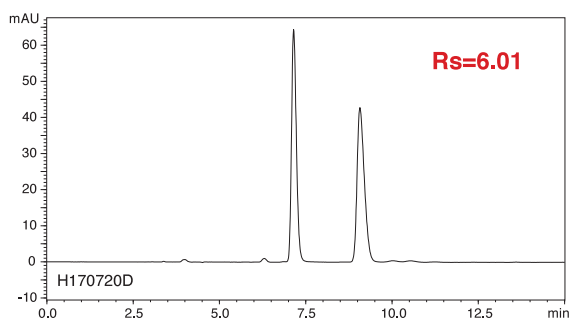
Method scouting is effective for method development of chiral compound separation. Rapid method development can be achieved by studying combination of mobile phases and columns comprehensively, and then optimizing a candidate condition.



Optimization



Column : 3 μ m, 75 X 3.0 mmI.D.
 Flow rate : 0.425 mL/min
 Gradient : 5-45%B (0-6 min), 45%B (6-10 min), 5%B (10-15 min)
 Temperature : 25°C
 Detection : UV at 270 nm
 Injection : 3 μ L (0.5 mg/mL)

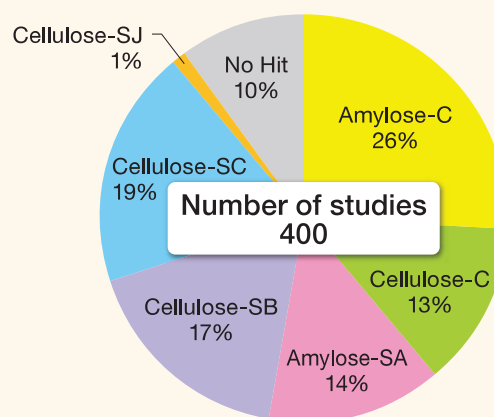


Column : CHIRAL ART Cellulose-SJ
 5 μ m, 250 X 4.6 mmI.D.
 Eluent : n-hexane/ethanol/diethylamine
 (95/5/0.1)
 Flow rate : 1.0 mL/min
 Temperature : 25°C
 Detection : UV at 270 nm
 Injection : 5 μ L (1.0 mg/mL)

Based on the result of method scouting, the elution mode was changed to isocratic and the particle size and the column size were optimized.

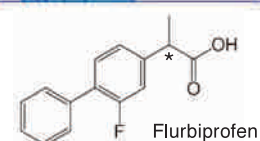
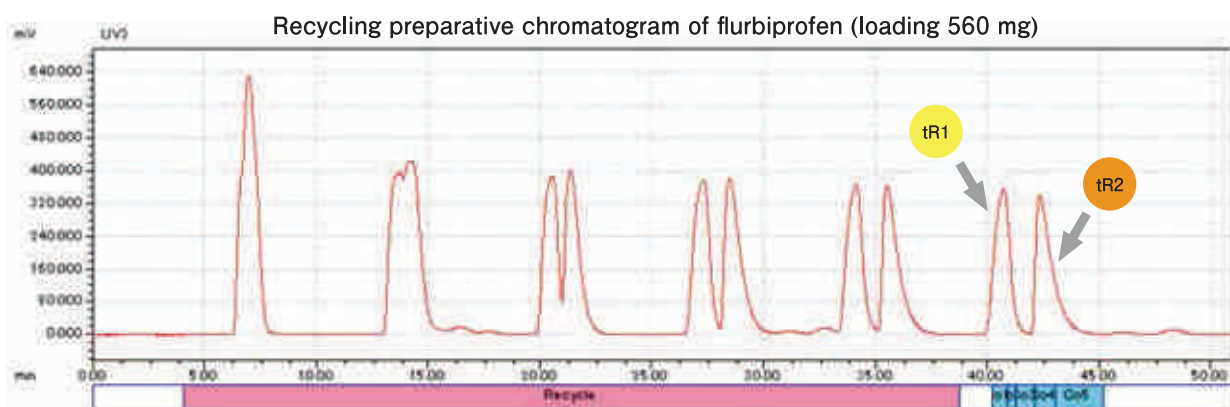
The result of screening using columns for chiral separation

Columns used for the optimized methods



Purification of Chiral Compounds

High Purity Preparative Purification of Optical Isomer Using Recycling HPLC



Productivity : about 3 times higher
Solvent consumption : about 1/10

	Single column		Recycling	
	tR1	tR2	tR1	tR2
Enantiomeric purity (%ee)	>99	>97	>99	99
Yield (%)	87	74	89	90
Productivity (mg product/hr)	122	103	335	336
Solvent consumption (L/g-product)	22	26	2.0	2.0

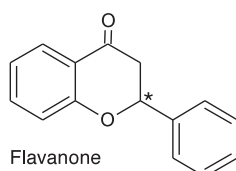
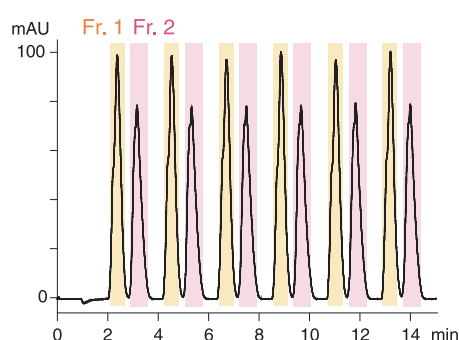
Productivity of single column preparation is estimated based on the stacking injection of the sample every 2.5 minutes

Column	: CHIRAL ART Cellulose-C 5 μ m, 250 X 30 mmI.D.
Eluent	: <i>n</i> -hexane/2-propanol/TFA (95/5/0.1)
Flow rate	: 45 mL/min
Detection	: UV at 280 nm
Injection	: 560 mg

Above is the result of preparative separation of optical isomer, flurbiprofen. Recycling preparation can achieve high purity and high yield on purification of the compound which is difficult to optimize preparative separation conditions using a single column method. Recycling preparation greatly contributes to reduction of solvent consumption and costs on purification as mobile phase is circulated during recycling mode.

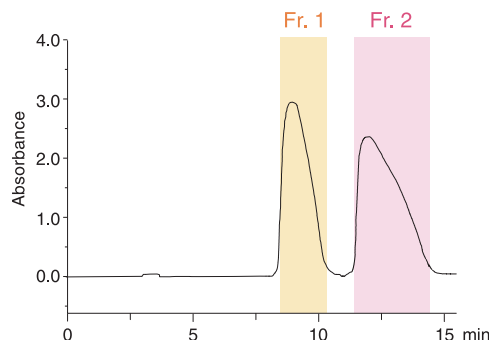
High Efficiency Preparation of Optical Isomer Using SFC

SFC



Alcyon SFC columns show excellent peak shape even on preparative separation at high loading condition. As a result, purification with high purity and high recovery will be achieved. Alcyon SFC columns offer purification with higher efficiency and lower solvent consumption.

HPLC



SFC	
Column	: Alcyon SFC CSP Amylose-C 5 μ m, 250 X 20 mmI.D.
Eluent	: CO ₂ /ethanol (80/20)
Flow rate	: 60 mL/min
Temperature	: 30°C
Detection	: UV at 280 nm
Back pressure	: 15 MPa (2180 psi)
Injection	: 1.5 mL (20 mg/mL)

HPLC	
Column	: CHIRAL ART Amylose-C 5 μ m, 250 X 20 mmI.D.
Eluent	: <i>n</i> -hexane/ethanol (90/10)
Flow rate	: 20 mL/min
Temperature	: ambient
Detection	: UV at 220 nm
Injection	: 3 mL (20 mg/mL)

Column : 250 × 20 mmI.D.	SFC		HPLC	
	Fr. 1	Fr. 2	Fr. 1	Fr. 2
Enantiomeric purity (%ee)	>99.9	99.8	>99.9	99.7
Yield (%)	94.5	95.6	95.7	93.7
Productivity (mg product/hr)	340	344	172	169
	Productivity is doubled			
Volume of purified fraction (L/g-product)	0.39	0.57	1.15	2.88
	Volume of purified fraction is 1/4, easy removal of residual solvent			
Solvent consumption (L/g-product)	ca. 2		ca. 7	
	Solvent consumption is about 1/3			
Cost (Yen/g product) (Mobile phase, waste liquid treatment)	5,000		12,000	
	Cost is half or lower			

Productivity is estimated based on the stacking injection of the sample every 9 minutes for HPLC and every 2.5 minutes for SFC.

Preparative HPLC Systems/Columns

YMC offer a wide range of product lineup such as a system featured a recycling preparation function which is useful for preparative purification of chiral compounds, and large scale preparative systems which can meet GMP requirements. We can propose the optimal systems and columns depending on the purification scale and its purposes.

Versatile Preparative HPLC Systems

LC-Forte/R



Features

- Recycling mode as a standard feature
- Laboratory-scale enantiomeric separation of a few grams of the target in one day
- Low cost preparative separation enabled by reducing solvent consumption
- Featured both HPLC and flash chromatography

Preparative HPLC Systems

K-Prep



Features

- Usable for a wide range of scale from a laboratory-scale to a plant-scale
- Fully-automatic operation by PC
- Maximum flow rate: up to 25 L/min
- GMP compliant and explosion proof type is also available

Dynamic Axial Compression Columns

DAD/DAU



Features

- Cost-effective self-packing dynamic axial compression columns
- Superior column performance, durability, and reproducibility provided by constant pressurization
- Inner diameter: 50 to 1000 mm
- GMP compliant and explosion proof type is also available

From Laboratory to Plant-Scale Separation/Purification Contract Purification



Features

- Purification method development is also available
- Fast service achieved by accumulated experience and knowledge
- Smooth transfer of the purification method and system to clients
- GMP compliant simulated moving bed (SMB) continuous chromatography equipment
- Prompt racemic resolution at a kilogram scale

Advantages of Contract Purification

Separation and purification using chromatography can require advanced technology, time, and cost. YMC provides purification services with our accumulated experience, know-how, and excellent equipment. In addition to ensuring qualification of a target substance according to your request, we will also propose an efficient separation method that may result in a cost reduction.

Customer

- Difficulty in purification method optimization
- Expensive columns and packing materials for purification
- No systems and facilities for preparative purification
- Shortage of time and labor

Outsourcing to YMC

- Accumulated experience and know-how of separation and purification
- Low-cost columns and packing materials manufactured in-house
- Large columns and preparative systems are available



High Purity Compounds

Quick Service

High Reliability

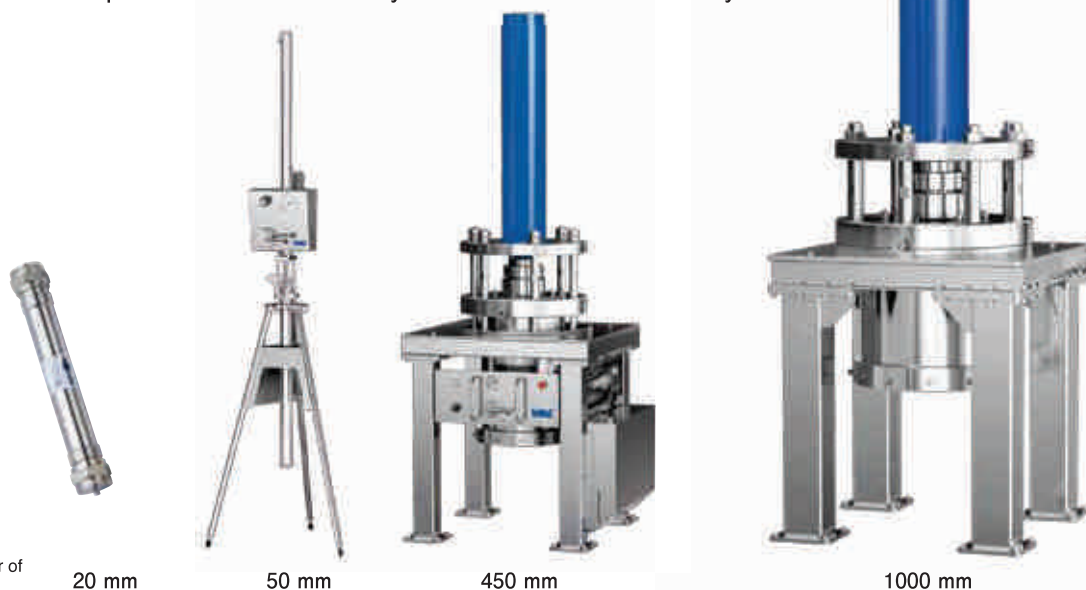
Low-Cost

Applicable Scale

GMP: grams to tons

non-GMP: milligrams to tons

- Seamless scale up according to the development stage.
- Easy transfer of the purification method and system to the customer's facility.



Inner diameter of the column

20 mm

50 mm

450 mm

1000 mm

R&D

Purification purpose

Production

mg

Scale

ton

NEW!

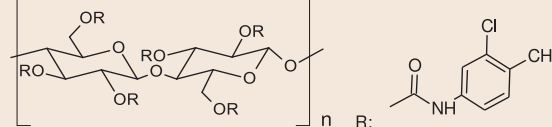
Chiral Separation Column

CHIRAL ART Cellulose-SZ

Features

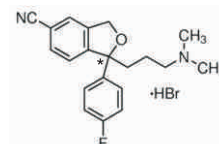
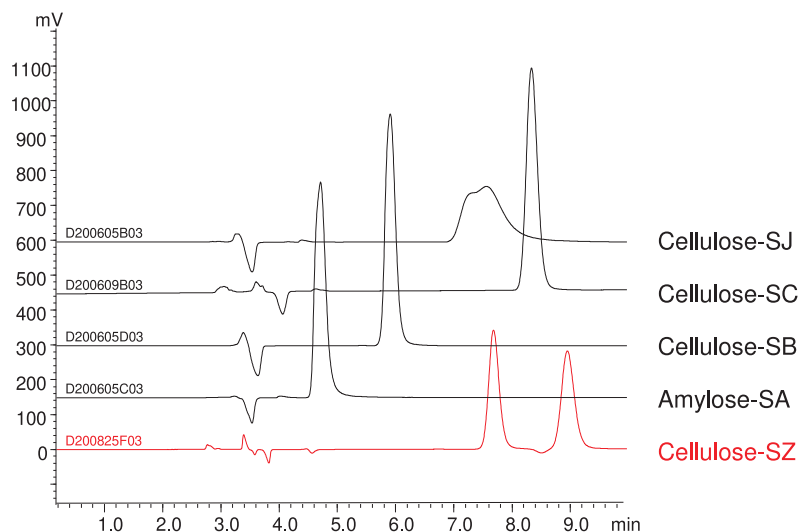
- New chiral selector as an immobilized type
- Wide applications and unique selectivity complementing other chiral selectors
- Compatible with various organic solvents
- High durability over a wide range of pH

Chiral Selector



Cellulose tris(3-chloro-4-methylphenylcarbamate)

Unique Selectivity Complementing Other Chiral Selectors



Citalopram hydrobromide

Column : 5 μ m, 250 X 4.6 mm I.D.
 Eluent : *n*-hexane/2-propanol/diethylamine (70/30/0.1)
 Flow rate : 1.0 mL/min
 Temperature : 25°C
 Detection : UV at 230 nm
 Injection : 5 μ L (1.0 mg/mL)

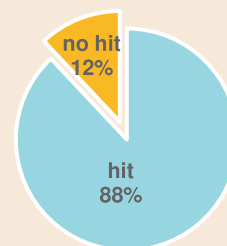
With unique stereoselectivity of CHIRAL ART Cellulose-SZ, it is expected that success rate of chiral separation is improved.

CHIRAL ART Family Products

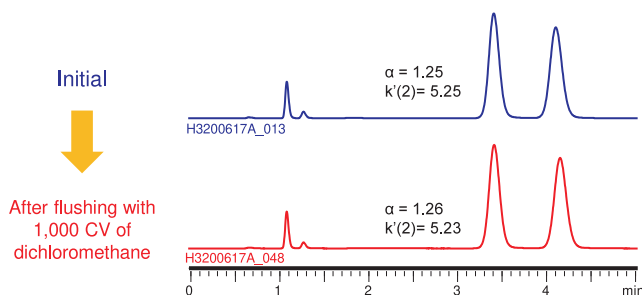
Type	Name	Chiral Selector
Immobilized	CHIRAL ART Amylose-SA	Amylose tris(3,5-dimethylphenylcarbamate)
	CHIRAL ART Cellulose-SB	Cellulose tris(3,5-dimethylphenylcarbamate)
	CHIRAL ART Cellulose-SC	Cellulose tris(3,5-dichlorophenylcarbamate)
	CHIRAL ART Cellulose-SJ	Cellulose tris(4-methylbenzoate)
	NEW CHIRAL ART Cellulose-SZ	Cellulose tris(3-chloro-4-methylphenylcarbamate)
Coated	CHIRAL ART Amylose-C Neo	Amylose tris(3,5-dimethylphenylcarbamate)
	CHIRAL ART Cellulose-C	Cellulose tris(3,5-dimethylphenylcarbamate)

CHIRAL ART Columns Screening Result

Adding Cellulose-SZ will raise success rate!



Wide Range of Usable Solvents



Initial
↓
After flushing with
1,000 CV of
dichloromethane

Column : 5 μ m, 50 X 4.6 mm I.D.
Eluent : *n*-hexane/2-propanol (95/5)
Flow rate : 1.0 mL/min
Temperature : 25°C
Sample : Benzoin

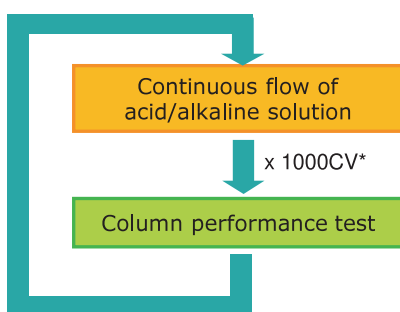
Retention rate of initial column performance
(after flushing with 1,000 CV of each solvent at 40°C)

Solvent	α	$k'(2)$
Ethyl acetate	100.2%	98.6%
Tetrahydrofuran	98.6%	98.4%
Dichloromethane	100.3%	99.5%

*CV=Column Volume

CHIRAL ART Cellulose-SZ has high resistance to various solvents. The change in column performance after exposure to each solvent was less than 2%.

Wide Usable pH Range



*CV=Column Volume

Continuous flow of acid/alkaline solution

Column : 5 μ m, 50 X 4.6 mm I.D.
Eluent : Buffer/methanol (90/10)
Flow rate : 1.0 mL/min

[Acidic condition]

Buffer : 0.1% H₃PO₄ (pH 2)
Temperature : 40°C

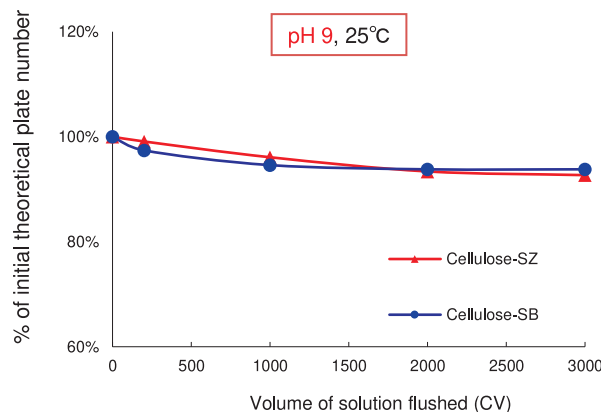
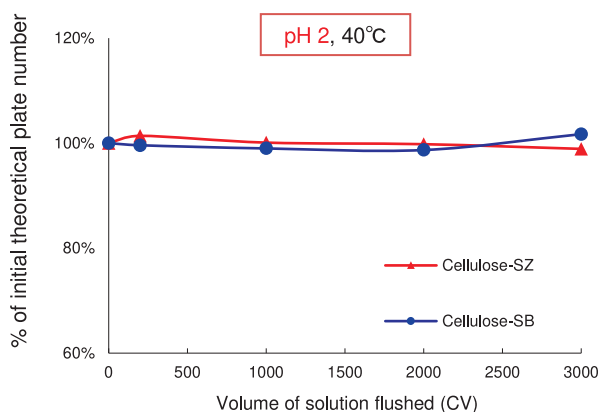
[Basic condition]

Buffer : 20 mM NH₄HCO₃-DEA* (pH 9)
Temperature : 25°C

*DEA=diethylamine

Column performance test

Column : 5 μ m, 50 X 4.6 mm I.D.
Eluent : acetonitrile/water (45/55)
for Cellulose-SZ
acetonitrile/water (30/70)
for Cellulose-SB
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 254 nm
Sample : *trans*-Stilbene oxide
for Cellulose-SZ
Benzoin for Cellulose-SB



CHIRAL ART Cellulose-SZ has excellent chemical durability and can be used across a wide range of pH. Cellulose-SZ offers stable and consistent performance in reversed phase mode.

Worldwide Availability

YMC America, Inc.
www.ymcamerica.com

YMC Europe GmbH
www.ymc.de

YMC Switzerland LLC
www.ymc-schweiz.ch

YMC Shanghai Rep. Office
www.ymcchina.com

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www.ymcindia.com

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