

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

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** 



- 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		Amylose tris(3,5-dimethylphenylcarbamate)	CH₃	L99
Cellulose-SB	3 5	Cellulose tris(3,5-dimethylphenylcarbamate)	NH CH <sub>3</sub> R: 3,5-Dimethylphenylcarbamate	_
Cellulose-SC	10 20	Cellulose tris(3,5-dichlorophenylcarbamate)	R: 3,5-Dichlorophenylcarbamate	_
Cellulose-SJ		Cellulose tris(4-methylbenzoate)	R: 4-Methylbenzoate	_

#### **Coated type**

## Columns/packing materials with high resolution for various compounds

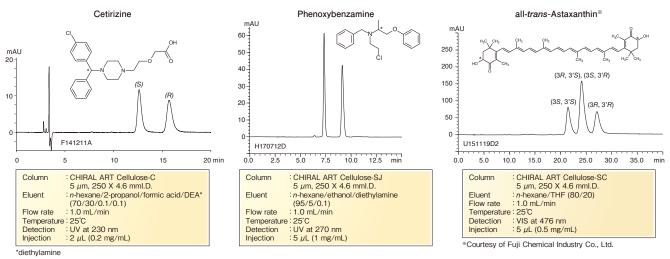
Column/ Packing material	Particle size (µm)	Chiral selector	USP Classification	
Amylose-C Amylose-C Neo	3 5	Amylose tris(3,5-dimethylphenylcarbamate)	CH <sub>3</sub>	L51
Cellulose-C	10 20	Cellulose tris(3,5-dimethylphenylcarbamate)	NH CH <sub>3</sub> R: 3,5-Dimethylphenylcarbamate	L40

<sup>\*</sup>Please see `Care and Use Instruction` of CHIRAL ART columns on our web site for usable solvents

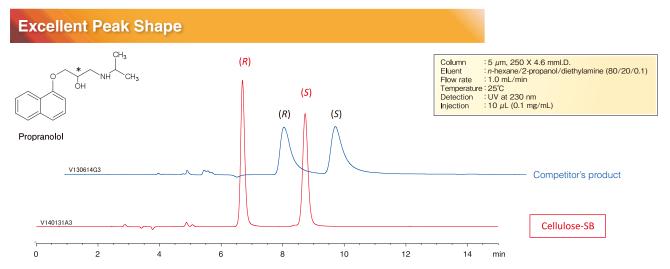
<sup>\*</sup>Amylose-C Neo columns/packing materials are upgraded products of Amylose-C

# HPLC Columns/Packing Materials CHIRAL ART

## **Useful for Separation of a Wide Range of Chiral Compounds**

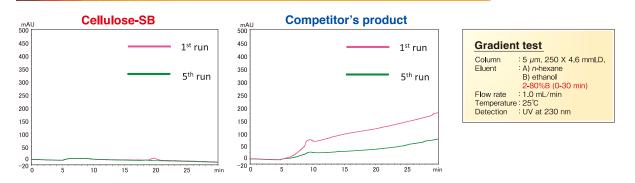


CHIRAL ART are suitable for separation of a wide range of compounds.



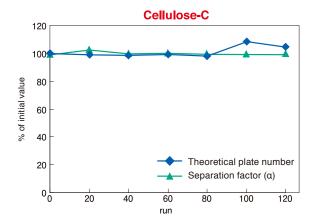
CHIRAL ART provide good peak shapes on ionic and metal coordination compounds.

## Low Column Bleeding (Immobilized Type)



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

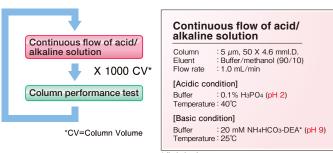
: 5 μm, 250 X 4.6 mml.D. Column 6 A) *n*-hexane, B) ethanol 0-100%B (0-15 min) Temperature: 37°C

## Column performance test

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

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 viscose solvents as a mobile phase on immobilized type columns.

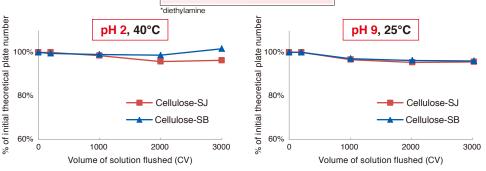
## Wide Usable pH Range (Immobilized Type)



## Column performance test

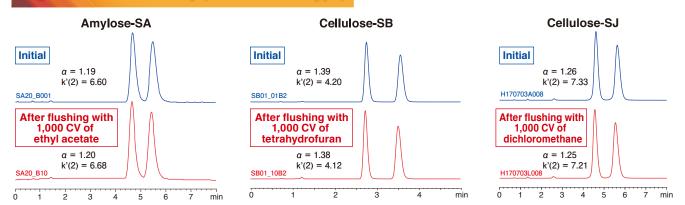
5 μm. 50 X 4.6 mml.D. Column methanol/water (70/30) for Cellulose-SJ acetonitrile/water (30/70) for Cellulose-SB Flow rate 1.0 mL/min Temperature : 25°C Detection : UV a

UV at 254 nm 1-(1-Naphthyl)ethanol for Cellulose-SJ Benzoin for Cellulose-SB Sample



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)

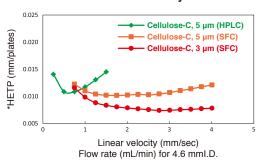
Retention rate of initial column performance (After flushing with 1,000 CV of each solvent at 40°C) *CV=Column Volume										
	Amylose-SA		Cellulose-SB		Cellulose-SJ					
	а	k'(2)	а	k'(2)	α	k'(2)				
Ethyl acetate	100.3%	101.2%	100.0%	99.1%	99.3%	99.0%				
Tetrahydrofuran	100.0%	100.0%	99.3%	98.0%	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**

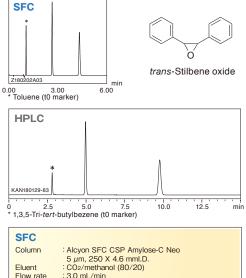
## Correlation between linear velocity and column efficiency



\*HETP: Column length/Theoretical plate number (smaller value shows better efficiency)

Temperature: 25°C
Detection: UV at 230 nm
Sample: trans-Stilbene oxide

## Example of fast separation with high resolution

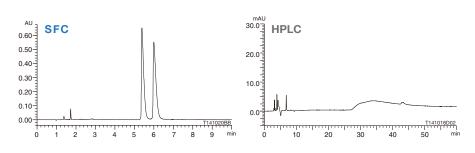


HPLC
Column
: CHIRAL ART Amylose-C Neo
5 µm, 250 X 4.6 mml.D.
Eluent
: n-hexane/2-propanol (90/10)
Flow rate
: 1.0 mL/min

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 mml.D.

Eluent : C02/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 mml.D.

Eluent : η-hexane/2-propanol (99/1)
Flow rate : 1.0 mL/min
Temperature : 25°C
Detection : UV at 220 nm

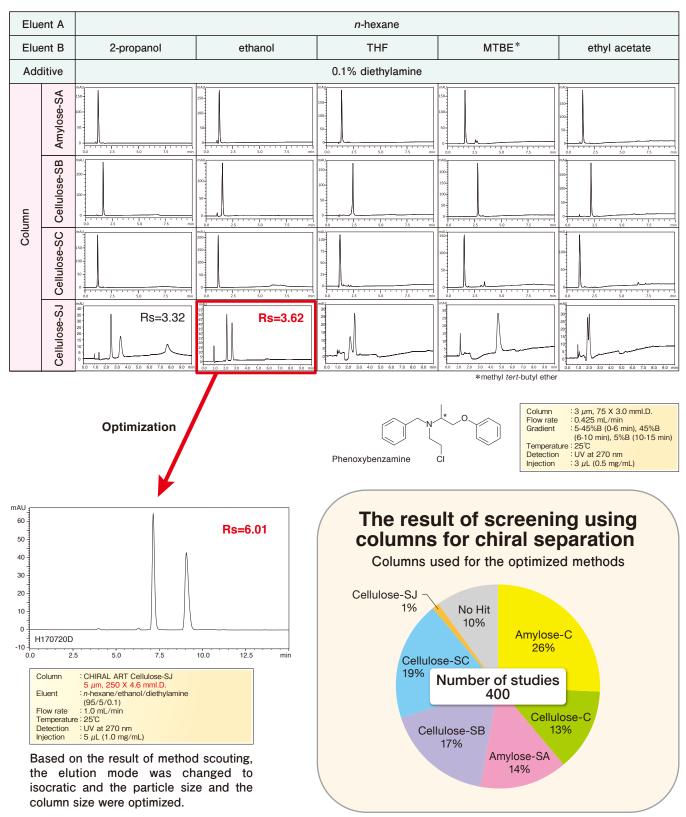
2-Phenylpropionic acid

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.

Excellent peak shape of 2-phenylpropionic acid is obtained on SFC chiral separation. In HPLC,

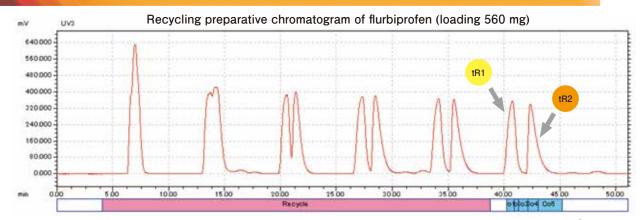
# **Example of Method Scouting**

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.



# **Purification of Chiral Compounds**

## High Purity Preparative Purification of Optical Isomer Using Recycling HPLC



	Single column		Recycling		ОН
	tR1	tR2	tR1	tR2	
Enantiomeric purity (%ee)	>99	>97	>99	99	F Flurbiprofen
Yield (%)	87	74	89	90	
Productivity (mg product/hr)	122	103	335	336	Productivity : about 3 times highe
Solvent consumption (L/g-product)	22	26	2.0	2.0	Solvent consumption : about 1/10

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

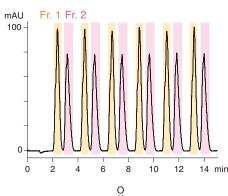
CHIRAL ART Cellulose-C 5  $\mu$ m, 250 X 30 mml.D. Eluent n-hexane/2-propanol/TFA (95/5/0.1) 45 mL/min

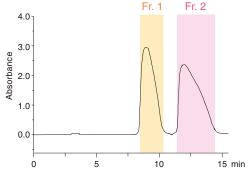
Detection UV at 280 nm

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.

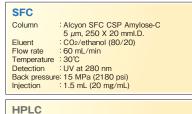
## High Efficiency Preparation of Optical Isomer Using SFC







(Mobile phase, waste liquid treatment)



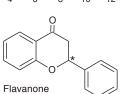
CHIRAL ART Amylose-C

5 μm, 250 X 20 mml.D. : n-hexane/ethanol (90/10)

20 mL/min ambient UV at 220 nm

Cost is half or lower

3 mL (20 mg/mL)



Flavanone

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.

O-lumin - 050 × 00 mml D	SF	-C	HPLC			
Column: $250 \times 20$ mml.D.	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		
Book at the Constant dead (b)	340	344	172	169		
Productivity (mg product/hr)	Productivity is doubled					
Volume of purified fraction	0.39	0.57	1.15	2.88		
(L/g-product)	Volume of purified fraction is 1/4, easy removal of residual solvent					
Solvent consumption	ca. 2 ca. 7					
(L/g-product)	Solv	ent consump	otion is about 1/3			
Cost (Yen/g product)	5,0	000	12,000			

Column

Flow rate Temperature

Detection

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**



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.

- 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** 

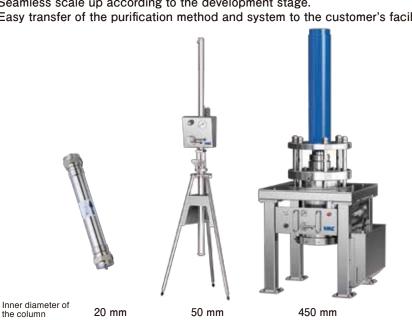
## Applicable Scale

GMP: grams to tons

non-GMP: milligrams to tons

I Seamless scale up according to the development stage.

Easy transfer of the purification method and system to the customer's facility.







## Flow of Purification Service

We respond flexibly to your need including confidentiality, GMP requirements, and budget. Please feel free to ask for consultation about purification of any scale from small production to mass production.

**Purification Request** 

- Consultation
- Signing a non-disclosure agreement
- Preliminary study of the sample provided (about a week)

**Preliminary Study Report** 

 Proposal and confirmation of the optimal column and the most efficient preparative separation method

Submission of a quote

 Submission of a quote according to the result of the preliminary study

**Purification** 

Preparative purification with the optimal method

charged depending on the contents of the study.

Purity test

**Delivery of Purified Product** and Submission of Report

\*Loading test is required for a more precise quote of a large-scale purification.
\*Preliminary study is basically free of charge, but some cases may be partly

## Facilities and Quality Assurance System



**API Purification Plant** 

Our GMP compliant API Purification Plant is equipped with large scale preparative HPLC systems and dynamic axial compression columns as well as a lyophilizer and various analytical instruments. Low-cost purification can be achieved by utilizing in-house products such as preparative chromatography systems, packing materials, and columns along with our experience and know-how in chromatography purification. We also established GMP quality management system for appropriate manufacturing control and quality control. Our quality assurance and quality control units are independent from our manufacturing control units, ensuring product quality and maintaining the quality system.



SMB preparative system



Dynamic axial compression HPLC column



Preparative HPLC system

## **Ordering Information**

## HPLC columns CHIRAL ART

#### Columns

Particle	Column size				Product number			
size	inner diameter x length		Immobili	zed type			Coated type	
(μm)	(mm)	Amylose-SA	Cellulose-SB	Cellulose-SC	Cellulose-SJ	Amylose-C	Amylose-C Neo	Cellulose-C
3	2.0 X 75	KSA99S03-L502WT	KSB99S03-L502WT	KSC99S03-L502WT	KSJ99S03-L502WT	KAN99S03-L502WT	KBN99S03-L502WT	KCN99S03-L502WT
	2.0 X 100	KSA99S03-1002WT	KSB99S03-1002WT	KSC99S03-1002WT	KSJ99S03-1002WT	KAN99S03-1002WT	KBN99S03-1002WT	KCN99S03-1002WT
	2.0 X 150	KSA99S03-1502WT	KSB99S03-1502WT	KSC99S03-1502WT	KSJ99S03-1502WT	KAN99S03-1502WT	KBN99S03-1502WT	KCN99S03-1502WT
	2.0 X 250	KSA99S03-2502WT	KSB99S03-2502WT	KSC99S03-2502WT	KSJ99S03-2502WT	KAN99S03-2502WT	KBN99S03-2502WT	KCN99S03-2502WT
	3.0 X 50	KSA99S03-0503WT	KSB99S03-0503WT	KSC99S03-0503WT	KSJ99S03-0503WT	KAN99S03-0503WT	KBN99S03-0503WT	KCN99S03-0503WT
	3.0 X 75	KSA99S03-L503WT	KSB99S03-L503WT	KSC99S03-L503WT	KSJ99S03-L503WT	KAN99S03-L503WT	KBN99S03-L503WT	KCN99S03-L503WT
	3.0 X 100	KSA99S03-1003WT	KSB99S03-1003WT	KSC99S03-1003WT	KSJ99S03-1003WT	KAN99S03-1003WT	KBN99S03-1003WT	KCN99S03-1003WT
	3.0 X 150	KSA99S03-1503WT	KSB99S03-1503WT	KSC99S03-1503WT	KSJ99S03-1503WT	KAN99S03-1503WT	KBN99S03-1503WT	KCN99S03-1503WT
	3.0 X 250	KSA99S03-2503WT	KSB99S03-2503WT	KSC99S03-2503WT	KSJ99S03-2503WT	KAN99S03-2503WT	KBN99S03-2503WT	KCN99S03-2503WT
	4.6 X 50	KSA99S03-0546WT	KSB99S03-0546WT	KSC99S03-0546WT	KSJ99S03-0546WT	KAN99S03-0546WT	KBN99S03-0546WT	KCN99S03-0546WT
	4.6 X 75	KSA99S03-L546WT	KSB99S03-L546WT	KSC99S03-L546WT	KSJ99S03-L546WT	KAN99S03-L546WT	KBN99S03-L546WT	KCN99S03-L546WT
	4.6 X 100	KSA99S03-1046WT	KSB99S03-1046WT	KSC99S03-1046WT	KSJ99S03-1046WT	KAN99S03-1046WT	KBN99S03-1046WT	KCN99S03-1046WT
	4.6 X 150	KSA99S03-1546WT	KSB99S03-1546WT	KSC99S03-1546WT	KSJ99S03-1546WT	KAN99S03-1546WT	KBN99S03-1546WT	KCN99S03-1546WT
	4.6 X 250	KSA99S03-2546WT	KSB99S03-2546WT	KSC99S03-2546WT	KSJ99S03-2546WT	KAN99S03-2546WT	KBN99S03-2546WT	KCN99S03-2546WT
5	4.6 X 150	KSA99S05-1546WT	KSB99S05-1546WT	KSC99S05-1546WT	KSJ99S05-1546WT	KAN99S05-1546WT	KBN99S05-1546WT	KCN99S05-1546WT
	4.6 X 250	KSA99S05-2546WT	KSB99S05-2546WT	KSC99S05-2546WT	KSJ99S05-2546WT	KAN99S05-2546WT	KBN99S05-2546WT	KCN99S05-2546WT
	10 X 250	KSA99S05-2510WT	KSB99S05-2510WT	KSC99S05-2510WT	KSJ99S05-2510WT	KAN99S05-2510WT	KBN99S05-2510WT	KCN99S05-2510WT
	20 X 250	KSA99S05-2520WX	KSB99S05-2520WX	KSC99S05-2520WX	KSJ99S05-2520WX	KAN99S05-2520WX	KBN99S05-2520WX	KCN99S05-2520WX
	30 X 250	KSA99S05-2530WX	KSB99S05-2530WX	KSC99S05-2530WX	KSJ99S05-2530WX	KAN99S05-2530WX	KBN99S05-2530WX	KCN99S05-2530WX

## Guard cartridge columns (inner diameter 4.0 mm or smaller: 5/pack, 10/20/30 mm: 2/pack)

Particle	Column size	Product number									
size	inner diameter x length		Immobili	zed type			Coated type				
(μm)	(mm)	Amylose-SA	Cellulose-SB	Cellulose-SC	Cellulose-SJ	Amylose-C	Amylose-C Neo	Cellulose-C			
3	2.1 X 10	KSA99S03-01Q1GC	KSB99S03-01Q1GC	KSC99S03-01Q1GC	KSJ99S03-01Q1GC	KAN99S03-01Q1GC	KBN99S03-01Q1GC	KCN99S03-01Q1GC			
	3.0 X 10	KSA99S03-0103GC	KSB99S03-0103GC	KSC99S03-0103GC	KSJ99S03-0103GC	KAN99S03-0103GC	KBN99S03-0103GC	KCN99S03-0103GC			
	4.0 X 10	KSA99S03-0104GC	KSB99S03-0104GC	KSC99S03-0104GC	KSJ99S03-0104GC	KAN99S03-0104GC	KBN99S03-0104GC	KCN99S03-0104GC			
5	4.0 X 10	KSA99S05-0104GC	KSB99S05-0104GC	KSC99S05-0104GC	KSJ99S05-0104GC	KAN99S05-0104GC	KBN99S05-0104GC	KCN99S05-0104GC			
	10 X 10	KSA99S05-0110CC	KSB99S05-0110CC	KSC99S05-0110CC	KSJ99S05-0110CC	KAN99S05-0110CC	KBN99S05-0110CC	KCN99S05-0110CC			
	20 X 10	KSA99S05-0120CC	KSB99S05-0120CC	KSC99S05-0120CC	KSJ99S05-0120CC	KAN99S05-0120CC	KBN99S05-0120CC	KCN99S05-0120CC			
	30 X 10	KSA99S05-0130CC	KSB99S05-0130CC	KSC99S05-0130CC	KSJ99S05-0130CC	KAN99S05-0130CC	KBN99S05-0130CC	KCN99S05-0130CC			

A cartridge holder will need to be purchased separately before using this product for the first time.

## SFC columns Alcyon SFC CSP Columns

Particle	Column size				Product number					
size	inner diameter x length		Immobili	zed type	d type		Coated type			
(μm)	(mm)	Amylose-SA	Cellulose-SB	Cellulose-SC	Cellulose-SJ	Amylose-C	Amylose-C Neo	Cellulose-C		
3	2.1 X 150	KSA99S03-15Q1WTS	KSB99S03-15Q1WTS	KSC99S03-15Q1WTS	KSJ99S03-15Q1WTS	KAN99S03-15Q1WTS	KBN99S03-15Q1WTS	KCN99S03-15Q1WTS		
	3.0 X 50	KSA99S03-0503WTS	KSB99S03-0503WTS	KSC99S03-0503WTS	KSJ99S03-0503WTS	KAN99S03-0503WTS	KBN99S03-0503WTS	KCN99S03-0503WTS		
	3.0 X 100	KSA99S03-1003WTS	KSB99S03-1003WTS	KSC99S03-1003WTS	KSJ99S03-1003WTS	KAN99S03-1003WTS	KBN99S03-1003WTS	KCN99S03-1003WTS		
	3.0 X 150	KSA99S03-1503WTS	KSB99S03-1503WTS	KSC99S03-1503WTS	KSJ99S03-1503WTS	KAN99S03-1503WTS	KBN99S03-1503WTS	KCN99S03-1503WTS		
	4.6 X 150	KSA99S03-1546WTS	KSB99S03-1546WTS	KSC99S03-1546WTS	KSJ99S03-1546WTS	KAN99S03-1546WTS	KBN99S03-1546WTS	KCN99S03-1546WTS		
	4.6 X 250	KSA99S03-2546WTS	KSB99S03-2546WTS	KSC99S03-2546WTS	KSJ99S03-2546WTS	KAN99S03-2546WTS	KBN99S03-2546WTS	KCN99S03-2546WTS		
5	2.1 X 150	KSA99S05-15Q1WTS	KSB99S05-15Q1WTS	KSC99S05-15Q1WTS	KSJ99S05-15Q1WTS	KAN99S05-15Q1WTS	KBN99S05-15Q1WTS	KCN99S05-15Q1WTS		
	4.6 X 150	KSA99S05-1546WTS	KSB99S05-1546WTS	KSC99S05-1546WTS	KSJ99S05-1546WTS	KAN99S05-1546WTS	KBN99S05-1546WTS	KCN99S05-1546WTS		
	4.6 X 250	KSA99S05-2546WTS	KSB99S05-2546WTS	KSC99S05-2546WTS	KSJ99S05-2546WTS	KAN99S05-2546WTS	KBN99S05-2546WTS	KCN99S05-2546WTS		
	10 X 250	KSA99S05-2510WTS	KSB99S05-2510WTS	KSC99S05-2510WTS	KSJ99S05-2510WTS	KAN99S05-2510WTS	KBN99S05-2510WTS	KCN99S05-2510WTS		
	20 X 250	KSA99S05-2520WTS	KSB99S05-2520WTS	KSC99S05-2520WTS	KSJ99S05-2520WTS	KAN99S05-2520WTS	KBN99S05-2520WTS	KCN99S05-2520WTS		

Before use (installation, operation, maintenance, or check-up) of our products, please read this instruction carefully and follow the safety rules and precautions in the manual.

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