

Introduction

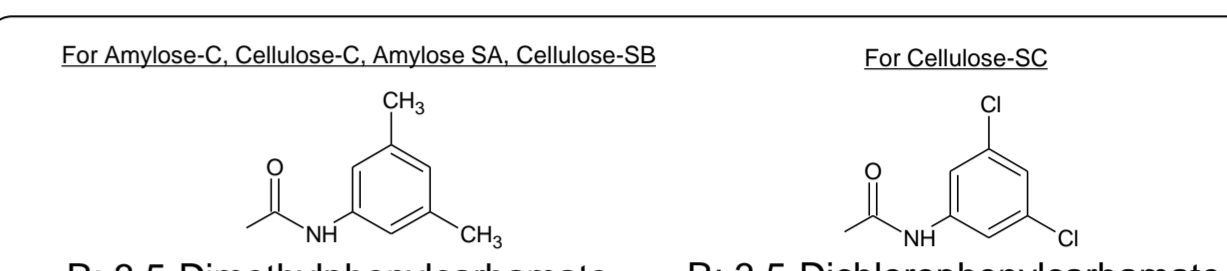
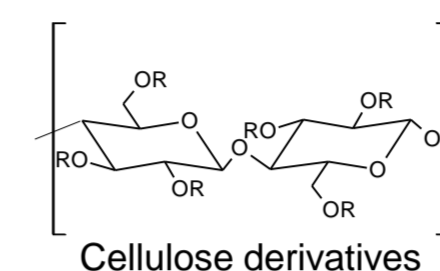
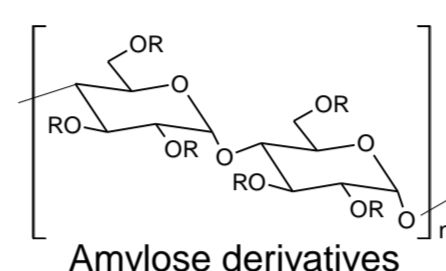
The role of chiral separation is becoming more and more important especially in pharmaceutical industry. And the demand for isolating enantiomers with high optical purity is increasing. To provide required amount of enantiomers rapidly and ensure high optical purity of them, novel chiral stationary phases (CSPs) and rational scale-up process is very important.

Recently we developed 5 kinds of CSPs consisting of polysaccharides derivatives coated/immobilized on 3, 5, 10, 20 μm silica particle sizes. They show excellent chiral separations for a wide range of racemic compounds such as neutral, acidic, and basic compounds. Furthermore, as they are designed to have the same separation characteristics across particles, reliable scale-up could be possible.

In this poster, we try to clarify advantages of our CSPs to make use for optical resolution process compared with competitor's. And for a laboratory scale preparation process, we study robustness and efficiency of the scale-up by using a standard sample.

Specification of novel stationary phases consisting of polysaccharide derivatives

Product name	Base material	Particle size(μm)	Chiral selector	Type	Usable pH range	Pressure limit
CHIRAL ART Amylose-C	Porous silica	3	Amylose tris (3,5-dimethylphenylcarbamate)	Coated	—	4350 psi (30 MPa)
CHIRAL ART Cellulose-C		5	Cellulose tris (3,5-dimethylphenylcarbamate)			
		10				
CHIRAL ART Amylose-SA	Porous silica	3	Amylose tris (3,5-dimethylphenylcarbamate)	Immobilized	2.0 – 9.0	4350 psi (30 MPa)
CHIRAL ART Cellulose-SB		5	Cellulose tris (3,5-dimethylphenylcarbamate)			
CHIRAL ART Cellulose-SC		10	Cellulose tris (3,5-dichlorophenylcarbamate)			



- Excellent mechanical stability based on novel high strength super-wide pore silica gel
- Available in 3, 5 μm packed columns for analytical to preparative separation and 10, 20 μm packed columns and bulk materials for scale-up
- Effective for cost reduction of analytical to preparative chiral separation

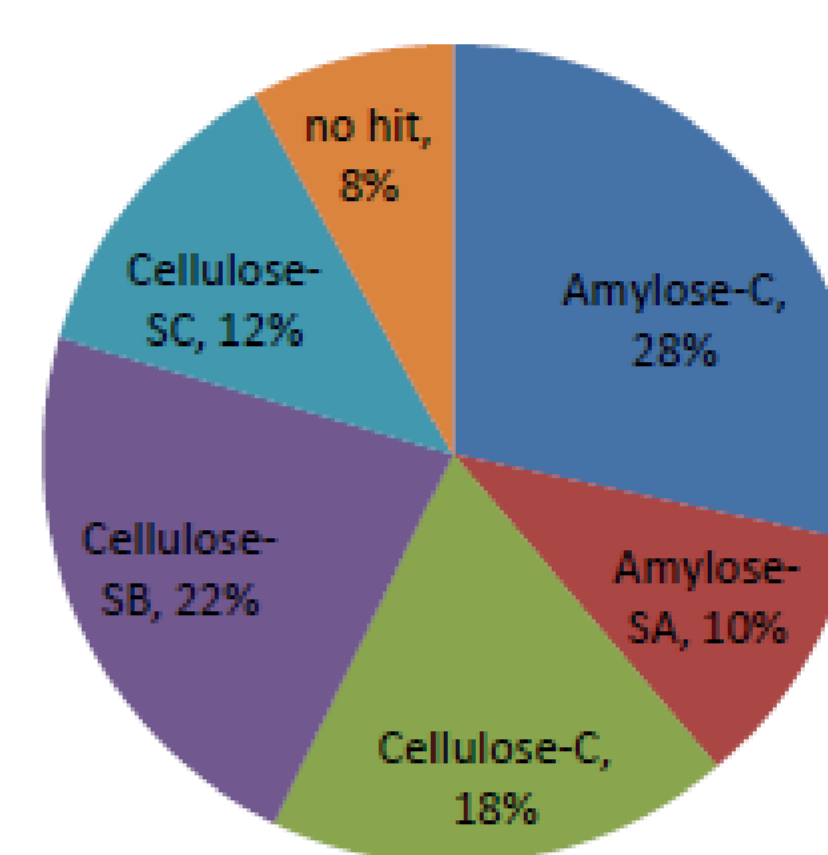
Comparison of chiral separation selectivity of a wide variety of racemic compounds

Coated type Separation factor (α)			
Compounds / Mobile phase	Amylose-C	Competitor's product	Competitor/ YMC
Benzoin Hex/IPA (90/10)	1.32	1.31	101%
N-CBZ-DL-Alanine Hex/IPA/TFA (80/20/0.1)	2.00	2.20	91%
Verapamil Hex/IPA/DEA (90/10/0.1)	1.30	1.30	100%

Immobilized type Separation factor (α)			
Compounds / Mobile phase	Amylose-SA	Competitor's product	Competitor/ YMC
Flavone Hex/EtOH (90/10)	1.72	1.72	100%
Flurbiprofen Hex/EtOH/TFA (95/5/0.1)	1.37	1.40	98%
Carbinoxamine Hex/IPA/DEA (90/10/0.1)	1.36	1.28	106%

Immobilized type Separation factor (α)			
Compounds / Mobile phase	Cellulose-SB	Competitor's product	Competitor/ YMC
trans-Stilbene oxide Hex/IPA (90/10)	2.30	2.20	105%
Ibuprofen Hex/IPA/TFA (99/1/0.1)	1.30	1.20	108%
Propranolol Hex/IPA/DEA (80/20/0.1)	2.00	1.80	111%

Analysis of the hit ratio of chiral selectors for various compounds



- Available 5 kinds of CSPs can cover >90% of chiral separation of racemates
- Hit ratio varied from 10% to 28% among 5 selectors

- Hit criteria: $R_s > 1.5$
- Hit database: Requested 125 samples in contract service

Immobilized type Separation factor (α)			
Compounds / Mobile phase	Amylose-SA	Competitor's product	Competitor/ YMC
2,2,2-Trifluoro-1-(9-anthryl)ethanol Hex/IPA (90/10)	2.87	2.48	116%
Ibuprofen Hex/IPA/TFA (99/1/0.1)	1.12	1.14	98%
Propranolol Hex/IPA/DEA (80/20/0.1)	1.53	1.40	109%

Immobilized type Separation factor (α)			
Compounds / Mobile phase	Cellulose-SC	Competitor's product	Competitor/ YMC
2-Phenylcyclohexanone Hex/IPA (90/10)	1.28	1.27	101%
Warfarin Hex/IPA/TFA (80/20/0.1)	1.59	1.57	101%
Tropicamide Hex/EtOH/DEA (55/45/0.1)	1.33	1.27	105%

- 5 kinds of CSPs showed identical separation factor (α) with competitor's (see representative chromatograms)
- Each selector showed good separation for a wide range of compounds such as neutral, acidic, and basic compounds

Comparison of loading capacities of Carbinoxamine on Amylose-SA, and Propranolol on Cellulose-SB

CHIRAL ART Amylose-SA			
Compounds / Mobile phase	Amylose-SA	Competitor's product	Competitor/ YMC
Carbinoxamine Hex/IPA/DEA (90/10/0.1)	2.9	1.5	1.9

CHIRAL ART Cellulose-SB			
Compounds / Mobile phase	Cellulose-SB	Competitor's product	Competitor/ YMC
Propranolol Hex/IPA/DEA (80/20/0.1)	3.1	0.3	10.3

* Calculated on repeated injection every 6 minutes (Amylose-SA) and every 8 minutes (competitor's product)
 Column: 5 μm, 250 X 4.6 mm i.d.
 Eluent: n-hexane/2-propanol/DEA (90/10/0.1)
 Flow rate: 0.5 ml/min
 Detection: UV at 230 nm
 Temperature: 25°C for analytical scale, ambient for preparative scale

* Calculated on repeated injection every 15 minutes (Cellulose-SB) and every 10 minutes (competitor's product)
 Column: 5 μm, 250 X 4.6 mm i.d.
 Eluent: n-hexane/2-propanol/DEA (80/20/0.1)
 Flow rate: 0.5 ml/min
 Detection: UV at 230 nm
 Temperature: 25°C for analytical scale, ambient for preparative scale

Scale-up study of purification of Propranolol on Cellulose-SB

Scale	Column	Flow rate	Linear velocity	Loading	Enantiomeric excess	Recovery
Analytical	5 μm, 250 X 4.6 mm i.d.	0.5 ml/min	0.5 mm/s	1.6 mg	>99.9% ee	99%
Semi-preparative	5 μm, 250 X 20 mm i.d.	9.5 ml/min	0.5 mm/s	30 mg	>99.9% ee	99%
Preparative	10 μm, 250 X 50 mm i.d.	59 ml/min	0.5 mm/s	188 mg	>99.9% ee	97%

Chiral stationary phase: Cellulose-SB
 Eluent: n-hexane/2-propanol/DEA (80/20/0.1)
 Flow rate: shown in below figures
 Detection: UV at 230 nm
 Temperature: ambient

Preparative column was packed with Dynamic Axial Compression.

	Analytical 250 X 4.6 mm i.d.		Semi-preparative 250 X 20 mm i.d.		Preparative 250 X 50 mm i.d.	
	1 st peak	2 nd peak	1 st peak	2 nd peak	1 st peak	2 nd peak
Enantiomeric excess	>99.9% ee	99.3% ee	99.9% ee	99.8% ee	99.1% ee	99.3% ee
Recovery	99%	99%	97%	99%	99%	94%

- Maximum loading amount was evaluated of 1.6 mg for 250 X 4.6 mm i.d. with maintaining enantiomeric excess of individual fraction $\geq 99\%$.
- Theoretical loading amount of 30mg for 250 X 20 mm i.d. and 188mg for 250 X 50 mm i.d. can be possible by examining their chromatograms and recovery amounts and enantiomeric excess of individual fractions.
- Dynamic Axial Compression Column self-packed with Cellulose-SB 10μm can be easily and linearly scale-up to purification.

Conclusions

- 90% hit coverage of chiral separation with our 5 kinds of CSPs
- 2-10 times higher loading capacities than competitor's in some cases
- robust scale-up from milligrams to kilograms