

Supersep™ Max:

Breakthrough multi-column SFC technology



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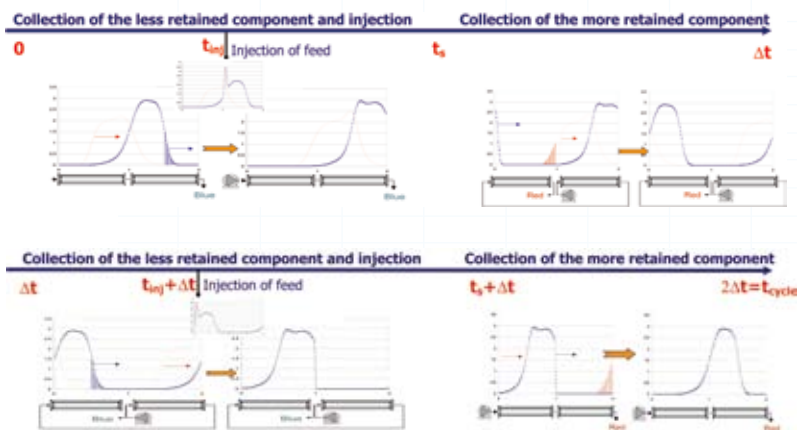
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Abstract

One of the most challenging problems encountered during the development of a new pharmaceutical compound is linked to purification. At early development stages, methods enabling fast and secure preparation of grams of drug candidates are required to quickly move to proof of concept. For late development and production, cost-effective, robust and environmentally-friendly routes are needed, while high yield and productivity are a prerequisite. Specially designed to separate from a few grams to kilograms of compounds, Supercritical Fluid Chromatography (SFC) systems perfectly match early development needs. SFC ensures very quick separation thanks to the low viscosity of supercritical carbon dioxide. Nevertheless, it is recognized that for binary separations of larger quantities, multi-column processes like SMB or Varicol® are solutions choice. A new process has recently been developed, combining both advantages of SFC and multi-column processes for kg to ten's of kg campaigns: Supersep™ Max.

Supersep™ Max: Process General Description

Supersep™ Max is a two-column process that can increase the productivity up to 5-fold compared with traditional SFC. Purified fractions are obtained with yields greater than 90% and product purity greater than 99%. Even if it is a two-column process, the amount of Chiral Stationary Phase (CSP) is not changed: one long packed bed is replaced by two short columns. The amount of stationary phase remains the same as in traditional SFC. The re-circulation of mixed fractions greatly increases the separation efficiency and results in the highest CSP productivity. Pure fractions are collected leaving mixed fractions to re-circulate through both columns while fresh racemate is periodically injected. The Supersep™ Max cycle is divided in two periods consisting of two stages:

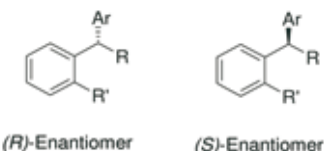


Experimental Results

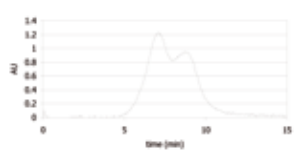
Chiral Separation

Analytical Injection

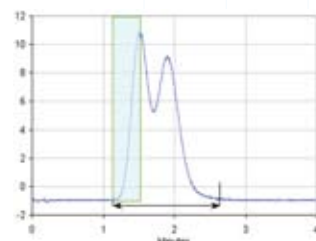
Preparative Classical SFC



Undisclosed API



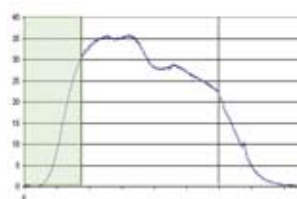
Chiralpak™ AD 20 μm, 80 bar
25 cm L x 0.46 cm I.D.
3 mL/min, 10% Methanol
(Chiralpak™ is a trademark of Daicel Chemical Industries).



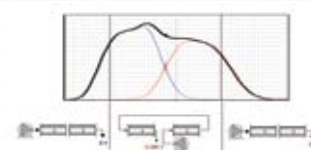
1 column 20 cm L x 2 cm I.D.
Flowrate = 150 g/min (10% Methanol)
1 mL/injection
Cycle Time = 110 s (stacked injections)

- Reaching high yield is impossible
- Recycle intermediate cuts & reprocess
- Loss of productivity

Supersep™ Max



2 columns 10 cm L x 2 cm I.D.
Flowrate = 300 g/min (10% Methanol)
0.8 mL/injection
Cycle Time = 70 s (stacked injections)



- High yield & high purity reached in one step
- High concentration of collected fractions (4 times higher than classical SFC)

	Preparative Classical SFC	Supersep™ Max
Purity	99%	99%
Yield	46%	94%
Productivity (kg enantiomer/kg CSP/day)	0.12	0.61
Methanol Consumption (L/g product)	5.98	2.33
Time to purify 100 g of desired enantiomer (h)	532	104

Conclusion

Supersep™ Max is an innovative SFC process that represents major advances in SFC. Supersep™ Max dramatically increases the productivity of chiral separations and enhances the yield for difficult separations. This technology is especially suited to purifying ten's of grams to ten's of kilograms. Supersep™ Max allows to obtain compounds faster and at a lower cost. It combines the advantages of an innovative two-column process (reduced production time, increased productivity and yield) with the benefits of Novasep's Supersep™ systems (green SFC systems, low organic solvent consumption, reduced evaporation requirements, CO₂ recycling).

