Productivity Optimisation in Chiral Chromatographic Processes.

Geoffrey B Cox, S Khattabi, J K Lee and R W Stringham,
Chiral Technologies Inc,
800 North Five Points Rd,
West Chester, PA 19380

The past few years have seen the implementation of several large scale production chromatographic processes for the preparation of single enantiomer drug products using Simulated Moving bed chromatography. The economic advantages of chromatographic processing generally increase over the alternative options as the productivity (measured as kg (enantiomer) / kg (stationary phase) / day) of the separation increases. Providing one compares like, optimised separation systems, productivity is a useful indicator of the more important cost per kg for the selection of a suitable separation for scale-up. As a rule of thumb, one can say that a separation having a productivity of greater than 1 kg/kg/day is likely to give potentially interesting production costs. Where the productivity is significantly below 1 kg/kg/day, other processes will probably be more economically attractive. Figure 1 shows a plot of cost per kg of isolated product as a function of productivity

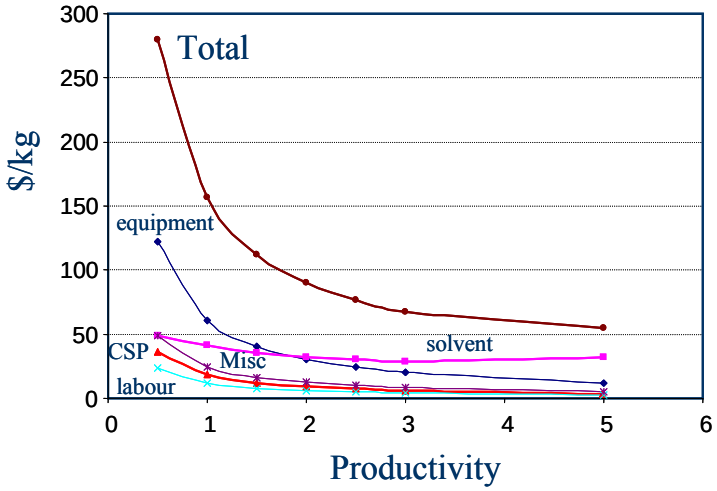

Figure 1.

There are a number of ways to improve the productivity of a separation. These include the selection of the appropriate chromatographic technique (HPLC, SFC or SMB), the optimum stationary phase – mobile phase combination, the speed of the separation and the overall column capacity. The major impact on productivity arises from the choice of the chromatographic technique and the stationary – mobile phase pair, and this paper addresses these two aspects.

Separation speed can increase the productivity dramatically, although the solvent economy is not much affected by this strategy. Table 1 shows the effect of flow rate on the productivity of the separation of guaiphenesin enantiomers.

Table 1.

Flow Rate	Productivity
(ml/min)	(kg (en)/kg/day)
50	0.24
100	0.32
200	1.3
400	2.1

Another method to increase the speed of the separation is to use Supercritical Fluid Chromatography (SFC). This technique uses very low viscosity mobile phases based on carbon dioxide, which allows high efficiency separations to be carried out at high speed with a low pressure drop across the column. Productivity values of between 2 and 4 are common in optimised SFC separations. Large scale SFC is currently limited by the lack of large scale equipment, although several separations are under development in the world that could bring this technique to the production scale.

The fastest way to reach high productivity separations is by the optimisation of the chiral stationary phase – mobile phase pair. This is conventionally carried out by screening large numbers of chiral stationary phases (CSPs) with a range of solvent systems. Figure 2 shows the result from a recent approach to this, screening 11 compounds using a library of 31 chiral stationary phases based on polysaccharides.

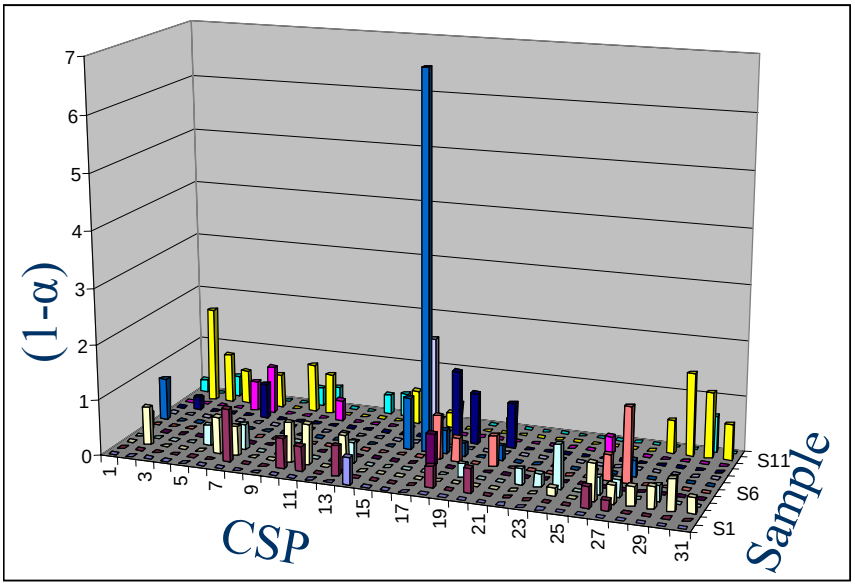

Figure 2.

Several of these developmental phases show high selectivity and productivity for certain separations, even though they are not generally useful in the same way as are commercially available CSPs. This approach can rapidly identify useful CSPs for a given separation for further optimisation. Table 2 shows the results of the screening of a

number of compounds on the CSP library relative to those from screening on commercially available CSPs.

Table 2.

Sample	CSP	Selectivity	Solvent	Best Commercial CSP	Selectivity
CT 1	"A"	2.28	ACN	AD	1.63
CT 2	"B"	2.35	ACN	OJ	1.92
CT 3	"C"	2.94	MeOH	OG	1.62
CT 4	"D"	4.09	MeOH	None	1.00
CT 5	"C"	2.23	ACN	OG	1.48
CT 6	"E"	1.78	ACN	AD	1.26

Optimisation of the selectivity has a large influence on the productivity of a separation. Although one can predict the effects for ideal cases, often the only way to determine the best conditions is by experiment, mostly because the adsorption isotherms of chiral compounds on CSPs rarely follows conventional isotherm models. Optimisation of the mobile phase is not only one of selectivity optimisation since other factors such as solvent viscosity and the solubility of the products in the mobile phase are often of equal importance.

A case study on the separation of 1-(2,4-dichlorophenyl-2-(1-imidazoyl)ethanol enantiomers has shown that in this case of a very high selectivity (9.2), the productivity using a SMB system is as high as 4.7 kg/kg/day. This high productivity translates into very low production costs: even with typical outsourcing costs it is possible to produce the pure enantiomer of miconazole starting from this intermediate at a cost per kg of around $100.