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Performance of simulated moving bed with conventional and monolith columns

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ABSTRACT

In this article the performances of different bed structures, i.e., conventional adsorbent beads (with different diameters) and monolithic columns, in the separation of chiral species by the simulated moving bed (SMB) technology are compared. In order to assess these different morphologies the equivalent particle size for monolithic structure was calculated based on equivalent permeabilities. The performance of the SMB units was compared for the conditions quantified by maximum productivity. The configuration of the SMB unit and the total system volume were not varied. The maximum operating pressure drop of 20 bar and the purity in both product streams over 99% were set as constraints in all computations. The true moving bed model was used as an analogy to simulated moving bed in order to reduce computation time. The productivity of the SMB unit using particle diameter of 27 μm can be slightly higher than of the SMB with particle diameter ≥50 μm but at the cost of higher eluent consumption. Moreover, there is no need to operate an SMB unit at its maximum pressure drop to get the best performance values, since in the presence of mass-transfer resistances, the contact time becomes the unit major limitation.

1. Introduction

It was common practice to market chiral drugs as racemates for many years. However, due to different biological activities of each enantiomer where one can be therapeutically active and the other may have antagonist properties there has been an increasing demand to supply enantiomerically pure drugs for therapeutic purposes [1].

Enantiomerically pure compounds are obtained using two main approaches. The racemic material is prepared and later on resolved into its enantiomeric forms or utilizing a stereoselective synthesis and producing only one enantiomer. However, this last approach is in the most cases not advantageous from an economical point of view, due to the numerous steps involved, high prices of enantiomeric reagents and low or moderate productivity [2].

Therefore, more comprehensive attention is being paid to adsorbent materials for purposes of preparative liquid chromatography due to the need to separate new drugs with complex chemical structures in adequate amount in the pharmaceutical and fine chemical industry. Higher productivity of a separation process on a certain column packed with spherical particles can be achieved by increasing the mobile phase velocity limited either by the maximum allowed system pressure drop or by the slow diffusional mass transfer.

The monolithic column represents a compromise between adsorbents with high permeability (lower hydraulic resistance) and high performance [3,4], a result of the independent control of the silica skeleton size and throughpores. The monolithic column as a new structure of stationary phase has attracted more and more interest in all areas of separation especially in preparative bioseparations [5–7]. Generally silica based monoliths contain a network of macropores with 1–2 μm macropore size, which represent approximately 80% of the total porosity and mesopores with size 5–25 nm which is approximately 10–15% of the total porosity [8].

To meet the high demand for pure enantiomers in pharmaceutical industries, large-scale chromatographic separations are required but the high cost of the adsorbent, the high products dilution and the large amounts of mobile phase needed in batch mode of preparative chromatography are the limiting factors. Nevertheless, these issues are considerably diminished by introducing the simulated moving bed (SMB) chromatography [9].

The SMB chromatography is a multi-column continuous chromatographic binary separation technique involving countercurrent movement of the adsorbent and liquid [10] and therefore, higher throughput, purity and recovery relative to the batch chromatography are achieved. After the scale-down of the simulated moving bed unit by Novasep in early 1990s this technology became an alternative to the up to now leading techniques [11–13].The pharma industry is still in the early stages of adopting SMB as

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Nomenclature

A, C	parameters to calculate HETP
A_c	cross-section area of the column (m^2)
b	equilibrium constant for the adsorption of enantiomers (m^3/kg)
B_0	permeability (m^2)
C	bulk liquid phase concentration (kg/m^3)
$\bar{C}_p$	average pore liquid concentration (kg/m^3)
d_c	diameter of the column (m)
d_p	diameter of particle (m)
D_L	axial dispersion coefficient (m^2/s)
D_m	molecular diffusion (m^2/s)
D_p	pore diffusion (m^2/s)
H	adsorption equilibrium constants of non-selective site
k_{ext}	external mass-transfer coefficient (m/s)
k_{int}	internal mass-transfer coefficient (m/s)
k_{ov}	overall mass-transfer coefficient (m/s)
K	adsorption equilibrium constants
L_c	column length (m)
n_j	number of columns per section
N	number of theoretical plate
N_c	total number of columns
ΔP	column pressure drop (Pa)
Pe	axial Peclet number
PR	productivity (g/m^3/h)
PU	purity (%)
q	average adsorbed phase concentration (kg/m^3)
q_m	adsorbed phase saturation concentration of component (kg/m^3)
Q	liquid flow rate (m^3/s)
RE	recovery (%)
SC	specific eluent consumption (m^3/g)
Sh	Sherwood number
t	time variable (s)
t^*	switching time (s)
t_R	retention time (s)
u_s	solid velocity (m/s)
V_c	volume of the column (m^3)
V_m	molar volume of the adsorbate at its normal boiling temperature (m^3/mol)
x	dimensionless axial coordinate
z	axial variable (m)

Greek letters

α	number of mass-transfer unit
ε	external porosity
ε_p	internal porosity
ε_T	total porosity
γ_j	ratio of fluid and solid velocity in section j
η	viscosity (Pa s)
ν	interstitial velocity (m/s)
θ	dimensionless time
ρ	fluid density (kg/m^3)

Subscripts and superscripts

E, F, Rf, X	eluent, feed, raffinate, extract stream
i	species in binary system (R,S *R*-α-Tetralol, *S*-α-Tetralol, respectively)
j	number of section (j = 1, 2, 3, 4)
*	operating conditions in SMB
in, out	inlet, outlet, respectively

a production technique, though activity has accelerated over the past years. Several pharmaceutical companies have been producing enantiomeric compounds by means of commercial-scale SMB units; examples are UCB Pharma (Belgium), H. Lundbeck (Denmark), AMPAC Fine Chemicals (USA), Ptizer (USA), Cephanon (USA), GlaxoSmithKline (UK), Bayer (Germany), CarboGen Laboratories (Switzerland), Chiral Technologies (USA), Daicel (Japan), and Merck (Germany) [14].

An SMB is essentially a binary separator, which allows the continuous injection and separation of binary mixtures. The simulated counter-current contact between the solid and liquid phases maximizes the mass-transfer driving force, leading to a significant reduction in mobile and stationary phases consumption when compared with conventional batch chromatography. Hence, with SMB technology, large-scale separations can now be carried out under cost-effective conditions.

The SMB operation is explained typically using the equivalent true moving bed (TMB) concept. In the TMB liquid and solid flow in opposite directions (Fig. 1), liquid and adsorbent streams are continuously recycled: the liquid flowing out of section 4 is recycled to section 1, while the solid coming out of section 1 is recycled to section 4. The feed is continuously injected in the middle of the

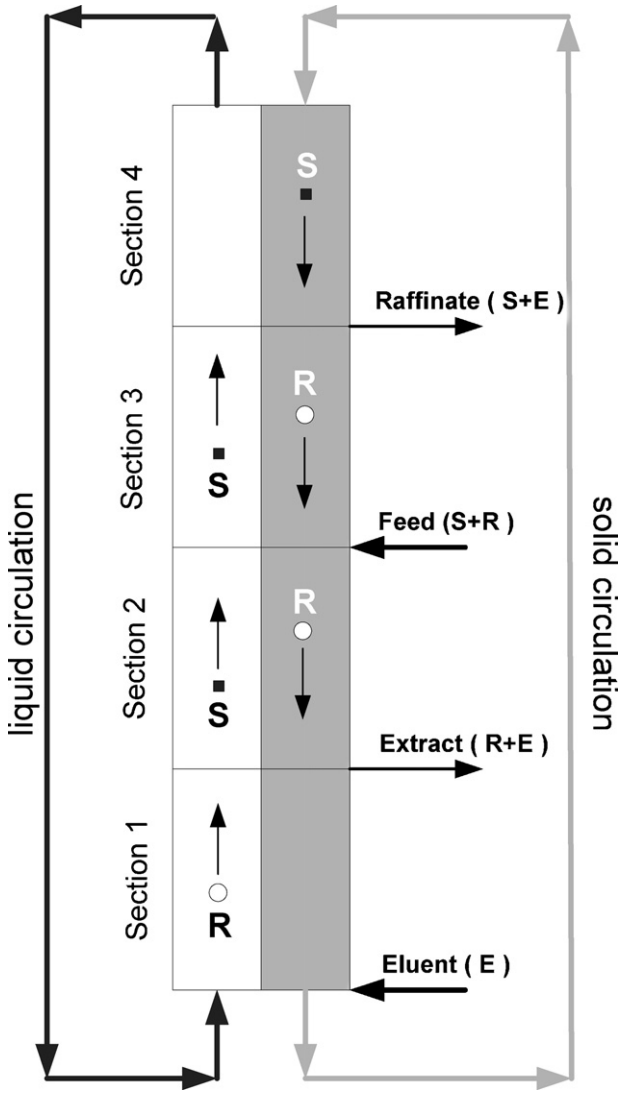

Fig. 1. Schematic diagram of a TMB unit.