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Possible resolution gain in enantioseparations afforded by core–shell particle technology

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ABSTRACT

Whether columns packed with core–shell particles may outperform those packed with fully porous particles for chiral separations is controversial. The potential advantages of such columns are investigated from a theoretical viewpoint. The height equivalent to a theoretical plate (HETP) associated to the slow adsorption-desorption process typical of chiral chromatography was derived from the Laplace transform of the general rate model of chromatography for core–shell particles. The relationship between the resolution factor and the core-to-particle diameter ratio is predicted at constant selectivity. The calculations are based on a complete set of actual kinetic parameters (longitudinal diffusion, eddy dispersion, intra-particle diffusivity, and adsorption-desorption constant) measured for a reference column packed with Lux Cellulose-1 fully porous particles. If we compare columns packed with the best procedure available in either case, the results demonstrate that those packed with core–shell particles may outperform to a degree those packed with fully porous particles. The minimum reduced HETP could decrease from 2.0 to 1.7. The maximum relative gain in resolution is about 10%, which is not negligible for critical enantioselective-separations. This gain is observed only if the packing uniformity of the core–shell particles is achieved.

1. Introduction

Recent fundamental work has brought a satisfactory understanding of the different contributions to band broadening in chromatographic columns [1–3]. Our knowledge of the different mass transfer resistance phenomena taking place in chromatographic columns is most important to design and prepare all types of columns in the new HPLC column generation, whether RPLC-C_{18}, HILIC, or chiral. The mass transfer mechanisms in RPLC-C_{18} and HILIC (silica) were already elucidated [4,5,1,6,7]. Accurate measurements of the three main contributions (longitudinal diffusion, eddy dispersion, and solid–liquid mass transfer resistance due to the finite diffusivity of the sample molecules across particles) to the total plate height are straightforward for small molecules in RPLC and HILIC retention modes for two reasons: (1) the diffusion coefficients of small molecules are sufficiently large to allow their fast, accurate measurement with the peak parking (PP) method [8–10]; and (2) the adsorption–desorption process of small molecules in RPLC and HILIC are rather fast. A comprehensive modeling of band transport in beds packed with non-porous particles under retained conditions shows that the adsorption rate constants are usually between 1×10^7 and $1 \times 10^8\ \mathrm{s}^{-1}$ [11]. For such large adsorption rate constants, the mass transfer resistance due to the adsorption–desorption process is negligible, so the mass transfer resistance in the stationary phase is essentially controlled by the finite rate of diffusion across the particles. The solid–liquid mass transfer resistance HETP term can then be obtained from the combination of the PP results and a valid model of effective diffusion in heterogeneous packed bed immersed in the eluent [12,13].

The complete mass transfer mechanism in chiral chromatography was recently investigated in the reversed phase retention mode (which uses RPLC-like or aqueous-organic eluent mixtures) for fully porous particles [14,15]. Unlike in RPLC and HILIC, the slow rate of the adsorption–desorption process onto chiral stationary phases (CSP) affects significantly the overall band broadening. Using *trans*-stilbene enantiomers, a cellulose-based CSP, and a methanol–water eluent (90/10, v/v), the relative contribution of this rate to the total plate height is nearly 30% at a reduced velocity of about 35. This largely exceeds the contribution of the solid–liquid mass transfer resistance due to diffusion (15% [14]). This result triggers the question of how the slow resistance to overall mass transport taking place inside fully porous particles would affect the efficiency of core–shell particles. Answering this question requires considering

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Nomenclature

$A(\nu)$	reduced eddy dispersion term
B	reduced longitudinal diffusion coefficient with reference to the interstitial linear velocity
c_s	sample concentration in the stationary phase (mol/m^3)
c_p	sample concentration in the internal bulk eluent (mol/m^3)
C_a	reduced solid–liquid mass transfer resistance coefficient due to adsorption–desorption kinetics
C_p	reduced solid–liquid mass transfer resistance coefficient due to finite rate of diffusion across the particles
d_c	average non-porous core diameter (m)
d_p	average particle diameter (m)
D	dimensionless number related to the adsorption–desorption kinetics
D_{eff}	effective diffusion coefficient of the analyte in the packed column (m^2/s)
D_m	bulk molecular diffusion coefficient (m^2/s)
D_p	sample diffusivity in the particle (m^2/s)
F_v	flow rate (m^3/s)
h	reduced plate height
k_{ads}	adsorption rate constant (s^{-1})
$h_{TC}(\nu)$	trans-column/border eddy dispersion reduced plate height
k'	retention factor
k'_1	retention factor of the least retained enantiomer
k'_2	retention factor of the most retained enantiomer
k_1	zone retention factor
K_a	equilibrium Henry constant for the sample adsorption–desorption between the solid phase and the liquid eluent phase
$K_{a,1}$	Henry constant of the least retained enantiomer
$K_{a,2}$	Henry constant of the most retained enantiomer
L	column length (m)
N_1	column efficiency for the least retained enantiomer
N_2	column efficiency for the most retained enantiomer
r_c	column inner radius (m)
R_S	resolution factor
u	interstitial linear velocity (m/s)

Greek letters

α	selectivity factor
β	parameter in Torquato's model of effective diffusion in packed beds defined by Eq. (8)
ϵ_e	external column porosity
ϵ_p	particle porosity
ϵ_t	total column porosity
η	eluent viscosity (Pa s)
γ_e	obstruction factor caused by randomly packed non-porous particles to the diffusion in the external bulk mobile phase
ν	reduced interstitial linear velocity
ρ	core-to-particle diameter ratio
Ω	ratio of the effective diffusivity of the sample in the porous particle to its bulk diffusion coefficient
ω_1	diffusion eddy dispersion coefficient related to trans-channel velocity bias in the infinite diameter column packed with non-porous particles
λ_1	flow eddy dispersion coefficient related to trans-channel velocity bias in the infinite diameter column packed with non-porous particles
ω_2	diffusion eddy dispersion coefficient related to short-range inter-channel velocity bias in the infinite diameter column packed with non-porous particles
λ_2	flow eddy dispersion coefficient related to short-range inter-channel trans-column velocity bias in the infinite diameter column packed with non-porous particles
ξ_2	adjustable parameter in Torquato's model of effective diffusion Eq. (7)

the well-known benefit of core–shell particles technology, e.g., the significant diminution of long-range eddy dispersion, e.g. the reduction of the transcolumn velocity biases and of border effects) [16–19,2]. However, experimental data are still scarce. Studies comparing enantioseparations made with polysaccharide based CSPs in columns packed with totally porous and core–shell silica particles were done in NP-HPLC with wide-bore (4.6 mm ×250 mm) [20] and open tubular (75 μm ×60 cm) [21] columns. The conclusions seem to depend on the column dimensions. A measurable improvement of the efficiency of 4.6 mm i.d. columns was reported at high flow rates for benzoin on 2,2-dihydroxy-6,6-dimethylbiphenyl [20] but no significant difference in plate heights was observed for thalidomide on open tubular columns (75 μm i.d.) [21]. Therefore, a fundamental, comprehensive description of the mass transfer mechanism in columns packed with core–shell particles and used in chiral chromatography is needed to draw clearer conclusions.

The goal of this work is to investigate whether columns packed with core–shell particles could outperform those packed with fully porous particles in chiral chromatography. In chiral chromatography, the adsorption isotherms of enantiomers usually involves adsorption on two types of sites: the weak non-selective sites onto which adsorption–desorption can be considered as fast and the stronger selective sites onto which the adsorption–desorption process is much slower. The analytical solution to this problem was derived by Giddings and Eyring, using the stochastic theory for a two-site system and is given as a probability distribution [22]. Alternately, a numerical solution could be obtained by extending the classical general rate model to a two-sites adsorption–desorption process [23]. However, the general rate model of chromatography involving mass transfer resistance due to a slow adsorption–desorption process was solved analytically only by a Laplace transform in the case of a homogeneous surface, thus with a unique adsorption rate constant k_{ads}.

In this work, for the sake of simplicity, we consider the ideal case in which there is no adsorption on the weak sites that do not contribute to retention. Only the strong active sites are responsible for retention of the analytes. The main goal of the present work is to assess whether the band broadening contribution of a small adsorption rate constant could potentially be compensated by the use of core–shell technology. It is not intended to account quantitatively for the description of a specific chiral separation but to show the expected and general trends that practitioners and column manufacturers can expect. This is why an apparent homogenous adsorption model is used rather. The HETP term related to a slow adsorption–desorption process (modeled with a first order Langmuir adsorption–desorption kinetics) is well documented for fully porous particles [24,23,25]. Applying the Laplace transform to the general rate model of chromatography in the case of core–shell particles, Kaczmarski [26] and Miyabe [27] derived the van Deemter equation in the presence of slow adsorption–desorption for a homogeneous adsorption process. This expression permits the