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Experimental validation of physico-chemical models of effective diffusion in chromatographic columns packed with superficially porous particles

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A R T I C L E I N F O

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A B S T R A C T

The effective diffusion coefficient of a non-retained compound (uracil) was measured with the peak parking (PP) method for two series (4.6 mm × 100 mm and 2.1 mm × 100 mm) of six replicate columns packed with the same batch of superficially porous 2.6 μm Kinetex-C_{18} particles. The abilities of four different models of effective diffusion in packed beds to account for the experimental data are compared. These models include the conventional Knox time-averaged model, the extension to molecular diffusion of the Landauer electrical conductance model, the Garnett diffusion model for the inclusion of core-shell spheres down to infinitesimal small sizes, and the stochastic Torquato model for a random dispersion of spheres in contact.

The choice of a non-retained compound for this purpose is justified by the facts that the diffusivity of this compound through the porous shell can be estimated independently from its internal porosity derived from inverse size-exclusion chromatography (ISEC) data, that the internal obstruction factor can be assessed by nuclear magnetic resonance (NMR) using the spin-echo pulsed field-gradient method, and that the hindrance diffusion factor can be estimated with either the Renkin or the Brenner correlations. The experimental effective diffusion coefficient of uracil was found to be in excellent agreement with the value predicted by Knox semi-empirical model, in good agreement with those predicted by Torquato and Landauer models while the Garnett model failed definitely. In conclusion, the longitudinal diffusion terms of columns packed with core-shell particles cannot yet be accurately predicted by any of the sophisticated, physically relevant models of effective diffusion actually available in the scientific literature.

1. Introduction

Chromatographic columns packed with superficially porous particles have attracted much attention during the last 5 years. After the long eclipse that followed early attempts at developing pellicular stationary phases (Horváth and Lipsky, 1969), which had found limited commercial success in the 1970s–1990s, Advanced Material Technologies (Wilmington, DE, USA), Phenomenex (Torrance, CA, USA), and Agilent Technologies (Little Fall, DE, USA) have mastered the production of columns packed of sub-3 μm shell particles with performance comparable to those of columns packed of sub-2 μm particles, with the advantage of operating at back pressures below 400 bar (DeStefano et al., 2007; Gritti et al., 2010a; Gritti and Guiochon, 2010a,b), with costless modifications of conventional HPLC systems to minimize their extra-column volume (Gritti et al., 2010b). This new core-shell technology has been thoroughly studied in academic laboratories and industrial companies (Kirkland et al., 2007; Schuster et al., 2010; Gritti and Guiochon, 2007a,b; Cavazzini et al., 2007; Marchetti et al., 2007; McCalley, 2008; Gritti et al., 2010a–c; Gritti and Guiochon, 2010b–e; Olah et al., 2010; Gritti and Guiochon, 2011a–c; McCalley, 2010; Omamogho et al., 2011; Jorgenson et al., 2010). Of particular interest are the three components of the column height equivalent to a theoretical plate (HETP) of these columns, those due to eddy dispersion, longitudinal or axial diffusion, and to the resistance to mass transfer, traditionally referred to in chromatography as the *A*, *B*, and *C* terms of the HETP (Giddings, 1965).

The mass transfer mechanism (the *C* term) in 4.6 and 2.1 mm I.D. columns packed with sub-3 μm particles has been deeply investigated (Gritti et al., 2010a,c; Gritti and Guiochon, 2010d,e, 2011b,c). The use of a well defined experimental protocol (Gritti and Guiochon, 2010f) permitted the demonstration that the recent breakthrough of the sub-3 μm shell particle technology is due to their low eddy diffusion and longitudinal diffusion contributions to band broadening (Gritti and Guiochon, 2010e), themselves due to the particle structure. In contrast, the

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reduction of the liquid–solid mass transfer resistance contribution to band broadening expected from the small diffusion length across the porous shells was found to be insignificant for low molecular weight solutes that have a high molecular diffusivity ($\simeq 10^{-5}$ cm^2/s) (Horváth and Lipsky, 1969; Kaczmarski and Guiochon, 2008; Felinger, 2011). Except possibly for large biomolecules, the HETP contribution of this term is so small that it does not control the mass transfer kinetics of solutes at high velocities (Gritti et al., 2010c; Gritti and Guiochon, 2010e).

Both experimental (Dewaele and Verzele, 1983; Endele et al., 1974; Unger et al., 1986; Gritti et al., 2010c) and theoretical (Carta, 1988; Carta and Bauer, 1990; Daneyko et al., 2011) investigations converge to demonstrate that the decrease of the HETP term (contribution to band broadening due to the unevenness of the interstitial eluent velocity, e.g., to eddy dispersion) measured for 4.6 mm I.D. columns packed with shell particles is not explained by the narrow particle size distribution of these particles. It is due the external roughness of these particles, resulting from the step-by-step growth process of the shell, that has a fundamental impact on the consolidation of the packed bed (Yew et al., 2003). The high shear stress between these rugged particles and between them and the column wall results in strains that affect bed homogeneity. The rougher the particles, the lesser the strains and the smaller the trans-column velocity biases across the packed column. In this work, we investigate the causes for the decrease of the plate height contribution associated to band broadening due to longitudinal diffusion of the sample during its migration along the column (the *B* term) in part due to the significant volume fraction of nonporous, spherical cores through which analyte molecules cannot diffuse but around which they must travel (obstruction). To explain this decrease, suitable models of longitudinal diffusion in packed beds made of core-shell particles immersed in a continuum liquid have been studied (Gritti and Guiochon, 2011d,e; Broeckhoven et al., 2006).

The most important issue raised in this study is how to validate or reject these different models, based on measurements of effective diffusion coefficients along packed columns, which can be described as ternary composite materials. Column beds include a solid impermeable spherical core surrounded by a concentric, uniform porous shell, core and shell forming the shell particles, which are in contact and randomly dispersed through a liquid phase. Two main difficulties are encountered in attempts to use liquid chromatography data for the validation of effective diffusion models: (1) the diffusion coefficients of analytes are known in the liquid phase (bulk molecular diffusion coefficients D_m are easily measured by the peak parking method, Gritti and Guiochon, 2011c); they are obviously equal to zero in the solid core; these coefficients are unknown in the porous shell for retained compounds, due to the contribution of surface diffusion; (2) no mathematical model of effective diffusivity in packed columns can account for the inherent disorder parameter, which affects longitudinal diffusion. Therefore, model validation is impossible unless other methods of independent experimental measurements of analyte diffusivity in the porous shell and of parameters precisely characterizing the structure disorder using morphology reconstruction (Hlushkou et al., 2010; Bruns and Tallarek, 2011). Accordingly, it seems *a priori* more judicious to consider a non-retained compound for which surface diffusion is strictly equal to zero, rather than retained ones. The diffusivity of a non-retained compound is simply accounted for by the accessible internal porosity of the porous stationary phase and by the restriction to diffusion along the tortuous, constricted, and narrow interconnected system of mesopores. Furthermore, in order to assess for the contribution of the packing disorder on the longitudinal diffusion *B* term, it was decided to use a large number of chromatographic columns (12) with two different inner diameters (2.1 and 4.6 mm I.D.), but packed with the same batch of particles.

In this work, we tested four different mathematical models of effective diffusion in packed beds made of ternary composite materials. These models are the conventional time-averaged diffusion model (Knox and Scott, 1983), the Davis diffusion model (Davis, 1977) derived from the extension of the effective medium theory of Landauer (Landauer, 1952) to molecular diffusion, the Garnett diffusion model accounting for the core-shell structure of the particles (Garnett, 1904), and the Garnett–Torquato diffusion model accounting for both the shell structure of the packed particles and the random dispersion of these spheres in contact with each other throughout the column bed (Torquato, 2002, 1985). Six 4.6×100 mm and as many 2.1×100 mm columns packed with the same batch of 2.6 μm Kinetex-C$_{18}$ shell particles were used for the evaluation of the disorder parameter, which necessarily varies from one column to the other because packing a column is by essence a random process. ISEC and the PP method were systematically applied to each of those 12 columns in order to measure the true effective diffusion coefficients (D_{eff}) of the non-retained compound uracil. The bulk molecular diffusion coefficient (D_m) of uracil was measured by the PP method using a 4.6×100 mm column packed with non-porous 3.3 μm silica cores. The diffusivity ($D_p = \Omega D_m$) of uracil through the porous Kinetex-C$_{18}$ shells was assessed from the combination of ISEC experiments for the measurement of the internal porosity (ε_p) and of nuclear magnetic resonance (NMR) using the spin-echo pulsed field-gradient method for the measurement of the hindrance diffusion factor (Mitzithras and Strange, 1992) due to the internal obstruction (γ) and the confined geometry throughout the narrow mesoporous network ($F(\lambda_m)$). These results lead to conclusions on the importance of the packing disorder on the longitudinal diffusion *B* term of commercial columns and on the most suitable model of effective diffusion in heterogeneous chromatographic beds packed with core-shell particles.

2. Theory

Shell particles are made of a solid, non-porous, spherical core surrounded by a concentric porous shell. The core-to-particle diameter ratio, ρ, ranges between 0.60 and 0.75 for commercially available shell particles. We define as ε_e the external porosity of the packed bed, D_m the bulk molecular diffusion coefficient of the analyte, and k_1 the zone retention factor extended to superficially porous particle, which is written (Guiochon et al., 2006)

$$k_1 = \frac{1-\varepsilon_e}{\varepsilon_e}[\varepsilon_p + (1-\varepsilon_p)K_a][1-\rho^3] \tag{1}$$

The apparent analyte diffusivity through the porous shells is $D_p = \varepsilon_p \gamma_i D_m = \Omega D_m$, where ε_p is the internal porosity of the porous shells and γ_i is the internal obstruction factor due to the tortuous constricted pathways that hinders the molecular motion of analytes along the mesopores. Four different theoretical diffusion models in packed columns were recently derived to account for the reduced longitudinal diffusion *B* term of columns packed with core-shell particles (Gritti and Guiochon, 2011d,e). In theory, this effective diffusion coefficient, D_{eff}, depends on the volume composition parameters (i.e., ε_e and ρ^3), on the diffusion coefficient of the analyte in each homogeneous phase of the composite material (D_m in the bulk phase and D_p in the porous shell), and on the structure and degree of disorder of the composite material (this variable cannot really be quantified and must be considered as a random factor, varying from one column to the other).