A Strategy for Tailored Design of Efficient and Low-Pressure Drop Packed Column Chromatography

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Packed chromatographic column, with higher efficiency and lower pressure drop is designed by using inert core adsorbents as stationary phase. The analytical solutions for moments and height equivalent to a theoretical plate (HETP) are given under the conditions of linear adsorption kinetics by taking into account of the axial dispersion, film mass-transfer resistance, intraparticle diffusion resistance, and the sorption rate for chromatographic column packed with inert core adsorbents. By minimizing HETP, a nonlinear algebraic equation was derived to predict the optimized value of the inert core radius. For a given adsorbent with the optimized inert core radius, a strategy was presented to tailor the design of new packed chromatographic column with higher efficiency and lower pressure drop. As an example for supercritical carbon dioxide chromatography, reduced equations in terms of dimensionless inert core radius were derived by "order of magnitude" analysis. The quantitative analysis shows that the major benefit of the inert core adsorbent is a shorter diffusion path compared to conventional fully porous particles. The shorter diffusion path reduces dispersion of solutes and minimizes peak broadening leading to lower pressure drop while maintaining high-separation efficiency. © 2010 American Institute of Chemical Engineers *AIChE J,* 56: 3091–3098, 2010

Keywords: inert core adsorbent, fixed bed, chromatography, pressure drop, separation efficiency, HETP

Introduction

Chromatography is a widely-used tool in analytical and preparative processes.[1] It is highly desirable to increase the packed column separation efficiency, while maintaining or reducing the pressure drop across the column. In order to maximize the separation efficiency in a column with a given length it is necessary to reduce the particle size as far as possible. The limit is set by pressure drop, which becomes unacceptably large if the particles are too small.[2] For example, a prepacked 250 mm long, 4 mm dia. Chiralcel-OD column with an average particle size of 20 μm from Chiral Technologies Europe, Illkrich-Cedex, France, was used for the resolution of 1-phenyl-1-propanol racemic mixture by

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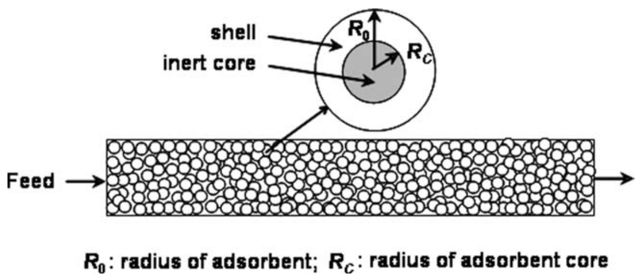

Figure 1. Scheme of chromatographic column and inert core adsorbent.

supercritical fluid chromatography. The pressure drop across the unit is up to 17.0 MPa leading to further compression of the beds which resulted in a reduction of the average column volume by 8%.[3]

Binding ligand inert core adsorbents are being used for the fast, high-performance liquid chromatography (HPLC), because of short diffusion path resulting in low-intraparticle diffusion resistance for biomacromolecules separation.[4–11] It may be advantageous in chromatographic column designed to specify inert core adsorbents instead of fully porous particles for bioseparation where the macromolecules diffusion rate in the adsorbents has significant influence on the mass-transfer kinetics. There are some commercial examples of such adsorbents. One example is Poroshell$^{\mathrm{TM}}$ 5 μm particle with a thin layer of porous silica on a solid core used for fast, high-resolution protein separation for analytical chromatography;[12] another example is HALO fused-core$^{\mathrm{TM}}$ particle technology for hyper-fast and super-rugged HPLC columns.[13]

Inert core adsorbents have fascinated chromatographers for nearly 40 years.[4–16] It is realized that the loading capacity of the columns packed with the inert core adsorbent is relatively low and appears to be a limitation of its application.[9,10,17,18] The optimal design of inert core adsorbents in the packed column is very important to enhance the column separation efficiency while maintaining or reducing the pressure drop across the column. A simple and efficient method applied for the analysis of chromatographic band profiles is the method of moments[1,2,6–9,15,19,20] which has been used for many years.[16,21,22] Recently, the group of Guiochon[6,7] proposed a moment solution for chromatographic columns packed with a pellicular adsorbent based on a general rate (GR) model that takes into account of the axial dispersion, film mass-transfer resistance and intraparticle diffusion resistance, and confirmed the technical improvement experimentally by using inert core adsorbents in chromatography.

Based on our previous work,[8,9,14] we present a rigorous approach that taking into account of the axial dispersion, film mass-transfer resistance, intraparticle diffusion resistance, and the sorption rate (adsorption/desorption kinetics) for chromatographic column packed with inert core adsorbents; we further derive a nonlinear algebraic equation to predict the optimized value of inert core radius based on the minimization of height equivalent to a theoretical plate (*HETP*). A new strategy is presented here to design higher efficient and with lower pressure drop packed column chromatography using inert core adsorbents as stationary phase. An example is presented for the case of supercritical carbon dioxide chromatography for resolution of 1-phenyl-1-propanol,[3] and quantitatively described for (1) how to lower the pressure drop to improve the chromatographic operation performance, (2) how to enhance the chromatographic separation efficiency, and (3) how to increase the treatment capability.

It should be pointed out that the separation efficiency depends on many factors. In addition to particle properties (particle size, porosity, ligand density and chemistry), affinity (adsorbent/target molecule interactions), and operating conditions (flow rate, temperature, mobile phase composition) can also play critical roles. There are many ways to improve separation efficiency; this work deals with one aspect of a very complex problem.

Mathematical Models

The scheme of the chromatographic column and the inert core adsorbent is shown in Figure 1.

It is assumed that the ligand-binding is uniform for the porous section of the adsorbent particle. If the particle radius is R_0 with a core radius R_c (column length L_0 with column dia. D_0), for GR model by taking into account the axial dispersion, film mass-transfer resistance, intraparticle diffusion resistance, and the sorption rate (adsorption/desorption kinetics), the expressions of the first absolute moment μ_1, and the second central moment μ_2', for Dirac input mode at the exit can be obtained as[7,14]

$$\mu_1 = \theta\left[1+\upsilon\left(1-\xi_C^3\right)(1+\xi_m)\right] \tag{1}$$

$$\mu_2' = 2\theta\upsilon\left(1-\xi_C^3\right)\left[\frac{(1+\xi_m)^2\left(1-\xi_C^3\right)}{3}\left(\frac{1}{\Theta}+\frac{1}{Bi}\right)+\frac{\xi_m}{\psi}\right] + \frac{2\theta^2\left[1+\upsilon\left(1-\xi_C^3\right)(1+\xi_m)\right]^2}{Pe} \tag{2}$$

in which $\xi_C = \frac{R_C}{R_0}$, the porosity ratio is $\upsilon = \left(\frac{1-\varepsilon_{B0}}{\varepsilon_{B0}}\right)\varepsilon_S$, the capacity factor is $\xi_m = \frac{K\rho_S}{\varepsilon_S}$, the dimensionless adsorption rate constant is $\psi = \frac{k_{\mathrm{ads}}R_0^2}{D_pK\rho_S}$, the Biot number is $Bi = \frac{k_{f0}R_0}{\varepsilon_S D_p}$, the ratio of time constants for convection in outer fluid and pore diffusion is $\theta = \frac{\varepsilon_{B0}L_0D_p}{u_0R_0^2}$, and the Pelect number based on column length is $Pe = \frac{u_0L_0}{\varepsilon_{B0}D_{L0}}$, and

$$\frac{1}{\Theta} = \frac{(1-\xi_C)^2}{\left(1-\xi_C^3\right)}\left[\xi_C + \frac{(1-\xi_C)^3}{5\left(1-\xi_C^3\right)}\right] \tag{3}$$

The first absolute moment and the second central moment give all the information available in the profiles on the thermodynamics of equilibrium between the mobile and the stationary phase, and on the mass-transfer kinetics between these two phases of the system. The theoretical plate number N_T can be calculated using the first absolute moment μ_1, and the second central moment μ_2'

$$N_T = \frac{\mu_1^2}{\mu_2'} \tag{4}$$

The *HETP* normalized by the column length is defined as

$$HETP = \frac{1}{N_T} \tag{5}$$

i.e.

$$HETP = \frac{2\upsilon\left(1-\xi_C^3\right)}{\theta\left[1+\upsilon\left(1-\xi_C^3\right)\left(1+\xi_m\right)\right]^2} \times \left[\frac{\left(1+\xi_m\right)^2\left(1-\xi_C^3\right)}{3}\left(\frac{1}{\Theta}+\frac{1}{Bi}\right)+\frac{\xi_m}{\psi}\right]+\frac{2}{Pe} \tag{6}$$

or in dimension form on the righthand side of Eq. 6

$$HETP = \frac{2\upsilon\left(1-\xi_C^3\right)}{\left[1+\upsilon\left(1-\xi_C^3\right)\left(1+\xi_m\right)\right]^2}\left(\frac{\varepsilon_S u_0 R_0^2}{\varepsilon_{B0} L_0}\right) \times \left[\frac{\left(1+\xi_m\right)^2\left(1-\xi_C^3\right)}{3}\left(\frac{1}{\Theta}\frac{1}{\varepsilon_S D_P}+\frac{1}{k_{f0}R_0}\right)+\frac{\xi_m^2}{R_0^2}\frac{1}{k_{\mathrm{ads}}}\right] + \frac{2\varepsilon_{B0}D_{L0}}{u_0 L_0} \tag{7}$$

The linear GR model represents the limiting cases of low concentrations or very strong adsorption (very large Henry constant) within the Henry's law region.

In general, we have the following simple form for *HETP*

$$HETP = \frac{2}{\left(1-\xi_C^3\right)\left(1-\varepsilon_{B0}\right)}\left(\frac{u_0 R_0^2}{L_0}\right) \times \left[\frac{\left(1-\xi_C^3\right)}{3}\left(\frac{1}{\Theta}\frac{1}{\varepsilon_S D_P}+\frac{1}{k_{f0}R_0}\right)+\frac{1}{R_0^2}\frac{1}{k_{\mathrm{ads}}}\right] + \frac{2\varepsilon_{B0}D_{L0}}{u_0 L_0} \quad (\xi_m >> 1) \tag{8}$$

The resolution is measured from the chromatogram by the degree of separation[23]

$$R_S = \frac{\sqrt{N_T}}{4}\left(\frac{k}{k+1}\right)\left(\frac{\alpha-1}{\alpha}\right) \tag{9}$$

where k is the retention factor calculated relative to the column void volume, and α is selectivity factor calculated from the ratio of retention factors; evidently, k and α are determined by the chemical properties of the system.

Axial dispersion coefficient D_{L0} and external mass-transfer coefficient k_{f0} are, respectively, evaluated by[2]

$$D_{L0} = \gamma_1 \varepsilon_{B0} D_M + 2\gamma_2 R_0 u_0 \tag{10}$$

in which $\gamma_1 = 0.45 + 0.55\varepsilon_S$ and $\gamma_2 \approx 0.5$.

$$\frac{2k_{f0}R_0}{D_M} = \frac{1.09}{\varepsilon_{B0}}\left(\frac{\mu_f}{\rho_f D_M}\right)^{0.33}\left(\frac{2R_0 u_0 \rho_f}{\mu_f}\right)^{0.33}, \quad \text{for } 0.0015 < \frac{2R_0 u_0 \rho_f}{\mu_f} < 50 \tag{11}$$

The pore diffusivity D_p is related to the molecular diffusivity D_M as[2]

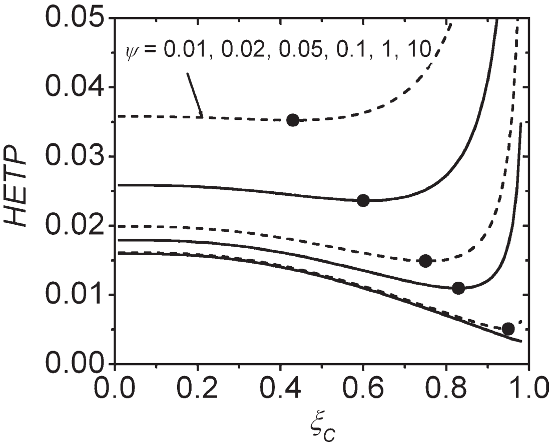

Figure 2. Effect of ξ_c on *HETP* for different adsorption-desorption rate ψ at typical conditions of $\xi_m = 10^3$, *Bi* = 10^2, and $\upsilon = 0.5$.

Circle Points: optimized value $\xi_{C,optimized}$ calculated by Eq. 15.

$$D_P = \frac{D_M}{\tau} \tag{12}$$

in which τ is the tortuosity factor.

The pressure drop ΔP_0 through the column can be estimated by[23]

$$\Delta P_0 \propto \frac{\eta L_0 Q_0}{D_0^2 R_0^2} \tag{13}$$

where η is solvent viscosity, Q_0 is the flow rate, and D_0 is the inner column diameter.

The optimized value ξ_c is based on the minimization of *HETP* of Eq. 6, i.e.,

$$\frac{\partial HETP}{\partial \xi_C} = 0 \tag{14}$$

Then, the optimized value $\xi_{C,optimized}$ is obtained by solving the nonlinear algebraic Eq. 15

$$\frac{3\upsilon\left(1+\xi_m\right)\left(1+3\xi_C+\xi_C^2\right)}{5}+\frac{1+2\xi_C}{1-\xi_C}+\frac{2}{Bi} = \frac{3\xi_m}{\psi\left(1+\xi_m\right)\left(1-\xi_C\right)^2}\left[\upsilon\left(1+\xi_C+\xi_C^2\right)-\frac{1}{\left(1+\xi_m\right)\left(1-\xi_C\right)}\right] \tag{15}$$

Equation 15 presents a general equation to predict the optimized value of inert core radius. With the optimized inert core radius, a packed-column can be designed to operate with higher separation efficiency and lower pressure drop.

Results and Discussion

When the adsorption rate is very fast, such as $\psi = 10$, local adsorption equilibrium can be attained immediately on the adsorbed surface of adsorbent; with increase of the inert core size in the adsorbent, the intraparticle diffusion

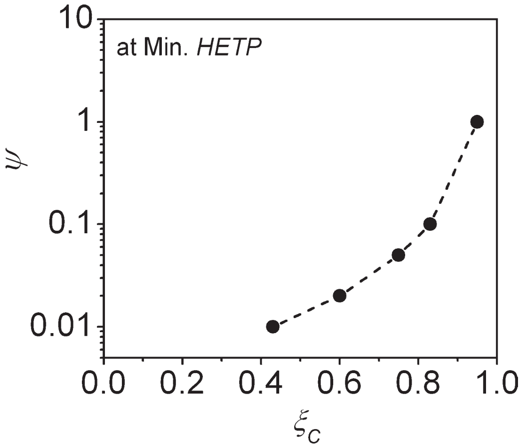

Figure 3. Minimum value of *HETP* changes with ξ_c and ψ calculated by Eq. 15 at typical conditions of $\xi_m = 10^3$, $Bi = 10^2$, and $\upsilon = 0.5$.

resistance is significantly decreased, which will enhance the column efficiency, *HETP* will decrease as shown in Figure 2 at typical values of $\xi_m = 10^3$, $Bi = 10^2$, and $\upsilon = 0.5$.[7,8] When the adsorption rate is slow for small ψ values, instantaneous adsorption equilibrium on the adsorbed surface of adsorbents is not attained; at constant ψ there is an optimum value of ξ_c leading to a maximum value of N_T.

Although the intraparticle diffusion resistance can be decreased significantly with the increase of inert core size, the decrease of the accessible surface area used for adsorption in adsorbents (shell volume decrease) will not favor the adsorption of solutes with slow adsorption rate. Therefore, at a given adsorption rate, there exists an optimum inert core size as shown in Figure 2; at this point, *HETP* is minimum and column operation is more efficient, as shown in Figure 3.

New strategy for tailored design of new chromatographic column based on the optimized value of the inert core dimensionless radius

Let us consider that a chromatographic column packed with fully porous particle with radius R_0, is now replaced by inert core particles with the same radius R_0; the optimized value of the inert core radius should be $R_0\xi_{C,optimized}$ based on Eq. 15. The loading capability of the column packed with inert core adsorbent is relatively low compared with fully porous particle with the same size.

It should be pointed out that there is no restriction to the sizes of inert core particles; hence, no limitation to their binding capacity unless other concerns come into play, such as particle rigidity and technical difficulties in producing bigger inert core particles. For the purpose of reducing the pressure drop across the column, while maintaining or increasing the separation efficiency, we propose a strategy for the design of new adsorbent as stationary phase based on the optimized value of the inert core radius. The procedure is shown in Figure 4 for design of new adsorbent based on the optimized value $\xi_{C,optimized}$.

Assuming the volume of the thin porous layer of the new adsorbent with radius R is φ_1 times to that of the fully porous particle with radius R_0, if the same value of $\xi_{C,\text{optimized}}$ is kept, we have

$$\varphi_1 \frac{4}{3}\pi R_0^3 = \frac{4}{3}\pi R^3 - \frac{4}{3}\pi\left(R\xi_{C,\text{optimized}}\right)^3 \tag{16}$$

That is

$$R = \lambda R_0 \tag{17}$$

where

$$\lambda = \left(\frac{\varphi_1}{1-\xi^3_{C,\text{optimized}}}\right)^{\frac{1}{3}} \tag{18}$$

Let n be the number of particles packed in the column, we have

$$\pi\frac{D_0^2}{4}L_0(1-\varepsilon_{B0}) = n\frac{4}{3}\pi R_0^3 \tag{19}$$

where ε_{B0} is the bed porosity.

Equation 19 leads to the result

$$n = \frac{3D_0^2 L_0(1-\varepsilon_{B0})}{16R_0^3} \tag{20}$$

Let the new column have a dia. $D = \varphi_2 D_0$ with φ_3 times loading amount of ligand, that is, to keep φ_3/φ_1 times number of packing particles, we, thus, have

$$\frac{\varphi_3}{\varphi_1} n \frac{4}{3}\pi R^3 = \pi\frac{D^2}{4}L(1-\varepsilon_B) \tag{21}$$

Equation 21 leads to the result

$$\frac{L}{L_0} = \frac{\varphi_3}{\varphi_1}\frac{(1-\varepsilon_{B0})}{(1-\varepsilon_B)}\left(\frac{D_0}{D}\right)^2\left(\frac{R}{R_0}\right)^3 = \frac{\varphi_3\lambda^3}{\varphi_1\varphi_2^2}\frac{(1-\varepsilon_{B0})}{(1-\varepsilon_B)} \tag{22}$$

If we keep the flow rate as $\varphi_4 Q_0$, the pressure drop is now

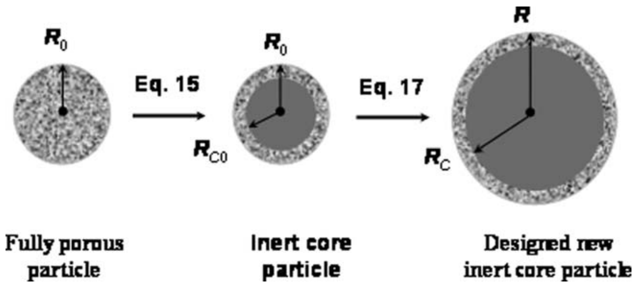

Figure 4. The procedure for design of new adsorbent based on the optimized value $\xi_{C,optimized}$.

Table 1. Pressure Drop, Resolution Ratio and Superficial Velocity for the New Column: Case of Inert Core Particle with the Same Ligand-Loading of the Fully Porous Particle

$\xi_{C,optimized}$	λ	Θ	Particle radius, R	Column diameter, D	Column length, L	Pressure drop, ΔP	Resolution ratio, η	Flow velocity, u
0	1	5	R_0	D_0	L_0	ΔP_0	1	u_0
$\xi_{C,optimized}$	Eq. 18	Eq. 3	λR_0	λD_0	λL_0	$\frac{1}{\lambda^3}\Delta P_0$	Eq. 36	$\frac{1}{\lambda^2}u_0$
0.6	1.08	7.95	$1.08\ R_0$	$1.08\ D_0$	$1.08\ L_0$	$\frac{1}{1.26}\Delta P_0$	1.09	$\frac{1}{1.17}u_0$
0.63*	1.10	8.51	$1.10\ R_0$	$1.10\ D_0$	$1.10\ L_0$	$\frac{1}{1.33}\Delta P_0$	1.11	$\frac{1}{1.21}u_0$
0.9	1.55	30.08	$1.55\ R_0$	$1.55\ D_0$	$1.55\ L_0$	$\frac{1}{3.72}\Delta P_0$	1.50	$\frac{1}{2.40}u_0$
0.95	1.91	60.06	$1.91\ R_0$	$1.91\ D_0$	$1.91\ L_0$	$\frac{1}{6.97}\Delta P_0$	1.78	$\frac{1}{3.65}u_0$

*Fused-Core$^{\text{TM}}$ particle.[13]

$$\Delta P = \varphi_4 \Delta P_0 \frac{\frac{L}{D^2R^2}}{\frac{L_0}{D_0^2R_0^2}} = \Delta P_0 \frac{\varphi_3\varphi_4\lambda}{\varphi_1\varphi_2^4}\frac{(1-\varepsilon_{B0})}{(1-\varepsilon_B)} \tag{23}$$

The superficial velocity u based on $\pi D^2 u = \varphi_4 \pi D_0^2 u_0$ is now

$$u = \varphi_4 \frac{D_0^2}{D^2} u_0 = \frac{\varphi_4}{\varphi_2^2} u_0 \tag{24}$$

Let us now consider the separation efficiency. For simplification, we take an example for the new inert core particle with the same volume and ligand-loading as that of the fully porous particle (i.e., $\varphi_1 = 1$ and $\varphi_3 = 1$), the new column with a dia. $D = \lambda D_0$ (i.e., $\varphi_2 = \lambda$).

For uniform particle the average porosity of the column is a function of R/D.[24] If $R/D = R_0/D_0$, we have

$$1 - \varepsilon_B = 1 - \varepsilon_{B0} \tag{25}$$

and then

$$L = \lambda^3 \frac{L_0}{\lambda^2} = \lambda L_0 \tag{26}$$

Case 1. Maintaining the same flow rate (i.e., $\varphi_4 = 1$)

The pressure drop is now

$$\Delta P = \Delta P_0 \frac{\varphi_3\varphi_4\lambda}{\varphi_1\varphi_2^4}\frac{(1-\varepsilon_{B0})}{(1-\varepsilon_B)} = \frac{1}{\lambda^3}\Delta P_0 \tag{27}$$

The superficial velocity u is

$$u = \frac{\varphi_4}{\varphi_2^2} u_0 = \frac{1}{\lambda^2} u_0 \tag{28}$$

(1) Axial dispersion coefficient D_L

Let, $\varepsilon_s = 0.35$,[2] we have

$$D_{L0} = 0.643\varepsilon_{B0}D_M + R_0u_0, \text{and } D_L = 0.643\varepsilon_{B0}D_M + \frac{1}{\lambda}R_0u_0 \tag{29}$$

(2) *HETP*

Based on Eq. 8, for $\xi_c = 0$, we have

$$HETP_0 = \frac{2}{(1-\varepsilon_{B0})}\left(\frac{u_0R_0^2}{L_0}\right) \times \left[\frac{1}{3}\left(\frac{1}{5}\frac{\tau}{\varepsilon_S D_M} + \frac{1}{k_{f0}R_0}\right) + \frac{1}{R_0^2}\frac{1}{k_{\text{ads}}}\right] + \frac{2\varepsilon_{B0}}{u_0L_0}(0.643\varepsilon_{B0}D_M + R_0u_0) \tag{30}$$

for the new column

$$HETP = \frac{2}{(1-\varepsilon_{B0})}\left(\frac{u_0R_0^2}{L_0}\right) \times \left[\frac{1}{3\lambda}\left(\frac{1}{\Theta}\frac{\tau}{\varepsilon_S D_M} + \frac{1}{\lambda^{0.66}k_{f0}R_0}\right) + \frac{1}{R_0^2}\frac{1}{k_{\text{ads}}}\right] + \frac{2\varepsilon_{B0}}{u_0L_0}(0.643\lambda\varepsilon_{B0}D_M + R_0u_0) \tag{31}$$

Let γ be the efficiency ratio of both the "new" and "old" columns (the ratio of theoretical plate number), we have

$$\gamma = \frac{N_T}{N_{T0}} = \frac{HETP_0}{HETP} \tag{32}$$

after arrangement

$$\gamma = \frac{\frac{1}{15}\frac{\tau R_0^2}{\varepsilon_S D_M} + \frac{1}{3}\frac{R_0}{k_{f0}} + \frac{1}{k_{\text{ads}}} + \varepsilon_{B0}(1-\varepsilon_{B0})\left(0.643\frac{\varepsilon_{B0}D_M}{u_0^2} + \frac{R_0}{u_0}\right)}{\frac{1}{3\lambda\Theta}\frac{\tau R_0^2}{\varepsilon_S D_M} + \frac{1}{3\lambda^{1.66}}\frac{R_0}{k_{f0}} + \frac{1}{k_{\text{ads}}} + \varepsilon_{B0}(1-\varepsilon_{B0})\left(0.643\lambda\frac{\varepsilon_{B0}D_M}{u_0^2} + \frac{R_0}{u_0}\right)} \tag{33}$$

Typically $\varepsilon_{B0} \approx 0.4$, $\tau \approx 2.5$,[2] we have

$$\gamma = \frac{\frac{7.14R_0^2}{D_M} + \frac{5R_0}{k_{f0}} + \frac{15}{k_{\text{ads}}} + \frac{0.925D_M}{u_0^2} + \frac{3.6R_0}{u_0}}{\frac{35.7}{\lambda\Theta}\frac{R_0^2}{D_M} + \frac{5}{\lambda^{1.66}}\frac{R_0}{k_{f0}} + \frac{15}{k_{\text{ads}}} + 0.925\lambda\frac{D_M}{u_0^2} + \frac{3.6R_0}{u_0}}. \tag{34}$$

For convenience, we only consider the case for supercritical fluid chromatography. Usually D_M, u_0, R_0, k_{f0} and k_{ads} has the following order of magnitude in supercritical fluid carbon dioxide.[2,3]

$D_M \sim 10^{-10}\text{m}^2/\text{s}, u_0 \sim 10^{-3}\text{m/s}, R_0 \sim 10^{-5}\text{m}, k_{f0} \sim 10^{-6}$ m/s, and $k_{\text{ads}} \sim 10s^{-1}$ (assumed) $\psi \sim 0.01$. Thus

$$\gamma = \frac{7.14 + 50 + 1.5 + 0.925 \times 10^{-4} + 0.036}{\frac{35.7}{\lambda\Theta} + \frac{50}{\lambda^{1.66}} + 1.5 + 0.925 \times 10^{-4}\lambda + 0.036} \approx \frac{58}{\frac{35}{\lambda\Theta} + \frac{50}{\lambda^{1.66}} + 1} \tag{35}$$

It is evident that the intraparticle diffusional resistance, the external mass-transfer resistance, and the sorption rate are dominant for resolution of racemates in supercritical fluid chromatography.

Therefore, the ratio of the resolution factors η, is

$$\eta = \frac{R_S}{R_{S0}} = \sqrt{\gamma} = \sqrt{\frac{58}{\frac{35}{\lambda\Theta} + \frac{50}{\lambda^{1.66}} + 1}} \tag{36}$$

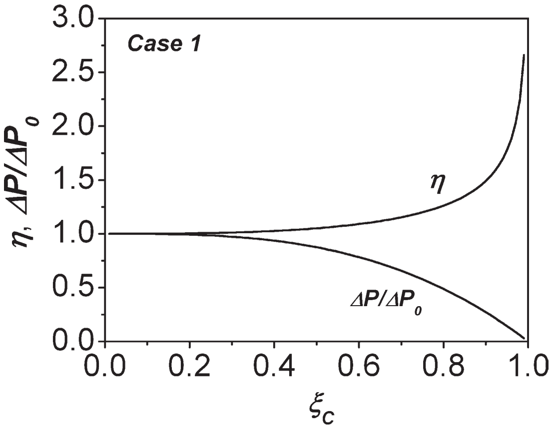

Figure 5. Effect of ξ_c on pressure drop $\Delta P/\Delta P_0$, and the ratio of the resolution factors η for *Case 1* (maintaining the same flow rate).

in which one assumed that retention factor k and α selectivity factor did not change, because for the inert core adsorbent those quantities are only related to the physical properties of the stationary phase.

Table 1 is the summary for the evaluation results for the case that keeps both the same loading amount of ligand and the same treatment capability (same feed flow rate).

The third row in Table 1 for $\xi_c = 0.6$, and particle radius $1.08R_0$ shows that if one sets a new column as dia. $1.08D_0$, length $1.08L_0$ with the same flow rate (the flow velocity is u_0/1.17), then pressure drop is ΔP_0/1.26, and the resolution factor increases 1.09 times. Furthermore, as shown in the fourth row in Table 1 for $\xi_c = 0.95$ and particle radius $1.91R_0$, if one sets a new column as diameter $1.91D_0$, length $1.91L_0$ with the same flow rate Q_0 (the flow velocity is u_0/3.65), then pressure drop is only ΔP_0/6.97, and the resolution factor increases 1.78 times.

The effect of ξ_c on the pressure drop $\Delta P/\Delta P_0$ and on the ratio of the resolution factor η for Case 1 (maintaining the same flow rate) is shown in Figure 5. The *HETP* is not sensitive to $\xi_{C,optimized}$ when $\psi < 0.01$, as shown in Figure 3; ξ_c can be choice in a wide range.

Increase of ξ_c favors the operation performance (lower the pressure drop); however, *HETP* increases greatly once apart from the optimized value ξ_c, as shown in Figure 2.

Case 2. Increasing feed flow rate to λQ_0 (i.e.,$\varepsilon_4 = \lambda$)

The pressure drop is now

$$\Delta P = \frac{1}{\lambda^2}\Delta P_0 \tag{37}$$

The superficial velocity is now $u = \frac{\varphi_4}{\varphi_2^2}u_0 = \frac{1}{\lambda}u_0$, and

$$D_{L0} = 0.643\varepsilon_{B0}D_M + R_0u_0, \text{and } \; D_L = 0.643\varepsilon_{B0}D_M + R_0u_0 \tag{38}$$

For the new column, the dimensionless *HEPT* is

$$HETP = \frac{2}{(1-\varepsilon_{B0})}\left(\frac{u_0R_0^2}{L_0}\right) \times \left[\frac{1}{3}\left(\frac{1}{\Theta}\frac{\tau}{\varepsilon_S D_M} + \frac{1}{k_{f0}R_0}\right) + \frac{\lambda}{R_0^2}\frac{1}{k_{\text{ads}}}\right] + \frac{2\varepsilon_{B0}}{u_0L_0}(0.643\varepsilon_{B0}D_M + R_0u_0) \tag{39}$$

Thus, similarly, we have

$$\gamma \approx \frac{58}{\frac{35}{\Theta} + 50 + \lambda} \tag{40}$$

and

$$\eta = \sqrt{\frac{58}{\frac{35}{\Theta} + 50 + \lambda}} \tag{41}$$

Table 2 is the summary for the evaluation results for the case that keeps the same loading amount of ligand, but where the treatment capability (feed flow rate) increases by a factor of λ.

The third row in Table 2 for $\xi_c = 0.60$, and particle radius $1.08Q_0$ shows that if one sets a new column as diameter $1.08D_0$, length $1.08L_0$ with the flow rate $1.08Q_0$ (the flow velocity is u_0/1.08), then the pressure drop is ΔP_0/1.17, and the resolution factor increases 1.02 times.

Furthermore, as shown in the fourth row in Table 2 for $\xi_c = 0.95$, and particle radius $1.91R_0$, if one sets a new column with diameter $1.91D_0$, length $1.91L_0$ with the flow rate $1.91Q_0$ (the flow velocity u_0/1.91), then the pressure drop is only ΔP_0/3.65, and the resolution factor increases 1.05 times.

Figure 6 shows the effect of ξ_c on the pressure drop ratio $\Delta P/\Delta P_0$, on the ratio of the resolution factors η, and on the flow rate ratio Q/Q_0 for Case 2 (increasing flow rate to λQ_0).

Table 2. Pressure Drop, Resolution Ratio and Superficial Velocity for the New Column: Case of Inert Core Particle with the Same Ligand-Loading of the Fully Porous Particle, but λ Times the Treatment Capability

$\xi_{C,optimized}$	λ	Θ	Particle radius, R	Column diameter, D	Column length, L	Pressure drop, ΔP	Resolution ratio, η	Flow rate, Q	Flow velocity, u
0	1	5	R_0	D_0	L_0	ΔP_0	1	Q_0	u_0
$\xi_{C,optimized}$	Eq. 18	Eq. 3	λR_0	λD_0	λL_0	$\frac{1}{\lambda^2}\Delta P_0$	Eq. 41	λQ_0	$\frac{1}{\lambda}u_0$
0.6	1.08	7.95	1.08 R_0	1.08 D_0	1.08 L_0	$\frac{1}{1.17}\Delta P_0$	1.02	1.08 Q_0	$\frac{1}{1.08}u_0$
0.63*	1.10	8.51	1.10 R_0	1.10 D_0	1.10 L_0	$\frac{1}{1.21}\Delta P_0$	1.03	1.10 Q_0	$\frac{1}{1.10}u_0$
0.9	1.55	30.08	1.55 R_0	1.55 D_0	1.55 L_0	$\frac{1}{2.40}\Delta P_0$	1.05	1.55 Q_0	$\frac{1}{1.55}u_0$
0.95	1.91	60.04	1.91 R_0	1.91 D_0	1.91 L_0	$\frac{1}{3.65}\Delta P_0$	1.05	1.91 Q_0	$\frac{1}{1.91}u_0$

*Fused-Core™ particle.[13]

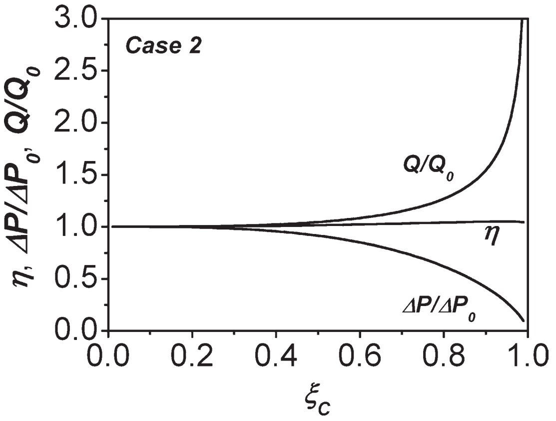

Figure 6. Effect of ξ_c on pressure drop $\Delta P/\Delta P_0$, the ratio of the resolution factors η, and flow rate Q/Q_0 for *Case 2* (increasing feed flow rate to λQ_0).

Conclusions

A new strategy was presented for tailored design of the column chromatography with higher efficiency and lower pressure drop by packing inert core adsorbents as stationary phase. The optimized value of inert core is obtained by solving a nonlinear algebraic equation, which is derived from a new expression for the height equivalent to a theoretical plate (*HETP*) under linear adsorption equilibrium by taking into account of the axial dispersion, film mass-transfer resistance, intraparticle diffusion resistance, and the sorption rate for chromatographic column packed with inert core adsorbents. As an example for supercritical carbon dioxide chromatography, reduced equations in terms of dimensionless core radius were derived by order of magnitude analysis. The quantitative analysis shows that the major benefit of the inert core adsorbent is small diffusion path compared to conventional fully porous particles. The shorter diffusion path reduces dispersion of solutes and minimizes peak broadening leading to lower pressure drop while maintaining high-separation efficiency.

In summary, the advantages of the packed chromatographic column with inert core adsorbents designed with the aforementioned strategy are (1) lower pressure drop across the column and higher efficiency, (2) higher resolution than in conventional HPLC, and increasing feed flow rate, and (3) more flexibility for designing the column.

It should be mentioned that the method can only be applied for linear chromatography, mainly for analytical purposes. In the case of preparative chromatography, the column works in nonlinear isotherm range.

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Notation

Bi = Biot number ($= k_f R/\varepsilon_s D_P$)
D = inner column diameter, m
D_L = longitudinal dispersion coefficient, $m^2 \cdot s^{-1}$
D_M = molecular diffusivity, $m^2 \cdot s^{-1}$
D_p = effective pore diffusivity, $m^2 \cdot s^{-1}$
K = Henry equilibrium constant, $m^3 \cdot kg^{-1}$
k = retention factor
k_{ads} = kinetic constant for adsorption, s^{-1}
k_f = external mass-transfer coefficient, $m \cdot s^{-1}$
L = length of column, m
N_T = theoretical plate number
Pe = Pelect number based on adsorber length ($= uL/\varepsilon_B D_L$)
Q = flow rate, $m^3 \cdot s^{-1}$
R = radius of the adsorbent, m
R_c = radius of adsorbent inert core, m
R_s = degree of separation
u = average velocity in the interparticle space in the column, $m \cdot s^{-1}$

Greek letters

α = selectivity factor
γ = the efficiency ratio of both the "new" and "old" columns
η = the ratio of the resolution factor
μ_1' = the first absolute moment
μ_2' = the second central moment
μ_f = viscosity of fluid, Pa·s
ε_B = voidage of column
ε_s = voidage of adsorbent shell
θ = ratio of time constants for convection in outer fluid and pore diffusion ($= LD_p/uR^2$)
λ = Eq. 18
ρ_f = density of fluid, $kg \cdot m^{-3}$
ρ_s = density of adsorbent shell, $kg \cdot m^{-3}$
ξ_c = dimensionless radius of adsorbent inert core ($= R_c/R_0$)
ξ_m = adsorption capacity factor ($= K\rho_s/\varepsilon_s$)
τ = tortuosity factor
υ = distribution ratio $[= (1 - \varepsilon_B)\varepsilon_S/\varepsilon_B]$
ψ = dimensionless adsorption rate constant $\left(= k_{\mathrm{ads}}R^2/D_p K \rho_S\right)$
ΔP = pressure drop across the column

Subscripts

0 = state for fully porous particle

Literature Cited

1. Guiochon G, Felinger A, Katti AM, Shirazi D. *Fundamentals of Preparative and Nonlinear Chromatography*. Amsterdam: Elsevier, 2006.
2. Ruthven DM. *Principles of Adsorption and Adsorption Processes*. New York: Wiley, 1984.
3. Rajendran A, Peper S, Johannsen M, Mazzotti M, Morbidelli M, Brunner G. Enantioseparation of 1-phenyl-1-propanol by supercritical fluid-simulated moving bed chromatography. *J Chromatogr A*. 2005;1092:55–64.
4. Kirkland JJ. Superficially porous silica microspheres for the fast high-performance liquid chromatography of macromolecules. *Anal Chem*. 1992;64:1239–1245.
5. Wang X, Barber WE, Carr PW. A practical approach to maximizing peak capacity by using long columns pocked with pellicular stationary phases for proteomic research. *J Chromatogr A*. 2006;1107:139–151.
6. Kaczmarski K, Guiochon G. Modeling of the mass-transfer kinetics in chromatographic columns packed with shell and pellicular particles. *Anal Chem*. 2007;79:4648–4656.
7. Cavazzini A, Gritti F, Kaczmarski K, Marchetti N, Guiochon G. Mass-transfer kinetics in a shell packing material for chromatography. *Anal Chem*. 2007;79:5972–5979.
8. Li P, Xiu GH, Rodrigues AE. Analytical breakthrough curves for inert core adsorbent with sorption kinetics. *AIChE J*. 2003;49:2974–2979.
9. Li P, Xiu GH, Rodrigues AE. Modeling breakthrough and elution curves in fixed-bed of inert core adsorbents: analytical and approximate solutions. *Chem Eng Sci*. 2004;59:3091–3103.

10. Kirkland JJ, Truszkowski FA, Dilks Jr CH, Engel GS. Superficially porous silica microspheres for fast high-performance liquid chromatography of macromolecules. *J Chromatogr A*. 2000;890:3–13.
11. DeStefano JJ, Langlois TJ, Kirkland JJ. Characteristics of superficially-porous silica particles for fast HPLC: Some performance comparisons with sub-2 μm particles. *J Chromatogr Sci*. 2008;46:254–260.
12. Ricker R. Using ZORBAX poroshell 300Extend-C18 to achieve unique selectivity at pH 2 and 10: Angiotensins. Agilent Technologies, publication 5989–0676EN. Available at: www.agilent.com/chem.
13. Halo^{TM}particles are designed for hyper-fast HPLC. www.mac-mod.com/pb/halo-pb.html.
14. Li P. *Proteins Separation and Purification by Expanded Bed Chromatography and Simulated Moving Bed Technology*. Ph.D. Thesis. Portugal: University of Porto, 2006.
15. Miyabe K, Guiochon G. The moment equations of chromatography for monolithic stationary phases. *J Phys Chem*. 2002;106:8898–8909.
16. Horvath CG, Lipsky SR. Peak capacity in chromatography. *Anal Chem*. 1967;39:1893–1899.
17. Owen RO, Chase HA. Modeling of the continuous counter-current expanded bed adsorber for the purification of proteins. *Chem Eng Sci*. 1999;54:3765–3781.
18. Hunter AK, Carta G. Protein adsorption on novel acrylamido-based polymeric ion exchangers. II. Adsorption rates and column behavior. *J Chromatogr A*. 2000;897:81–97.
19. Suzuki M. *Adsorption Engineering*. Amsterdam: Elsevier, 1990.
20. Rodrigues AE, Ramos AMD, Loureiro JM, Diaz M, Lu ZP. Influence of adsorption-desorption kinetics on the performance of chromatographic processes using large-pore supports. *Chem Eng Sci*. 1992;47:4405–4413.
21. Giddings JC. *Dynamics of Chromatography*. New York: Marcel Dekker, 1960.
22. Kucera E. Contribution to the theory of chromatography. *J Chromatogr*. 1965;19:237–248.
23. Dong MW. *Modern HPLC for Practicing Scientists*. New York: Wiley, 2006.
24. Mueller GE. Radial void fraction distributions in randomly packed fixed beds of uniformly sized spheres in cylindrical containers. *Powder Technol*. 1992;72:269–275.

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