

Pore diffusion and solid diffusion models: Application in countercurrent chromatographic separation process

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Abstract—Difference and equivalence of two approaches for countercurrent chromatographic separation process were discussed. Although the two approaches are different in the TCC process in terms of model equations and definition of phase concentrations and flow rate ratios as well as complete separation regions expressed by flow rate ratios etc., they are equivalent in the SMB process. Experimental and simulation results are consistent with theoretical analysis. In application of the SMB process, it is of crucial importance to use these two approaches consistently.

Key words: Separation, Simulated Moving Bed (SMB) Chromatography, True Counter-Current (TCC) Chromatography, Zone Flow Rate Ratios, Microporous Particles

INTRODUCTION

Due to continuous operation and efficient use of stationary and mobile phases, the countercurrent chromatographic process, especially simulated moving bed (SMB) technique, exhibits a number of advantages in terms of desorbent requirement and productivity. Applied for almost forty years in the hydrocarbon and sugar industries for large-scale separations, SMB technology has recently been down-scaled to apply in the areas of biotechnology, pharmaceuticals and fine chemical applications as well as chiral separations [Houwing et al., 2002; Lee et al., 2006; Muhlbachler et al., 2004; Park et al., 2005; Zhang et al., 2004], due to technique progress and availability of new reliable stationary phases [Abel et al., 2002; Erdem et al., 2006; Zhang et al., 2004]. The first successful chromatographic enantioseparation by applying the SMB principle was published by Negawa and Shoji who separated 1-phenylethanol on Chiralcel OD. This application opened the field of SMB chromatography in the enantioseparation, witnessed by the large number of chiral SMB separations reported in the literature in recent years [Pedferri et al., 1999; Schulte and Strube, 2001].

One of the key issues in operating the SMB process is the determination of zone flow rates and column switching time. Safety margin method, standing wave design method and triangle theory are extensively applied approaches. Among them, safety margin method [Zhong and Guiochon, 1997] and triangle theory [Mazzotti et al., 1997; Storti et al., 1993] are developed in the frame of equilibrium theory, which neglects the effect of axial mixing and mass transfer resistances. In both methods, development of SMB resorts to its corresponding hypothetical true counter-current (TCC) process and the conversion of TCC operation parameters to an SMB unit, using the geometric and kinematic equivalence between the SMB and TCC process. It is worth noting that the solid phase used in SMB is usually microporous particles regardless of the fast development of

mesoporous silica such as MCM and FSM [Kresge et al., 1992]. To date, silica gel bonded chiral stationary phases (CSPs) are still the most important substance for chiral separations. Considering the pore size and dimension of the adsorbate molecular, the liquid phase entrapped by micropores of solid particles (i.e., intra-particle voidage of a column) can be regarded as parts of either a mobile phase or stationary phase. In other words, the adsorbent is described as porous particles and homogeneous particles, respectively (which corresponds to pore diffusion and solid diffusion model, respectively). In batch chromatographic separation, the equivalence of pore diffusion and solid diffusion model is well known. In the TCC process, however, there are two different ways to define liquid to solid flow rate ratios (m_j' or m_j , $j=1, 2, 3, 4$), and thus complete separation regions expressed by m_j' or m_j ($j=1, 2, 3, 4$) for linear TCC operation as well as TCC to SMB conversion rules are different. Nevertheless, it is shown in this paper that the two approaches are equivalent in terms of SMB operations. In summary, the equivalence and difference of the two approaches in SMB separation is elucidated in this paper, and the importance of their consistent application in the design and operation of SMB process is also discussed.

DIFFERENT APPROACHES IN TCC PROCESS

In batch chromatography, the pore-diffusion model and solid-diffusion model are well known models. The difference between the two models is in the description of the intraparticle morphology: the particle has pores large enough to contain adsorbate molecular in the first case and a single concentration is present inside the particle (i.e., the particle is homogeneous in nature) in the second case. In TCC and its equivalent SMB process, the two models result in different definitions of flow rate ratios and thus different expressions of complete separation regions. Their difference is discussed in this section.

1. Intra-particle Fluid with Liquid Phase Concentration

The following partial differential equation for the generic j th section of ideal 4-zone TCC unit (with no axial dispersion and mass

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transfer resistances) can be derived based on differential mass balance:

$$\frac{\partial C_i^j}{\partial t} + \frac{(1-\varepsilon^*)}{\varepsilon^*} \frac{\partial q_i^j}{\partial t} + \frac{[v_L \varepsilon - v_s(1-\varepsilon)\varepsilon_p]}{\varepsilon^*} \frac{\partial C_i^j}{\partial z} - \frac{v_s(1-\varepsilon)(1-\varepsilon_p)}{\varepsilon^*} \frac{\partial q_i^j}{\partial z} = 0 \quad (1)$$

where the concentration of stationary phase, q_i^j , refers to that of the real "solid" part of the porous particle; the liquid entrapped by porous particles has liquid phase concentration of C_i^j . Note that Eq. (1) becomes dimensionless if one defines $\tau = tQ_s/V$ and $\xi = Az/V$ as the dimensionless time and space coordinates, respectively [Mazzotti et al., 1997]. In Eq. (1), v_L and v_s are the interstitial velocity of liquid phase and solid phase, respectively; $\varepsilon^* = \varepsilon + \varepsilon_p(1-\varepsilon)$ is the overall void fraction of the bed, whereas ε_p is the intraparticle porosity and ε is the bed voidage; i refers to the species to be separated ($i=A, B$) and j to the four sections of the TCC unit ($j=1, 2, 3, 4$). By considering fluid phase to be entrapped by intra-particle micropores, flow rate ratio, m_j^i , is defined as the net fluid flow rate over the solid phase flow rate since liquid entrapped by intraparticle of solid phase moves counter-currently with respect to the bulk liquid phase in the unit:

$$m_j^i = \frac{Q_j^{TCC} - Q_s \varepsilon_p}{Q_s(1-\varepsilon_p)} \quad (2)$$

The steady-state behavior of a TCC unit is determined only by its flow rate ratios. The necessary and sufficient conditions to achieve complete separation of binary mixture of A and B are as follows (A is the more adsorbed species while B is the less adsorbed one) for linear isotherms:

$$H_A < m_1 < \infty \quad (3)$$

$$H_B < m_2 < H_A \quad (4)$$

$$H_B < m_3 < H_A \quad (5)$$

$$m_4 < H_B \quad (6)$$

Based on the equivalence between the SMB and TCC process [Ruthven and Ching, 1989], one has

$$m_j^i = \frac{Q_j^{SMB} t^* - V \varepsilon^*}{V(1-\varepsilon^*)} \quad (7)$$

which relates operating parameters of an SMB unit with its equivalent TCC process. Based on m_j^i of TCC process, one can obtain SMB zone flow rates, Q_j^{SMB} , provided the switching time has been determined (which is a compromise between SMB productivity and system maximum operation pressure).

The equilibrium constant H in Eqs. (3)-(6) can be evaluated from a series of pulse tests at different flow rates in the batch chromatography process:

$$t_R = t_0 \left(\frac{\varepsilon^*}{\varepsilon} + \frac{1-\varepsilon^*}{\varepsilon} H \right) \quad (8)$$

Eq. (8) is readily derived from the fact that retention time, t_R , and dead time, t_0 , are inversely proportional to particle velocity of a solute, v_p , and interstitial velocity of mobile phase, v , respectively. Note that a solute molecule makes its way out of column at the velocity of mobile phase, v , only during the fraction of time they spend in that phase rather than on (or in) the stationary adsorbent. There-

fore, the particle velocity of component i is:

$$v_i = \frac{v}{\frac{\varepsilon^*}{\varepsilon} + \frac{1-\varepsilon^*}{\varepsilon} H_i} \quad (9)$$

2. Intra-particle Fluid with Solid Phase Concentration

In TCC and SMB processes, the liquid entrapped by intra-particles of porous adsorbent can be assumed to have a concentration of solid phase, $C_{s,i}^j$, which suggests that the particle is without micropores [Nicolao et al., 2001]. Accordingly, the following differential mass balance equation of compound i can be derived:

$$\frac{\partial C_i^j}{\partial t} + F \frac{\partial C_{s,i}^j}{\partial t} + v_L \frac{\partial C_i^j}{\partial z} - v_s F \frac{\partial C_{s,i}^j}{\partial z} = 0 \quad (10)$$

where F is the phase ratio and equals to $(1-\varepsilon)/\varepsilon$.

Note that the flow rate ratio m_j of the unit is now defined as:

$$m_j = \frac{Q_j^{TCC}}{Q_s} = \frac{v_L \varepsilon}{v_s(1-\varepsilon)} \quad (11)$$

Combining Eqs. (10) and (11), at steady state, we have:

$$\frac{\partial}{\partial z} (m_j C_i^j - C_{s,i}^j) = 0 \quad (12)$$

To achieve complete separation, the following inequalities should be fulfilled in the linear isotherm region:

$$K_A < m_1 < \infty \quad (13)$$

$$K_B < m_2 < K_A \quad (14)$$

$$K_B < m_3 < K_A \quad (15)$$

$$m_4 < K_B \quad (16)$$

Based on the equivalence between SMB and TCC processes, one can obtain SMB zone flow rates, Q_j^{SMB} based on following equation:

$$m_j = \frac{Q_j^{SMB} t^* - V \varepsilon}{V(1-\varepsilon)} \quad (17)$$

Similarly, as in the previous approach, the equilibrium constant K can be evaluated from a series of pulse tests at different flow rates in the batch chromatography process:

$$t_R = t_0 \left(1 + \frac{1-\varepsilon}{\varepsilon} K \right) \quad (18)$$

which can also be derived from particle velocity of component i :

$$v_i = \frac{v}{1 + \frac{1-\varepsilon}{\varepsilon} K_i} \quad (19)$$

The difference between the two approaches is summarized in Tables 1 and 2, which compare the definition of liquid and solid phase concentrations and the application equations of these two approaches in the TCC process. Both are equilibrium based approaches, i.e., they neglect mass transfer resistances and axial dispersion effects. It is easily noted that the two mass balance equations differ only in the coefficients. In fact, the two approaches become identical (e.g., definition of flow rate ratios, mass balance equations, reten-

Table 1. Liquid and solid phase definition in TCC and SMB process

Column voidage		TCC & SMB approaches	
Different void inside column	Fraction of column	Approach 1 (pore diffusion)	Approach 2 (solid diffusion)
Bed (inter-particle) voidage	ε	Liquid phase concentration, c_i^j	Liquid phase concentration, c_i^j
Micropore of porous adsorbent (intra-particle voidage)	$\varepsilon_p(1-\varepsilon)$	Liquid phase concentration, c_i^j	Solid phase concentration, $C_{s,i}^j$
“Solid” part of adsorbent	$(1-\varepsilon_p)(1-\varepsilon)$	Solid phase concentration, q_i^j	Solid phase concentration, $C_{s,i}^j$

Table 2. Comparison of the two approaches in continuous counter-current chromatographic process

Definition of equations	Approach 1	Approach 2
Definition of flow rate ratios	$m_j = \frac{Q_j^{TCC} - Q_s \varepsilon_p}{Q_s(1-\varepsilon_p)}$	$m_j = \frac{Q_j^{TCC}}{Q_s} = \frac{v_L \varepsilon}{v_s(1-\varepsilon)}$
Model equations	$\frac{\partial C_i^j}{\partial t} + \frac{(1-\varepsilon)}{\varepsilon} \frac{\partial q_i^j}{\partial t} + \left[\frac{v_L \varepsilon - v_s(1-\varepsilon) \varepsilon_p}{\varepsilon} \right] \frac{\partial C_i^j}{\partial z} - \frac{v_s(1-\varepsilon)(1-\varepsilon_p)}{\varepsilon} \frac{\partial q_i^j}{\partial z} = 0$	$\frac{\partial C_i^j}{\partial t} + F \frac{\partial C_{s,i}^j}{\partial t} + v_L \frac{\partial C_i^j}{\partial z} - v_s F \frac{\partial C_{s,i}^j}{\partial z} = 0$
Complete separation regions (in linear isotherm region)	$H_A < m_1 < \infty$ $H_B < m_2 < H_A$ $H_B < m_3 < H_A$ $m_4 < H_B$	$K_A < m_1 < \infty$ $K_B < m_2 < K_A$ $K_B < m_3 < K_A$ $m_4 < H_B$
Retention time in fixed bed	$t_R = t_0 \left(\frac{\varepsilon}{\varepsilon} + \frac{1-\varepsilon}{\varepsilon} H \right)$	$t_R = t_0 \left(1 + \frac{1-\varepsilon}{\varepsilon} K \right)$
Physical meaning of equilibrium constant	$H = \frac{q_i}{C_i}$	$K = \frac{C_{s,i}}{C_i}$
Linear isotherm coefficients	$H = \frac{S - V \varepsilon^*}{V(1-\varepsilon^*)}$	$K = \frac{S - V \varepsilon}{V(1-\varepsilon)}$
Particle velocity of solute i	$v_i = \frac{v}{\frac{\varepsilon}{\varepsilon} + \frac{1-\varepsilon}{\varepsilon} \frac{q_i}{C_i}}$	$v_i = \frac{v}{1 + \frac{1-\varepsilon}{\varepsilon} \frac{C_{s,i}}{C_i}}$
Wave velocity of concentration i	$v_{w(i)} = \frac{v}{\frac{\varepsilon}{\varepsilon} + \frac{1-\varepsilon}{\varepsilon} \frac{dq_i}{dC_i}}$	$v_{w(i)} = \frac{v}{1 + \frac{1-\varepsilon}{\varepsilon} \frac{dC_{s,i}}{dC_i}}$
Switching time in SMB	$t^* = \frac{V(1-\varepsilon)}{Q_s}$	$t^* = \frac{V(1-\varepsilon)}{Q_s}$
Equivalence of TCC and SMB	$m_j = \frac{Q_j^{SMB} t^* - V \varepsilon^*}{V(1-\varepsilon^*)}$	$m_j = \frac{Q_j^{SMB} t^* - V \varepsilon}{V(1-\varepsilon)}$

tion time expressions, TCC and SMB equivalence equations, etc.) if one applies porous solid (pore diffusion model) to the limiting case of homogeneous solid (solid diffusion model) by setting $\varepsilon_p=0$.

EQUIVALENCE OF TWO APPROACHES IN SMB PROCESS

In practical applications ε_p is not equal to 0 and there always exist two different approaches arising from different model assumptions. As a result, the definitions of flow rate ratio, model equations as well as the expressions for complete separation region in the TCC process are different. It is worth noticing the difference and applying either approach consistently. However, it will be shown in this section that the two approaches give the same zone flow rates at the optimal operation condition for the same chromatographic system (sample-column-mobile phase).

Assuming that adsorbent and fluid are regenerated properly in sections 1 and 4 of the four-zone SMB, respectively, it is rather use-

ful to consider the projection of the 4-dimensional spaces of separation region onto the (m_2, m_3) plane, where the triangle-shaped complete separation region is defined. When plotting the experimental retention time of the two eluted components against the reciprocal of mobile phase flow rate, two straight lines can be obtained by fitting the experimental points. From the slopes of the lines, linear equilibrium constants can be determined for the two approaches, respectively, which have different values as shown in Table 2. However, at the optimal SMB operation conditions ($m_2=H_B$, $m_3=H_A$ for approach 1 and $m_2=K_B$, $m_3=K_A$ for approach 2), the SMB unit has the same zone flow rates for these two approaches:

$$Q_2^{SMB} = \frac{S_B}{t^*} \quad (20)$$

$$Q_3^{SMB} = \frac{S_A}{t^*} \quad (21)$$

where S_A and S_B represent the slope of the fitted t_R-1/V lines (V is

mobile phase flow rate) for the more adsorbed and less adsorbed species, respectively.

It can also be shown that at the other two vertexes of the triangle-shaped complete separation region (the vertexes are located at the diagonal line), both approaches obtain the same SMB zone flow rates provided the switching time of columns is identical (i.e., the hypothetical solid moving rate in SMB is identical). Furthermore, it can also be shown (details not given) that both approaches give exactly the same operation conditions for the five-zone SMB process provided the switching time of columns is identical and the safety margin factor is adjusted accordingly. Thus, the two design approaches are equivalent in the SMB process because equal zone flow rates at the optimal operation condition can be obtained for the same chromatographic system. Besides, the SMB operation ranges are also identical for the two approaches.

EXPERIMENTAL AND SIMULATION RESULTS OF A SMB SEPARATION

4-zone SMB separation of the chiral drug propranolol was performed based on the complete separation regions obtained from equilibrium and column parameters [Wang et al., 2006]. Eight columns (250 mm×10 mm, average total porosity 0.66, bed voidage 0.38) packed with perphenyl carbamoylated-CD bonded silica gel were used for the separation. Feed concentration of propranolol was 0.15 mg/ml (which was found to be in the linear isotherm region). The equilibrium constants K_i were found to be 4.36 and 6.31 for (S)- and (R)-propranolol, respectively. Table 3 shows some typical experimental results. In Run 1, proper values of m_1 to m_4 were selected based on the complete separation region by approach 2 while attempts were made to maintain the robustness of operation. From the m_i ($i=1, \dots, 4$) and switching time t^* decided, SMB and TCC conversion rule (bed voidage ε was used) of approach 2 was used to determine the liquid flow rate of SMB and thus the inlet and outlet streams' flow rates. High purity of both raffinate and extract product was found. Complete separation of target drug was also achieved in Run 2 applying approach 1. In Run 3, however, if one applied the conversion rule of approach 1 (total porosity ε^* was used) using the same values of m_1 to m_4 as in Run 1, no separations were found in both product streams. This is due to the inconsistent application of the two approaches. Actually, if one converted the obtained Q_1 to Q_4 in Run 3 to the corresponding liquid to flow rate ratios m' using SMB and TCC conversion rule of approach 1, it can be easily found that the operation conditions were not in complete separation expressed by m' . Simulation of the separation was also conducted, and cyclic steady-state concentration profile for operations at Run 1 and 3 are shown in Fig. 1. Complete separation was found in Run 1 while no separation was achieved in Run 3, which is inconsistent

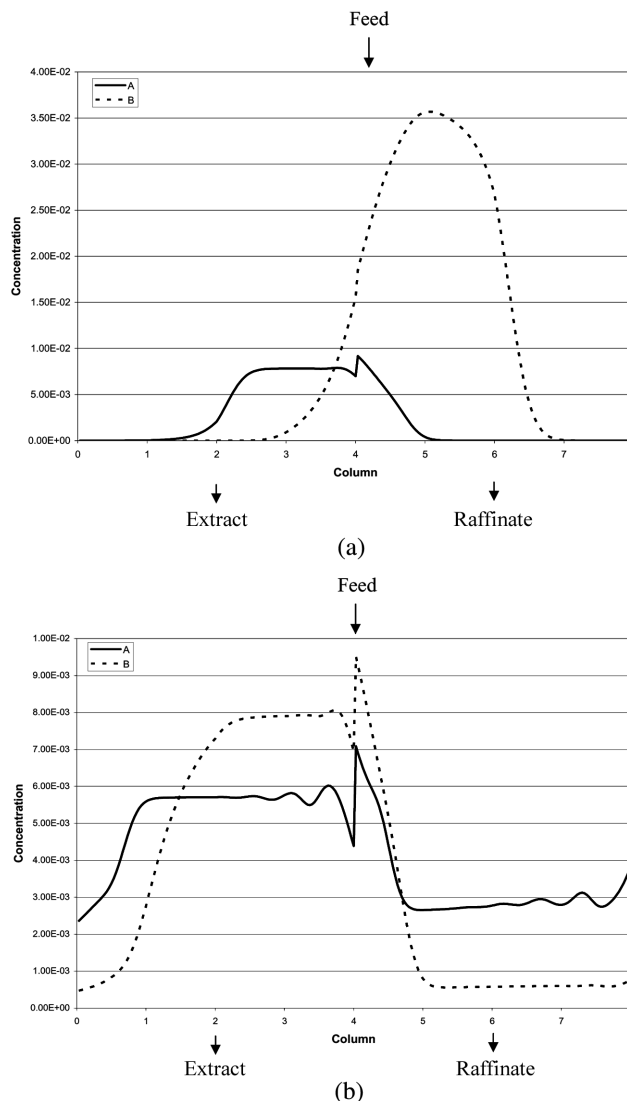


Fig. 1. Steady state concentration distribution profile for propranolol separation in the SMB (A, B represent the more and less retained enantiomer of propranolol hydrochloride, respectively). (a) Run 1; (b) Run 3.

with experimental results. This example shows the importance of understanding the difference of the two approaches in SMB separation, and one should always apply the two models consistently in SMB development.

CONCLUSIONS

We discussed in this paper the difference and equivalence of two

Table 3. Operating conditions and separation results of SMB experiments

Run	Flow rate ratios				Switch time t^* (min)	Flow rates (ml/min)				Product purity (%)	
	m_1	m_2	m_3	m_4		Q_1	Q_F	Q_R	Q_E	Raf	Ext
1	7.19	4.76	4.96	3.58	15	6.33	0.16	1.12	1.97	99.9	99.8
2	12.72	8.5	8.8	5.92	15	6.53	0.13	1.28	1.88	99.8	99.8
3	7.19	4.76	4.96	3.58	10	6.1	0.13	0.92	1.62	46.3	18.5

approaches for countercurrent chromatographic separation process arising from the different definitions of intra-particle liquid concentration. Experimental and simulation results are consistent with theoretical analysis. In application of the SMB process, it is of crucial importance to use TCC to SMB conversion and linear isotherm coefficients expressions consistently. It should be pointed out that the discussion is based on equilibrium theory, which is only applicable for an ideal system. For a nonideal system (whether for linear or nonlinear isotherm), a series of distorted triangular regions can be generated by computer simulations to include mass transfer and axial dispersion effects neglected by the triangle method [Azevedo and Rodriguez, 1999]. Alternately, one can apply the standing wave design method, which provides unique solutions to guarantee high purity and yield operation of SMB process [Mallmann et al., 1998].

NOMENCLATURE

A	: cross section area of chromatographic column
c_i^j	: liquid phase concentration of component i in section j of TCC and SMB
$C_{s,b}$: concentration in stationary phase (mg/ml), refer to Table 1
F	: phase ratio, equal to $(1 - \varepsilon)/\varepsilon$
H	: equilibrium constant (dimensionless), defined by Eq. (8)
K	: equilibrium constant (dimensionless), defined by Eq. (18)
m_j	: fluid phase flow rate over solid phase flow rate in j section of the TCC and SMB unit, defined by Eq. (11)
m_j'	: net fluid phase flow rate over solid phase flow rate in j section of the TCC and SMB unit, defined by Eq. (2)
q_i^j	: concentration of component i on stationary phase in section j of TCC and SMB
$Q_j (Q_j^{SMB})$: liquid phase flow rate in j section of SMB process ($j=1, 2, 3, 4$)
Q_j^{TCC}	: liquid phase flow rate in j section of TCC process
Q_s	: solid phase flow rate in TCC process
Q_E	: extract flow rate of SMB process
Q_F	: feed flow rate of SMB process
Q_R	: raffinate flow rate of SMB process
t	: time coordinate
t_0	: mean retention time of an unretained compound [min]
t_R	: retention time of a component [min]
t^*	: switching time in SMB process [min]
v	: interstitial velocity of mobile phase in a fixed column
v_i	: particle velocity of a solute i
v_L	: interstitial velocity of the fluid phase in TCC and SMB process
v_s	: solid velocity in TCC process
V	: column volume
\dot{V}	: volumetric flow rate of mobile phase
z	: space coordinate
S_A, S_B	: slope of the fitted $t_R - 1/V$ lines

Greek Letters

ε	: bed voidage
ε_p	: intra-particle porosity
ε^*	: total porosity of column
τ	: dimensionless time coordinates ($\tau = tQ_s/V$)
ξ	: dimensionless space coordinates ($\xi = Az/V$)

Subscripts and Superscripts

A	: the more adsorbed component
B	: the less adsorbed component
D	: desorbent
E	: extract product of SMB
R	: raffinate product of SMB
i	: component i
j	: j section of TCC and SMB ($j=1, 2, 3, 4$)
L	: liquid phase
S	: solid phase
SMB	: simulated moving bed chromatography
TCC	: true counter-current chromatography

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