*CHROMATOGRAPHY, Vol.31 No.1 (2010)*

Focusing Review

# Development of New Strategy for Analysis of Chromatographic Behavior on the Basis of Moment Theory

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**Abstract**

The moment theory was used for the analysis of chromatographic behavior. Information about the characteristics and mechanism of chromatographic separation in RPLC mode was quantitatively derived by analyzing experimental data of pulse response (PR) measurements from kinetic and thermodynamic points of view. Especially, some fundamentals of surface diffusion were studied in detail because it has a predominant contribution to the mass transfer in the stationary phase, hence a significant influence on the column efficiency at high flow velocity (fast chromatography). New moment equations were developed for various packing materials having different structural characteristics of shapes and porosities, such as monoliths and shell-type particles, for high speed separations. The peak parking (PP) method was also used for the kinetic study on the molecular migration in the columns and for the development of some experimental techniques relating to the kinetic study on chromatography. The PR and PP methods complement each other. The combination of the two methods and the moment theory leads to a comprehensive strategy for studying the mass transfer kinetics in chromatography.

*Key Words*: Moment analysis, Mass transfer kinetics, Reversed-phase liquid chromatography, Surface diffusion, Pulse response method, Peak parking method

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## 1. Introduction

High performance liquid chromatography (HPLC) has already been essential as a powerful tool for fine separations. However, still now, some apparatuses, e.g., high pressure pumps and high performance columns, have rapidly been developed in order to establish fast chromatography techniques with high efficiency. On the other hand, the further progress of chromatographic technologies needs the pursuit of fundamental studies on the separation mechanism. Chromatographic behavior, such as the sample retention, band broadening, elution peak profile, column efficiency, separation performance, and so on, depends on both the retention equilibrium and mass transfer kinetics in the column. A great number of research works have been carried out so far on the retention equilibrium in chromatography. However, chromatographic behavior has not so abundantly been investigated from kinetic points of view because of some essential difficulties concerning the kinetic study. Additionally, in contrast with the extensive applications of various HPLC instruments and separation media developed in recent decades, it seems that arrangements of theoretical bases and experimental strategies relating to the kinetic study are not well recognized by most chromatographers. Now, it is required to develop a new strategy for the analysis of chromatographic behavior beyond the ordinary “plate theory” and “rate theory” of chromatography [1−3].

The author has developed an analytical system based on the “moment theory” [3−5], which contributes to the kinetic study on chromatographic behavior, and applied the new approach to the experimental study on separation mechanism. Some fundamentals of

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chromatographic separation have also been clarified from the theoretical analyses of the experimental data from the various viewpoints of the retention equilibrium, mass transfer kinetics, and thermodynamic properties. In this review, some items of information about the moment analysis (MA) method and the concrete examples about the mass transfer kinetics derived by the MA method are provided. The progress of some strategies for the kinetic study on chromatography is also introduced.

In the section 2, it is explained why the kinetic study on chromatographic behavior is essentially difficult in comparison with the study on the retention equilibrium. A brief explanation about a framework of the MA method is provided in the section 3. In the section 4, it is described what kind of new information about chromatographic behavior can be obtained by the MA from elution peak profiles experimentally measured. The section 5 is devoted to indicate the results of some characteristics and mechanism of surface diffusion, which has not appropriately been recognized for several decades in the community of chromatography. The recent progress of some strategies for the kinetic study on chromatography is also introduced in the section 6.

There are semantic discussions about the retention mechanism of chromatography, for example, “partition” or “adsorption” in RPLC. However, in this review, it is regarded as adsorption phenomena in a wide sense that sample molecules migrate between the mobile and stationary phases and that the sample molecules are consequently concentrated on the stationary phase surface. It is not intended to discuss the retention mechanism. The author would like to focus the main subject of this review on the quantitative analysis of the kinetic aspects in chromatography.

## 2. Background of the kinetic study on chromatography

Fundamental studies on chromatographic behavior have so far been mainly pursued from the viewpoint of the retention equilibrium because chromatography primarily depends on the phase equilibrium thermodynamics [3]. In comparison with a great number of research works on the chromatographic retention, the kinetic study on chromatography has not sufficiently been carried out. Mass transfer taking place in HPLC columns and stationary phases should quantitatively be studied in more detail for well understanding some important characteristics of chromatographic separations.

It is the most conventional approach for the kinetic study on chromatography to analyze the flow rate dependence of HETP ($H$). Some ordinary rate equations, such as the van Deemter equation and the Knox equation, have extensively been used to account for the dependence of HETP on the mobile phase flow velocity [1−3]. It has also been recognized that band broadening rests on the contributions of several mass transfer processes in the column. For example, as illustrated in Figure 1, the four kinetic processes are taken into account in the general rate (GR) model of chromatography [3−10], i.e., (1) the axial mixing in the bulk mobile phase percolating between packing materials (axial dispersion), (2) the diffusive migration of sample molecules between bulk mobile phase and the external surface of stationary phase (external mass transfer), (3) the diffusive migration of sample molecules through pores inside separation media (intra-stationary phase diffusion), and (4) the adsorption-desorption process at actual reaction sites on the stationary phase surface (adsorption-desorption kinetics). The flow rate dependence of HETP must provide some items of significant information about the mass transfer kinetics in the column and in the stationary phase. However, it is hard to extract the important information about the mass transfer kinetics from the curved profile representing the dependence of $H$ on the mobile phase flow velocity. As indicated in Table 1, it seems that fundamental studies on the mass transfer kinetics are more difficult than those of the retention

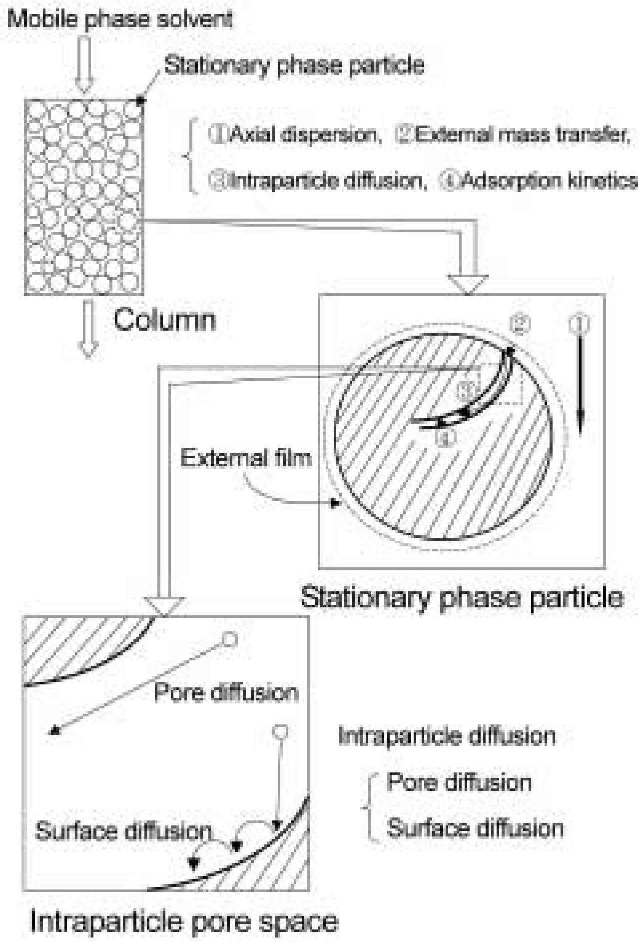

**Figure 1.** Schematic illustration of the mass transfer processes in the column. [Reproduced with permission from [7], K. Miyabe, G. Guiochon: Measurement of the parameters of the mass transfer kinetics in high performance liquid chromatography. J. Sep. Sci. 2003. 26. 155−173. Copyright Wiley-VCH Verlag GmbH & Co. KGaA].

**Table 1.** Comparison of the study on the retention equilibrium with that on the mass transfer kinetics in chromatography

| | Retention equilibrium | Mass transfer kinetics |
|---|---|---|
| Theory | Thermodynamics | Rate theory of chromatography<br>Moment analysis |
| Experimental data | | |
| Type | Retention time ($t_R$)<br>First absolute moment ($\mu_1$) | Peak variance ($\sigma^2$)<br>Second central moment ($\mu_2$') |
| Accuracy | High | Relatively low |
| Precision | High | Relatively low |
| Number | A few | Many |

equilibrium. There would be the following three barriers, which prevent the progress of kinetic studies on chromatography.

At first, in principle, it is required for the kinetic study to measure far more experimental data than the study on the chromatographic retention. The latter needs the information about only the chromatographic retention, i.e., the retention time ($t_R$) or first absolute moment ($\mu_1$) of an elution peak. On the other hand, the former needs the information about the band broadening, i.e., the variance ($\sigma^2$) or second central moment ($\mu_2$') of the peak, other than $t_R$ or $\mu_1$. Additionally, a number of chromatographic data must be measured in a wide range of the mobile phase flow velocity in order to sufficiently represent the flow rate dependence of HETP. It is required to experimentally measure elution peaks as many as possible because the whole profile of the curved correlation between HETP and the mobile phase flow velocity is essential to accurately determine some related kinetic parameters. In contrast with the kinetic study, we could go so far as to say that an equilibrium parameter, such as the retention equilibrium constant ($K_a$ or $K$) and the retention factor ($k$), can be obtained from only one datum of elution peak. The number of experimental data for the kinetic study on chromatography is much more than that for the retention equilibrium.

Second, accurate measurement of $\sigma^2$ or $\mu_2$' is more difficult than that of $t_R$ or $\mu_1$. This means that the error for the experimental measurement of $H$ is larger than that for $K_a$ or $K$ and $k$. Although the values of $\mu_1$ and $\mu_2$' are obtained by integrating an elution peak profile in a range of time, the integration time range required for the determination of $\mu_2$' is wider than that of $\mu_1$. The difficulty in the measurement of accurate value of $\mu_2$' leads to the error of the second moment analysis. Ultimately, it is more difficult to accurately measure the flow rate dependence of HETP than the determination of $K_a$ or $K$ and $k$. On the other hand, it is not so difficult to measure the equilibrium parameters with the relative standard deviation (RSD) less than 1%. However, it seems that the RSD for the measurement of the HETP and the number of theoretical plates is around several percent.

Third, the study on the retention equilibrium rests on the solid basis, i.e., thermodynamics. On the other hand, the conventional rate equations are not sufficient for the detailed analysis of the mass transfer kinetics in chromatography from the curved profile of the flow rate dependence of HETP. Although they are quite popular [1−3], they are empirical and contain several fitting parameters, of which the physical definition and meanings are not necessarily clear. Consequently, they do not provide sufficiently quantitative information about some kinetic parameters relating to the mass transfer processes in chromatography.

## 3. Moment Analysis Theory

There are other theories and models for analyzing chromatographic behavior. The MA method is one of them. It is based on the GR model of chromatography [3−8]. The information about the retention equilibrium and the mass transfer kinetics in the column is derived from $\mu_1$ and $\mu_2$' of elution peaks experimentally measured, respectively. Similar to the ordinary manner of kinetic studies of chromatography using the conventional rate equations, the flow rate dependence of HETP is analyzed for deriving the kinetic information. It is also assumed in the MA theory that the HETP consists of the contributions of several mass transfer processes in the column. On the other hand, the physical meanings of all the parameters included in the moment equations are clearly defined because they are mathematically derived on the basis of the GR model of chromatography. The information about the mass transfer kinetics in the column and the stationary phase can quantitatively be obtained with physically sound justification. This is the most important difference between the MA method of chromatography and the ordinary kinetic study with the conventional rate equations.

The MA method has been introduced in some previous literature [3−8]. However, it is not probably recognized that the MA method is an effective approach for the kinetic study of chromatography. It is not so familiar with most chromatographers because it is difficult to find the detailed information about the fundamentals of the MA method and the practical MA procedure in the conventional literature and textbooks of chromatography. For the sake of readers, some basic information about the framework of the MA method is briefly explained in the following.

### 3.1. Moment Equations

The moment equations are mathematically derived from the basic equations of the GR model of chromatography, which are the partially differential equations representing the material balance and the mass transfer rates in the column and in the stationary phase [3−8, 11, 12]. When full-porous spherical particles are used as the stationary phase, the moment equations are represented as follows. At first, $\mu_1$ represents the position of an elution peak and is correlated with $K_a$.

$$\mu_1 = \frac{\int_0^\infty Ce(t)\,t\,dt}{\int_0^\infty Ce(t)\,dt} = \frac{L}{u_0}\left[\varepsilon_e + (1-\varepsilon_e)\{\varepsilon_i + (1-\varepsilon_i)K_a\}\right] \qquad (1)$$

where Ce($t$) is the concentration profile of the sample compound at the exit of the column as a function of time ($t$), $L$ the length of the column, $u_0$ the superficial velocity of the mobile phase solvent, $\varepsilon_e$ the void fraction of the column (external porosity), and $\varepsilon_i$ the porosity of the stationary phase (internal porosity). Although Eq. (1) appears to be slightly complicated, it indicates the same correlation as the following equation when the elution peak is symmetrical. Equation (2) is well known in the community of chromatography.

$$t_R = t_0(1+k) \qquad (2)$$

where $t_0$ is the elution time of an inert tracer. When the elution peak has a symmetrical profile, $\mu_1$ is equal to $t_R$. On the other hand, $\mu_2'$ is represented as follows.

$$\mu_2' = \frac{\int_0^\infty Ce(t)(t-\mu_1)^2\,dt}{\int_0^\infty Ce(t)\,dt} = \frac{2L}{u_0}(\delta_{ax} + \delta_f + \delta_d + \delta_{ads}) \qquad (3)$$

$$\delta_0 = \varepsilon_e + (1-\varepsilon_e)\{\varepsilon_i + (1-\varepsilon_i)K_a\} \qquad (4)$$

$$\delta_{ax} = \left(\frac{\varepsilon_e D_L}{u_0^2}\right)\delta_0^2 \qquad (5)$$

$$\delta_f = (1-\varepsilon_e)\left(\frac{R_p}{3k_f}\right)\{\varepsilon_i + (1-\varepsilon_i)K_a\}^2 \qquad (6)$$

$$\delta_d = (1-\varepsilon_e)\left(\frac{R_p^2}{15D_e}\right)\{\varepsilon_i + (1-\varepsilon_i)K_a\}^2 \qquad (7)$$

$$\delta_{ads} = (1-\varepsilon_e)(1-\varepsilon_i)\frac{K_a^2}{k_{ads}} \qquad (8)$$

where $D_L$ is the axial dispersion coefficient, $k_f$ the external mass transfer coefficient, $D_e$ the intraparticle diffusivity, $k_{ads}$ the adsorption rate coefficient, $R_p$ the radius of stationary phase particle and $\delta$ the contribution of each mass transfer process to $\mu_2'$. The subscripts ax, f, d, and ads denote the axial dispersion, external mass transfer, intraparticle diffusion, and adsorption-desorption kinetics, respectively. Similar to $\mu_1$, $\mu_2'$ is equal to the variance ($\sigma^2$) of an elution peak, which is one of well known chromatographic parameters. Equations (3)−(8) indicate that the band broadening originates from the contributions of the several mass transfer processes in the column. However, it seems that the contribution of the adsorption-desorption kinetics to the total mass transfer resistance is usually assumed to be negligibly small in the case of RPLC because the reaction rate of physical adsorption is fast enough [5].

### 3.2. Moment analysis procedure

#### 3.2.1. First moment analysis

The following equations are derived from Eqs. (1) and (2).

$$\frac{\mu_1 - t_0}{1-\varepsilon_e} = \frac{L}{u_0}(1-\varepsilon_i)K_a \qquad (9)$$

$$t_0 = \frac{L}{u_0}\{\varepsilon_e + (1-\varepsilon_e)\varepsilon_i\} \qquad (10)$$

A plot of the left hand side of Eq. (9) versus $L/u_0$ should be a straight line passing through the origin of the coordinates. The value of $K_a$ is derived from the slope of the straight line. In the MA method, the pulse response experiments are carried out while changing the mobile phase flow velocity because the flow rate dependence of HETP is analyzed in order to extract some kinetic parameters from $\mu_2'$ in the second moment analysis as explained in the next section. When the linear correlation between $(\mu_1-t_0)/(1-\varepsilon_e)$ and $L/u_0$ passing through the origin is observed, it seems that the temperature conditions are homogeneously controlled in the column. The residence time of the sample band is different in the column when the mobile phase flow velocity is changed.

### 3.2.2. Second moment analysis

Similar to the conventional kinetic studies based on the ordinary rate equations, the flow rate dependence of HETP is analyzed in the MA procedure. The value of $H$ is calculated from Eqs. (1)−(8) as follows. The value of HETP is expressed as $H_{total}$ because it consists of the contributions of the several mass transfer processes in the column.

$$H_{total} = \frac{\mu_2'}{\mu_1^2} L = \frac{2\varepsilon_e D_L}{u_0} + \frac{2u_0}{\delta_0^2}\delta_f + \frac{2u_0}{\delta_0^2}\delta_d = H_{ax} + H_f + H_d \quad (11)$$

As shown in Eq. (11), the contribution of the axial dispersion ($H_{ax}$) can be separated from those of both the external mass transfer ($H_f$) and the diffusive migration of sample molecules inside the stationary phase ($H_d$) by taking advantage of the difference in their flow rate dependence. The following correlation is derived from Eq. (11).

$$H_{total} - H_f = H_{ax} + H_d = \frac{2\varepsilon_e D_L}{u_0} + \frac{2u_0}{\delta_0^2}\delta_d \quad (12)$$

The axial dispersion coefficient ($D_L$) of the conventional HPLC columns packed with spherical particles is usually accounted for by assuming that axial dispersion consists of two main mechanisms, i.e., molecular diffusion and eddy diffusion [3].

$$D_L = \gamma_1 D_m + \gamma_2 d_p u \quad (13)$$

where $\gamma_1$ and $\gamma_2$ are the two geometrical coefficients, $d_p$ the particle diameter, and $u$ the interstitial velocity of the mobile phase solvent (= $u_0/\varepsilon_e$). Equation (12) is modified as follows by substituting Eq. (13) into Eq. (12).

$$H_{total} - H_f = \frac{2\varepsilon_e \gamma_1 D_m}{u_0} + 2\gamma_2 d_p + \frac{2u_0}{\delta_0^2}\delta_d = \frac{B}{u_0} + A + C u_0 \quad (14)$$

Equation (14) indicates that the correlation between ($H_{total}-H_f$) and $u_0$ is represented by the same formula as the van Deemter equation with three coefficients. However, Eq. (14) is essentially different from the conventional rate equation in terms of the following two points. At first, the contribution of the external mass transfer to $H_{total}$ is also taken into account in Eq. (14). Second, the definition and physical meanings of the parameter $C$ in Eq. (14) are clearly explained. As shown in Eqs. (7) and (14), quantitative information about the mass transfer kinetics in the stationary phase can strictly be obtained as $D_e$ from the coefficient $C$. These are obvious differences between the ordinary rate equations and the moment equations.

As illustrated in Figure 1, the diffusive molecular migration in intraparticle pore space is usually assumed to consist of the parallel contributions of pore diffusion and surface diffusion [4, 5]. The value of $D_e$ is accounted for as follows.

$$D_e = D_p + (1 - \varepsilon_i) K_a D_s \quad (15)$$

Surface diffusion coefficient ($D_s$) is calculated by subtracting the contribution of pore diffusion to $D_e$. Pore diffusivity ($D_p$) is estimated from molecular diffusivity ($D_m$) and some related parameters [3−5]. Detailed information about these parameters can be found out in other literature [3−8, 13]. The second term in the right hand side of Eq. (15) represents the contribution of surface diffusion to intraparticle diffusion.

## 4. Analysis of chromatographic behavior on the basis of the moment theory

Fundamental studies on the characteristics and mechanism of chromatography have been conducted in RPLC systems because it is the most popular mode of HPLC. The pulse response (PR) and peak parking (PP) experiments were carried out under different RPLC conditions concerning the type, concentration, and composition of the stationary phase, mobile phase, and sample compound. The temperature conditions were also changed. Experimental data thus measured were analyzed by the method of moments to study chromatographic behavior from the viewpoints of the retention equilibrium, mass transfer kinetics, and related thermodynamic properties.

### 4.1. Retention equilibrium

The retention behavior in RPLC systems was studied on the basis of the solvophobic theory [14]. Chromatographic equilibrium parameters, i.e., the retention equilibrium constant and the enthalpy change due to retention, were quantitatively analyzed [15]. We also experimentally demonstrated the influence of solvent on the retention behavior in RPLC by comparing the equilibrium parameters between gas-solid and liquid-solid phase systems [16]. On the basis of these results, the retention equilibrium in RPLC was studied from thermodynamic points of view. In addition, a convenient procedure was proposed for the practical measurement of adsorption isotherm, which is based on the Elution by Characteristic Point [17].

### 4.2. Mass transfer kinetics

Elution peak profiles simultaneously indicate us the information about the retention equilibrium and mass transfer kinetics. However, we have not completely derived the kinetic information from chromatograms because the ordinary rate equations of chromatography are not suitable for this purpose. The author applied the MA method to the derivation of the important information about the molecular migration dynamics in the column, which could not be extracted by the ordinary rate equations [16, 18−28].

For example, Figure 2 [27] illustrates the flow rate dependence

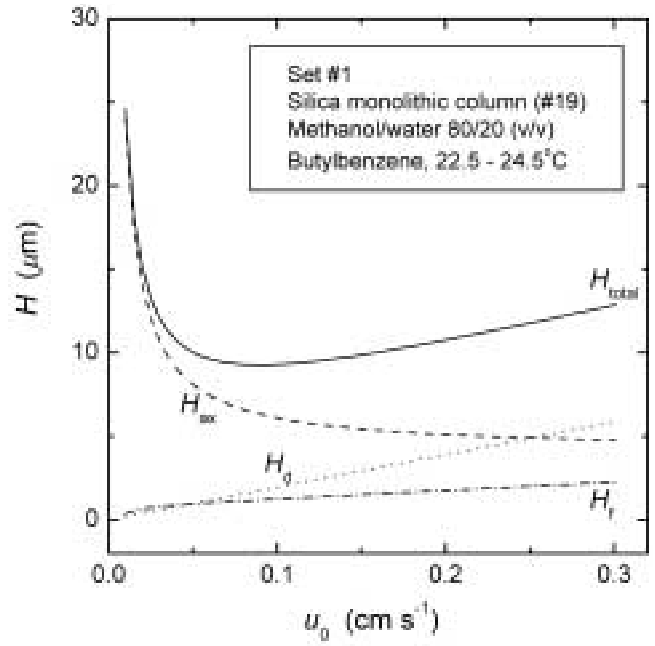

**Figure 2.** Contribution of the three mass-transfer processes in the $C_{18}$-silica monolithic column (contributions of axial dispersion, $H_{ax}$, external mass transfer, $H_f$, and intra-skeleton diffusive transfer, $H_d$) to the correlation between HETP and $u_0$ for the experimental set 1. The value of the external mass-transfer coefficient, $k_f$ was calculated using the penetration theory. Reproduced from [27] with permission.

of the contributions of the three mass transfer processes, i.e., axial dispersion, external mass transfer, and intra-stationary phase diffusion, to $H_{total}$ of a $C_{18}$−silica monolithic column. Band broadening in the column was quantitatively studied by analyzing the mass transfer rate in the three kinetic steps.

In Figure 3 [16], the contributions of the three mass transfer processes ($\delta_{ax}$, $\delta_f$, and $\delta_d$) to $\mu_2$’ were compared with each other under different experimental conditions. The values in parentheses indicate the adsorption equilibrium constant ($K$). The total length of each bar indicates the sum of $\delta_{ax}$, $\delta_f$, and $\delta_d$. Figure 3 indicates that the contributions of the three mass transfer steps to band broadening can quantitatively be evaluated. Similar results have been reported in other literature [6−8, 27].

As indicated in Eq. (15), it has usually been assumed that the mass transfer in porous adsorbents rests on the contributions of the two parallel mechanisms, i.e., pore and surface diffusion. Figure 4 [16] illustrates the comparison of the contributions between the two diffusive molecular migration mechanisms to the overall mass transfer in the stationary phase. The number in parentheses again indicates the value of $K$. The total length of each bar represents the value of $D_e$. The hatched part corresponds to the contribution of pore diffusion. It is obvious in Figure 4 that $D_e$ is much larger than $D_p$ in all the RPLC and GC systems. This means that surface diffusion plays a predominant role for the mass flux inside the stationary phase and most sample molecules migrate by surface diffusion.

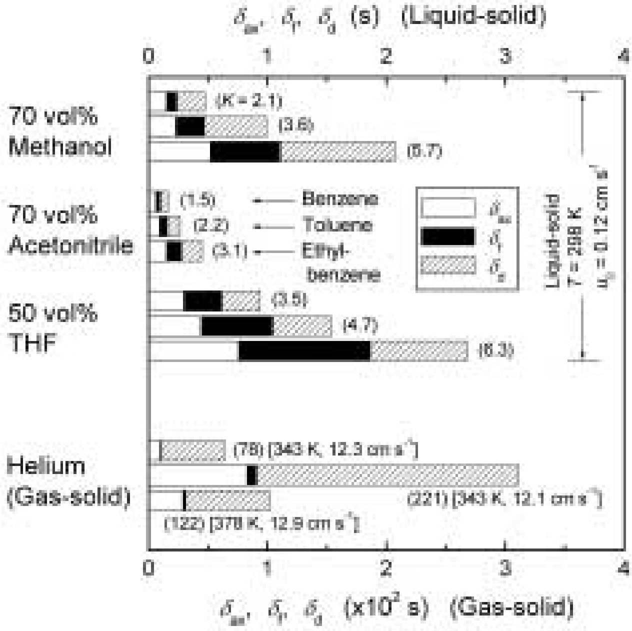

**Figure 3.** Comparison of the contributions of axial dispersion, external mass transfer, and intraparticle diffusion to the second central moment. Reproduced from [16] with permission.

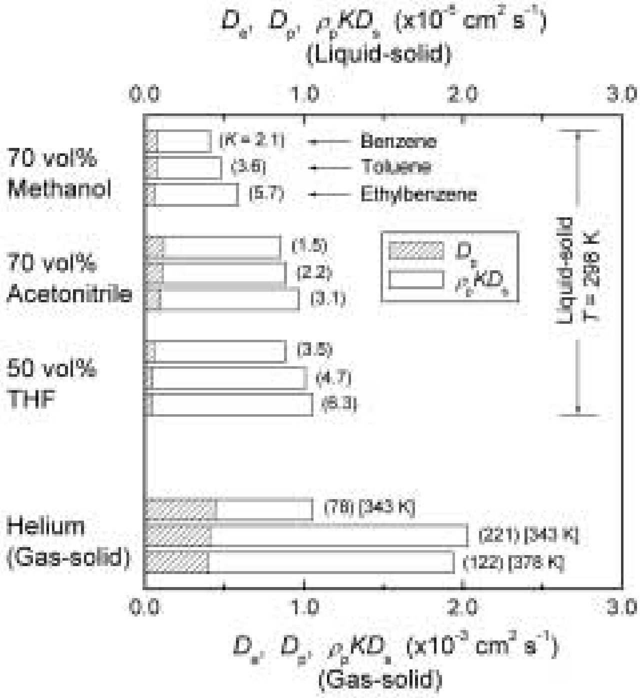

**Figure 4.** Comparison of the contributions of pore diffusion and surface diffusion to intraparticle diffusion. Reproduced from [16] with permission.

The significant contribution of surface diffusion to the intra-stationary phase diffusion has also been reported in other literature [6−8, 27, 28]. Figure 4 indicates that the MA method is also effective for the kinetic study on the molecular migration in porous materials. To the best of our knowledge, surface diffusion in chromatography has not so frequently been studied in detail in the field of chromatography. Some results concerning surface diffusion will be explained in the following.

### 4.3. Thermodynamic properties

The characteristics and mechanism of the retention equilibrium and surface diffusion in RPLC systems were studied from the thermodynamic points of view by analyzing related experimental data, i.e., the enthalpy change due to retention, the frequency factor and activation energy of surface diffusion, and so on [6]. The retention behavior and surface diffusion in RPLC were studied from the viewpoints of two extrathermodynamic relationships, i.e., enthalpy-entropy compensation (EEC) and linear free energy relationship (LFER) [29−34]. At first, the values of $K$ and $D_s$ were analyzed in detail in order to demonstrate that a real EEC of the retention equilibrium and surface diffusion originate from substantial physicochemical effects. Then, we developed a new thermodynamic model based on the EEC to explain the LFER between the retention equilibria, between surface diffusion phenomena, and between the retention equilibrium and surface diffusion under different RPLC conditions. The model is effective for explaining the variation of $K$ and $D_s$ due to change in the RPLC conditions and the temperature dependence of the LFER.

## 5. Study on the fundamentals of surface diffusion

Chromatographic separation is influenced by the variation in the HPLC conditions of the stationary and mobile phases, sample compounds, and others (e.g., temperature). When chromatographic behavior is studied from kinetic points of view, we can choose surface diffusion as an informative rate process [35−40]. Surface diffusion data experimentally measured by the PR and PP methods under various HPLC conditions were analyzed on the basis of the absolute rate theory [41].

Surface diffusion is always affected by the retention behavior of the sample molecules because they migrate in the vicinity of the stationary phase surface under adsorbed state. It is usually assumed to be an activated mass transfer process taking place in a potential field of adsorption [4, 5, 42, 43]. It seems that the manner of surface diffusion directly reflects the change in the chromatographic behavior. Additionally, as explained above, surface diffusion has an important contribution to the mass transfer in the stationary phase. The results of a series of studies on surface diffusion let us to conclude that the characteristics and mechanism of surface diffusion should be studied in detail.

### 5.1. Drawbacks of the conventional model for surface diffusion

There have been some research subjects relating to the values of $D_s$ and thermodynamic properties of surface diffusion, which have not been solved. Table 2 [28] lists the experimental data of the retention equilibrium constant ($K$), the isosteric heat of adsorption ($Q_{st}$), $D_s$, and the activation energy of surface diffusion ($E_s$) measured in the RPLC system consisting of a $C_{18}$-silica gel and 70 vol% methanol and those in the GC system using the same type of packing materials and helium.

One of subjects is the unreasonable correlation between the experimental values of $E_s$ and $Q_{st}$. As illustrated in Figure 5 [9], the ratio $E_s/(-Q_{st})$ should be smaller than unity because surface diffu-

**Table 2.** Comparison of thermodynamic properties in liquid-solid and gas-solid phase systems

| Phase system | Liquid-solid | | | | Liquid-solid | | | | Gas-solid | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stationary phase | $C_{18}$-silica gel | | | | $C_{18}$-silica gel | | | | $C_{18}$-silica gel | | | |
| Mobile phase | Methanol/water (70/30, v/v) | | | | Acetonitrile/water (70/30, v/v) | | | | Helium | | | |
| | ln $K^a$ | $-Q_{st}$ (kJ mol$^{-1}$) | ln $D_s^a$ | $E_s$ (kJ mol$^{-1}$) | ln $K^a$ | $-Q_{st}$ (kJ mol$^{-1}$) | ln $D_s^a$ | $E_s$ (kJ mol$^{-1}$) | ln $K^a$ | $-Q_{st}$ (kJ mol$^{-1}$) | ln $D_s^a$ | $E_s$ (kJ mol$^{-1}$) |
| Benzene | 0.73 | 6.7 | −12.8 | 19.4 | 0.43 | 5.8 | −12.0 | 14.6 | 6.08 | 35.3 | −12.4 | 13.5 |
| Toluene | 1.28 | 8.7 | −13.0 | 20.5 | 0.79 | 5.8 | −12.3 | 16.2 | 7.42 | 40.7 | −12.7 | 17.5 |
| Ethylbenzene | 1.75 | 9.7 | −13.2 | 22.0 | 1.12 | 6.1 | −12.6 | 16.6 | 8.30 | 43.8 | −13.2 | 23.2 |
| *p*-Xylene | 1.87 | 10.3 | −13.1 | 23.4 | 1.17 | 6.5 | −12.6 | 13.9 | 8.48 | 44.6 | −13.0 | 21.1 |
| *n*-Pentane | 2.35 | 11.8 | –[b] | –[b] | 1.78 | 6.2 | –[b] | –[b] | 4.66 | 31.7 | −12.0 | 10.2 |
| *n*-Hexane | 2.90 | 12.6 | –[b] | –[b] | 2.19 | 8.2 | –[b] | –[b] | 5.75 | 33.4 | −12.1 | 14.1 |
| *n*-Heptane | 3.43 | 14.8 | –[b] | –[b] | 2.62 | 9.6 | –[b] | –[b] | 6.94 | 38.2 | −12.2 | 14.4 |
| *n*-Octane | 3.98 | 17.2 | –[b] | –[b] | 3.05 | 10.9 | –[b] | –[b] | 8.16 | 43.4 | −12.5 | 17.1 |
| Cyclohexane | 2.45 | 10.4 | −13.6 | 22.2 | 1.88 | 6.7 | –[b] | –[b] | 5.92 | 33.0 | −12.5 | 15.6 |
| Chlorobenzene | 1.20 | 8.1 | −13.0 | 22.6 | 0.77 | 5.9 | −12.4 | 13.8 | 7.74 | 40.5 | −13.4 | 25.7 |

[a] At 298 K. [b] Not determined.

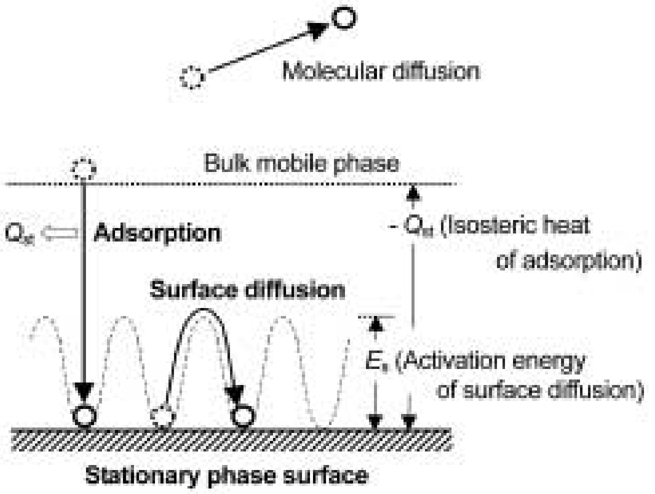

**Figure 5.** Schematic illustration of the thermodynamic properties relating to the retention and surface diffusion of sample molecules on the stationary phase surface. Reproduced from [9] with permission.

sion is a mass transfer process of adsorbate molecules under adsorbed state. The molecules do not need to be completely desorbed from the surface to the bulk liquid phase. Some characteristics and mechanism of surface diffusion have ordinarily been investigated on the basis of an Arrhenius type equation [5].

$$D_s = D_{s0} \exp\left[\frac{-\alpha(-Q_{st})}{RT}\right] \tag{16}$$

where $\alpha$ is the ratio $E_s/(-Q_{st})$, $R$ the gas constant, and $T$ the absolute temperature. However, Table 2 indicates that $E_s$ is larger than $-Q_{st}$ in the RPLC systems [6]. This means that surface diffusion does not take place.

Another subject is related with the value of $D_s$ under weak retention conditions. It has been observed that the frequency factor of surface diffusion ($D_{s0}$) ranges between ca. $10^{-3}$ and $10^{-2}$ cm$^2$ s$^{-1}$ in the RPLC systems [6]. Equation (16) indicates that, if the value of $\alpha$ is constant, $D_s$ approaches $D_{s0}$ when $Q_{st}$ tends toward zero. This means that $D_s$ is several orders of magnitude larger than molecular diffusivity ($D_m$) when the sample retention is weak because $D_m$ is usually of the order of ca. $10^{-6}$−$10^{-5}$ cm$^2$ s$^{-1}$ in liquid phase systems [1, 3−5, 13]. This conclusion is unreasonable because surface diffusion must be slower than molecular diffusion. Neither theory nor model has been developed for comprehensively explaining the unreasonable experimental results, i.e., $D_s$ larger than $D_m$ and the correlations between $E_s$ and $Q_{st}$.

In this study, we analyzed some experimental data from various points of view in order to clarify some important characteristics and mechanism of surface diffusion [35−40]. At first, the influence of temperature and the amount of adsorbate adsorbed on $D_s$ has ordinarily been studied [18]. Additionally, we studied surface diffusion by analyzing (1) the dependence of $D_s$ on the retention strength [38], (2) the correlation between $D_s$ and $D_m$ [40], (3) some thermodynamic and extrathermodynamic properties of surface diffusion [30, 31, 33] on the basis of the absolute rate theory [41], and (4) the difference of surface diffusion in the liquid-solid (RPLC) and the gas-solid (GC) systems [16, 19, 20]. These are new approaches for the study on surface diffusion.

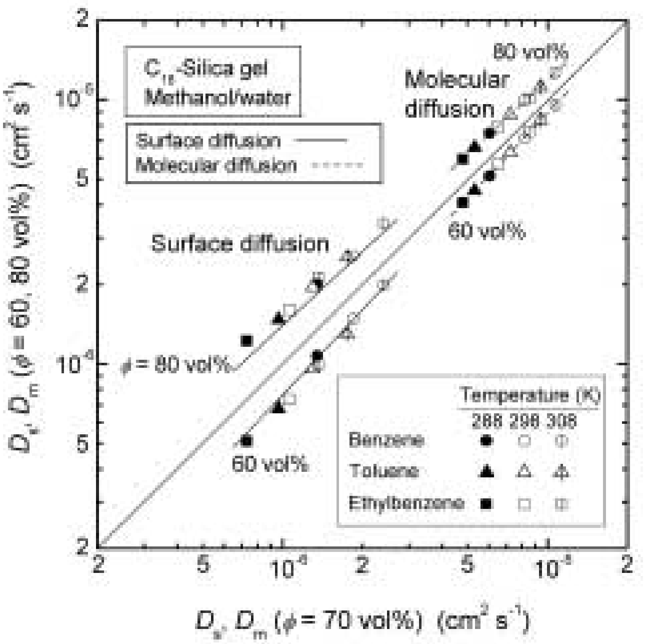

**Figure 6.** Comparison of the dependence of surface diffusion coefficient on the mobile phase composition with that of molecular diffusivity. Reprodeced from [44] with permission.

Figure 6 [44] illustrates the influence of the composition of methanol ($\phi$) in the mobile phase ranging from 60 to 80 vol% on $D_s$ and $D_m$. It is indicated that $D_s$ increases with increasing $\phi$ irrespective of the sample compounds and temperature. In addition, most data points fluctuate around the solid straight lines. Figure 6 also shows the correlation of $D_m$ in the mobile phase solvents of the different compositions. The $D_m$ values were estimated by the Wilke-Chang equation [13]. All the plots of $D_m$ are located on the linear dashed lines, of which the slope is almost unity. Similar to $D_s$, $D_m$ increases with increasing $\phi$. This result is reasonable because the viscosity of an aqueous solution of methanol decreases almost linearly with increasing $\phi$ in the range between 60 and 80 vol% [3]. The two solid lines are the extrapolation of the corresponding dashed lines, suggesting that the variation in $D_s$ due to the change in $\phi$ results primarily from the corresponding variation in $D_m$. The results in Figure 6 demonstrate that the influence of the mobile phase composition on surface diffusion and molecular diffusion are similar and that there is an intimate correlation between $D_s$ and $D_m$. The same conclusion is also obtained in other RPLC systems [35−

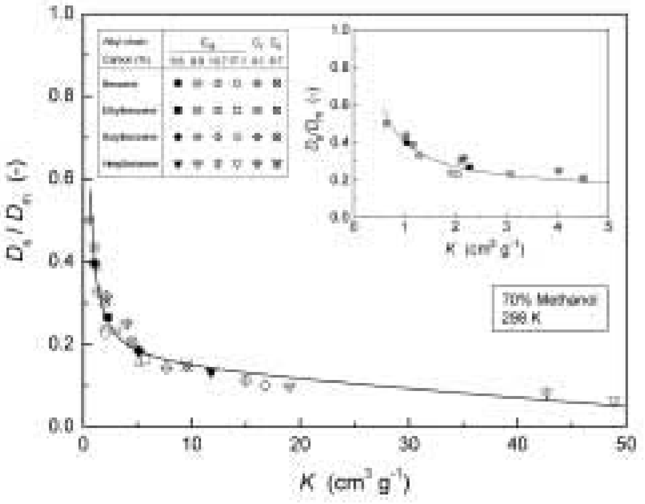

**Figure 7.** Ratio of the surface diffusion coefficient to the molecular diffusivity versus the adsorption equilibrium constant. Inset: enlargement of the plots in the range of the small $K$ values. Reproduced from [38] with permission.

40, 44].

Figure 7 [38] illustrates $D_s$ as a function of $K$. The inset shows the enlargement of the plots in the range of $K$ smaller than 5. Figure 7 indicates three important points concerning the correlation between $D_s$ and $K$. At first, all the data measured under various RPLC conditions are plotted around a single curved line. This means that the mechanism of surface diffusion is similar irrespective of the sample compounds and the modification conditions of the stationary phase surface. Second, $D_s$ decreases with increasing $K$, suggesting that surface diffusion is restricted by the retention strength. Finally, although the extrapolation is not so exact, it seems that $D_s$ approximately approaches corresponding value of $D_m$ as $K$ decreases. This result also suggests that surface diffusion is intimately correlated with molecular diffusion.

The ratio of $D_s$ to $D_m$ is plotted against $-Q_{st}$ in Figure 8 [39]. Although Figure 8 shows some scatter, the plots fluctuate around a single straight line, indicating the presence of a linear correlation between ln ($D_s/D_m$) and $-Q_{st}$. The ratio $D_s/D_m$ at $Q_{st}$ = 0 kJ mol$^{-1}$ is 0.54. Although $D_s$ is not completely equal to $D_m$ at $Q_{st}$ = 0 kJ mol$^{-1}$, it is likely that $D_s$ is of the same order of magnitude with $D_m$. Figure 8 also indicates the restriction of surface diffusion due to the sample retention and the intimate correlation between surface diffusion and molecular diffusion. It seems that the small difference between the intercept and unity is due to some specific structural and chemical conditions of the mobile phase solvent in the vicinity of the stationary phase surface, in which surface diffusion takes place. It is easily imaged that the conditions near the stationary phase surface are different from those in the bulk mobile phase.

The results of these studies ultimately lead to the conclusion that there is an intimate correlation between surface diffusion and molecular diffusion and that surface diffusion is regarded as the mass transfer, which is originally similar to molecular diffusion, but restricted in the potential field of adsorption. This conclusion is quite contrast with the ordinary concept and model of surface diffusion [4, 5, 42, 43]. It has commonly been recognized that surface diffusion is completely different from molecular diffusion and that there is no correlation between the two mass transfer mechanisms. On the other hand, the thermodynamic study on surface diffusion indicates that $E_s$ consists of the contributions of the hole-making and jumping steps, which are correlated with the evaporation energy ($\Delta E_v$) of the mobile phase solvent and $-Q_{st}$ in liquid-solid phase systems, respectively [35, 36]. In addition, the comparison of the surface diffusion data measured in both the RPLC and GC systems provided the information about the influence of the mobile phase solvents on the chromatographic behavior in RPLC [16].

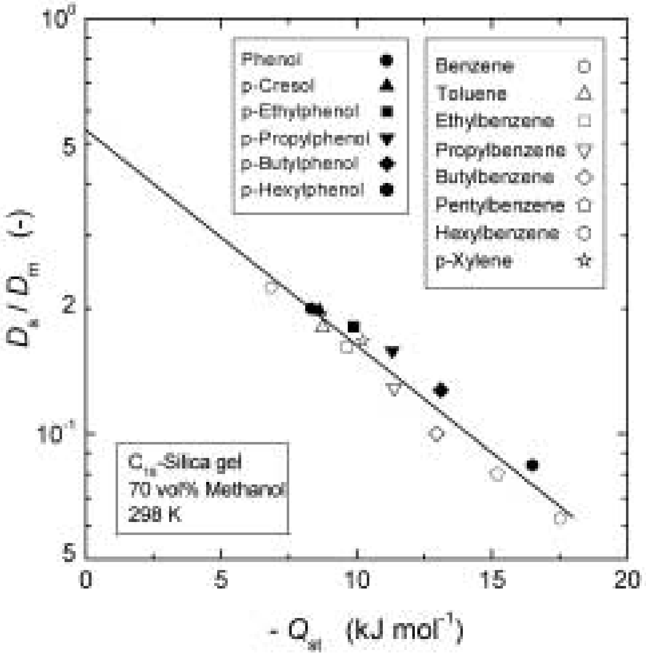

**Figure 8.** Correlation between the ratio of the surface diffusion coefficient to the molecular diffusivity and the isosteric heat of adsorption. Reproduced from [39] with permission.

On the basis of the experimental results, a surface-restricted molecular diffusion model [6−8, 28, 35−40, 44] was proposed as a first approximation for the mechanism of surface diffusion and formulated by applying the absolute rate theory [41].

$$D_s = D_{s0} \exp\left[\frac{-\{E_m + \beta(-Q_{st})\}}{RT}\right] \tag{17}$$

where $E_m$ is the activation energy of molecular diffusion and β the proportional coefficient. In the absolute rate theory [41], it is assumed that surface diffusion consists of two mechanisms, i.e., a hole-making process and a jumping (bond-breaking) one. In Eq. (17), $E_m$ and $\beta(-Q_{st})$ correspond to the contribution to $E_s$ of the hole-making and the jumping (bond-breaking) one, respectively [41].

### 5.2. Interpretation of various correlations between $E_s$ and $Q_{st}$

Figure 9 [28] illustrates the experimental data of $E_s$ against $-Q_{st}$. As listed in Table 2 [28], the values of $E_s$ are larger than those of $-Q_{st}$ in the RPLC system consisting of a $C_{18}$-silica gel column and aqueous mixtures of methanol or acetonitrile (70 vol%). A similar situation is also observed in other liquid-solid adsorption systems [6, 28]. No surface diffusion is expected under such conditions. On the contrary, $E_s$ smaller than $-Q_{st}$ has also been reported even in liquid-solid phase adsorption [6, 28]. The contradictory two correlations between $E_s$ and $Q_{st}$ in liquid-solid phase systems can be explained on the basis of Eq. (17).

The two dashed lines in Figure 9 indicate that $E_m$ is around 15 kJ mol$^{-1}$. This value is reasonable because it is not required to completely eliminate solvent molecules when the hole is constructed for diffusive molecular migration. The ratio of $E_m/\Delta E_v$ is about 1/3−1/2 because $\Delta E_v$ of various solvents is usually ranging from about 30 to 40 kJ mol$^{-1}$. On the other hand, the dashed lines indicate that β is about 0.5. This result is also reasonable because it is not required that molecules adsorbed are completely desorbed from the stationary phase surface to the bulk mobile phase when they migrate by surface diffusion. It is a diffusive molecular migration process under adsorbed state.

The dashed lines intersect the diagonal line at around $Q_{st} = -40$ kJ mol$^{-1}$. This means that $E_s$ is smaller than $-Q_{st}$ when $-Q_{st}$ is larger than about 40 kJ mol$^{-1}$. The explanation is supported by a few experimental data in Figure 9. By contrast, the value of $-Q_{st}$ in the RPLC systems usually ranges from ca. 10 to 20 kJ mol$^{-1}$, as listed in Table 2, which is smaller than the threshold. On the other hand, there is no solvent effect on $Q_{st}$ in the gas-solid phase adsorption. This is the reason why the ratio of $E_s/(-Q_{st})$ in gas-solid adsorption is smaller than unity as listed in Table 2 [28, 30].

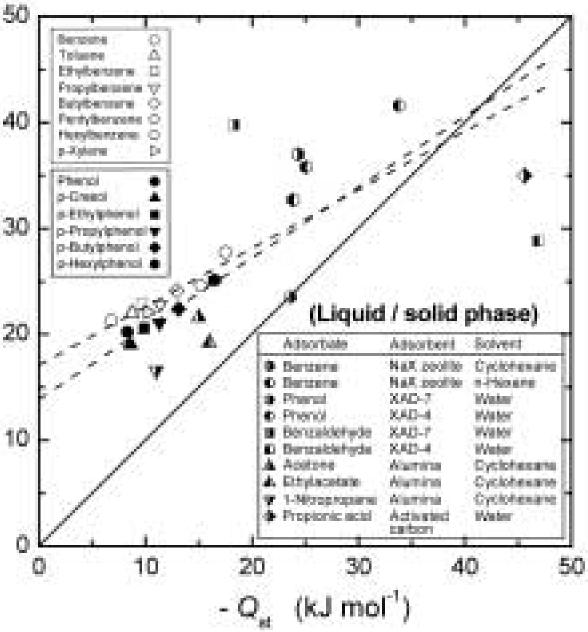

**Figure 9.** Correlation between activation energy of surface diffusion and isosteric heat of adsorption. Reproduced from [28] with permission.

The surface-restricted molecular diffusion model is also effective for explaining the second subject concerning the $D_s$ values under weak retention conditions. Equation (17) suggests that $D_s$ is equal to $D_{s0}\exp(-E_m/RT)$ under such conditions. This value is of the same order of magnitude with $D_m$. This is consistent with the results in Figures 7 and 8 that $D_s$ approaches the corresponding value of $D_m$ when $K$ and $Q_{st}$ tend toward zero. In addition, the surface-restricted molecular diffusion model is also effective for the quantitative explanation of some intrinsic characteristics and mechanism of surface diffusion [6−8, 28, 35−40, 44].

## 6. Advance in analytical strategy of chromatographic behavior

Different types of separation media having various structural characteristics have been developed for attaining fast chromatography with high efficiency, e.g., monolithic stationary phases [45], pellicular (shell) particles, and non-porous particles. Alternatively, ultra-high pressure LC systems have also been developed for this purpose, which use columns packed with full-porous spherical particles of the diameter around 2 μm. We need to quantitatively analyze chromatographic behavior in the different stationary phases under very high efficiency conditions. Some items of information relating to the topics are picked up in this section.

### 6.1. New moment equations for chromatography

About 30−40 years ago, the moment equations have already been proposed for the conventional columns packed with full-porous spherical particles [3−8, 11, 12]. However, they cannot be used for the different separation media because their structural characteristics are significantly different from those of full-porous spherical particles. The author has systematically developed a framework of new moment equations for chromatography using the various types of packing materials having different structural characteristics, i.e., shape (spherical particle, cylindrical fiber, flat plate, and hollow tube) and porous structure (full-porous, superficially porous (pellicular or shell), and non-porous) [27, 45−48]. Figure 10 [47] shows the schematic illustration of the structural characteristics of the different packing materials.

A set of basic equations of the GR model of chromatography, which represent the mass balance and the mass transfer kinetics in a column, were analytically solved in the Laplace domain. The moment equations in the real time domain for μ₁ and μ₂' of elution peaks were derived from the analytical solution in the Laplace domain. For example, Equations (18) and (19) are the moment equations of μ₁ and μ₂' for chromatography using the full-porous stationary phases, i.e., spherical particles, cylindrical fibers, and flat plates [47, 48].

$$\frac{\mu_1 - \frac{\tau}{2}}{\frac{L}{u}} = 1 + \frac{1-\varepsilon_e}{\varepsilon_e}\{\varepsilon_i + (1-\varepsilon_i)K_a\} \tag{18}$$

$$\frac{\mu_2' - \frac{\tau^2}{12}}{\frac{L}{u}} = \frac{2D_L}{u^2}[1 + \frac{1-\varepsilon_e}{\varepsilon_e}\{\varepsilon_i + (1-\varepsilon_i)K_a\}]^2 + \frac{2(1-\varepsilon_e)}{\varepsilon_e}[(1-\varepsilon_i)\frac{K_a^2}{k_{ads}} + (\frac{\xi}{\theta k_f} + \frac{\xi^2}{\sigma D_e})\{\varepsilon_i + (1-\varepsilon_i)K_a\}^2] \tag{19}$$

where τ is the width of the rectangular sample injection pulse, *u* the interstitial velocity, ξ the diffusion distance, and θ and σ the numerical coefficients. At first, the first moment equation is completely identical irrespective of the shapes of the packing materials. On the other hand, the second moment equation depends on their shapes, although their basic formula is the same for all the packing materials. Only two numerical coefficients, i. e., θ and σ, which are attached with the external mass transfer coefficient ($k_f$) and the intra-stationary phase diffusivity ($D_e$) are systematically changed, i. e., 3 and 15 for the spherical particles, 2 and 8 for the cylindrical fibers, and 1 and 3 for the flat plates. It seems that the θ value well represents the dimension of the mass transfer in the stationary phases. The ratio of σ to θ is also systematically changed, i. e., 5, 4, and 3. The numerical values must reflect the geometrical difference between the packing materials. The diffusion distance (ξ) is also different depending on the shape of the separation media, i.e., radius for the spherical particles and cylindrical fibers, and thickness for the flat plates.

### 6.2. Peak parking method

It was demonstrated that the peak parking (PP) (stopped flow or arrested flow) method is effective for the quantitative analysis of chromatographic behavior, as well as the pulse response (PR) method. The PR method has been used as one of powerful strategies for the kinetic study on chromatography. It is carried out under dynamic conditions by intentionally selecting a range of moderate to high flow velocities of the mobile phase solvent. A non-equilibrium situation of the solute distribution between the mobile and stationary phases is intentionally generated. It is a "dynamic method" because the information about intra-stationary phase diffusion is derived by analyzing the band broadening, which takes place under the non-equilibrium conditions. On the other hand, the PP method is a "static method". In contrast with the PR method, the band broadening due to axial molecular diffusion in the PP experiments takes place under equilibrium conditions of the solute

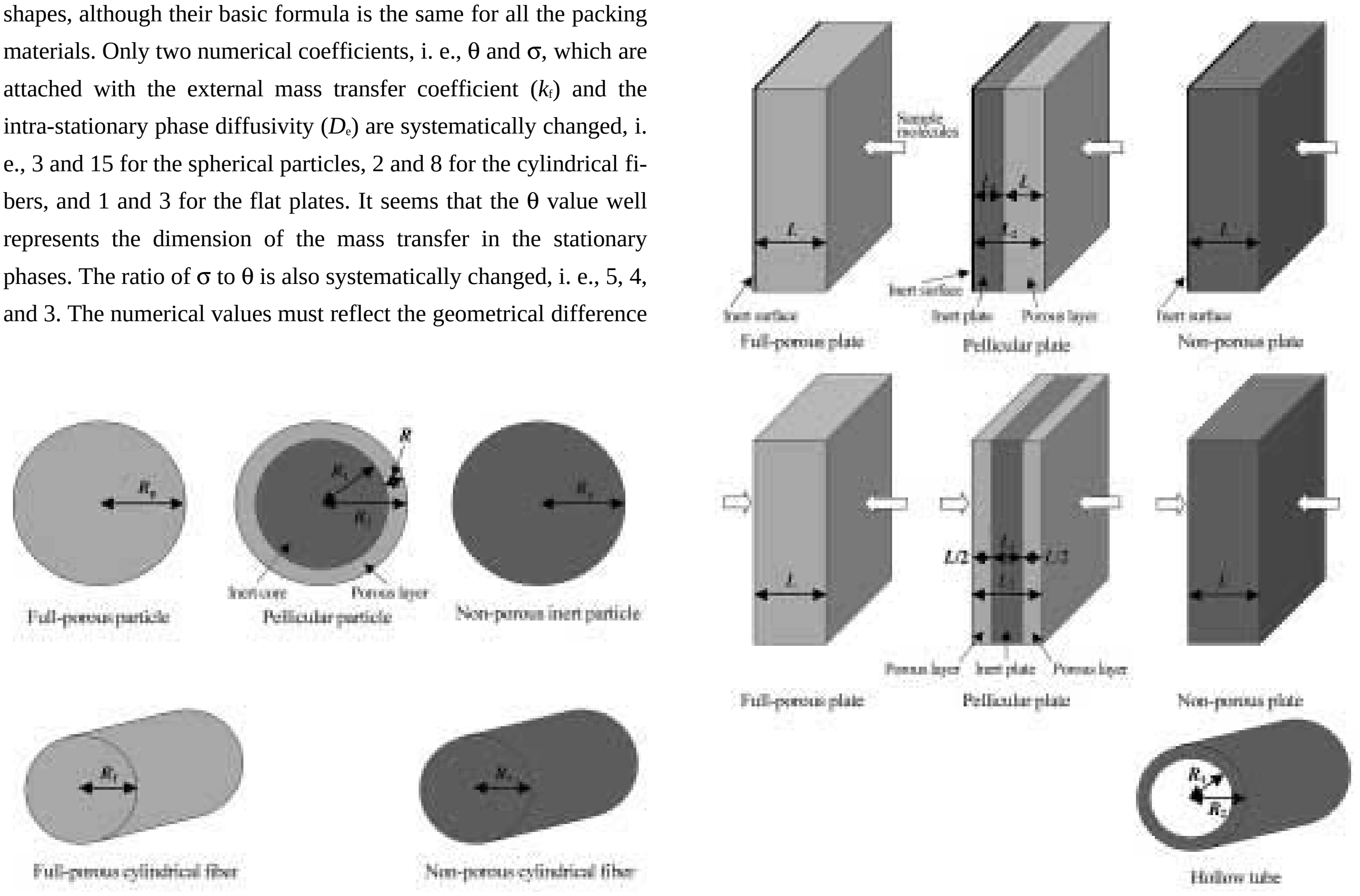

**Figure 10.** Schematic illustration of the structural characteristics of various packing materials and separation media. Reproduced from [47] with permission.

distribution between the stationary and mobile phases because there is no convective flow of the mobile phase during the peak parking period ($t_p$) [10, 49−51].

Figure 11 [51] illustrates the comparison of the PP method with the PR method. In the case of the PR approach, the chromatographic process is continuously conducted after the injection of a small sample pulse. On the other hand, in the case of the PP method, the elution of the sample band identically injected into the column is intentionally interrupted for a while in the course of the chromatographic process. The sample band naturally diffuses in the longitudinal direction of the column during $t_p$. Subsequently, the elution chromatography is resumed and continued until the chromatographic peak is completely eluted. There are some differences in the elution peak profiles measured by the two methods. At first, as illustrated in Figure 11, the difference in the elution time of the two peaks is equal to $t_p$. Second, the elution peak measured by the PP method is broader than that by the PR method (dotted peak in Figure 11). The information about the mass transfer kinetics in the stationary phase is derived by analyzing the additional band broadening due to the diffusive axial molecular migration during $t_p$.

The characteristics of the two methods are contrary with each other because their basic concept for the analysis of molecular dynamics is completely opposite. Table 3 [51] lists the comparison of

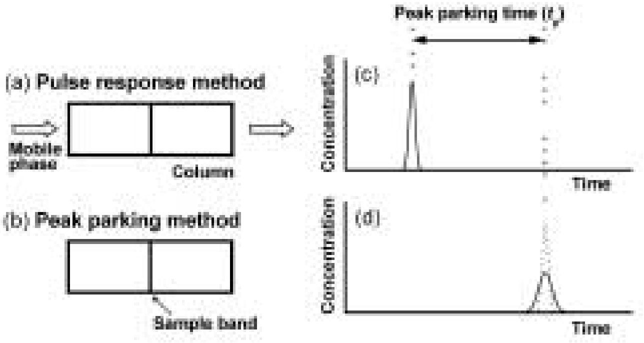

**Figure 11.** Schematic illustration of the band broadening phenomena and the elution peak profiles in the pulse response and peak parking experiments. (a) Intermediate situation in the pulse response method. The mobile phase flows continuously through the column, at a constant flow rate. (b) Intermediate situation in the peak parking method. The mobile-phase flow is arrested for the peak parking period. (c) Elution peak profile in the pulse response method. (d) Elution peak profile in the peak parking method (solid line) compared to the elution peak profile in elution, shifted for the peak parking time (dotted line). Reproduced from [51] with permission.

**Table 3.** Comparison of the peak parking − moment analysis method with the pulse response − moment analysis method

| Pulse response − moment analysis method | Peak parking − moment analysis method |
|---|---|
| [Disadvantages] | [Advantages] |
| 1. The procedure of the data analysis is relatively complicated. | 1. The procedure of the data analyses is quite simple. |
| 2. Estimation of $k_f$ and $D_p$ is required for the data analysis. | 2. No estimation of $k_f$ and $D_p$ is required for the data analysis. |
| 3. Accurate values of $\mu_1$ and $\mu_2'$ are essential. | 3. Accurate values of $\mu_1$ and $\mu_2'$ are not necessarily essential. |
| 4. Some corrections are necessary to determine the accurate values of $\mu_1$ and $\mu_2'$. | 4. The corrections are not necessarily required. |
| (1) Asymmetric (tailing and fronting) peak profiles | (1) The asymmetric peak profiles and extra-column pipes provide little influence on the data analysis. |
| (2) Extra-column pipes | (2) The longer the peak parking time is, the smaller their influence on the results becomes, because the sample band symmetrically broadens out in the axial direction of the column during the peak parking period. |
| 5. It is hard to derive the kinetic information about the mass transfer in small packing materials. | 5. The kinetic information about the mass transfer in small separation media can be obtained. |
| 6. Acquire of many experimental data is preferable. | 6. The kinetic information can be derived from a small number of experimental data. |
| 7. The experimental procedure is sometimes tedious and time−consuming. | 7. Although the experimental procedure is time−consuming, it is easy to conduct and labor-saving. |
| 8. Accurate information about the size of the packing materials is required. | 8. No information about the size of packing materials is required for the data analysis. |
| [Advantage] | [Disadvantage] |
| 1. The kinetic information about the mass transfer in large packing materials can be obtained. | 1. It takes long time to derive the kinetic information about the mass transfer in large separation media. |

some characteristics of the PR and PP methods. It is obvious that the two methods are complementary to each other. A disadvantage of one method can be covered by an advantage of the other method. The combination of the two methods leads to a comprehensive strategy for the kinetic study on chromatographic behavior irrespective of HPLC conditions. According to experimental conditions and research objects, we can choose one of them as a suitable approach. The PP method has been applied to the analysis of surface diffusion [51] and to the experimental measurements of various kinetic parameters as follows.

### 6.3. Development of various related methods for the kinetic study on chromatography

In order to establish a framework of the experimental methods for the kinetic study on chromatography, we developed some related methods, which are essential for the accurate analysis of chromatographic behavior. For example, the methods for the experimental measurement of the following kinetic parameters were developed, i.e., (1) molecular diffusivity in liquid phase (the PP method using capillary flow channels) [52], (2) external mass transfer coefficient (the PR method using a column packed with non-porous particles and the combination of the PR and PP methods using a column packed with full-porous particles) [53], and (3) pore diffusivity (the PP method in SEC mode using benzene and polystyrene of large molecular weight).

### 6.4. Numerical method for the analysis of asymmetrical peak profiles

A numerical approach was proposed for the estimations of the true efficiency and of the radial heterogeneity of a column from the asymmetrical (tailing and fronting) profiles of elution peaks experimentally measured [54−57].

Experimental chromatographic data are usually analyzed on the assumption that the peak profiles under linear equilibrium isotherm conditions are also represented by the Gaussian distribution function. In addition, most theoretical models of chromatography are based on this assumption. In practice, however, asymmetrical (tailing or fronting) peaks are frequently observed even under linear isotherm conditions. In such a case, the information about the true performance and characteristics of chromatographic behavior cannot properly be evaluated from the analysis of the asymmetrical peak profiles because these profiles are not Gaussian curves. We need to develop a new strategy for appropriately analyzing asymmetrical peak profiles in order to derive the accurate information about chromatographic behavior because the packing structure of most columns are not homogeneous in the column radial direction. It has been shown previously that most columns exhibit the radial distributions of the mobile phase flow velocity and the local efficiency [3]. The column radial heterogeneity is an important source of asymmetry of elution peaks. We do not know how columns can homogeneously be prepared. It is probably impossible to completely eliminate this source of peak asymmetry due to the radial distributions of the flow velocity and the column efficiency.

At first, we considered the mechanism of the peak distortion by a numerical approach [54−57]. The numerical calculation of elution peaks shows how the peak asymmetry is related to the characteristics of the distributions of the flow velocity and local column efficiency in the radial direction of the column. Then, we developed an inverse numerical method, which allows the estimation of the true column efficiency and of the column radial heterogeneity from some parameters of peaks experimentally recorded even when they show asymmetrical profiles [57].

## 7. Conclusion

Still now, the development of HPLC technologies quite rapidly proceeds. In the future, chromatographic behavior could not completely be represented by the conventional models nor properly analyzed on the basis of the ordinary HPLC theories. It must be required to establish an appropriate analytical strategy for the advanced chromatography and to more accurately understand the fundamentals of chromatographic separation. In this review, the MA method was introduced as one of the candidates for constructing the effective strategy for the kinetic study on chromatography. The new theories and models must contribute to the development of some innovatory technologies of chromatography from theoretical points of view. The author wishes that some results of this study contribute to the further progress of fundamental research works concerning the mechanism of HPLC separations and to the more accurate understanding of some essential characteristics of chromatography.

## Acknowledgment

The author would like to express his sincere gratitude to Professor Georges Guiochon (The university of Tennessee and Oak Ridge National Laboratory). He kindly evaluates the research works and gives him a great number of beneficial suggestions and many pieces of instructive advice as a co-researcher. The author is also grateful to Professor Katsumi Goto (Professor Emeritus, University of Toyama) and Professor Motoyuki Suzuki (Professor Emeritus, The university of Tokyo) for their kind supervision. The author gratefully acknowledges all collaborators, coworkers, and colleagues for their kind supports and comments in the course of the research works.

Financial supports from the Ministry of Education, Culture, Sports, Science and Technology, the Japan Science and Technology Agency (JST), University of Toyama, and also from private companies are gratefully acknowledged.

The author would like to make a grateful acknowledgment for the Society for Chromatographic Sciences (SCS) for presenting the Award of SCS in 2009 to him and for giving him an opportunity to publish this review paper.

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