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SIGNIFICANCE AND ESTIMATION OF CHROMATOGRAPHIC PARAMETERS

A. M. LENHOFF

Department of Chemical Engineering, University of Delaware, Newark, DE 19716 (U.S.A.)

SUMMARY

An analytical solution to the equations providing a mechanistic description of linear chromatography is used to examine the predicted effects of different parameters. The mechanisms accounted for are convection, axial dispersion, mass transfer to and within the particles, and sorption-desorption kinetics. Intraparticle rate limitations, *i.e.*, slow intraparticle diffusion and sorption kinetics, are found to produce similar chromatographic results, making it difficult to distinguish their effects. In both cases the resulting peaks are symmetric, in contrast to the pronounced tailing which is shown to arise from secondary sorption.

Calculation of plate heights from the model results indicates that moment determinations are susceptible to appreciable error; estimation of mechanistic parameters should therefore be performed using the time-domain results. The utility of several limiting approximations is demonstrated using both direct comparison with the analytical solution as well as order-of-magnitude estimates of the characteristic times of the different processes in the column.

INTRODUCTION

The mechanisms underlying chromatography in packed columns are well understood qualitatively and have been extensively investigated quantitatively as well. Nevertheless, a theoretical description adequate for detailed analysis in the time domain has not yet been applied to chromatography in a systematic fashion. The usual framework of theoretical plates not only lacks a realistic physical basis, but also lumps all the information present in a chromatographic peak into a relatively small number of quantities representing its most important characteristics, namely the peak area (zeroth moment), retention time (first moment) and peak width (second moment). A preferred approach is one based on the thermodynamic, transport and kinetic processes occurring in the column, the mechanisms of which are reasonably well understood. Such treatments have, of course, been used before, but generally with the results expressed in terms of the moments^{1,2} or related to the usual theoretical plates analysis³. In this paper use is made of the complete analytical time-domain solutions to the describing equations to elucidate the effects of the parameters of greatest interest and to ascertain under which conditions limiting approximations

to the full analysis provide sufficient accuracy. In addition, implications of measurement errors in experimental application of the theoretical plates method are examined.

Strong motivation for this study comes from the existing and potential uses of liquid chromatography (LC) for preparative and process scale separations in, for example, the pharmaceutical industry. Here the frequent operation under mass overloading adds the additional complicating feature of non-linear sorption isotherms to the obvious problem of scale, and techniques appropriate for determination of optimal operating conditions in analytical chromatography lose their utility. While we intend to extend our study to the non-linear situation, this paper is restricted to linear chromatography.

THEORETICAL BASIS

Problem statement

The phenomena considered to be of importance in column LC are axial convection, convective dispersion ("eddy diffusion"), mass transfer to the particle surface and within the particle and sorption-desorption kinetics. The corresponding describing equations have appeared in various previous studies (e.g., refs. 2 and 3) with small differences in some details, particularly in the boundary conditions. They are simply solute continuity equations for the mobile phase (c_m) and stationary phase (pores, c_s , and surface, c_a) concentrations, expressed as functions of time, t , axial position, z , and intraparticle radial position, r :

mobile phase

$$\frac{\partial c_m}{\partial t} + u \frac{\partial c_m}{\partial z} = \mathcal{D}_m \frac{\partial^2 c_m}{\partial z^2} - \frac{3(1 - \epsilon) k_m}{\epsilon R} (c_m - Kc_s |_{r=R})$$

intraparticle

$$\epsilon_i \frac{\partial c_s}{\partial t} = \mathcal{D}_s \frac{1}{r^2} \frac{\partial}{\partial r} r^2 \frac{\partial c_s}{\partial r} - kS_v(c_s - \alpha'c_a)$$

surface

$$\frac{\partial c_a}{\partial t} = k(c_s - \alpha'c_a)$$

with boundary conditions:

mobile phase

$$uc_m - \mathcal{D}_m \frac{\partial c_m}{\partial z} = 0 \quad \text{at } z = 0$$

$$\frac{\partial c_m}{\partial z} = 0 \quad \text{at } z = L$$

particle

$$\frac{\partial c_s}{\partial r} = 0 \quad \text{at } r = 0$$

$$\mathcal{D}_s \frac{\partial c_s}{\partial r} = k_m(c_m - Kc_s) \quad \text{at } r = R$$

and initial conditions

$$c_m = c_0 L \delta(z), \quad c_s = c_a = 0 \quad \text{at } t = 0$$

where u = mean interstitial mobile phase velocity; \mathcal{D}_m = axial dispersion coefficient (includes "eddy diffusion"); ε = column void fraction; k_m = external mass transfer coefficient (mobile phase to particle surface); R = particle radius = $d_p/2$; K = size-exclusion distribution coefficient; ε_i = particle porosity; D_s = intraparticle effective diffusivity; k = sorption rate constant; L = column length; S_v = specific surface area available for sorption; α' = sorption partition coefficient.

The axial boundary conditions are those of Danckwerts⁴, which preclude diffusive transport across the boundaries of the column. Under typical chromatographic conditions axial transport is overwhelmingly convective, and the use of alternative boundary conditions makes little difference to the final outcome.

The problem statement is scaled relative to appropriate characteristic quantities in such a way that the concentrations $\Theta_m = c_m/c_0$, $\Theta_s = c_s/c_0$, and $\Theta_a = c_a S_v/c_0$ are functions of dimensionless time $\tau = tu/L$ and position $\zeta = z/L$ and $\eta = r/R$, as well as the following dimensionless parameters:

$$v = \frac{d_p u}{\mathcal{D}} = \text{Péclet number (reduced velocity);}$$

$$\delta = \frac{d_p}{L} = \text{particle size-column length ratio;}$$

$$E_m = \frac{\mathcal{D}_m}{\mathcal{D}} = \text{scaled dispersion coefficient;}$$

$$E_s = \frac{\mathcal{D}_s}{\mathcal{D}} = \text{scaled intraparticle effective diffusivity;}$$

$$\text{Sh} = \frac{k_m d_p}{\mathcal{D}} = \text{Sherwood number;}$$

$$D = \frac{k S_v d_p}{u} = \text{Damköhler number;}$$

$$\alpha = \frac{\alpha'}{S_v} = \text{scaled sorption partition coefficient.}$$

The significance of these parameters and their importance in the analysis will be discussed later.

Analytical solution

The scaled equations and boundary and initial conditions, which are not shown here, can be solved in either of two ways. The first, using separation of variables, leads to an eigenfunction expansion which is not, however, amenable to numerical evaluation, because of the very large value of $v\delta/E_m$ typical of column chromatography. The alternative approach makes use of the solution in Laplace transform domain, with inversion accomplished by contour integration in the complex plane. This method, used by Rosen⁵ with a simplified model of chromatography, has been applied by Rasmuson⁶ to computing breakthrough curves using essentially the same model as that given above. The resulting solution for effluent mobile phase concentration is

$$\Theta_m(\tau) |_{z=1} = \frac{1}{\pi} \int_0^{\infty} \Re(\bar{\Theta}_m(i\omega) |_{z=1} e^{i\omega\tau}) d\omega$$

where the overbar denotes the Laplace transform, and \Re denotes the real part. $\bar{\Theta}_m |_{z=1}$ is given by

$$\bar{\Theta}_m(s) |_{z=1} = \frac{b e^{\bar{v}m_2}}{m_1^2 - m_2^2 e^{-\bar{v}b}}$$

where

$$m_{1,2} = \frac{1}{2} (1 \pm b)$$

$$\bar{v} = \frac{v}{\delta E_m}$$

$$b = \sqrt{1 - 4\psi/\bar{v}^2}$$

$$\psi = -s\bar{v} - \frac{6(1 - \varepsilon)\text{Sh}}{\varepsilon\delta^2 E_m} \frac{w \coth w - 1}{\text{Sh}K/2E_s + w \coth w - 1}$$

$$w^2 = \frac{\delta v s}{4E_s} \left(\varepsilon_i + \frac{D}{s + D\alpha} \right)$$

This solution, which can be implemented numerically, forms the basis for the rest of the work described here. The solution in Laplace transform domain can, however, also be used to obtain the moments of the elution curve, from which the retention time, t_R , and the reduced plate height, h , can be found:

$$t_R = \frac{L}{u} \left[1 + \frac{1 - \varepsilon}{\varepsilon K} \left(\varepsilon_i + \frac{1}{\alpha} \right) \right]$$

$$h = \frac{2E_m}{v} + \left[\left(\frac{v}{30E_s} + \frac{v}{3K\text{Sh}} \right) \left(\varepsilon_i + \frac{1}{\alpha} \right)^2 + \frac{2}{D\alpha^2} \right] \frac{(1 - \varepsilon)}{\varepsilon K} \left(\frac{L}{ut_R} \right)^2$$

The expression for t_R contains three terms: the quantity 1 represents the mobile phase residence time, the term in ε_i the (intraparticle) pore residence time and that in α the contribution of the sorbed fraction. The observed value of the distribution ratio k' is therefore given by

$$1 + k' = \frac{1 + \frac{1 - \varepsilon}{\varepsilon K} \left(\varepsilon_i + \frac{1}{\alpha} \right)}{1 + \frac{1 - \varepsilon}{\varepsilon K} \varepsilon_i}$$

The expression for the reduced plate height neglects terms in $e^{-\bar{v}}$; it is based on the expressions given by Kučera² and differs only slightly from that given by Horváth and Lin³. The four terms represent the contributions of axial dispersion, external mass transfer, intraparticle diffusion and sorption-desorption kinetics respectively to band broadening. While the relative contributions of these effects can be evaluated from the equation, similar conclusions and much insight can be obtained by examining the relative characteristic times for the different processes. This is discussed in the next section.

Orders of magnitude and characteristic time scales

Much can be learned and understood about chromatography from order-of-magnitude arguments, which can be invaluable in the planning and interpretation of both modelling and experiment. These concepts are successfully used, for example, by Giddings⁷ in formulating his plate height equations.

The most natural basis for a preliminary analysis is the set of time scales characterizing the system and the processes to which it is subjected. For the present description of LC these are: convection, $t_{\text{conv}} = d_p/u$; external mass transfer, $t_{\text{MT}} = d_p/k_m$; intraparticle diffusion, $t_{\text{diff}} = d_p^2/D_s$; sorption, $t_{\text{sorp}} = 1/kS_v$;

These characteristic times arise naturally, and their ratios form the dimensionless parameters already introduced. For example, $t_{\text{diff}}/t_{\text{conv}} = v/E_s$, $t_{\text{diff}}/t_{\text{MT}} = \text{Sh}/E_s$ and $t_{\text{conv}}/t_{\text{sorp}} = D$. Since system behaviour depends on the relative speeds of the different processes, it may be characterised in terms of these dimensionless parameters. One example of this is well known to all chromatographers: the minimum reduced plate height occurs at a Péclet number (reduced velocity) between 1 and 10, where the flow-rate through the column is more or less comparable in speed to the rate of solute transport inside the particle, the latter usually being rate-limiting in chromatography

A generalisation of this observation follows from consideration of the mechanisms of band broadening and the framework within which they are described, but it is important to distinguish between the lateral transport mechanisms and axial dispersion. Lateral transport contributes to band broadening only as a result of its interaction with axial convection, and an evaluation of the magnitude of the contribution can come only from a consideration of this interaction. Therefore, appreciable band broadening will be observed if lateral transport is much slower than axial convection, a comparison which is made directly in the respective ratios of characteristic times: $t_{\text{MT}}/t_{\text{conv}} = v/\text{Sh}$, $t_{\text{diff}}/t_{\text{conv}} = v/E_s$ and $t_{\text{sorp}}/t_{\text{conv}} = 1/D$. Substantial band broadening is to be expected if any one of these ratios is much larger than unity. It is also

worth noting that these three lateral transport processes take place in series, so they will be dominated by any one which may be significantly slower than the other two. This forms the basis of one way for developing simpler, more efficient limiting approximations later in this paper.

Axial dispersion or eddy diffusion is accounted for by an explicit axial transport term into which all mobile phase dispersive effects are lumped; these generally originate in convective non-uniformities resulting from the geometry of and the hydrodynamics in the packed bed. Band broadening can occur by axial dispersion or by the essentially parallel mechanism resulting from the coupling of slow lateral transport with axial convection. The respective increases l in peak width during time

period t_{conv} may be estimated as $l_{\text{disp}} \approx \sqrt{\mathcal{D}_m d_p / u}$ and $l_{\text{lat}} \approx ut_{\text{lat}}$, where t_{lat} is a characteristic lateral transport time. Since the faster of two parallel processes is dominant (*cf.* the serial steps in lateral transport), band broadening will be dominated by axial dispersion if $l_{\text{disp}}/l_{\text{lat}} \gg 1$, and *vice versa*. This criterion may be rearranged to give $\mathcal{D}_m d_p / u^3 t_{\text{lat}}^2 \gg 1$ which becomes, for instance, $\text{Sh}^2 E_m / \nu^3 \gg 1$, $E_m E_s^2 / \nu^3 \gg 1$ or $D^2 E_m / \nu \gg 1$ if lateral transport is limited by external mass transfer, intraparticle diffusion or sorption, respectively.

When certain geometric or thermodynamic parameters take on extreme values, they may affect the time constants, so that the discussion above requires slight modifications. For example, very small values of α' (strong binding) do not affect sorption rates, but imply that desorption is slow. This clearly has an effect on the rate of lateral transport and consequently on band broadening, and is important in, for example, affinity chromatography. In this case the appropriate ratio of characteristic times changes from $1/D$ to $1/D\alpha$. The combination of the ratios of time constants with the thermodynamic and geometric parameters leads to terms such as those in the equation describing the reduced plate height; a comparison of the plate height and order-of-magnitude analyses demonstrates that they lead to the same conclusions regarding the limiting processes in chromatography.

RESULTS AND DISCUSSION

Parameter values

The dimensionless parameters can be divided into two categories for the purpose of selecting suitable base values. The kinetic quantities ν , E_s and D have all been assigned base values of unity, the rationale for this selection becoming apparent when the discussion above of characteristic times is taken into account: the parameters have been chosen so as to make the rates of the different processes of approximately equal orders of magnitude, *i.e.*, no single transport step is rate-limiting. E_m , describing axial dispersion, and Sh , describing external mass transfer, are also kinetic parameters. The extensive studies of these two effects make it possible to depend with sufficient confidence on literature correlations to estimate appropriate parameter values. The equation of Hiby⁸ has been used for describing axial dispersion

$$E_m = \frac{\mathcal{D}_m}{\mathcal{D}} = 0.67 + \frac{0.65\nu}{1 + 7\nu^{1/2}}$$

and that of Pfeffer⁹ for external mass transfer

$$\text{Sh} = \frac{k_m d_p}{\mathcal{D}} = \mathcal{A} v^{1/3} \quad A \approx 1$$

The second class of parameters conveys geometric and thermodynamic information. Realistic values are $\varepsilon = 0.35$, $\varepsilon_i = 0.3$, $K = 1$, $\alpha = 0.5$ and $\delta = 0.0001$, leading to a k' value of 3.39. Note that $K = 1$ implies that there is no size-exclusion effect.

It is, of course, possible to examine the system response throughout the parameter space. Instead, the emphasis here will be on the two mechanisms which are probably least understood, yet most often prove to be limiting in modern LC: intraparticle diffusion and sorption-desorption kinetics. That intraparticle diffusion is often limiting is apparent from the common situation, mentioned earlier, where the minimum reduced plate height is at a Péclet number of approximately order unity. Sorption-desorption kinetics have been studied less extensively, but the results of Horváth and Lin³ suggest that they may be limiting in reversed-phase chromatography, while the strong binding associated with affinity systems makes desorption limiting there in the absence of solvent changes.

Time-domain calculations

Figs. 1 and 2 show the effects of the two parameters of greatest importance to the present discussion, namely E_s and D ; dimensionless concentration is shown as a function of dimensionless time, *i.e.*, scaled relative to the extraparticle residence time L/u . The base case, for the parameters given above, gives a relatively narrow, sym-

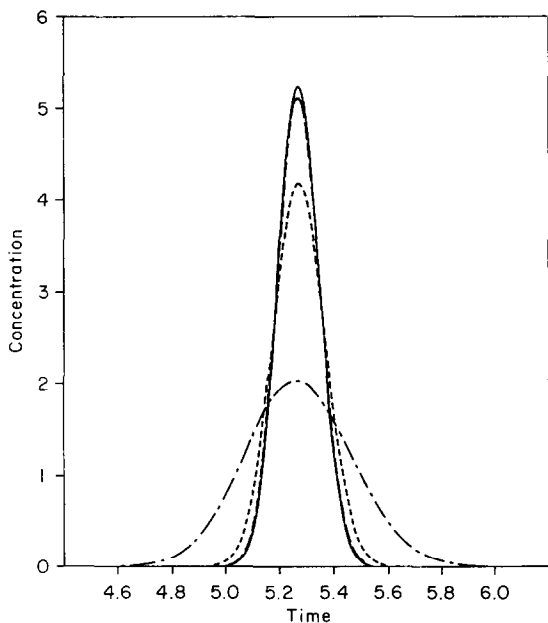


Fig. 1. Effect of intraparticle diffusivity on chromatography. Diffusivity ratio: (—) = 1; (---) = 0.1; (- · -) = 0.01; (···) = 0.001.

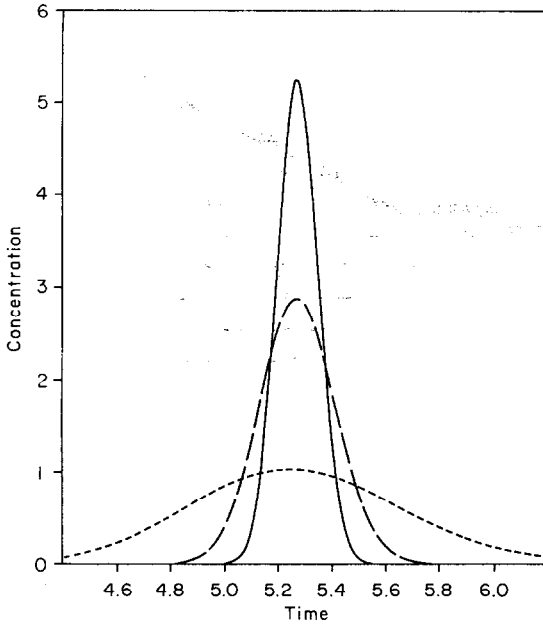


Fig. 2. Effect of sorption kinetics on chromatography. (—) $D = 1$; (---) $D = 0.1$; (- - -) $D = 0.01$.

metric peak, as expected with convection and all the processes contributing to band broadening approximately equally rapid. As either E_s or D decreases, *i.e.*, as resistance to lateral transport increases, the peak becomes broader, again as expected: the

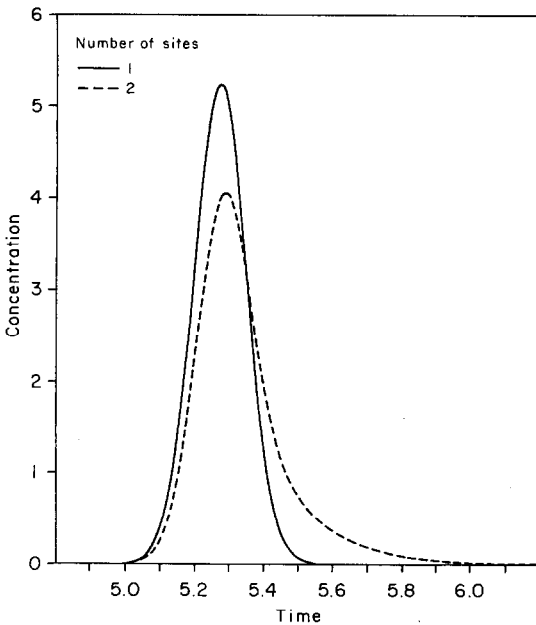


Fig. 3. Tailing resulting from sorption on secondary sites. (—) One site; (- - -) two sites.

ratios $t_{\text{diff}}/t_{\text{conv}} = v/E_s$ and $t_{\text{sorp}}/t_{\text{conv}} = 1/D$, respectively, become significantly greater than unity. A similar quantitative prediction of when appreciable band broadening increases will result from the various components of the lateral transport resistance can be obtained from the reduced plate height equation.

The similarity of the results for intraparticle diffusion and sorption limitations indicates that these two effects can not be distinguished by operating, for example, at different flow-rates: either particle size or sorption chemistry must be manipulated. It is particularly notable that peak symmetry does not appear to be lost in the range of parameters discussed here. Other results not shown do display some asymmetry when lateral transport resistance is high; this occurs at higher k' values (> 10), but the peaks are so broad as to be uncharacteristic of the asymmetric peaks often observed in, for example, reversed-phase systems. This suggests that slow sorption kinetics cannot alone account for appreciable asymmetry in chromatographic peaks, as is sometimes suggested¹⁰. Other suspected causes of asymmetry¹⁰ include extra-column effects and sorption on secondary sites. It is possible to modify the model used here to test the second of these, by adding a second class of sorption sites characterised by different values of D and α , *i.e.*, by different sorption kinetics and thermodynamics. The analytical solution can be obtained by a straightforward extension of the approach used for the single-site model. Fig. 3 shows the effect of adding secondary sites to the base case given by the values in above; the parameters associated with the secondary sorption are $D_2 = 3 \cdot 10^{-5}$ and $\alpha_2 = 30$. Because of the appearance of the specific surface area S_v in both these dimensionless parameters, the physical significance of this pair of values cannot be determined unambiguously. For example, both weak, slow binding on a large number of sites (large α' , S_v ; small k) as well as strong, fast binding on a small number of sites (small α' , S_v ; large k) are compatible with the (D, α) pair given, although the latter situation is what would be expected to apply to secondary sorption.

The effect of the secondary sites is primarily to add a tail to the peak, with the result being in qualitative agreement with what is often observed experimentally in, for example, reversed-phase chromatography. While the value of t_R determined from the peak value is not affected appreciably by the tail, the actual mean residence time is about 5.33 (*cf.* the different values of mean, median and mode of a skewed statistical distribution). The tail similarly affects the second moment more than is reflected by, for example, the peak width at half peak height. In the two-site situation, the values of t_R and h obtained from the moments are, strictly speaking, more representative of the full peak, but since the tail may contain relatively little material, the crude values based on peak height and width may often be adequate.

Moments of elution peaks

The usual approach to analysing linear chromatography involves determining a reduced plate height h from the response time and shape of the chromatographic peak. The variation of h with the reduced velocity or Péclet number v can provide information on the rate-limiting mechanism and on how well the column is packed, by use of the Van Deemter or Knox equation. The information provided by any peak is, however, reduced in this way to two quantities, *viz.* t_R and h , and even the multiple runs required for the h vs. v plot do not fully compensate for this lumping of information. In the case of skewed peaks, for example, t_R and h can still be calculated,

but the peak skewness is not reflected in either quantity; the third moment is required for this. On the other hand, the full analytical solution in the time domain conveys much more complete information regarding the peak in that it permits use of each point in the chromatographic profile.

Despite the disadvantages of the plate height approach, it continues to be used, and it is therefore important to be aware of possible sources of difficulty. Several studies of the susceptibility to error of moment and plate height calculations have been performed¹¹⁻¹⁵; effects examined include extra-column effects, noise, baseline drift, tail truncation and peak skewness. In all these studies, however, it was impossible to relate the empirically observed shape of the chromatographic peak, whether simulated or actually measured experimentally, to mechanistically relevant parameters. The usual way of doing this in chromatography is by analysing h vs. v plots, but no previous studies seem to have generated these from purely mechanistic models solved in the time domain. It has therefore not been possible to separate the effects of errors in experimental measurements from errors in data processing. In what follows, then, the effects of data processing errors on h vs. v curves generated from exact analytical time-domain solutions will be examined.

The situation to be studied is the relatively simple one based on the parameters given previously, except that the diffusivity ratio, E_s , is taken to have the value 0.1. As is clear from Fig. 1, the resulting chromatographic peak is narrow and symmetric, and one would expect relatively few problems in applying moments to this system. Fig. 4 shows the dependence of h on v predicted by the exact plate height equation, as well as the values at some selected values of v found from the moments

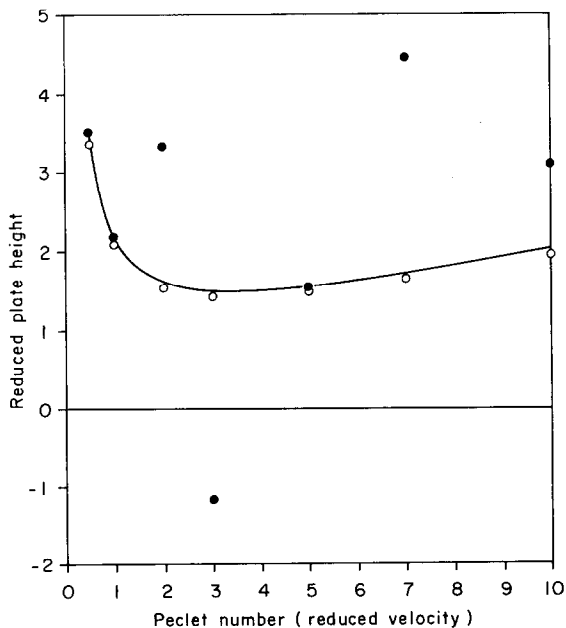


Fig. 4. Effects of integration error on computed value of reduced plate height. (—) Predicted by exact plate height equation; (●) 0.1% accuracy; (○) truncation at 2% of peak.

of the analytical time-domain solution evaluated by numerical integration. If the integration is performed accurately, agreement between the two methods is excellent. However, Fig. 4 also shows the effect of inaccurate integration. The solid circles denote points determined by integrating with an upper bound on integration error of 0.1%, using an adaptive quadrature package¹⁶. The extremely large errors are a consequence of the relationship between the plate height and the moments: h is proportional to $\mu_2 - \mu_1^2$, where μ_n ($n = 1, 2$) is the n th moment about the origin of the normalised chromatogram. Since the difference between μ_2 and μ_1^2 is typically small, small errors in integration can be significant, as is clearly demonstrated by the results. In principle, less accurate integration can, of course, give rise to still larger errors, but these are often masked by the correlation among the errors in the moments if, for example, trapezoidal integration is used.

The other possible source of error examined here is that of tail truncation, which has been examined previously^{12,15}. The results obtained by truncating at 2% of peak height, shown by the open circles in Fig. 4, indicate a systematically slightly low value of h . The relatively small magnitude of the error is a consequence of the absence of a significant tail in the peak considered, but the effect is much more severe when tailing is appreciable. Correlation among the errors in the three moments also reduces the discrepancy in h .

It may thus be concluded, as have others previously, that calculations of plate heights from the moments are susceptible to appreciable errors. Use of peak width measurements appears from other studies to be, if anything, even less reliable. It is particularly difficult to estimate mechanistic parameters from plate height determinations, and use of the full time-domain results with the matching model solution is the preferred approach.

Limiting approximations

Matching experimental results to the analytical solution in the time domain requires the latter to be computed efficiently and accurately. For this purpose it is useful to consider approximate descriptions of the chromatographic process valid for certain limiting ranges of parameter values, since the solutions are typically more computationally efficient while still acceptably accurate. Four such cases are considered here.

The first approximation¹⁷ involves lumping intraparticle diffusion into a mass transfer term. Solute concentration within the particle is assumed to be uniform, and solute influx across the external surface is given by $k_{\text{int}}(c_{\text{s|R}} - c_{\text{s}})$, where k_{int} is an internal mass transfer coefficient usually assumed to be given by $B\mathcal{D}_s/d_p$, where B is a constant between 0.5 and 2.5. This approximation would be expected to be reasonable when intraparticle diffusion is rapid, *i.e.*, when t_{diff} is not large relative to the other two lateral transport times (t_{MT} and t_{sorp}) or to the convection time t_{conv} . This is borne out by detailed calculations, of which Fig. 5 is representative: the lumped mass transfer description is accurate for $E_s = 1$ but not for $E_s = 0.001$.

An approximation which is very often valid is that which assumes sorption kinetics to be fast relative to the other lateral transport steps; in the limit, sorption equilibrium may be assumed to apply within the particle ($c_{\text{s}} = \alpha'c_{\text{a}}$), corresponding to an infinite Damköhler number D . The effect of increasing Damköhler number is shown in Fig. 6, from which it is apparent that for values of D as small as 10 the

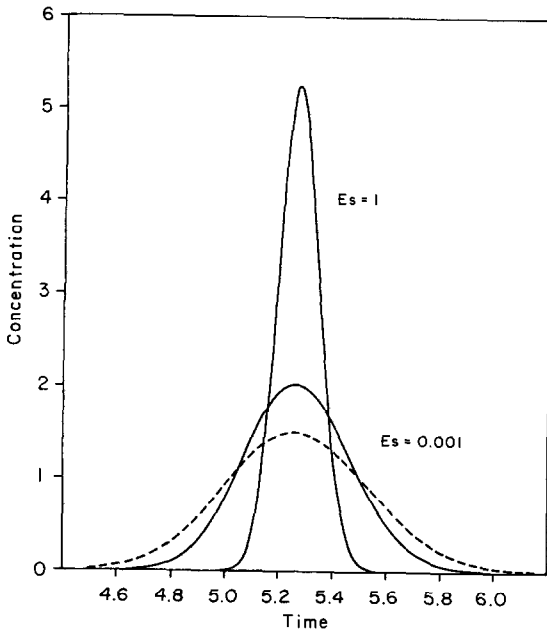


Fig. 5. Effect on model accuracy of lumping intraparticle diffusion. (—) Distributed mass transfer; (- -) lumped mass transfer.

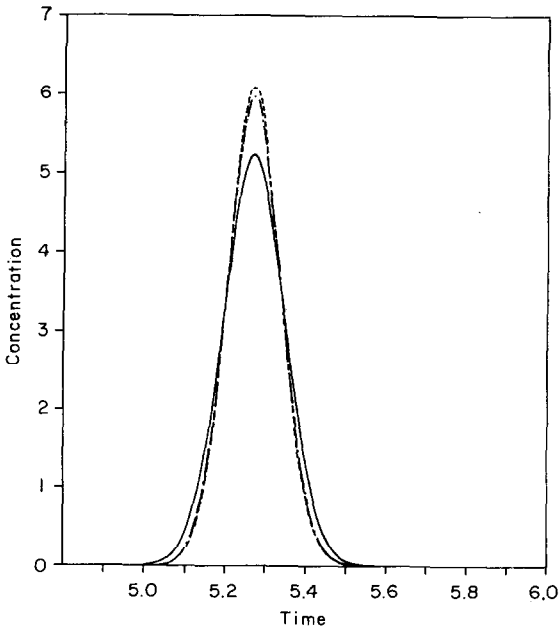


Fig. 6. Limiting approximation for instantaneous sorption and desorption. (—) $D = 1$; (- -) $D = 10$; (- · -) $D = \infty$.

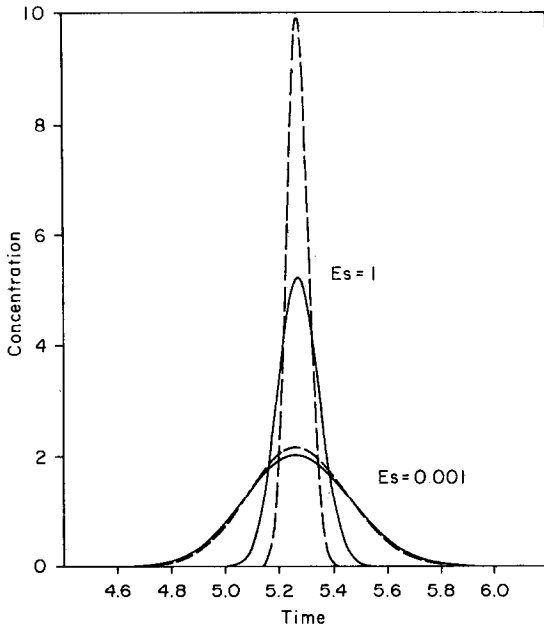


Fig. 7. Effect of neglecting axial dispersion. (—) With axial dispersion; (---) without axial dispersion.

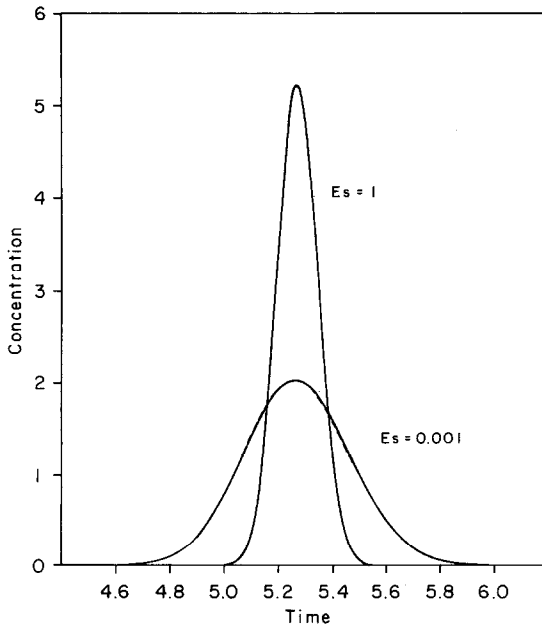


Fig. 8. Effect of lumping all band broadening mechanisms into single-phase effective dispersion coefficient (—) Exact solution; (---) approximate solution.

assumption of equilibrium is reasonable. This is in agreement with the predictions of the order-of-magnitude analysis.

The neglect of axial dispersion may be reasonable if its contribution to band broadening is much smaller than that of the interaction between convection and lateral transport. Fig. 7 shows situations where this does and does not apply, with the intraparticle diffusivity being the manipulated parameter. Clearly at the lower value of E_s lateral transport is slow enough to cause enough band broadening to dominate the axial dispersive contribution. Again the order-of-magnitude analysis is in accord with this result.

Finally, an approximate solution can be developed on the basis of the observed symmetry of the chromatographic peaks over a wide range of parameter values. This symmetry suggests that the interaction between lateral transport and axial convection can be described in terms of an effective axial dispersion coefficient, \mathcal{D}_{eff} , in single-phase dispersed plug flow at an effective velocity, u_{eff} . The velocity is found from the solute mean residence time given by the first moment, μ_1 , while \mathcal{D}_{eff} can be found explicitly using the equation for reduced plate height h : $\mathcal{D}_{\text{eff}} = d_p u_{\text{eff}} h / 2$. The concentration profile can then be calculated using either the short column asymptotic result¹⁸ or the long column Gaussian result; the differences are small for normal chromatographic situations. As shown in Fig. 8, the agreement between the approximate and exact solutions is excellent over a wide range of values of E_s ; similar results are observed when other parameters are varied.

CONCLUSIONS

The availability of the full analytical solution allows testing of several assumptions and procedures commonly used in linear chromatography. As has been shown, for example, slow lateral transport, whether diffusive or sorptive in origin, does not usually cause peak skewness. Secondary sorption, on the other hand, indeed appears to be a plausible cause of peak skewness. Other causes, not considered here, arise from extra-column effects such as dispersion in feeder tubes.

The use of moments to determine plate heights is susceptible to appreciable integration errors. In practice, this problem may be ameliorated to some extent by correlations among the errors in the three moments, but the use of plate heights remains a risky procedure. It would be much safer to perform parameter estimation using the full chromatographic peak in the time domain, thereby allowing a much more rigorous use of experimental data. For this purpose the modified single-phase dispersed plug flow model is accurate and efficient for chromatographic systems described by the model used here. It should be emphasised, however, that extra-column effects should be accounted for in the modelling process, since they can contribute to band broadening. For instance, for the parameter values given earlier it is possible to have reduced plate heights as low as about 1. Such low values are inconsistent with normal experimental observations, and extra-column effects are largely responsible.

Finally, it should be noted again that the plate height approach loses all validity in the non-linear region one would expect to encounter in many preparative situations. The full time-domain description would be needed here, and the procedures discussed here for linear chromatography may provide a basic framework which can be extended to non-linear systems.

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