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Production Rate in Preparative Elution Chromatography—A Simplified Basic Equation

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Summary

An expression for the production rate in preparative elution chromatography, based on a simplified model, is derived, and is used to illustrate the roles played by the relevant variables.

Several important papers on the more fundamental aspects of preparative efficiency in chromatography have been published (e.g., *1–5*). These reflect the widely differing views on how capacity, resolution, and speed are best to be optimized. This paper continues the approach developed in these laboratories over a period of years (e.g., *6–11*). In essence an attempt has been made to obtain a relatively simple analytical expression from which several salient features of preparative chromatography are more clearly evident. This has been done by considering a relatively restricted area of preparative chromatography. Preparative efficiency is taken simply as production rate, i.e., the mass of a component of a specified purity that can be recovered per unit time; only chromatography in columns is considered and development is restricted to the elution technique; the sample mixture contains only two equimolar components, of which the least retarded is recovered; repetitive injection is employed in such a way that cross-contamination between samples is negligible; the desired component is recovered by making a single cut in the valley between eluted peaks; carrier flow is laminar; temperature and flow programming techniques are not employed; distribution

isotherms are linear; and the inlet sample profile is treated as an equivalent Gaussian (EG) profile.

DERIVATION OF THE BASIC EQUATIONS

The mass rate at which a Component 1 of total mass m_1 is produced at the column outlet per unit sample injected is given by

$$E_p = \frac{(m_1 - \Delta m_1)u_0}{w_{t0}(1 + k_1)} \tag{1}$$

where u_0 is the carrier flow velocity at the outlet, w_{t0} is the total width of the injected sample within the column at the column outlet, Δm_1 is the mass that has to be discarded to meet the required purity specification, and k_1 is the mass distribution coefficient.

This equation also applies to the continuous production rate if, as will be assumed throughout, samples are introduced repetitively. The task is now to transcribe Eq. (1) to variables that have practical significance. The problematic factors in this connection are $(m_1 - \Delta m_1)$ and w_{t0}.

It is evident that Δm_1 can arise from two sources; the overlap with other components within a specific sample and the overlap between successive samples (see Fig. 1). The values of Δm_1 and w_{t0} depend, evidently, on the positions of the cuts, on the separating ability of the column, and on the number of components contained in the sample. However, for the purpose of studying the influence of various variables on the inherent efficiency of a preparative column, the essentials are brought out by considering the simple case of an equimolar two-component mixture. These results would serve as a useful guideline for estimating the production rate where more complicated samples are resolved.

An important matter is the definition of an appropriate unit in terms of which w_{t0} can be measured. The general differential equation which describes the motion of an arbitrary concentration distribution along the axial coordinate x is

$$\frac{\partial c}{\partial t} = -\frac{u}{1 + k}\frac{\partial c}{\partial x} + D_{eff}\frac{\partial^2 c}{\partial x^2} \tag{2}$$

which, when operated upon by the operator

$$\int_{-\infty}^{+\infty} (x - \langle x \rangle)^2\, dx \Big/ \int_{-\infty}^{+\infty} c(x)\, dx$$

yields

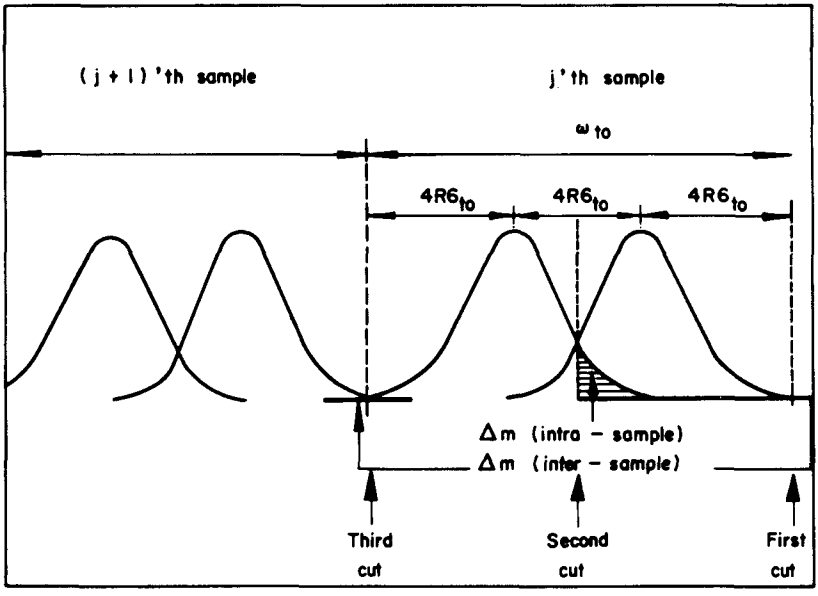

FIG. 1. Illustration of the cut points and impurities in preparative elution chromatography with repetitive sample inlet.

$$d\sigma^2/dt = 2D_{\text{eff}} \tag{3}$$

where σ^2 is the second moment or variance of the distribution defined by

$$\sigma^2 = \int_{-\infty}^{+\infty} c(x - \langle x \rangle)^2 \, dx \Big/ \int_{-\infty}^{+\infty} c \, dx$$

and

$$\langle x \rangle = \int_{-\infty}^{+\infty} cx \, dx \Big/ \int_{-\infty}^{+\infty} c \, dx$$

is the first moment.

D_{eff} is the effective diffusion coefficient and is related to the local plate height $H(x)$ by

$$H(x) = \frac{2D_{\text{eff}}(1 + k)}{u(x)}$$

σ is a measure of the peak width and would seem to be a natural unit to choose. The problem is that, although straightforward methods are available for measuring this quantity for Gaussian peaks, this does not hold for arbitrary peaks. Now when Eq. (3) is integrated [assuming $H(x)$ constant over the column length] one finds

$$\sigma_{t0}^2 = H(x)l + \sigma_{ti}^2 \tag{4}$$

The column contribution $\sigma_c^2 = H(x)l$ is Gaussian but σ_{ti}^2, the input variance within the column, depends on the form of the input. In order to facilitate the mathematical treatment an important assumption will now be made, namely, that the second moment of the actual input be replaced by that of the equivalent Gaussian inlet. The latter inlet function is uniquely defined as that Gaussian inlet which has the same area (i.e., represents the same mass) and maximum concentration as that of the actual inlet function. It can be shown (*12*) that this procedure is satisfactory when the system is operated near the maximum production rate.

Provided that the peaks at the outlet are Gaussian in shape, there is a well-defined relationship between the number of σ_{t0}'s between the peak maxima within the sample and the purity. In the same way, cross-contamination between samples can be specified in terms of the distance between them as measured in units of σ_{t0}. For example, in the special equimolar two-component case which is being considered here, a distance of $4\sigma_{t0}$ between peaks would lead to a contamination of about 2% while a $6\sigma_{t0}$ interval between samples would give an impurity of about 0.15%. It will always be assumed in the following that the frequency of sample injection has been regulated to make the cross-contamination negligible in comparison with the overlap within the sample. This is ensured by taking the distance between samples as equal to twice the distance between the two peaks within the sample, i.e.

$$w_{t0} = (2R + R)4\sigma_{t0} = 12R\sigma_{t0} \tag{5}$$

An expression for $(m_1 - \Delta m_1)$ is now given by

$$(m_1 - \Delta m_1) = \frac{m_1}{2}\{1 + \operatorname{erf}\sqrt{2}R\} \tag{6}$$

The mass m_1 itself can be related to the equivalent Gaussian variance. Consider a plug input. Then

$$m_1 = C_i V_i \tag{7}$$

where C_i is the concentration, at the inlet pressure, of m_1 in the volume V_i. If equilibration of the solute between the phases is instantaneous within the column, the plug length is reduced by a factor $1/(1 + k_1)$ during introduction into the column. Under these

conditions the concentration in the mobile phase, C_m, becomes equal to C_i. From the definition of the EG-inlet it follows that

$$w_{ii} = \sqrt{2\pi}\sigma_{ii} \tag{8}$$

where w_{ii} is the width of the plug within the column at the inlet if it is assumed that the time of introduction is short enough for peak-form deviations due to plate-height effects to be negligible. If the porosity ϵ is defined as the void fraction in the column, viz.

$$\epsilon = \frac{\text{volume of mobile phase}}{\text{total volume available for packing}}$$

the expression for m_1 can be written as

$$m_1 = (1 + k_1)c_i\pi r_c\epsilon \sqrt{2\pi}\sigma_{ii} \tag{9}$$

i.e.

$$V_1 = (1 + k_1)\pi r_c^2\epsilon \sqrt{2\pi}\sigma_{ii} \tag{10}$$

where V_c is the internal radius of the column. E_p thus becomes

$$E_p = \frac{\pi^{3/2}c_i r_c^2\epsilon\sigma_{ii}u_0\{1 + \text{erf } \sqrt{2}R\}}{24R\sigma_{t0}} \tag{11}$$

It remains to relate σ_{t0} and σ_{ii} to useful practical parameters. This can be effected by means of the resolution function R, which for equimolar peaks, is given by

$$R = \frac{\text{distance between peak maxima}}{4\sigma_{t0}}$$

A general expression for R, which takes variations along the column axis into account, can be derived (*12*) as

$$R = \frac{(\alpha - 1)k_1u_0 \int_0^l dx/u(x)}{4(1 + k_1)\left\{\int_0^l \frac{P^2(x)}{P_0^2} H(x)\, dx + p^2\sigma_{ii}^2\right\}^{1/2}} \tag{12}$$

where $P(x)$ = pressure at x, P_i = inlet pressure, P_0 = outlet pressure, $p = P_i/P_0$, and α = relative volatility.

When the indicated integrations are carried out and the resulting equation is solved for σ_{ii}, one finds

$$\sigma_{ii} = \beta\left[\left\{\frac{(\alpha - 1)lk_1}{4R(1 + k_1)}\right\}^2 - Hl\right]^{1/2} \tag{13}$$

where

$$\beta = 2(p^3 - 1)/3p(p^2 - 1)$$

is a pressure correction associated with σ_{ii} and H is the HETP including pressure corrections.

The bracket factor in Eq. (12) is just σ_{t0}, so that this quantity follows directly as

$$\sigma_{t0} = \frac{\delta(\alpha - 1)lk_1}{4R(1 + k_1)} \tag{14}$$

with the pressure correction δ given by

$$\delta = \frac{u_0}{l}\int_0^l \frac{dx}{u(x)} = p\beta = \frac{2(p^3 - 1)}{3(p^2 - 1)} \tag{15}$$

Substitution of Eqs. (13) and (14) in Eq. (11) yields the required expression for E_p as

$$E_p = \left\{\frac{\sqrt{2\pi}c_i\epsilon\pi r_c^2 u_i}{24R}\right\}\left\{1 - \frac{16(1 + k_1)^2R^2H}{k_1^2(\alpha - 1)^2l}\right\}^{1/2}\{1 + \text{erf}\,\sqrt{2}R\}$$
$$= \{f_A\}\{f_B\}\{f_C\} \tag{16}$$

DISCUSSION

Several interesting deductions may be made from the general properties of Eq. (16). In particular, the roles played by the variables in the present situation may be compared to those in the analytical case.

(a) The Plate-Height (H)

It is evident from Eq. (16) that H plays only a secondary role in preparative work in contrast to its dominant role in the analytical efficiency function. Theories of preparative chromatography based on the plate height as efficiency function should therefore be considered as inadequate.

(b) The Concentration (C_i)

Since E_p is directly proportional to C_i, the maximum concentration should be used if maximum production rate is to be achieved. This maximum is determined by the linearity of the distribution isotherm if operation is restricted to linear chromatography. This does not imply that it would necessarily be deleterious to operate the column

in the nonlinear region since a fair amount of skewing may be tolerated in view of the gain in mass. In fact, preliminary theoretical investigations indicate that such a procedure may considerably enhance the production rate of a preparative column. A complete discussion of these effects is, however, not possible at the moment.

(c) The Concentration Distribution Coefficient (K)

It is evident that E_p is only relatively weakly dependent on K through the f_B factor. This might appear surprising in view of the observation that increase in K should lead to a shorter initial plug length and corresponding increase in production rate. This effect is, however, exactly offset by the reduction in the velocity at the column outlet so that f_A is independent of K.

(d) The Column Length (l)

Inspection of Eq. (16) shows that a critical length, l_a, has to be reached before production can start. This should correspond to zero inlet volume, i.e., l_a should be equal to the analytical length. That this is indeed the case is seen by equating the bracketed term to zero and solving for l_a. The result is

$$l_a = \frac{16R^2H(1 + k_1)^2}{(\alpha - 1)^2k_1^2}$$

which is simply the expression for the analytical length. When l is increased beyond l_a, larger inlet volumes may be used and E_p increases.

(e) The Velocity (u_i)

The velocity appears both explicitly and implicitly (through H), and these dependences have opposite effects on the production rate. This leads to an optimum flow velocity for production rate in preparative chromatography, the value of which will exceed that for the corresponding analytical case. This may be seen by noting that the shortest critical length, l_{am}, is obtained by making H a minimum. The flow velocity at which this occurs is the usual optimum flow velocity for analytical work. For every $l > l_{am}$ there will therefore be an optimum flow velocity for preparative work which will exceed that of the analytical value by a factor which will increase with increasing length.

(f) The Inlet Volume (V_i)

The actual functional dependence of the inlet volume is found by substituting Eq. (13) into Eq. (10).

$$V_i = (1 + k_1)\pi r_c^2 \epsilon \sqrt{2\pi\beta} \left[\left\{ \frac{(\alpha - 1)fk_1}{4R(1 + k_1)} \right\}^2 - Hl \right]^{1/2}$$

It is evident that the determination of V_i requires, apart from l and u_i which are respectively given and optimized, the specification of the column radius, which may, or may not, be fixed by an optimum.

(g) The Resolution (R)

R appears in all three factors of Eq. (16). In f_C it expresses the fact that increase in R will lead to an increase in the amount of substance recovered with a corresponding increase in the efficiency. Its presence in f_B indicates that a price has to be paid for this increase in terms of an increase in length (the other variables are considered as remaining constant). The R in the numerator of f_A merely takes into account the increased width of the sample (and consequently reduced E_p) with increasing R.

The effect of the stationary phase loading and the column radius cannot be assessed by inspection of Eq. (16) since they are related to (α, k, and H), and H, respectively. Their relationship to the plate height is particularly involved and will be dealt with in separate communications on the production rate of open tubular and packed columns. The role of temperature will also be dealt with separately.

List of Symbols

β	pressure correction defined by Eq. (13)
c	concentration of component at x parameter defined by Eq. (15)
D_{eff}	effective longitudinal diffusion coefficient (axial dispersion coefficient)
E_p	production rate of ith component by elution development for two-fraction technique
ϵ	void fraction
$H(x)$	local HETP
l	column length
l_a	column length required for the separation of an infinitesimally small sample

l_{am}	minimum of l_a
m_i	total mass of ith component in sample
P_i	inlet pressure
P_0	outlet pressure
p	P_i/P_0
R	resolution $= \Delta x/4\sigma$
r_c	inside radius of column
σ^2	second moment (variance) of concentration distribution
σ_{ii}^2	variance at inlet within column
σ_{t0}^2	total variance at column outlet within the column
u_0	linear carrier velocity at outlet
V_i	inlet volume at the pressure existing at the inlet but without the column
w_{ii}	width of plug within column at inlet
w_{t0}	total width of fraction cut out at outlet within column

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