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Journal of Chromatography A, 1006 (2003) 45–60
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Efficiency of preparative and process column distribution systems

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Abstract

An analytical method for computing the residence time distribution of the liquid distribution system in chromatography columns is described. The impact of the distributor design on the separation efficiency is predicted as a function of media properties and packed bed dimensions. The efficiency loss due to the distributor when increasing column diameter during scale-up is quantified. It is shown that this loss can be compensated by modulating the local bed height via a moderate inclination of the bed support. It is concluded that the selection of an appropriate distributor design concept with optimised dimensions enables a scale-up of chromatographic separations without any significant loss of chromatographic efficiency due to the distribution system.

Keywords: Residence time distribution; Efficiency; Preparative chromatography; Distribution system; Column packing; Mathematical modelling

1. Introduction

It is well known that the efficiency of a chromatographic separation may suffer from the fluid transfer in the column peripherals as well as from an unfavourable design of the fluid distribution system [1]. Moreover, heterogeneities in the packed bed can have a significant negative impact on the fluid flow and packed bed efficiency [2]. In general, such non-ideal conditions should introduce as little sample dispersion as possible to superimpose on the characteristic dispersion of the chromatography medium in a homogeneous ideal packing, often referred as ideal ‘‘band-broadening’’. The term ‘‘medium’’ shall be used in the following to denote the chromatographic efficiency as well as material properties of the stationary phase for the ideal state where particle and packed bed properties are considered constant and isotropic.

While fluid transfer in the peripherals upstream and downstream the column is not affected by the design and the properties of the column, there is a distinct connection between the column distribution system and the fluid flow within the packed bed. This is due to the fact that the fluid distribution system represents the boundary conditions for the packed bed at the inlet and outlet side. The fluid distribution system is, therefore, the most critical design element of a chromatographic column. To avoid introducing excessive dispersion in the apparent RTD (residence time distribution) of the chromatographic unit, the design of the distribution system has to be adjusted to the properties of the medium and the dimensions of the packed bed [3]. However, these requirements apply to the operating mode of the distributor when liquid is fed to the

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0021-9673/03/$ – see front matter
doi:10.1016/S0021-9673(03)00177-8

packed bed. In addition, the functionality of the distributor during column packing is of interest. Here, excess liquid has to be removed during the initial bed formation process and a uniform velocity field at the bed support is desirable to facilitate a uniform initial growth of the bed. To strengthen the ''design by calculation'' of chromatographic columns and processes, the availability of a straightforward analytical approach for an efficiency analysis of distribution systems is of great interest for selecting design alternatives as well as for dimensioning. Such an approximative analytical method is the objective of this study.

2. Chromatographic efficiency

2.1. Dispersion

Deterioration in chromatographic efficiency is usually determined from a deviation in the column response compared to predictions obtained from idealised models. The most frequently used idealised model for efficiency analysis is the elution of a tracer signal under conditions that inhibit any sorptive interaction between sample and media, so-called ''non-retaining'' conditions. This involves evaluating the RTD (residence time distribution) of a tracer eluted as pulse or front, which is also a common method for the installation qualification of chromatographic systems. The dispersion is quantified as HETP (height equivalent of a theoretical plate) calculated from the characteristic moments of the RTD [3,4]. For this condition, the dispersion or band-broadening expected for the stationary phase packed to an ideal and homogeneous bed can be described with a Van Deemter type equation. The latter considers stoichiometry (bed voidage and intraparticle porosity), dispersion and diffusional mass transfer for tracer and packed bed under the condition of an infinitesimal sample volume; a detailed description can be found elsewhere [4].

To facilitate a generic analysis of chromatographic efficiency, the use of the dimensionless reduced plate height $h = \mathrm{HETP}/d_\mathrm{p}$ is preferable. As a rule of thumb, the characteristic dispersion of the medium typically gives a reduced plate height in the range $h = 1.5–2.0$ at an optimised superficial velocity when considering the highly porous media used for protein chromatography in biotechnological downstream processing [3]. The ideal efficiency of the medium has to be compared to the experimentally determined efficiency of the chromatographic system, where an increase in the reduced plate height is a result of additional dispersion from peripherals, sample volume, bed heterogeneities and distribution system. In practice, a typical standard installation qualification of a chromatographic unit (whole system including the packed column) used in ion-exchange separations of proteins is an experimentally determined reduced plate height of $h_{\mathrm{Unit,\ Apparent}} < 3.0$ [5]. For high resolution size exclusion chromatography of proteins, a unit with optimal efficiency should exhibit a reduced plate height of $h_{\mathrm{Unit,\ Apparent}} \approx 2.0$ [6].

Dispersion is often determined with help of the peak width w_h at half the height of the eluted peak, as shown in Fig. 1. This procedure is an approximation valid for the Gaussian-shaped curves that are expected for the ideal condition. In practice, eluted peaks often deviate from this ideal shape and peak skewness is described qualitatively by a so-called asymmetry factor A_f, where ''leading'' in the RTD is indicated by $A_\mathrm{f} < 1$ and ''tailing'' by $A_\mathrm{f} > 1$. Commonly applied acceptance criteria for the asymmetry factor are $0.8 < A_\mathrm{f} < 1.5–1.8$, depending on the type of application.

$$h = \frac{\mathrm{HETP}}{d_\mathrm{p}} = \frac{L}{d_\mathrm{p}} \cdot \frac{\sigma^2}{\mu_1^2} \approx \frac{L}{d_\mathrm{p}} \cdot \frac{1}{5.54} \cdot \left(\frac{w_h}{V_\mathrm{R}}\right)^2 \tag{1}$$

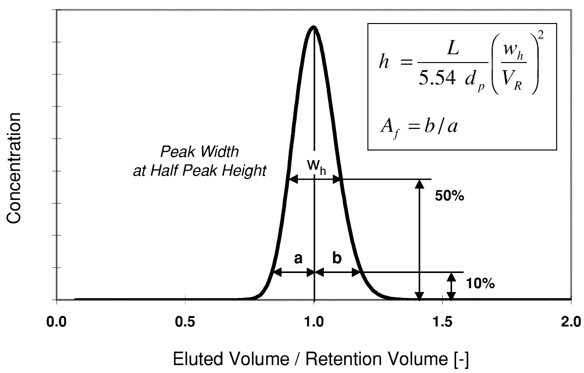

Fig. 1. Approximative method for calculating the reduced plate height and asymmetry factor from an eluted peak.

$$A_f = b/a \quad (2)$$

As mentioned above, the mathematically correct description of dispersion is the variance in the RTD determined from integration. However, results obtained by integration can be misleading as deviations from the idealised Gaussian model are common. This explains why the rather pragmatic evaluation of peak width and asymmetry factor is often preferred for the installation qualification of systems in the field. It should, however, be mentioned that modified models for Gaussian distributions accounting for peak skewness have been proposed, which may increase the applicability of the integration methods, primarily for modelling and simulation purposes [1].

For the RTD test condition, the additivity relationship of the characteristic moments can be used to analyse the impact of different sources of dispersion upon the apparent reduced plate height:

$$h_{\text{Unit, Apparent}} = \frac{L}{d_p} \cdot \frac{\sum_{i=1}^{n} \sigma_i^2}{\left(\sum_{i=1}^{n} \mu_{1\,i}\right)^2} \quad (3)$$

For the scope of this study, as well as for the analysis of chromatographic efficiency in general, the quantification and control of the terms in Eq. (3) is of major interest. For example, the dispersion introduced by the volume of a tracer pulse can be approximated for sample volumes smaller than 5% of the packed bed volume [7]:

$$\sigma^2_{\text{Sample}} \approx \left(\frac{1}{3} \cdot \frac{V_{\text{Sample}}}{V_{\text{Bed}}}\right)^2 \quad (4)$$

In contrast, dispersion by the peripherals depends strongly on the dimensions of the pipework and valves, as well as on the flow regimes (laminar or turbulent). In practice, the experimental analysis of dispersion in the peripherals by bypassing the column is therefore strongly recommended. Neither can dispersion and peak asymmetry resulting from packing heterogeneities be predicted by general empirical rules. On the other hand, the dispersion from packing heterogeneities can be quantified as soon as the impact of the liquid distribution system is known. In regard to such an analysis, the characterisation of the distribution system is of major interest.

2.2. Efficiency of the distribution system

Following Eq. (3) and considering the most important sources of dispersion in the chromatographic system, the deterioration in the reduced plate height due to the distribution system can be described as

$$\begin{aligned} h_{\text{Distribution system}} &= \frac{L}{d_p} \\ &\cdot \left(\frac{\sigma^2_{\text{Medium}} + \sigma^2_{\text{Distribution system}} + \sigma^2_{\text{Peripherals}} + \sigma^2_{\text{Sample}} + \sigma^2_{\text{Packing heterogeneity}}}{(\mu_{1\,\text{Medium}} + \mu_{1\,\text{Distribution system}} + \mu_{1\,\text{Peripherals}} + \mu_{1\,\text{Sample}} + \mu_{1\,\text{Packing heterogeneity}})^2}\right) \\ &- \frac{L}{d_p}\left(\frac{\sigma^2_{\text{Medium}} + \sigma^2_{\text{Peripherals}} + \sigma^2_{\text{Sample}} + \sigma^2_{\text{Packing heterogeneity}}}{(\mu_{1\,\text{Medium}} + \mu_{1\,\text{Peripherals}} + \mu_{1\,\text{Sample}} + \mu_{1\,\text{Packing heterogeneity}})^2}\right) \end{aligned} \quad (5)$$

Note that the contribution of the liquid distribution system to the overall dispersion is a relative figure when described in terms of a reduced plate height because there is no additivity relationship for reduced plate heights! An expression like Eq. (5) is therefore seldom applied, although it facilitates a very comprehensive analysis, as shown in the following. To reduce complexity for the purpose of column design, we consider only the dispersion by the medium and the distribution system. We thus calculate the distributor impact on this apparent efficiency as

$$\begin{aligned} h_D &= \frac{L}{d_p} \cdot \left(\frac{\sigma^2_{\text{Apparent}}}{\mu^2_{1_{\text{Apparent}}}} - \frac{\sigma^2_{\text{Medium}}}{\mu^2_{1_{\text{Medium}}}}\right) \\ &= \frac{L}{d_p} \cdot \left(\frac{\sigma^2_{\text{Medium}} + \sigma^2_{\text{Distribution system}}}{(\mu_{1_{\text{Medium}}} + \mu_{1_{\text{Distribution system}}})^2} - \frac{\sigma^2_{\text{Medium}}}{\mu^2_{1_{\text{Medium}}}}\right) \end{aligned} \quad (6)$$

In most situations, this simplification will be a conservative assessment of the distributor impact because $h_{\text{Distribution system}} \leq h_D$. To eliminate the impact of the superficial velocity, and to make the analysis more transparent, we set the reduced plate height of the medium by definition to $h_{\text{Medium}} = 2$. The first moment for an inert tracer passing the ideal packed bed is calculated from the bed voidage ε_b, intra-particle porosity ε_p, and size exclusion coefficient K_e:

$$\mu_{1_{\text{Medium}}} = \varepsilon_b + (1 - \varepsilon_b)\varepsilon_p K_e \quad (7)$$

For the RTD test condition, it is assumed that a non-adsorbed low-molecular mass tracer is used that completely penetrates the intraparticle volume, which leads to the assumption of $K_e = 1$.

Hence, the variance of the medium $\sigma^2_{\mathrm{Medium}}$ normalised in term of reduced residence time can be calculated from the relationship:

$$h_{\mathrm{Medium}} = \frac{L}{d_p} \cdot \frac{\sigma^2_{\mathrm{Medium}}}{\mu^2_{1_{\mathrm{Medium}}}} \equiv 2.0 \tag{8}$$

The method described in the following will provide the characteristic moments of the RTD generated by the distribution system for the analysis of the distributor efficiency in terms of the parameter h_D using Eqs. (6)–(8). Furthermore, we will also present a method for computing the apparent RTD by medium and distribution system. The apparent RTD has to be derived for an analysis of peak asymmetry, for example. Note that the theoretical analysis considers the case of a non-constant packed bed height. In this situation, the packed bed height L in the equations above has to be replaced by the average bed height $\hat{L}$.

3. Theory

3.1. Distributor geometry

We restrict the analysis to geometries that are essentially rotational symmetric. Fig. 2 shows a standard design of a distribution system with a central inlet, a plenum chamber between the column end plate and the particle-retaining bed support (filter or net). It is assumed that the design of the distribution system at the column inlet is identical to that at the liquid collection system at the outlet. In a first approach, we neglect the bed support with regard to its hold-up volume, dispersion and pressure drop. The height of the distribution channel $y_{\mathrm{Channel}}(r)$ does not have to be constant as long as the assumptions made for the channel are not violated. For the analysis in this study, the height of the distribution channel follows a linear function determined by the channel height at the column radius $y_{\mathrm{Channel},\, r=R}$ and a channel height $y_{\mathrm{Channel},\, r=0}$ projected to the centreline. To account for the central mobile phase inlet/outlet as well as for a fillet at the edge between the nozzle and distribution channel, we will make assumptions for the pressure field for the range $r/R < 0.1$. In addition, the figure illustrates a modulation in the packed bed height by an inclination of the bed support. This modulation is described by the distance $y_{\mathrm{Bed\ support}}$ specifying the axial displacement at the centreline relative to the nominal packed bed height L found at the column wall. For the analysis in this study, the position of the bed support $y_{\mathrm{Bed\ support}}(r)$ is represented as a linear function. For a bed support inclination with $y_{\mathrm{Bed\ support}} > 0$, the total height of the packed bed at

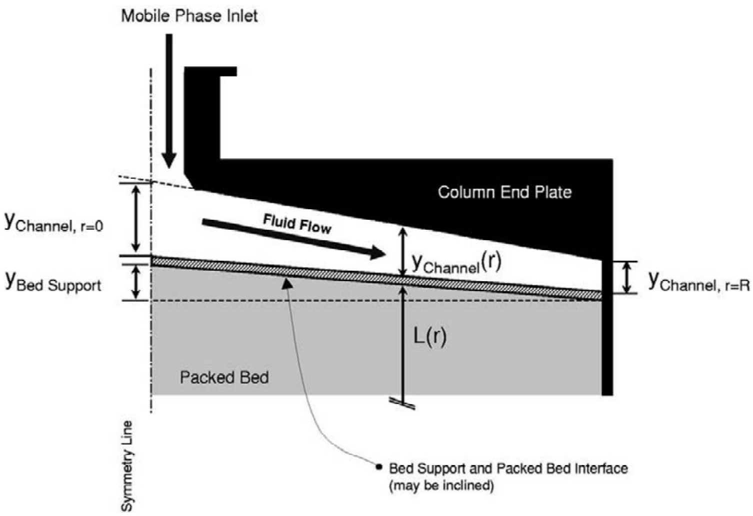

Fig. 2. Schematic view of distributor geometry and geometrical input parameters of the distributor analysis.

the column centreline is $L(r) = L + 2y_{\text{Bed support}}$ such that the average height of the packed bed as well as the average bed volume will increase slightly.

3.2. Assumptions

The main assumption required for establishing an analytical method is that the deviation from a uniform velocity field in the packed bed region is negligible with respect to the computation of the volume flux at the inlet and outlet of the packed bed. This means that the volumetric flow in the liquid distribution channel feeding the packed bed is known and constant. For an axi-symmetric distribution system with a distribution channel extending from the central mobile phase inlet to the column radius R, this approximation yields:

$$\dot{V}_{\text{Channel}}(r) \approx u_{\text{s}} \pi R^2 \cdot \left(1 - \left(\frac{r}{R}\right)^2\right) \tag{9}$$

From numerical parameter studies using CFD (computational fluid dynamics) methods, we have found that this approximation is justified for all cases where the design of the distribution system is appropriate in terms of introduced dispersion.

The following assumptions are made for the description of pressure and flow in the distribution channel:

(1) the radial volume flux in the channel follows Eq. (9);

(2) the flow in the distribution channel is steady, incompressible viscous laminar flow;

(3) the channel is very narrow and ideal, which means that the liquid is confined by a top and bottom surface only (impermeable end plate and filter at the packed bed interface);

(4) the channel is permeable towards the packed bed at the surface of the bed support.

For the description of pressure and flow in the packed bed, it is assumed that:

(1) the flow in the packed bed region is porous media flow according to Darcy's law;

(2) the packed bed permeability is constant and isotropic;

(3) the flow is assumed to be one-dimensional and in the direction of the column symmetry line.

3.3. Computation of RTD for distribution system

Based on these assumptions, an analytical method is developed that describes deviations from the ideal RTD due to:

(1) differences in the residence time due to a radial pressure gradient in the distribution and collection channel inducing a gradient in the axial velocity over the packed bed;

(2) differences in residence time between fluid elements moving radially in the distribution and collection channel and thus passing the packed bed at different radial positions.

From a mass and momentum balance, we derived an equation for the pressure field in an ideal channel extending from the centreline of the column towards the column radius ($r = R$). We assume that pressure in the narrow channel is a function of r only and that the radial flow is decelerating (from mass balance). Qualitatively then, we expect the velocity profile to be steeper near the walls than the parabolic profile in fully developed two-dimensional channel flow. In other words, the shear stress on the channel wall is higher than if the flow is a fully developed two-dimensional channel flow. From full-scale CFD simulations, we obtain a good estimation of the wall shear stress. A force balance between pressure, shear stress and inertia derived from the Navier–Stokes equation making use of the estimation of the shear stress gives an approximation of the pressure distribution in the channel:

$$\begin{aligned} p(r) = {} & \left(\frac{12\mu N(r) Q_0(r)}{y_{\text{Channel}}(r)^2 R^2} - \frac{\rho N(r)^2 Q_0(r)^2}{2R^2}\right)(r^2 - R^2) \\ & + \frac{24\mu N(r) Q_0(r)}{y_{\text{Channel}}(r)^2} \ln\left(\frac{R}{r}\right) \\ & + 0.5\rho N(r)^2 Q_0(r)^2 \left(\frac{1}{R^2} - \frac{1}{r^2}\right) \end{aligned} \tag{10}$$

with radial position in the channel r, column radius R, local channel height $y_{\text{Channel}}(r)$, constant fluid dynamic viscosity μ, constant fluid density ρ, $N(r) = R^2/(R^2 - r^2)$, and $Q_0(r) = u_{\text{m}}(r) \cdot r$ with mean velocity in the channel $u_{\text{m}}(r)$. Employing Eq. (9), the mean velocity in the channel calculates with the superficial velocity u_{s} to

$$u_{\text{m}}(r) = \frac{u_{\text{s}}}{2ry_{\text{Channel}}(r)} \cdot (R^2 - r^2) \tag{11}$$

Eq. (10) was originally developed for a constant channel height and needs to be modified depending on the shape of the channel. For simplification, the equation shall be applied in this study for channels with non-constant channel height, too. However, for all design cases discussed in this study, we have verified that errors in the distributor impact h_D resulting from this simplification are negligible. The channel pressure $p(r)$ according to Eq. (10) superimposes the nominal pressure gradient over the packed bed that is computed with Darcy's law as

$$\Delta P_{\mathrm{Bed}} = \frac{u_s \mu L}{\kappa} \tag{12}$$

For a constant hydraulic permeability κ of the porous medium, packed bed height L and fluid viscosity μ, the superficial velocity u_s over the packed bed is proportional to the pressure difference ΔP over the bed. The non-linearity in pressure–flow curves that can be found with compressible media is not considered in this study as we assume that permeability and voidage are constant and isotropic. In case of compressible media, the appropriate data for the average permeability and voidage needs to be provided for the specific operating conditions, i.e., column diameter, bed height and fluid velocity. The pressure drop over the bed supports is in practice often negligible, but may be added to the pressure over the bed.

For a bed support inclination with $y_{\mathrm{Bed\ support}} > 0$, the average bed height $\hat{L}$ has to be determined by integration and an average pressure drop over the packed bed has to be calculated:

$$\Delta \hat{P}_{\mathrm{Bed}} = \frac{\hat{L}}{L_{\mathrm{Nominal}}} \cdot \Delta P_{\mathrm{Bed}} \tag{13}$$

For a chromatographic column having a liquid distribution system consisting of a single channel extending from the central inlet towards the column wall, the pressure in the distribution channel typically decreases with increasing radius. In contrast, for a liquid collection channel at the outlet that has identical dimensions, the pressure will increase with radial position as $p(r)_{\mathrm{Distribution\ channel}} = -p(r)_{\mathrm{Collection\ channel}}$ with $p(R) = 0$. As the pressure gradient over the packed bed is the driving force for the flow, the following axial velocity in the packed bed as function of radius can be derived with the assumption that the pressure fields in the distribution and collection channel are identical:

$$\frac{u_{\mathrm{axial}}(r)}{\hat{u}_s} = \left(\frac{L(r)}{\hat{L}}\right)^{-1} \cdot \frac{2p(r) + \Delta \hat{P}_{\mathrm{Bed}}}{\frac{2\pi}{\pi R^2} \int_0^R (2p(r) + \Delta \hat{P}_{\mathrm{Bed}}) r \, \mathrm{d}r} \tag{14}$$

For a flush bed support ($y_{\mathrm{Bed\ support}} = 0$), this equation simplifies to:

$$\frac{u_{\mathrm{axial}}(r)}{\hat{u}_s} = \frac{2p(r) + \Delta P_{\mathrm{Bed}}}{\frac{2\pi}{\pi R^2} \int_0^R (2p(r) + \Delta P_{\mathrm{Bed}}) r \, \mathrm{d}r} \tag{15}$$

However, an approximation for the pressure at the mobile phase inlet and outlet has to be made as Eq. (10) does not hold for the inlet region. The mobile phase inlet is typically $r_i/R < 0.05$ and in most cases a fillet or radius is applied to avoid any throttling of fluid in the transition region between mobile phase inlet and distribution channel. Thus, we make the assumption that

$$p(r) = p(r/R = 0.1) \text{ for } r/R < 0.1 \tag{16}$$

Now, a dimensionless residence time as function on radial position can be calculated:

$$\tau_{\mathrm{axial}}(r) = \frac{L(r)}{\hat{L}} \cdot \left(\frac{u_{\mathrm{axial}}(r)}{\hat{u}_s}\right)^{-1} = \left(\frac{L(r)}{\hat{L}}\right)^2 \cdot \left(\frac{2p(r) + \Delta \hat{P}_{\mathrm{Bed}}}{\frac{2\pi}{\pi R^2} \int_0^R (2p(r) + \Delta \hat{P}_{\mathrm{Bed}}) r \, \mathrm{d}r}\right)^{-1} \tag{17}$$

which, for a flush bed support ($y_{\mathrm{Bed\ support}} = 0$), simplifies to

$$\tau_{\mathrm{axial}}(r) = \left(\frac{u_{\mathrm{axial}}(r)}{\hat{u}_s}\right)^{-1} = \left(\frac{2p(r) + \Delta \hat{P}_{\mathrm{Bed}}}{\frac{2\pi}{\pi R^2} \int_0^R (2p(r) + \Delta \hat{P}_{\mathrm{Bed}}) r \, \mathrm{d}r}\right)^{-1} \tag{18}$$

The residence time $\tau_{\mathrm{radial}}(r)$ due to a lateral fluid transfer between the mobile phase inlet/outlet at the column centreline and a radial position r within the fluid distribution and collection channels can be derived from the average radial velocity in the channel as:

$$\tau_{\text{radial}}(r) = \frac{2u_s}{\hat{L}} \int_0^r \frac{1}{u_m(r)}\,\mathrm{d}r \tag{19}$$

For the non-retained tracer condition discussed here, the resulting dimensionless residence time as function of radial position over the column becomes:

$$\tau_{\text{sum}}(r) = \tau_{\text{axial}}(r) + \tau_{\text{radial}}(r) \tag{20}$$

Now the RTD over the column can be derived by integration over the packed bed cross-sectional area:

$$F_{\text{Distribution}}(\tau) = C(\tau)/C_0 = \frac{2\pi}{\pi R^2} \int_0^R \tau'_{\text{sum}}(r) r\,\mathrm{d}r,$$
$$\tau'_{\text{sum}} \in (0,\tau) \tag{21}$$

To apply Eq. (6), we need the characteristic moments of the computed breakthrough curve at the column outlet. The first moment is,

$$\mu_{1,\text{Distribution}} = \int_0^1 \tau dF_{\text{Distribution}}(\tau) \tag{22}$$

To derive the characteristic moment of the distribution system, this first moment has to be corrected for the packed bed volume, which gives:

$$\mu_{1,\text{Distribution System}} = \int_0^1 \tau dF_{\text{Distribution}}(\tau) - 1 \tag{23}$$

The dispersion by the distribution system in terms of the normalised variance is calculated on the basis of reduced time $\tau_r = \tau/\mu_1$ to:

$$\sigma^2_{\text{Distribution System}}(\tau_r) = \int_0^1 (\tau_r - 1)^2 dF_{\text{Distribution}}(\tau_r) \tag{24}$$

We have already discussed the problem of yielding a relevant figure for dispersion when analysing RTD signals that deviate from the gaussian shape. In contrast to the peak response of a packed bed under ideal conditions, an ideal sigmoidal shape of the distributor RTD breakthrough curve $F_{\text{Distribution}}(\tau)$ cannot be expected. However, we found that arbitrary defined integration boundaries of [0.02, 0.98] applied to Eq. (24) are in most cases appropriate to derive a good estimate of dispersion by the distribution system as long as the distributor design is favourable. Under these conditions, we found that predictions by Eq. (24) are also in reasonable agreement with the determination of the dispersion from the apparent RTD. Determining the apparent RTD is generally a more robust method as skewness and asymmetry in the apparent RTD are usually small compared with the skewness in the RTD for the distribution system alone. Determining the apparent RTD allows the alternative of determining the peak width at half height of the peak for non-symmetric peaks. However, the advantage of determining dispersion from the distributor RTD curve lies in a higher computation speed facilitating a quick assessment of a wider range of media and bed heights when applying the simplified integration procedure described in the following. For this procedure, the RTD age function is calculated as:

$$F^*_{\text{Distribution}}(\tau) = \frac{1}{\mu_{1,\text{Distribution}}} \frac{2\pi}{\pi R^2} \int_0^r \tau_{\text{sum}}(r) r\,\mathrm{d}r \tag{25}$$

with the first moment determined as

$$\mu_{1,\text{Distribution}} = \frac{2\pi}{\pi R^2} \int_0^R \tau_{\text{sum}}(r) r\,\mathrm{d}r \tag{26}$$

Physically, this RTD age function is only correct as long as $\tau_{\text{sum}}(r)$ is monotonically increasing. However, determining dispersion by Eq. (24) on the basis of this age function is mathematically correct as long as the integration boundaries are not restricted. This facilitates the use of the simplified approach for an initial design optimisation prior to the computation of the apparent RTD. For clarity, we re-write the equation that will be used subsequently within this study to determine the dispersion by the distributor and the distributor impact on efficiency, respectively:

$$\sigma^2_{\text{Distribution system}}(\tau_r) \approx \int_{0.02}^{0.98} (\tau_r - 1)^2 dF^*_{\text{Distribution}}(\tau_r) \quad (27)$$

3.4. Computation of apparent RTD

As mentioned above, the alternative to evaluating the RTD for the distribution system alone is analysis of the apparent RTD for the combination of medium and distribution system. Furthermore, this approach is required for an assessment of the asymmetry factor A_f. The following integrals provide the impulse function $E_{\text{apparent}}(\tau)$ as well as the age function $F_{\text{apparent}}(\tau)$ for the non-retaining test conditions:

$$E_{\text{Apparent}}(\tau) = \frac{2\pi}{\pi R^2} \int_0^R E_{\text{Medium}}\left(\frac{\tau}{\tau_{\text{axial}}(r)} - \tau_{\text{radial}}(r)\right) \mathrm{d}r \quad (28)$$

$$F_{\text{Apparent}}(\tau) = \frac{2\pi}{\pi R^2} \int_0^R F_{\text{Medium}}\left(\frac{\tau}{\tau_{\text{axial}}(r)} - \tau_{\text{radial}}(r)\right) \mathrm{d}r \quad (29)$$

with the Gaussian RTD impulse function for the medium

$$E_{\text{Medium}}(\tau) = \frac{1}{\mu_{1_{\text{Medium}}}} \cdot \sqrt{\frac{\text{Bo}_{\text{Medium}} \mu_{1_{\text{Medium}}}}{4\pi\tau}} \cdot \exp\left(- \frac{\text{Bo}_{\text{Medium}} \mu_{1_{\text{Medium}}}}{4\tau} \cdot \left(1 - \frac{\tau}{\mu_{1_{\text{Medium}}}}\right)^2 \right) \quad (30)$$

and the corresponding sigmoidal RTD age function

$$F_{\text{Medium}}(\tau) = \frac{1}{2} \cdot \left(1 - \text{erf}\left(\sqrt{\frac{\text{Bo}_{\text{Medium}}}{4\mu^2_{1_{\text{Medium}}}}} \frac{\mu_{1_{\text{Medium}}} - \tau}{\sqrt{\tau}}\right)\right) \quad (31)$$

In general, the relationship $E(\tau) = \partial F(\tau)/\partial t$ applies. In the equations above, the dispersion of the medium is given by the Bodenstein number

$$\text{Bo}_{\text{Medium}} \approx \frac{2\mu^2_{1_{\text{Medium}}}}{\sigma^2_{\text{Medium}}} = \frac{2\hat{L}}{\text{HETP}_{\text{Medium}}} = \frac{2\hat{L}}{h_{\text{Medium}} d_p} \quad (32)$$

The first and second moment of the apparent RTD function for evaluating the distributor impact with Eq. (6) are calculated as:

$$\mu_{1_{\text{Apparent}}} = \int_0^\infty \tau E_{\text{Apparent}}(\tau) \mathrm{d}\tau \quad (33)$$

$$\sigma^2_{\text{Apparent}} = \int_0^\infty (\tau - \mu_{1_{\text{Apparent}}})^2 E_{\text{Apparent}}(\tau) \mathrm{d}\tau \quad (34)$$

Note that determining the apparent dispersion for the medium and distribution system by integration is not problematic as long as the design of the distribution system is optimised for the specific case studied because this implies that peak skewness in the apparent RTD is usually negligible. In a situation where peak skewness has to be considered, the method of determining the dispersion from the peak width at half peak height can be an alternative.

3.5. Impact of bed support

The bed support (see Fig. 2) has primarily a particle-retaining function. For columns that are used at process scale in biopharmaceutical downstream processing, bed supports of extremely low permeability are usually avoided for reasons of fouling. The impact of the bed support may therefore be neglected for the operating mode. If the hold-up volume of the bed support is significant in comparison to the bed volume, one may add the thickness of both bed supports to the nominal packed bed height and thereby adjust Eq. (6) and Eq. (7) as well as Eq. (12) for a first approximation. For analytical columns with frits of considerable thickness or of significantly lower hydraulic permeability than the packed bed, the extension of Eq. (6) with the characteristic moments of the bed supports is required, and Eq. (14) has to account for the pressure drop over the bed supports as well. A more detailed approach is also required for bed supports of non-constant thickness or a variable hydraulic permeability [8].

However, for analysing distributor functionality in the column packing mode, the pressure drop over the bed support is nevertheless of great interest as the pressure drop over the packed bed is infinitesimal during the initial bed formation. Here, a minimum pressure drop over the outlet bed support is required to achieve a uniform velocity as well as uniform formation and growth of the bed. The velocity field at the bed support becomes

$$\frac{u_{\mathrm{axial}}(r)}{\hat{u}_{\mathrm{s}}} = \frac{p(r) + \Delta P_{\mathrm{Bed\ support}}}{\frac{2\pi}{\pi R^2}\int_0^R (p(r) + \Delta P_{\mathrm{Bed\ support}}) r \, \mathrm{d}r} \tag{35}$$

Again, we assume that the pressure at $r/R < 0.1$ can be approximated by Eq. (16). This analysis is valid as long as the deviation from the uniform velocity field is small. In practice, it should though be possible to approximate the velocity field for a ratio of maximum to average velocity up to $u_{\mathrm{axial}}(r)/\hat{u}_{\mathrm{s}} < 1.2$. To guarantee scalability of a distributor in the packing mode, a maximum deviation in the velocity field for the ‘‘empty’’ column must not be exceeded irrespective of column diameter.

4. Results

4.1. Input data

The required medium input data for the packed bed is particle size, hydraulic permeability, voidage and intraparticle porosity. The parameters used in this study are found in Table 1 and are typical values derived from experimental data at process scale. The size exclusion coefficient required in Eq. (7) is set to $K_{\mathrm{e}} = 1$ as default. As mentioned above, the permeability of the packed bed has to be adjusted according to the degree of bed compression and column size. As this is a critical parameter, a sensitivity analysis is recommended when no exact experimental permeability data is available. The fluid is assumed to be an aqueous solution; data are listed in Table 2. The superficial velocity in the packed bed is set to 100 cm/h for all calculations. Note that the superficial velocity selected for analysis of the distributor impact is allowed to deviate from the optimal RTD test velocity for the specific medium as long as the dynamic pressure in Eq. (10) is negligible. The dimensions of the column distributors analysed in this study are summarised in Table 3; the characteristic heights for distribution channel and bed support displacement are illustrated in Fig. 2. As mentioned above, the channel height and the bed support inclination follow linear functions.

Table 2
Mobile phase properties

Dynamic fluid viscosity	$\eta = 0.001$ Ns/m^2
Fluid density	$\rho = 1000$ kg/m^3
Superficial velocity	$u_{\mathrm{s}} = 100$ cm/h

4.2. Parameter study, 200-mm column diameter

The analysis of channel pressure, axial velocity

Table 1
Typical values for properties of chromatography media families (Amersham Biosciences) and their ideal homogeneous packings at process scale

Chromatography medium	Bead size, d_{p} (μm)	Particle porosity, ε_{p} (–)	Bed voidage, ε_{b} (–)	Bed permeability, κ (m^2)
Sepharose Big Beads	180	0.9	0.32	1.0e–11
Sepharose Fast Flow	90	0.9	0.32	2.0e–12
Sephacryl	50	0.9	0.32	1.0e–12
Sepharose HP	34	0.9	0.32	5.5e–13
SOURCE 30	30	0.6	0.32	4.8e–13
SOURCE 15	15	0.6	0.32	1.2e–13
SOURCE 5	5	0.6	0.32	1.5e–14

Table 3
Geometrical data of the design alternatives analysed (compare with Fig. 2)

Design code		Column diameter (mm)	$y_{\mathrm{Channel},\ r=0}$ (mm)	$y_{\mathrm{Channel},\ r=R}$ (mm)	$y_{\mathrm{Bed\ Support}}$ (mm)
200/0.9–0.9/0.0	A	200	0.9	0.9	0.0
200/0.9–0.4/0.0	B	200	0.9	0.4	0.0
200/0.9–0.4/0.5	C	200	0.9	0.4	0.5
200/0.3–0.15/0.5	D	200	0.3	0.15	0.5
1000/3.8–0.6/2.5	–	1000	3.8	0.6	2.5
2000/4.5–0.9/3.5	–	2000	4.5	0.9	3.5
2000/4.5–0.9/0.0	–	2000	4.5	0.9	0.0

field and residence time is illustrated for four design variants of a 200-mm diameter distributor (designs A–D, see Table 3). The pressure in the inlet distribution channel according to Eq. (10) is plotted in Fig. 3. The large channel height of designs A–C gives a moderate lateral pressure drop in the channel, while the thin channel of design D gives a maximum pressure of approximately 1.7 kPa at the inlet. For design C, the resulting velocity field in the packed bed according to Eq. (14) is plotted in Fig. 4 for three media with different particle sizes and hydraulic permeabilities. Among these three, the 34-μm medium gives the smallest deviation from the uniform velocity field for the considered packed bed geometry as the pressure drop over the packed bed is largest. The curve for the 34-μm medium also reveals the impact of the bed support inclination at design C on the velocity field because the local velocity at the column wall (lower local bed height) is larger than at the column centreline. For the 90-μm medium, the local residence time according to Eq. (20) is plotted in Fig. 5 for the four design variants. Design C is most favourable for this combination of medium and bed height due to a more uniform local residence time. As shown in the figure, design D, with its small channel dimensions, is not at all appropriate for media of large particle size. Finally, integration over the local residence time with Eq. (21) yields the corresponding RTD curves plotted in Fig. 6.

Once the RTD is available, evaluating the characteristic moments with Eqs. (26) and (27) yields the distributor impact h_D according to Eq. (6), which has been summarised in Fig. 7a–d as distributor performance profiles for each design. This graphical representation of the data gives a comprehensive

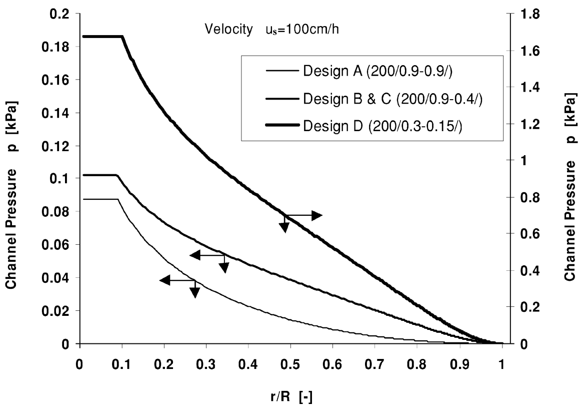

Fig. 3. Pressure in distribution channels according predicted according to Eq. (10); geometries according to Table 3.

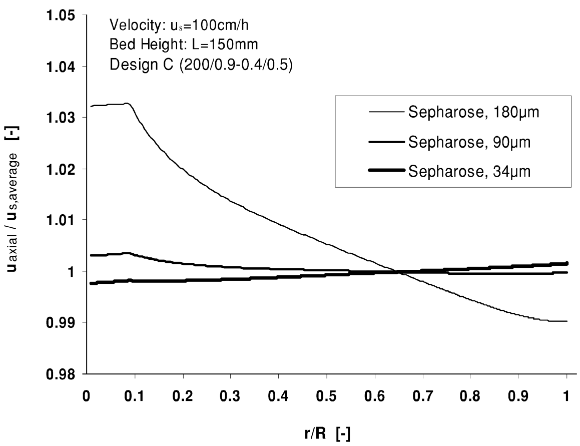

Fig. 4. Axial velocity normalised to average velocity in packed bed predicted according to Eq. (14); media parameters according to Table 1.

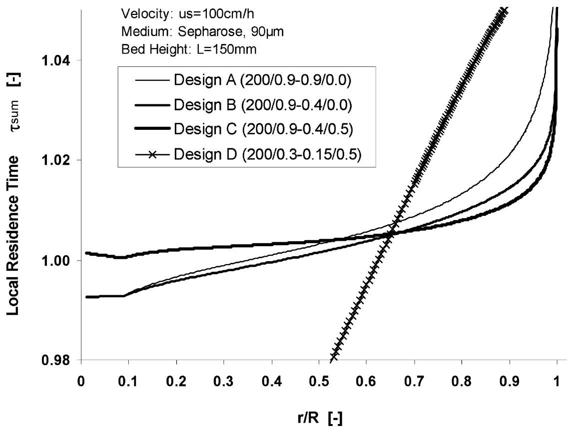

Fig. 5. Local residence time predicted according to Eq. (20).

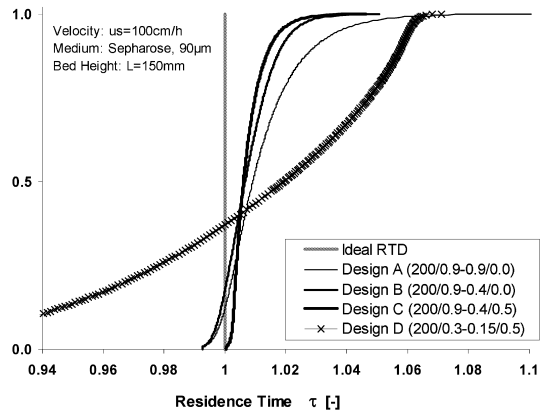

Fig. 6. RTD (residence time distribution) predicted according to Eq. (21).

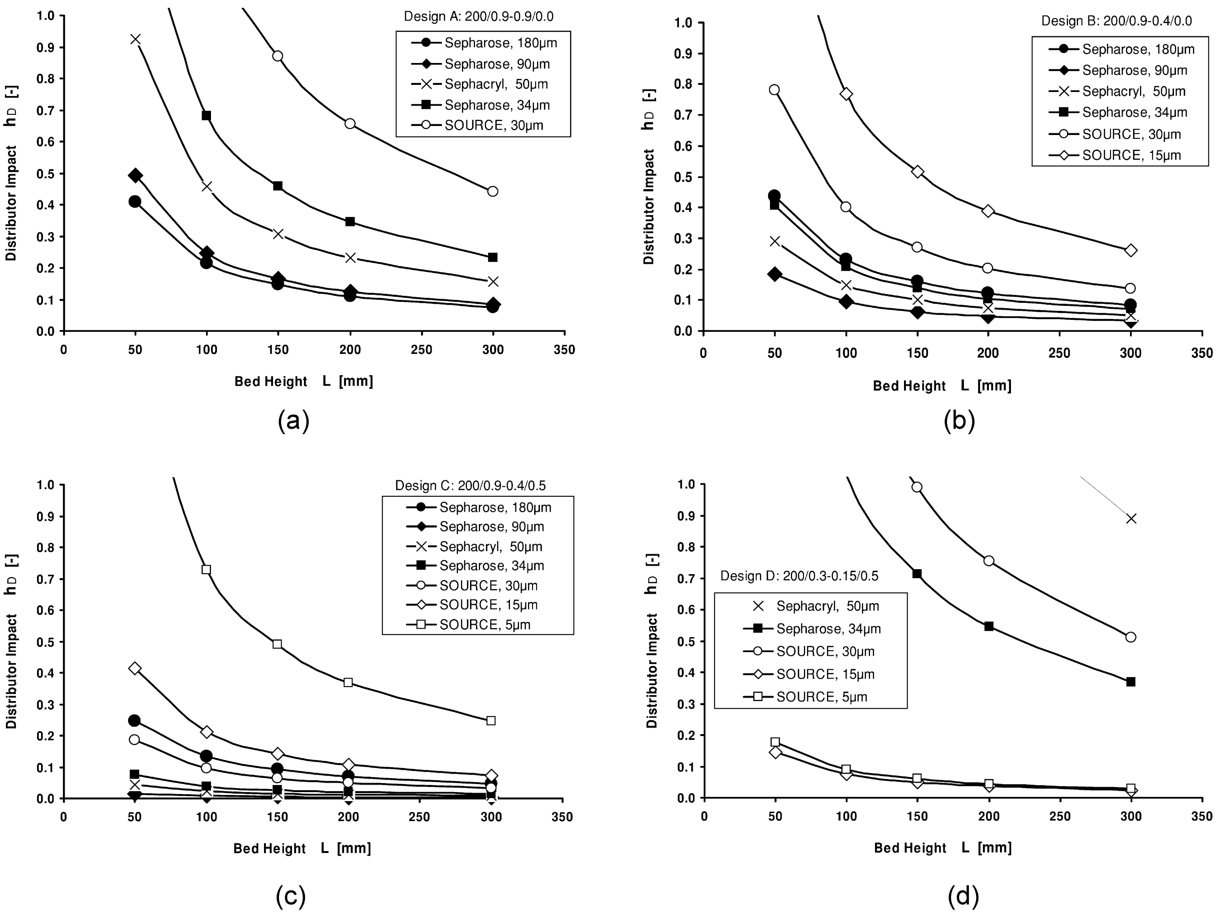

Fig. 7. Predicted performance profiles for 200-mm distributors: (a) design A, (b) design B, (c) design C, (d) design D.

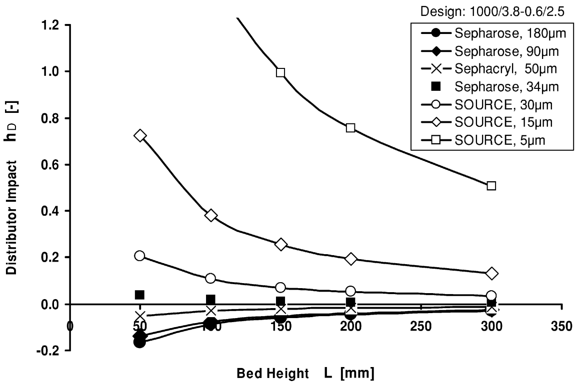

Fig. 8. Predicted performance profile for 1000-mm distributor.

correlation between distributor design and impact on chromatographic efficiency. The lower the distributor impact h_D, the better the apparent efficiency of the chromatographic unit. Note that this impact refers to the RTD test condition with the assumption $h_{media} = 2$. The performance profiles illustrate that the distributor impact is generally more critical at low bed heights. Theoretically, the distributor impact can become negative if the hold-up volume of the distributor is significant, but dispersion is small compared with the dispersion of the media.

From the comparison of design alternatives A–C, we can conclude that a conically shaped distribution channel improves the efficiency significantly compared with a distribution channel of constant height. The inclination in the bed support does improve efficiency furthermore. Design D (Fig. 7d) illustrates

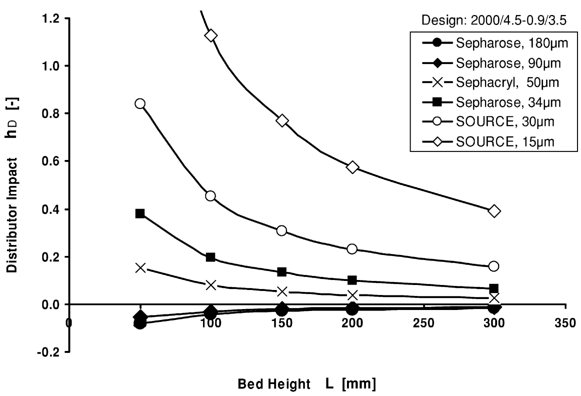

Fig. 9. Predicted performance profile for 2000-mm distributor, bed support inclination.

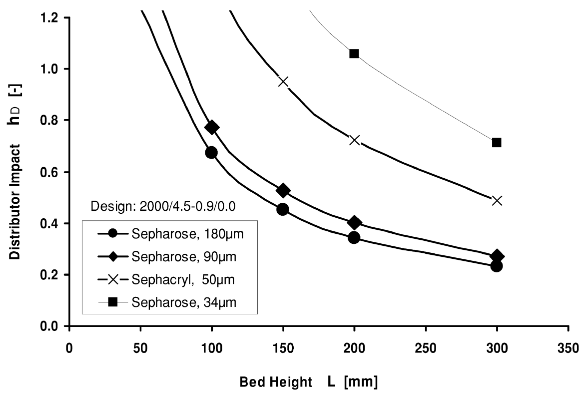

Fig. 10. Predicted performance profile for 2000-mm distributor, flush bed support.

that adjusting the dimensions may facilitate operation with 5-μm particles in a 200-mm diameter column without a significant distributor impact. On the other hand, design D reduces the ‘‘bandwidth’’ for different media compared with design C, which has more the character of a general purpose design.

4.3. Scale-up to 2000-mm column diameter

Appropriate dimensioning of the distributor, which includes optimising the bed support inclination, allows for the design of general purpose distributors

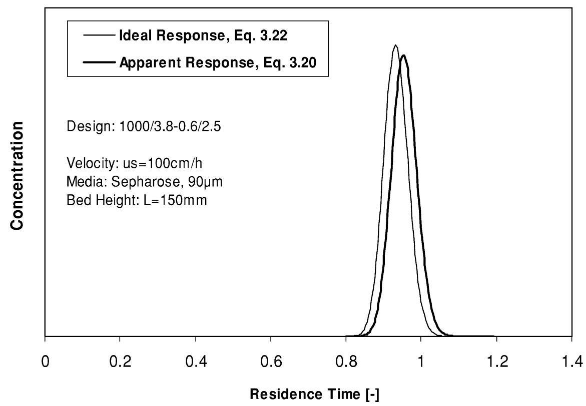

Fig. 11. Predicted apparent residence time distribution according to Eq. (28) and predicted ideal peak response according to Eq. (30) for 90-μm agarose medium, 1000-mm distributor (compare with Fig. 8).

with high ‘‘bandwidths’’ for the media commonly used at process scale. This is illustrated by the two performance profiles for columns of 1000 and 2000 mm shown in Figs. 8 and 9, respectively. Finally, the poor performance profile for the 2000-mm distributor with a flush bed support is shown for comparison in Fig. 10.

4.4. Asymmetry in apparent RTD

When analysing the shape of the RTDs for the 200-mm distributor (Fig. 6), it becomes evident that the distributor variants in designs A–C will introduce ‘‘tailing’’ to the apparent RTD of the chromatographic unit. In contrast, a distribution channel with dimensions too small with regard to the packed bed properties will introduce ‘‘leading’’ in the apparent RTD, as indicated by the curve for design D in Fig. 6. However, it should be noted that this rule of thumb for the impact on asymmetry is only applicable to the standard design of a distributor with a single distribution channel as illustrated in Fig. 2.

From our analysis of a large number of parameter sets for distributors and media, we conclude that a distribution system optimised to give a small impact on efficiency h_D will typically introduce moderate ‘‘tailing’’ in the apparent RTD curve. To determine the asymmetry, evaluation of Eq. (28) is required. A prediction of the apparent RTD curve for the 90-μm agarose medium operated with the 1000-mm distributor (compare Fig. 8) is shown in Fig. 11. For smaller column diameters, the hold-up volume of the distributor will be reduced and the first moment for the combined system can be expected to be closer to the first moment of the medium alone. For all cases analysed that were based on an appropriate distributor design, we found asymmetry factors that were typically in the range $1.0 < A_f < 1.1$. On the other hand, it is obvious that a distributor of unfavourable design may cause significant skewness in the peak response of the chromatographic system. However, we conclude that the optimisation of the distributor design for an ideal asymmetry factor is not a primary objective because a design optimised for a small impact on efficiency will usually minimise asymmetry in the apparent RTD impulse function as well.

5. Discussion

The performance profiles in Figs. 7–10 summarize the distributor impact for the RTD test condition that is used for the installation qualification of chromatographic units. The distributor impact is therefore the most important criteria for the distributor design. However, as discussed above, additional requirements for the distributor have to be met, such as the need for a uniform velocity field in the packing mode according to Eq. (35). Especially in biopharmaceutical processing, the risk for fouling may set a lower limit for the pore size of a bed support. Thus, hydraulic resistance and pressure drop over the bed support may only be adjustable within certain limits, which may suggest to increase channel dimensions despite the negative consequence of a larger distributor impact. An alternative can be to add an orifice plate that increases the pressure drop in axial direction while keeping channel dimensions optimal for the operating conditions and the distributor impact. A third criterion for distributor dimensioning is a possible trade-off between the figure of the distributor impact and the uniformity of the axial residence time $\tau_{axial}(r)$ in the packed bed. This is relevant for separations that require high peak resolution in combination with large peak retention factors. In practice, this design criterion will only be crucial for the largest scale HPLC columns.

In summary, it is the combined analysis of three key properties that gives an optimal distributor design for the very specific combination of column diameter, medium properties, packed bed height and application requirements. These properties are:

(1) distributor impact for RTD test condition in operating mode (RTD test velocity);

(2) velocity field in packing mode (packing velocity);

(3) velocity field and axial residence time $\tau_{axial}(r)$ in operating mode (operating velocity).

For quantifying the distributor impact, computation of the RTD for the distribution system alone can be used in a first approach to the design optimisation for reasons of computation time, especially when applying the simplified integration according to Eq. (25). For a detailed analysis of a specific application with known bed height, analysing the peak response of medium and distribution system by calculating the apparent RTD impulse function is preferable. In practice, an acceptance criterion has to be defined for distributor impact as the installation qualification is compulsory. We consider a figure of $h_D < 0.2–0.4$ to be appropriate, depending on the type of application. For crude capture applications, the accepted distributor impact might be significantly larger, i.e., if a large number of column volumes are required to saturate the column. In this situation, the deviation in local residence time due to the lateral fluid transfer in the channels $\tau_{radial}(r)$ has a negligible impact on the apparent RTD and thus the packed bed capacity, even if efficiency in the elution step might be affected. For a detailed analysis of the distributor impact in sorption chromatography, an approach described by Miyabe and Guiochon [9] could be used in combination with the theory presented here. Finally, it shall be mentioned that a distributor design with bed support inclination will have an impact on the local bed voidage for the case of axial compression packing. To account for this, a relative permeability as function of radius can be derived with the compression factor for the specific medium and the nominal bed height. This relative permeability has to be considered in Eq. (14) for calculation of the axial velocity in the packed bed.

5.1. Alternative design solutions and technical considerations

In this study, a linear function is considered for the height of the distribution channel in the range $0.1 < r/R < 1.0$. From parameter studies, we have found that this linear shape is close to ideal with regard to the resulting chromatographic efficiency and the pressure field in the channel as long as the transition region between the central inlet and the distribution channel is of appropriate design. However, a potential problem that has to be considered for process scale columns is the deviation from the ideal distribution channel that has been assumed in the computation method. This is usually due to requirements on the positioning of the bed support so that sufficient strength and rigidity in the design is achieved. A small impact on the channel geometry may be achieved when positioning the bed support by help of a perforated plate. The plate may have a minimum number of protrusions to define the height of the distribution channel. Another standard solution is a rib pattern machined in the end plate or into a laminated liner. For such rib designs, deviation from the ideal channel is given primarily by an increase in zero-velocity surface area by the walls of the ribs. To extend the described computation method to such a design, the introduction of an appropriate correction factor $f(r)$ in the viscous terms of the pressure field equation Eq. (10) is required, in combination with the computation of an equivalent effective channel height for the ideal channel.

A summary of rotational symmetric distributor design concepts is shown schematically in Fig. 12 with a qualitative positioning according to efficiency and complexity. A comparison with Fig. 2 shows that the concepts classified as 0PF, 0CF and 0CC are variants covered by the design method described in this study (compare with design variants A–C in Table 3). In practice, there might be a reduced technical complexity of the 0PF variant as a distribution channel of constant height is easy to produce as, for example, a perforated plate with dimples of constant depth on its surface. Common to these three variants is that the mobile phase is introduced into a single distribution channel extending from the centreline to the column wall. As an alternative, a pre-distribution of liquid can be employed, typically by means of an external manifold that feeds the liquid to multiple inlets at the column

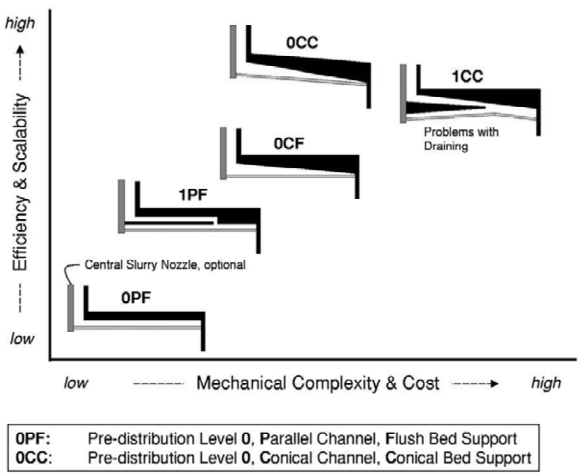

Fig. 12. Comparison of rotational symmetric design variants with regard to efficiency and complexity.

end plate. However, pre-distribution can also be achieved in a rotational symmetric manner by means of a solid impermeable disk that feeds the liquid into an annular pre-distribution slot. The authors have investigated systems based on this rotational symmetric pre-distribution by numerical CFD analysis as well as by an extension of the theoretical approach described in this paper. For the latter, the pre-distribution system was approximated as two parallel columns that represent the central and peripheral region. The residence time distribution for each system was calculated according to the framework described above and the overall dispersion was determined. Equivalence of static pressure in both distribution channels has been prescribed as a coupling condition at the position of the pre-distribution slot. It was found that the efficiency of the 1PF system is generally lower than with the 0CF system when trying to optimise the performance profiles of the distribution system for use with a wider range of media. However, the simplicity of the 1PF variant is of interest for inexpensive capture cartridges for example. When dedicated to a specific medium, bed height, column diameter, etc., the efficiency of this design concept can be sufficient even at large scale.

Theoretically, there is the rather efficient variant 1CC yielding a maximum bed height at the position of the annular feeding slot. In practice, this variant might lead to problems with unpacking and draining of the column when using pack-in-place technology at large scale. In contrast, the unpacking of columns equipped with the 0CC variant is facilitated by virtue of the bed support inclination when mounting a pack-in-place slurry valve in the column centreline [10]. With regard to an efficient draining of the 0CC design variant, it needs to be mentioned that there is no need for an identical bed support inclination at both top and bottom distributor as long as the sum of bed support inclination at the top and bottom equals $2y_{\text{Bed support}}$.

6. Conclusions

An analytical framework for analysing a column liquid distribution system is described. The approach is applicable for a rotational symmetric system and allows for efficient dimensioning of the column distributor as well as for the evaluation of design alternatives. It is shown that the standard design of a distributor with a central inlet/outlet for the mobile phase and a single conical distribution channel can be scaled without a significant loss in chromatographic efficiency if a moderate bed support inclination is applied. The most important criterion for design optimisation is the distributor impact at the RTD test condition. However, deviations from a uniform velocity field in the column need to be considered as well, both for the packing and operating modes. This analytical approach permits a detailed and quantitative theoretical analysis. It needs to be pointed out that the discussion of distributor efficiency is based on the assumption of a homogeneous packed bed. In practice, deviations from this assumption due to column packing techniques and media properties are found [2]. Until now, it has been a problem to quantify and identify the impact of the distribution system and the impact of the packed bed homogeneity independently when analysing the efficiency of packed columns [11]. The approach described in this study can improve an analysis of packing quality because the distribution system can be designed such that the distributor impact is known and the packed bed efficiency is not negatively affected from the distributor.

7. Nomenclature

7.1. Symbols

A_f	asymmetry factor
Bo	Bodenstein number
C	concentration
d_p	particle diameter
$E(\tau)$	RTD, impulse function
$F(\tau)$	RTD, age function
f	correction factor
h	reduced plate height
h_D	distributor impact for RTD test condition
K_e	distribution coefficient (‘‘size-exclusion’’ coefficient)
L	bed height
$N(r)$	geometry factor $(=R^2/(R^2-r^2))$
P	pressure

p	pressure in distribution channel
Q_0	channel flux $(=u_m(r)\cdot r)$
R	column radius
r	radius
t	time
u_m	mean fluid velocity in distribution channel
u_s	superficial velocity in packed bed
V_R	retention volume
w_h	peak width at 50% of max. peak height
y	height

7.2. Greek

ε_b	void fraction of bed, inter-particle porosity
ε_p	intra-particle porosity
κ	hydraulic permeability
η	fluid viscosity
μ_1	mean residence time, first moment of RTD
ρ	fluid density
σ^2	variance, second moment of RTD, normalised in terms of reduced residence time
τ	residence time $(=t\ u_s/L)$
τ_r	reduced residence time $(=\tau/\mu 1)$

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