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Mathematical modelling and evaluation of performance of cuboid packed-bed devices for chromatographic separations

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ABSTRACT

In a recent paper, box-shaped or cuboid packed bed devices have been proposed as alternative to columns for chromatographic separations. We first propose a mathematical model for residence time distribution in such devices. Based on it, we examine factors likely to affect separation performance, and verify the predictions of our mathematical model by conducting tracer experiments. We then compare the performance of two commercial columns with their respective equivalent cuboid packed-bed devices, i.e. containing the same chromatographic media, and having the same bed-height and bed-volume. Parameters compared include the number of theoretical plates, attributes of flow-through and eluted protein peaks, and resolution in model binary protein separations. For each of these metrics examined, the cuboid packed-bed device outperformed its equivalent commercial column. Other potential advantages likely to be gained from using a cuboid packed-bed instead of a column are elucidated.

1. Introduction

Packed-beds are used for a wide range of separations, including chromatography [1–5]. By default, the shape of a packed-bed used for chromatographic separations is cylindrical, i.e. in the form of a column, within which the particles comprising the packed-bed are simply held together by containment. A column represents a very simple format for facilitating contact between solutes present in a fluid with a solid surface, as required in chromatography. This is why columns have been so successfully used for a wide range of separations [1–5]. However, columns used for process-scale chromatography, such as those used for purifying biopharmaceutical products have relatively small bed-height to diameter ratios [6–10]. This attribute is required to minimize the pressure drop, and compaction of chromatographic resins, and to maximize the productivity. Also, a common scale-up strategy used in process-scale chromatography of biopharmaceutical products is to keep the bed height constant while increasing the diameter [6–8]. Non-uniform flow distribution is a major problem with such wide columns as it results in broad flow-through peaks, and broad and poorly resolved eluted peaks [11–20]. In addition to lowering purity and slowing down the separation, peak broadening results in dilution of the flow-through or the eluate fractions, which in turn could necessitate further downstream concentration enrichment steps. This could further affect recovery and productivity of these separation processes.

Flow maldistribution in columns with small bed height to diameter ratios has been widely examined and discussed [11–28]. The two most important challenges with such devices are fluid scaling [27,28] and achieving uniformity in resin packing [16,17]. Non-uniform flow distribution due to poor fluid scaling in large diameter columns results in distortion of the solute front as demonstrated in numerous studies [13–28]. The decrease in efficiency of chromatographic separation with increase in column diameter is also well documented [6,22–26]. Flow maldistribution could affect the elution process due to distortion of the eluent front [15–17]. Non-uniform resin packing and non-uniform resin compaction during separation could also adversely affect separation performance [15–17]. The factors discussed above along with some others such as the jetting effect at the inlet, ultimately lead to low purity, recovery and productivity. Flow maldistribution in process chromatography columns have been primarily addressed through improvements in column header design, including the use of headers of different shapes, and the use of collimators, manifolds anti-jetting features [16,18,27–32]. Alternative configurations such as the radial-flow column [33,34], segmented parallel flow column [35], and curtain flow column [36] have also been reported in the literature.

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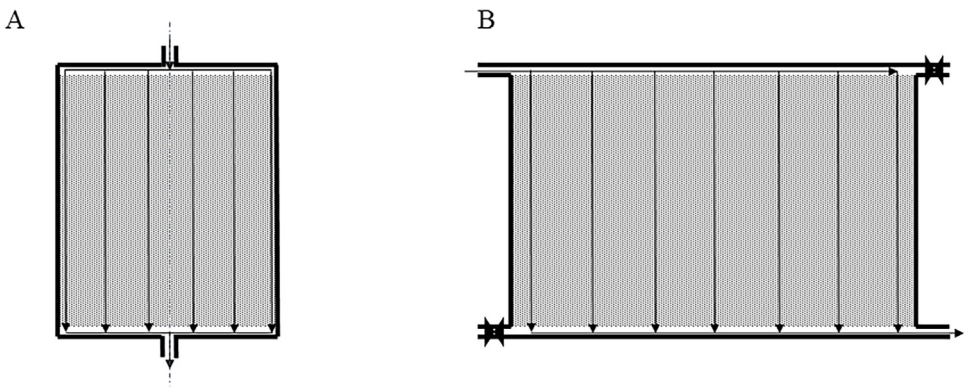

Fig. 1. Idealized flow paths in a column (A) and in a cuboid packed-bed (B).

In a recent paper, a radically different approach from those discussed above, i.e. the use of a "chromatography-box" device, housing within it, a cuboid packed-bed has been proposed [20]. In such devices, a set of lateral flow channels similar to those used in laterally-fed membrane chromatography or LFMC [37–40] are used to distribute the influent liquid into the packed-bed and collect the liquid from it on the other side. This flow arrangement facilitates pressure-drop balancing and thereby ensure uniformity in superficial velocity. It also ensures uniformity in solute flow path lengths, thereby narrowing the residence time distribution. Fig. 1 shows the sectional views of a column (A) and a cuboid packed-bed (B), in each case, showing the idealized flow-paths within these devices. A combination of variability in flow path lengths, and variability in velocity along these respective flow paths results in a very significant variability in solute residence time within a column [15–17,20]. This contributes towards peak broadening and loss of peak-resolution in separation. On the other hand, the flow path lengths within a cuboid packed-bed are fairly similar and the velocities along these do not vary that significantly. Consequently the solute residence distribution is narrower [20]. Aspects examined in the paper [20] include the separation of model proteins using cuboid packed-bed devices and their equivalent columns and performance metrics such as the number of theoretical plates, peak width, asymmetry and resolution in multi-protein separation. The cuboid packed-beds outperformed their equivalent columns (i.e. with same media, bed height and area of cross-section) in terms of all these metrics. This was primarily attributed to superior hydraulics and consequent lower dispersion effects within the cuboid packed-bed devices. The results discussed in the paper [20] suggest that some of the separation challenges in biopharmaceutical manufacturing involving columns having small bed-height to diameter ratios could potentially be addressed by using cuboid packed-bed devices. Also, as can be seen in Fig. 1B, the inlet of the upper lateral channel is located offset from the cuboid packed-bed. This design attribute prevents the direct jetting of the feed into the packed-bed, as usually happens in a column (see Fig. 1A).

In this paper, we have examined factors likely to affect the separation performance of cuboid packed-bed devices by building on and extending the mathematical model for solute residence time distribution described in our previous paper [20]. Tracer experiments using unbound coloured protein samples were carried out to verify the predictions based on the mathematical model. Also, in our previous paper [20], we had focused on custom-designed columns having bed-height to diameter ratios less than 1 and their equivalent cuboid packed-bed devices. In this paper, we have compared the performance of two commercial columns (5 mL HiTrap Capto Q and 5 mL HiTrap Capto S; both having a bed-height to diameter ratio of 1.56) with their equivalent cuboid packed-bed devices, i.e. containing the same chromatographic resin, and having the same bed-height and bed-volume. The performance metrics compared in the current study include the number of theoretical plates, shape and height of flow-through and eluted peaks, and resolution in model binary protein separations. The results obtained are discussed.

2. Materials and methods

HiTrap Capto Q (5 mL, product number 11-0013-03) and HiTrap Capto S (5 mL, product number 17-5441-2) columns, and Capto S (product number 17-5441-01) and Capto Q (product number 17-5316-02) chromatographic media were purchased from GE Healthcare Biosciences, QC, Canada. Capto Q is a quaternary amine group based strong anion exchanger while Capto S is a sulfonate group based strong cation exchanger. Both resins have average particle size of 90 μm. Cytochrome C (equine, pI = 10–10.5, catalog number C2867), lysozyme (pI = 11.0, catalog number L6876), bovine serum albumin (pI = 4.8, catalog number A7906), myoglobin (from horse heart, pI = 6.8 and 7.2, catalogue number M1882), ribonuclease A (from bovine pancreas, pI = 9.6, catalogue number R6513) and chemicals used to prepare buffer were purchased from Sigma-Aldrich (St. Louis, MO, USA). All buffers and the solutions were prepared using water obtained from a SIMPLICITY 185 water purification unit Millipore (Molsheim, France). Buffers and solutions used in chromatography experiments were micro-filtered and degassed using PVDF micro-filter (VVLP04700, 0.1 μm pore size, Millipore, Billerica, MA, USA).

The cuboid packed-bed device used in this study (see Fig. 2A) was designed and fabricated in our workshop. The basic design was based on that reported in our previous paper [20]. The central frame of the device for housing the cuboid packed-bed was made of polyvinyl chloride (PVC) while the upper and lower plates were made of acrylic (transparent). The upper and lower plates had pillared lateral channels for flow distribution and collection respectively. The detailed design of the lateral channel in a plate is shown in Fig. 2B. The lateral channels were designed such that the resistance to flow within these was low compared to that in the packed-bed. An earlier study on LFMC systems [39] has shown this to be critically important for efficient functioning of devices based on such flow arrangement. The cuboid packed-bed dimensions were 25 mm (length) × 8 mm (width) × 25 mm (height), the effective bed volume being 5 mL. The packed-bed was separated from the lateral channels using nylon meshes (0.002 inch opening, product number 9318T48, McMaster Carr, USA) for retaining the chromatographic media. The cuboid packed-bed devices were packed by slurry filtration under suction flow at 0.5 mL/min. The slurry was first topped up until the level was flush with the top of the device frame. The device was assembled and appropriate buffer was pumped through the device at 5 mL/min. The device was then