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On the workings of laterally-fed membrane chromatography

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ABSTRACT

Membrane chromatography has significant potential for use in biopharmaceutical purification processes. However, currently available membrane chromatography devices give poor resolution and therefore their use is restricted to polishing applications, typically carried out in the flow-through mode. Laterally-fed membrane chromatography (or LFMC) was developed specifically for carrying high-resolution multi-component protein separations. Recent studies have shown that resolution obtained with LFMC is comparable to that obtained with equivalent resin-based packed bed chromatography. Therefore, LFMC combines high-resolution with high-productivity, a highly desirable attribute in any purification technique. In this paper we explain the workings of LFMC based on theoretical and experimental analysis of hydraulic flow-path and residence time distribution. Factors likely to affect efficiency of LFMC are discussed using a simple electrical circuit analogy.

1. Introduction

Membrane chromatography has been proposed as an alternative to packed-bed or column chromatography [1–5]. The advantages of this technique have been explained in term of enhanced mass transport in flow-through pores [6–14]. Diffusion, which plays a rate-limiting role in packed-bed chromatography, limits productivity [6–14]. For biopharmaceuticals, longer separation time implies greater likelihood of product denaturation and other forms of degradation, and aggregation. In membrane chromatography, transport of solutes and eluent species takes place predominantly by convection [6–14]. Therefore, separation is typical faster by an order of magnitude. This technique has been used quite successfully for the removal of viruses, endotoxins, prions and host cell proteins from biopharmaceuticals in a flow-through mode [15–18]. However, membrane chromatography is not widely used for high-resolution multi-component separations in the bind-and-elute mode as currently available devices give broad and poorly resolved eluted peaks which diminish the quality of separation and also result in significant product dilution.

Currently available membrane chromatography devices have not been designed specifically for chromatographic separations. For instance, the design of a stacked-disc device is based on syringe-filters routinely used in research laboratories for small-volume microfiltration. While stacked-disc devices are widely used for preliminary laboratory-scale separations, they are totally unsuitable for large-scale applications. Any attempt to make these devices bigger by increasing their diameter leads to huge variability in the flow path lengths, which in turn adversely affects the quality of separation. Stacked-disc devices incorporating flow distribution and collection channels have been shown to be suitable for high-resolution protein fractionation [8,19]. However, even with such efficiency enhancing features, these devices do not work very well then the disc diameter exceeds 50 mm. A typical stacked-disc device has very large void volume relative to the membrane volume and this factor also contributes toward poor separation performance.

The design of a radial-flow device is based on a depth filtration cartridge. It has a large membrane area to bed volume ratio, and can therefore be operated at very high flow rates with low back pressure, and is reasonably scalable. A radial-flow device is used in the flow-through mode for removal of impurities that are present in relatively small amounts. It has large dead volumes, both on the feed and the permeate sides, which results in significant back-mixing. Also, the flow path is convoluted and flow behaviour is therefore difficult to characterize [20–22]. Liquid entering the device is first fed in a radially outward direction into the annular space surrounding a membrane roll. Within this space, the liquid flows in an axial direction, before being forced into the membrane roll in a radially inward direction. The liquid is then collected on the grooved outer surface of a central core and directed towards the outlet. Subtle changes in device orientation can significantly affect the flow behaviour in a radial-flow device. The factors discussed above are perhaps not that important in flow-through separations, but make the radial-flow device unsuitable for high-resolution, multi-component, bind-and-elute separations.

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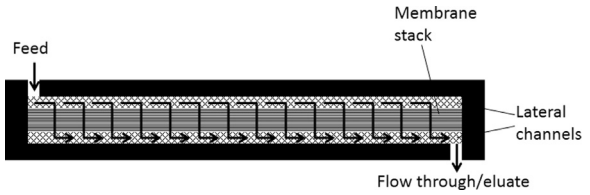

Fig. 1. Diagram of laterally-fed membrane chromatography (or LFMC) device.

Laterally-fed membrane chromatography (LFMC) devices have been designed specifically for high-resolution multi-component protein separations [21–24]. In an LFMC device (see Fig. 1) a lateral flow channel is first used to distribute the liquid over the feed-side of a rectangular membrane stack. The permeate is collected on the other side of the stack using another lateral flow channel having similar hydraulic resistance. This type of flow arrangement makes it easy to balance the pressure-drop across the membrane stack and thereby ensure uniformity of permeate flux (or superficial velocity) along the length of the device. This flow arrangement also ensures that the flow-path lengths are similar throughout the device. Our previous studies have shown that resolution obtained with the LFMC device is superior to those obtained with other type of membrane chromatography devices [21,22]. More recently, we have shown that the resolution is similar to that obtained with resin-based columns [23]. These devices therefore represent a win-win situation, i.e. combination of high-productivity with high-resolution. Therefore, we feel that the LFMC device has significant potential for application in the biotechnology industry.

In this paper, we have analysed in detail, the flow behaviour in an LFMC device and have used this to explain its superior performances vis-à-vis other membrane chromatography devices. Mass balance based mathematical models were developed to analyse the residence time distribution in the LFMC device and carefully designed experiments were carried out to validate these. Factors likely to affect efficiency of LFMC were also examined using a simple electrical circuit analogy.

2. Materials and methods

Red food dye purchased from (McCormick, Sparks, MD, USA) was used as tracer to compare the performance of an LFMC device with a stacked-disc device. Hydrophilized PVDF membrane (0.22 μm; GVWP) housed in the above membrane devices for the tracer experiments was purchased from Millipore (Billerica, MA, USA). Sample solutions were prepared using ultra-pure water (18.2 MΩ cm) obtained from a SIMPLICITY 185 water purification unit (Millipore, Molsheim, France).

The detailed designs of the stacked-disc and the LFMC devices used for tracer dye experiments are described in our previous paper [21]. These were made of acrylic to facilitate tracking of the tracer dye. The effective membrane diameter in the stacked-disc device was 40 mm whereas the effective length and breadth of the membrane housed within the LFMC device were 157 mm and 8 mm respectively. Therefore, both of these devices had the same effective membrane area, i.e. 12.57 cm^2. A single layer of hydrophilized PVDF membrane was fitted in each of these devices. The depth of the lateral channels in the LFMC device and the depth of the headers on the stacked-disc device were identical (0.508 mm). The tracer dye consisted of food colour solution diluted one in ten in water. Degassed microfiltered water, used as mobile phase in these experiments was pumped at a flow rate of 10 mL/min from a tank to the membrane modules using a HiLoad P-50 pump (GE Healthcare, Piscataway, NJ, USA). The effective volumetric permeate flux value in these experiments was 1.326×10^{-4} m/s. A sample injector fitted with a 250 μL loop was used to inject the tracer into the membrane devices. A digital camera (Sony Cybershot, Model DSC-WX7, Japan) was used to obtain video clips of the feed side of the devices during these experiments. These were recorded in MTS format. Snapshots were obtained at the rate of one per 0.25 s using Windows Live Movie Maker, and these were processed using Image J freeware (http://imagej.nih.gov/ij/). The gray scale intensities of the snapshots were measured by coding macros and normalizing by subtracting the base line intensity for each pixel. The radial velocity in the feed-side header of the stacked-disc device was measured by determining the precise radial location of the tracer dye front at a given time by plotting the grayscale intensity versus the radius. In a similar way, the velocity in the feed-side lateral channel LFMC device was measured by determining the precise lateral location of the tracer dye front at a given time by plotting the grayscale intensity versus the length of the channel.

3. Results and discussion

One of the main attributes of membrane chromatography is the high membrane bed cross-sectional area to bed height ratio. While this allows separation to be carried out at low transmembrane pressure, it creates a major set of challenges, i.e. uniform flow distribution on the inlet or feed side and collection on the outlet or permeate side. As discussed in detail in our earlier papers, this problem exits with both the commonly used configurations, i.e. stacked-disc and radial flow [21,22]. Fig. 2 shows a section of a stacked-disc device, clearly showing the considerable variability in hydraulic path length. Path 1, being closer to the centre, would have a smaller length than path 2, which is closer to the periphery of the membrane stack:

$$l_2 > l_1 \tag{1}$$

As shown in Fig. 3(A), liquid is distributed in a stacked-disc device in a radially outward direction in the feed space over the membrane stack (i.e. the top header) and is collected in a radially inward direction in the permeate space below the membrane stack (i.e. the bottom header). The liquid velocity would decrease in a radially outward direction in the top header due to increase in cross-sectional area for the flowing liquid, and loss of liquid by permeation through the membrane. The liquid velocity in the bottom header would increase in a radially inward direction due to decrease in cross-sectional area, and cumulative collection of permeate from the membrane. Based on the above, it could be argued that the average fluid velocity along path 1 would be greater than that along path 2 (see Fig. 2):

$$v_1 > v_2 \tag{2}$$

Based on (1) and (2), it could be shown that the hydraulic

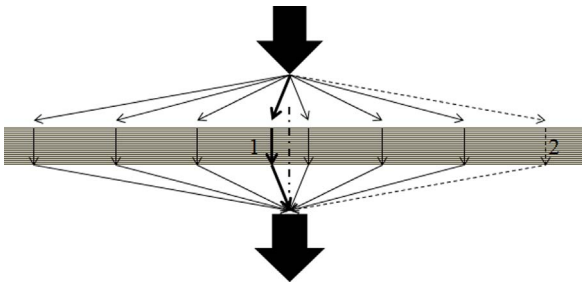

Fig. 2. Flow distribution and collection challenges in stacked-disc membrane chromatography device (1: flow path close to centre, 2: flow path close to periphery).