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Coiled fiber membrane chromatography

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ABSTRACT

A new type of particle-loaded membrane adsorber module was prepared by coiling adsorptive fibers. In order to characterize the material and predict the module performance, the protein accessibility and mass flux of single fibers were tested in incubation experiments. The coil's layout spacing and winding tension are useful parameters for tailoring the module for stabilization, polishing, or pharmaceutical applications. Decreasing the distance between two adjacent fibers during the coiling process affects the flow resistance and the dynamic adsorption capacity of the module. Higher flow resistance creates a higher convective flow through the fibers resulting in faster adsorption processes. Exerting a high winding tension causes fiber deformation, resulting in modules with high packing density. The feed flow is then forced through the fibers to a greater extent, thereby reducing the diffusive distance to the active sites located in the interior of the fiber, which results in steeper breakthrough curves and better ligand utilization.

1. Introduction

Chromatography is undoubtedly the workhorse of downstream processes, affording high resolution for bioseparations. At the same time, it has the notoriety of being a low-throughput operation, and the single largest expense in downstream processing. Consequently, 'chromatographic alternatives' are an attractive proposition, even if only a reduction in the extent of use of packed beds can be realized [1].

This motive explains why much research is focused on chromatographic systems that are highly convective-controlled, operate at low pressure, have low fouling and plugging sensitivity, maintain constant bed quality, and possess high dynamic capacity.

In the separation and purification steps in the production of biomolecules, the manufacturers face two critical parameters: adsorption capacity and flow uniformity. The main disadvantages of chromatographic columns, especially when using gel type resins, are non-uniformity of flow, bed compression and slow diffusion rates. Depending on how a column is packed, flow paths and therefore flow rates can vary in different parts of a column, resulting in different adsorption and desorption rates. In a "worst-case" scenario one part of a column may be saturated with the target molecule, while other parts of the column may still have free binding sites, resulting in product binding and breakthrough occurring simultaneously, destroying the resolving power of the column [2].

1.1. Monoliths

Monoliths can be operated at much higher mobile phase flow rates than packed-bed systems, with minimal loss in resolution, because of their significantly reduced mass transfer resistance. Scaling monoliths is hampered by the difficulty of preparing high-volume monoliths with uniform pore structure, owing to the exothermic nature of the polymerization reaction. This problem was circumvented by preparing tubular monoliths. Currently, the largest available modules are 800 mL [1,3]. The 1–5 μm sized pores have the advantage of a low flow resistance however these big pores are accompanied by a low active surface area and thus a low adsorption capacity.

1.2. Expanded bed adsorption

In an expanded bed, a particulate adsorbent in a column is allowed to rise from its settled state by applying an upward flow. This increases the space between the adsorbent particles, allowing cells and cell debris to flow through without blocking the bed. Usually the size of the adsorbents in an expanded bed range from 50 to 400 μm. Smaller beads cause overexpansion even at low flow rates while larger beads require very high flow velocities to expand the bed sufficiently. In either situation the productivity of the bed is low due to low flow rates or due to restricted diffusion into the beads. Another serious problem is back-mixing, which decreases the efficiency of the adsorption process. Expanded beds are often not able to meet the requirements of the biopharmaceutical industry in terms of productivity and hygiene [4].

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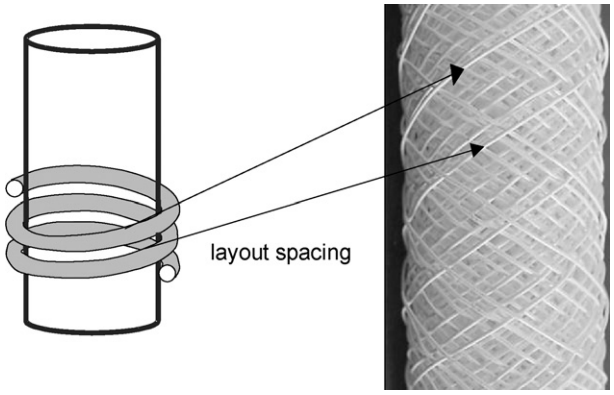

Fig. 1. Schematic drawing and photograph of a very open coiled PLM-fibers in order to illustrate the concept and the distance between two adjacent loops (the 'pitch' or 'layout spacing').

1.3. Membrane chromatography

Membrane chromatography with chemically functionalized microfiltration membranes has proven to be a very attractive alternative for packed-bed systems containing large particles. The dynamic capacity for big biomolecules is at least one order of magnitude higher than those of traditional packed-bed chromatography. However, this advantage is less pronounced for small target molecules. One benefit of adsorptive membranes is the absence of the long diffusion times that often occur in packed-bed chromatography. A second feature of a typical membrane bed is the large cross-sectional area relative to the bed length, which allows high velocities and large volumetric capacities. A large diameter to length ratio, however, introduces the challenge of achieving uniform flow distribution across the membrane. Flow maldistribution can reduce the membrane efficiency to the level of packed-bed chromatography [5].

1.4. Particle-loaded membrane chromatography

The advantage of the particle-loaded membrane (PLM) adsorbers over packed-bed systems and chemically functionalized membrane adsorbers for protein recovery and purification processes is the combination of both a high flow rate and a high capacity. This is because macroporous membranes have low flow resistance compared to chromatographic beads. The large pores in the membrane structure ensure convective transport of the target molecules to the active binding sites located on the surface of the embedded particles. Meanwhile, the use of small particles creates a high adsorption/affinity area per unit of column volume. Embedding particles in a macroporous matrix makes the column insensitive to possible particle deformation [6–8].

This paper reports the process performance of coiled PLM-fibers (depicted in Fig. 1). A coiled fiber module is prepared by coiling a particle-loaded fiber around a core. When the coiled layer is sufficiently thick, the core and coiled fiber are inserted into an outer shell, and potted in order to fix the fiber pack and fill dead volumes. The flow performance of a coiled fiber module can be tailored by adjusting the layout spacing (distance between two adjacent loops) and the winding tension (the force exerted on the fiber during the coiling process).

The coiled fiber modules can easily be scaled by changing the fiber package diameter or the module length. A disadvantage of the coiled fiber module is the challenge of balancing the convective flow around and through the fibers. It is highly desirable to be able to predict whether the adsorption fiber has adequate adsorption performance, even before starting the coiling process. We hereby present an algorithm to correlate the adsorption kinetics from an incubation experiment with the dynamic breakthrough performance of a coiled fiber module.

2. Background

Membrane chromatography is a promising technique for the isolation, the purification and the recovery of biomolecules. When compared to traditional bead chromatography, the process is much faster, easier in processing and more robust. In addition it is also easier to set up and to scale up [9–11].

2.1. Kinetics from incubation

The binding of ligate molecules occurs by adsorption from the liquid phase onto the ligands present on the surface or in the pores of a solid support material. In the case of a protein as the ligate (P) and a vacant immobilized ligand (S), the following reaction scheme applies:

$$P + S \leftrightarrow PS \tag{1}$$

where PS represents the protein–ligand complex. In a second-order rate expression, Eq. (1) can be written as:

$$\frac{\partial c_s}{\partial t} = k_a c(c_l - c_s) - k_d c_s \tag{2}$$

where t is the time in (s), c the feed concentration (mg/l), c_s the protein–ligand complex concentration in (mg/mL), c_l the ligand capacity (mg/mL), k_a the forming constant of complex PS (mL/mg s) and k_d the dissociation constant of complex PS (1/s).

The mass balance across a membrane section can be described by two continuity equations: one for the liquid phase and the other for the solid phase [12–14].

Where the four terms represent the unsteady state, convection, axial diffusion and adsorption, respectively.

$$\varepsilon \frac{\partial c}{\partial t} + \varepsilon \cdot u \frac{\partial c}{\partial x} = \varepsilon \cdot D_{ax} \frac{\partial^2 c}{\partial x^2} - (1-\varepsilon)\frac{\partial c_s}{\partial t} \tag{3}$$

In these equations ε is the void fraction, u the linear flow velocity (m/s), a the exchange area and K the adsorption reaction coefficient ($1/s\,m^2$).

The concentration gradients in the radial direction are assumed to be negligible because the time scale of radial diffusion is much less than that of axial convection. For mixed matrix systems using one component and assuming that at initial conditions there is no protein in the membrane, initially Eq. (3) becomes for the liquid phase,

$$\varepsilon \frac{\partial c}{\partial t} = aK(c_s - c) \tag{4}$$

and for the solid phase,

$$(1-\varepsilon)\frac{\partial c_s}{\partial t} = -aK(c_s - c). \tag{5}$$

a is the specific adsorption area (m^2/mL), and K is the adsorption reaction coefficient a (mL/s m^2). The factor aK, a lumping parameter including the diffusion and the adsorption kinetics and the protein unfolding and rearrangements during the adsorption process, can be deduced from the kinetics of an incubation experiment in which the bulk concentration is plotted as a function of time. The initial slope of this kinetic depletion process describes the mass flow in the adsorption process if there is only diffusion (j) occurring (Eq. (6)).

$$j = V \cdot a \cdot K \cdot \Delta c \tag{6}$$

where j is the mass flow (mg/s), V is the reactor volume (m^3), and Δc the difference in concentration (mg/m^3).