

Chapter 6 Conclusions

6.1 Summary of findings

This study is in two parts. The larger investigates a novel design for separating cellular material from liquids. Screw-threaded inserts that are a loose fit concentrically within tubular membranes had already been shown to improve filtration flux, but lacked a thorough examination. Key parameters for efficient and economical operation are therefore assessed here for inserts of several different diameters, with screw-threads of both one and two starts. Pressure drop, axial mixing, shear stress and turbulence are all addressed. The second half of the investigation concerns affinity separations. A model system of a representative protein molecule, bovine serum albumin, and an ion-exchange membrane is studied under both static and dynamic modes of operation. The rate-limiting steps are investigated and procedures established that will aid the understanding of other systems, such as an exciting new technique for antibody removal using highly specific, synthetic, ligands.

It has already been established that screw-thread flow promoters can improve microfiltration flux, but this study seeks to explain and produce evidence for the mechanisms responsible for this improvement. Taken together, several different experimental methods point towards the existence of a ‘sweet spot’ for each insert when operation is most efficient. It is argued that shear stress and frequency measurements show that vortices generated by both the helical and axial flow components alternately dominate, leading to the dividing streamline between the two flows either extending far into the annular flow or retreating deep into the helical cross-section, and therefore when averaged over the length of a filter, good exchange of fluid between the two flow-paths is achieved. This good cross-stream mixing ensures that plug flow is approximated, as residence time distribution measurements show.

Experiments confirm that pressure-drop is minimised by increasing the clearance between insert and membrane, and more dramatically by the use of a twin-start helical insert. The measured pressure gradient around helical flow promoters is bounded with an accuracy of $\pm 50\%$ by the two simple models considered in Chapter 2. The models superimpose a helical flow and an axial flow, matching the overall pressure-drop in each channel. They are easy to implement, are valid for single- and twin-start inserts and are therefore useful design tools. The models reveal that as total flow rate increases, the proportion following a helical path steadily decreases.

Platinum thin film gauges measured wall shear stress in two positions, and in addition yielded valuable information concerning vortex strength and frequency, and flow repeatability. Measured shear stresses are shown to be consistent with filtration fluxes observed in previous studies, and also the pressure-drop model described above.

Although mean shear rates were comparatively high, and at certain flow rates the vortex structure appeared unstable, there was no turbulence. Pringpuangkeo⁹¹ had observed no haemolysis, and the predictions arising from the laminar computer simulation of Costigan¹⁶ agreed with values measured here. The nature of turbulent flow is such that lysis is not caused simply by high mean shear, but is due to short-duration, localised peaks in shear stress being large enough, and in eddies of the right length scale, to disrupt cell membranes. Helical flow promoters therefore generate high wall shear stresses (to reduce flux decline in microfiltration), yet the haemolysis problems associated with conventional, turbulence-promoting methods of improving filtration flux are absent.

For high-volume, bulk processing applications, reducing power input is the most critical consideration. A typical industrial membrane filtration process⁷⁶ uses 18 membranes, each 4 metres in length, connected in series and operated at a flow rate of 30 l/min. The low

pressure-drop characteristics of helical inserts are recognised only at flow rates of the order of 1 l/min, so existing filter module designs would require extensive modifications. Only by greatly reducing operating costs can the increased capital cost be recouped. In cases such as these, a twin-start insert with a large clearance gap, such as 0.75 mm, would be recommended.

Conversely, for medical applications or high-value separations, maximising filtrate flux is the prime concern so the appropriate helical insert is the one which generates the highest wall shear stress. A single-start insert with as small a clearance as is practicable—depending on the manufacturing tolerances of a given membrane tube, typically 0.3 to 0.5 mm—is best in this respect. A feed flow rate of around 300 ml/min leads to the closest approximation to plug flow for such an insert.

In contrast to much published work, which is limited by slow reaction kinetics and modelled with the Thomas model of adsorption¹⁰⁹, the affinity system studied here is controlled by a rate-limiting surface diffusion mechanism. Membrane holders of two sizes are described and the fluid dynamics of both are satisfactory, as assessed by non-adsorptive operation. Breakthrough curves are used to characterise the adsorption process, and form the basis for a definition of membrane efficiency. The preferred operating conditions for the efficient removal of protein from a feed solution are described. Capacity is maximised by loading a short stack of large-diameter membrane discs at a low flow rate, and efficiency is greatest when the concentration of the feed solution is low. The total protein then adsorbed is around 45 mg/ml of membrane, which compares favourably with published data.

A key recommendation is that an open mind is necessary when optimising other affinity processes, as different rate-limiting mechanisms require different operating strategies for fast, efficient protein capture. Conditions that give adequate performance with one system may

certainly not be assumed without further investigation to apply equally well to other combinations of ligand and target protein.

6.2 Suggestions for future work

Flow visualisation techniques are desirable to seek confirmation of the proposed relationships between shear stress, mixing and flow rate. If there is indeed an optimum flow rate for each insert when vortices created by both helical and leakage flow are present, giving good mixing, it should be possible to observe them. The method of Ralph⁹² forms a good starting point for experiments. Still photographs would be taken for a range of flow rates, using a large-scale model of the helical flow promoter, the flow being seeded with reflective particles. The insert casing would be formed with a square exterior section to minimise the lens effect, and steps should be taken to match the refractive indices of the test section and the fluid within it.

The residence time distribution analysis described here provides useful information about the nature of mixing around helical flow promoters. The fact that the conductivity probe which was used to measure concentration was located outside of the insert holder was unsatisfactory, however, as the effect of the insert could not be distinguished from the effect of the insert holder. A preferable arrangement would be a pair of conductivity probes mounted within the test section, close to inlet and outlet. With two measurements, the spreading of the tracer solution would be obvious.

Bellhouse *et al.*¹⁰ showed that the orientation of a thin film gauge affects its response to shear stress. By mounting a gauge in a holder that can be rotated, the extent to which the flow direction deviates from axial could be measured. Clearly there will be some deviation due to the helical flow entraining fluid particles in the perimeter annulus. In conjunction with an estimate of the mean residence time, knowledge of the flow direction in the annular gap

would make an estimate possible of the proportion of the flow following the annular and helical paths.

It is not deemed to be productive to further pursue the model affinity system described in this study, since it is of limited practical use. However, when specific ligands can be manufactured and successfully attached to a membrane, a similar course of work as described here is advocated to determine the operating conditions of flow rate, concentration and membrane thickness for efficient separations. Initial experiments should focus on solutions of the target protein alone, but subsequently tests will be necessary to verify that non-specific adsorption is low, to assess the extent to which the adsorption is modified when other proteins are present, and to address issues of elution.

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