SURFACE ENGINEERING FOR DEVELOPING NEW MEMBRANE ADSORBERS

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Significant increases in product titers during cell culture means that development of purification processes that can efficiently recover and purify high titer feed streams is a major challenge in the biopharmaceutical industry. On the other hand, introduction of new unit operations is complicated by the significant cost involved in meeting the regulatory requirements for validation and approval of a new unit operation. Recently the development of bio-similars or clones of products for which patent protection has expired, has provided an added competitive incentive for the development of low cost, high efficiency purification processes.

Membrane adsorbers are routinely used in the downstream processing of biopharmaceuticals in flow through mode to remove contaminants e.g. host cell proteins, DNA and virus particles. Membrane adsorbers overcome the limitations of resin-based chromatography. Convective flow through the membrane pores overcomes the problems associated with slow internal pore diffusion that plagues resin particles. In addition, scale up of membrane devices is simpler than packed beds. Nevertheless use of membrane adsorbers in bind and elute mode remains limited. This presentation focuses on the importance of engineering membrane surface ligands in order to maximize capacity and recovery in bind and elute operation. Two examples are presented.

Bisphosphonate derived ligands have been grafted from the surface of regenerated cellulose membranes. The capacity and flexibility of the ligands are enhanced by copolymerization of N(2-hydroxypropyl) methacrylamide (HPMA). These ligands selectively bind arginine rich proteins. Binding studies indicate the importance of tailoring the three dimensional structure of the ligands in order to maximize capacity and recovery. The mechanism for poly(bisphosphonate-*co*-polyHMPA) binding has been determined by molecular dynamic simulations. The results obtained highlight the importance of the phosphonate groups as well as HPMA for strong binding interactions and high recoveries.

The second example uses responsive ligands that change their conformation in response to changes in external conditions. Membrane based hydrophobic interaction chromatography (HIC) has been conducted using poly(N-vinylcaprolactam) (PVCL) and its copolymers grafted from the surface of regenerated cellulose membranes. PVCL displays a lower critical solution temperature (LCST). The LCST depends on salt type and concentration. At high salt concentration e.g. 1.8 M $(NH_4)_2SO_4$, used during loading in HIC, the ligand is above its LCST. Consequently it adopts a dehydrated conformation enhancing protein binding. At low ionic strength, during elution, the ligand is below its LCST. It adopts a hydrated conformation leading to protein desorption.