Refining Process Separation Procedures with Prepacked Chromatography Columns

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An increasing global demand for precise therapeutics to address unmet medical needs has paved the way for the development and approval of novel biopharmaceuticals. Consequently, the global biopharmaceuticals market is estimated to reach 650 billion USD by 2027, with an annual growth rate of approximately 7% [1]. The biopharmaceutical industry is addressing this demand by accelerating the development of new therapeutics and vaccines, improving downstream processes (DSPs) and increasing the production of current therapeutics, without compromising safety, purity, or effectivity.

Downstream processing includes a series of steps, aiming to recover and purify the molecule of interest from a complex mixture of host cell proteins (HCPs), debris, and cell culture by-products following development. Chromatography is widely used in DSPs across the biopharmaceutical industry due to its ability to selectively isolate and purify target molecules while removing impurities. Different types of chromatography resins can be employed depending on the specific requirements of the molecule being purified, leveraging various modes of interaction such as affinity, ion exchange (IEX), size-exclusion (SEC), and hydrophobic interaction (HIC). Combining multiple chromatography modalities in a single resin has given rise to multimodal (mixed-mode) chromatography, which is highly selective, robust, and capable of removing a range of impurities in one purification step. Multimodal chromatography has therefore become an attractive option for the biopharmaceutical industry, as it helps to improve the yield and purity of target proteins in fewer steps, leading to reduced processing time and cost [2].

The last decade has seen advances in DSP, focusing on optimising drug development and production processes whilst improving overall process total cost. This has been achieved by the adoption and implementation of single-use and disposable technologies, such as prepacked chromatography columns.

Prepacked columns have played a crucial role in achieving optimal purification while bringing down production costs and speeding up the manufacturing process. This can be especially beneficial for large-scale manufacturing of biopharmaceuticals, such as monoclonal antibodies, purified or recombinant proteins or gene therapy products, where efficiency and cost-effectiveness are important considerations.

Downstream Processing Challenges

As the diversity and complexity of biopharmaceutical products continue to grow, so do the challenges facing DSP, such as increased production cost due to process complexity, use of larger footprint space, and increased requirements of processing resources (e.g., in column packing). Ensuring that these processes are suitable for large-scale manufacturing is key to ensuring timely production and market entry while adhering to stringent purity standards set up by regulatory bodies.

Purification strategies need to be tailored to each product's needs, aimed at producing high purity end product by removing impurities, such as HCPs and DNA, endotoxins, viruses, and protein aggregates, while remaining cost-effective. In many cases, DSP requires the use of multiple chromatography steps, leading to costly production. Scaling-up chromatography workflows from laboratory to manufacturing scale can also be challenging due to differences in column size, flow rate and resin behaviour - thus operating conditions identified at the small scale might be suboptimal for large-scale DSPs [3].

Columns are a fundamental part of chromatography and are used throughout DSP, including resin screening, process development and production. Therefore, using a good quality column is crucial to establishing an excellent DSP. A typical column packing process involves several steps, such as calculating the appropriate slurry concentration required for a desired column bed volume, column packing, testing, qualification following by cleaning, unpacking and resin storage after use in production.

However, the complexity of the process introduces several challenges associated with each stage. Potential hurdles include column preparation, resin availability, hardware availability and storage, user expertise and training, column quantification and failure.

Packing larger or multiple columns could create a bottleneck in the process workflow, due to facility space and storage limitations, since clean columns should be available for use throughout DSP. Additionally, reusing the same column hardware for different processes creates the need for stringent cleaning protocols, as packing resins and cleaning columns by hand can increase the risk of contamination.

As well as facility space, loose resin packing, slurry and buffer preparations and column cleaning require specialist knowledge and expertise, which can vary from person to person, potentially leading to variability in column quality and performance. Introducing a variability between batches makes it difficult to obtain reproducible data, as well as challenging to ensure that the same packing and column cleaning methods and approved quality standards are followed consistently.

Moreover, DSP teams work with different resins from different suppliers, with each supplier providing their own resin packing recommendations. This introduces another degree of variability in the column packing process, which could lead to inconsistent results or process failure. Process failure can also occur from a packed column not passing a set of qualifications and approval requirements. If a column fails to meet internal specifications, the packing process would need to be repeated.

With global supply chain issues and shipping delays, resin availability is another factor that could impact column packing and DSP schedule.

Streamlining Downstream Processes with Prepacked Columns

Issues associated with in-house resin packing can be mitigated by using prepacked chromatography columns [3]. Prepacked column vendors offer ready-to-use, qualified, Good Manufacturing Practice (GMP) compliant columns, accompanied by specific instructions and documentations. Vendors provide different sized columns, prefilled with a variety of different resins, as well as the column hardware, making them compatible with a variety of chromatography systems. The end-user expectation for a prepacked column is that its performance should be as good or better than columns packed in-house, and that it meets the required specifications to allow ease of scale-up.

Manufactured under controlled conditions, prepacked columns ensure reproducibility and reduce contamination by alleviating errors potentially introduced when packed in-house. This allows facility to achieve higher yields and more reliable results. Moreover, the use of prepacked columns can provide significant time savings as they are easy to set up and ready-to-use. Because of this, they allow for increased productivity and less downtime while eliminating the need for expert specialists or specialised equipment, which is often a concern in smaller laboratories. Additionally, the use of prepacked columns can also help minimise the risk of cross-contamination between batches, making it a popular choice for biopharmaceutical production.

Outsourcing the entire column packing process is an alternative solution to the key challenges in column packing, with the end user receiving a ready-to-use column. Outsourcing has the potential to free resources and improve process productivity and throughput, and may be the more appropriate choice for when vendor's do not have a prepacked option.

However, purchasing prepacked columns from vendors still ultimately presents the best solution to onsite packing challenges, due to the following:

- The vendor would have the best knowledge of the resin and column packing conditions - as such, optimal resin packing conditions would be used to pack columns to provide the best possible performance
- A prepacked column offered by the vendor would be its own product, streamlining the ordering process
- The vendor does not rely on an additional service or supplier to provide the resin, eliminating potential delays in resin availability and reducing the number of parties involved
- With the vendor, there would be the single point of contact, for ordering, technical and commercial support — this eliminates the need for the end-user to work with two different companies (i.e., when ordering a resin, and then requesting a packing service)
- The vendor would have the prepacked columns available in a shorter lead time or, in some cases, already available in stock, increasing process throughput by reducing potential schedule delays resulting from column availability

Regulatory Requirements for Prepacked Columns

Prepacked chromatography columns used for the production of biopharmaceuticals are subject to regulatory requirements designed to ensure the quality, safety, and efficacy of these products. The regulations for prepacked chromatography columns vary depending on the country and the intended use of the columns. For example, in the United States, the Food and Drug Administration (FDA) requires that biopharmaceutical products must be manufactured in compliance with GMPs, designed to guarantee that products are produced in a controlled environment using standardised processes. The FDA also requires that biopharmaceuticals be tested and validated to ensure their quality and purity. In addition, prepacked chromatography columns used in biopharmaceutical production must be validated to ensure their reliability and consistency, including validation of their packing, performance, and compatibility with the target molecule.

GMP prepacked columns offering a variety of column diameters, bed heights and resins to choose from, such as the Foresight and Foresight Pro columns, can support DSP chromatography applications across multiple stages of biological drug development and manufacturing [5]. This includes a wide variety of purification and polishing applications for vaccines, monoclonal antibodies, and recombinant proteins.

Conclusions

The biopharmaceutical industry is continuously exploring new and innovative methods to streamline the purification process and increase efficiency. One such method is the use of prepacked columns which are becoming increasingly mainstream in DSP.

Prepacked columns enable streamlined, easy to scale-up purification processes, with a better use of resources and improved throughput, which are critical for biopharmaceutical production. Moreover, they reduce the risk of column-to-column variability and provide a consistent and reliable purification outcome, contributing to the quality and consistency of the final biopharmaceutical product.

References:

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