

WHITE PAPER

The Impact of Packed Bed Height on Efficiency and Quality



Introduction

When performing liquid chromatography, there are numerous process parameters that impact chromatographic performance, process efficiency, and final product quality. While many of these parameters cannot be easily or immediately changed, several can be optimized for improved performance. This white paper focuses on one such parameter — packed chromatography column bed height.

Historically, a 20 cm packed bed height has been recommended for bind and elute liquid chromatography. There are two main reasons for this: mass transfer and dynamic binding capacity.

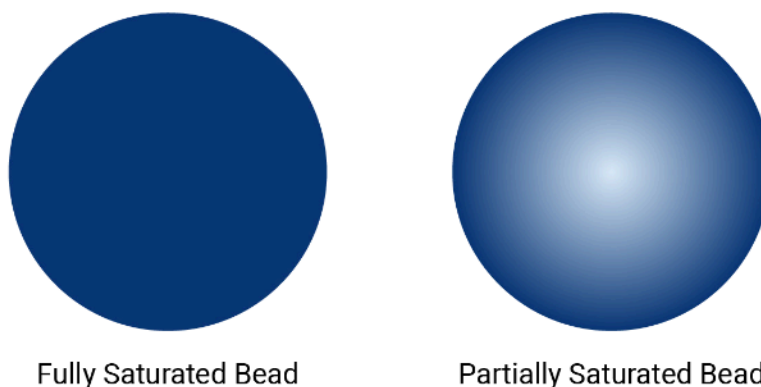
Mass Transfer

Legacy chromatography resins typically possess slow mass transfer characteristics. Mass transfer is the movement of mass from one location to another, usually from a region of higher concentration to a region of lower concentration. For protein liquid chromatography, this would be the process where proteins enter a chromatography resin bead from the surrounding process stream. The rate of mass transfer is largely dependent upon the physical structure of the resin bead, the size of the diffusing molecule, the temperature and the viscosity of the liquid.

Due to the size of biomolecules, it takes time for a chromatography resin bead to become saturated with target molecules. If the resin is exposed to the process stream for too short a time, the resin will only be partially saturated.

Figure 1

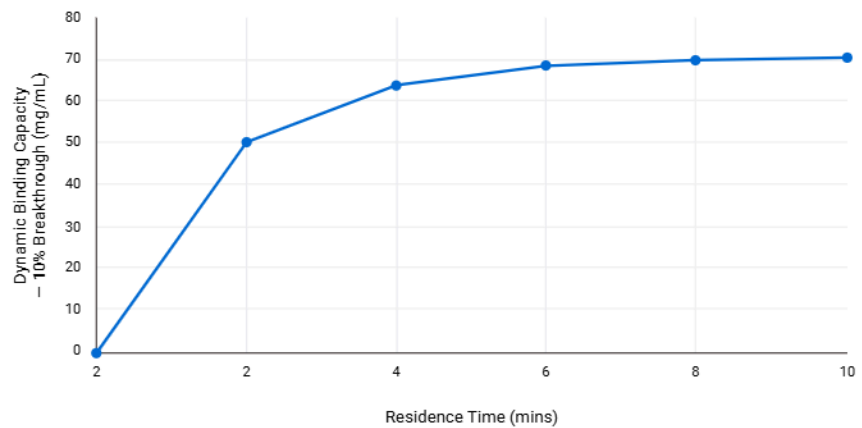
Effect of Insufficient Residence Time on Resin Saturation



The time the packed bed is exposed to the sample is known as the residence time. During process development, residence times should be explored to understand the total capacity available at various residence times. A chart can then be plotted.

Figure 2

Effect of Residence Time on Dynamic Binding Capacity

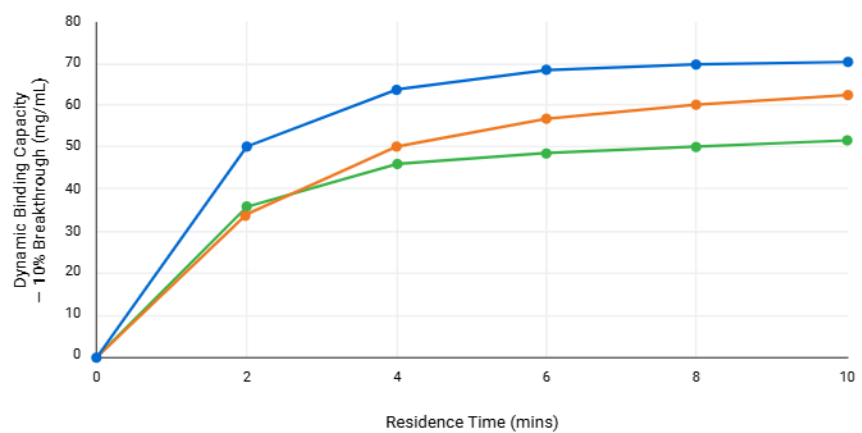


As can be seen in the plot, capacity increases with residence time but starts to level off around four to five minutes, indicating that the resin is fully saturated. Therefore, there is little benefit in using longer residence times.

Modern chromatography resins tend to possess faster mass transfer characteristics. For example, Purolite™ Resin, Praesto™ Jetted A50, reaches high capacities at shorter residence times compared to alternative protein A resins.

Figure 3

Impact of Mass Transfer Base Matrices on the Time Required to Fully Saturate a Packed Bed



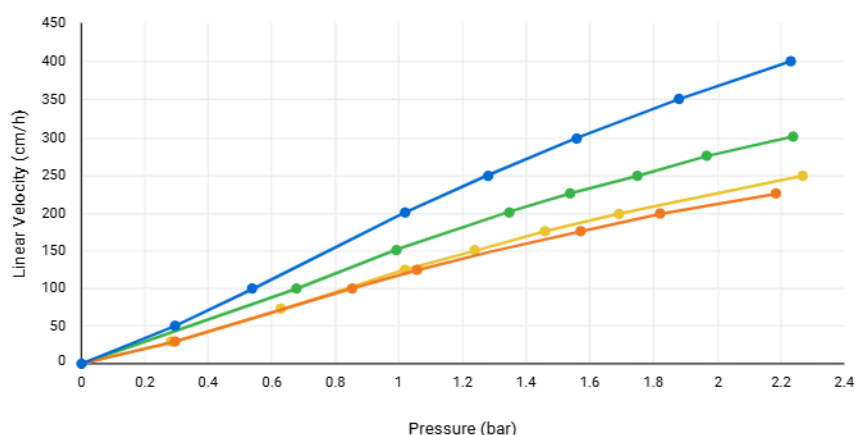
Having a short residence time maximizes productivity as a larger volume can be processed per unit time.

However, high flow rates will increase the pressure drop across the packed bed. Increased pressure can over-compress the packed bed and effect the resolution of the column, damaging the resin. In addition, the column hardware's pressure limit may be exceeded, resulting in the catastrophic failure of the column hardware.

The pressure in a packed bed is closely related to the height of the column bed. Lowering the bed height enables higher flow rates without surpassing the pressure limits of the packed bed.

Figure 4

Pressure/Flow Characteristics at Various Bed Heights



Dynamic Binding Capacity

In liquid chromatography, the dynamic binding capacity (DBC) offered by protein A resins has traditionally support the use of large bed height. Due to the comparatively lower DBC offered by legacy resins, large amounts of resins are required to capture the necessary amount of the target protein.

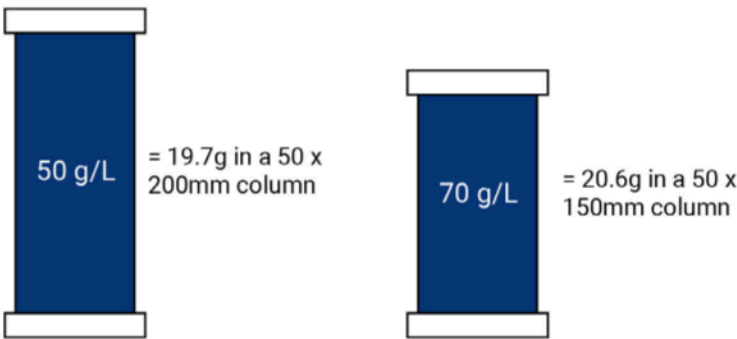
With limited bench or floor space available in many facilities, increasing column bed height is commonly used to maximize total DBC of a column.

However, leveraging a resin with higher DBC allows for the same amount of target protein to be purified while using less resin and a shorter bed height.

Figure 5

Impact of High DBC Resin

In this example, roughly the same amount of protein can be bound by using a high DBC resin at a shorter bed height.



The ability to perform protein purification at high speed – while maintaining DBC – allows for more cycles to be run per hour. Lowering bed height helps to facilitate this process.

TABLE 1 Productivity Impact Using Reduced Bed Heights

Resin	Residence Time (mins)	DBC (g/L)	Cycles	Column Dimension (ID x BH cm)	Buffer Volume (L)	Total Processing Time (H)	Total Resin Cost (\$)*	Productivity (g/L/H)
Praesto Jetted A50	2	50.4 (40.3)	8	60 x 10	3845	7	\$465,034	51.3
Competitor A	4	45.9 (36.7)	4	60 x 20	3845	7	\$1,252,023	25.7
Competitor B	4	50.2 (40.2)	4	60 x 20	3845	7	\$1,252,023	25.7

Practical Considerations for Process Scaling

The use of shorter bed heights — in conjunction with a high DBC resin — significantly benefits productivity. Ideally, these benefits would be maintained when scaling production.

Typically, when scaling, column bed height remains consistent while column diameter is increased. In addition, a constant linear flow rate is used at each scale. Maintaining bed height and linear flow rate when scaling keeps residence time — and capacity — constant.

However, practical issues, such as the limitation of available column sizes, must be considered when scaling.

While chromatography columns are available in a variety of diameters; size limitations may prevent exact scaling. Using a column that is not exact to scaling without making the proper alterations may result in some binding capacity remaining unused.

In addition, efficiency is critical when processing large volumes of sample. Utilizing all required capacity is preferred to improve process efficiency — four cycles is more efficient than 4.5.

One strategy commonly utilized in membrane chromatography is to scale based on column volumes per hour (CV/h). This strategy allows the same residence time to be used when scaling, with CV/h remaining constant rather than cm/h.

In addition, the aspect ratio (bed height: column diameter) can be easily adjusted — provided the flow rate is adjusted to maintain the same CV/h. The main obstacle when using this strategy is ensuring the operation is performed under the same pressure flow constraints for the packed bed.

Strategy Benefits

- **Facility Fit:** Ensure smooth tech transfer
- **Goal Optimization:** Column size can be adjusted according to the overarching process goal (i.e. reducing COGs)
- **Pre-clinical Scales:** Reducing the bed height of pre-clinical scales can accommodate higher resin binding capacities and shorter residence times, compensating for the increased time needed due to reduced resin volume while requiring fewer cycles as titers rise.

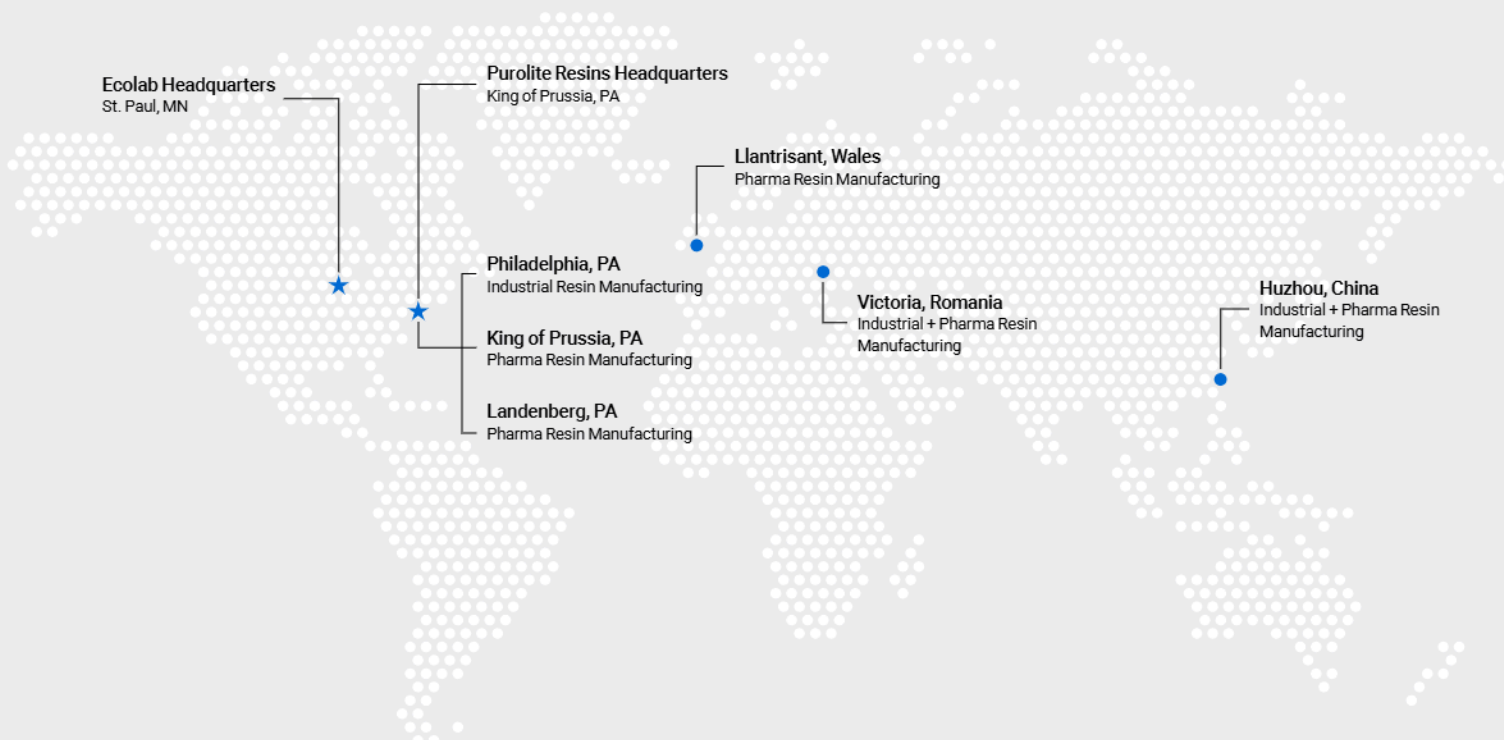
These benefits are particularly important for affinity chromatography, where protein A steps account for a substantial portion of the overall costs involved in manufacturing a biological product.

When varied in liquid chromatography, column bed height significantly impacts process efficiency and product quality. Optimizing bed height can achieve faster mass transfer, higher DBC, and improved efficiency. This strategy, however, must be supported by next-generation chromatography resins that allow for shorter residence time and offer high capacity.

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