Technical Tip

Who Does Preparative Chromatography and Why

In the pharmaceutical and life science industry preparative chromatography techniques are used at many different scales ranging from mg up to metric quantities of product to be purified. Basically we can differentiate between 3 types of scales:

1. Laboratory Scale

This scale is performed in almost any pharmaceutical company in medicinal chemistry, for lead finding, high throughput screening, to create combinatorial libraries, for the isolation and characterization of impurities and to prepare reference standards. The applications are not limited to any specific group of compounds. The quantities of product to be purified are in the mg – g range. As a large number of compounds have to be purified the methods used are mostly generic and little effort is paid to optimize the methods because speed and efficiency are more important than cost savings. The hardware used is either an analytical columns or a prepacked column up to a diameter of typically 20 – 30 mm.

2. Pilot Scale

At this scale g up to kg quantities of APIs or intermediates are purified to produce drug candidates for clinical phase trials. Pharmaceutical companies are eager to speed up the duration of clinical phase trials, but at such early stage the upstream processes are often not fully optimized so that prep chromatography is an effective tool to purify these compounds. Speed and efficiency are still more important than the purification cost. As the upstream process may be refined at a later stage or because alternative purification methods will be found, not all projects will necessarily require prep chromatography at production scale which makes this a spot business market. This particularly applies for small molecules, whereas peptide manufacturers will always need to apply a RP-HPLC purification step in order to remove impurities closely related to the target compound as failure sequences from the solid phase synthesis. For smaller molecules often NP chromatography is preferred. The hardware used at this scale may be a larger prepacked column (e. g. 5 cm inner diameter) or a self packer column of 5 – 20 cm inner diameter.

3. Production scale

Depending on the potency of the drug production scale quantities can range between kg and metric tons. The columns used are almost exclusively self packers with an inner diameter of 10 cm up to > 1 m. At this scale it is absolutely mandatory to optimize the process in order to minimize the purification cost. There are relatively few examples of small molecules which are purified by preparative HPLC. Examples include taxols, prostaglandins, steroids and natural products. Often medium pressure media are used for such applications but generally NP methods are preferred. Peptides (including insulin as the most prominent example) always require a RP-HPLC step, sometimes in combination with an ion exchange purification step. Proteins also require purification by preparative chromatography, often a combination of different modes such as ion exchange, affinity, HIC chromatography is used. RP-HPLC is in some cases applied as a final polishing step.

Key words: Preparative, bulk, scale-up

Author: Guido Krautz