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Dare To Use Preparative Chromatography at Industrial Scale for Your API:

Maximize Purity, Efficiency, and Sustainability

BioProcess International
SPECIAL REPORT

Dare To Use Preparative Chromatography at Industrial Scale for Your API

Maximize Purity, Efficiency, and Sustainability

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Pharmaceutical development is evolving at an unprecedented pace, with active pharmaceutical ingredients (APIs) becoming increasingly complex and specialized. Such drugs require intricate methods for chemical synthesis or bioproduction, and such processes can yield impurities that closely resemble target molecules. Standard purification approaches (e.g., crystallization and liquid–liquid extraction) frequently fall short in removing such challenging contaminants.

Concurrently, the prevalence of chronic diseases is projected to grow around the world. Diabetes alone is expected to affect 578 million people worldwide by 2030. Surges in patient needs propelled the global market for glucagon-like peptide 1 (GLP-1) agonists to about US$24.4 billion in 2022, with an anticipated compound annual growth rate (CAGR) of 33.2% through 2032. Such projections underscore the urgent need for efficient and scalable purification methods that deliver safe, high-quality APIs to patients worldwide.

A batch-chromatography process at Axplora's facility in Pompey, France

Chromatography in API Purification

Synthetic APIs: Cutting-edge techniques for chemical synthesis enable sophisticated API designs but also generate structurally similar impurities that can be difficult to separate from target molecules. Preparative chromatography excels with complex impurity profiles, making it an indispensable method for peptides (e.g., GLP-1 agonists), oligonucleotides, lipids used in lipid-nanoparticle (LNP) formulations, and more. When conventional techniques fail to achieve required levels of purity or efficiency, preparative chromatography fills the gap and ensures patient safety.

Biologic APIs: Production of biologic APIs through microbial fermentation or animal and plant cell culture generates both *process-related impurities* — e.g., host-cell proteins and DNA (HCPs, hcDNA), leached ligands from affinity-chromatography resins, and residual solvents and detergents — and *product-related impurities*, such as truncated proteins. Downstream biologics processing almost always involves one or more chromatographic steps.

Extracting biologic APIs from plants, nonhuman animals, and humans (e.g., blood plasma) usually starts with several centrifugation and precipitation steps. Thereafter, preparative chromatography often

Figure 1: Comparing equipment configurations for (LEFT) batch and (RIGHT) continuous-chromatography operations

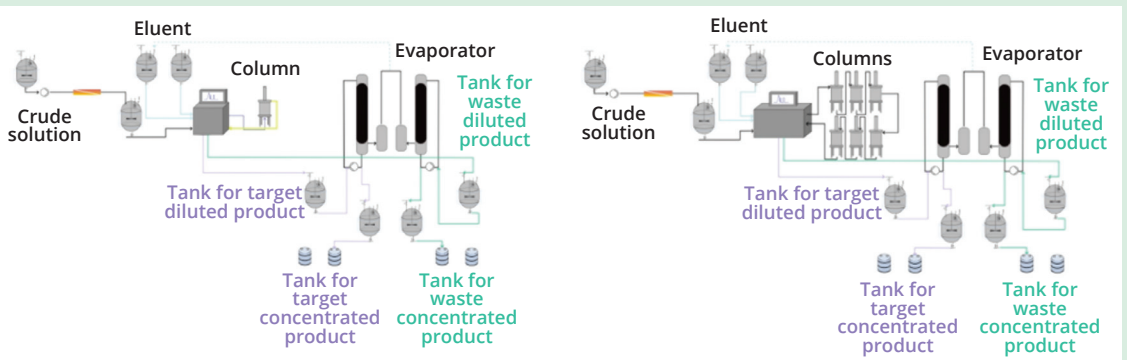
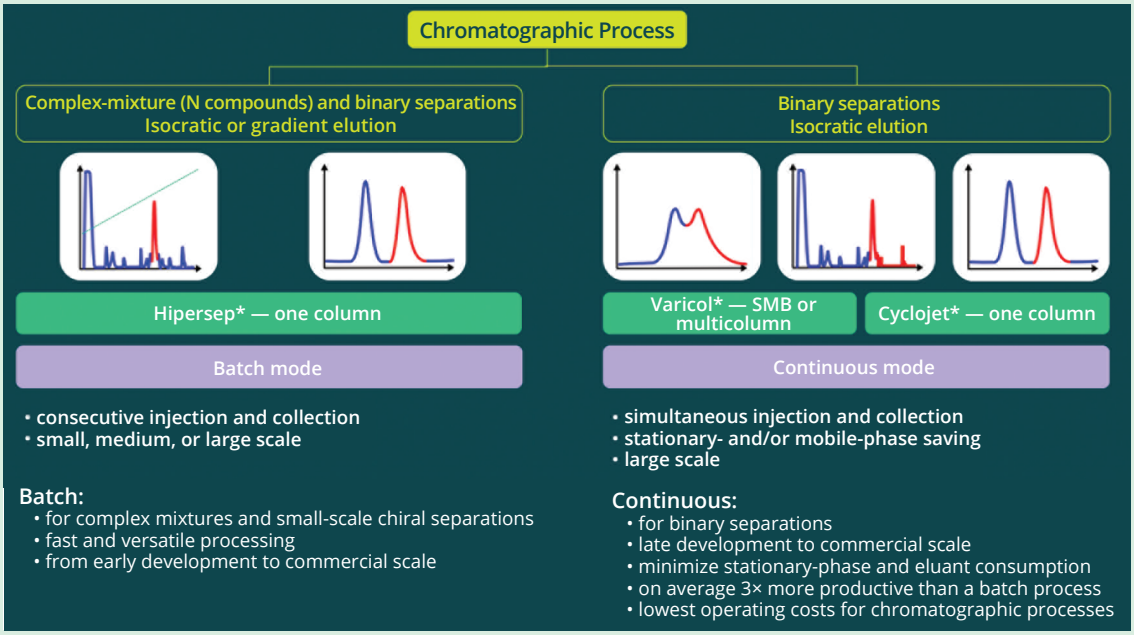


Figure 2: Comparing applications for (LEFT) batch and (RIGHT) continuous-chromatography operations (SMB = simulated moving bed, * = trademark of Sartorius)



is required to complete removal of product- and process-related impurities. Ion-exchange (IEX), reversed-phase (RP), and other chromatography methods also are applied to reduce viral and endotoxin loads. Such measures are critical to the safety of injectable drug products.

Curiosity Is Key: The above examples demonstrate the potential of preparative chromatography. Yet truly unlocking the method's power requires a willingness to explore the full breadth of chromatographic modes. Rather than limiting development to "standard" approaches, process scientists and engineers can gain significant advantages — e.g., higher yields, fewer steps, and improved productivity — by testing alternative chromatography techniques or switching from low-pressure to high-pressure formats.

The Power of Preparative Chromatography

Separation Mechanisms: There is no one-size-fits-all method in industrial chromatography. Selecting an optimal retention mechanism to purify a given API is critical. For instance, IEX chromatography exploits charge differences to separate target molecules and impurities. Affinity chromatography provides for selective binding of APIs to specific ligands. Chiral chromatography effects separation based on molecules' conformational symmetry or asymmetry. Adsorption chromatography can involve normal-phase processing of material over bare silica or with polar bonding. Alternatively, RP adsorption methods involve hydrophobic bonded silicas or polymeric resins. Process engineers also can leverage molecules' hydrophilic and hydrophobic properties, as is the case with hydrophobic-interaction (HIC) and hydrophilic-interaction (HILIC) chromatography methods.

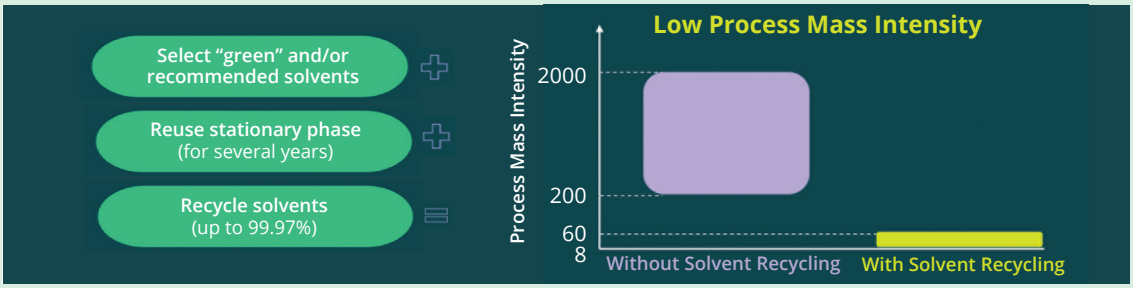
Multimodal Chromatography: Some advanced processes combine multiple mechanisms. For instance, mixed-mode stationary phases merge IEX characteristics with hydrophobic interactions, and hydroxyapatite (HA) relies on both electrostatic and metal-affinity properties. The choice of matrix — from agarose cross-linked resins and silica to ceramics (e.g., HA) and polymeric resins — determines a process's operating pressure, flow rates, and overall system productivity. Bespoke combinations of chromatography modes should be tested systematically and tailored to a therapeutic's unique features.

Exploring New Methods

RP Chromatography for Proteins: Why not explore other modes such as RP chromatography with organic solvents? Scientists have used that approach for decades to purify insulin: After an initial IEX step, RP chromatography is applied as an orthogonal method. Using one or two RP steps to purify proteins can reduce the required number of chromatography steps significantly while increasing productivity and yield.

Essential Infrastructure: Moving beyond traditional purification methods requires specialized equipment, including sanitary low- and high-pressure chromatography systems in areas classified for good manufacturing practice (GMP) and atmosphères

Figure 3: Chromatography — a sustainable process



explosibles (ATEX) operations. Such infrastructure is indispensable for handling a breadth of solvents and reagents safely while complying with stringent regulatory requirements.

Intensification Strategies

Continuous and Sequential-Continuous Approaches: Once separation parameters are optimized, the next frontier is *process intensification*, purifying more product in less time using fewer resources (Figures 1 and 2). Simulated moving bed (SMB) chromatography is a prime example. Known for its utility in chiral separations, SMB also excels at binary separation of complex mixtures. For example, Axplora uses SMB to purify hundreds of tons of ethyl eicosapentaenoic acid (E-EPA) annually at one of its sites in France. By continuously shifting material across columns, SMB methods can reduce solvent use and resin requirements significantly. Process-simulation tools built on batch-column data can be applied to quantify expected productivity gains and cost savings.

Eluent Recycling and Solvent Reduction: Sustainability goals and cost pressures are accelerating adoption of high-efficiency solvent recycling (Figure 3). Frequently, users can achieve >99% recovery without carryover. Innovative chromatographic processes also can be designed to prevent fouling or "poisoning" of stationary phases, extending their operational lifetime and improving process mass intensity (PMI) levels.

PMI measures the total mass of material used to produce one kilogram of API or intermediate. The American Chemical Society's Green Chemistry Institute has selected PMI as the key mass-based metric to benchmark process ecofriendliness. Solvent selection and recycling at production scale can drive solvent PMI close to zero. By turning chromatography into a sustainable operation, manufacturers reduce both environmental impact and operating expenses.

Axplora, Your Partner in Purification

Industrial-scale preparative chromatography is a powerful solution for challenging purifications but requires deep expertise, specialized equipment, and a willingness to innovate. Building on the Novasep legacy, Axplora has over 30 years of experience developing, scaling up, and commercializing chromatography processes at facilities inspected by the US Food and Drug Administration (FDA). With more than 20 validated manufacturing processes that incorporate chromatography, Axplora stands ready to purify nearly any molecule — synthetic or biological — in quantities from grams to hundreds of metric tons.

A company designing complex APIs should select a contract development and manufacturing organization (CDMO) with a proven track record and key capabilities. Those should include expertise in both small- and large-molecule purification, advanced infrastructure for continuous and high-pressure chromatography approaches, agile project management to accelerate development and commercialization, and the ability to establish customized and high-performance processes that meet stringent quality requirements.

Embrace Collaboration, Drive Innovation: Considering the growing diversity and complexity of pharmaceutical molecules, preparative chromatography is a critical enabler of efficient API manufacturing. By bringing together cross-disciplinary talent in process engineering, biology, biochemistry, and chemistry, Axplora develops fit-for-purpose, intensified chromatography processes that deliver high yields of well-purified products in a reliable supply.

Whether you want to optimize a purification process, explore novel chromatographic modes, or seamlessly scale production, Axplora has the experience and capabilities needed to bring your project to success. Let's dare to innovate and realize the full potential of preparative chromatography at industrial scale.

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