BACHEM

PUSHING THE BOUNDARIES

MCSGP for efficiency and sustainability

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The pharmaceutical industry is currently witnessing a surge in demand for therapeutic peptides and oligonucleotides (TIDES), driven by breakthrough treatments for conditions like obesity. This growth brings about immense challenges in manufacturing efficiency, sustainability, speed, and cost-effectiveness. Bachem, a leading peptide manufacturer, has risen to meet these challenges with an innovative approach to API purification: Multi-Column Solvent Gradient Purification (MCSGP) technology.

This case study explores Bachem's implementation of MCSGP, a continuous chromatography process that promises to redefine large-scale TIDES purification. By transitioning from traditional batch processing to this cutting-edge continuous method, Bachem is setting new standards for sustainable, efficient, and scalable pharmaceutical production.

The TIDES Revolution

Continuous processing and market growth

Intensification of production processes has been a driving force in the 20th century for many manufacturing industries. So much so, that the pharmaceutical sector is now embracing a significant shift from batch-wise production towards continuous processing, a trend that has already transformed various sectors from oil refining, to food production, to chemicals. This evolution is much more than just an upgrade; it's a strategic overhaul that meets the ever-growing demand for cost-effective, large-scale production of new drug modalities.

While flow chemistry is still far from universally displacing batch synthesis of most biopharmaceuticals, the last five years have seen a notable move towards continuous processes(1), especially in chromatographic purification of active pharmaceutical ingredients (APIs) – including large biopharmaceuticals, such as monoclonal antibodies(2).

This shift is particularly necessary in the rapidly expanding TIDES market. These large synthetic molecules, with their high specificity and potency, have emerged as vital tools in treating a range of diseases, from metabolic disorders to cancers, to immunology and rare diseases.

Projected to reach $50.6 billion by 2026 with a CAGR of 8.2%, the TIDES sector is driven significantly by breakthrough anti-obesity treatments. The anti-obesity drug market alone reached $6 billion earlier this year and is expected to grow to $100 billion by 2030(3). Driving this trend are next-generation GLP-1RA based drugs, which include numerous dual and/or triple agonists (cagrisema, retatrutide, mazdutide and survodutide) currently in phase 3 trials as potential treatments for obesity and its metabolic complications4,5

To meet this unprecedented demand, manufacturers need to gear up for large-scale manufacturing challenges and make peptide manufacturing faster, greener and cheaper. Bachem has been a first mover in adopting innovative technologies like MCSGP. These continuous chromatography methods address critical challenges in TIDES production, particularly high Process Mass Intensity (PMI). By optimizing resource utilization and reducing waste, these advancements not only meet rising demand but also strive to reach the latest sustainability goals, marking a new era in pharmaceutical manufacturing.

The challenges

Scaling up sustainably

The pharmaceutical industry is currently under enormous pressure to scale up peptide API production to meet burgeoning demand, with targets set at several hundred kilograms per year. However, the crux of the issue lies in the sheer volume of chemicals required for production. Take, for instance, the manufacture of glucagon-like peptides (GLPs), commonly used in diabetes and obesity treatments. The process demands up to 16,000 kg of chemicals for every kilogram of API produced, highlighting the resource-intensive nature of these operations. This chemical-heavy approach leads to two critical issues, with the purification step being particularly problematic:

- High solvent consumption
- Substantial waste generation

As a result, pharmaceutical companies are actively seeking manufacturing partners who can balance large-scale API production with environmental responsibility. The ideal partner must demonstrate capabilities in three key areas: minimizing the environmental footprint associated with large-scale purification, particularly in solvent use and waste production; enhancing throughput and productivity to accelerate manufacturing timelines; and increasing yield while maintaining target purity levels.

This balancing act represents one of the most pressing challenges in modern pharmaceutical production.

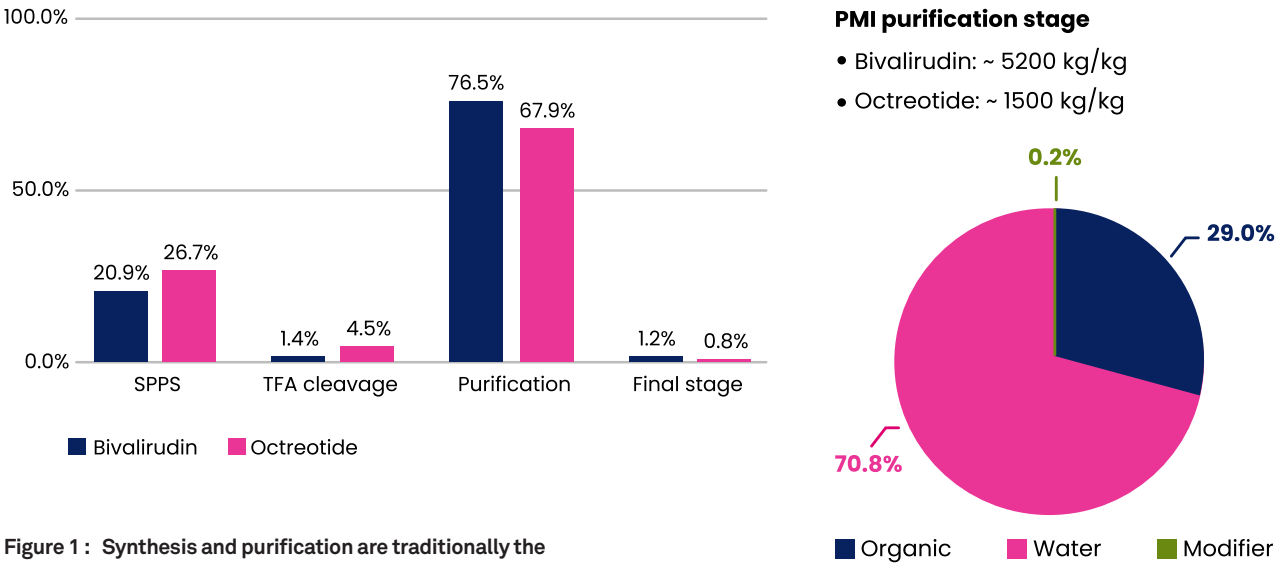

Figure 1 : Synthesis and purification are traditionally the largest contributors to process mass intensity for TIDES injected into MCSGP.

Overcoming the Pareto barrier

In peptide API production, manufacturers face a persistent challenge known as the Pareto barrier - a tradeoff between yield and purity. This barrier is particularly pronounced in chromatography, where column load defines the Pareto curve due to band broadening, tag-along, and displacement effects. Consequently, every purification step inevitably results in product co-eluting with related substances, creating "side-cuts" - fractions containing products that aren't pure enough for further processing.

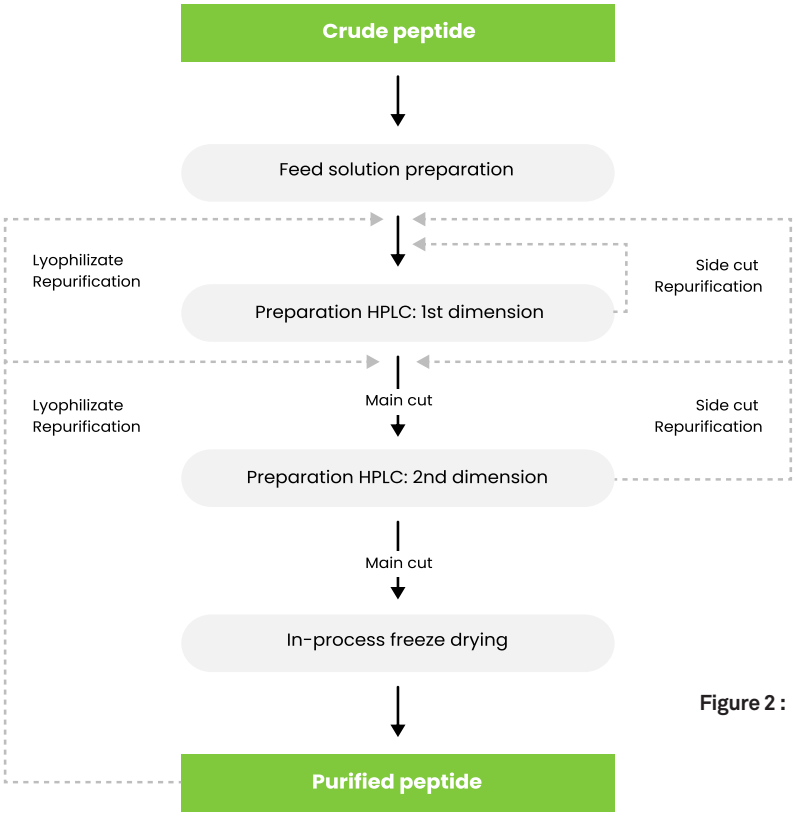

Figure 2 : Schematic illustration of purification with side-cut recycling for batch chromatography.

By re-purifying these collected side-cuts with the same purification conditions, overall yields can be increased significantly (between 10 – 30%)[1], an option desired by customers. In batch processing, side cuts need to be collected iteratively and stored. Once enough side-cut fractions have been collected, they can be pooled and run again with the same parameters. However, this batch-wise recycling of side-cuts puts a strain on the manufacturing system, from storage space and solvent consumption to manpower and analytical capacity.

How it works

MCSGP: Revolutionizing peptide purification

Bachem's MCSGP(6) technology represents a staggering breakthrough in addressing the challenges of peptide manufacturing. This continuous chromatographic process utilizes two columns in countercurrent mode, enabling automatic side-cut recycling within the same purification system.

The MCSGP process efficiently separates impurities from the product. Here's how it works:

1. Weak adsorbing side-cut fractions elute from column 1
2. These fractions are diluted and transferred to column 2 (called a "switch")
3. Simultaneously, new crude solution is fed onto column 2
4. The product elutes from column 1
5. After product collection, strongly adsorbing side-cut fractions are diluted and transferred to column 2
6. The process then repeats with column 2.

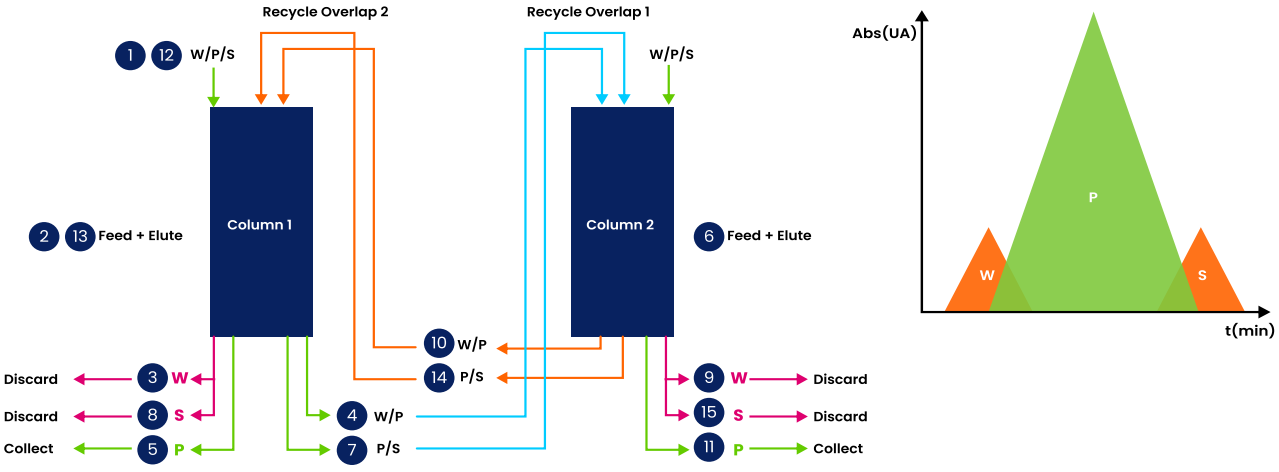

Figure 3 : Process scheme of MCSGP (P = pure product; W = weakly adsorbing impurities; S = strongly adsorbing impurities; W/P = weakly adsorbing impurities overlapping with the product; P/S = product is overlapping with strongly adsorbing impurities). The numbers indicate theoretical steps in the process. The right part of the figure represents the UV profile of the feed injected into MCSGP

One technical challenge of MCSGP purification is the need to be robust towards minor disturbances of flow rate, column load, crude purity, and eluent composition. In-process controls should be in place during the start-up phase of the system to ensure a smooth launch into a steady state. Due to the high level of automation, however, the systems are capable of running overnight without any supervision.

Each individual run is inherently lower efficiency compared to batch mode, but this is compensated for during recycling, as the side-cuts are constantly mixed with the crude product, which increases yield compared to traditional batch re-purification. Another advantage of continuous chromatography versus batch re-purification is the significantly shorter campaign time, reducing operation time from five days to 24 hours.

When it comes to solvent savings, the potential gains are often a function of the performance of the underlying batch mode, with MCSGP seeing modest gains against very optimized batch processes, but significant solvent savings in less efficient processes. Exploring these potentials can really move the needle on pharmaceutical sustainability targets.

The results

Greener manufacturing at scale

Bachem's research into MCSGP has revealed significant advancements in continuous chromatography for TIDES, highlighting the application of chromatographic conditions that are not viable in batch purification, such as steeper gradients and green solvents. This capability addresses many of the shortcomings associated with traditional batch-mode systems and opens up new possibilities for more sustainable manufacturing processes.

One of the most notable outcomes of this research is the substantial improvement in sustainability metrics.[1] **In some projects, the overall API process mass intensity was reduced by up to 70% (from 5700 kg/kg to 1600 kg/kg), while solvent consumption decreased on average by 30%**—with the potential for even greater reductions depending on the process being replaced. Yields also improved, averaging 10% higher than with batch methods. Additionally, the process is automated, reducing the need for manpower and speeding up throughput, which contributes to overall cost savings.

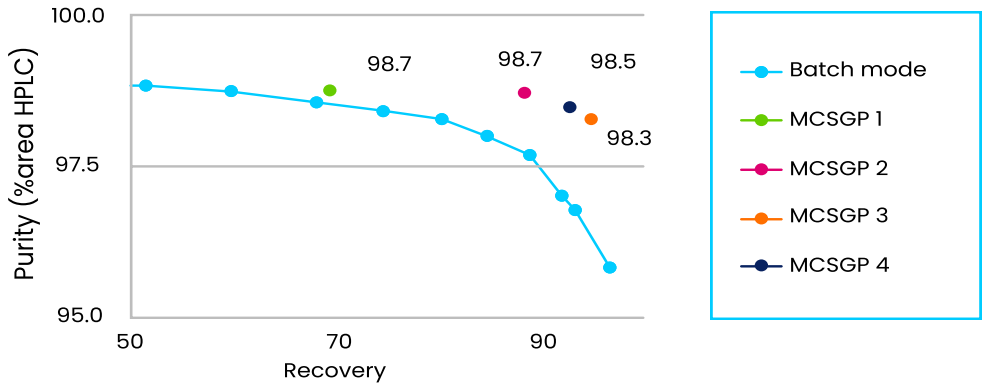

Figure 4 : Side-cut recycling by MCSGP allows purification processes to break the pareto-barrier. Shown /above: Yield and purity of four different automation setups for MCSGP.

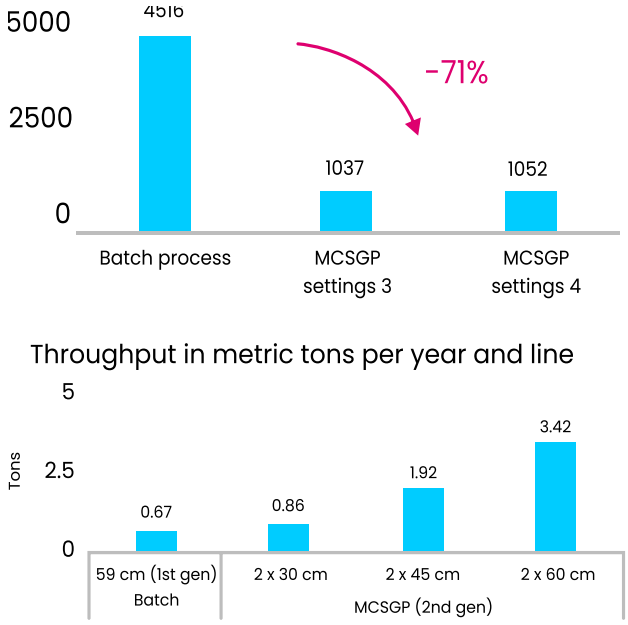

Figure 5 : Illustrative example based on real data, highlighting PMI and throughput differences for batch and MCSGP purification.

The improved quality of crude material obtained from the second-generation API process played a crucial role in these advancements. It enabled the development of a one-dimensional purification method, further streamlining the process. In testing, three out of four MCSGP conditions examined were able to significantly overcome the Pareto barrier of the batch process, demonstrating the technique's potential to push beyond traditional limitations.

One very promising avenue for MCSGP is the possibility to explore the use of greener solvents that would not be efficient enough for classical batch purification methods.

However, it's important to note that continuous chromatography for TIDES has not yet reached innovation saturation. There remain several promising avenues for further improvement, including the use of mechanistic modelling to accelerate process development and parameter optimization. Looking ahead, future research could focus on conducting robustness studies and exploring the design space of operating parameters to further increase yields, reduce waste, and enhance solvent recycling efficiency.

A new era of continuous chromatography

Pharmaceutical manufacturing is increasingly intensifying at the level of drug substance manufacturers and contract development and manufacturing organizations (CDMOs). Continuous chromatography for TIDES is now a reality, offering a fast, scalable, cost-effective, and highly efficient alternative to traditional batch processing. However, it requires specialised equipment and process expertise for successful implementation.

Bachem has pioneered the MCSGP technology—a fully automated, GMP-compliant continuous chromatography system for large-scale TIDES purification. This innovation sets a new industry benchmark, significantly reducing solvent consumption and process mass intensity while increasing manufacturing throughput. [1]

In 2023, Bachem released the first GMP drug substances purified by MCSGP for both therapeutic peptides and oligonucleotides, demonstrating its practical potential.

Given these successes, other CDMOs are now trying to catch up with implementing continuous chromatography solutions, indirectly shaping the whole industry towards more sustainable manufacturing of peptides.

Although implementing MCSGP demands specific expertise, the benefits are clear. It provides a more sustainable and efficient solution for drug production without compromising on quality. As pharmaceutical companies and CDMOs look to enhance sustainability, continuous chromatography for TIDES offers a forward-thinking approach to greener and more streamlined manufacturing.

Bachem stands at the forefront of innovating TIDES manufacturing. Our commitment to cutting-edge technologies like MCSGP positions us uniquely to address the evolving needs of the biopharma sector. We don't just meet current demands; we anticipate future challenges for our customers and proactively develop solutions. Whether you're looking to scale up production, enhance purification yields, or explore novel synthesis possibilities, Bachem is equipped to turn your ambitious projects into reality. Contact Bachem today to discover how our innovative approach can[1] add value and ensure your project will succeed in a rapidly changing market.

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GLOBAL BUSINESS

Bachem facilities are located in Switzerland, the UK, and in the US. All cGMP manufacturing sites are inspected by the US-FDA and national authorities.

About Bachem:

Bachem is a leading, innovation-driven company specializing in the development and manufacture of peptides and oligonucleotides. The company, which has over 50 years of experience and expertise, provides products for research, clinical development, and commercial application to pharmaceutical and biotechnology companies worldwide and offers a comprehensive range of services. Bachem operates internationally with headquarters in Switzerland and locations in Europe, the US and Asia. The company is listed on the SIX Swiss Exchange. For further information, see www.bachem.com.

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