BACHEM

INNOVATIONS
FOR TIDES

Powders, Processes and Progress
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LIST OF ABBREVIATIONS

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AEX</td>
<td>Anion Exchange Chromatography</td>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient (drug substance in medicines)</td>
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<tr>
<td>CDMO</td>
<td>Contract Development and Manufacturing Organization</td>
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<tr>
<td>CEPS</td>
<td>Chemo-Enzymatic Peptide Synthesis</td>
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<td>CMR</td>
<td>Carcinogenic, Mutagenic, or toxic for Reproduction</td>
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<tr>
<td>DMF</td>
<td>Dimethyl formamide (solvent used in SPPS)</td>
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<tr>
<td>Fmoc</td>
<td>9-Fluorenylmethoxycarbonyl (temporary amino-protecting group used for peptide synthesis)</td>
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<tr>
<td>GMP*</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>cGMP</td>
<td>current Good Manufacturing Practice</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography (method of analysis and purification)</td>
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<tr>
<td>LPPS</td>
<td>Liquid-phase Peptide Synthesis</td>
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<tr>
<td>MES</td>
<td>Manufacturing Execution System</td>
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<tr>
<td>MCSGP</td>
<td>Multicolumn Counter-current Solvent Gradient Purification</td>
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<tr>
<td>MS/MS</td>
<td>Tandem Mass Spectrometry</td>
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<tr>
<td>NCE</td>
<td>New Chemical Entities (drug substance not yet licensed)</td>
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<tr>
<td>NMP</td>
<td>N-methyl-2-pyrolidone (solvent used in SPPS)</td>
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<tr>
<td>PMI</td>
<td>Process Mass Intensity</td>
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<td>SBT</td>
<td>Stirred-bed Technology</td>
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<tr>
<td>SPPS</td>
<td>Solid-phase Peptide Synthesis</td>
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<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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* GMP = Good Manufacturing Practice, production guidelines that aid quality assurance. These guidelines must be followed when manufacturing substances to be used in humans. Adherence is regularly checked by specialist authorities (such as Swiss-medic in Switzerland or the FDA in the USA). Drug substances in medicines, ingredients in cosmetics and additives in foods are some of the items that are sold under these guidelines.
Peptides and oligonucleotides (TIDES) have the potential to expand the space of "druggable" targets. The growing number of TIDES – under investigation in clinical trials and used as therapeutics – is accompanied by an increasing need for efficient and cost-effective routes for their large-scale manufacture. However, manufacturing of these substances involves many challenges from decreasing yields for longer TIDES to the enormous volumes of potentially hazardous reagents and solvents for synthesis and purification. The only way to produce these therapeutic powders in the highest quality in an efficient and sustainable way is to improve the manufacturing processes. This can be achieved either through process optimizations or by new innovative technologies.

As a trailblazing CDMO Bachem has implemented a new level of automation and digitalization of solid-phase peptide synthesis to meet the predicted rise in demand of capacity and compliance. We have boosted our processes efficiency in terms of time, cost, safety, and reliability as you can read on the next page.

Shorter peptides can be produced without hazardous solvents, more efficient scale-up and enhanced process controls using Molecular Hiving™ technology. For that we signed an exclusive licensing agreement with our partner Jitsubo Co., LTD: Jitsubo’s experts develop selected manufacturing processes using this technology and transfer these processes to Bachem. Further optimizations, scale-up, and commercial production are done at Bachem. The details are described on pages 6–7.

Just like Molecular Hiving™, our newly developed tag-assisted one-pot liquid-phase oligonucleotide synthesis (TOP LOPS) necessitates fewer washing and filtration steps contrasting with classical methods, resulting, in a remarkable reduction of solvents. TOP LOPS uses liquid anchor molecules, called tags or pseudo-solid phase protection groups, on which the growing oligonucleotide is assembled as you can learn from page 10 on.

Furthermore, like the stirred-bed technology (SBT) for solid-phase oligonucleotide synthesis (SPOS), it is a favorable technology when it comes to large-scale production due to its limitless scalability. SBT is an economical engineering solution with a simple reactor design and adapted chemistry, as detailed on pages 12–13.

In the production of larger peptides with more than 40 amino acids or even the production of small proteins, peptiligase enzymes offer a scalable alternative for large-scale manufacturing. We are investigating this together with our partner EnzyTag. As described on pages 8–9, peptiligases enable a more economical manufacturing not only of large linear peptides, but also of cyclic peptide drugs and (bio)conjugates like peptide-oligonucleotide conjugates.

Purification can be a bottleneck in the production of oligonucleotides and peptides, because of the enormous amounts of solvents involved. We addressed these challenges with different approaches. We set up the first continuous chromatography system for center cut purification of peptides and oligonucleotides at industrial scale, as you can see on page 14.

Our technological leadership and innovative strength have been the cornerstones of our success since the very beginning of our company more than 50 years ago. We are innovating TIDES manufacturing as we must! We hope this brochure can show you how your project could benefit from the innovative processes we are developing with our partners.
Industry 4.0 refers to the automation and digitalization of traditional industrial processes through smart technology and integration. An “Industry 4.0-smart factory” is characterized by machines that are interconnected, interoperable, and can process data autonomously. More automation leads to shorter production cycles, more consistent product quality, higher efficacy, and more precise documentation.

Bachem, known for establishing industry standards in innovative and efficient large-scale manufacturing processes for active pharmaceutical ingredients (API), is constantly improving its degree of automation. For example, our automated SPPS process allows operations to be carried out with minimal human intervention. This improved the reliability of the process, the reproducibility of its results and its safety, while significantly increasing its cost-effectiveness. We have also invested in digitalization of the production process. As results documentation can be conducted in a paper-free way, improved first-time right rates can be attained, and by – implementing a plant information system – data analytics is possible.

How it works
Our first robotic operator, the Bachem amino acid loading unit or BALU, was designed and programmed for mid commercial scale GMP SPPS (150 L vessel size). BALU performs all the tasks shown in the figure on page 5 without the involvement of a human operator and thus 24 hours, 7 days a week independent from shift systems. A barcode scanner that reads the labels placed on the amino acid containers ensures correct handling. The process control system of the factory floor with the robot is integrated with a manufacturing execution system (MES), that shares production data seamlessly across Bachem. Fast and efficient responses to any variations in the production process are therefore possible.

Another innovative feature of our fully automated SPPS process is process analytical technology (PAT), which performs inline analytics after key steps. PAT removes the need for manual in-process controls, thus decreasing the need for human input, and provides better control of critical process parameters. This increases process safety, reproducibility, and...
accuracy. Implementing PAT for our process control decreases the need for human input and the cost of goods and leads to higher reproducibility in preventing side reactions.

The digitalization of our SPPS process started by integrating the process control system into the MES. The MES governs the process control system by defining the sequence of operations that must be performed, as written in a MES recipe, also called the Master Batch Record. Furthermore, the MES records all events, process values, alarms, as they happen during the process. Finally, the MES generates an electronic batch report. This means all equipment is managed without the need for physical logbooks. MES documentation is completely paperless while remaining fully GMP-compliant!

Full digitalization was achieved by connecting the MES to our enterprise resource planning system. Execution of process orders, automatic take-out and stock creation, material flow, and inventory control are thus also fully automated and paperless. Finally, our digitalization strategy includes real-time logging and long-term archiving of data on a Historian platform. This plant information system allows for real-time and remote monitoring of the factory floor and easy access to data for trend and batch-to-batch comparisons. In addition, it provides the basis for future predictive and prescriptive data analytics.

At Bachem, further digitalization and automation initiatives are on the horizon. Through these innovations, we will maintain our technological leadership and set a high industry standard for customers.

Benefits
• Automation and digitalization are increasing our capacities with more flexible, reliable, and scalable manufacturing processes delivering consistently high-quality API.
• Thanks to our full automation of the SPPS process we can optimize equipment usage and reduce operating times.
• Full digitalization of the SPPS process allows for paperless documentation, improved first-time-right rates, data analytics and improved data safety and integrity.
• Our GMP documentation has been simplified and improved.

More Information
We aim to redesign our processes to minimize the use or generation of hazardous substances and their environmental impact. For this reason, we have implemented innovative solutions for greener peptide synthesis by replacing potentially harmful solvents whenever possible. Jitsubo’s Molecular Hiving™ technology is one example of that approach. This technique is most advantageous for shorter peptides with up to 10 to 15 amino acids, that are required in larger quantities with batch sizes of 5 to 10 kg.

With Molecular Hiving™, fewer washing and filtration steps are needed compared to classic peptide synthesis, resulting in a reduction up to 60% in the use of organic solvents. Additionally, solvents and reagents classified as carcinogenic, mutagenic, or toxic for reproduction (CMR substances) can be entirely avoided. This makes the peptide products manufactured using this technology highly attractive for the pharmaceutical and cosmetics industries. Molecular Hiving™ can be applied for both GMP and non-GMP products and processes.

How it works
Molecular Hiving™ is a method of liquid-phase peptide synthesis using a hydrophobic anchor, onto which the peptide is assembled in the same way as on the resin in SPPS. This anchor, also called a tag, is soluble in organic solvents but insoluble in aqueous solutions. This is especially important, as all applied reagents, excess amino acid derivatives, and other byproducts are removed by aqueous extractions during synthesis. The anchor-bound peptide always remains in the organic phase, and only at the very end, when it has been fully assembled, is the peptide on its anchor isolated from the solution through a precipitation step. Cleavage of the peptide from the anchor and of the protecting groups from the peptide are performed in an analogous way to SPPS, using a trifluoroacetic acid (TFA) cleavage cocktail. The solubility of the peptide on the tag defines the length of the synthesized peptides, as issues regarding solubility in non-water miscible solvents are often observed for longer peptides and the peptide must remain soluble in the organic phase throughout the entire process. However, longer peptides can also also be made using a fragment approach.
The Fmoc amino acid derivatives are coupled by adding them directly to the solution (step 1). Thus, direct monitoring of the reaction’s progress is possible using HPLC. There is always a certain amount of water in the organic phase, and because of that, this technology is not suitable for water-sensitive coupling reagents. However, there is a wide range of coupling reagents available that can be used for Molecular Hiving™. Typically, fewer equivalents of Fmoc amino acid derivatives are needed than in normal SPPS, as the reaction in solution has a faster conversion rate.

When the coupling is complete, Fmoc cleavage (step 2) is performed by adding a suitable base. Again, monitoring by HPLC is possible, so it is easy to directly control whether all Fmoc protecting groups are cleaved. After this, aqueous extractions (step 3) will remove the excess amino acids, coupling reagents, and bases.

Steps 1 to 3 are repeated depending on the length of the desired peptide, each cycle adding one amino acid to the chain. After the peptide is fully assembled, the protected peptide on the tag is isolated by means of a precipitation process (step 4). Finally, the peptide is cleaved from the tag, along with its protecting groups, and purified if necessary.

**Benefits**
- This is a CMR free process by which peptides can be synthesized without the use of DMF, NMP, or any other hazardous solvents and reagents.
- There is a significant reduction in solvent consumption compared to SPPS processes, and to traditional peptide synthesis in solution (LPPS).
- Compared to SPPS, fewer equivalents of Fmoc amino acid derivatives and coupling reagents are required.
- Direct in-process control is possible, e.g., by HPLC.

**More Information**

**Webinar:**
WHEN ENZYMES DO A BETTER JOB: CHEMO-ENZYMATIC PEPTIDE SYNTHESIS

Therapeutic peptides are becoming ever longer and more complex. To make these peptides in large quantities we are working with our industry partner EnzyTag to develop an efficient enzymatic ligation tool called chemo-enzymatic peptide synthesis, or CEPS. It is a state-of-the-art, greener, and more sustainable synthetic way to make cyclic or long peptides or even small proteins that are difficult to express recombinantly. For that purpose, CEPS uses a peptide ligation enzyme, also known as peptiligase, to form longer peptides by coupling shorter peptide chains previously produced by SPPS.

Fmoc-based SPPS routinely delivers peptides with a length of 50 to 60 amino acids. Longer sequences are difficult to make because of the impurity levels. CEPS enables the synthesis of peptide sequences well above 100 amino acids. Due to the fragment approach the impurity profile is excellent. The process runs under aqueous conditions at near neutral pH as the enzyme is active in the pH range of 7 to 8.5. The enzyme is derived from an endotoxic-free biotechnological process in Bacillus subtilis bacteria, which are generally regarded as safe (GRAS) organisms.

How it works
Peptiligase originates from a serine protease – an enzyme that normally cleaves peptide bonds. The enzyme has been engineered in such a way that it now creates peptide bonds. This was achieved by substituting the active site serine with a cysteine. Peptiligase was also designed to recognize multiple sequences of amino acids, making CEPS a traceless technology without the need to insert a specific recognition sequence. Furthermore, the enzyme shows good activity and stability in the presence of organic co-solvents or denaturing agents, which enables the efficient ligation of hydrophobic and/or folded peptides.

To make a peptide by CEPS, at least two peptide fragments are used. The first fragment is a synthetic peptide that needs to have an oxo- or thioester at its C-terminus. The ligation starts with the reaction between the ester and the thiol of the active site cysteine (step 1 in figure above). As a result, organic alcohol leaves the active site (step 2), and the peptide is covalently attached to the peptiligase via a thioester. The amine fragment (synthetic or recombinant) then comes in and replaces the thioester, forming the product (steps 3 and 4). The peptiligase is then free.

Ester fragment requires 4 amino acids for proper docking
Amine fragment requires 2 amino acids for proper docking
(most amino acids are tolerated except proline)
Peptiligase requires six amino acids for proper docking: four amino acids in the ester fragment and two in the amine fragment. The full range of canonical amino acids, including hydrophobic amino acids, is tolerated in the active site. Outside of the active site, non-canonical amino acids and non-peptide motifs can also be included in the peptide sequence. To produce cyclic peptides and cyclotides, peptiligase needs at least twelve amino acids for cyclization, given that six amino acids are needed for recognition in the reaction pocket of the enzyme and another six are needed to close the loop.

**Benefits**

- **CEPS** enables the regio- and stereoselective synthesis of peptides that cannot be (efficiently) manufactured by stepwise SPPS.
- In combination with SPPS long peptides with more than 40 amino acids and cyclic peptides with more than twelve amino acids can be made in high purity.
- Protection of side-chain functionalities is not necessary, as side reactions and racemization are absent.
- CEPS is more environmentally friendly, as the consumption of organic solvents is reduced.
- This is a scalable process applicable for GMP manufacturing.
- It is capable of synthesizing > 90% of marketed pharmaceutical peptides.

More Information

**Webinars:**

**Publications:**
A more sustainable and scalable oligonucleotide synthesis using fewer solvents, and solvents that are halogen-free can be achieved by combining the positive aspects of solution-phase oligonucleotide synthesis and solid-phase oligonucleotide synthesis (SPOS). This hybrid approach uses liquid anchor molecules, also called tags or pseudo-solid phase protection groups, on which the growing oligonucleotide is assembled instead of a solid-phase resin. The reactor is also used for liquid-phase oligonucleotide synthesis (LPOS) and not a fixed-bed one. This means the advantages of solution-phase oligonucleotide synthesis that are preserved in such a tag-assisted one-pot liquid-phase oligonucleotide synthesis (TOP LPOS) are as follows:

- Linear reaction kinetics in homogeneous solution
- Reagents and building blocks; that can be used mostly in stoichiometric amounts and not in excess and
- Relatively simple one-pot reactor design

**Detritylation** = Deprotection: Removal of the acid-labile 5’-DMT (4,4’ Dimethoxytrityl) protecting group from the first nucleoside bound on a solid support (5’-DMT prevents polymerization of the nucleoside) with an acid.

**Activation and Coupling:** The free 5’-OH of the first nucleoside reacts with the phosphor and replaces the diisopropyl amine group.

**Oxidation or Thiolation** (X=S): Transforming the unstable phosphate triester into a more stable phosphate triester.

**Capping:** Unreacted solid phase bound 5’-OH groups are permanently blocked from further chain elongation by transforming the OH-group into an acetylated (inactive) group.

**Deprotection:** Removal of the protecting group of the second nucleoside.

**Cleavage:** After synthesis of the desired oligonucleotide when all building blocks are added after several cycles, it must be cleaved from the solid support and conditioned for further downstream processing.

* SPOS and LPOS differ regarding the reactor types, the organic solvent systems used, washing and extraction steps, existing or non-existing supports on which the growing oligonucleotide chains are assembled, and the product isolation steps.
The main advantage of solid-phase synthesis however, which is the separation of the product from byproducts and reagents is preserved using the tag. Limitations of SPOS such as a restricted loading capacity of the solid-phase resin is not a factor. That’s why a higher volume yield can be achieved.

Concerning synthesis chemistry, the same repetitive chemical steps are used as in classic fixed-bed flow through SPOS, shown in the image on page 10. However, excessive washing steps after each cycle are not necessary. Reaction debris is removed by aqueous extraction.

**How it works**

Currently, standard LPOS is performed in halogenated solvents and isolation after each reaction cycle typically requires tedious and time-consuming precipitation and filtration. Using a soluble support containing long-alkyl chains (tag) enables product isolation also by extraction. We were able to develop an LPOS process using halogen-free solvents and aqueous extraction to separate the product from byproducts and excess reagents. That means this one-pot process is characterized by coupling cycles avoiding solid-liquid separation i.e., precipitation or filtration. Instead, the separation of the growing oligonucleotide and reaction debris is done by liquid-liquid separation i.e., aqueous extractions. The non-halogenated CMR-free organic solvent system retains the growing mid-sized, tagged oligonucleotide by providing sufficient solubility and aqueous extractability for the tagged oligonucleotide. The newly developed tags (structures shown in the image below) do not interfere with the standard oligonucleotide synthesis shown in the image above. They are cleaved after elongation of the oligonucleotide under basic global deprotection conditions.

The coupling conditions, scavenger and extraction conditions were further fine-tuned. As for all LPOS technologies, non-destructive analytical methods such as HPLC can be used for process control. This is a clear advantage in comparison to SPOS, where one must first remove the solid support to be able to perform analysis.

A considerable reduction in process mass intensity (PMI) compared to automated classic SPOS can be expected as half of PMI during the synthesis is derived from the solvents used in washing steps.

**Benefits**

- TOP LPOS uses extraction to remove reaction debris, avoiding precipitation and filtration steps and therefore has high potential for low organic solvent consumption.
- The non-heterogeneous process is ideally suited for large-scale manufacturing due to its one-pot design and limitless scalability.
- This technology is ideal for the synthesis of oligonucleotide fragments which are then used for enzymatic ligation reactions.

**Selection of developed tags:** Two distinct families were established, based on either a carbonate linkage (to the nucleoside) or ester linkage. Both linkers are stable during oligonucleotide synthesis and are cleaved under classic basic global deprotection conditions.

**More Information**

To address a potential metric ton demand for oligonucleotides, it is essential to develop more efficient, more sustainable, and highly scalable manufacturing techniques. With stirred-bed technology (SBT) for solid-phase oligonucleotide synthesis (SPOS), ton-scale commercial oligonucleotide API manufacture with unmatched process mass intensity (PMI)* is within reach.

Based on decades of experience in applying stirred-bed reactors for making peptides, we investigated whether these could be used for the manufacturing of oligonucleotides as well. Like peptides, oligonucleotides are typically synthesized by solid-phase synthesis using an automated synthesizer. However, the scalability of the manufacturing with flow-through synthesizers is limited by many factors like the sizes of the pumps generating the flow or the thickness of the solid-phase resin bed (bed height). This thickness is critical because only an optimal bed height for a given flow in those synthesizers ensures that the reaction mixture flows evenly through the resin, allowing completion of chemical reactions. Swelling of the solid-phase resins for general applications is usually not exploitable. That’s why a scale of over 2 mol of oligonucleotide per batch – corresponding to a double digit-kilogram-scale for an average oligonucleotide – is so far unprecedented.

In addition, there is another important disadvantage of this technology: the concentration gradient over the column, as seen in Figure 2, resulting in batch inhomogeneity to some extent. Better batch homogeneity can be achieved by getting away from the flow-through column principle to agitated-bed systems.

### Fixed bed flow-through SPOS versus stirred-bed batch SPOS.

- Scalability limited by flow (pumps)
- Bed-height and flow critical
- Resin swelling not tolerated

This inhomogeneity of conventional packed bed flow SPOS is completely omitted in the SBT-SPOS due to uniform reagent contact time and distribution.

### How it works

We use a comparably simple type of equipment with stirred vessels, standard coupling chemistry

*Process Mass Intensity (PMI) = Mass going into the process / Mass of the product."
(see page 10) and optimized deprotection protocols solving the problem of a side reaction that occurs when the protecting groups are removed in the repetitive process of SPOS. This side reaction, the loss of purine nucleobases in the produced oligonucleotides, as shown in the figure above occurs due to the acidic conditions during the removal of the protecting groups and decreases yields and purity. Both chemical and engineering adaptations of the detritylation step were made in stirred-bed synthesizers to control this side reaction in such a way that there is only a minimum of depurination. As a result of thorough investigations our experts moved away from using the common dichloroacetic acid in toluene during deprotection. Instead, they used a cocktail based on an acid with a higher pKa value, a mixture of toluene with trifluoroethanol and special scavengers for the deprotection.

SBT is not only suitable for making full-length product sequences. It is also ideal for hybrid approaches: short fragment synthesis with typically less than 15 nucleotides at the hundred-kilogram scale followed by either chemical or enzymatic ligations with no chromatography steps involved.

With SBT, a drastic reduction of solvent consumption and PMI can be achieved by using higher loading of the solid phase resin and the reduction of solvents used for washing.

Benefits
- SBT is one of the methods of choice to make metric ton quantities of oligonucleotides with unbeaten PMI.
- It is an economical engineering solution with a simple reactor design and adapted chemistry omitting inhomogeneity of conventional packed bed flow SPOS due to uniform reagent contact time and distribution as well as flow-independent chemistry.
- SBT is very effective when combined with MCSGP purification.
Pioneering Continuous Chromatography

Highly efficient and cost-effective process for large-scale purification

Automated 24/7 system allowing a significant decrease of campaign duration

What are the benefits for peptides and oligonucleotides purification?

1.

2.

3.

4.

Sustainable process with decreased solvent consumption and PMI

Higher yield and purity even for complicated separation due to recycling of fractions

Continuous chromatography: a game-changer for large-scale production of peptides and oligonucleotides.

Purification is not only paramount for achieving high purity but also a major determinant of the productivity of the entire API manufacturing process. The innovative multicolumn countercurrent solvent gradient purification (MCSGP) technology represents great progress in the downstream process for peptide and oligonucleotide manufacturing. Compared to single-column batch purification, solvent consumption is typically decreased by over 30%, thus contributing to a higher level of sustainability. The process has a higher capacity and often reaches the target product purity often with a higher yield, typically 10% more. The automated system runs 24/7 and has the potential for additional reductions in cycle time. In 2021, Bachem acquired the first two process scale MCSGP systems for the high-performance liquid chromatography (HPLC) and anion exchange chromatography (AEX) purification of peptides and oligonucleotides using 20 and 30 cm diameter columns. These systems are qualified for GMP use, and first purifications at scale have been successfully performed.

How it works

MCSGP is a fully automated system using two columns that are operated in countercurrent mode. It internally re-purifies side-fractions, called side-cuts, while eluting product fractions by changing from one column to the other. During gradient purification, weak and strong adsorbing impurities are separated from the product.

We have proved that MCSGP technology is cost-effective and reduces waste. Sharing the benefits of continuous chromatography with the pharma or biotech companies that rely on us for their products’ excellence is part of our mission. MCSGP is a greener, economical, and more sustainable process.
Continuous chromatography equipment for API purification at the Bachem site in Bubendorf.

Benefits

- MCSGP increases the capacity, quality, and sustainability of the purification process.
- It is a scalable, highly efficient technology, that is particularly useful for large-scale production.
- Using an automated system, it can run 24/7, allowing a significant decrease in purification campaign cycle times.
- More sustainable purification is possible with MCSGP, as it reduces solvent consumption and process mass intensity.
- It deploys standard chromatographic conditions, and API quality is not adversely affected by changing from batch mode to continuous mode.

More Information

Webinar:

Whitepaper:
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 USA and Asia. The company is listed on the SIX Swiss Exchange. For further information, see www.bachem.com.

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