SK pharmteco

White Paper

Simulated Moving Bed (SMB) Technology: Optimizing API Purification

Introduction

The pharmaceutical industry is rapidly diversifying, with a growing demand for solutions providing efficiency, high-purity, and scalability in the production of active pharmaceutical ingredients (APIs) production at the same time controlling costs.

Simulated Moving Bed (SMB) technology is a powerful continuous chromatographic purification technique that checks all the boxes. Despite the numerous recognized advantages of chromatography, misconceptions about complexity, cost, and scalability have hindered its widespread adoption. This white paper aims to address these topics and highlight SMB's transformative benefits over traditional purification methods.

SMB Overview

SMB is a continuous chromatographic separation process designed to optimize the purification of binary-like mixtures, such as enantiomers, diastereomers, or structurally related impurities difficult to resolve by simple crystallization. Unlike batch chromatography, SMB operates truly continuously, offering cost savings, enhanced efficiency, and environmental benefits.

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Common Misconceptions & Barriers

The SMB technology was developed in the 1950s for the petroleum industry (large adsorption columns) and was later adapted for the purification of sugar molasses at multi metric tons per day using large ion exchange columns and water as mobile phase. The SMB technology was then transferred to the pharmaceutical industry in the early 1990s for the purification of chiral compounds. Despite a long history of successes, the technology still suffers from misconceptions and misunderstandings.

SMB is a well-established technology

While SMB requires initial optimization, advancements in automation and simulation tools have simplified its design and improved the robustness of its operation. With proper training or collaboration with experienced providers, SMB can be seamlessly integrated into manufacturing processes. Process development for SMB can be done within a couple of weeks (screening using an HPLC unit) to identify the separation conditions and, using well-established modelling software, the process parameters can be easily calculated with a few loading data points. Demonstration at small scale (bench top mini-SMB units) can also be performed in 2-3 weeks, resulting in a high confidence prediction of the performance at larger scale due to the simplicity of the process scale-up.

SMB can be used beyond chiral separations

SMB is versatile and effective for a wide range of applications, including separating structurally similar compounds and high-purity recovery of non-chiral APIs.

SMB equipment is available for manufacturing at commercial scale

While the initial investment in SMB systems may be higher, the total cost of operation is significantly reduced due to the high automation (low manpower requirement), the large savings in solvents usage (99.9% recycling demonstrated at commercial scale) and the resulting reduced waste generated, and the improved robustness of the process significantly reducing the rate of rejection for a batch. The investment in chiral stationary phase (CSP), while quite large, can be amortized over several campaigns and years of production. New enhanced chiral media are robust and solvent resistant allowing use of the CSP for over 5 years (up to 10 years demonstrated) of constant manufacturing resulting in a cost contribution for the CSP of a few dollars per kg of API produced.

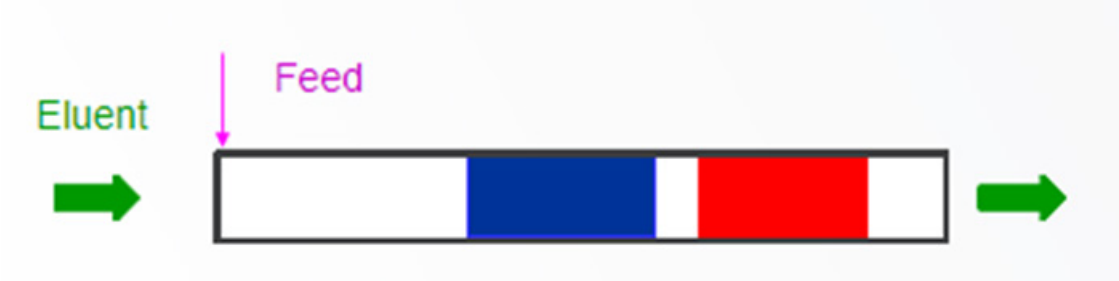
SMB Process

The process is based on liquid solid equilibrium achieved in a counter current fashion. Many parallels can be drawn with continuous distillation (Liquide vapor equilibrium) as the two processes are very closely related from a chemical engineering standpoint.

Step 1

SMB is a chromatographic technique based on the same fundamental principles of batch chromatography. In the batch chromatography process, a binary mixture is injected onto the column and is eluted with a mobile phase, a separation of the components of the mixtures occurs because each compound has a different affinity with the solid support packed within the column. These compounds can be collected individually at the end of the column.

Figure 1: Batch Chromatography Principle

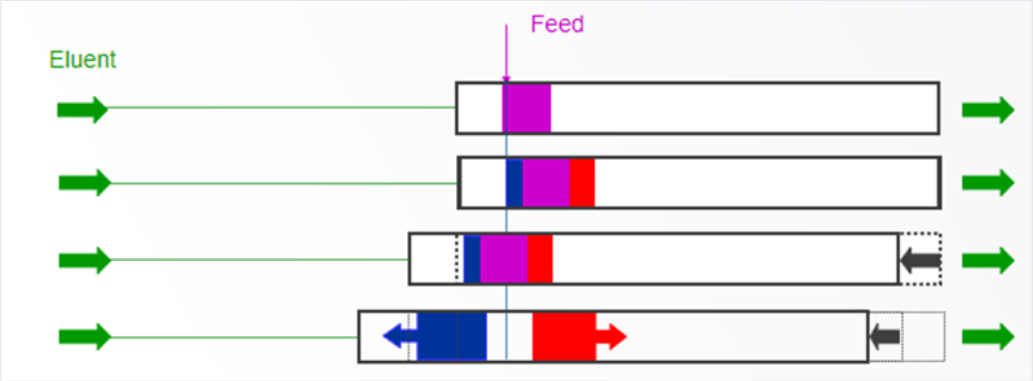


Batch processes are typically time consuming and require a large quantity of chromatographic media and solvent to separate small amounts of material at a time. While techniques such as stacked injections and gradient elution can improve the throughput, a batch process presents some limitations in overall efficiency. Converting a batch process to a continuous process can be challenging but will result in improved performance and throughput.

Step 2

The chromatographic process can be significantly improved if a continuous flow is considered. Starting from the same column configuration, one can imagine that if the column is moved in the opposite direction of the flow, at an intermediate velocity between the two compounds of interest, the slow compound will appear to be moving with the column for an observer located at the point of injection, while the fast moving one will still move in the direction of the elution (See **Figure 2**). A gap is forming and is growing between the two components as shown in the figure below.

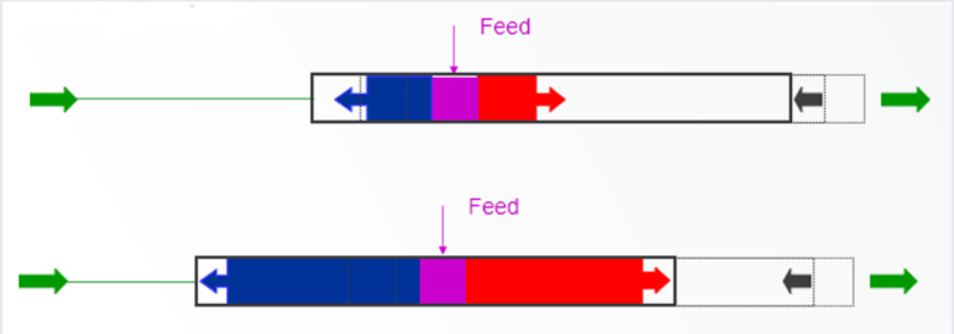
Figure 2: SMB Chromatography Principle – Relative Movement



Step 3

This “gap” generated by the relative movement of the compounds can be leveraged to add more feed solution. Eventually, because the column is not infinite, the separation will run out of “space” and the column will be saturated with product.

Figure 3: SMB Chromatography Principle – Continuous Feed



Step 4

The two products must be removed from the column and new column sections must be added to continue the process.

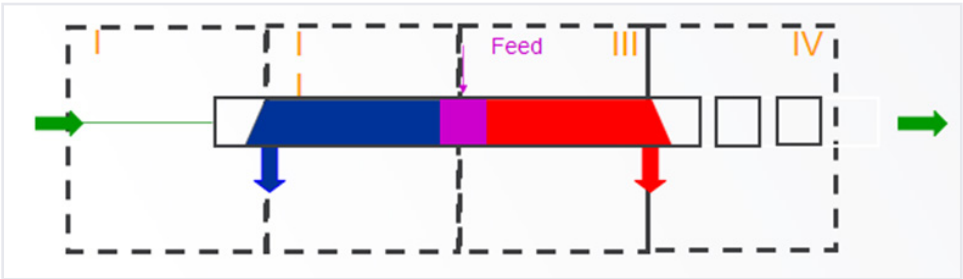
Figure 4: SMB Chromatography Principle – Multiple Columns and Outlets

Because of the mass balance, the amount of feed added to the system must equate to the sum of the material removed from the process.

Step 5

The process can be separated into four distinct zones as indicated in the figure below. The Zone I on the left requires a large flow rate to "push" harder the strongly retained compound towards the right, by increasing its speed. The strongly retained compound is then forced to exit the system at the stream located between Zone I and Zone II. The Zones II and III located in the middle are designed to have the strongly retained compound move with the column to the left while the fast eluting one is still moving to the right with the mobile phase. Therefore, it is important to carefully select the flow rates in these zones as well as the feed load to control the relative velocities (note the elution velocity of a compound is also influenced by concentration). Finally, Zone IV has the lowest flow rate resulting in an increased retention of the fast-eluting compound causing a reverse elution and forcing it to be recovered in the stream located between Zone III and Zone IV. As a result, the left-over mobile phase coming out of Zone IV is "clean" and can be recycled into Zone I.

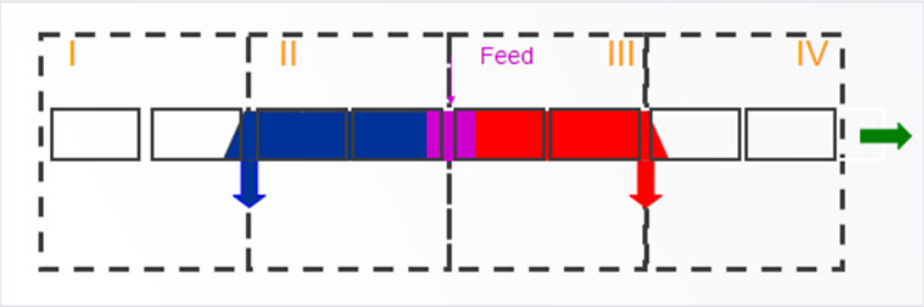
Figure 5: SMB Chromatography Principle – 4 Zones Defined



Step 6

For practical reasons, the “column” is broken down into smaller identical units. To “simulate” the continuous flow of solid material, the columns are moved at regular constant time intervals known as the “switch time”.

Figure 6: SMB Chromatography Principle – Process Design



The feed concentration, the flow rates and the switch times must be selected carefully to ensure complete separation in Zones II and III. But also, the zone I flow rate must be selected to ensure that the strongly retained compound is completely removed from the column in position 1 so the column can be “moved” to the end of Zone IV when the switch occurs. Similarly, the flow rate in Zone IV must be low enough to ensure that the mobile phase coming out of Zone IV can be recycled to the top of Zone I.

Limitations and Advantages of SMB

The conversion of an intrinsically batch process into a continuous process comes with a cost.

- The separation must be stable over time. The separation process relies heavily on the stability of the retention times and, therefore, any source of change in the retention behavior must be identified and delt with before scale-up. For example, any impurity that potentially accumulates on the stationary phase could reduce the media performance resulting in a reduction of retention capacity.

- The mobile phase can only be of a single composition (i.e. isocratic) and the feed mixture must be dissolved in the same mobile phase as recycling of the mobile phase is an integral part of the process.

- The continuous process results in the production of two streams and, therefore, is only separating “binary” mixtures (e.g. enantiomers or specific impurity from a mixture - see below).

The benefits of the technology are:

1. A continuous flow of mixture is being separated, eliminating the batch downtime between injections and, therefore, increasing the potential throughput of the process.

2. The overall usage of chromatographic media has significantly increased, reducing the operating cost associated with the packing material.

3. The process produces more concentrated product streams than typical batch elution, reducing the solvent consumption and contributing to a more cost-effective process.

4. Easy scale-up. Like any chromatographic process, scaling-up SMB relies on the ratio of the column cross sections to maintain the relative velocity at the particle constant to ensure the same mass transfer and equilibrium. This simple rule makes the scale-up very reliable and easy. For example, processing 50 g of feed a day on a 10 mm diameter SMB unit will correspond to processing 320 kg of feed a day on a 800 mm SMB unit $((800/10)^2$ x 50 g/1000) providing that the column length, the chromatographic media, the mobile phase composition, and the feed concentration are maintained the same.

The continuous nature of the process and the simplicity to scale-up make it an ideal candidate for large commercial-scale manufacturing of “blockbuster” drugs. Its ability to handle high feed rates, to produce high-purity products efficiently, and to achieve high productivity translates into significantly lower manufacturing costs.

SMB Applications

While it is a binary separation technique, SMB still benefits from a wide range of applications making it a powerful process that excels in a variety of challenging separations, including:

Chiral Separations:

SMB is particularly adapted for the separation of enantiomers (including regioisomers, rotational isomers (atropisomers), and cis/trans mixtures), which are mirror-image molecules with identical chemical properties but distinct biological activities. Recent advances in chiral stationary phases allow the use of a broad range of solvents enabling SMB technology to achieve high enantiomeric purity with high throughput and high recovery, resulting in a competitive process compared to traditional chiral resolution or asymmetric synthesis. When combined with racemization of the undesired enantiomer (either in batch or in flow), the SMB process becomes exceptionally efficient in terms of waste generation and process mass intensity metric (PMI), making the process one of the most sustainable unit operations in the industry.

Diastereoisomer Separations:

Similar to chiral separations, diastereoisomers can be separated using SMB technology providing that the desired isomer is first or last eluting from the diastereomeric mixture, the other isomers being recovered in the other SMB stream.

Complex Separations:

SMB can be used successfully even with complex mixtures such as extracts from natural products (i.e. Paclitaxel from yew tree extract) as long as the impurities are gathered on one side of the elution profile and can be recovered either in the extract (most retained) or the raffinate (less retained) stream, while the enriched desired product is recovered in the other stream with high purity and yield.

Structurally Similar Impurities:

SMB can also leverage the power of chromatography to resolve effectively structurally similar impurities that would otherwise be difficult to remove by traditional crystallization methods without a significant hit on the yield. The output of the SMB process ensures purity of the APIs with removal of the undesired impurities to a controlled level in a single step without the need of a base line resolution separation.

Product Recovery (SMB Mining™):

SMB can also be used to remove troublesome impurities in the recovered mother liquors from a crystallization step to provide a second crop of “crude” product that can, in turn, be crystallized with the exact same method to enhance the overall yield of the process without a significant impact on the regulatory aspect.

Alternative Purification Solutions

Technique	Advantages	Limitations	Why Choose Chromatography
Crystallization	Cost-effective, scalable	Ineffective for similar solubility properties	Superior yield for closely related impurities
Membrane Separation	Simple, size-based filtration	Limited resolution for compounds with similar molecular sizes	Higher precision in challenging separations
Liquid-Liquid Extraction	Effective for solubility-based separations	Precision issues with closely related compounds	Ensures higher purity
Precipitation Techniques	Useful for APIs with selective solubility properties	Impurities may co-precipitate, requiring further purification	Ideal for complex separations
Ion Exchange	Effective for APIs with ionic functional groups	Limited utility for neutral or non-ionic compounds	Superior for ionic compounds and functional group separations

Advantages of SMB Over Other Techniques

Flow Process: As a continuous flow process, SMB offers a smaller footprint, making it ideal for space-efficient operations. It is fully automated which reduces labor requirements, lowers operational costs, and enhances efficiency.

Sustainable: SMB strongly aligns with the green chemistry principles. Through the implementation of solvent recovery and reuse strategies, the process can generate significantly less waste. For example, SK pharmteco produced a large volume API for 20 years using large scale SMB and recycled consistently more than 99.9% of the mobile phase resulting in a PMI of less than 1 for the process while typical chiral resolutions are in the 10 to 40 range. In addition, adding the racemization of the undesired enantiomer via batch or a flow process further improves the process PMI, making this unit operation the lowest PMI in the industry. Finally, the long-term stability of chiral stationary phases (CSPs) minimizes material usage and waste, enhancing the process sustainability further.

High Recovery: Chromatography is a powerful separation technique affording very high recovery while maintaining high purity. It is typical to target a 48% recovery out of a maximum of 50% for a chiral separation. This can be further increased when racemization of the undesired enantiomer can be performed, augmenting the overall yield for each racemization cycle.

High Purity: SMB offers higher purity through binary separations, allowing for precise tuning of the process to meet specific separation needs. This high purity can be achieved even with separation with low selectivity without the need of a baseline separation at contrario to batch chromatography. Unfortunately, the higher the chiral purity target, the lower the productivity of the process to ensure robustness. However, chiral enhancement during downstream crystallization may help to relax the purity target at the SMB step allowing for a higher throughput.

Reduction in Waste and Raw Materials: Because of internal recycling, the process in itself is more concentrated and uses less solvent than batch chromatography. Typically, the SMB outlet streams are also associated with falling film evaporators (pilot and commercial scale) allowing for about 85-90% of the solvent to be recycled as eluent. The concentrated material can be further processed in large conical driers to remove the remaining solvent that can be recycled in the SMB process resulting in less than 0.1% solvent to be added to the process corresponding to a PMI of less than 0.2. In addition, potential racemization of the undesired enantiomer either in batch or in flow can further reduce the need for fresh feed, adding another positive contribution to the overall process PMI. SKPT has demonstrated several racemization processes in batch; such as a

simple stirring with a base to “flip” the chiral center, or a complex two-step chemistry to deconstruct and rebuild the chiral center. SKPT has also demonstrated the racemization of atropisomers in flow using PFR at 180°C and high pressure at kilo scale under CGMP.

Cost Benefits: SMB offers significant cost benefits. Solvent recovery reduces procurement and waste disposal expenses for long-term savings.

- High yield
- Potential for racemization
- Low labor via automation
- Simpler synthetic route
- No metal catalyst
- CSP can be used for many years (> 5)

Rapid Development: The development of chiral chromatographic separations typically requires 2 or 3 weeks of screening to identify the best set of separation conditions. At the end of the screening, loading studies are performed to obtain the liquid solid equilibrium data required to model the process. Once the model is defined, in-silico optimization using robust and well-established mathematical models allows for a rapid evaluation of the large-scale performance and the resulting manufacturing cost with a high level of confidence.

Demonstration at bench top scale (mini-SMB) in an additional 2-3 weeks provides confirmation of estimated parameters from modelling for accurate scale-up pricing and also provides access to both enantiomers for further downstream development.

Scalability: As said earlier, scale up of chromatographic process is simply based on the ratio of the columns cross section as long as column length, packing media, mobile phase composition and feed concentration are maintained. For example, a 50 g feed processed on the mini-SMB equipped with 8 columns of 10 mm diameter will correspond to 20 kg of feed processed on the SMB with 8 columns of 200 mm in diameter ((200/10)^2x50/1000). With a large selection of SMB units SK pharmteco is capable to scale-up rapidly the process from the benchtop SMB unit to any of the pilot or commercial scale units.

Figure 7: SMB Scale-up Capabilities at SK pharmteco – California Manufacturing Site

SK pharmteco's Value Proposition

As a recognized leader in Simulated Moving Bed (SMB) technology, SK pharmteco combines unmatched technical expertise with decades of experience. From early-stage development to commercial-scale production, we offer tailored solutions designed to meet the unique needs of every program.

Comprehensive Capabilities

We operate 7 SMB units, including the largest SMB unit (5 x 1000 mm) in North America. These are all located on a single site in California, enabling seamless scalability from gram-level R&D batches to multi-ton commercial production.

Expertise by the Numbers

- 25+ years of process development & commercial manufacturing expertise using SMB
- Developed 50+ processes & validated multiple APIs at a commercial scale
- In-house equipment building and automation expertise
- Produced 2,000+ MT of product using SMB technology over 20 years
- 4 commercial products validated at scale
- Over 30 API and intermediates produced at pilot scale using SMB for clinical trials
- 100+ chiral compounds screening and separated at bench top.

U.S.-Based Supplier

As the only U.S.-based CDMO offering CGMP-certified SMB separation from gram scale to ton scale, we provide unparalleled regional access and supply chain security for our customers.

Regulatory Excellence

Our validated API production processes and regulatory inspections demonstrate our commitment to quality and compliance.

Our team is available to evaluate your synthetic route, help simplify your supply chain, accelerate time-to-market, and serve as a reliable CDMO partner to help you achieve your goals.

Conclusion

SMB technology offers unmatched benefits in API purification, including high purity, high yield, high throughput, easy scalability to multi metric tons annually providing a cost efficient, and environmentally friendly solution for your manufacturing needs. While there are common misconceptions, advances in SMB and growing awareness of its versatility are driving adoption in the pharmaceutical industry.

Discover how SMB can revolutionize your purification needs. Contact us to discuss your project needs and learn how we can deliver unmatched excellence.

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