inke

Supercritical Fluid Chromatography (SFC) as a Next-Generation Platform for HPAPI Purification:

Enhancing Efficiency, Sustainability and Speed-to-Market

Knowledge Center



01
Abstract

Supercritical Fluid Chromatography (SFC) is emerging as a highly promising alternative and complementary technology to conventional liquid chromatography for the purification of Active Pharmaceutical Ingredients (APIs), including Highly Potent Active Pharmaceutical Ingredients (HPAPIs).

While traditionally underutilized at industrial scale, recent advances in instrumentation, process control and scale-up methodologies have positioned SFC as a powerful tool for both analytical characterization and preparative purification.

This paper presents the role of SFC within the evolving purification strategy at Inke Ophthalmics, highlighting its potential as a next step in downstream process optimization. Particular focus is given to its advantages in analytical resolution, preparative productivity, reduction of solvent consumption, waste minimization and enhancement of product quality.

Additionally, the paper explores the applicability of SFC in GMP high-containment environments, including its relevance for early-stage development of novel APIs where toxicological uncertainty and speed-to-market are critical factors. The integration of SFC within purification strategies demonstrates how sustainable technologies can simultaneously improve operational efficiency, reduce environmental impact and enhance overall business performance.

Keywords

HPAPI; Supercritical Fluid Chromatography (SFC); Downstream Processing; Green Chemistry; Preparative Chromatography; Process Optimization; Sustainability; GMP; High Containment; Early Drug Development; Scale-Up; Productivity

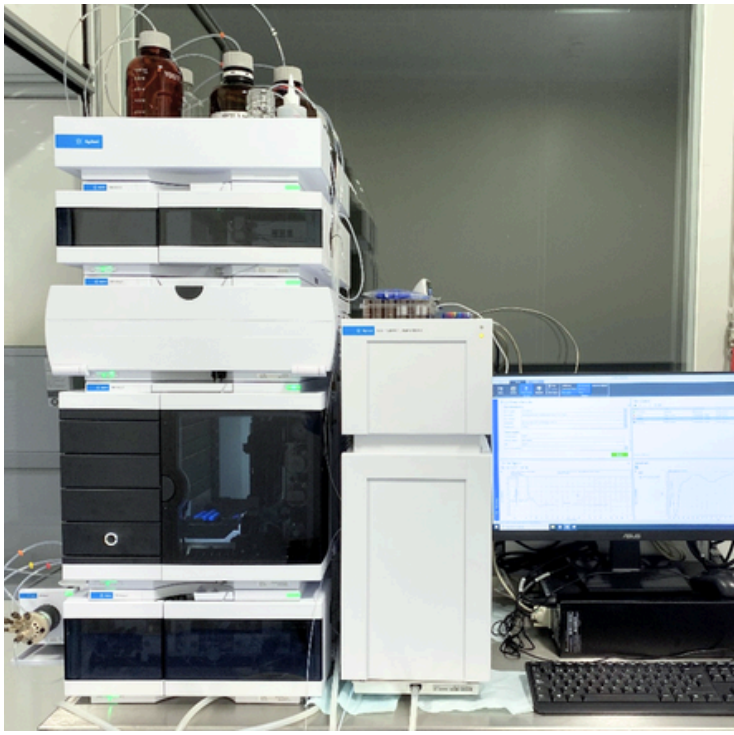
02
SFC as the Next Step in Chromatographic Evolution

In HPAPI manufacturing, the increasing complexity of molecules and the growing demand for higher purity levels are driving continuous innovation in downstream processing. While preparative HPLC and Flash chromatography have traditionally dominated purification strategies, these technologies often require large volumes of organic solvents, generate significant waste, and can impose operational and economic burdens, particularly in high-containment environments.

In this context, SFC emerges as a natural evolution of chromatographic technologies, offering a fundamentally different approach to purification. By using supercritical CO_2 as the primary mobile phase, SFC reduces reliance on organic solvents while enabling faster mass transfer and separation dynamics.

At Inke Ophthalmics, SFC is evaluated not as a replacement for existing technologies, but as a complementary and strategic extension of the purification toolbox, broadening the range of options available to address the specific requirements of complex and highly potent APIs.

A strategic extension of chromatographic purification capabilities.



Analytical SFC system at Inke Ophthalmics

When could SFC make a difference?

SFC can be particularly valuable when purification challenges involve:

- Chiral separations
- Complex impurity profiles and difficult separations
- Solvent-intensive purification processes
- Thermolabile compounds
- High-value natural products
- Limited material availability during early development

03
Analytical Advantages of SFC: Resolution, Selectivity and Speed

From an analytical perspective, SFC provides several key advantages over conventional liquid chromatography, particularly in terms of resolution, selectivity and analysis speed.

Enhanced Resolution and Selectivity

Supercritical fluids exhibit lower viscosity and higher diffusivity, enabling improved interaction kinetics between the analyte and the stationary phase. These properties can enhance chromatographic resolution and facilitate the separation of structurally similar impurities, isomers and closely related compounds.

This is particularly relevant for HPAPIs, where impurity profiles are often complex and minor structural differences can significantly influence biological activity.

Faster Analysis Time

The lower backpressure associated with SFC enables higher optimal flow rates and shorter run times without compromising resolution. This can support faster screening of chromatographic conditions and accelerate process development, allowing suitable separation strategies to be identified more efficiently.

Improved Method Development Efficiency

SFC can also improve method development efficiency by enabling rapid condition scouting, better discrimination between impurity families and greater flexibility in tuning separation parameters. Together, these capabilities provide a deeper understanding of impurity behavior within a shorter development timeframe.

SFC enables a deeper understanding of impurity behavior in a shorter timeframe.

04
Preparative SFC: A Step Change in Downstream Efficiency

While the analytical advantages of SFC are well established, its most transformative impact lies in preparative applications, where improvements in productivity, solvent consumption, waste generation and product quality can directly enhance downstream processing.

4.1 Increased Productivity

Preparative SFC enables higher throughput through faster cycle times and an increased number of injections per unit time, supporting more efficient use of chromatographic equipment. These advantages translate into higher productivity per system and shorter batch processing times, improving overall downstream efficiency.

4.2 Reduced Mobile Phase Consumption

One of the most significant advantages of preparative SFC is the reduction in organic solvent consumption. With CO_2 acting as the primary mobile phase, organic modifiers can be used in significantly lower quantities than in conventional liquid chromatography.

The resulting lower solvent evaporation volumes can also reduce thermal stress on the product during downstream processing. In addition, reduced reliance on organic solvents can lower the associated requirements and costs of solvent procurement, storage, handling, recovery and disposal, while simplifying the overall management of the chromatographic process.

4.3 Waste Reduction and Sustainability

The use of supercritical CO_2 can also contribute to a reduced environmental footprint by decreasing the generation of hazardous solvent waste and simplifying waste management. These benefits are aligned with green chemistry principles and increasingly stringent corporate and regulatory sustainability requirements.

SFC therefore not only improves process efficiency but also supports a more sustainable approach to pharmaceutical manufacturing.

4.4 Improved Product Quality

SFC can enhance final product quality by providing improved resolution between closely related impurities, reducing the risk of co-elution and enabling better control of impurity profiles.
This is particularly important in HPAPI manufacturing, where small changes in impurity levels can have significant toxicological implications, while regulatory and customer requirements continue to become increasingly stringent.

05
Integration into GMP High-Containment Environments

The application of SFC in high-containment GMP environments introduces both opportunities and specific operational considerations, particularly when handling highly potent compounds.

5.1 Compatibility with Containment Strategy

SFC systems can be integrated into existing containment strategies through closed-loop CO_2 systems, controlled injection and collection points, and reduced liquid handling compared with conventional liquid chromatography. Together, these characteristics can contribute to lower operator exposure and simplify certain handling steps within high-containment operations.

5.2 Reduction of Liquid Handling Risks

Compared with conventional liquid chromatography, SFC requires lower volumes of liquid solvents and generates reduced liquid waste streams. This can be particularly beneficial in HPAPI environments, where liquid handling may introduce secondary exposure risks and waste management can be both complex and costly.

5.3 Operational Considerations

Safe and efficient implementation of SFC requires appropriate equipment design, operator training and integration with existing GMP workflows. These requirements must be considered when introducing the technology into a high-containment manufacturing environment.

However, the associated investment can be balanced by increased productivity, reduced operating costs and improved environmental performance, supporting both operational efficiency and more sustainable downstream processing.

Integrating efficiency with high-containment requirements.

06
Application in Early Development: Speed and Flexibility

One of the most promising applications of SFC lies in the early-stage development of new APIs, where limited material availability, evolving toxicological knowledge and the need for rapid development require flexible and efficient purification strategies.

6.1 Managing Toxicological Uncertainty

During early development phases, toxicological data may still be incomplete and compound potency may not yet be fully characterized. In this context, SFC can provide an efficient approach to analytical and purification activities, helping to shorten development and purification timelines while reducing the extent of material handling required.

6.2 Accelerating go-to-market

Speed is a critical factor in early development. SFC can enable faster analytical development, rapid transition to preparative conditions and shorter overall development cycles, helping accelerate progression toward clinical development and, ultimately, supporting shorter time-to-market.

6.3 Economic Benefits in Development Phases

SFC can also contribute to lower material consumption, reduced development costs and a lower waste-management burden. These advantages are particularly valuable when working with limited quantities of new compounds or conducting iterative development cycles, where efficient use of both material and time becomes especially important.



07
SFC as Part of a Hybrid Purification Strategy

At Inke Ophthalmics, SFC is not considered an isolated technology, but rather part of an integrated purification strategy alongside preparative HPLC, Flash chromatography and hybrid purification approaches.

This combination enables the most appropriate purification technique to be selected for each stage of the process, providing flexibility to adapt the strategy to specific compound characteristics while supporting the continuous optimization of downstream processing.

By extending the design space of chromatographic purification, SFC can enable solutions beyond those accessible with conventional liquid chromatography alone.



Preparative SFC capabilities at Inke Ophthalmics

08
Continuous Optimization and Future Potential

The integration of SFC reflects a broader philosophy of continuous improvement in HPAPI purification. Future opportunities include increasing scale-up capabilities, integrating SFC with continuous processing, further reducing environmental impact and expanding its applicability across a broader range of compound classes.

In this context, SFC represents not only a technological advancement, but also a step toward more sustainable, efficient and adaptable downstream manufacturing systems.

09
Conclusions

The evaluation and implementation of Supercritical Fluid Chromatography at Inke Ophthalmics demonstrates its potential as a versatile technology for HPAPI purification, with relevant advantages across both analytical and preparative applications.

By combining higher productivity with reduced solvent consumption and waste generation, SFC can contribute to more efficient and sustainable downstream processing while supporting improved separation performance and impurity control. Its speed and flexibility also make it particularly suitable for early-stage development, while its integration into high-containment GMP environments expands its potential across different stages of pharmaceutical development and manufacturing.

Ultimately, SFC should not be viewed as a niche technology, but as a strategic enabler for next-generation purification processes, supporting faster, more sustainable and economically efficient pharmaceutical development.

A strategic enabler for faster, more sustainable and efficient pharmaceutical development.



About the Author



Gastón Estruch

Site Director Inke Ophthalmics

As Site Director at Inke Ophthalmics, Gastón Estruch oversees multidisciplinary operations spanning R&D, production, quality and engineering, supporting the development and manufacturing activities of the site.

Advancing Complex API Purification

Inke Ophthalmics combines expertise in highly potent APIs with advanced chromatographic purification capabilities, including preparative HPLC and SFC from development to commercial scale. Our approach integrates high-containment manufacturing, process development and purification technologies to address the specific requirements of complex APIs. Facing a difficult API purification challenge? Let's explore the right purification approach. Talk to our team

Scan the QR code to learn more.

inke

Inke is a pharmaceutical company specialized in the development and manufacturing of complex APIs, with extensive expertise in highly potent and micronized compounds. From its GMP manufacturing sites in Spain, Inke combines advanced process technologies, high-containment capabilities and strong regulatory expertise to support pharmaceutical partners worldwide across respiratory, CNS, ophthalmic and other specialty therapeutic areas.