Flash SFC with Bare Silica: Bridging Traditional Flash and Preparative SFC Workflows

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Abstract

Traditional normal phase (NP) purification on silica and reversed phase (RP) purification on C18 remain central to preparative workflows across industrial, government, and academic laboratories. While preparative supercritical fluid chromatography (SFC) has been widely adopted for chiral separations, broader use for achiral purification has progressed more slowly despite clear advantages in throughput, reduced solvent use, simplified fraction dry-down, and improved sustainability.

A persistent barrier to routine achiral SFC is the perceived complexity of method development, including the need to screen multiple bonded stationary phases and co-solvent/additive combinations. In this work, we revisit bare silica as a familiar, versatile stationary phase for achiral CO_2-based separations, positioning it as a practical bridge between established NP/RP workflows and modern SFC approaches. Bare silica can be used with and without acidic or basic modifiers, enabling selectivity tuning while retaining a workflow that is conceptually aligned with silica-based purification practices already common in many labs.

We pose two questions relevant to today's preparative landscape: (1) Can silica-based CO_2 separations reduce reliance on alkane-rich NP methods and chlorinated solvents such as dichloromethane under increasing regulatory pressure? (2) Can CO_2-based purification more frequently complement or substitute RP methods that depend on large volumes of water and acetonitrile, both of which contribute to extended dry-down time and energy use?

Finally, we discuss how silica-based SFC workflows can be extended across a continuum of operating scales and column formats, including single-use, prepacked silica cartridges commonly used for rapid purification, enabling familiar 'load-run-collect' operation in what we describe as Flash SFC—a workflow that combines the simplicity of flash chromatography with the speed and sustainability benefits of CO_2-based separations. This perspective highlights bare silica as a unifying stationary phase that can lower adoption barriers and broaden the role of SFC within modern preparative chromatography workflows.

Background

Traditional normal-phase (NP) flash chromatography and preparative HPLC commonly utilize silica-based stationary phases with solvent systems such as heptane/ethyl acetate and related organic solvent mixtures. While these approaches are widely used and highly effective, method development often requires optimization of solvent composition, additives, and gradient conditions. Efforts have also been made to reduce reliance on chlorinated solvents and replace them with greener alternatives [1,5]. Reverse-phase (RP) flash chromatography and preparative HPLC typically employ water/acetonitrile or water/alcohol mobile phases on C18 stationary phases. Method development is often simplified through the availability of analytical RP-HPLC instrumentation; however, removal of aqueous mobile phase components after purification can significantly increase processing time and drying requirements. Preparative SFC offers an alternative purification approach capable of reducing organic solvent consumption, minimizing dry down burden, and providing rapid separations. Despite these advantages, broader adoption of achiral SFC has been limited by the perception that method development requires specialized expertise and analytical SFC instrumentation. To simplify method development, Teledyne LABS purification platforms utilize a scout- and focused-gradient workflow in which a low-loading scouting experiment performed directly on the preparative instrument is used to automatically generate optimized purification conditions through the Focused Gradient Generator algorithm [2].

Previous studies have investigated the relationship between TLC retention behavior and SFC selectivity, demonstrating that while useful trends may sometimes be observed, direct extrapolation from TLC to SFC is not universally reliable and can be highly dependent on analyte class, stationary phase, and modifier conditions [3,4]. Similar challenges can be encountered when attempting to predict SFC behavior from RP-HPLC data. Because bare silica stationary phases are widely used in normal-phase flash chromatography and are also highly effective for many achiral SFC separations, they provide a unique opportunity to establish a common chromatographic platform across multiple purification modalities [7, 8]. Flash SFC was developed to combine the workflow simplicity of flash chromatography with the selectivity and solvent advantages of preparative SFC. Previous work demonstrated flash-scale SFC purification and alternative sample-loading approaches for pharmaceutical medicinal chemistry applications [3]. The examples presented here explore how silica-based stationary phases can bridge traditional flash chromatography, Flash SFC, and preparative SFC workflows while simplifying the transition between these purification approaches.

Experimental

A variety of pharmaceuticals, natural products, steroids, and other small molecules were evaluated using traditional flash chromatography, analytical SFC, preparative SFC, and Flash SFC workflows. Silica-based separations were performed using Redi*Sep* Gold® Silica columns and cartridges to evaluate the utility of bare silica as a common stationary phase across these purification approaches. Method development was performed using either analytical SFC instrumentation or a scout-and-focused-gradient workflow directly on Teledyne LABS ACC*QPrep*® SFC and Combi*Flash*® SFC systems. For scout-based development, a low-loading gradient screening run was performed directly on the preparative instrument and used to generate optimized purification conditions through the Focused Gradient Generator algorithm [2]. Preparative SFC experiments were conducted on an ACC*QPrep* SFC system, while Flash SFC evaluations were performed on a Combi*Flash* SFC system. Both approaches utilized CO_2 with alcohol modifiers on silica stationary phases.

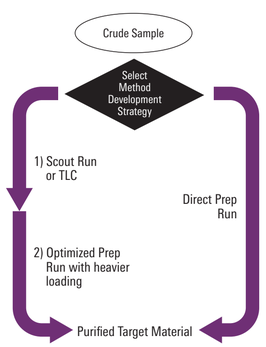
Traditional flash chromatography experiments were performed using a Combi*Flash* NextGen system equipped with Redi*Sep* Gold Silica cartridges and standard load-run-collect workflows. Traditional preparative HPLC runs were conducted on an ACC*QPrep* HP150 instrument. Representative examples were selected to compare purification strategies across multiple compound classes and evaluate whether bare silica can serve as a practical bridge between traditional flash chromatography, preparative HPLC, preparative SFC, and Flash SFC workflows.

Introduction to Teledyne CombiFlash® SFC

Flash SFC combines the ease of flash chromatography with the unique selectivity and solvent advantages of supercritical fluid chromatography

Standardized and Optimized Purification Workflows for Flash and Flash SFC

PeakTrak™ Focus Gradient Generator



Optimized Method Development Workflow

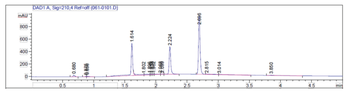
TLC	Scout Gradient	
	Analytical	PeakTrak FGG
Screen stationary phase & mobile phase systems, & determine isocratic conditions	Expert, custom screening & method development	Run Scout on Analytical or Flash System

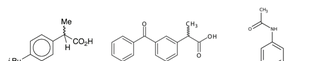
"One-shot" Direct Purification with broad, standardized gradients

NP Flash	SFC
0-100% Hex/EA or 0-30% DCM/MeOH	0-70% CO_2/co-solvent (e.g. MeOH

Both traditional flash chromatography and Flash SFC can be performed using broad-gradient "one-shot" purification workflows or optimized scouting-based method development workflows, with PeakTrak Focused Gradient Generator enabling rapid gradient refinement from scout data. TLC to SFC screening and method development relationships are still being investigated.

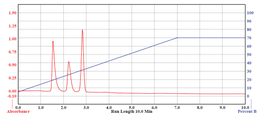
Analytical SFC to Flash SFC Examples with Several Drug Molecules



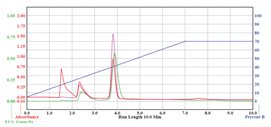


Analytical SFC run on a 4.6 x 150 mm Redi*Sep* Prep Silica column, 5 µm, 5-40% CO_2/MeOH from 0-3 minutes @ 5 mL/min, 100 bar, 40 °C: ibuprofen, ketoprofen, acetaminophen mixture (listed by elution order)

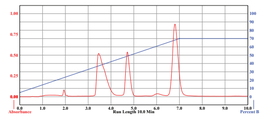
- Both profens require acetic acid with n-hexane/ethyl acetate for NP Flash chromatography (not shown)
- Phenolic hydrogen also acidic on acetaminophen



Flash SFC run on a 12 g, Redi*Sep* Gold Silica column, 5-70% CO_2/MeOH from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in MeOH: ibuprofen, ketoprofen, cetaminophen mixture (listed by elution order)

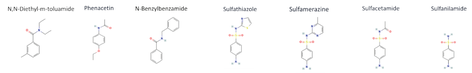


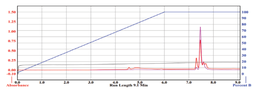
Flash SFC run on a 12 g, 19.5 mm x 50 mm, 20 µm Redi*Sep* Gold Silica column, 5-70% CO_2/IPA from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in IPA: ibuprofen, ketoprofen, acetaminophen mixture (listed by elution order)



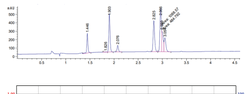
Flash SFC run on a 12 g, Redi*Sep* Gold Silica column, 5-70% CO_2/IPA from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, solid load cartridge: ibuprofen, ketoprofen, acetaminophen mixture (listed by elution order)

Comparison of NP HPLC, Analytical SFC, and Flash SFC for Seven Bioactive Molecules

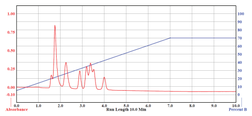




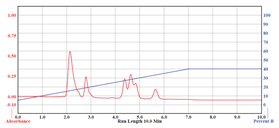
NP HPLC run on a 20 mm x 150 mm, 5 µm Redi*Sep* Prep Silica column, 0-100% hexane/ethyl acetate from 0-6 minutes @ 18.9 mL/min: ibuprofen, ketoprofen, acetaminophen mixture (listed by elution order)



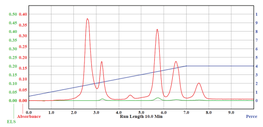
Analytical SFC run on a 4.6 x 150 mm Redi*Sep* Prep Silica column, 5 µm, 5-40% CO_2/MeOH from 0-3 minutes @ 5 mL/min, 100 bar, 40 °C



Flash SFC run on a 12 g, Redi*Sep* Gold Silica column, 5-70% CO_2 /MeOH from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in MeOH



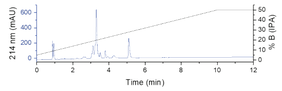
Flash SFC run on a 12 g, Redi*Sep* Gold Silica column, 5-40% CO_2 /MeOH from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in MeOH



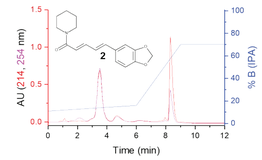
Flash SFC run on a 12 g, Redi*Sep* Gold Silica column, 5-40% CO_2 /IPA from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in IPA

SFC and a Natural Product Extract

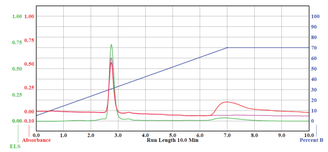
- Piperine is a naturally occurring alkaloid molecule from black pepper.
- Has been shown to have various therapeutic effects and continues to be studied.
- A focused gradient was calculated and the compound purified on preparative SFC.
- This result was obtained from a cosolvent screen. Methanol was evaluated first but did not provide sufficient selectivity.



Analytical SFC chromatogram of piperine extract with 2-propanol on silica



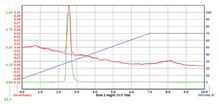
Preparative SFC focused-gradient purification of piperine extract using 2-propanol on silica



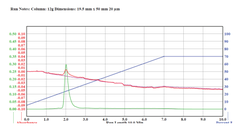
Flash SFC run on a 12 g, Redi*Sep* Gold Silica column, 5-70% CO_2 /IPA from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in IPA

Flash SFC and Steroids

- Steroids are commonly run with dichloromethane in flash chromatography
- Cholesterol is easily run on SFC and silica with ELSD detection
- 2-propanol was the eluting solvent—no DCM needed!

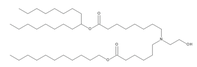


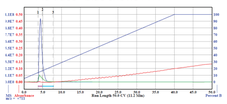
- Stigmasterol is a phytosterol
- It also runs on SFC and silica with no dichloromethane needed
- Again, the eluting solvent was 2-propanol and it is easily detected with ELSD



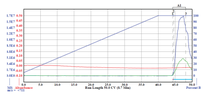
Comparison of NP Flash, RP Flash, Flash SFC, and Prep SFC for SM-102 Using Alternative Stationary Phases

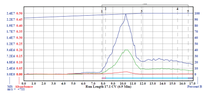
- SM-102 is a synthetic amino lipid that forms nanoparticles in conjunction with other compounds
- SM-102 forms part of the delivery system for some mRNA vaccines including some COVID vaccines
- Tested it via NP flash chromatography
  - DCM/methanol on an amine column
  - Impurity co-elutes (ELSD trace-green)
  - MS trace- blue shows M+H



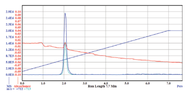


- SM-102 is commonly run on reverse phase; this is on a 5.5 g Redi*Sep* Gold C18 20 µm column with water/acetonitrile with 0.1% formic acid.
- 2 mg sample loading on scout run; 10 mg on focus run.
- With no chromophores, SM-102 requires ELSD or MS for detection
- Sample elutes from reverse phase with poor peak shape.

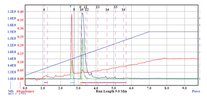




Flash SFC run on a 15.5 g Redi*Sep* Gold Amine column, 5-70% CO_2/MeOH from 0-7 minutes @ 50 mL/min, 40 °C, 100 bar, liquid loading in MeOH



- Silica screened along with other 5 µm SFC columns and alcohols
- Redi*Sep* Prep SFC Diamine similar to the amine column used for flash chromatography
- Ethanol used as a co-solvent
- Good peak shape in scout run
- Well resolved from impurity
- No additive required



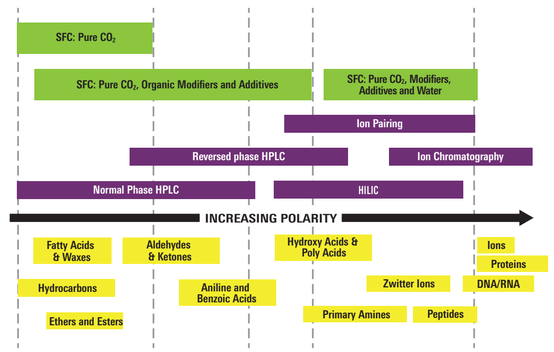
Results and Discussion

- Representative pharmaceuticals, bioactive compounds, steroids, natural products, and lipids were successfully evaluated using flash chromatography, Flash SFC, preparative HPLC, and preparative SFC workflows.
- Bare silica served as a common stationary phase across traditional NP flash chromatography, NP HPLC, Flash SFC, and preparative SFC workflows, enabling comparison of chromatographic behavior across purification modalities.
- Clear differences in retention behavior, elution order, and peak spacing were observed when transitioning from conventional flash solvent systems to CO_2-based SFC mobile phases.
- Flash SFC provided complementary selectivity while maintaining a familiar load-run-collect purification workflow.
- Scout- and focused-gradient workflows enabled method development directly on preparative instrumentation, reducing the need for dedicated analytical SFC method development.
- Flash SFC can reduce reliance on chlorinated solvents, decrease organic solvent consumption and drying burden, and expand the available preparative separation space.

Conclusion

The examples presented in this study demonstrate that bare silica can serve as a common stationary phase across traditional flash chromatography, Flash SFC, and preparative SFC. Although the stationary phase remained constant, substantial differences in retention behavior, elution order, and resolution were frequently observed when transitioning from conventional flash solvent systems to CO_2-based mobile phases. Flash SFC therefore provides access to complementary chromatographic selectivity while preserving a familiar purification workflow.

SFC can Access Much of the Chemical Space Addressed by LC



[9]

References

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[2] Silver J. Overview of Analytical-to-Preparative Liquid Chromatography Method Development. *ACS Comb Sci.* **2019** Sep 9; *21* (9):609-613.

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[5] Xiao, H.; Silver, J. Supercritical Fluid Chromatography (SFC) replaces chlorinated solvents for Chinese Traditional Medicine compound purification! Poster presentation at the American Society for Pharmacognosy conference in Grand Rapids, MI, August 2025.

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[7] Ashraf-Khorassani, M.; Taylor, L.T.; Seest, E. Screening strategies for achiral supercritical fluid chromatography employing hydrophilic interaction liquid chromatography-like parameters. *Journal of Chromatography A, 1229* **(2012)** 237–248.

[8] Taylor, L.T.; Ashraf-Khorassani, M. Bare Silica Has a Future in Supercritical Fluid Chromatography, *LCGC Europe* **(July 1, 2010)** *23* (7), 352-357.

[9] Chart from the SFC primer written by Terry Berger-https://www.agilent.com/cs/library/primers/public/5991-5509EN.pdf]

ACS Fall Sept 2026