ACS Green Chemistry Institute
Pharmaceutical Roundtable

2019 ACS GCI Pharmaceutical Roundtable Research Grant
Proposal to Determine the Potential Scope and Environmental Impact of Analytical and Preparative-Scale Supercritical Fluid Chromatography Processes

The ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) is seeking to fund a 12-month R&D collaboration to support the goal of the roundtable's analytical chemistry initiative to clearly define sustainable chromatographic analytical and purification methodologies applied across the pharmaceutical industry. GCIPR has developed an analytical method greenness score (AMGS) calculator which is shared among the roundtable companies.[1] In the process, we have identified a critical gap in the metrics knowledge base in the literature with respect to the various forms of CO_2 used in applications ranging from small scale analytical to larger scale preparative and QC-based processes. As a result, the lack of current information about the properties of pressurized CO_2-based mobile phases (referred to as supercritical in industry) that contain organic modifiers and occasionally an acidic or basic additive impedes the accurate determination of the overall greenness of these phases. This includes safety during handling, the post-extraction atmospheric release, and the energy demands of recycling/recovery or ventilation. Without this experimental data, it is difficult to provide appropriate guidance to the pharmaceutical industry for the selection and assessment of the most applicable green and sustainable methods with respect to the use of CO_2. To address this, we are seeking proposals that outline a combination of statistical, experimental and theoretical approaches (including the research of peer-reviewed literature data) for establishing unequivocal environmental, health and safety (EHS) benefits and cumulative energy demand (CED) coefficients for pressurized CO_2 used for supercritical fluid chromatography (SFC) as well as in supercritical fluid extraction (SFE) processes. A life cycle analysis (LCA) of pressurized carbon dioxide is needed, including how it is sourced, the cost of infrastructure for early boundary expansion[2], as well as the use of pressurized CO_2-organic mixtures for analytical and preparative SFC applications in future pharmaceutical research up to and including its potential use in manufacturing. Additionally, the team hopes to provide a more comprehensive assessment of the environmental impact and safety risks for scale up considerations. These include commonly used acidic and basic solvent modifiers often added to the pressurized CO_2 mobile phases as well as any background processes that support the delivery of CO_2 during operations. Since SFC is a widely used method of choice for chiral separations and the use of derivatizing agents and/or protecting groups are often used to enhance chiral separation capability, an evaluation of the environmental efficiency of these steps in the synthetic protocol would be useful.

Proposals are invited from public and private institutions of higher education worldwide. This collaborative project is intended for an individual within the selected Principal Investigator's research group with knowledge of and experience with pressurized CO_2 and SFC applications. One grant will be awarded to support execution of research for a period of 12 months. Deadline for receipt of proposals is **July 1, 2019** at 5 p.m. EDT (GMT- 4). Proposals must be received by the deadline to be considered. Submissions must be a single PDF file submitted to gcipr@acs.org. GCIPR will notify the PI of the selected proposal in **August 2019.** We expect research to commence in the principal investigator's lab upon transfer of funds (**expected by October 1, 2019**) and last approximately 12 months.

Requirements for Submission:

Proposals will only be accepted from public and private institutions of higher education worldwide. Proposals must be submitted to gcipr@acs.org through the appropriate institutional office for external funding. For international submissions with no comparable office, submit a PDF file of a letter signed by an appropriate university official recognizing the terms of the grant.

Detailed Project Description:

The past decade has witnessed the inception of Green Analytical Chemistry[3,4] with the subsequent formalization of the 12 principles of Green Analytical Chemistry[5] to mirror those previously established in both the Green Chemistry and Green Chemical Engineering space[6]. To parallel this initiative, the GCIPR recently created an Analytical sub-team comprised of members from nine different pharmaceutical roundtable companies. This sub-team is tasked with not only the evaluation of emerging greener analytical technologies, but also with benchmarking and comparing various established analytical methodologies associated with commonly used analytical instrumentation. Since analysis and purification activities play a vital role in the drug lifecycle, solvent usage and waste generation, especially for scale-up activities, is a major concern. Despite a steady increase in recognition of the importance of greener and more sustainable methods[6], there is still a tendency within the analytical chemistry community to prioritize chromatographic integrity (e.g. resolution, accuracy and robustness), over environmental impact when it comes to selecting a suitable separation method. This trend appears to be gradually shifting towards greener methods as industry-wide pressure is being applied to challenge pharmaceutical companies to commit to and invest in more sustainable processes. While this is promising, the focus herein has been on the development of greener analytical methods specifically using more sustainable raw materials, such as the utilization of greener solvents as a mobile phase[7,8] rather than an all-encompassing benchmarking of the established analytical technique itself. In a recent attempt to address this, Plotka-Wasylka reported on the Green Analytical Procedure Index (GAPI), which provides a visual approach for the comparison of analytical techniques[9]. Despite this being a valuable advancement towards green analytical chemistry, the evaluation of the various aspects of each technique is only semi-quantitative, with further refinement being achieved through a "penalty-based" system incorporating known literature risks associated with the reagents being utilized. The use of CO_2 as a mobile phase was not considered for this assessment. It is, therefore, the goal of the analytical GCIPR sub-team to provide the pharmaceutical industry with a comprehensive and quantitative assessment of EHS parameters across a range of analytical methodologies including SFC so that they can be considered in the method selection process in addition to chromatographic parameters.

Supercritical fluid chromatography continues to grow steadily as the separations technique of choice for chiral applications in many analytical laboratories due to the use of pressurized CO_2 as the main component of the mobile phase.[10] When mixed with an organic solvent, the resultant lower viscosity translates to higher flow rates and thus faster separations relative to HPLC. In addition, CO_2 itself has reduced toxicity and contributes little to waste generation relative to commonly used normal phase organic solvents.[11] Despite these advantages, there is still an on-going debate within the literature amongst experts in the field as to whether SFC is a "green" technique[12], and why this technology has not yet been more globally adopted as a "greener" methodology. In order to address some of these debated questions, the life cycle analysis (LCA) of CO_2 obtained from various sources and waste streams should be considered. Commercial CO_2 used by the pharmaceutical industry could be retrieved from one of these sources: 1) as a byproduct of ammonia production; 2) as a byproduct of the hydrogen refinery process; and 3) from natural underground reservoirs. Carbon dioxide is initially retrieved in gaseous form and then converted to liquid for commercial use[13]. To fully assess the greenness of pressurized CO_2 used in analytical processes, identification of the specific source of CO_2 obtained by most pharmaceutical companies is required to determine the full environmental impact of CO_2 production, including costs associated with infrastructure changes for liquification of CO_2. Likewise, pressurized CO_2-based waste streams from analytical processes must be included and quantitatively compared to those containing water and organic solvents. While CO_2 from these processes is most likely amongst the most recoverable material when compared to water and organic solvents, the energy required to recycle post-separation CO_2 should be considered and compared to a non-recycled approach. Our goal is to provide a more definitive measure of greenness for pressurized CO_2 used in different analytical processes but primarily for SFC.

Driving change in analytical method development approaches towards greener methods necessitates the ability to determine specific coefficients for various EHS factors as well as the CED for the various solvents and additives used in chromatography applications. The EHS and CED values for many pharmaceutically-relevant solvents used in this tool can be found in the literature[14,15]. Additionally, the acid and base selection guide published by GSK in 2014 includes EHS and green chemistry scores for a list of acids and bases that are used in Medicinal Chemistry, as well as those that are generally recognized as safe (GRAS) by the US Food and Drug Administration (FDA). (16) While this guide may help provide more sustainable alternatives for chemistry applications, it is not an all-inclusive list and thus not all commonly used acidic and basic chromatography additives are addressed. While dilution of some acids in mobile phases may only produce negligible changes in overall greenness scores, a discussion of other factors for choosing a greener acid and/or base such as potential waste disposal issues will be useful.

Using a custom green and sustainable science calculator, such as the one developed by members of the GCIPR[1], EHS and CED values are then applied and a quantitative "greenness" score is assigned to a specific chromatographic technique and method used to analyze a compound. These scores are then used to benchmark the different techniques to enable users to make a judicious selection of the appropriate and greener analytical technique for a specific separation. However, the greenness calculator tool is limited in its ability to accurately quantify the greenness score for CO_2, much less pressurized CO_2 applications, and thus hinders "like-for-like" comparison with other chromatographic techniques such as reverse phase and normal phase HPLC and UHPLC, as well as their associated methods. Due to these current limitations, the values for CO_2 in SFC methods are currently approximated to those of either hexanes (based on its non-polar nature), or even water (due to its low toxicity). Comparing the bulk properties of water and hexanes (as well as looking at the various available solvent guides) quickly demonstrates that this is an unreasonable assumption to make (17). In these applications CO_2, which is considered supercritical when pressurization reaches a critical temperature and pressure, is commonly paired with an organic solvent modifier such as an alcohol. Beyond this critical point, the composition of the CO_2-based mobile phase will be one phase, while below it, it will exist as two phases. The physicochemical properties of the one-phase and two-phase mixtures are different, due to differences in density and viscosity, for example[13]. However, there is still debate about the actual state of CO_2 (subcritical vs. supercritical) within the working zone at which most SFC instruments operate and should thus be considered. Compression of the CO_2-based solvent requires additional equipment and background processes such as CO_2 delivery system (e.g. bulk, dewar, tank), chiller, and a purifier, all of which contribute to the overall CED for the system. The energy required to pressurize the mobile phase at supercritical vs. subcritical states needs to be compared. Therefore, LCA studies of the different states of CO_2 during the analysis should be performed. The source of CO_2 and typical infrastructure data as available should be included in the life cycle assessment.

To summarize, the proposed, multifaceted research plan is to investigate the EHS benefits and determine the CED coefficients for supercritical fluid chromatography (pressurized CO_2) with respect to its use during drug discovery and manufacturing. Subsequently, these values will then be integrated into the new AMGS calculator, enabling SFC to be quantitatively compared with reverse phase, normal phase, and even ultra high-performance chromatography (UHPLC). The need to provide an improved metric for these modifiers (CO_2, acids, and bases) has, to date, been unexplored and results could be expanded and applied to those using SFE and large manufacturing-scale preparative separations. LCA studies to determine the environmental impact of the different states of CO_2 during analytical and preparative SFC should be performed, considering the source of CO_2, the composition of the CO_2-based mobile phase, waste stream (renewable), and the energy requirements relating to CO_2 delivery and pressurization.

<u>Project Goal:</u>

Through a combination of literature research and experimental measurements the environmental, health and safety (EHS) benefits will be evaluated and the cumulative energy demand (CED) coefficients for supercritical fluid chromatography (supercritical CO_2) and related processes (e.g. derivatization) will be determined; the environmental impact of pressurized CO_2-organic mixtures used during analytical and preparative SFC will be assessed; the amount of waste generated between pressurized CO_2 processes, reverse phase, normal phase, and UHPLC will be quantitatively compared; and the energy requirements of other upstream processes relating to CO_2 delivery will be evaluated. Finally, the corresponding EHS and CED values will then be integrated into the custom greenness calculator for an accurate assessment of the greenness of pressurized CO_2 processes including SFC.

<u>Project Timeline:</u>

It is expected that 12 months of research support will be sufficient to enable completion of the specified project.

<u>Proposal Format:</u>

A maximum of 6 pages, as described below, plus CVs is requested. All information below must be submitted as a single PDF file. All components described in sections A, B, and C must be included in the same PDF file to assure the proposal is reviewed in its entirety.

A) Title Page (1 page, 12 pt font, 1-inch margins)

1. Project Title
2. Principal Investigator
3. Title / Position(s)
4. Telephone Number(s)
5. Fax Number(s)
6. Postal Mailing Address
7. E-Mail Address
8. Research Group website

B) Proposed Plan of Work *(5 pages, 12 pt font, 1-inch margins)*

1. Abstract: Summary statement of how the proposed work meets the overall criteria for the determination of the environmental, health and safety (EHS) benefits and cumulative energy demand (CED) coefficients for pressurized CO_2 used in SFC and related processes (e.g. SFE, etc.) during drug discovery and manufacturing; quantitative comparison of the greenness of SFC relative to reverse phase, normal phase, or even ultra-high performance chromatography (UHPLC) using a custom calculator tool; LCA studies to determine the environmental impact of the different states of CO_2 during analytical and preparative SFC while factoring in the source of CO_2, the composition of the CO_2-based mobile phase, waste stream (renewable), and the energy requirements relating to CO_2 delivery and pressurization (500 words or less).
2. Background: Provide a brief assessment of the proposed project in the context of the current state of knowledge (limit to 1 page or less).
3. Objectives: Briefly state the project objectives.
4. Project Approach: Include specific aims, investigations planned and preliminary results.
5. References
6. Project Timeline
7. Estimated Budget: Please provide a budget for this work.
   a. Overhead should be restricted to ≤ 10% of the total budget.
   b. Funding would start in **October 2019**, or as agreed between the Principal Investigator and the Roundtable.
   c. Post-doctoral associate salary and benefits are supported.
   d. Graduate student stipend and benefits are supported. Proposals for support of advanced graduate students are highly favored.
   e. PI salary supplements will not be supported.
   f. Laboratory supplies and instrument use charges are supported.
   g. No funds may be allocated for travel, equipment purchase or repair, or administrative support.

8. Current funding list for the PI including title of grant award, agency, award amount and duration – limit to 1 page or less.
9. Brief facilities description for the PI – limit to one page or less.
10. Listing of any existing background intellectual property and/or collaborations that might limit the freedom to operate any of the results arising from any research funded by ACS GCI.

C) Curriculum Vitae of Project Team Members: Please submit a two-page curriculum vitae of all project team members. (Does not count toward your page limit.)

Report Requirements:

- As a collaborative research project, the Roundtable will work with the principal investigator(s) to assay progress and provide industrial direction, when appropriate, in a manner that respects the independence of the researcher/student.
    - Teleconferences with Roundtable members will be held monthly to discuss project status, provide suggestions and feedback pertaining status of the project.
    - A written progress update will be due 12 months from initiation of research to enable the GCIPR to ascertain whether additional funding may be required for a project extension.

- A final comprehensive report including research outcomes and final budget is due one month after the end of the grant period.
    - The report must be submitted as a PDF document to gcipr@acs.org. The report will be shared with the member companies of the Roundtable.
    - The results contained within the report will be utilized for publication in a peer review technical journal within six months of the conclusion of the research. As a collaborative research project, the portion of the manuscript pertaining to this project will be written by the principal investigator and student(s) performing the work, with the Roundtable as co-authors.

Intellectual Property, Publication Acknowledgement, and Terms of the Grant:

- The primary purpose of this grant is to publish research to make information publicly available.
- Every patent, United States or foreign, that results from research funded (in part or in its entirety) by the ACS GCI PR Research Grant shall be immediately dedicated to the public, royalty free.
- Each publication prepared in connection with an ACS GCIPR Grant shall make acknowledgement in the following manner: "This manuscript was developed with the support of the ACS GCIPR (https://www.acsgcipr.org). The ACS GCI is a not-for-profit organization whose mission is to catalyze and enable the implementation of green and sustainable chemistry throughout the global chemistry enterprise. The ACS GCI Pharmaceutical Roundtable is composed of pharmaceutical and biotechnology companies and was established to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its member's shared belief that the pursuit of green chemistry and engineering is imperative for business and environmental sustainability."
- Acceptance of an ACS GCIPR Research Grant will be conditioned upon agreement by the grantee institution that in the event the principal investigator is unable for any reason to conduct the research

proposed, the funds, if previously paid by the Roundtable, shall, upon demand, be returned in full to the Roundtable, and further, that in the event the PI is unable for any reason to continue with the research after it has commenced, this grant shall be terminated forthwith and the unexpended and unencumbered balance of any funds theretofore advanced shall be returned to the Roundtable.

- The grantee institution, by acceptance of this grant, provides assurance that support normally provided by the institution for research of the faculty member will not be diminished.
- Applicants may have only one research grant with the ACS GCIPR at a time. In order to close a grant, the ACS GCIPR must receive and approve the required reports.

For additional information:
Website: https://www.acsgcipr.org
Email: gcipr@acs.org

References

1) *Green Chem.*, **2019**, DOI: 10.1039/C8GC03875A.
2) *J. Chem. Technol. Biotechnol.*, **2007**, *82*, 1023–1038.
3) *Trends in Analytical Chem.*, **2008**, *27*, 497.
4) *Chem. Rev.*, **2007**, *107*, 2695.
5) *Trends in Analytical Chem.*, **2013**, *50*, 78.
6) *Green Chem.*, **2008**, *10*, 268.
7) *ACS Sustainable Chem. Eng.*, **2017**, *5*, 5618.
8) *Molecules*, **2018**, *23*, 1065.
9) *Talanta*, **2018**, *181*, 204.
10) *J. Chrom. A.*, **2017**, *27*, 76.
11) *Am. Pharm. Rev.,* **2017**, https://www.americanpharmaceuticalreview.com/Featured-Articles/335411-Supercritical-Fluid-Chromatography-An-Essential-Tool-in-Drug-Discovery/
12) *Analytical Scientist*, **2013**, https://theanalyticalscientist.com/techniques-tools/greening-sfc
13) The Application of Green Solvents in Separation Processes, Ch 7 - Supercritical Fluids and Gas-Expanded Liquids, 2017, 155-214.
14) *Green Chem.*, **2014**, *16*, 3045.
15) *Green Chem.*, **2007**, *9*, 927.
16) *Green Chem.*, **2015**, *17*, 945.
17) *Sustainable Chemical Processes*, **2016**, https://doi.org/10.1186/s40508-016-0051-z.