2022 ACS GCI Pharmaceutical Roundtable Research Grant to Investigate Utilization of GC for Separation of Higher Molecular Weight Compounds to Reduce Solvent Waste

The ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) is a partnership between the ACS Green Chemistry Institute® and pharmaceutical-related corporations united by a shared commitment to integrate the principles of green chemistry and engineering into the business of drug discovery and production. Current members are AbbVie, Amgen, AstraZeneca, Bayer, Biogen, Biohaven Pharmaceuticals, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Gilead, GlaxoSmithKline, Ipsen, Johnson & Johnson, Merck & Co., Neurocrine, Novartis, Novo Nordisk, Pfizer, Takeda, UCB Pharma, Vertex, and the ACS Green Chemistry Institute. Associate members are Ampac Fine Chemicals, Asymchem, Bachem, CatSci, Codexis, Hikal, Hovione, InnoSyn, Kaneka, Novasep, Pharmaron, Polypeptide, Porton, Sai Life Sciences, Solara Active Pharma Sciences Ltd., and WuXi AppTec. Corteva Agriscience, EnzyTag, and PHT International Inc. are affiliate members.

The ACS GCIPR is seeking a one-year R&D commitment to assist the Roundtable's Analytical Chemistry focus team. The focus of the R&D will be toward investigating the sustainability of a range of chromatographic analytical and purification methodologies commonly applied in the pharmaceutical industry. Proposals are invited from public and private institutions of higher education worldwide. This project is intended for a student within the selected Principal Investigator's research group. One grant is planned to be awarded, and the total award is limited to $50,000 for a grant period of 12 months. Interested PIs are required to provide a written proposal describing the investigator's capability to carry out the Roundtable's proposed research. The deadline for receipt of proposals is **May 15, 2022, at 5 p.m. EDT**. 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 selected PI by **September 6, 2022**. It is expected that research will commence in the Principal Investigator's lab no later than **October 3, 2022,** and last approximately 12 months.

Requirements for Submission

Proposals will be accepted from public and private institutions of higher education. The grant is not limited to institutions in the United States. Proposals must be submitted through the appropriate institutional office for external funding. For international submissions, if there is no comparable office, submit a PDF 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 (1, 2) with the subsequent formalization of the 12 principles of Green Analytical Chemistry (3) to mirror those previously established in both the Green Chemistry and Green Chemical Engineering space (4). To parallel this initiative, the GCIPR has established an Analytical sub-team tasked with not only the evaluation of emergent greener analytical technologies, but also to benchmark and compare various established analytical methodologies associated with commonly employed analytical instrumentation.

Gas Chromatography (GC) is a powerful analytical tool used for the analysis of pharmaceutical raw materials, residual solvents, and other low molecular compounds. Higher molecular range compounds are generally thought not to be compatible with GC because of a perceived current maximum operating temperature of GC columns of ca. 320°C. However, more recent developments in stationary phase technology (e.g., Phenomenex Zebron Inferno (5), Agilent 'ht' line of columns (6) etc.) have increased the maximum operating temperature of GC columns to ~400°C. Combining these new columns with carrier-gas-flow-programming and judicious selection of carrier gas potentially broadens the application space of GC analysis to compounds of much higher molecular weight (see Figure 1 for an example GC analysis of reserpine, MW 608).

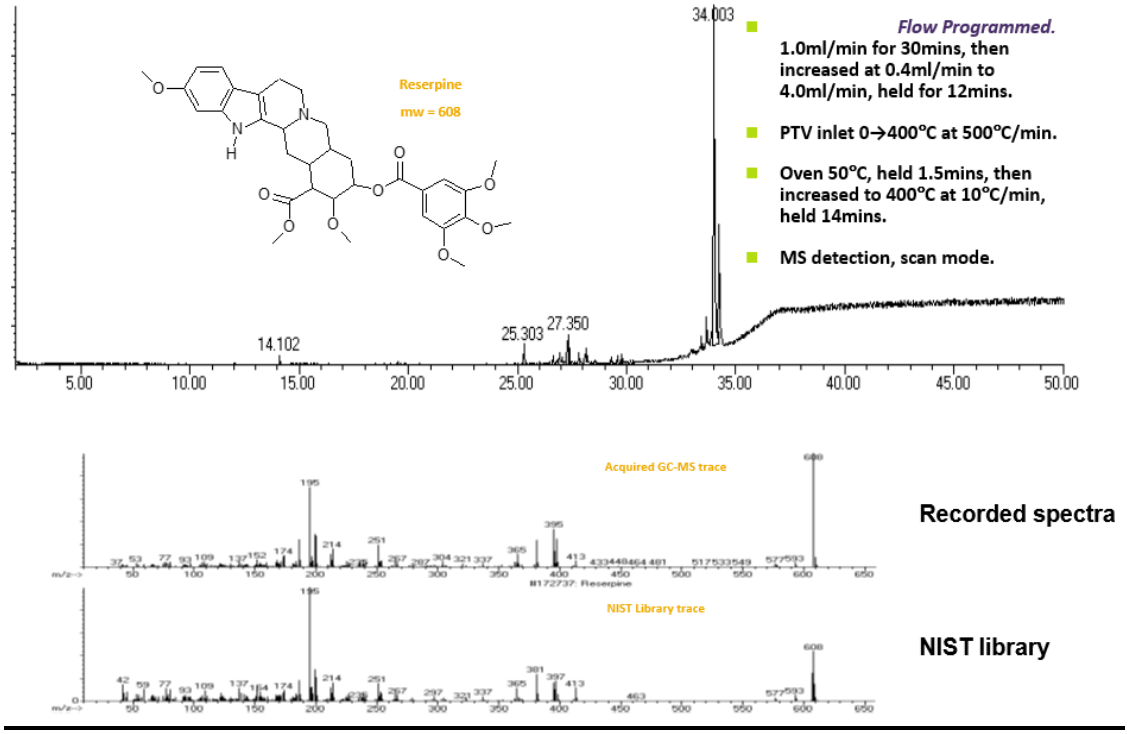

Figure 1. Analysis of reserpine using high temperature GC (Phenomenex Zebron Inferno 5-HT column), Helium carrier gas.

Currently the primary technique for analysis of higher molecular weight compounds is reversed phase liquid chromatography (RPLC). However, limitations of sample or eluent matrix combined with the choice of detectors means RPLC is not always the best approach for an analysis. Additionally, RPLC utilizes significantly higher volumes of organic solvent (which also requires disposal) and often has long analysis times compared to GC (potentially implying higher energy usage and CO_2 production per analysis).

High temperature GC could be seen as a superior technique to Liquid Chromatography (LC) for a number of reasons.

- It is a highly efficient separation technique and can give superior peak shapes compared to LC for some molecule types.
- Method development is often simpler in GC than LC with less variables to optimize - which is favourable in terms of number of experiments required and waste.
- LC primarily uses UV detection which requires the compound to have a chromophore. GC is compatible with a wide range of robust, quantitative and sensitive detectors (it is suggested that only FID and/or MS be used in this work programme).
- Uses significantly less organic solvent than LC (solvents are typically only used in GC during sample preparation).
- By replacing the commonly used (and unsustainable) helium carrier gas with either nitrogen or hydrogen, GC becomes a much greener separation technique than LC.

The focus of the proposed research is four-fold:

- Understand the application range of nitrogen and hydrogen (*not* helium) as carrier gas on chromatographic peak capacity (value inherently encompasses an assessment of peak shape) and analysis time for pharmaceutical compounds.
- Determine the upper molecular weight range for pharmaceutical compounds analyzable with modern high-temperature GC columns (which may include the use of flow/pressure programming to elute higher MW analytes).
- Identify approaches to minimize on-column degradation of analytes under these higher temperature conditions (e.g., use of cool-on-column (CoC) or programmed temperature vaporization (PTV) inlet techniques, minimization of on-column residence times through use of smaller i.d./column lengths etc).
- A critical assessment of the benefits of using GC over liquid chromatography (LC – most likely UHPLC) for the same compounds (e.g., through a quantitative assessment if solvent use, average analysis time, instrument energy consumption, CO_2 production per analysis etc). This data may be used in the next iteration of the AMGS calculator (7, 8).

Successful delivery of this research program would provide an alternative avenue for analyzing a broader range of compounds and lead to less reliance on traditional LC-based approaches. This would have a significant impact on reducing organic solvent use and waste for analysis of a wide range of pharmaceutically relevant compounds.

References

1) *Trends in Analytical Chem.* **2008**, *27*, 497.
2) *Chem. Rev*. **2007**, *107*, 2695.
3) *TrAC*. **2013**, *50*, 78.
4) *Green Chem*. **2008**, *10*, 268.
5) https://www.phenomenex.com/Info/Page/gchightemptip
6) https://www.agilent.com/cs/library/eseminars/Public/High%20Temperature%20GC%20Analysis.pdf
7) *Green Chem*.,**2019**, *21*, 1816. https://doi.org/10.1039/C8GC03875A
8) https://www.acsgcipr.org/amgs/

Project Goal

Through a combination of literature research and experimental measurements, the goal of the project is to determine the application space of higher temperature GC for pharmaceutical compounds and generate a quantitative analysis of the benefits of this approach versus LC analysis.

Project Timeline

It is anticipated that one year of research support will be sufficient to provide progress toward intended goals.

Proposal Format (Maximum 3 pages as described below + CVs)

All of the 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. Email Address:
8. Research Group Website:

B) Proposed Plan of Work *(2 pages, 12 pt. font, 1-inch margins)*

1. Objectives: Briefly state the project objectives
2. Project Approach: Include specific aims and investigations planned
3. Proposed milestone deliveries with brief description of the manner in which the researcher intends to achieve them
4. Brief description of the PI's research facilities and summary of the student's (undergraduate, graduate student and /or postdoc) capabilities to perform the proposed work
5. References (does not count toward your page limit)

Note: The PI should list any existing background intellectual property and/or collaborations they are aware of that might limit the freedom to operate any of the results arising from any research funded by ACS GCIPR. The priority of the Roundtable is to encourage research utilizing reaction conditions that are commercially available with the freedom to use.

C) Detailed Estimated Budget: The total amount requested would include all direct costs, student assistantships, etc. The total award is limited to $50,000 for a grant period of up to 12 months. This does not count toward your page limit.

1. Institutional overhead costs (indirect costs) should not be more than 10% of the total budget.
2. Post-doctoral associate salary and benefits are supported.
3. Student stipend and benefits are supported. Proposals for support of advanced graduate students are highly favored.
4. PI salary supplements will not be supported.
5. Laboratory supplies and instrument use charges are supported.
6. No funds may be allocated for travel, equipment purchase or repair, or administrative support.

D) Curriculum Vitae of Project Team Members: Please submit a curriculum vitae of each project team member (up to two pages per team member). This does not count toward your page limit.

Report Requirements

- Progress reports or updates are due monthly or bi-monthly from initiation of research and will be discussed in arranged web-conferences. Reports will be shared with the member companies of the Roundtable.
- Reports are to include research milestones/significant outcomes, summary of progress to date noting any deviations from the proposal, and research plans for upcoming months.
- A final comprehensive report is due one month after the end of the grant period. This report must be submitted as a PDF document electronically to gcipr@acs.org. In addition, the content of the report should be targeted for publication in a peer-reviewed technical journal. The paper will be co-authored by the principal investigator and student(s) performing the work with the guidance of member companies of the ACS GCIPR.

Intellectual Property, Publication Acknowledgement, and Terms of the Grant

- The primary purpose of this grant is the public dissemination of research through publication.
- Every patent, United States or foreign, that results from research funded (in part or in its entirety) by the ACS GCIPR Research Grant shall be immediately dedicated to the public, royalty free.
- Publication of results is expected within 6 months of work completion.
- Each publication prepared in connection with the ACS GCIPR Research Grant shall make acknowledgement in the following manner: "This manuscript was developed with the support of the American Chemical Society Green Chemistry Institute

Pharmaceutical Roundtable (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, composed of pharmaceutical and related industries, was established in 2005 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 a Roundtable Grant will be conditional 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: www.acsgcipr.org
Email: gcipr@acs.org