Smart Decision Making in Pharmaceutical Development Leveraging Automated Platforms

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Introduction

Automation can benefit pharmaceutical development by enabling the accelerated assessment of the physico-chemical characteristics of investigational new drugs utilizing high-throughput screens. Two major advantages to automation are preventing scientific staff from performing repetitive labor intensive tasks and reducing the amount of compound required for testing. The automation group at GSK routinely performs solubility, stability, excipient compatibility and kinetic reaction screens to identify drug development challenges and supports smart, data-driven decision making with a wider range of experiments than could be achieved manually.

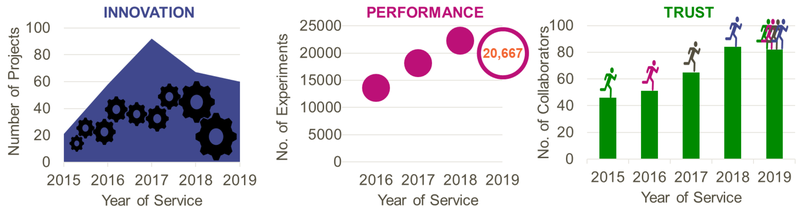

Figure 1. Automation supports projects across the portfolio as demonstrated through trends in innovation, performance and trust.

Instrumentation

The Unchained Labs Core Module 3 (CM3) is an automated platform that has both solid and liquid dispense capabilities combined with temperature controlled magnetic stir decks, all in one system. The integration of a miniaturized LC (Axcend FocusLC) with the CM3 is demonstrated to deliver efficiency in kinetic reaction screening.

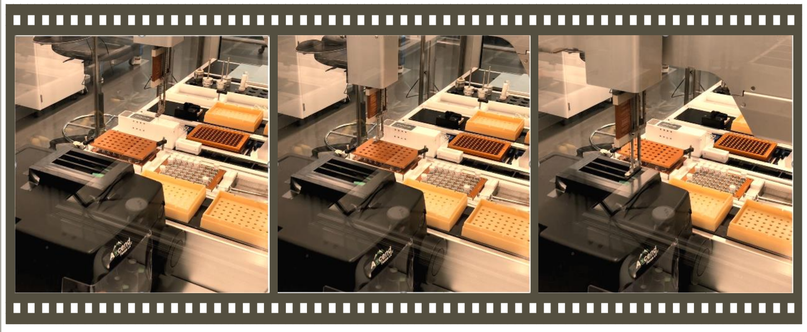

Figure 2. The extendable syringe needle on the CM3 robotic platform draws liquid from a plate and injects the sample onto the Axcend FocusLC.

LC performance evaluation

Peak capacity was determined for the reversed-phase separation of a 13-component mixture. A 5-95%B linear gradient, a range of gradient times (0.5-20 minutes) and several flow rates (1-3 µL) were evaluated on a system with a 40 nL sample loop, 10 cm x 150 µm capillary column packed with CoAnn 1.7 um C18 Particles, and an on-column absorbance detector at 255 nm.

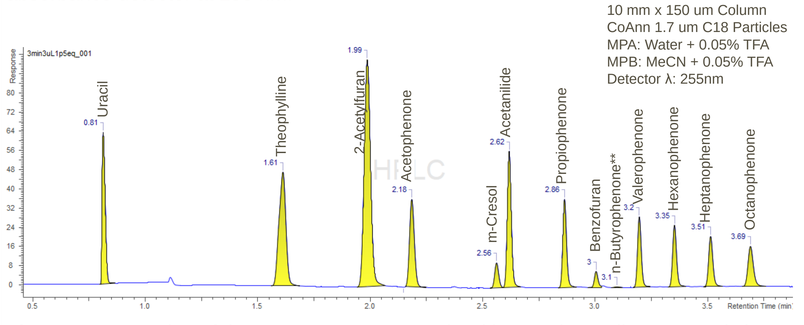

Figure 3. Separation of the 13-component test mix with a 3 min gradient at 3 µL/min.

Peak Capacity Results

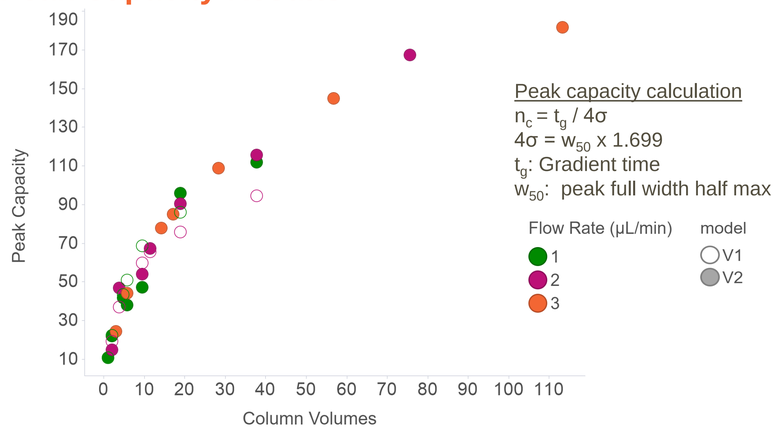

Figure 4. Experimental peak capacity in response to gradients of increasing column volumes exhibits the higher peak capacities achievable with the higher pressure limits available with the FocusLC V2.

Kinetic Reaction Screen

Method

In the Optimization Sampling Reactor (OSR) module of a CM3, six reaction vessels were charged with active pharmaceutical ingredient intermediate grade (API IG). The solvent composition, temperature, and stir rate of each vessel were programmed to model a specific step of the crystallization process. Each vessel was sampled 11 times over 24 hours. In total, 66 samples were collected and analyzed by HPLC (Agilent 1260).

Results

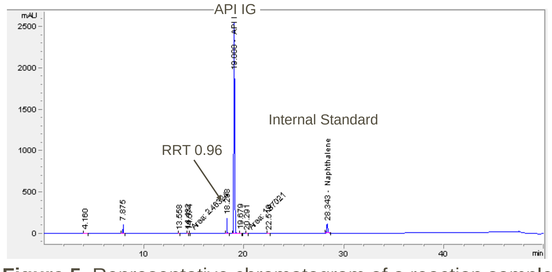

Figure 5. Representative chromatogram of a reaction sample from a 1260 HPLC.

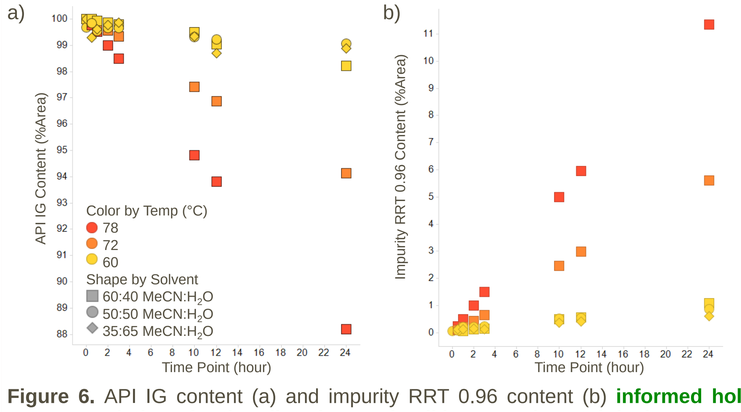

Figure 6. API IG content (a) and impurity RRT 0.96 content (b) **informed hold-time recommendations for the pilot plant and spiking experimental design.** Analyzing 66 samples with a 50 min HPLC method required 3300 minutes (or 138 hours) of instrument time. Operating the HPLC at 1 mL/min for 3300 minutes consumed 3.3 L solvent.

Integration of Miniature LC with Robotic Platform

Method

With the capability to operate at higher pressures (9000 psi), higher resolution separations are achievable in less time and consume less solvent with the implementation of capillary columns packed with sub-2 µm particles. The separation in Figure 5 was adapted for the FocusLC using chromatographic theory to maintain resolution while reducing other method parameters such as flow rate, gradient time and column dimensions. Samples from the kinetic reaction screen were analyzed by the FocusLC using the CM3 to inject the sample.

Results

- Linear range: 0.005 – 1.0 mg/mL (R^2 ≥0.999)
- $S/N_{peak\text{-}to\text{-}peak}$ > 8 for 0.005 mg/mL standard (2 pg on column)
- Retention time variability:
  ≤0.05 min standard deviation
  ≤0.8% RSD

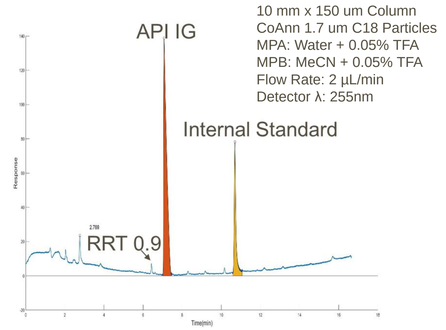

Figure 7. Representative chromatogram of kinetic reaction screen sample analyzed by the FocusLC. Anal 66 samples with a 17.7 min LC method required 1170 minutes (or 19.5 hours) of instrument time. Operating the LC at 2 µL/min for 1170 minutes consumed 2.3 mL solvent.

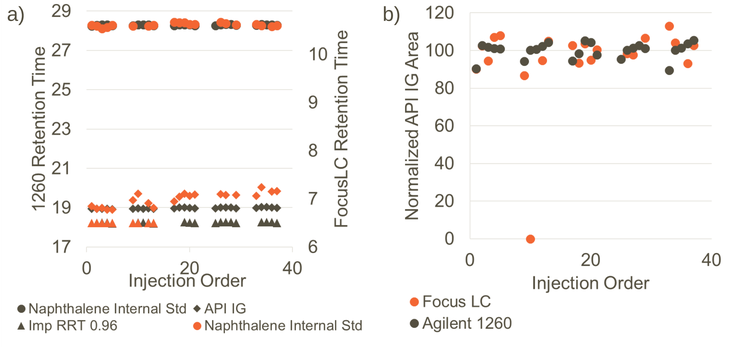

Figure 8. Retention time repeatability (a) and area response repeatability (b) were similar for separations on both the 1260 HPLC and FocusLC.

Conclusions

Automation Accelerates Data-Driven Decision Making in Pharmaceutical R&D

- Time saved completing tedious tasks
- Scientist freed to focus on the science
- Compound consumption minimized with plate-based assays
- Larger design space increased project knowledge earlier in development
- Integration of analytical equipment on automated platforms via a miniaturized LC reduced analysis time **3x** and mobile phase consumption **1400x**
- **More Data Earlier = Smarter Decisions**

Acknowledgements

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