Integrating automation and DOE to streamline and accelerate Quality by Design activities for process chemistry

Introduction

Getting drugs to market is hard! Modern drug development organizations face many business and environmental challenges. Billions of dollars are spent on new molecules or vaccine discoveries that can fail at any point in development, during the manufacturing process or in clinical trials. It is critical to design safe drug products and develop robust processes that minimize project risk as a candidate moves through development, out to the plant and into humans. In addition, in the eyes of the regulator, the application of Quality by Design (QbD) principals will soon become mandatory in drug submissions.

The International Conference on Harmonization (ICH) Tripartate guidelines for the implementation of QbD in the pharmaceutical industry (ICH Q8, Q9 and Q10) state:

- Products must be designed to meet patient safety and efficacy needs and performance requirements
- Processes must be designed to consistently meet product quality attributes
- The impact of starting raw materials and process parameters on product quality must be understood
- Critical sources of process variability must be identified and controlled
- The process is continually monitored and updated to allow for consistent quality over time and to have a stable process

How do you implement QbD with only the resources and capacity you have today?

Modern DOE offers a great tool for better characterizing products and processes. However, multiple response factors that need to be explored and non-linear responses often result in the need for experimentation that is beyond what a scientist can effectively manage or even complete. This results in informed guesswork rather than detailed knowledge about a product or process. The Big Kahuna and the Junior systems configured for reaction screening facilitate automated execution of complex experiment designs, including sample processing, reaction sampling and analytical work up – all in a plate-based screen with unattended operation. Hundreds of reaction conditions may be characterized per day, with very little material needed. In this way, the product and process knowledge space may be quickly defined. Scientists can study interactions that may not have previously been available due to time or material constraints.

Unchained Labs' tools translate complex experiments into executable methods

Scientists have a myriad of experimental design tools at their disposal. However, there is still an extra layer of translation needed to take the design from the DOE software package and convert it into an experimental script or method the automation can understand. The DOE import tool in Unchained Labs' Library Studio (part of the Lab Execution and Analysis (LEA) software) was designed to bridge that gap and provide an easy way for users to quickly generate Library Designs from the tabular data files output from their DOE software of choice. It accepts data in .CSV or .XLSX formats, so it is readily compatible with any software that can export into those formats. Today, scientists use Library Studio with Microsoft Excel, JMP, MODDE, Minitab

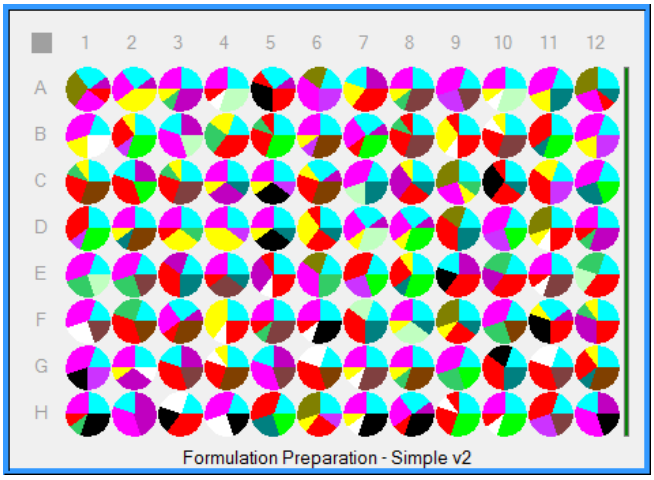


Figure 1: Library Studio 96-well plate based design. Each section of the pie chart represents a component of a formulation that is being tested.

and Design-Expert, making it easy for R&D labs using different DOE software packages to create and share information easily. Once the design has been imported into Library Studio, an intuitive and easy-to-use graphical user interface provides multiple options ranging from specifying materials, control parameters (such as temperature, pressure, pH, etc.) and order-of-addition. These recipes can be saved in an easy-to-read, easy-to-share format (Figure 1). Upon completion of the experiments and acquisition of analytical results, the design and responses may be exported from LEA in a format suitable for easy import into the user's DOE package. This automated formatting and reporting minimizes the risks of data corruption during transfer to the DOE software.

Filling in your design space

The Big Kahuna and Junior with Library Studio can have a dramatic effect on the size of the design space that a scientist can evaluate during development. As the Big Kahuna and Junior allow the number of factors that may be investigated per screen to be greatly magnified, scientists may now investigate the impact of many different raw materials and process parameters on product quality as is required by QbD.

A clear benefit to QbD and a wide design space is the regulatory cost savings post-approval. Changes within the design space don't require regulatory submission and approval. This means no FDA headaches and no delay. In short, the bigger the design space, the more likely it is that the compound will avoid the regulatory post-approval change process.

> The bigger the design space, the more likely the compound will avoid the regulatory post-approval change process. Combining DOE with Unchained Labs automation will lead to much wider knowledge of a product's design space, a better characterized process and thus a much better understood product.

Optimization Sampling Reactor for process monitoring and control

ICH guidelines require processes to be continually monitored and updated to allow for consistent quality over time and to have a stable process. The Optimization Sampling Reactor (OSR) designed for studying reactions over time is perfect for this purpose.

About the OSR

The OSR module itself is comprised of eight 40 mL overhead stirred reactors with working volumes ranging from 16–25 mL (Figure 2). Each reaction vessel is independently heated (up to 200 °C), cooled (down to –20 °C) and pressurized (ambient to 400 psi) to tightly controlled limits. This, coupled with tight process control, provides good inter– and intra–run repeatability. All results and process data are funneled down to the Renaissance Application Server (RAS), Unchained Labs' enterprise data solution. RAS allows scientists to view all experiment processing and analytical data together – from anywhere – for seamless

Figure 2: The OSR with controlled atmosphere sampling port technology.

knowledge sharing and efficient reporting of results.

Time-point quenching, workup and isolation for downstream analysis may be automated by the Big Kahuna and Junior platforms. Using the OSR, scientists may study reactions for as long or as short a time as needed while taking carefully managed time point samples from all reactions and preparing them for analysis. With time truly unlocked as a variable that can now be studied, scientists can widen their design and control spaces with no additional effort.

The OSR enables scientists to fully study the continuous variables of a reaction and study its kinetics in parallel. This is facilitated by the OSR's ability to automatically dispense and sample at pressure and temperature without risk of sample loss using the innovative controlled atmosphere sampling port technology. Samples are immediately quenched and worked up for analysis so the variability in results is minimized. The OSR is able to measure reaction progress by gas uptake with its ability to supply two process gas sources to each reactor (single quench gas source).

Coupling the Big Kahuna and the OSR with LEA software and modern DOE techniques supports an automated DOE approach to QbD implementation. With careful planning, hundreds of data points gathered may quickly turn into thousands of insightful data points. This approach allows for scientists to fully realize a QbD strategy while streamlining their experimental workflows and accelerating development:

- Plan experiment strategies that assess and ultimately manage true risk based on best science, not on time or material limitations
- Characterize hundreds of conditions per day, with minimal materials consumed – improving and documenting product and process knowledge
- Easily pull data back into the DOE package so that transfer functions are updated and refined in an ongoing process

An automated DOE approach to QbD implementation: hundreds of data points gathered may quickly turn into thousands of insightful data points.

Example of efficient study of reaction kinetics using the OSR

Understanding the kinetics of a reaction can be a critical part of a scale-up control strategy. In the following example, the ability of the OSR to track conversion and determine reaction endpoint was demonstrated with a well-documented reaction. *Trans*-cinnamic acid was hydrogenated in the presence of a 5% Pd catalyst on carbon in a solution of 2-methyltetrahydrofuran at 40 °C and hydrogen at 50 psi (Figure 3). The reaction was run for two hours, taking time point samples from each of the eight reactors every 24 minutes, for a total of 48 unique samples (six from each reactor). All samples were analyzed using HPLC.

The Library Studio design for this experiment is shown in Figure 4.

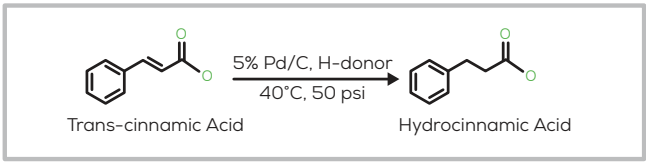
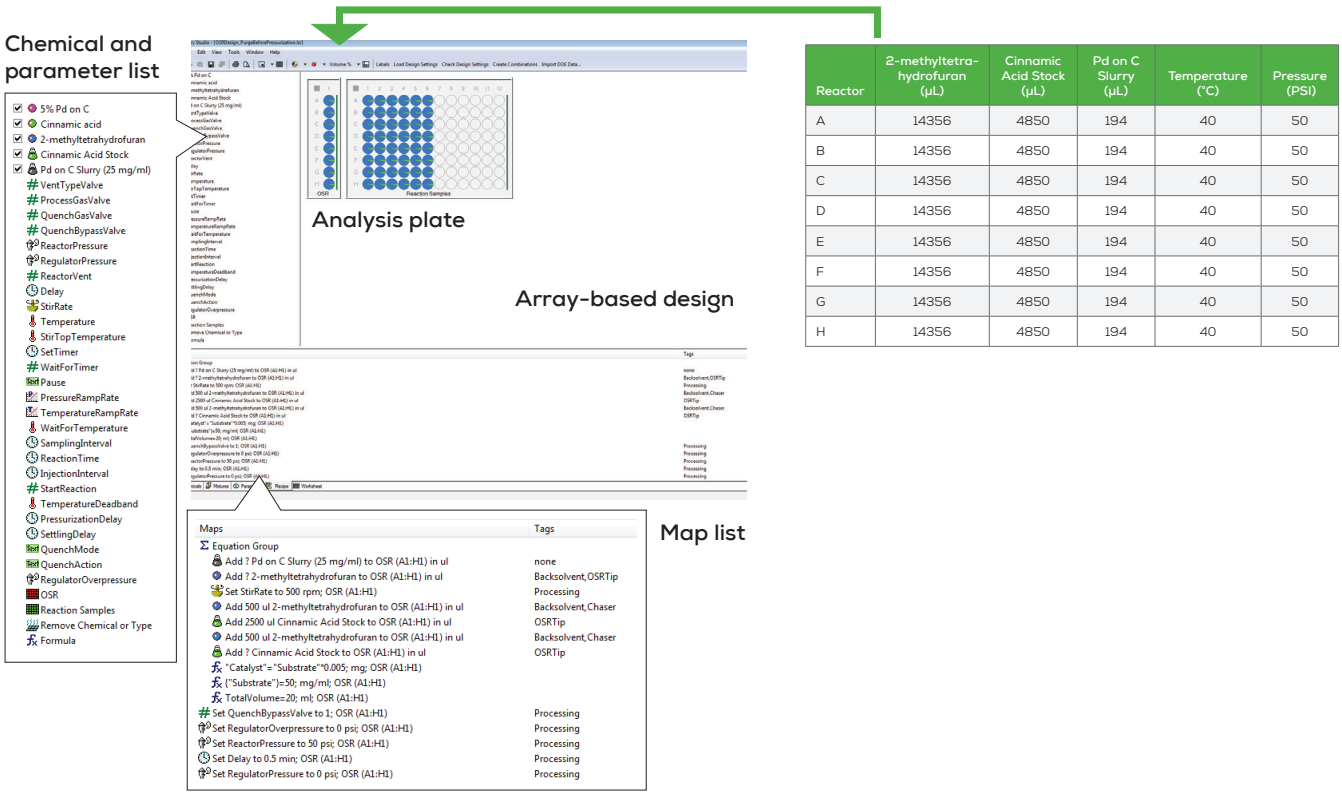


Figure 3: Hydrogenation of *Trans*-cinnamic acid.



Reactor	2-methyltetra-hydrofuran (µL)	Cinnamic Acid Stock (µL)	Pd on C Slurry (µL)	Temperature (°C)	Pressure (PSI)
A	14356	4850	194	40	50
B	14356	4850	194	40	50
C	14356	4850	194	40	50
D	14356	4850	194	40	50
E	14356	4850	194	40	50
F	14356	4850	194	40	50
G	14356	4850	194	40	50
H	14356	4850	194	40	50

Figure 4: Library Studio showing the design used for the hydrogenation of cinnamic acid OSR experiment.

Results

Under these experimental conditions, the reaction was completed in 96 minutes. At each time point taken, the % RSD conversion across all reactors showed a variation of less than 5%. The ability of the OSR to sample at elevated temperature and pressure during the experiment allowed the kinetic profiles to be identified efficiently (Figure 5).

Comparison to traditional methods

Using a traditional reactor would have required a scientist to setup 40 separate reactions (excluding T=0), quenching each at the desired time point. Thus, the total cumulative reaction time to gather the same volume of data points would be six days (it would take 18 hours to get just three replicates), assuming eight replicates were needed at each time point (Figure 6), and would require significantly more material than was consumed in this test. There would also be more room for human error and likely less consistency across the data set.

The comparison table below shows the actual materials and time required to repeat the same kinetic study of this reaction using the OSR, versus a traditional reactor, or a two-channel reactor (Table 1):

Using a traditional flask would have required the scientist to set up 40 separate reactions, quenching each at the desired time point and would have taken six working days.

In comparison, the automated approach with the OSR took only two hours to complete the study.

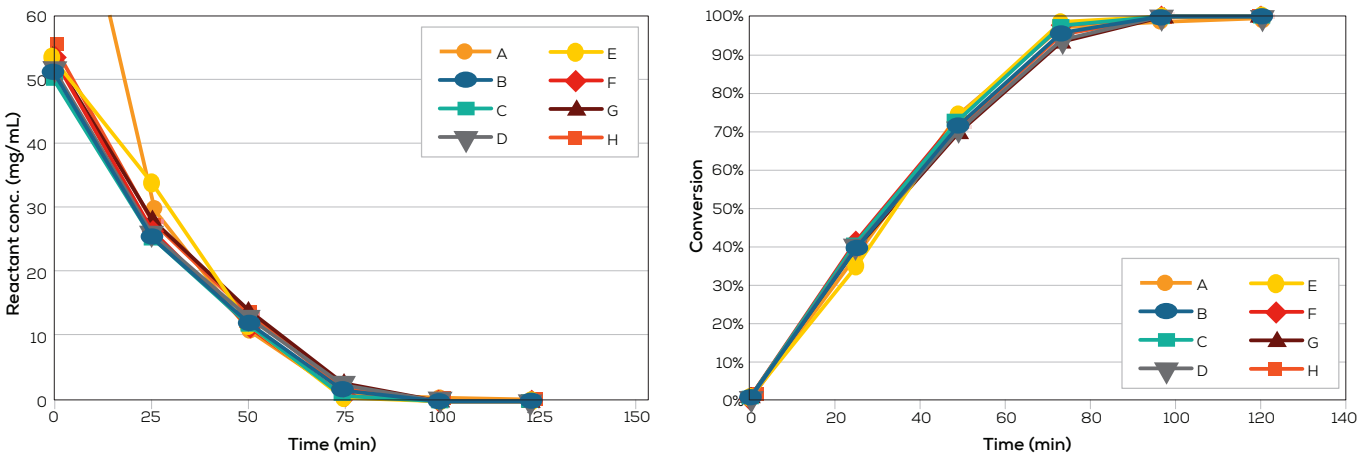


Figure 5: Graphs illustrate that the drop in reactant concentration and rise in percent conversion as the reaction progresses is very consistent, with the reaction completing at 96 minutes.

The traditional approach also requires the scientist to be in regular attendance for the six days of reaction time; it is simply a more labor-intensive process. Further, as the comparison table shows, 8 g of substrate (cinnamic acid) was consumed with the OSR approach versus 40 g for the traditional method. This is a significant material saving, particularly where proprietary, multi-step intermediates are concerned. In terms of time and materials consumed, building this kind of process and product knowledge with technology other than the OSR is prohibitively expensive.

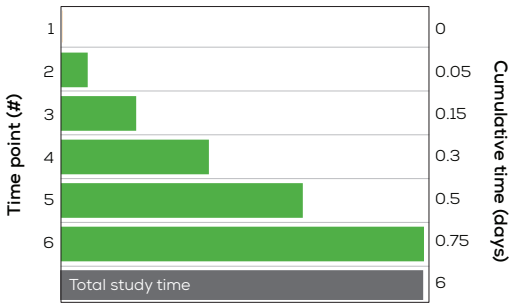


Figure 6: Cumulative time needed to get a single replicate at each of the six time points from a single reactor using traditional methods.

	Name	Role	Amount (mL)	Amount (mg)	Time (hrs)
OSR	2-methyltetra-hydrofuran	Solvent	153.6		2
	Cinnamic acid	Substrate		8000.0	
	5% Pd on C	Catalyst		40.0	
One-channel reactor (8 replicates)	2-methyltetra-hydrofuran	Solvent	767.8		48
	Cinnamic acid	Substrate		40000.0	
	5% Pd on C	Catalyst		200.0	
Two-channel reactor (8 replicates)	2-methyltetra-hydrofuran	Solvent	767.8		24
	Cinnamic acid	Substrate		40000.0	
	5% Pd on C	Catalyst		200.0	

Table 1: Consumption and time estimates for running the same study using comparable techniques.

		ICH Guidelines		
Unchained Labs' tool	**Activity**	**ICH Q8 (R2): pharmaceutical development-related activities**	**ICH Q9: quality risk management-related activities**	**ICH Q10: pharmaceutical quality system-related integrated activities**
Reaction screening system (Big Kahuna or Junior)	Process screening	Characterizing many combinations of reaction conditions and compositions to widen design space	Characterization results help determine failure modes	
		Characterizing process intermediates	Characterization results help determine risk factors for unit operations and rank risks	
Optimization Sample Reactor (OSR)	Process development and optimization (lab scale)	OSR with DOE to study critical process parameters and interactions with material attributes	OSR and automated DOE to characterize risk assessment to determine potential parameters impacting product quality	
		Test operational ranges of continuously variable parameters (e.g., temperature and pressure)	OSR reactors can help highlight potential issues of scale for example impurity generation	
		Implement studies to build understanding of critical process operations	Determine critical process steps, process parameters and product attributes (e.g., FMEA)	
LEA - Polyview	Reporting			Create batch report forms for records that feed operational guidelines for manufacturing
				Easily export data for detailed tech transfer reporting

Table 2: ICH guidelines that Unchained Labs' technology can impact.

Big impact on ICH activities

ICH guidelines Q8, Q9 and Q10 are designed to work together throughput the product life cycle, ensuring a robust process, where risks to product quality are managed. Unchained Labs' tools were designed by scientists, for scientists who need to rapidly build product understanding without having to burn through excessive time or money. Scientists can use these tools to build robust processes and products earlier in the development lifecycle and with more confidence. Table 2 shows how Unchained Labs' technology maps to process development activities within the framework of the ICH guidelines and accelerates each process.

Conclusion

Achieving robust processes and quality drug products as laid out in ICH guidelines Q8, Q9 and Q10 is critical. Unchained Labs' automation systems, in combination with LEA software, allow scientists to exploit automated DOE techniques to characterize hundreds of conditions per day under a wide variety of variables. Process parameters can be quickly defined and optimized using minimal amounts of materials. In addition, LEA software easily allows seamless integration of DOE and high-throughput automation. With a QbD strategy more fully realized, pharmaceutical labs can develop more robust processes that minimize project risk as a drug moves through development and out to the plant, and can do it with the same resources and capacity they have today.

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