Achieving Product and Process Understanding by Execution of Design of Experiments in a Quality by Design Approach in Developing a Generic Topical Product

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Introduction

The US Food and Drug Administration (FDA) has repeatedly asked pharmaceutical companies to include components of Quality by Design (QbD) in ANDA product filings during the development phase of product lifecycles. This case study demonstrates how incorporating QbD, a "*systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management*", can enhance product and process knowledge and enable sponsors to include statistical design of experiments (DoE) in process development. Specifically, this work describes how statistically designed experiments were utilized during development of a generic topical product. For generic pharmaceutical products, comprehensive or powerful DoE may not be feasible due to aggressive project timelines and lack of resources. However, using a risk and science based approach is feasible for many critical processes, enabling generic product development within the QbD paradigm.

SAS JMP was used as a tool to implement QbD in process development. An Ishikawa diagram was created and used as a starting point to take into account potential risks that would impact product quality, safety, purity, and efficacy. Potential critical quality attributes and process parameters were explored by different methods, including: prior product and process knowledge, Quality Risk Management, and DoE. A container-filling process DoE was planned and executed for process optimization and design space generation. This approach not only optimized the container-filling process, but also simplified technology transfer and accelerated product scale-up, therefore decreasing overall development time.

Software and Equipment

- JMP Version 8.0
- Mettler Toledo Analytical Balance
- IPN Container-Filling Machine

Experiment Design

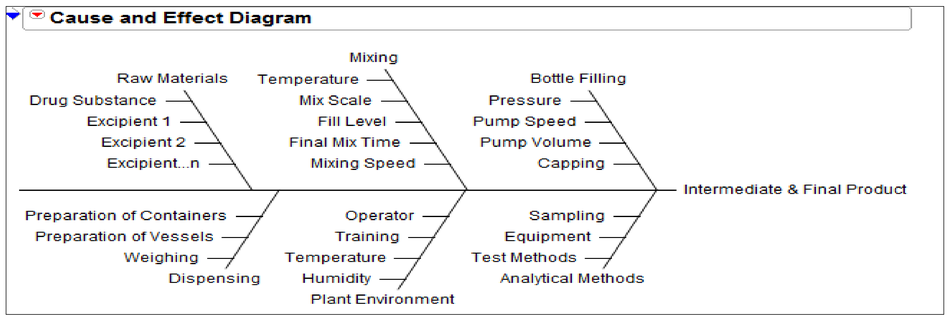
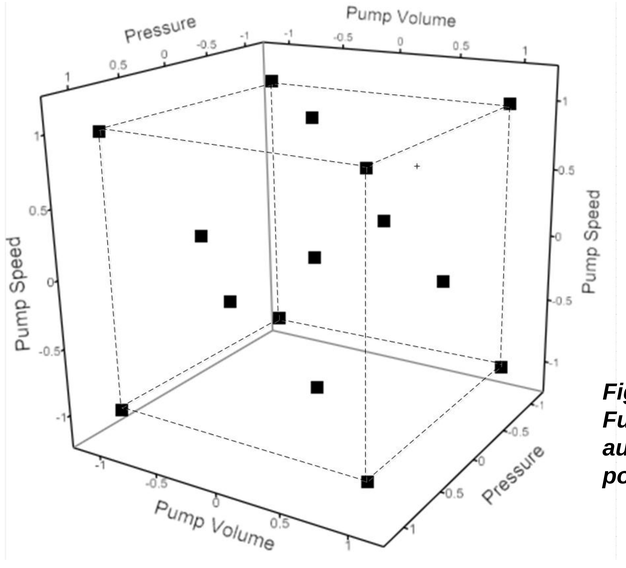


Figure 1. Ishikawa Diagram of Overall Manufacturing Process

Objectives	Prior Knowledge	Experiment Input Factors	Experiment Output Responses
• Understand main & interaction effects of inputs on outputs • Rank key CPPs • Create Design Space	• Equipment Train • Process Parameters	• Pump Volume • Pump Speed • Vessel Pressure	Container Fill Weight

Table 1. Experimental Design for Container-Filling Process



Experiment Design:

Power: 0.80
S/N: 1.0
α = 0.05

Figure 2 . Box Plot of DoE: FCC Full Factorial , all interactions, augmented to axial with 2 center points, yielding 16 runs.

Results & Discussion

The information gained was significant: all main effects are significant, no interaction effects significant; the design space (combinations of critical process parameters which will yield acceptable product) and knowledge space (ranges of critical process parameters which can yield acceptable product, representing the target ranges in which the process is controlled) were established. Using the prediction profiler, optimal process parameters were recommended. Process design verification was performed using the recommended settings via large trial runs and the exhibit batch to the FDA. The results the samples pulled from these manufacturing events confirmed the process parameter ranges.

Sorted Parameter Estimates

Term	Estimate	Std Error	t Ratio	Prob>|t|
Pump Volume(90,150)	19.298667	0.880555	21.92	<.0001*
Pressure (psi)(10,20)	10.879667	0.880555	12.36	<.0001*
Pump Speed (%)(20,40)	-9.526667	0.880555	-10.82	<.0001*
Pump Speed (%)*Pressure (psi)	-2.187083	1.017873	-2.15	0.0639
Pump Volume*Pump Speed (%)	-1.362083	1.017873	-1.34	0.2176
Pump Volume*Pressure (psi)	0.9820833	1.017873	0.96	0.3629

Figure 3. Main & Interaction Effects of Critical Process Parameters on Fill Volume

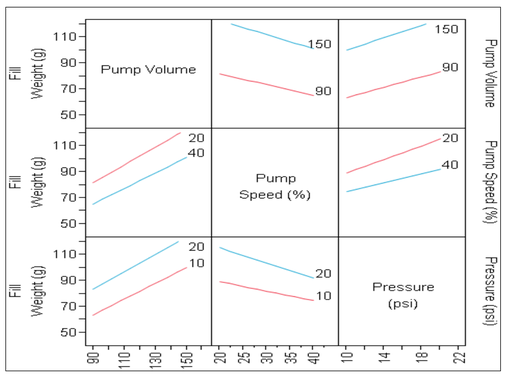


Figure 4. Main & Interaction Effects of CPPs on Fill Weight

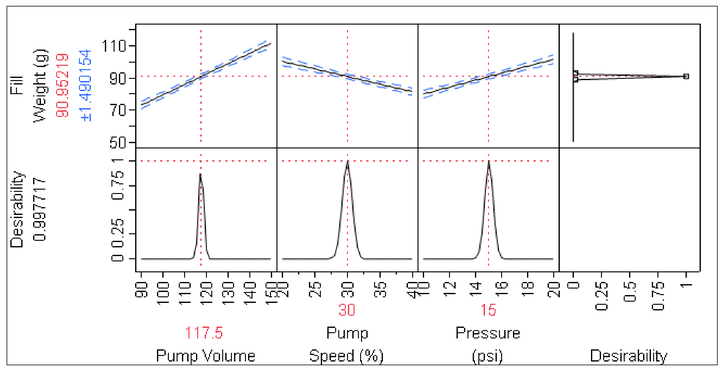


Figure 5. Prediction Profiler: Optimization of Container-Filling Process

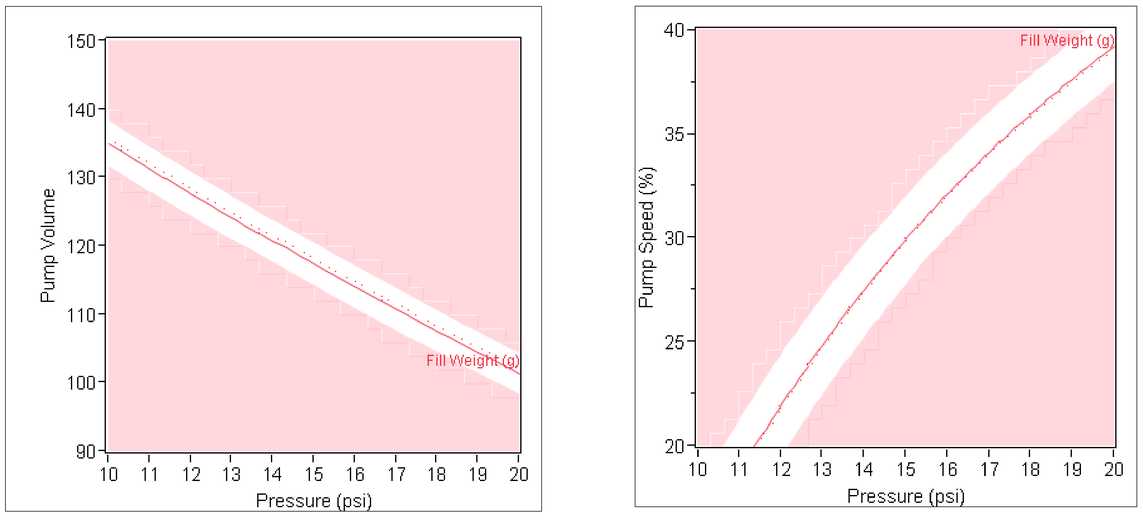


Figure 6. Design Space: Container-Filling Process

Conclusion

The DoE performed for the container filling process development resulted in more knowledge gained than from one variable-at-a-time process trials. Not only were main effects of parameters linked to output CQAs, but also interactions were linked and well understood. This resulted in enhanced product and process understanding, and showed that some powerful experiments can be performed in aggressive timelines. This approach not only optimized the container-filling process, but also decreased overall development time.

Reference

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, "ICH Harmonised Tripartite Guideline, Pharmaceutical Development – Q8(R2)", *August 2009*, www.ich.org.

Acknowledgements

- Actavis, Inc.
- Heath Rushing, SAS Institute & Adsurgo, LLC