Design of Experiments Helps Optimize Pharmaceutical Coating Process

Upsher-Smith Laboratories faced a problem with a fluid bed coating process that produced inconsistent results. Many of the coating parameters interacted with each other, so conventional one-factor-at-a-time (OFAT) experiments were unable to resolve the issue. Sarah Betterman, Scientist for Upsher-Smith, used design of experiments (DOE) to determine how the key coating process parameters affect dissolution, the critical response. The designed experiment explained the inconsistency of the original process by showing that slight variations in atomization air volume, at those conditions, would have a large impact on dissolution. It recommended several scenarios with the potential to provide consistent coating performance. Upsher-Smith tested the three scenarios. They identified one that is consistently delivering results within specifications in production.

Coating of a particulate using the Fluid Bed Wűrster HS™ Coating System involves repetitive movement of particles through an atomized spray region. During each cycle the particles are sprayed with a coating solution and then dried. Mass and heat are transferred between the three different phases involved in the operation – solid particles, liquid coating solution and gas jets. The complexity of the process is increased by the zones with high and low particle concentrations as well as high and low velocities. For example, too much atomization leads to premature drying of the coating material while too little may lead to overwetting and agglomeration. As a result, many coupled parameters affect the coating process.

Initial coating parameters provided inconsistent results

Upsher-Smith developed a commercial-scale manufacturing process for a new product based on a limited number of batches. As the company made more batches, inconsistencies appeared during the scaleup process. Betterman, who leads an initiative to implement DOE at the company, identified the application as well-suited for DOE because of the large number of factors involved and their complex interactions. “It would take forever to try and optimize this operation using one-factor-at-a-time experiments because every time you changed a factor, you would have to re-optimize all of the other factors,” Betterman said. “Design of experiments examines all of the variables simultaneously so it enabled us to identify the

optimum values for the factors much more quickly. At the same time, we captured information that gives us a better understanding of how the factors interact."

"The goal of DOE is to solve problems, not to become immersed in statistics," Betterman said. "That's why I decided it was worth making a small investment in a software package that is designed specifically to apply DOE in an industrial setting. Design-Expert® software (from Stat-Ease, Inc., Minneapolis, Minnesota) provides a full range of experimental designs and statistical analysis behind a very simple user interface. So I can spend my time running experiments and interpreting the results rather than crunching numbers."

Design of Box-Behnken experiment

Betterman identified three factors that had historically been demonstrated to have the most impact on dissolution. They included:

A. Product temperature
B. Spray rate
C. Atomization air volume

The responses were product dissolution as measured at five different time points. The dissolution was measured by immersing the product in dissolution media and quantifying the amount of the active ingredient that has been dissolved at each time point.

Std	Run	Factor 1 A: Product Temp deg C	Factor 2 B: Spray Rate g/min	Factor 3 C: Atomization Air Vol cfm
1	10	-	-	0
2	4	+	-	0
3	16	-	+	0
4	2	+	+	0
5	6	-	0	0
6	1	+	0	0
7	5	-	0	+
8	3	+	0	+
9	11	0	-	-
10	12	0	+	-
11	13	0	-	+
12	15	0	+	+
13	8	0	0	0
14	9	0	0	0
15	7	0	0	0
16	14	0	0	0

Figure 1: Experimental design

Betterman selected a Box-Behnken design, a response surface method (RSM) well suited to the goal of process optimization. The software developed a 16-run design which included 12 combinations of the factors plus four center points used to estimate pure error. A common bead blend was used to coat sixteen batches in a fluid bed coater with a Wűrster insert.

Results shed light on multiple factor interactions

Analysis of variance (ANOVA) revealed that a reduced quadratic model provides a good prediction of the percentage of drug releases at time point 1. The significant model terms ($p<0.05$) were A, B, C, AB, AC, BC and C^2.

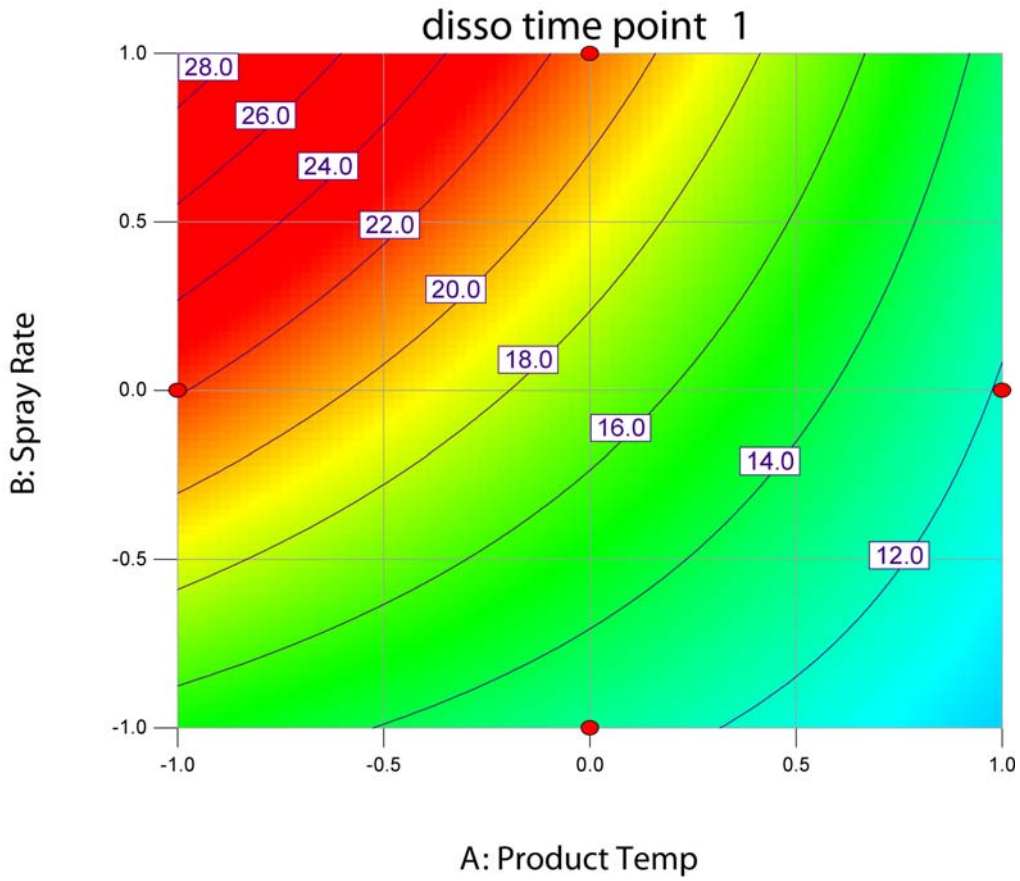

Figure 2: Contour plot for dissolution time point 1 with C at low level

The A and B effects can be examined graphically by looking at contour plots at various levels of C, for example, time point 1 with C at its low level as seen in Figure 2. This plot shows that a higher percentage of the product is released when product temperature (A) is low, spray rate (B) is high and atomization air volume (C) is low (the upper left corner of the graph). These results were surprising because theory suggests that such wet conditions should reduce or eliminate spray drying, create a uniform film coat, and provide a slow release. Further examination of the product indicated that the coating film was compromised, most likely due to agglomeration under the wet processing conditions. The agglomerates broke apart during the process, causing picking. Picking creates small cavities in the surface of the film, resulting in a fast release.

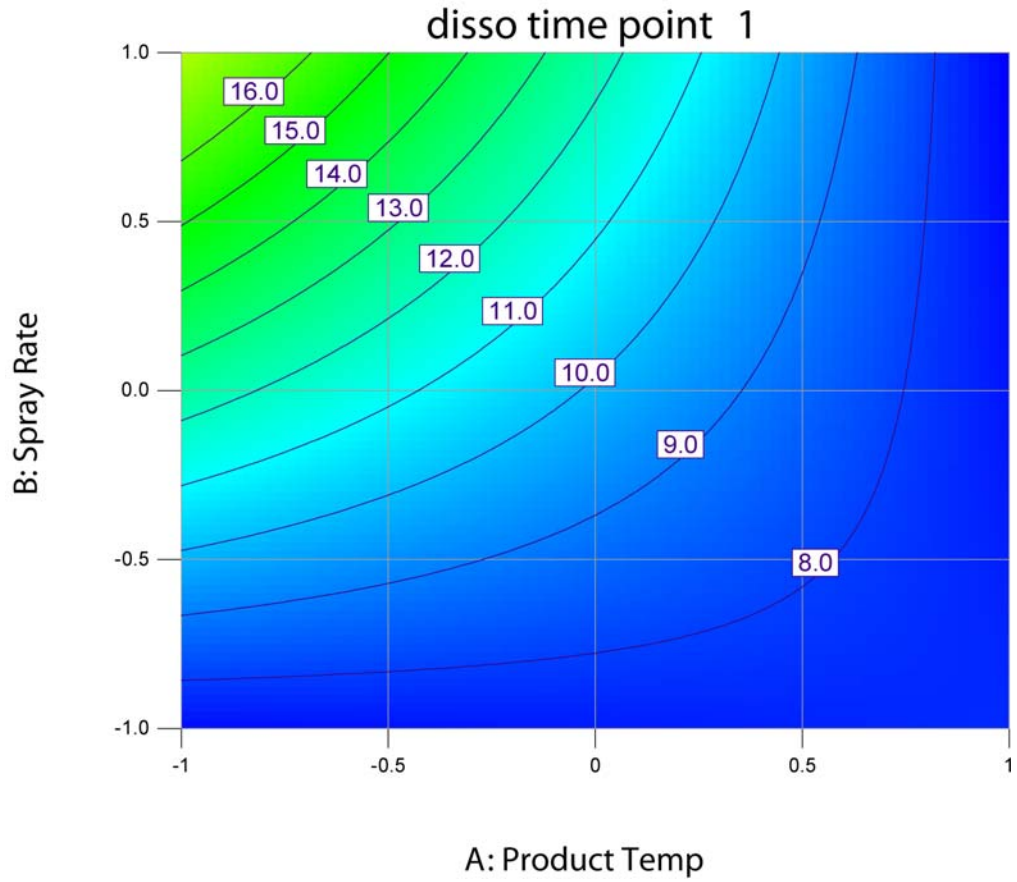

Figure 3: Contour plot for dissolution time point 1 with C at middle level

As the atomization air volume is increased to its middle value, the shape of the contours (Figure 3) remains the same but percent released decreases. The droplets are now smaller so the beads are not getting as wet and picking occurs less often.

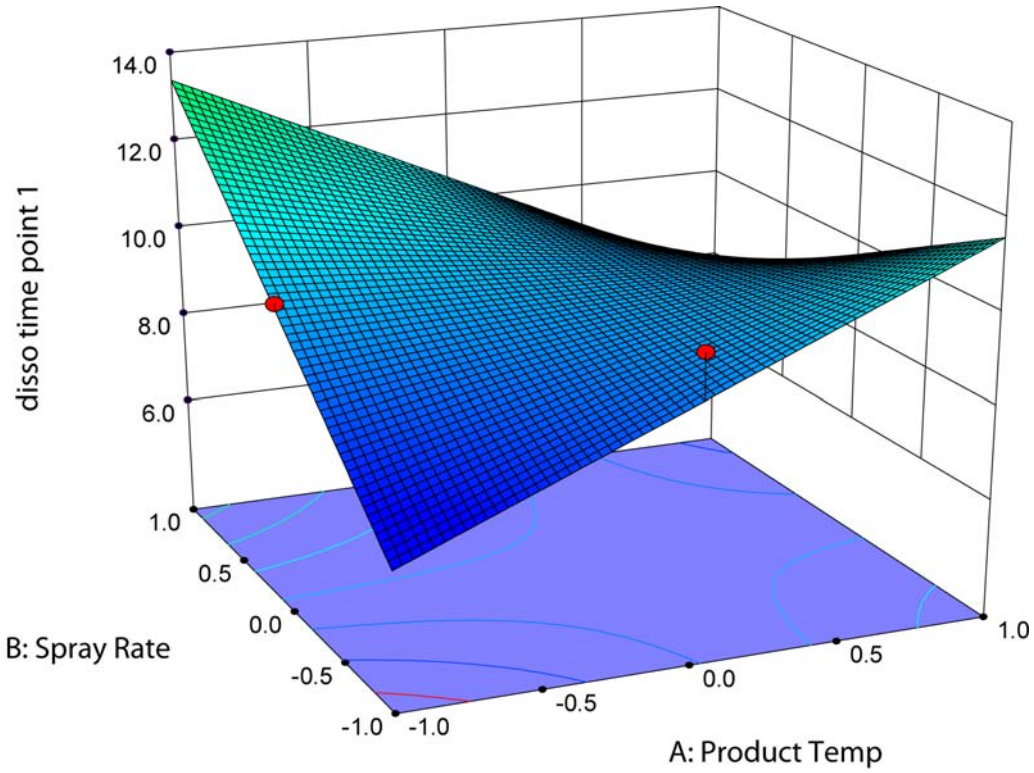

Figure 4: 3D surface plot for dissolution point 1 with C at high level

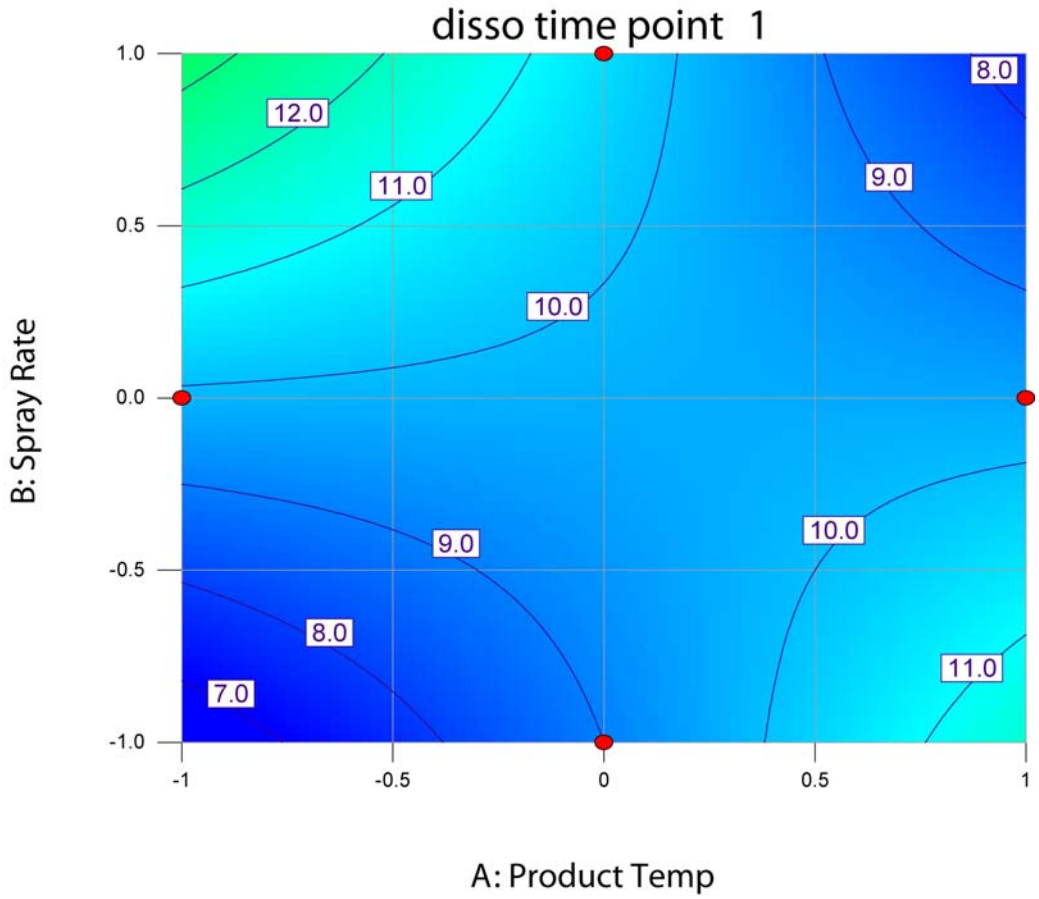

Figure 5: Contour plot for dissolution point 1 with C at high level

At a high atomization air volume, this response changes to having saddle behavior as shown in Figure 4. A contour plot of this situation is shown in Figure 5. This plot shows a smaller gradient through the design space, having a range of about 7% as compared to 19% with the atomization air volume at its low level. Also, the percentage released continues to decrease with an increase in the atomization air volume. Figure 5 shows that there are two areas with faster release, one most likely due to spray drying and the other most likely due to picking.

Optimizing the coating process

The DOE study demonstrated that at low- to mid-levels of atomization air volumes, a small change has a drastic effect on dissolution. On the other hand, at high levels, changes in atomization air volumes have a much smaller impact. This explained why the initial operating conditions provided inconsistent results.

The models generated during the data analysis were used to optimize the coating process with the goal of consistently meeting the dissolution release specifications. The optimization generated six distinct scenarios, or sets of coating parameters, that were predicted to give good results. After examining the six suggested setups, three were selected to try on a production-scale process. One setup showed high variability, causing the dissolution results to fall outside 95% confidence intervals, due to the low level of atomization air volume suggested. Another gave consistent results that closely followed the model's predictions but the dissolution times were too slow, failing drug release specifications. However, one particular setup recommended by the software gave consistent results that passed specifications with little variability. The decision was made to use this for production. It has provided excellent results ever since.

For more information, contact:

--Upsher-Smith Laboratories, Web site: http://www.upsher-smith.com/

--Stat-Ease, Inc.; 2021 E. Hennepin Avenue, Ste. 480, Minneapolis, MN 55413-2726. Ph: 612-378-9449, Fax: 612-746-2069, E-mail: info@statease.com, Web site: http://www.statease.com