Process Optimization Using Design of Experiments

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The use of design of experiments (DOE) software and methods allowed the authors to quantify the effects of changes in coating process conditions on the quality and performance of film-coated tablets. The application of DOE has the potential to allow rapid optimization of coating performance in a wide range of customer application environments to meet changing customer needs.

Aqueous film-coating processes can influence many quality aspects of the final coated product, including coated-tablet moisture content, surface roughness, gloss, coating efficiency, and coating uniformity. Colorcon's aqueous tablet-coating formulations must be capable of meeting these and other customer requirements in different application environments around the world using various types of coating process equipment.

Many different tablet coating machines are on the market, each with different configuration options and different controllable process parameters. Further, different configuration options can be non-numeric. For example, some machines can be configured with one or more spray guns. This situation can result in discontinuous effects on coated-product quality and performance. One critical consequence is that it is not possible to define one process operating specification that is optimal for all coating conditions.

The wide range of coating conditions (operating parameters, equipment, and configuration options) also has a profound consequence in terms of the development of robust coating formulations. Such a robust formulation is one that is insensitive to "normal" coating process variation. The first level of normal variation is the operating tolerances of the controllable process parameters. However, normal variation should be extended to include the likely range of uncontrollable environmental factors known to affect product

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Table I: Response variables listed in order of importance.

Response Variable Name	Variable Units
Coating uniformity (CU)	milligrams
% LOD	%
Coating process efficiency (CPE)	%
Surface roughness	Rz
Process exhaust temperature	°C
Gloss	GU (gloss units)

Table II: Study variables and ranges/levels.

Experiment Variable Name	Variable Units	Range or Levels
Suspension % solids	% (weight/weight)	10–20
Drying (inlet) air temperature	°C	60–90
Fluid delivery (spray) rate	grams/min	35–75
Atomizing air pressure	psi	22–60
Pan speed	rpm	8–20
Number of spray guns	number	1 or 2

Table III: Fixed operating settings.

Operating Parameter	Description
Pan loading	15 kg of 300-mg placebo tablets
Process drying air	Inlet: 250 cfm, exhaust: 300 cfm
Coating formulation	Opadry Y-22-12656
Coating level	Theoretical 3.0% weight gain
Spray gun pattern air	30.0 psi

Table IV: Comparison statistics of % cv and SD.

Data Set	Error %	R^2-adj
% cv	27.2	0.77
SD	2.1	0.93

quality and performance. Examples of such factors are ambient temperature and humidity. The range of operating conditions and discontinuous configuration options makes it difficult to develop a coating formulation that is sufficiently robust for all the various coating conditions that a particular product might experience.

The challenge posed by the consequences described above led us to seek a capability that would facilitate optimization of coating quality and performance under any specific set of coating conditions. Further, because coating conditions and customer requirements do change, the capability needed to be flexible, allowing quick reoptimization. Obviously, developing this capability required a clear understanding of coating-process effects. Therefore, the technical goal of this work was to quantitatively define the effects of critical process parameters on coating quality and performance over the range of operating conditions that our coatings could experience worldwide. The technical goal supported two critical business goals. The first was the creation of baseline operating parameters that would yield compatibility and reproducibility throughout our global technical departments. The second was the ability to rapidly optimize coating performance under customer application environments that are not always readily anticipated up front and are subject to change over time.

EXPERIMENTATION

Experiment design. Our experience has shown that process operating conditions significantly affect coating quality and performance. In many cases these effects are not strictly additive — process parameters can interact both synergistically and antagonistically. Although successive approximation experiments can yield incremental improvement in quality or performance, the data from these experiments do not usually enable the researcher to positively identify and quantify interaction effects. Also, studying several process parameters by trial and error is extremely inefficient.

Over the years, Colorcon has successfully used design of experiments (DOE) methods on many important projects in both the technical services area and in R&D. DOE overcomes the information limitations of successive approximation experiments and quickly gives the kind of understanding and results that are needed. Most important, as opposed to the only certain goal of trial and error — incremental improvement — the underlying DOE goal of quantitatively defining cause and effect was completely in concert with the stated goals for this program. The DOE approach was therefore the obvious choice.

DOE is a multivariate approach to experimenting, i.e., two or more variables (sometimes called factors) are always studied in one experiment. It is the most efficient method of experimenting when one's goal requires a clear definition of variable effects. As this article shows, obtaining clear cause-and-effect definition also supports the goal of product/process optimization.

Even with DOE, however, the amount of work increases significantly as the number of study variables increases. Therefore, we carried out a Pareto-type analysis to select the most important process parameters for study from among the candidates. We first selected six product quality and performance characteristics (response variables), shown in Table I, that are of primary importance to our customers.

We next identified 11 controllable process parameters that we knew affected the key response variables. By group consensus each parameter was then assigned a rank of either A or B, depending on the assumed strength of its effect relative to the other 10 variables in the list. The list was divided equally in terms of A and B assignments. Given 11 variables, we restricted the number of A assignments to six. The six A-ranked process parameters became our experiment variables. Table II presents these six variables and their experiment ranges or levels.

Colorcon uses the CARD software package by S-Matrix (Cupertino, CA) for DOE. The package enables us to combine correctly numeric variables such as temperature and pressure with the non-numeric variable (number of spray guns). The software package can design classical (factorial type) designs as well as

Table V: Experiment variable term ranking — CU response.

Model Term Name	Model Term Range	Coefficient Value	Model Term Effect	Model Term Rank
Pan speed	12	−0.0497	−0.5958	1.00
FD rate	40	0.0079	0.3157	0.53
Inlet temperature × number of guns	2	−0.1520	−0.3041	0.51
(Inlet temperature)^2	1	0.2404	0.2404	0.40
Number of guns	1	−0.2146	−0.2146	0.36
Inlet temperature	30	0.0046	0.1392	0.23
Percent solids	10	0.0134	0.1343	0.23
Atomizing air × percent solids	2	0.0499	0.0999	0.17
Atomizing air	38	0.0021	0.0811	0.14

algorithm (optimality type) designs, including mixture designs, which is important to our formulation studies (1,2).

For this study the software's Navigator Wizard guided us to an algorithm design as the correct statistical design type for our variables and goals. The statistical design selection logic is as follows. Our optimization goal required that we quantify all significant variable effects, including curvilinear (simple deviations from straight-line behavior) and nonlinear effects. At least three experiment levels are required to quantify even simple curvilinear effects. Thus, classical two-level designs were not appropriate. The non-numeric variable ruled out the use of classical three-level designs, because only two levels were available (one or two guns). Also, the information properties of classical three-level designs are based on all experiment variables being numeric. Analysis of data from these designs cannot provide correct effects estimation for non-numeric variables, the effects of which are discontinuous by nature (2). The algorithm design accommodated our variable types and our goals. In addition, it is advantageous to define numeric variables as continuous variables when possible, because fewer experiment trials are required to define completely cause and effect. Therefore, defining our numeric variables as continuous and using an algorithm design resulted in a smaller number of trials than would have been required by a classical design.

Experiment equipment. We used an O'Hara Technologies (Scarborough, ON, Canada) Labcoat II coating machine (fitted with a 24-in. pan and accommodating one or two spray guns) in this study. The five B-ranked process parameters were assigned constant operating conditions for the experiment. Table III presents these five parameters and their constant conditions.

Each coating trial in this experiment used 300-mg, round placebo tablets. The tablet core (uncoated tablet) consisted of modified starch (49.75%), microcrystalline cellulose (49.75%), magnesium stearate (0.25%), and colloidal silicon dioxide (0.25%).

An aqueous Colorcon coating (Opadry Y-22-12656) formulated with a yellow pigment was used in this study. We chose yellow to allow us to track specific tablet cores through the coating process. For each experiment trial, we numbered 100 individual tablet cores using a black marker before coating. Each marked core was then dried to constant weight and the weight was recorded. The marked tablets were then added to the 15-kg tablet load before coating. After application of the coating (to a theoretical 3% weight gain), the tablets were sorted, each marked, coated tablet was again dried to constant weight, and the weight was recorded. The difference in weight is the actual weight gain, i.e., the number of milligrams of coating applied to the core.

Tracking individual tablet cores and drying the marked tablets to constant weight before and after coating allowed us to eliminate weight gain measurement errors due to changes in moisture content, thereby yielding an accurate measure of weight gain for each experiment trial (3). The more accurate weight gain data resulted in better cause-and-effect definition for the coating uniformity response.

RESULTS AND DISCUSSION

Our full study addressed all six responses listed in Table I. However, the results presented here were obtained from analysis of the first three key responses listed in the table, namely coating uniformity (CU), tablet moisture content after coating (percent loss on drying [% LOD]), and coating process efficiency (CPE). These responses are critically important because they affect drug release profiles, drug and core stability, and the economics of the coating process.

Coating uniformity (CU) is of primary importance, especially when the coating functions as a major factor in influencing drug release. For example, a tablet that has received too little coating will release drug too rapidly (possibly causing "dose dumping"), while drug release from a tablet that has received too much coating material will almost certainly release drug more slowly than expected. Wide variations in the amount of coating received by individual tablets within a batch may also have some effect on the dissolution rate of drug even from immediate-release tablets.

CU is generally defined as the variation in weight gain of coated tablets within a coating trial. The commonly reported measure of CU is the coefficient of variation (% cv), which is calculated as

$$\%\,\mathrm{cv} = \frac{\sqrt{\dfrac{\Sigma\left[\left(wt_{a_i} - wt_{b_i}\right) - \bar{x}\right]^2}{n-1}}}{\bar{x}} \qquad [1]$$

where wt_{ai} and wt_{bi} are the weights of tablet i after and before coating, respectively, corrected for moisture content by drying to final weight; n is the number of tablets measured; and $\bar{x}$ is the average weight gain of the n measured tablets from the coating trial (4). Note that the numerator in the equation is simply the first standard deviation (SD) of the variation in weight gain within a trial.

A dependent relationship exists between weight gain and CU typically at weight gains <2%. The CU can be >40% at a weight gain of 1%, and drop well below 20% as the weight gain increases to 2%. However, at weight gains >2% this dependency breaks down, and the mean weight gain no longer imparts a constant bias to the variation in weight gain. In other words, at weight gains >2% there is no relationship between mean weight gain and weight gain variation. (The dependency be-

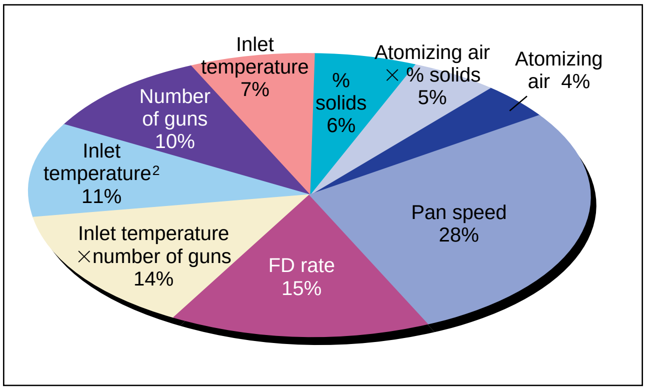

Figure 1: *Experiment variable term ranking — CU response.*

tween weight gain and CU is actually an artifact of coating time. Higher weight gain requires a longer coating time, so individual tablets have more opportunity to become evenly coated.)

As a result of the dependency breakdown, dividing the SD by the mean weight gain (to obtain the % cv) introduces a random error component into the % cv calculation, causing the % cv data to have more error than the SD data from which it is derived. This result in turn compromises data analysis. Therefore, when the weight gains in a data set are ⩾2%, the SD is a better measure of CU than % cv.

In our data set the measured weight gain ranged from 0.79% to the 3% target. However, more than 80% of the data showed weight gains >1.75%. To confirm that the SD is a more accurate representation of CU than % cv in our data set, we analyzed both. Two key statistics — the adjusted R square (R^2-Adj) and the error percent — obtained from each analysis are presented in Table IV. The R^2-Adj is the decimal equivalent of the percent of the response data variation that is explainable by the current analysis model. The error percent is the percent of the response data variation that can be attributable to overall experimental error.

When one compares the statistics in Table IV, it is clear that SD is a more accurate representation of CU. Therefore, for the remainder of this article the CU response is defined as the first standard deviation of weight gain variation (in milligrams).

In the CU analyses the software package identified two of the trials as outliers and recommended that it be allowed to drop the trial data from the data set before continuing the analysis. An outlier is an observed response value for a given trial that disagrees significantly with the corresponding model-predicted value based on the estimated variable effects. The outliers corresponded to trials that we suspected had problems due to exposure to moisture during weighing.

The CARD software automatically executes several interrelated analyses and cross-compares the results as part of its overall analysis function. Based on its internal cross-comparison, the software identified the response data as nonlinear and the correct transformation required before continuing the analysis. The nonlinear character of the response data arises from the dependency between mean coating weight gain and variation in weight gain. Recall that this dependency affects ~20% of the data with mean weight gains <1.75%, resulting in a relative (nonlinear) error. We therefore accepted the recommendation and let the package transform the data. Fortunately, we were not required to interpret analysis results corresponding to a transformed mathematical space, because it automatically back-transformed the completed analysis results into real-world terms.

The software's default analysis settings provide a final response model that contains only statistically valid variable effect terms. As part of the analysis output, it ranks these terms based on the relative strengths of their effects on the response being analyzed. Table V shows the variable-term ranking for the CU analysis results. In the table, a given term's rank is based on its effect on the response across its experiment range relative to the effect of the strongest effecting term. To illustrate, the spray rate, or fluid delivery (FD) rate, has a relative rank of 0.53, which means that its direct effect on CU across its range was 53% of the direct effect of pan speed, the strongest effector. Note that the interaction between the inlet air temperature and the number of guns (inlet temperature × number of guns) is the third strongest effector of CU.

The ranking is also presented graphically in Figure 1, which is a translation of the numerical ranking in Table V into a pie chart. The chart shows the effect of each experiment variable term across its range as a percent of the total combined effects of all variables across their ranges. The ranking pie chart also identifies pan speed as the largest direct effector of CU, followed by FD rate, drying air temperature (inlet temperature), and number of guns (5).

The linear, interaction, and curvilinear effects of the experiment variables in the ranking table are best visualized using response surface graphs. Figure 2 is a response surface graph showing the effects of both pan speed (*x* axis) and inlet temperature (*y* axis) on CU (*z* axis) across their experiment ranges. The figure clearly shows that increasing the pan speed reduces weight gain variation. For example, given an inlet temperature of 60 °C, the CU (weight gain SD) changes from ±1.9 mg at 8 rpm to ±1.0 mg at 20 rpm. Figure 2 also shows the curvilinear effect of inlet temperature, which results in high weight gain variation at the low and high end of its experiment range relative to the middle of the range.

The CU response ranking table (Table V) also reveals that the number of guns strongly interacts with the inlet air temperature. Recall that this interaction is the third strongest effector of CU. By definition an interaction between two variables means that the effect of one variable on a given response across its range is different at different level settings of the other interacting variable. Interactions therefore express dependent relationships between variables — the observed effect of one variable depends on the level setting of the other variable.

As stated earlier, interactions between variables are best visualized graphically. However, the fact that the number of guns is a non-numeric variable means that two response surface graphs are needed to see the interaction effect. Figure 3 is a second response surface graph of pan speed and inlet temperature. In this case we have changed the number of guns to two. By comparing Figures 2 and 3 we can see the direct and interaction effects of increasing the number of guns. The response surface is lower overall in Figure 3 (two guns) relative to Figure 2 (one gun).

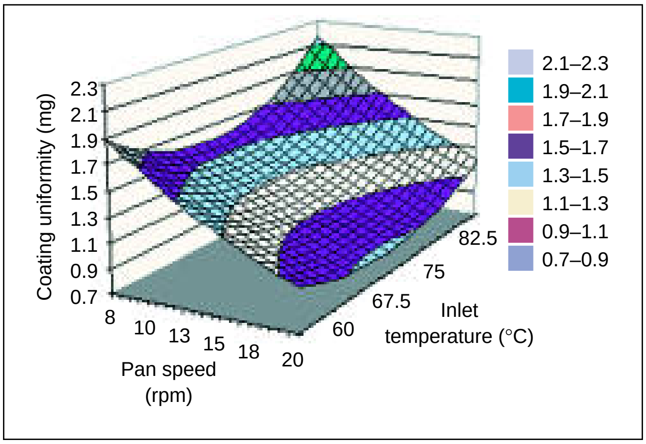

Figure 2: *CU response surface for one spray gun.*

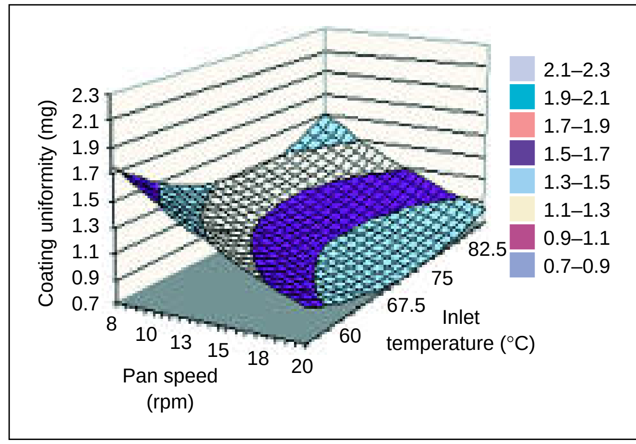

Figure 3: *CU response surface for two spray guns.*

These results show that changing from one spray gun to two directly reduces weight gain variation. The flatness of the response surface in Figure 3 relative to Figure 2 illustrates the interaction effect — increasing the number of guns dampens the strong curvilinear effect of inlet temperature.

The flatter response surface in Figure 3 relative to Figure 2 means that CU is less sensitive to variation in inlet temperature when two guns are used. This has an important consequence in terms of CU robustness when considering the influence of process variation on CU. More than half of the response surface in Figure 2 corresponds to combinations of pan speed and inlet temperature when the CU exceeds ±1.3 mg. An SD of ±1.3 mg corresponds to 95% confidence limits of ±2.6 mg. Given a 300-mg tablet core, this equals a ±0.86% variation in weight gain. Thus, more than half of all combinations result in a coated tablet weight gain variation that exceeds ±0.86% when one spray gun is used. In contrast, almost the entire response surface in Figure 3 corresponds to level setting combinations of pan speed and inlet temperature when the CU is well below ±1.3 mg. Thus, almost all combinations result in weight gain variation below ±0.86% when two spray guns are used.

% LOD is a measure of the moisture content of the tablet. It can be extremely important to both tablet core and drug stability. % LOD is a process-driven property that expresses overwetting or overdrying of the core during coating. The ideal circumstance is to have no net gain or loss of core moisture content due to coating.

% LOD is the moisture content of the coated tablet expressed as percent weight. % LOD is calculated as

$$\%\,\mathrm{LOD} = \left(\frac{wt_b - wt_a}{wt_b}\right) \times 100\% \qquad [2]$$

where wt_b and wt_a are the coated tablet weights before and after drying, respectively. In this case we used a 4-oz. retain jar of tablets. The tablets were weighed, dried at 60 °C for 24 h, then reweighed. All placebo tablet cores used in this study had an initial (uncoated) moisture content of 3%.

In this study the % LOD response ranged from 0.10% to 5.33%, indicating that one or more of the experiment variables had a substantial effect on this response. In other words, the coating conditions in the experiment design expressed a broad range from severe overdrying to severe overwetting. The experiment variable ranges were deliberately set sufficiently wide to allow a broad response range. Remember that the goal of a designed experiment is not incremental improvement in quality but clear quantification of cause and effect. Overly restrictive experiment variable ranges translate into small response ranges, thus making it difficult for data analysis to distinguish variable effects from background error variation.

Figure 4 graphically presents CARD's experiment variable term ranking for the % LOD analysis results. This ranking identifies inlet temperature as the largest direct effector of % LOD, followed by FD rate and number of guns. Note that the concentration of suspension solids (% solids) interacts with inlet temperature, number of guns, and FD rate. These direct and interaction effects are important in terms of coating quality versus batch processing time. A high % solids reduces the batch processing time, as does a high FD rate. However, faster batch processing times must not come at the expense of coated-product quality. An optimized coating process is one in which the batch processing time is minimized while appropriate product quality is achieved.

At this point we used the software's Optimizer Wizard function to evaluate the potential to optimize the coating process for both CU and % LOD over a range of % solids and FD rates. To do this we set the response goals in the Wizard to minimize CU while simultaneously hitting a 3% target for % LOD. We carried out optimizations in which we looked at all combinations of % solids and FD rate for both one and two spray guns. The Optimizer Wizard defined coating conditions that would achieve the 3% target for % LOD under all combinations of % solids and FD rate across their experiment ranges while keeping the CU below ±1.0 mg. However, the optimization analysis defined that in every case a better CU (smaller SD) would be achieved by using two spray guns.

Coating process efficiency (CPE) is a measure of the actual amount of coating applied to the tablets relative to the theoretical quantity of coating applied. It can therefore be another indicator of overwetting or overdrying. When overwetting occurs, material can potentially be transferred from the surface of the tablets to the walls of the coating pan, thus reducing CPE. Con-

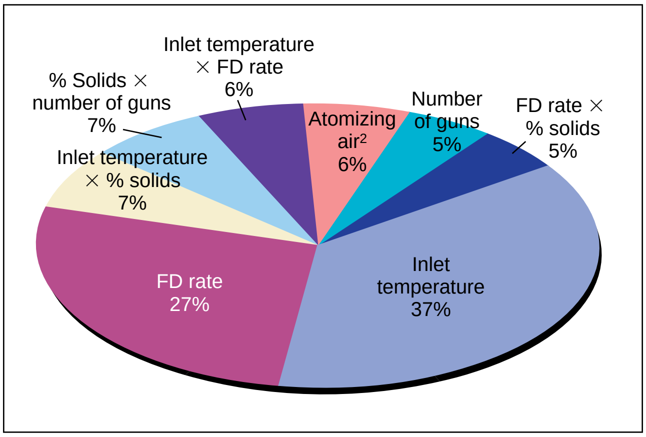

Figure 4: *Experiment variable term ranking — % LOD response.*

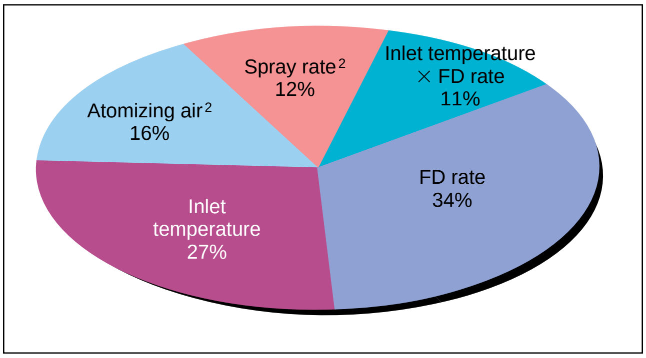

Figure 5: *Experiment variable term ranking — CPE response.*

versely, when overdrying occurs, coating solution can dry prematurely in the air stream (commonly called spray drying) and be lost into the exhaust air stream instead of being transferred to the tablets. These circumstances have the same implications as those previously mentioned for moisture content (% LOD), with the additional obvious economic issue of lost coating.

CPE is generally defined as the actual percent weight gain relative to the theoretical percent; a theoretical 100% transfer of coating to the tablets would mean no lost coating. CPE is computed as

$$\mathrm{CPE} = \left(\frac{\%\, wg_a}{\%\, wg_t}\right) \times 100\% \qquad [3]$$

where wg_t is the theoretical percent weight gain, which in this experiment was 3% in every coating trial, and wg_a is the actual percent weight gain, which is computed as

$$\text{Processing}\,\%\, wg_a = \left(\frac{wt_a - wt_b}{wt_b}\right) \times 100\% \qquad [4]$$

where wt_b and wt_a are the total batch weights before and after coating, respectively.

In this study the CPE response ranged from 25% to almost 100%, indicating a broad range from extremely inefficient (75% of coating lost) to almost perfect efficiency (no coating lost).

The experiment variable term ranking for the CPE analysis results is presented graphically in Figure 5. The ranking identifies FD rate as the largest direct effector of CPE, followed by inlet temperature and atomizing air pressure. In fact, the direct, interaction, and curvilinear effects of these three variables are responsible for all of the variation in the CPE data beyond that attributable to experimental error. It is noteworthy that FD rate and inlet temperature were the two main effectors of % LOD and were two of the three main effectors of CU (the third being pan speed).

The fact that critical responses have effector variables in common is not necessarily desirable from an optimization standpoint, because changing a variable level setting to improve one response will certainly change the other critical responses it affects. In many cases a variable's effects on different responses can be competing, i.e., a change that improves one response will degrade another (5). This can be the case for FD rate in terms of the CPE and % LOD responses. FD rate can be a positive effector of CPE (increasing the spray rate can improve coating efficiency). However, FD rate can simultaneously be a negative effector of % LOD (increasing the spray rate can cause overwetting). This circumstance is complicated further by the presence of interactions between variables. Interactions can cause a variable effect to switch from competing to complimentary, depending on the level settings of the variables involved in the interaction.

It is the complexity of variable effects on critical responses that makes multiple response optimization difficult. Adding to the difficulty are changing application environments and customer needs. Before acquiring automated optimization software, we were forced to compare manually the numerical analysis results and graphs for each critical property. This was a tremendously laborious process at best, and often not enough time was available to explore all possible opportunities.

However, the present situation is profoundly improved. We can now simply integrate the analysis results for all our properties through CARD's multiple response Optimizer Wizard, set our response goals, and let the computer do the work. For example, by adding the goal of ≥80% for CPE to the previously defined optimization goals (minimize CU, 3% LOD) and re-executing the optimization feature, the software identified experiment variable levels that would yield a CU of ±0.85 mg, a 3% LOD, and a CPE of 85%. We can also easily evaluate tradeoffs such as allowing slight flexibility in the target % LOD to improve coating efficiency, or relaxing the coating efficiency goal to see what improvement might be gained in coating uniformity.

CONCLUSIONS

The results we obtained from this work clearly defined the baseline operating parameters that yield compatibility and reproducibility throughout our global technical departments — our first stated goal of this program. Unambiguous quantitative results of this kind are required to replace partial understanding and conventional wisdom, which can vary from lab to lab. The need for, and value of, hard data in this area was emphasized by a call we recently received from a major pharmaceutical manufacturer that wanted to know if we had any specific data on the relative merits of using one versus two spray guns in coating machines configured with 24-in. pans.

Our customers' coating processes and product quality needs will certainly change over time. It will also almost always be true that more than one process parameter or product quality will change at a time. Thus our achievement of a multiple response optimization capability — our second program goal — will be a valuable tool in helping to deal with these circumstances. Colorcon has deployed the CARD software package and these program results throughout its global technical departments so that it can optimize coating performance to meet changing customer needs and application environments.

A recurrent objection to DOE is that it requires too many experiments. Our analysis of work done over long periods concludes that for many R&D and technical services programs, what appeared as many small focused experiments in fact constituted very large experiments conducted a few trials at a time. However, as opposed to efficient, statistically designed experiments, these disjointed cycles of work, which translated into many more experiments overall, did not yield the same unambiguous quantitative results. The excellent results we achieved on this program underscore the value Colorcon achieves through DOE. Although in many instances the results obtained were generally anticipated, there were important instances in which the results were equally unexpected. These important results would almost certainly not have been obtained by conventional-wisdom-driven trial-and-error experiments. We get an additional benefit from DOE with CARD — the ability to build upon historical data. As an example, we will use the results of the additional responses not described in this article as a baseline for future product development projects.

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