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DOE (Design of Experiments) in Development Chemistry: Potential Obstacles

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Abstract:

There are often issues associated with challenging accepted working practices through the introduction of statistical tools. This paper outlines common objections to the use of DOE (design of experiments) and our standard responses to overcome these obstacles.

Introduction

The development chemist faces a complex task in taking a drug candidate all the way from discovery to establishing a secure supply of manufacture on a production scale. The route of manufacture involves not only the preparation of intermediates and final drug substance, but also the isolation and the measurement of quality.

We would like to carry out this often lengthy process more efficiently in order to reduce the time it takes to bring a drug to market. Experimental design is an established and proven methodology for product and process improvement in the pharmaceutical industry.[1] We have found the design of experiments (DOE) an invaluable tool in identifying critical parameters, optimizing chemical processes, and identifying robust operating regions for our processes (see Figures 1−3). Screening designs can be used to identify which of a host of factors are critical to the process (Figure 1). Response surface designs can be used to optimize and then identify robust operating regions (Figures 2 and 3).

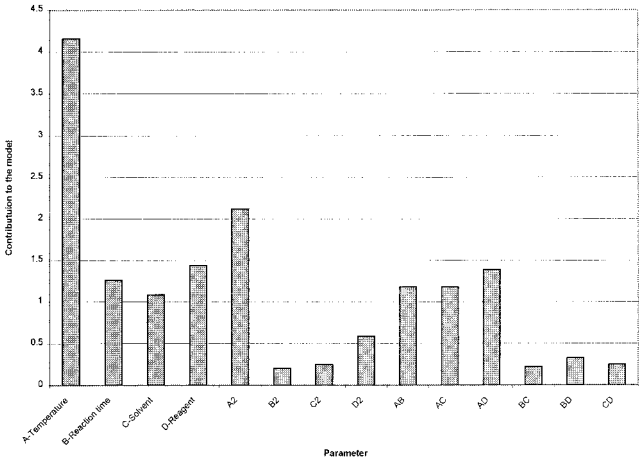

Figure 1. **Screening design. This Pareto plot ranks the importance of each factor and factor interaction effects. The higher the magnitude, the greater the influence of these terms on response. The graph shows the relative magnitude of the linear terms (A, B, C, D), the quadratic terms (A2, B2, C2, D2), and the interaction terms (AB, AC, AD, BC, BD, CD) that are used to fit the mathematical model.**

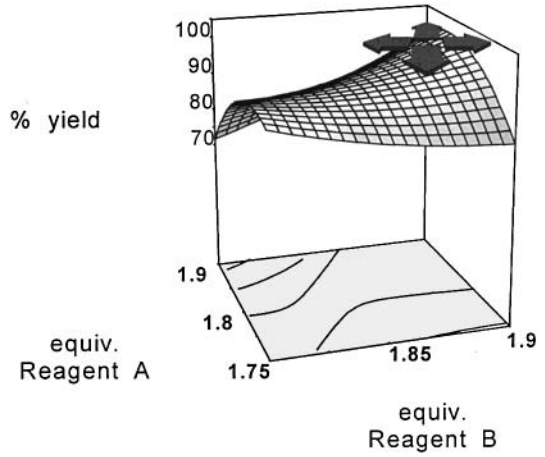

Figure 2. **Response surface design. In this example, the location of highest point of the response surface represents the conditions required to generate the maximum yield. Note how easy it is to see the interaction effects between the ratios of reagent A and B relative to a third componant C (1 equiv).**

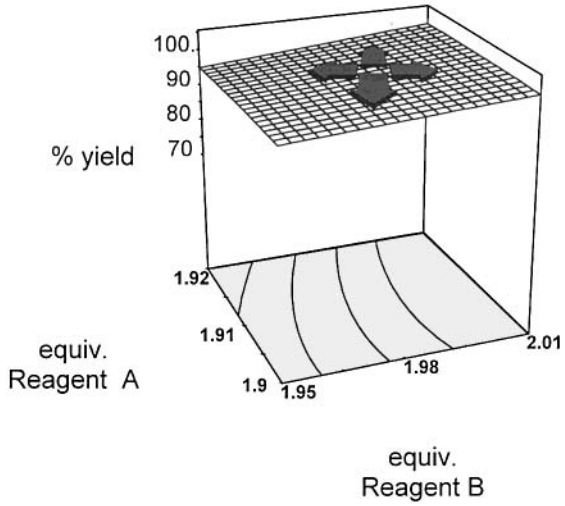

Figure 3. **Process operating ranges evaluation. A flat response surface indicates a robust method within the parameter range indicated.**

Despite the obvious benefits of experimental design, in introducing DOE methods, we have encountered resistance

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to the use of the techniques. As with any new technology, resistance to using DOE is inevitable, but we have found a simple brainstorm of "potential obstacles to implementation" an important way of getting that resistance "out on the table".

Here are some of the perceived obstacles and our standard responses!

Lack of Management Support

This obstacle is variously expressed as management resistance, lack of management support, or just "managers!"

Management support is essential if DOE is to become part of the standard toolbox of the development chemist. The one thing all managers will respond to is success. And DOE is very successful. The key is to try the techniques and demonstrate success. If you do not try it you will never know.

Insufficient Resources

This objection manifests itself in many ways, resources being defined loosely as time, money, starting materials, access to equipment, etc.

This would indeed be a worrying objection, if it were true. In fact, experimental design is an extraordinarily efficient method of identifying critical parameters, identifying settings that will optimise responses, and identifying robust regions of chemical space. In contrast we have found that people grossly underestimate the resources consumed by the traditional approach to arrive at what is best an incomplete answer. Those companies who have performed a formal cost-benefit analysis of a designed approach compared to the traditional "only alter one factor at a time" approach have invariably come down in favour of a designed approach. Frequently, a designed approach requires no more resource than the traditional approach. The difference is that with experimental design, because we plan to spend the resource up front, it is more visible.

We Agree That DOE Needs To Be Done—but Not by Us. Why Can't We Leave This to Someone Else Further Downstream in Development?

This is usually a corollary of resource issues. The implicit assumption is that this involves spending more resources than the traditional approach. Not so. We simply underestimate the resources spent using the traditional approach. Build quality in at the start! It is more effective to ensure that an optimised process is taken into the plant right at the start, rather than using a "make do" process because of limited investigation time. Once a process moves towards a production method, it becomes progressively more difficult to introduce radical change in the method. The benefits of applying a designed approach diminish as time goes on, as more and more resources are consumed producing an incomplete picture using a traditional approach. That is not to say that DOE techniques cannot be used as a valuable firefighting tool to troubleshoot late-stage processes. It is just better to avoid firefighting.

Why Waste Time Definitively Optimising a Process Stage, If the Route Is Still "Up for Grabs"?

We agree—timing is a critical issue. It is important to tailor your design so that it is "fit for purpose" for the current point in the project's life-cycle. Use small pilot studies to evaluate appropriate levels of factors and the reproducibility of controls. Apply screening designs (such as a fractional factorial) as early as possible to identify the correct choice of discrete factors (such as solvent and reagent) and the most important continuous variables (such as time and temperature). Then apply response surface designs (such as central composite) to optimise the key continuous variables. As a potential manufacturing process is identified, use a robustness design to establish process operating conditions. Throughout, carry out confirmation experiments to provide reality checks and identify scale-up issues.

Can We Apply DOE without Statistical Support?

Yes. But we believe it is much easier with good statistical support from an experienced statistician and practising experimenter. Good software is also an advantage, but again, not critical. Some of our first designed experiments were developed on the back of an envelope.

"It Ain't Broke...so Why Fix It?"

Rubbish. If this were true, then projects would never be late, critical parameters would never be overlooked, the development process itself would proceed smoothly, and transfer of products and processes would proceed without a hitch. In reality projects are late, critical factors are overlooked, drug development is a rocky road to travel, and new product introduction and technology transfer are fraught with hazards.

Or "Why Bother When the Results Are Blindingly Obvious?"

Intuition feels good. In reality, however, the results are often more complex than intuition would suggest. Woolly statements can be quantified, and the effect of several (often conflicting) responses can be visualised. We have found that the results are only blindingly obvious after they come in. "Obvious results" are much more difficult to predict up front.

Will It Work?

Sometimes people seek assurance that DOE will work. We cannot offer that assurance, and it would be foolish to make such promises. What we can say is that for a quantifiable amount of resource DOE will allow you to screen a list of factors you suspect may be critical to your product or process and identify a region within the design space where you will get reasonable results. And DOE techniques will do this time, after time, after time.

With several hundred industrial experiments under our belts we can count the number of "failures" on the fingers of one hand.

What If We Miss a Factor? Will My DOE Work Not Be Wasted?

If a critical factor is not included in the list of potential factors for investigation, then it will be missed, but the same is also true of traditional approaches. Fortunately, Experimental Design provides a set of diagnostic tools such as lack

of fit tests and residual analysis which allow the presence of a lurking variable to be detected. With traditional approaches we might accidentally stumble upon a missing factor, but more often than not it goes undetected.

In Chemical Development we Have a Large Number of Factors Affecting a Reaction. Will This Really Work with Multiple Factors?

Yes. DOE was developed specifically to look at large complex problems with many factors with complex interactions. Our experience has been that it works really well.

How Can Experimental Design Give Me the Right Synthetic Route?

It can't. Nobody believes it can, and that is not a label claim for DOE. These techniques work best in conjunction with your own knowledge of the chemistry. DOE is not a substitute for creative chemistry. Although DOE will not salvage a flawed multistage route, it may identify why a particular stage is flawed. It can also show how to get the best out of a flawed stage, where no other options are possible.

How Can DOE Possibly Handle Both Reaction and Work-Up?

Usually it makes sense not to attempt this. Before embarking on the design, it is usually preferable to look at the whole process (i.e., reaction and work-up) first to establish the overall issues. Then carry out a study to establish the best reaction conditions—the purer the process stream, the easier the work-up. Sometimes work-up and reaction are inextricably linked, in which case the study needs to cover both work-up and reaction. As a result, the design will inevitably be harder to control and more time-consuming to implement, but there is no alternative.

I Do Not Have a Reliable, Robust and Meaningful Way To Measure Responses.

Well, let's face it, you're going to have problems whether you use a traditional approach or a DOE approach! Good experimentation demands a good measurement technique, otherwise you might just as well be wearing a blindfold as well as your lab coat. DOE will often alert you to the fact that your response measurement technique is flawed. It may be some time before you realise this with a traditional approach as you could easily attribute the response noise to an experimental variable. Time spent in establishing a meaningful response measurement before you start a study is rarely wasted, and of course, DOE is an ideal way of proving that the response method is robust.

What about Scale-Up?

It is important to carry out a DOE study on an appropriate scale, using appropriate technology. In reality at the preliminary stages of exploration, amounts of starting material are very limited. It makes good sense to carry out the initial designs easily and quickly on a small scale in the laboratory. These reactions *should* provide a basis for scale-up to large-scale laboratory and ultimately industrial-scale production levels. It is important to verify this as early as possible using jacketed vessels, reaction calorimeters, or small plant reactors. However, some processes such as crystallisation, exothermic, and phase-transfer reactions can be very scale-dependent, due to bulk-transfer and heat-transfer effects. In these cases, it is more appropriate to use small-scale experimentation as a guide to identifying the important factors and work on a larger scale to obtain the more predictive model. Never forget that, if you don't understand the critical factors at the current scale, then scaling up isn't going to fix it.

Most scale-up issues can be anticipated but most organizations do a very poor job of capturing those issues and sharing them between project teams. Experimental design provides a framework for capturing and sharing that information in a learning organisation.

Regulatory

Fears about whether an experimental design approach would be welcomed by the regulators is often raised as a potential objection. An experimental design approach is totally consistent with the need of the regulators to see "evidence of a structured approach". Our experience has been that regulators welcome the simplicity, clarity, and obvious good, common sense underlying a designed approach.

Will I Need a Lot of Expensive Automated Equipment To Carry Out the Experiments?

Automation is not critical to experimental design; it just makes it easier to obtain better control and is more efficient to implement.[2] DOE highlights the presence of background noise that is rarely appreciated (although of course, it is still present!) when using a traditional approach. As a result, attention is drawn to the importance of process control. It may be necessary to alter the way we work or the technology we use. In GlaxoWellcome, we have developed the DART[3] and PROSPER[4] systems to enable us to carry out reactions in parallel and to give us better process control.

Other technology is rapidly emerging or becoming more accessible. To exploit this more effectively, an understanding of DOE is essential.

Isn't Simplex a More Direct Statistical Approach for Optimising a Process?

The simplex approach[5] is an alternative iterative approach to optimising the response of several parameters. The search algorithm is based on an evolutionary ("hill-climbing") optimisation procedure. If there is a lot of "background noise", in other words, if there are other uncontrolled factors contributing to the response variation, it may take some time

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(5) Bayne, C. K.; Rubin, I. B. *Practical Experimental Designs and Optimisation Methods for Chemists*; VCH Publishers: Deerfield Beach, FL, 1986.

before the whereabouts of the true summit becomes apparent. There are also possibilities that two hills exist on the response surface and the lower peak is climbed, rather than the higher. As with the traditional "one factor at a time" approach, the simplex technique is less well suited if there are many conflicting responses to be optimised. In addition, the sequential nature of this process mandates the use of a linear sequence of experiments. If there is a long reaction time (e.g., greater than 24 h), the actual time to "climb the hill" can be many days, and it is not clear at the outset how much resource will be consumed before the outcome is resolved.

Conclusions

We often liken the use of experimental design tools to the use of any other tool. We draw an analogy with the use of hammers. We can present the theory of hammers, we can present successful applications of hammers from a variety of industries, we can present a cost-benefit analysis of the use of hammers as opposed to other tools such as sticks and stones. None of these will convince you to switch to hammers. The one thing that is going to convince people is if they pick up the hammer and try it themselves. Very quickly you will get a feel for how the hammer works. We recommend that the first few times you try it you seek help from an experienced statistician—when you wield the hammer for the first time its as well to get someone else to hold the nail! Pick up the hammer, try DOE. You will never want to go back to doing things the way you used to do them.

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