Find the Most Favorable Formulations

Here's how to discover "sweet spots" — blends that best meet multiple product specifications.

This is the second of two articles on design of experiments. The first ("Optimize Your Process Optimization Efforts," Dec. 1996, pp. 51–60) provided tools for factor screening via two-level designs, plus tools for process optimization via response surface methods.

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Design of experiments (DOE) techniques provide an efficient means for you to optimize your process. But, you shouldn't restrict your studies only to process factors. Adjustments in the formulation may prove to be beneficial, as well. A simple but effective strategy of experimentation involves:

1. Optimizing the formulation via mixture design; and

2. Optimizing the process with factorial design and response surface methods *(1)*.

This article shows you how to apply DOE methods to your formulation. A case study gives you a template for action.

Why factorial methods may fail

Industrial experimenters typically turn to two-level factorials as their first attempt at DOE. These designs consist of all combinations of each factor at its high and low levels. With large numbers of factors, only a fraction of the runs need to be completed to produce estimates of main effects and simple interactions. However, when the response depends upon proportions of ingredients, such as in chemical or food formulations, factorial designs may not make sense. For example, look at what happens with experiments on lemonade (Table 1).

Run 1 (both factors low) and Run 4 (both factors high) taste the same. It makes more sense to look at taste as a function of the *proportion* of lemons to water, not the amount. Mixture design accounts for the dependence of response on proportionality of ingredients. If you experiment on formulations where only proportions matter, not the amount, factorials won't work. Use a mixture design.

Assessing mixtures

To illustrate how to apply mixture design, let's look at a relatively simple study that involves three surfactants (see Table 2) *(2)*. The experimenters measured the effects of these mixture components on an aqueous dispersion of polymeric nanospheres. They also studied the film-forming properties of this pharmaceutical preparation.

Table 3 details the experimental design, a second-degree augmented simplex lattice *(3)*. The scale goes from zero to one based on the relative proportions of the three ingredients. The experimenters held the total of the surfactants and all other ingredients at fixed levels.

Figure 1 shows the location of the points in the mixture space. (Ignore the contours for now.) In this triangular layout, the apexes represent the use of only a single, specific surfactant. Binary blends, which provide estimates of second-order effects, occur at the midpoints of the sides on the triangle. The points in the interior, which the experimenters added to augment the design, represent three-part blends. The centroid point contains equal amounts of all three ingredients. The interior points between the centroid and each apex represent axial check blends. These three-component mixtures contain two-thirds

of one respective component and one-sixth each of the other two components. The individual proportions go from zero to one from base to apex in each of the three axes.

The design includes one replicate of the centroid blend. This provides only a single statistical measure of pure error (one "degree of freedom" for estimation). We recommend that you also replicate the single-component runs to get a worthwhile estimate of pure error.

You can introduce constraints on individual components. However, this adds complications that go beyond the scope of this article; Ref. 3 provides the mathematical details. Software packages can set up optimal designs within constrained mixture regions *(4)*.

Creating a mathematical model

The experimenters desired minimal particle size for better dispersion. They also hoped to minimize the glass transition temperature for improved film forming. The two responses were fitted via least-squares regression to canonical mixture models. These polynomials account for the overall constraint that all mixture components must sum to one. They can be recognized by lack of an intercept. In an unconstrained mixture, first-order coefficients indicate response for the pure components. If a linear model proves sufficient, you can use these terms to determine the relative efficacy of each material. If higher-order terms must be employed, however, the picture gets complicated. The second-order terms in mixture models, such as AB, reveal interactions. For responses where higher is better, positive interaction coefficients indicate synergism while negative interaction coefficients signify antagonism. For responses where lower is better, such as the two responses in this case, the inverse is true: positive coefficients on interactions demonstrate antagonism and negative coefficients show synergism. In this case, by augmenting their design with interior points, the experimenters ran enough unique blends to allow estimation of a third-order term, ABC. This term, called a "special cubic," reveals any three-component interaction. When you work with chemical formulations, be prepared for complex interactions of this degree. Choose a design accordingly.

Mixture design is appropriate only when your response varies as a function of the proportions, not the total amount, of ingredients.

Table 4 shows the mixture models for particle size and glass transition temperature. The model coefficients came from a statistical software package that supports mixture design. Case statistics revealed that Blend 10 produced an unexpectedly low particle size (see Table 3). The statistics show this to be a highly significant outlier. However, because the original article does not reveal a special cause for this unusual deviation, we decided to keep the suspected outlier. If you uncover a questionable point, be sure to look for a possible reason, such a breakdown in equipment or mistake in making up the blend. Often, the cause of an outlier can be simply an error in data entry. If you cannot find a cause, be very cautious about modeling the response without that questionable point. It may pay to analyze the responses with and without the questionable point. If it makes no material impact on your decisions (which is what we observed in the particle-size response), keep the point. Also, we saw no sign of any outliers in the other response, glass transition temperature. This makes it less likely that there's anything unusual about Blend 10.

Optimizing via graphical techniques

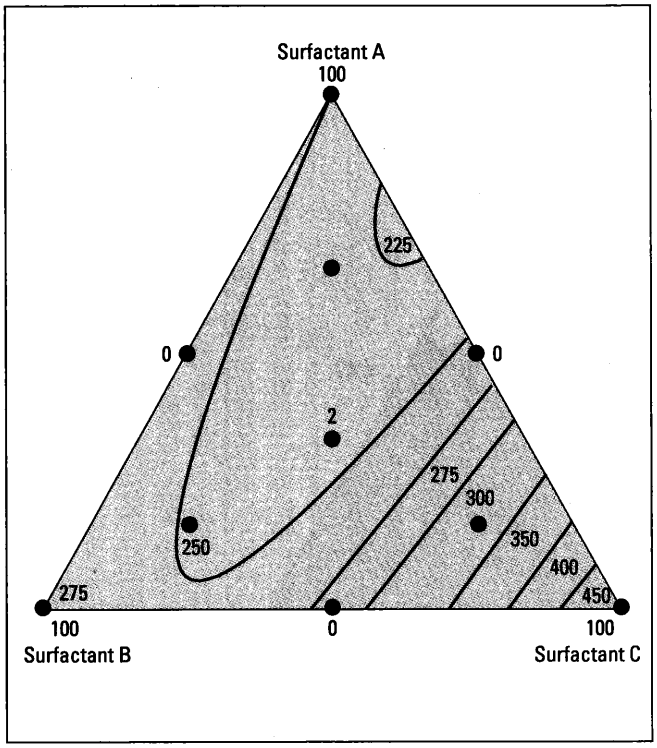
Given a statistically significant

Table 1. Misleading factorial design for lemonade.

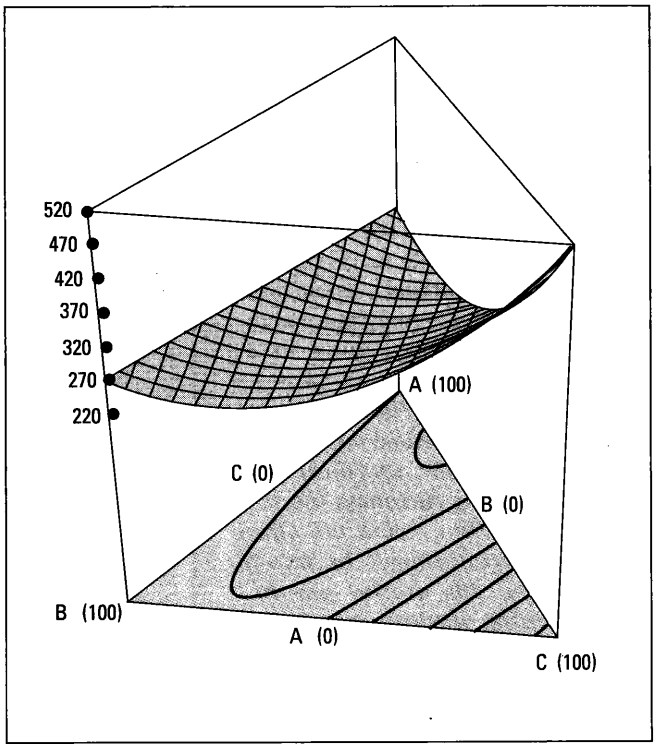
Run	Lemons	Water (cups)	Ratio of Lemons to Water	Taste
1	1	1	1.0	Good
2	2	1	2.0	Sour
3	1	2	0.5	Weak
4	2	2	1.0	Good

Table 2. Mixture components studied in surfactant experiment.

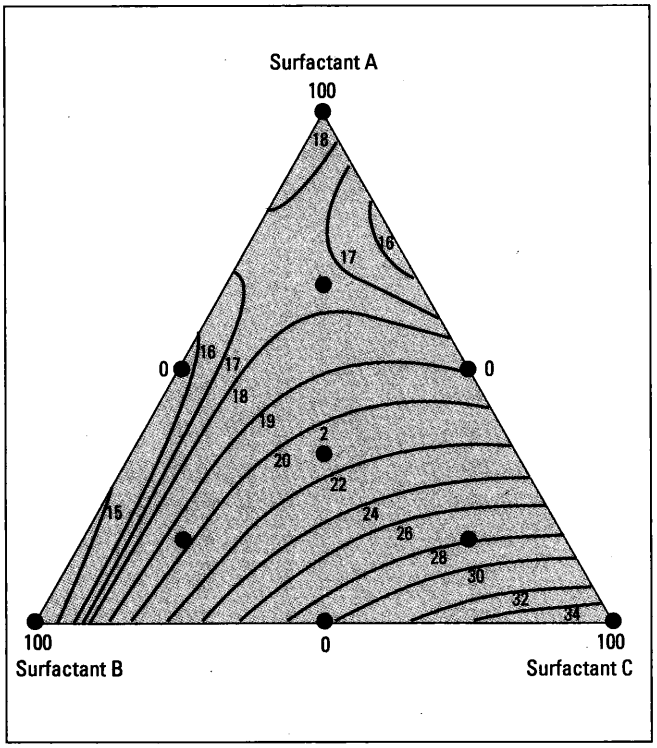
Component	Description
A	Poloxamer 188 NF
B	Polyoxyethylene 40 monostearate NF
C	Polyoxyethylene sorbitan fatty acid ester NF



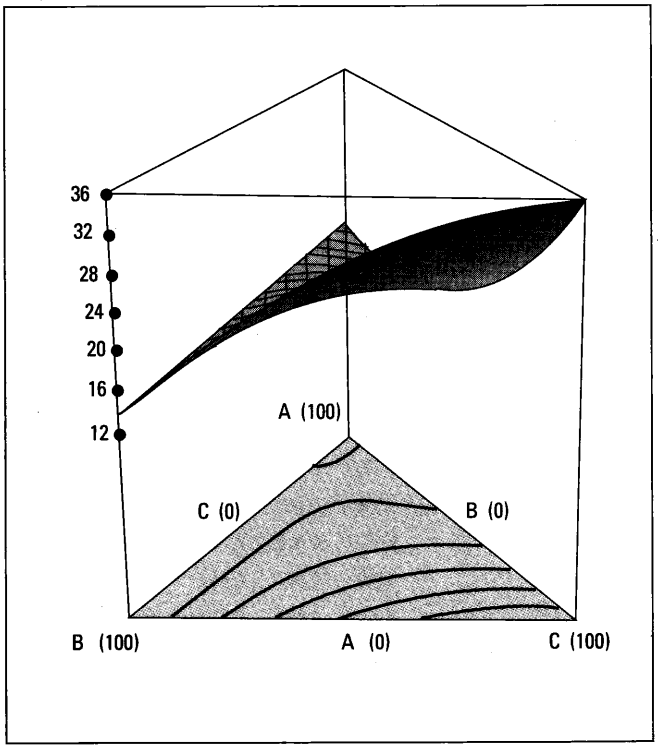
■ *Figure 1. Contour plot of particle size (from augmented simplex lattice mixture design).*



■ *Figure 2. Three-dimensional view of particle size.*

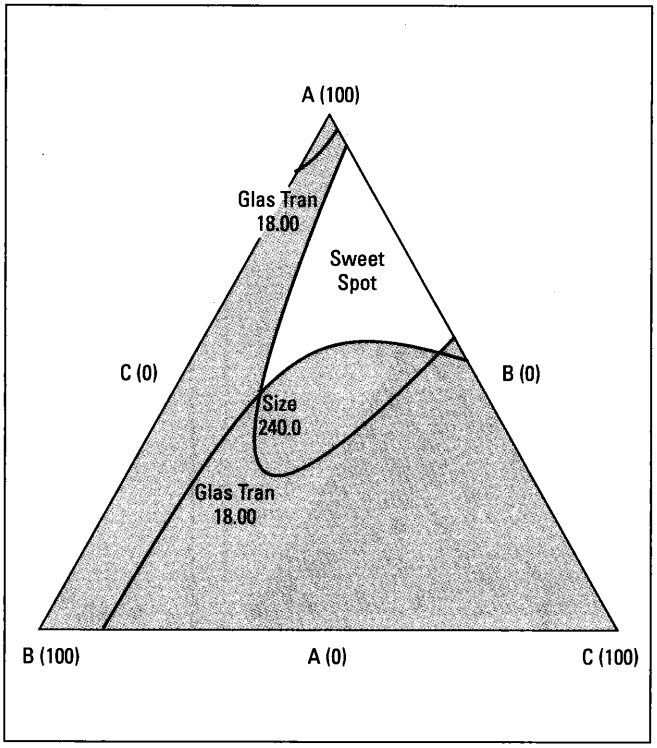


■ *Figure 3. Contour plot of glass transition temperature.*



■ *Figure 4. Three-dimensional view of glass transition temperature.*

fit, the mixture models become the basis for response surface graphs. These graphs provide valuable insights about your formulation. Figures 1 and 3 depict contour plots for particle size and glass transition temperature, respectively, from the surfactant mixtures. The three-dimensional representations (Figures 2 and 4) make it clear that particle size and glass transition temperature both can be minimized by going to a blend that is rich in Surfactant A (Poloxamer 188 NF). Figure 5 shows the contour plots overlaid with hypothetical maximum specifications. Areas not meeting maximum specifications are shaded, while the clear area meets specifications. As shown in the figure, this overlay plot reveals operating windows where you can hit the "sweet spot" and meet all customer specifications. When you work with more than three components or more than two process factors, it may become difficult to find the window because you must search through multidimensional space. Numerical search algorithms then become a necessity *(5)*.



■ *Figure 5. Overlay contour plot of particle size and glass transition temperature.*

Cost should be considered during this phase of the analysis. For formulations, it's easy. Just enter a cost equation as a function of the compo-

Table 3. Design matrix and data for surfactant study.

Blend No.*	Component Proportion			Blend Type	Particle Size†,	Glass Transition Temperature†,
	A	B	C		nm	°C
1	1.000	0.000	0.000	Pure A	250.1	18.9
2	0.000	1.000	0.000	Pure B	274.1	15.2
3	0.000	0.000	1.000	Pure C	533.5	35.0
4	0.500	0.500	0.000	Binary AB	255.2	16.1
5	0.500	0.000	0.500	Binary AC	267.3	18.9
6	0.000	0.500	0.500	Binary BC	294.3	31.2
7	0.333	0.333	0.333	Centroid	250.5	19.3
8	0.666	0.167	0.167	Check	232.5	18.2
9	0.167	0.666	0.167	Check	251.0	17.7
10	0.167	0.167	0.666	Check	276.0‡	30.1
11	0.333	0.333	0.333	Centroid**	255.0	19.0

* Actual run order randomized
**Replicate run
† Product is a controlled-release polymeric drug called poly(DL-lactdide)
‡ Statistical outlier

nent levels. Then, treat cost as an additional response on your overlay plot or numerical multiple-response optimization.

Relying on ratios

As an alternative to working in proportional scale and using mixture models, consider using ratios. For example, after settling on a surfactant, the pharmaceutical experimenters performed a standard response-surface study at varying ratios of polymer to surfactant while simultaneously varying the ratio of solid to liquid. With mixture variables expressed as ratios, you can add in to your experiment process factors such as agitation rate, temperature, and the like. When setting up ratios, be careful to follow these rules:

1. The number of ratios must be one less than the number of components.

2. Each ratio must include at least one component in at least one other ratio.

For more details on using ratios, see Ref. 3. The methods for combining process factors and mixture components remain relatively undeveloped, however.

Other caveats

Mixture design is appropriate only when your response varies as a function of the proportions, not the total amount, of ingredients. In some cases, such as application of coatings, this assumption cannot be satisfied and you must use an alternative approach for your DOE. Cornell *(3)* provides details on "mixture amount" designs. You also can use the ratio approach outlined above with amount added as a separate factor.

In addition, you must consider whether it's reasonable to vary each ingredient over a range of 0 to 100%. In many situations, you will need to impose constraints on one of more of the ingredients or on some combination of them. Good software for mixture design should easily accommodate a variety of constraints. Your constraints may form complex regions that cannot be covered by the standard mixture designs; so, you should select software that can set up optimal designs that will fit the polynomial you anticipate will be needed to model the response.

Finally, if you will be focusing primarily on process factors and wish to include concentration of a single chemical, then feel free to use a standard factorial or response surface design. For example, you might study time, temperature, and concentration in a 2^3 factorial with 8 runs. This keeps things as simple as possible.

A powerful tool

DOE methods can be applied to formulations if you account for the unique aspects of mixtures. By using appropriate designs, you greatly accelerate your exploration of alternative blends. Then, with the aid of response surface graphics based on mixture models, you can discover the winning component combination. CEP

Table 4 . Mathematical predictive models for surfactant study.

Particle size, nm

$Y_1 = 252\ A + 276\ B + 519\ C - 517\ AC - 456\ BC$

(Overall F* = 30 with p† < 0.001 ⇒ >99.9% confidence)

Glass transition temperature, °C

$Y_2 = 18.5\ A + 13.9\ B + 36.1\ C - 35.2\ AC + 19.6\ BC$

(Overall F* = 30 with p† < 0.001 ⇒ >99.9% confidence)

* F = F-test, ratio of signal to noise.

† p = probability of getting F if only random variability is at work — that is, the risk of a false positive outcome.

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