Find the Optimal Formulation for Mixtures

Discover "sweet spots" where multiple product specifications can be met in a most desirable way.

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(Writer's note: this is the second of a series on design of experiments. Part one provided tools for factor screening via two-level designs plus tools for process optimization via response surface methods.)

Design of experiments techniques provide an efficient means for you to optimize your process.[1] 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
2. Optimize the process with factorial design and response surface methods

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

Why factorial methods don't work well for mixtures

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 needs to be completed to produce estimates of main effects and simple interactions. However, when the response depends on 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 high) and run 4 (both factors low) 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.

Case study illustrates how to apply mixture design

To illustrate how to apply mixture design, we present a relatively simple study that involves three surfactants[2] (see Table 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 shows the experimental design, a second-degree augmented simplex lattice.[3] The scale goes from zero to one based on relative proportions of the three ingredients. The experimenters held the total of the surfactants and all other ingredients at fixed levels. 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 replicate the pure component runs also to get a worthwhile estimate of pure error.

Figure 1 shows the location of the points in the mixture space. (Ignore the contours for now). In this triangular layout, the apexes represent pure component blends. 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 2/3rds of each respective component and 1/6th each of the other two components. The individual proportions go from zero to one from base to apex in each of the three axes.

You can introduce constraints on individual components. This introduces complications that go beyond the scope of this article. The reference by Cornell 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. However, if higher order terms must be employed, 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. Negative interaction coefficients indicate antagonism. For responses where lower is better, such as the two responses in this case, the inverse is true: positive coefficients on interactions indicate antagonism and negative coefficients show synergism. In this case, by augmenting their design with interior points, the experimenter 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.

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. The statistics show this to be a highly significant outlier. However, since the original article does not reveal a special cause for this unusual deviation, we decided to keep the suspected outlier. If you uncover a suspected outlier, be sure to look for a special cause, such a breakdown in equipment, or mistake in making up the blend. Often the cause of an outlier can be simple an error in data entry. If you cannot find a cause, be very cautious about modeling the response without the questionable point. You could analyze the responses with and without the questionable point. If it makes no

material impact on your decisions, keep the point. This is what we observed in the particle size response. 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.

Multiple response optimization

Given a statistically significant fit, the mixture models become the basis for response surface graphs. The graphs provide valuable insights about your formulation. Figures 1 and 3 show contour plots for the two responses from the surfactant mixtures. The 3D representations (Figures 2 and 4) make it clear that particle size and glass transition temperature can both be minimized by going to a blend that's rich in surfactant A (poloxamer 188 NF). Figure 5 shows the contour plots overlaid with hypothetical maximum specifications. The 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] 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 component levels. Then treat cost as an additional response on your overlay plot or numerical multiple response optimization.

Option for mixtures: use 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 process factors such as agitation rate, temperature and the like to your experiment. You must be careful when setting up ratios 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 the reference by Cornell. The methods for combining process factors and mixture components remain relatively undeveloped. When the state-of-the-art progesses further, we may develop a how-to article on process/mixture optimization via DOE.

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 to your DOE. The reference by Cornell provides details on "mixture-amount" designs. You can also use the ratio approach outlined above, with amount added as a separate factor.

You must also consider whether it's reasonable to vary each ingredient over a range of 0 to 100 per cent. In many situations, you will need to impose constraints on one of more of the ingredients, or on some combination of ingredients. 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.

Conclusion

Design of experiment 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 will discover the winning component combination.

Literature Cited

(1) Anderson, M.J., Whitcomb, P.J., "Optimize Your Process-Optimization Efforts," *Chemical Engineering Progress*, December 1996.

(2) Frisbee, S.E., McGinity, J.W., "Influence of Nonionic Surfactants on the Physical and Chemical Properties of a Biodegradable Pseudolatex," *European Journal of Pharmaceutics and Biopharmaceutics, Vol. 40, No. 6* (December 1994).

(3) Cornell, *Experiments with Mixtures*, 2nd ed., John Wiley & Sons, Inc, New York, 1990.

(4) *1996 CEP Software Directory*, "Mathematics, Statistics" section.

(5) Anderson, M.J., Whitcomb, P.J., "Optimizing Formulation Performance with Desirability Functions", Quebec Metallurgical Conference, 1993.

Table 1: Misleading Factorial Design for Lemonade

Run	Lemons	Water (cups)	Ratio Lemons/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 (X_1)	**Poloxamer 188 NF**
B (X_2)	**Polyoxyethylene 40 monostearate NF**
C (X_3)	**Polyoxyethylene sorbitan fatty acid ester NF**

Table 3. Design Matrix and Data for Surfactant Study

Blend #[a]	A	B	C	Blend Type	Particle Size[b] (nm)	Glass Transition[b] (°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[c]	30.1
11	0.333	0.333	0.333	Centroid[d]	255.0	19.0

[a](Actual run order randomized)
[b](Product is a controlled-release polymeric drug[3] called poly(DL-lactdide))
[c](Statistical outlier.)
[d](Replicate run.)

Table 4 - Mathematical Predictive Models for Surfactant Study

Particle Size (nanometers):

$Y_1 = 252\ A + 276\ B + 519\ C - 517\ AC - 456\ BC$
(Overall F=30 with $p < 0.001 \Rightarrow$ >99.9% confidence)

Glass Transition:

$Y_2 = 18.5\ A + 13.9\ B + 36.1\ C - 35.2\ AC + 19.6\ BC$
(Overall F=30 with $p < 0.001 \Rightarrow$ >99.9% confidence)

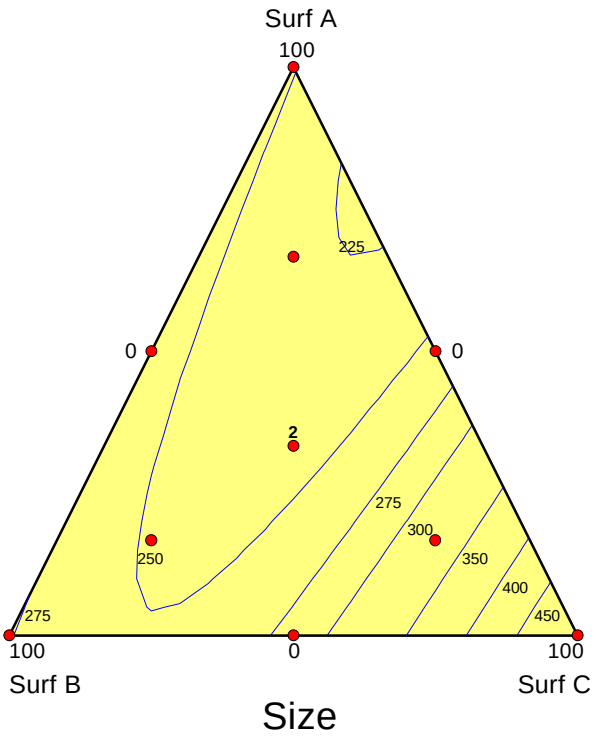

*Figure 1. Contour Plot of Particle Size**
**(from Augmented Simplex Lattice Mixture Design)*

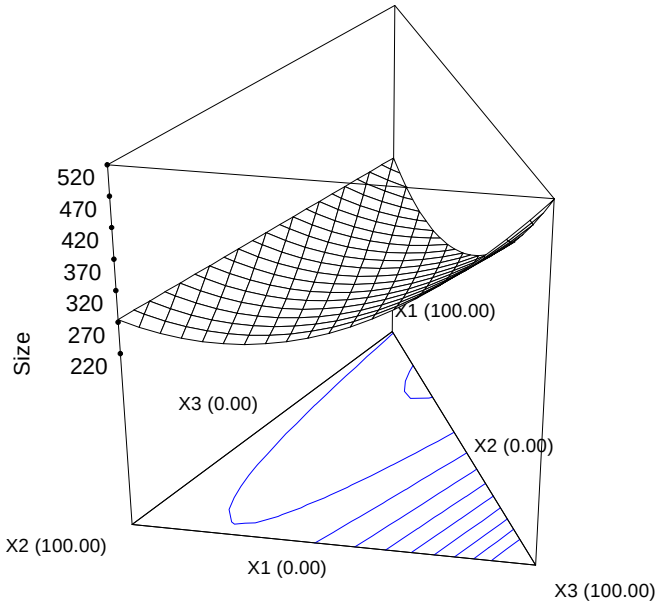

Figure 2. 3D View of Particle Size

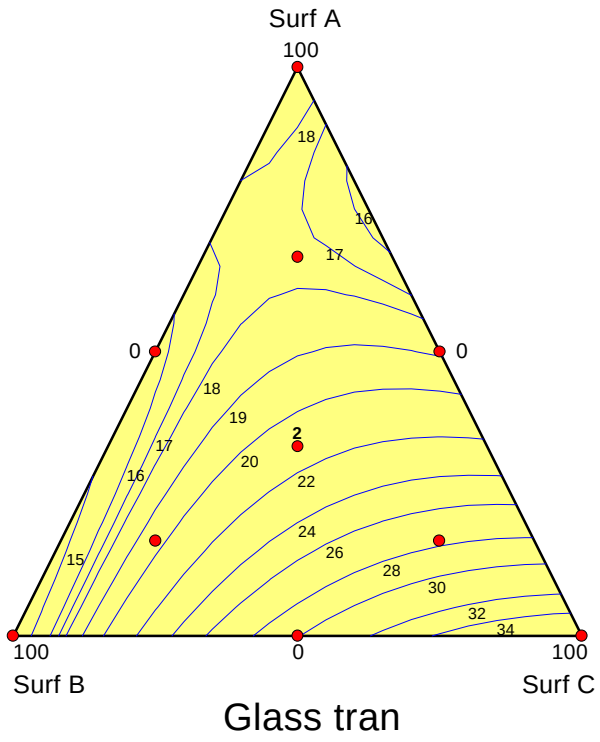

Figure 3. Contour Plot of Glass Transition Temperature

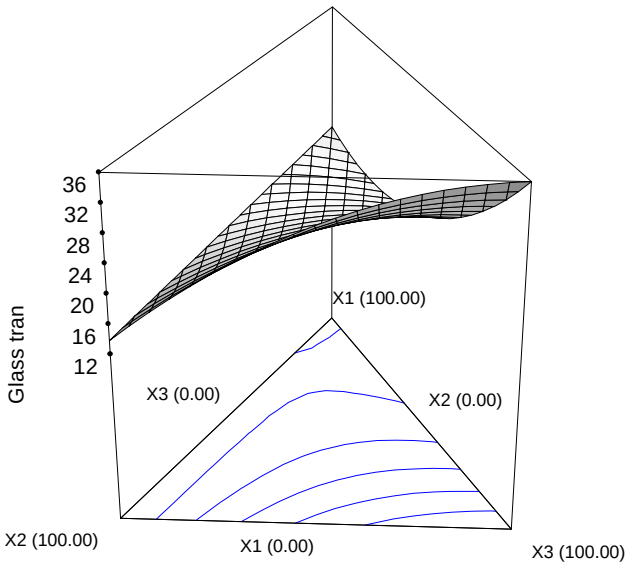

Figure 4. 3D View of Glass Transition Temperature

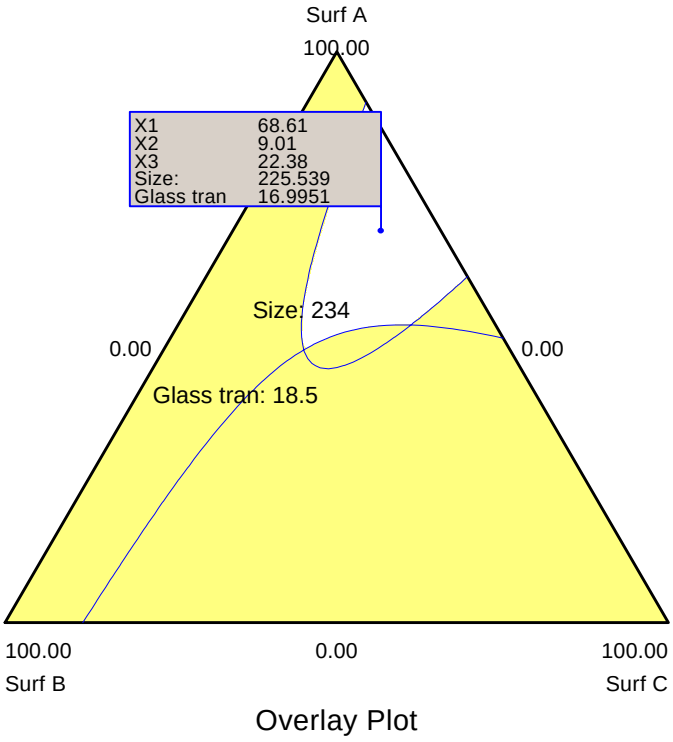

Figure 5. Overlay Contour Plot of Particle Size and Glass Transition Temperature