JMP Academic Case Study 055

Increasing Bioavailability of a Drug Using SMEDDS

Custom Mixture (Formulation) Design, Optimization, and Design Space

Produced by

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Key Ideas

This case study requires the use of design of experiments (DOE) – specifically, mixture or formulation design – to structure a smarter experiment for increasing the bioavailability of a drug. Since this drug has low solubility and bioavailability, it is challenging to formulate it using conventional development techniques. This problem can be solved with the help of JMP's unique design of experiments (DOE), which includes Custom Design for formulations.

Background

Bioavailability is an important factor in determining the efficacy of a drug. It is defined as the amount of the drug that reaches the bloodstream and thereby elicits action. There are many approaches to enhancing bioavailability, and one such is SMEDDS (self micro-emulsifying drug delivery system). SMEDDS are lipid-based drug delivery systems designed to improve medication dissolution in the gastrointestinal tract.

A pharmaceutical company (name kept confidential) is working on a pharmaceutical formulation to improve the bioavailability of a hard-to-dissolve active pharmaceutical ingredient (API). The company follows a Quality by Design (QbD) framework for development. An understanding of the critical quality attributes (CQAs) is a regulatory requirement and defines the quality target product profile (QTPP).

The API used in this formulation belongs to the biopharmaceutical classification system class of low solubility and permeability, which in turn constrains bioavailability. This formulation is a three-component system, comprising oil, surfactant, and cosurfactant. As part of the process, the API is solubilized in the oil and is emulsified using a surfactant and cosurfactant system to enhance the bioavailability of the drug. Thus, the drug-loaded micro-oil emulsified droplets have a better bioavailability profile than normally administered drugs. Bioavailability is a surrogate measure and can be influenced by oil droplet size, emulsification time, the amount of drug loaded in the oil, and the amount of drug released.

The Task

The development team has been tasked with creating a formulation that improves bioavailability. From domain expertise, it is understood that the lower the droplet size and emulsification time, the higher the bioavailability. At the same time, the amount of drug loaded in the oil and the amount of drug released upon administration have a direct influence on bioavailability. The team has the following tasks:

- To create an experimental design to conduct the trials. The team has a limited budget and can afford only 10 trial formulations.
- To identify the optimal mix of ingredients (oil, surfactant, and cosurfactant) to maximize the bioavailability.

With this background, the team decided to leverage DOE, a scientific way to actively learn, perform smarter experiments, and find the optimal factor settings.

The descriptions of the responses and factors, along with the limits, are presented below. (The limits were chosen based on the pre-formulation studies conducted prior to the DOE runs.)

Exhibit 1 Responses and Factors for Designing Experiment

Responses	Goal	Lower Limit	Upper Limit
Drug release at 15 min (%)	Maximize	70	100
Drug loading (mg/ml)	Maximize	90	100
Emulsification time (seconds)	Minimize	20	60
Droplet size (nm)	Minimize	50	300

Mixture Ingredients/Factors	Role	Lower Limit	Upper Limit
Capryol 90 (cosurfactant)	Mixture	0.12	0.32
Tween 80 (surfactant)	Mixture	0.51	0.67
Transcutol HP (oil)	Mixture	0.18	0.23

Please note that Capryol 90 is a nonionic cosurfactant used in oral lipid-based formulations for SMEDDS. Tween 80 is a widely used surfactant, and Transcutol HP is an oil-based solubilizer used for bioavailability enhancement.

Designing the Experiment

JMP can create classical mixture designs including simplex centroid, simplex lattice, extreme vertices, ABCD, and space filling. Since there was a constraint on the budget and number of runs, the team leveraged the Custom Design feature of JMP.

Custom Design: Custom Design in JMP generates a design suited to your problem (using an optimal design) so you don't have to push your problem to match a textbook design. Custom Design maximizes experimental budgets. Using its computer-generated designs, you can:

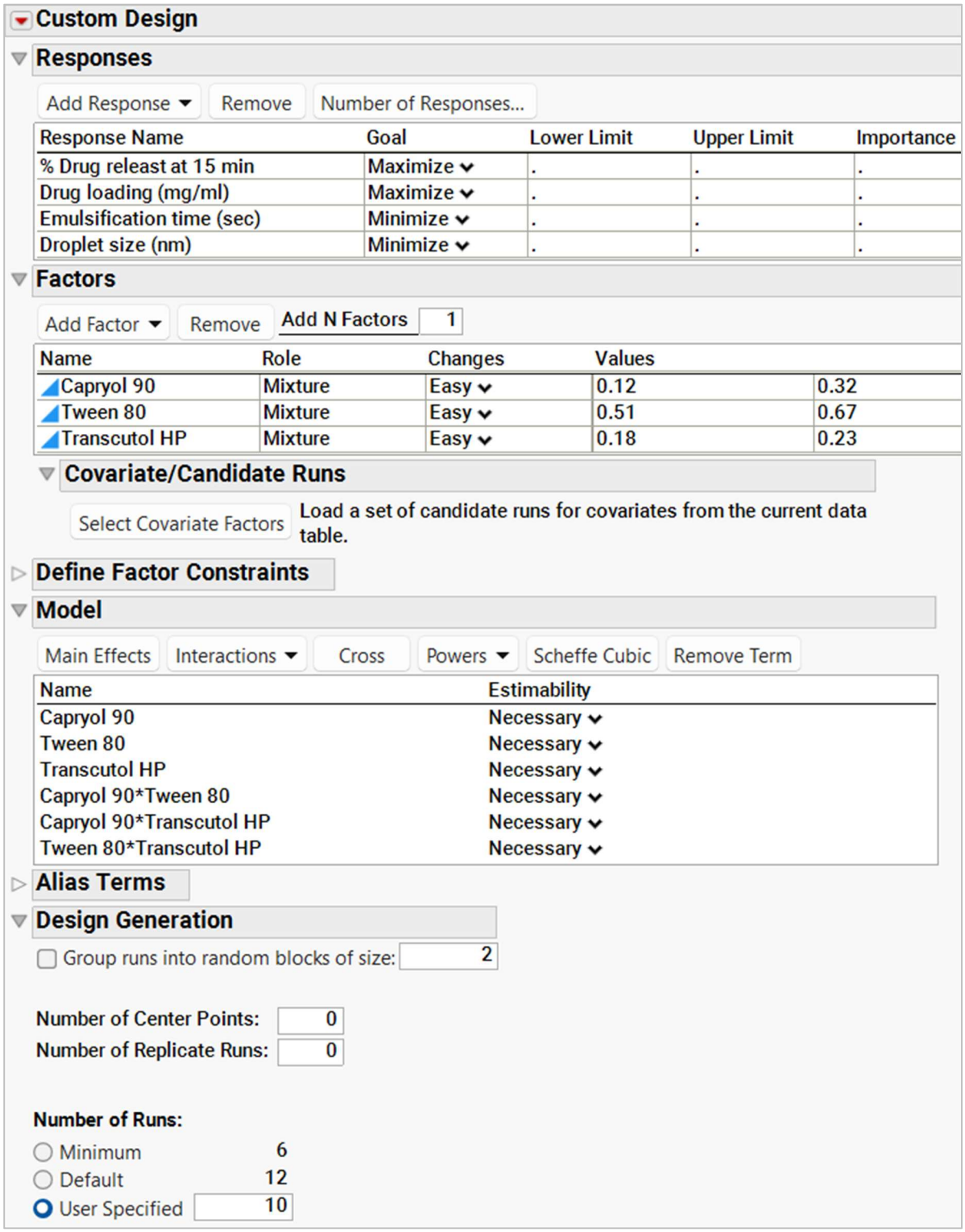
- Solve a variety of issues, including continuous, multilevel categorical, and mixture factors in the same design
- Define hard-to-change variables for automatic split-plot, split-split, and strip-strip designs
- Establish factor constraints, model effects, and interactions
- Include center points or replicate runs

Custom Design lets you run sample size and power calculations and see alias structures to help you determine if your experimental investment will be profitable and helps you construct designs fast and efficiently to save time, effort, and experimental resources.

Construction of Custom Mixture Design

Since this is a mixture design with constraints on the number of runs, the team applied Custom Design. Exhibit 2 shows the specifications for Custom Design.

Exhibit 2 Custom Design for Mixture Experiments



(DOE > Custom Design > Add four responses and select appropriate Goals for each of them. Specify the Lower Limit and Upper Limit as per the given data. Add the three continuous mixture factors and populate the lower and upper values. Under Model, select the Interactions drop-down and select the option "2nd". This will add two-way interactions to the model. Ensure the number of blocks is 2 and the user-specified number of runs is 10. > Make Design > Make Table. To replicate the design, use a random seed of 12345, which is available under the red triangle next to Custom Design.)

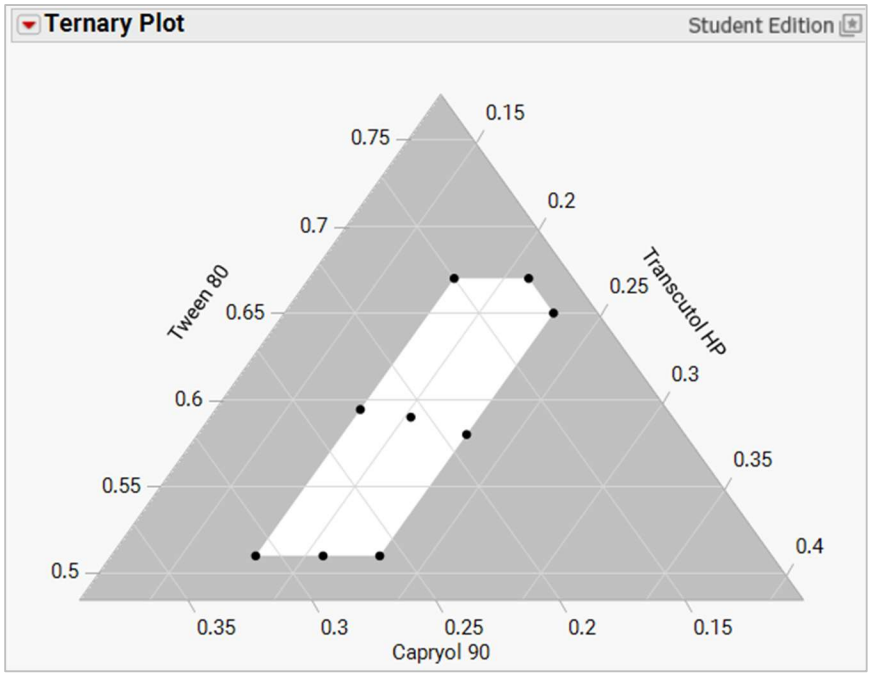
Input the responses and factors, followed by model specifications. After you select the model parameters, JMP gives you some guidance on the number of runs. The minimum number is the number of terms in the model; using it creates a saturated design. The default number is based on heuristics for creating a balanced design with at least four runs greater than the number of terms. This allows for an estimate of model error that has at least four degrees of freedom. (We had a constraint on the number of runs at 10.) As specified by the user, JMP will create an optimal design customized to the requirements or problem. It also provides metrics for design evaluation. Click Make Table to generate a table that gives the factor setting details of the 10 experiments and to populate the results.

The team conducted the experiment as generated by the custom mixture design, and the results are populated (as shown in Exhibit 3). The results are available in **smedds.jmp**. The team also visualized the design points using a ternary plot. Exhibit 4 shows the ternary plot (zoomed section) of the experimental runs.

Exhibit 3 Custom Design for Mixture Experiments with 10 Runs, Along with Responses

	Capryol 90	Tween 80	Transcutol HP	% Drug release at 15 min	Drug loading (mg/ml)	Emulsification time (sec)	Droplet size (nm)
1	0.21	0.59	0.20	84.1	98.1	40.7	240.2
2	0.19	0.58	0.23	87.11	98.44	42.33	253.67
3	0.15	0.67	0.18	86.14	98	41.33	248.53
4	0.12	0.65	0.23	93.68	100.11	26.33	188.7
5	0.26	0.51	0.23	79.91	97.44	45.67	260
6	0.31	0.51	0.18	74.24	97.11	57	290.73
7	0.23	0.59	0.18	85.89	98.33	45.33	257
8	0.31	0.51	0.18	74.24	97.11	57	290.73
9	0.28	0.51	0.21	77.4	97	55.67	278.2
10	0.12	0.67	0.21	89.92	100.11	34.33	227.2

Exhibit 4 Ternary Plot of Experimental Space

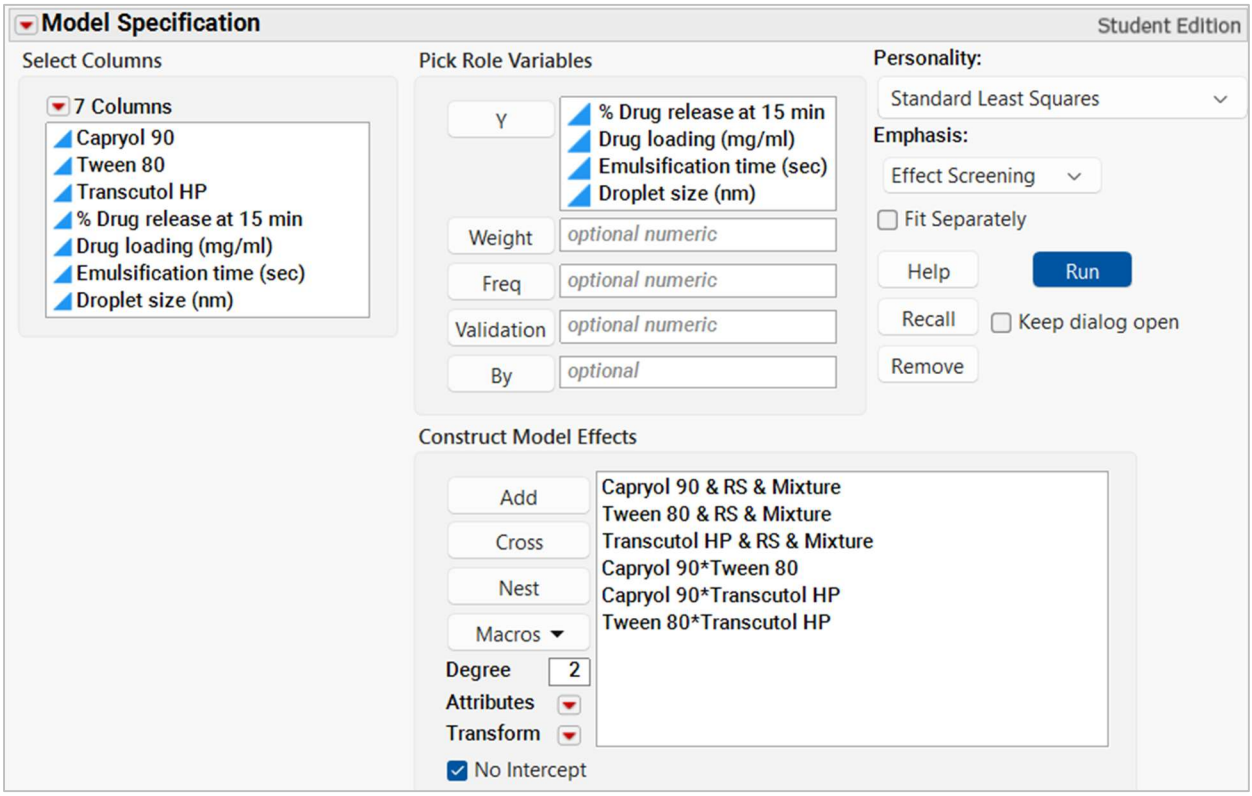


(Graph > Ternary Plot > Add all three factors (Capryol 90, Tween 80, and Transcutol) to the X plotting.)

Regression Analysis

JMP's Fit Model dialog, shown in Exhibit 5, enables us to explore the relationship between factors and responses.

Exhibit 5 Regression Analysis Using Fit Model

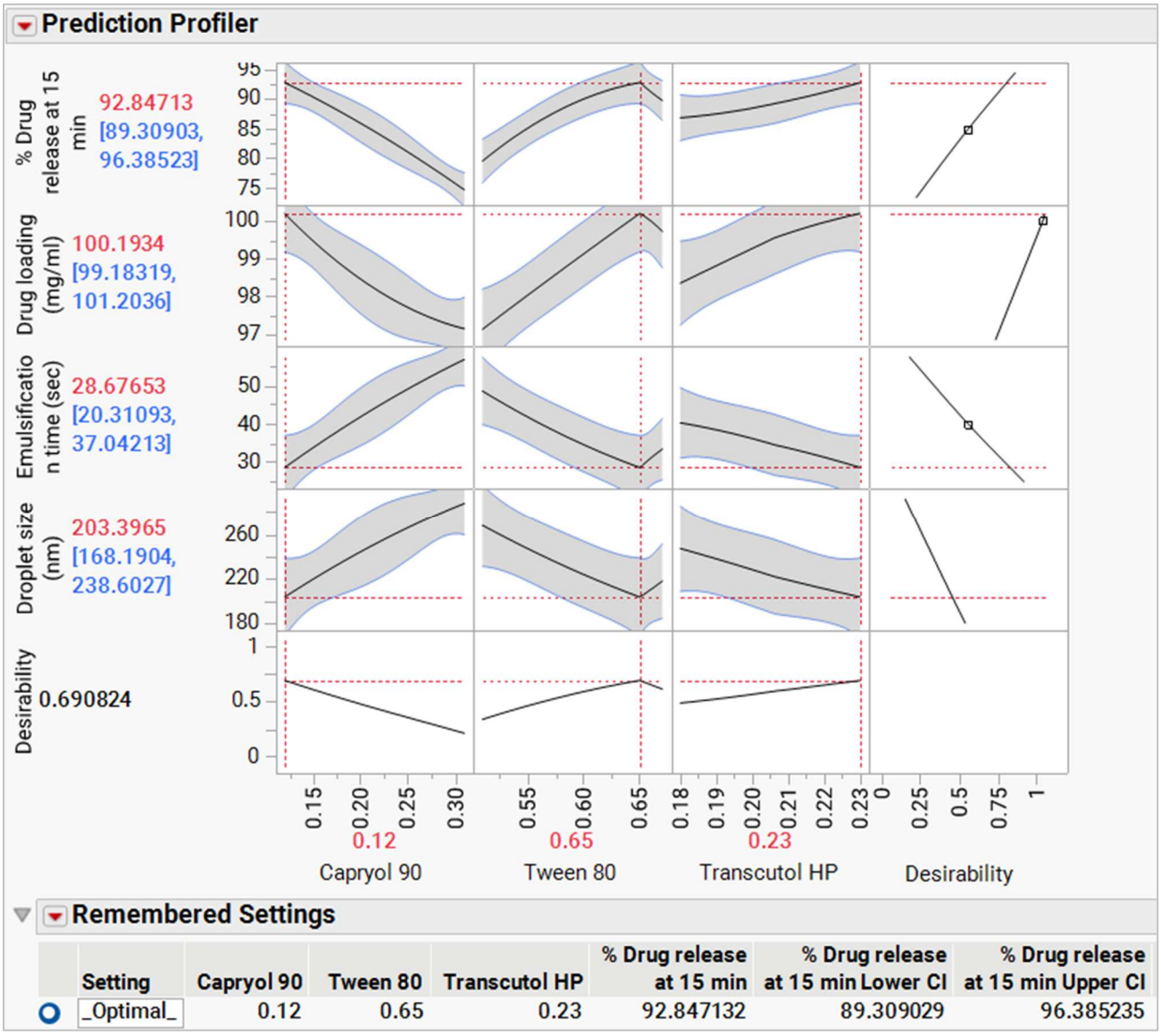


(Analyze> Fit Model> Select all the response variables and add to Y variables. select Capryol 90, Tween 80, and Transcutol HP and choose the Mixture Response Surface option under Macros. This will add all the main and two-way interactions as Model Effects. Select Standard Least Squares from the personality and click Run. One can also directly click the Model script that is generated by JMP from the data table.)

The regression output contains an effect summary followed by various metrics and diagnostic measures for each of the response variables. The red triangle next to Least Square Fit gives the option to choose from among multiple profilers, including Prediction, Contour, and Mixture, that enable visual exploration and regression understanding.

The Prediction Profiler (shown in Exhibit 6) is an interactive and dynamic graphical representation of the regression model. You can adjust one factor at a time with the Prediction Profiler to see how the anticipated responses change. (Note: If you change the value of any one of the factors using the slide, the other factors also change by maintaining their relative proportions.) Around the prediction trace, you can see the 95% confidence interval for the predicted values.

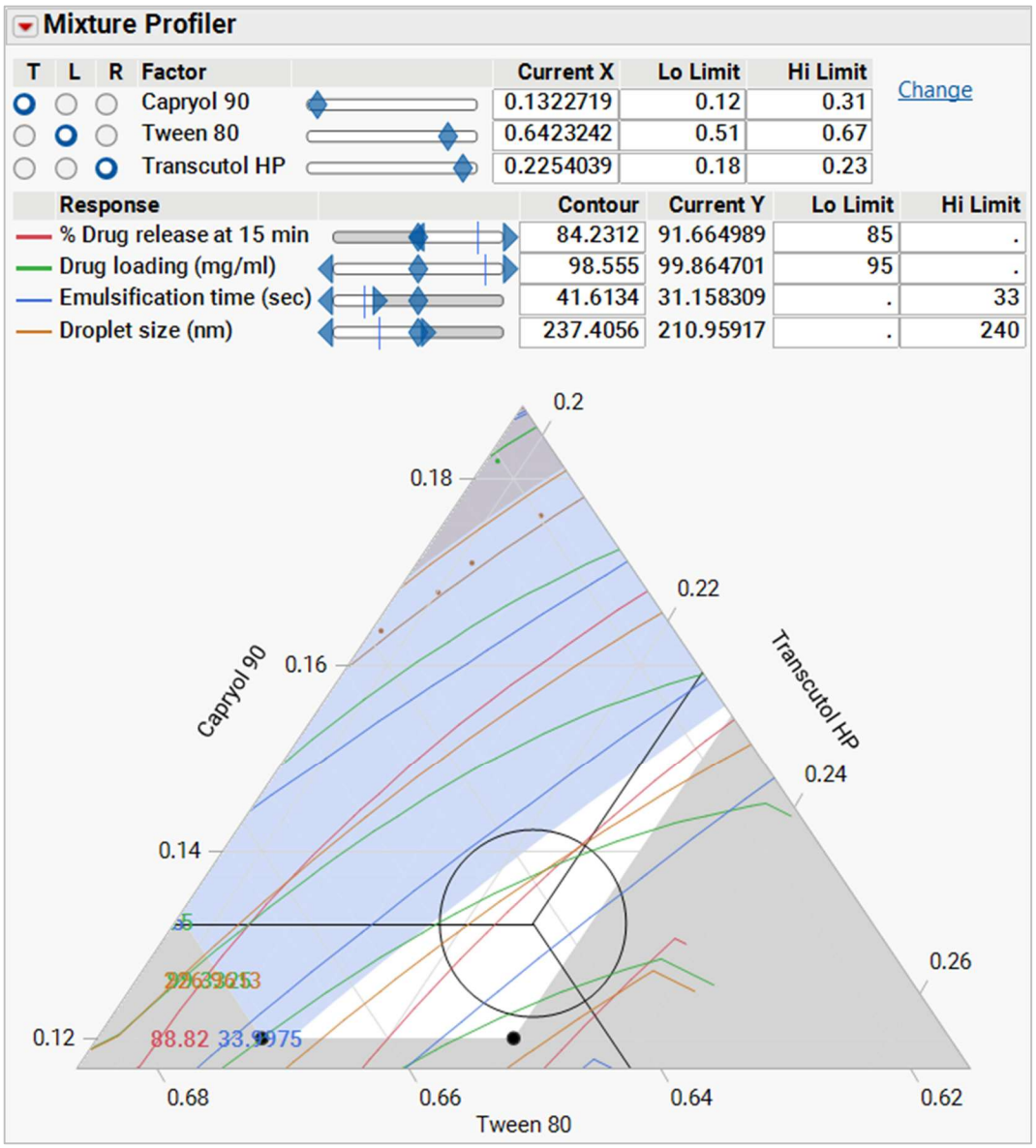
Exhibit 6 Prediction Profiler



The Prediction Profiler has additional built-in features. Maximize Desirability determines one combination of factor settings that results in a predicted response that optimizes our desirability (as set in Response Limits). (Note: There can be different factor level combinations that also maximize the desirability.) After selecting the option of maximizing desirability, the optimal factor settings and the corresponding response values are shown in Exhibit 6. The overall desirability is around 69%. (Note: The optimal factor settings might change each time you maximize desirability.) You can also explore other features like Simulation and Sensitivity Analysis.

The Mixture Profiler (shown in Exhibit 7) is useful for visualizing and optimizing response surfaces resulting from mixture experiments. It displays response contours on a ternary plot for mixture models, where all three factors in the model are components (ingredients) in a mixture. While the Prediction Profiler helps to optimize numerically, the Mixture Profiler helps you explore how the feasible region of a response is impacted by mixture components. We can also specify the constraints on the levels of the mixture components.

Exhibit 7 Mixture Profiler



As highlighted in Exhibit 7, we set the lower limits (for maximization functions) and higher limits (minimization functions) for responses using the slider controls or contour edit boxes. The Mixture Profiler shows the response contours of mixture experiment models on a ternary plot. The Mixture Profiler helps you see and optimize the response surfaces of your experiment. We magnified the region of interest using the magnifier from the Tools menu to visually explore the optimal solutions. Shading is used to exclude infeasible regions, and the white-colored zone depicts the design space or the possible optimal solutions. Use the Mixture Profiler's red triangle and select Factor Settings > Remember Settings to save the settings.

Summary

Statistical Insights

A well-designed experiment aids in active learning and understanding of the effect of changes in factor proportions on formulation responses. This case familiarized the creation of a formulation/mixture design. A constraint was presented (in terms of the number of runs), thus leading to the application of Custom Design instead of classical mixture designs. Output from regression helped in finding the optimal values of mixture components.

Managerial Implications

Applying Custom Design helps reduce the timelines and experimental effort needed to formulate a pharmaceutical product with a well-enunciated design space. Custom Design lets you experiment well and meet multiple response goals, which helps you stay in compliance with regulations.

JMP Features and Hints

This case used the DOE platform to create a design and analysis platform to fit a regression model. The Prediction Profiler was used to ascertain the optimal factor settings. A ternary plot was leveraged to visualize the design space.

Exercises

1. Using the tables below, create a mixture design. The number of runs must be exactly 12. Use a random seed of 12345 while creating your design.

Responses	Goal	Lower Limit	Upper Limit
Drug release at 15 min (%)	Maximize	70	100
Drug loading (mg/ml)	Maximize	90	100
Emulsification time (seconds)	Minimize	20	60
Droplet size (nm)	Minimize	50	300

Mixture Ingredients	Role	Lower Limit	Upper Limit
PEG 400 (cosurfactant)	Mixture	0.11	0.33
Tween 20 (surfactant)	Mixture	0.49	0.68
Captex 355 (oil)	Mixture	0.16	0.24

2. Use the **Mixtureexercise.jmp** dataset and perform the following tasks.

   - Visualize the experimental design data using the ternary plot.
   - Fit a regression model (considering main effects and two-way interactions) and find the optimal factor settings using the Prediction Profiler.