

Strategies for Formulations Development

A Step-by-Step Guide Using JMP®



Ronald D. Snee • Roger W. Hoerl



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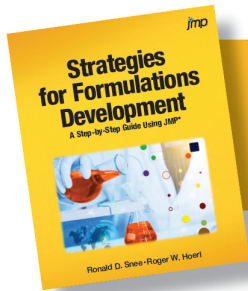
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Introduction to Formulations Development

“Manufacturers would often experiment, changing their formulas after tests of a finished powder proved it was not giving the results desired”.

Norman B. Wilkinson, *Explosives in History*, 1966

Overview

Many products are created by mixing or blending several components or ingredients. In the statistical literature the term *mixture* is used to define a formulation, blend, or composition. In this chapter, we discuss some examples of formulation and how to display formulations graphically. We also present some case studies that illustrate the problems addressed in formulation studies and show how such problems are resolved.

By the end of this chapter, here is what you will have:

- An introduction to formulations
- An understanding of how formulations are different from other types of experimentation
- Examples of formulations from various fields of study

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1.1 Examples of Formulations

Here are some examples of well-known products that are formulated by mixing together two or more ingredients or components:

- Pharmaceutical Tablets
- Food
- Gasoline Blends
- Metal Alloys
- Rocket Propellants
- Aerosol Formulations
- Paints
- Textile Fiber Blends
- Concrete
- Dyes
- Rubber
- Cocktails

This list illustrates the variety of scientific areas in which mixture experimentation is used. Here are some details.

Pharmaceutical Tablets – The tablets that we take are formulated by mixing the active ingredient (the compound used to treat the disease) with a number of other ingredients to form and manufacture the tablet. The ingredients include diluents, disintegrates, lubricants, glidants, binders, and fillers. How well the tablet dissolves is often a function of one or more of these ingredients.

Food – A variety of foods are manufactured by mixing several ingredients. For example, the development of cake mixes usually involves considerable mixture experimentation in the laboratory to determine the proportions of ingredients that will produce a cake with the proper appearance, moistness, texture, and flavor.

Gasoline Blends – Gasoline (for example, 91 octane) is a blend of different gasoline stocks derived from various refining processes (catalytic cracking, alkylation, catalytic reforming, polymerization, isomerization, and hydrocracking) plus small amounts of additives designed to further improve the overall efficiency and reliability of the internal combustion engine. The petroleum engineer's problem is to find the proportions of the various stocks and additives that will produce the 91 octane at minimum cost.

Metal Alloys – The physical properties of an alloy depend on the various percentages of metal components in it. How does one determine the proper percentages of each component to produce an alloy with the desired properties? Many important alloys have properties that are not easily predicted from the properties of the component metals. For example, small variations in the proportional amounts of its components can produce remarkable changes in the strength and hardness of steel.

Rocket Propellants – An early application of mixture design methodology involved the making of rocket propellants at a U.S. Naval Ordnance Test Station (Kurotori 1966). A rocket propellant contains a fuel, an oxidizer, a binder, and other components. A rocket propellant study is discussed in Chapter 5.

Aerosol Formulations – Numerous products, such as paints, clear plastic solutions, fire-extinguishing compounds, insecticides, waxes, and cleaners, are dispensed by aerosols. Food products, such as whipped cream, are also packaged in aerosol cans. To ensure that the formulation passes through the aerosol valve, you must usually add surface-active agents, stabilizers, and solvents. Such a formulation, then, is a complex mixture of propellants, active ingredients, additives, and solvents. When developing a new aerosol formulation, it is often of interest to know how well the formulation comes out of the can, what type of product properties it has, and whether it is safe to use.

Paints – Paints are also complex mixtures of pigment, binder, dispersant, surfactant, biocide, antioxidant, solvent, or water. These components are blended to produce a paint that does not drip, is washable, has the correct color value, and does not attract dirt. Manufacturers want to know what proportions of the various ingredients produce these desired properties.

Textile Fiber Blends – This is a different type of mixture. For example, in making a good polyester-cotton shirt, one has to determine the proper proportions of synthetic and natural fibers. One objective is to find a compromise between the wearability of the shirt and the aesthetic properties. A 100% cotton shirt generally does not wear long, and is very difficult to iron. By contrast, a 100% polyester shirt has great wearability but is not as comfortable. A 65% polyester-35% cotton compromise is often used to balance these two properties.

Concrete – Some scientists are developing reinforced concrete (a mixture of cement, sand, water, and mineral aggregates) with additives such as fiberglass (also called a fiber-reinforced composite). Such studies might determine whether the optimum proportions of cement, sand, and so on, are the same for two candidate additives.

Dyes – Anytime you see color on a substrate, whether your clothing, the carpet, or the wall, it will undoubtedly be a mixture of dyes blended in particular proportions to produce a certain hue, brightness, wash fastness, light fastness, and color value.

Rubber – One may be interested in measuring the tensile properties of various compositions of natural, butadiene, and isoprene-type rubber for automobile tires and other purposes.

Cocktails – A martini is a mixture of five parts gin and one part vermouth. In fact, most of our cocktails are mixtures of two or more liquors, plus juices, flavorings, and perhaps water or ice. The martini illustrates the unique property of a mixture system. The response is a function of the proportions of the components in the mixture and not the total amount of the mixture. The taste of a martini made from 5 ounces of gin and 1 ounce of vermouth is the same as one made from 5 liters of gin and 1 liter of vermouth. Of course, the consumption of the total amounts of the two mixtures would have vastly different effects.

1.2 How Formulation Experiments are Different

It should be recognized at the outset that experimenting with formulations is different from experimenting with other types of variables. In this book we address formulations in which the properties of the formulation are a function of the proportions of the different ingredients in the formulation, and not the total amount of the ingredients. As Table 1.1 illustrates, a formulation made by mixing four parts of ingredient A and one part of ingredient B would have the same performance no matter whether the product was formulated with 4 pounds of ingredient A and 1 pound of ingredient B or 8 pounds of ingredient A and 2 pounds of ingredient B. That is, the performance of the two formulations would be the same because the ratio of the two ingredients is 4:1 in both.

Table 1.1 – Formulation Proportions

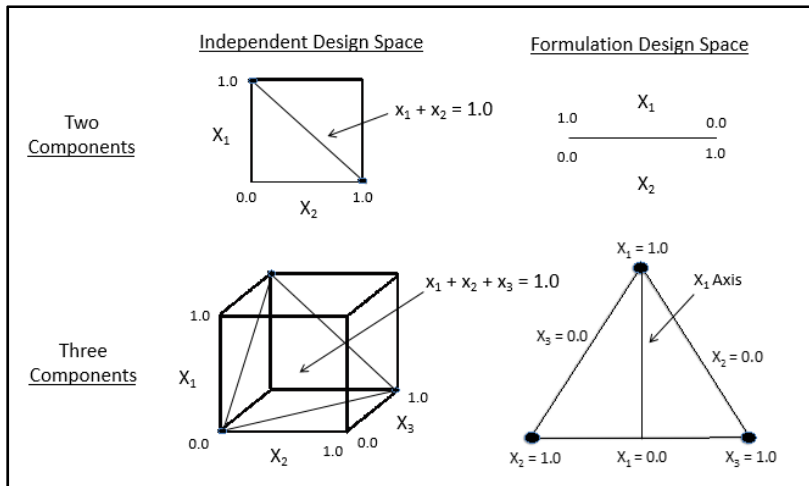
Formulation	Ratio
4A + 1B	4:1
8A + 2B	4:1

On a proportional basis the formulation consists of 0.8 ingredient A and 0.2 ingredient B; this is sometimes referred to as an 80:20 formulation of ingredients A and B. The proportions of the components sum to 1.0. It is this characteristic that sets formulations apart from other types of products. In the case of q components in the formulation, if we know the levels of all the components but one, we can compute the level of the remaining component by knowing that all components sum to 1.0:

$$x_1 + x_2 + \dots + x_q = 1, \text{ hence } x_q = 1 - (x_1 + x_2 + x_3 + \dots + x_{q-1})$$

The summation constraint has the effect of modifying the geometry of the experimental region and reducing the dimensionality. This effect can be seen in Figure 1.1. Note that for two independent variables (non-formulations), the typical factorial designs are based on a two-dimensional square. With formulations, however, the second component must be one minus the first component. Hence, the available design space becomes a line instead of a square. Therefore, there is only one true dimension in the formulation design space, or one fewer than the dimensionality of the factorial space.

Figure 1.1 – Geometry of Formulation Experimental Regions



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When experimenting with three independent (non-formulation) variables, the typical factorial designs are based on a three-dimensional cube. The three formulation components must sum to 1.0. However, once the proportions of the first two components have been determined, the third must be 1.0 minus these. Therefore, the available design space becomes a two-dimensional triangle, or *simplex*. Chapter 3 discusses in detail the effect of the formulation constraint on the resulting experiment designs.

Displaying Formulation Compositions Using Trilinear Coordinates

The first effect of the formulation constraint is how the formulations are displayed graphically. This is particularly important as graphical display and analysis are critical to the successful design, analysis, and interpretation of formulation experiments and data. Trilinear coordinates are used to display formulation compositions. When all the components vary from 0 – 1, the region is referred to as a simplex. The region for three components is shown in Figures 1.2a, 1.2b, and 1.2c.

Figure 1.2a – Three-Component Simplex: x_1 Component Axis

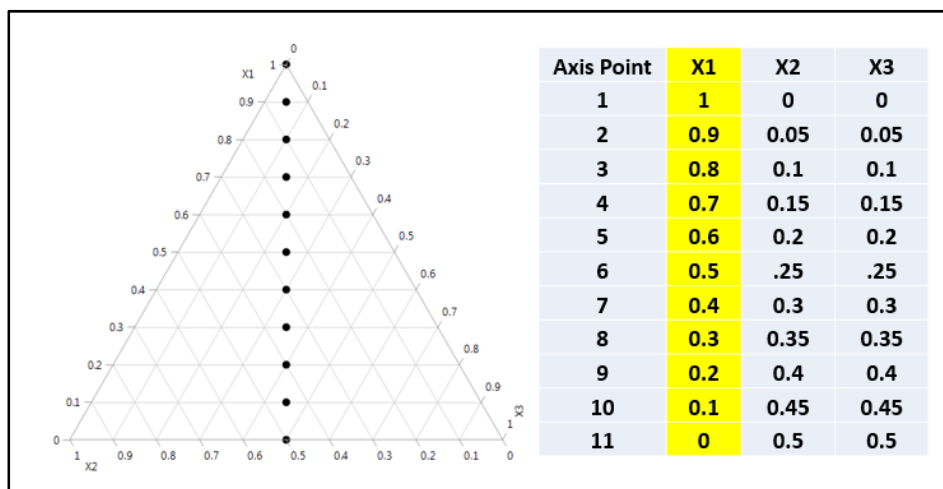
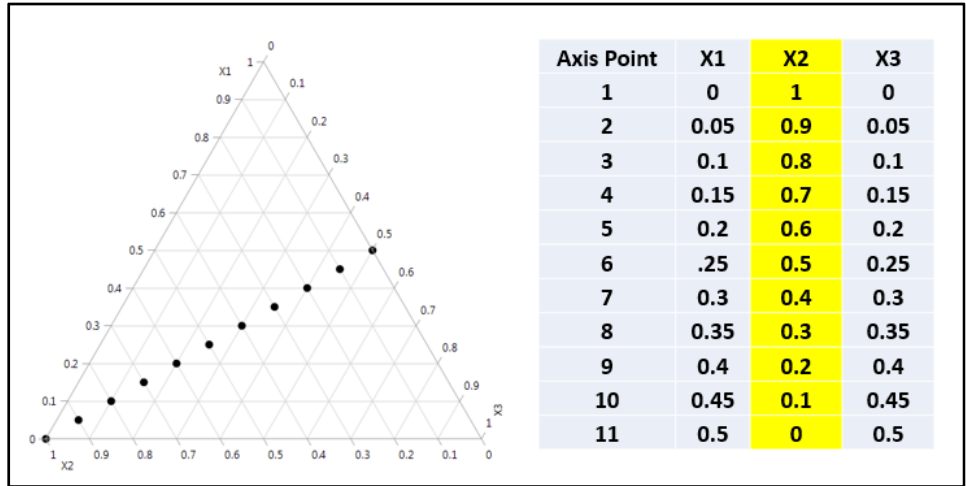
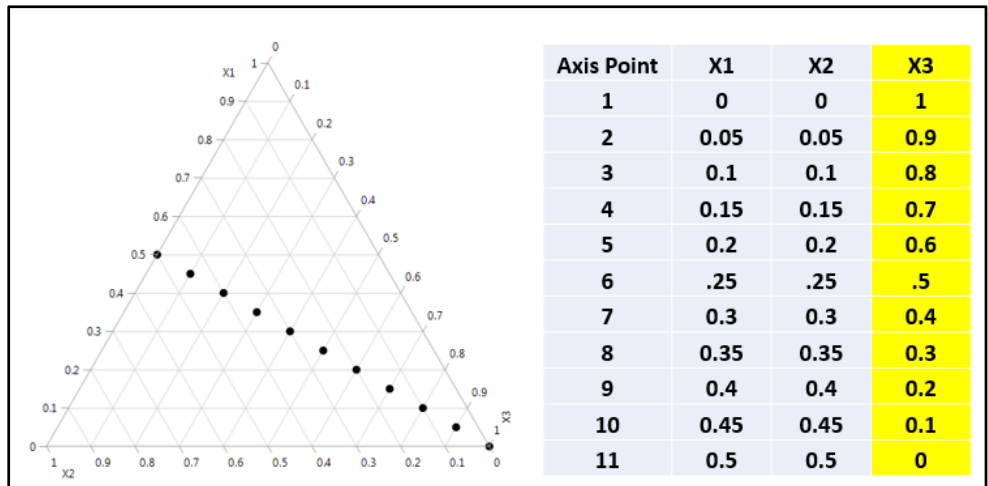
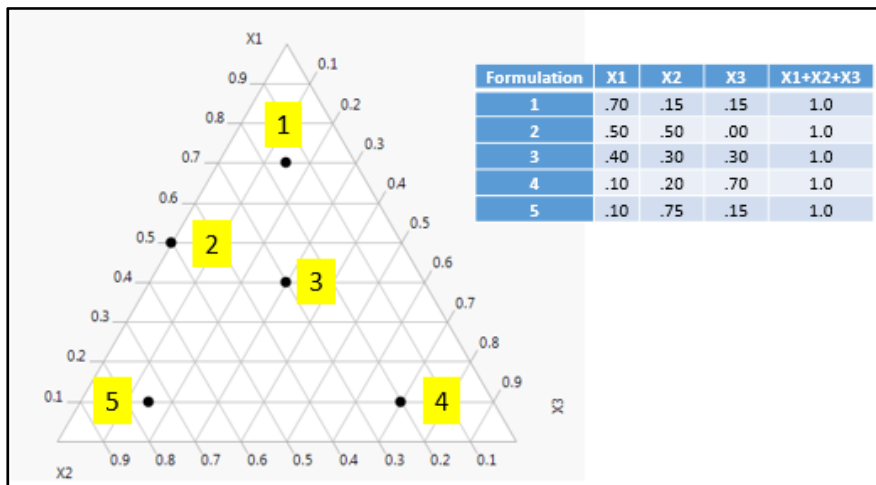


Figure 1.2b – Three-Component Simplex: x_2 Component AxisFigure 1.2c – Three-Component Simplex: x_3 Component Axis

The region is a triangle that has three vertices and three edges. The x_1 component axis runs vertically from the bottom ($x_1=0$) to the top ($x_1=1$) of the triangle (Figure 1.2a). The x_2 component axis varies from the right-hand side of Figure 1.2b ($x_2=0$) to the lower left of the figure ($x_2=1$). The x_3 component axis varies from the left-hand side of Figure 1.2c ($x_3=0$) to the lower right of the figure ($x_3=1$). Lines of constant x_1 , x_2 , and x_3 run parallel to the bottom, right, and left sides of the triangle, respectively. All coordinates of all the points in the figure sum to 1.0 ($x_1+x_2+x_3=1$).

The compositions of five formulations are shown in Figure 1.3.

Figure 1.3 – Trilinear Coordinates Examples



The point, or composition (0.7, 0.15, 0.15), is the intersection of the line $x_1 = .7$, which is 0.7 of the distance from the top and the bottom of the triangle; the line $x_2 = 0.15$, which is 0.15 of the distance from the right side to the left corner; and the line $x_3 = .15$, which is 0.15 of the distance from the left side to the lower right corner. In three-component mixtures, $x_1 + x_2 + x_3 = 1$. Hence, the third coordinate is one minus the sum of the other two. The resulting triangle has only two independent dimensions, and the intersection of any two lines defines a point. For example, the point (.4, .3, .3) is the intersection of the lines $x_1 = .4$ and $x_2 = .3$, or $x_1 = .4$ and $x_3 = .3$, or the intersection of $x_2 = .3$ and $x_3 = .3$. The use of trilinear coordinates to display formulations will be discussed further in Chapter 3 and used throughout the book.

In the case of more than three components (dimensions) the space is still referred to as a *simplex*. The constraint that the sum of the components (x 's) is a constant (in most cases 1) still holds. As a result, the x 's cannot be varied independently of each other. In the case of q components, we can calculate the level of any component in the formulation, given the levels of the other components in the formulation. As a result, the regression model used to describe the data does not have an intercept term, and the quadratic (non-linear blending) model does not have squared terms. These models are discussed in detail in Chapter 4.

1.3 Formulation Case Studies

This section introduces four case studies to illustrate the problems addressed in formulation studies and how these problems are resolved. The methods to produce the designs, analyses, and results are discussed in the following chapters.

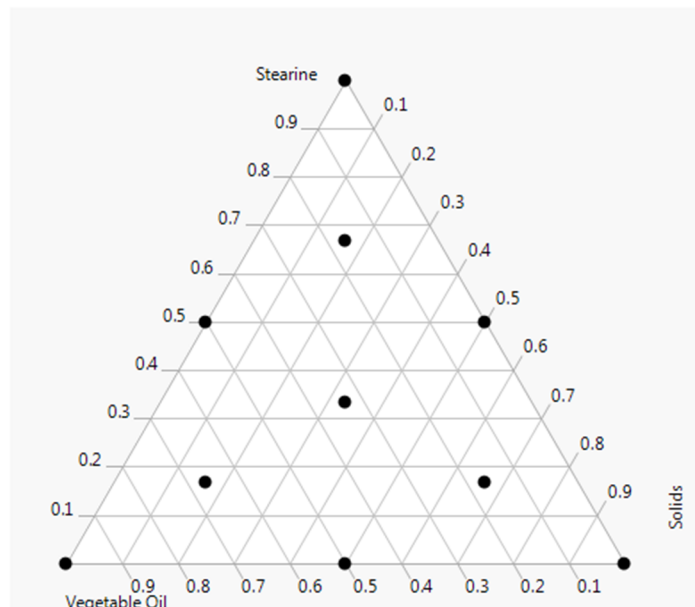
Food Product

Hare (1974) describes a three-component study whose objective was to study the blending behavior of three components on the performance of a vegetable oil as measured by the solid fat index (y). Ten formulations were prepared as summarized in Table 1.2 and displayed graphically in Figure 1.4.

Table 1.2 – Vegetable Oil Formulation Experimental Design Blends

Blend	Stearine	Vegetable Oil	Solids	Solid Fat Index
1	1	0	0	4.6
2	0	1	0	35.5
3	0	0	1	55.5
4	1/2	1/2	0	14.5
5	1/2	0	1/2	25.7
6	0	1/2	1/2	46.1
7	1/3	1/3	1/3	27.4
8	2/3	1/6	1/6	14.5
9	1/6	2/3	1/6	32.0
10	1/6	1/6	2/3	42.5

Figure 1.4 – Vegetable Oil Formulation Experimental Design



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The three components were x_1 =Stearine (vegetable oil solids of one type of oil), x_2 =vegetable oil (a different oil type) and x_3 =vegetable oil solids of yet a third type of oil. The objective of the experiment was to find compositions that would produce a solid fat index of 40.

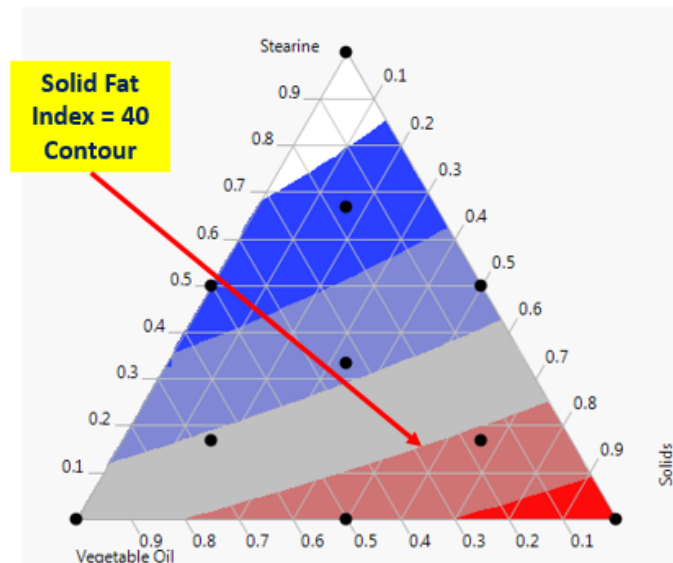
Regression analysis was used to create the prediction equation that enables one to calculate the solid fat index for any composition of the three components studied:

$$E(y) = 4.61x_1 - 35.9x_2 + 56.0x_3 - 21.5x_1x_2 - 16.6x_1x_3$$

We note here that a cross-product term such as x_1x_2 describes the non-linear blending characteristics of components 1 and 2 (the response function is curved). It is not referred to as an interaction term as in models for process variables. Blending characteristics are discussed in detail in Chapter 4.

An effective way to understand the blending behavior of the components is to construct a response surface contour plot as shown in Figure 1.5.

Figure 1.5 – Vegetable Oil Contour Plot



Here we see that there are a number of compositions to choose from to produce a solid fat index of 40.

Formulation	Stearine (%)	Vegetable Oil (%)	Vegetable Oil Solids (%)	Predicted Solid Fat Index
1	10	45	45	40
2	20	15	65	40

In Table 1.2 we saw that Blend 10 (1/6, 1/6, 2/3) had a measured solid fat index of 42.5. We also saw that there are a number of possible tradeoffs between the components. The different components have different costs. The composition selected was the most cost effective formulation.

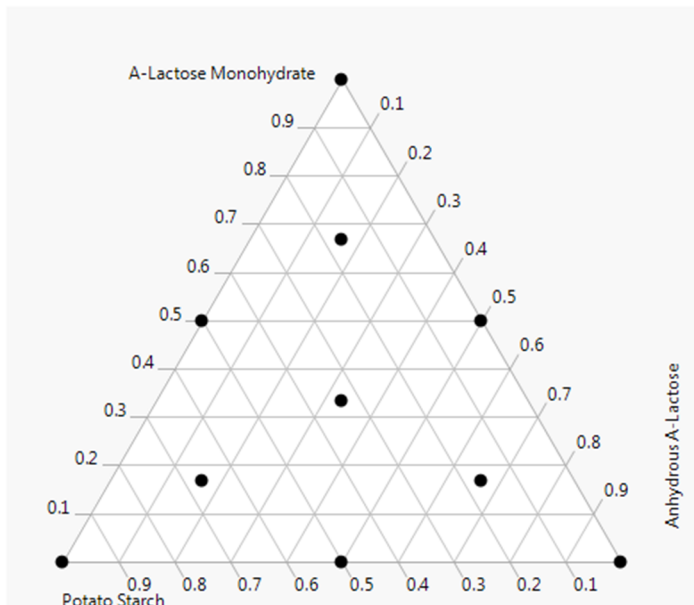
Pharmaceutical Tablet Formulation

Huisman et al. (1984) discuss the development of a pharmaceutical tablet containing up to three diluents: Alpha-Lactose Monohydrate, Potato Starch, and Anhydrous Alpha-Lactose. The lubricant Magnesium Stearate was held constant in the study. The objective of the study was to find a formulation with tablet strength >80N (Newton) and disintegration time <60 seconds at minimum cost. The formulation design and response data are summarized in Table 1.3 and displayed in Figure 1.6.

Table 1.3 – Pharmaceutical Placebo Formulation Experiment Design

Blend	Alpha Lactose Monohydrate	Potato Starch	Anhydrous Alpha-Lactose	Tablet Strength	Disintegration Time
1	1	0	0	55.8	13
2	0	1	0	36.4	22
3	0	0	1	152.8	561
4	1/2	1/2	0	68.8	25
5	1/2	0	1/2	91	548
6	0	1/2	1/2	125	141
7	1/3	1/3	1/3	94.6	22
8	2/3	1/6	1/6	70.4	13
9	1/6	2/3	1/6	80	34
10	1/6	1/6	2/3	130	385

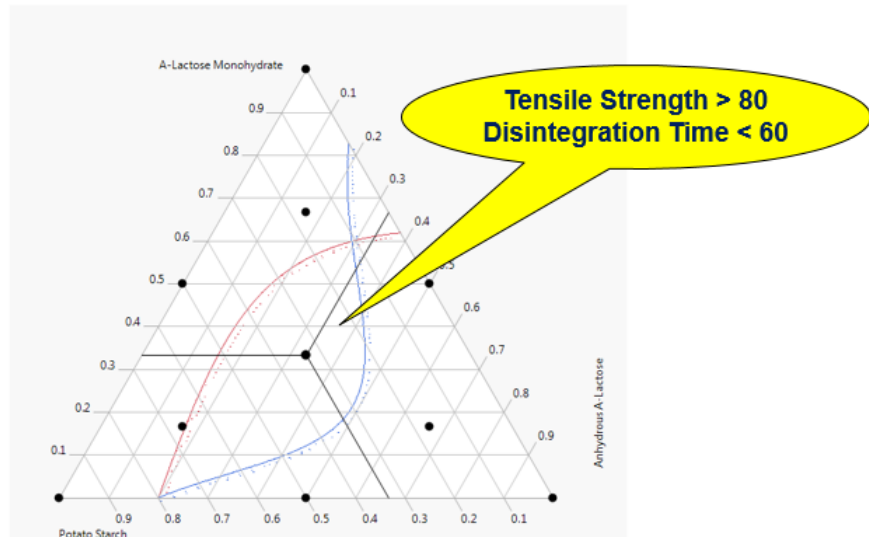
Figure 1.6 – Placebo Tablet Formulation Experiment Design



As we saw in Table 1.3, this study used the same formulation experiment design as the food product example discussed above. One major difference in this case is that there were two responses that needed to be considered: tablet strength and tablet disintegration time. It is typical that formulations will have several responses of interest.

Figure 1.7 shows the formulations that will meet the desired levels for strength and disintegration time--namely a region centered at a 1/3:1/3:1/3 (equal proportions) blend of Alpha-Lactose Monohydrate, Potato Starch, and Anhydrous Alpha-Lactose. When cost is considered, the blend chosen for the tablet would likely change depending on the cost of the components.

Figure 1.7 – Placebo Tablet Design Space



Lubricant Formulation

A group of chemical engineers were engaged in a lubricant blending study, whose objective was to determine how much of an additive to use to ensure that a formulation of three components would have the desired performance (Snee 1975). There were several uses for the formulation, each requiring a different amount of the additive. It was decided to conduct an experiment to generate data. The generated data would enable them to construct a prediction equation, and that equation would permit them to calculate the amount of additive needed to produce the desired performance for a given application.

Here are the four components and ranges studied:

- x_1 = Additive 0.07 - 0.18
- x_2 = Component A 0.00 – 0.30
- x_3 = Component B 0.37 – 0.70
- x_4 = Component C 0.00 – 0.15

These ranges were used to create an 18-blend extreme vertices design as shown in Table 1.4. The design included the viscosity (y) for each blend. Extreme vertices designs will be discussed in Chapters 7 and 8.

Table 1.4 – Lubricant Formulation Design

Blend	Additive	A	B	C	Viscosity
1	0.15	0	0.7	0.15	13.89
2	0.18	0.3	0.37	0.15	13.99
3	0.07	0.23	0.7	0	7.60
4	0.07	0.08	0.7	0.15	9.45
5	0.18	0.12	0.7	0	12.93
6	0.07	0.3	0.63	0	7.38
7	0.07	0.3	0.48	0.15	8.58
8	0.18	0	0.67	0.15	15.65
9	0.18	0.3	0.52	0	11.94
10	0.18	0	0.7	0.12	15.24
11	0.07	0.2275	0.6275	0.075	8.24
12	0.18	0.144	0.592	0.084	13.84
13	0.125	0.3	0.5	0.075	10.08
14	0.13	0.086	0.7	0.084	11.48
15	0.125	0.2375	0.6375	0	9.64
16	0.13	0.136	0.584	0.15	11.94
17	0.133	0.163	0.617	0.087	11.25
18	0.18	0.15	0.52	0.15	14.65

This data was used to generate the following 10-coefficient quadratic blending model:

$$E(y) = b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{14}x_1x_4 + b_{23}x_2x_3 + b_{24}x_2x_4 + b_{34}x_3x_4$$

Linear Blending	Non-Linear Blending	Non-Linear Blending
b1 = 126.9	b12 = -115.0	b23 = -5.80
b2 = 6.7	b13 = -99.0	b24 = -8.7
b3 = 7.0	b14 = -56.4	b34 = -6.7
b4 = 16.2		

Given the levels of Components A, B, and C and the desired viscosity for a given application, the equation was used to calculate the amount of additive needed to create the desired formulation.

In Table 1.5 we see the results for the first eight applications of the model, which produced formulations for eight different customers.

Table 1.5 – Lubricant Application Blends

Batch	Additive	A	B	C	Y Obsd	Y Pred	Difference
1	0.0923	0.0741	0.6975	0.1361	10.35	10.32	0.03
2	0.1035	0.0846	0.6774	0.1345	10.8	10.75	0.05
3	0.1389	0.1244	0.6075	0.1292	12.2	12.22	-0.02
4	0.1793	0.1765	0.5211	0.1231	14.07	14.12	-0.05
5	0.1924	0.1936	0.4929	0.1211	14.72	14.8	-0.08
6	0.105	0.05	0.735	0.11	10.83	10.79	0.04
7	0.137	0.1	0.643	0.12	12.2	12.15	0.05
8	0.175	0.2	0.485	0.14	13.93	13.97	-0.04

The prediction standard deviation was 0.047, which was essentially equal to the viscosity measurement variation. The engineers were very pleased with the performance of the model and used it extensively in creating products for a variety of customers and applications.

Pharmaceutical Tablet Compactability

Martinello et al. (2006) describe a study that investigated a formulation involving the compound paracetamol, which was known to have poor flowability and compressibility properties. The study involved seven ingredients:

Component	Low Level	High Level
Microcel	0.50	0.88
KollydonVA64	0.10	0.25
Flowlac	0	0.25
KollydonCL30	0	0.10
PEG 400	0	0.10
Aerosil	0	0.03
MgSt	0.005	0.025

Nine responses were measured. Of particular interest were repose angle, compressibility, disintegration time, and friability (tendency of a pharmaceutical tablet to chip, crumble, or break).

A 19-blend extreme vertices design shown in Table 1.6 was used to design the formulations to be tested.

Table 1.6 – Pharmaceutical Tablet Compactability Study Blends

Blend	Microcel	Kollydon VA64	Flowlac	Kollydon CL30	Peg 400	Aerosil	MgSt
1	0.58	0.165	0.125	0.05	0.05	0.015	0.015
2	0.615	0.25	0	0	0.1	0.03	0.005
3	0.5	0.25	0.245	0	0	0	0.005
4	0.5	0.25	0.025	0.1	0.1	0	0.025
5	0.595	0.25	0	0.1	0	0.03	0.025
6	0.5	0.1	0.245	0	0.1	0.03	0.025
7	0.875	0.1	0	0	0	0	0.025
8	0.58	0.165	0.125	0.05	0.05	0.015	0.015
9	0.5	0.1	0.245	0.1	0	0.03	0.025
10	0.525	0.1	0.25	0	0.1	0	0.025
11	0.865	0.1	0	0	0	0.03	0.005
12	0.595	0.25	0	0	0.1	0.03	0.025
13	0.58	0.165	0.125	0.05	0.05	0.015	0.015
14	0.5	0.25	0.245	0	0	0	0.005
15	0.695	0.1	0	0.1	0.1	0	0.005
16	0.58	0.165	0.125	0.05	0.05	0.015	0.015
17	0.695	0.1	0	0.1	0.1	0	0.005
18	0.515	0.1	0.25	0.1	0	0.03	0.005
19	0.58	0.165	0.125	0.05	0.05	0.015	0.015

A seven-term linear blending model was fit to the data and used to develop an optimal formulation. When tested, the formulation produced measured responses that were very close to those predicted by the linear blending model, as shown in Table 1.7. A linear blending model (only linear terms in the model) has a response function that is a straight line (two components) or a plane (> 2 components). Blending characteristics are discussed in detail in Chapter 4.

Table 1.7 – Pharmaceutical Tablet Compactability Optimal Formulation

Response	Predicted	Measured
Compressibility (%)	32.0	29.8
Water Content (%)	2.3	2.1
Repose Angle (deg)	21	18
Weight Variation (mg)	700	724
Hardness (kgf)	11.2	16.0
Friability (%)	1.03	0.91
Paracetamol Content (%)	99.7	97.4
Disintegration Time (min)	2.3	2.6
Dissolution (%)	91.9	92.0

The authors concluded “the optimal formulation showed good flowability, no lamination, and also met all official pharmaceutical specifications.” (Martinello et al, p. 95).

1.4 Summary and Looking Forward

In this chapter we have introduced a *formulation* as a product or entity produced by mixing or blending two or more components or ingredients. We have shown how experimenting with formulations is different from experimenting with process variables and other type of factors that can be varied independently of one another. Examples from different fields have been introduced, including four published applications that illustrate some of the problems formulators and formulation scientists encounter. In the next chapter we discuss the basics of experimentation that relate to formulations development.

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About This Book

Purpose

This book is based on decades of real life practical experience. The authors have been designing and analyzing formulation studies over most of their careers, including fundamental research and developing better ways to conduct formulation studies.

This book will help you:

- Approach the formulation development process from a strategic viewpoint, with the overall end in mind
- Focus on identifying components that have a dominant effect on the formulation and deepening understanding of how the components blend together
- Design and analyze screening experiments to identify those components that are most important to the performance of the formulation
- Analyze both screening and optimization experiments using graphical and numerical methods
- Optimize multiple criteria, such as the quality, cost, and performance of product formulations
- Design and analyze formulation studies that involve both formulation components and process variables using recently published methods that reduce the required experimentation by up to 50%
- Develop formulations robust to deviations from ingredient targets
- Provide step-by-step instructions on how to use JMP to replicate all analyses presented

We designed this book to be used in a number of different ways for different purposes. It can be used as a step-by-step guide by scientists as they develop formulations. Associated roadmaps are provided at various points in the book. Detailed examples should also provide useful guidance.

The book can also serve as a reference on specific experimental designs and tools used in experimenting with mixtures and formulations including analysis, interpretation and how to report and present results.

The authors have also taught design of experiments courses in which approximately 10% of the time is devoted to experimenting with formulations. Chapters 1-5 provide material useful for such teaching purposes.

This book is unique in that it tells formulation scientists *what they need to know to successfully conduct formulation studies*, not what is nice to know, or everything there is to know. By integrating JMP software into the book, we guide the reader on the software implementation of the proposed methodology.

What scientists need to know includes how to:

- Define a strategy for formulation experimentation – a strategic view of how to:
 - Increase your probability of success
 - Identify components having a large effect on formulation performance
- Speed up the development of formulations
- Conduct screening experiments to identify the most important components thereby taking advantage of the “Pareto Principle” (Juran and Godfrey 1999), which states that the majority of the variation will be due to a vital few components
- Cut the experimentation required for the simultaneous optimization of formulation components and process variables by as much as 50%
- Use computer generated experiment designs when the classical designs will not suffice given the physical and economic constraints of the given experiential environments
- Conduct formulation robustness studies
- Use software to effectively and efficiently design and analyze formulation experiments
- Learn from case studies and examples from many different fields

Case studies and examples provided are from a variety of industries including: pharmaceutical, biotech, chemical, petroleum, and food, to name a few.

Is This Book for You?

This book is written for:

- Scientists and engineers working on formulation development
- Targeted industries include pharmaceutical, biotechnology, chemical, food, plastics, electronics, paint, coating and glass
- Users of JMP and SAS with beginning to intermediate level of JMP expertise

This book will help scientists engaged in formulation work to solve real formulation problems, including how to:

- Develop formulation strategies that will speed up the formulation development cycle
- Develop screening experiments to identify those ingredients/components that have the largest effect and are most important to the performance of the formulation
- Optimize quality and performance of product formulations using mixture response surface methods, analytical models and use of regression analysis
- Develop a design space (operating window) for the manufacture of a formulation
- Minimize the amount of experimentation required to develop and optimize a formulation
- Design formulations that are robust to deviations from ingredient targets
- Design and analyze formulation studies that involve both formulation variables and process variables using methods that reduce the required experimentation by as much as 50%
 - Models are created that enhance the understanding of the formulations and the effects of manufacturing process variables, thereby enabling the combined optimization of formulations and the associated manufacturing processes
- Use computer generated experiment designs when the classical design will not suffice given the physical and economic constraints of the given experiential environment
- Use graphics to explore, analyze and communicate results

This book discusses concepts, methods, and tools that enable scientists to develop formulations (mixtures) that are effective and efficient from a cost perspective. The reader of this book will be able to:

- Develop strategies that will speed up formulation development and minimize the amount of experimentation required to create and optimize formulations
- Develop screening experiments to identify those ingredients/components that are most important to the performance of the formulation
- Optimize quality and performance of product formulations
- Design and analyze experiments that involve both formulation variables and process variables using methods that reduce the required experimentation by as much as 50%
- Use computer generated experimental designs when the classical designs will not suffice given the physical and economic constraints of the given experiential environment
- Build models that deepen understanding of the scientific fundamentals of formulations
- Use graphics to explore, analyze and communicate results

One of the unique features of this book is that these insights are combined into a roadmap that formulation scientist can use to create and develop product formulations.

Prerequisites

We recommend the reader have:

- Rudimentary knowledge of what a formulation/mixture is
- Rudimentary knowledge of basic statistics

Scope of This Book

The principle topics covered in this book include experiment design, analysis, modelling and interpretation of results in the following areas:

- Formulation screening designs and identification of major components:
- Formulation optimization using response surface experiments
- Optimization of formulations - Graphical and mathematical approaches
- Product formulation when components have lower and upper bounds

- Computer aided design of formulation experiments
- Formulation experiments involving formulation components and processing variables

The information in this book provides a formulation scientist with the concepts, methods and tools required to effectively experiment with and develop formulations.

This book is organized into four main sections as summarized in the following table, beginning with the basics and concluding with additional and more advanced material.

Section	Content
I. Fundamentals	Introduction to mixtures, blends, and formulations, including case studies and a discussion of the basics of experimentation and response surface exploration
II. Design and Analysis of Formulation Experiments	How to design and analyze formulation studies using analytical and graphical tools. Topics discussed include the geometry of the experimental region and the details of how response surface methodology is used in formulation studies.
III. Experimenting with Constrained Systems	Formulations involving single component and multiple component constraints are introduced and techniques to experiment with such systems are illustrated and discussed. The techniques utilize both screening experiments and response surface exploration. Both analytical and graphical techniques are utilized. The use of computer-aided design of experiments is discussed and illustrated.
IV. Further Extensions	This part of the book extends the topics discussed in Parts I, II and III. Topics addressed include design and analysis of experiments involving mixture and process variables, model simplification, mathematical response optimization, multi-response optimization and how to address multicollinearity of mixture variables.

The table below describes a chapter by chapter summary of the book.

Chapter	Topic	Content
1	Mixtures, Blends and Formulations	Introduction to formulations, how formulations differ from other types of experimentation and examples of formulations from various fields
2	Basics of Response Surface Methodology and experimentation	Experimentation fundamentals, developing empirical models, strategy and a roadmap for sequential experimentation and modeling.
3	Experimental Designs for Formulations	Geometry of the experimental region, basic simplex designs, introduction to screening and response surface designs
4	Modeling Formulation Data	The model building process, plots of response versus component levels, basic mixture models, interpretation of model coefficients, residual analysis and transformations
5	Screening Experiments	Screening concepts, screening designs, graphical analysis, calculation of effects, estimation of experimental error (variation)
6	Constrained Mixture Systems	Reasons for constraints, geometry of constrained mixture systems, pseudocomponents, multiple component constraints and identifying the design space.
7	Screening with Constrained Systems	Strategy and objectives, screening designs with constraints, graphical analysis, calculation of component effects, roadmap for screening
8	Response Surface Modeling with Constraints	Strategy and objectives, designs to support response surface models, fitting constrained response surface models, multicollinearity and other challenges. The use of computer algorithms in the design of formulation experiments is illustrated and discussed.
9	Experiments Involving Formulation and Process Variables	Experimental environment, strategy and objectives, full crossed designs, fractional designs, non-linear approaches, integrated models
10	Additional and Advanced Topics	Model simplification, more advanced model forms, numerical response optimization, experimenting with multiple responses, addressing multicollinearity

This book does not cover mathematical derivations or underlying theory. The concepts, methods, and tools presented and discussed are all based on sound statistical theory.

About the Examples

Software Used to Develop the Book's Content

JMP 13 has been used in this book.

Example Code and Data

You can access the example code and data for this book by linking to its author page at <http://support.sas.com/publishing/authors>. Select the name of the author. Then, look for the cover thumbnail of this book, and select Example Code and Data to display the JMP programs that are included in this book.

Data and associated references for additional case studies are also included in the website to show other areas in which the methodology in this book has been applied.

If you are unable to access the code through the Web site, send e-mail to saspress@sas.com.

Output and Graphics Used in This Book

All computer output and graphics were produced with JMP 13.

JMP Platforms and commands for each analysis are included in the book near the associated output and graphics.

Additional Help

Although this book illustrates many analyses regularly performed in businesses across industries, questions specific to your aims and issues may arise. To fully support you, SAS Institute and SAS Press offer you the following help resources:

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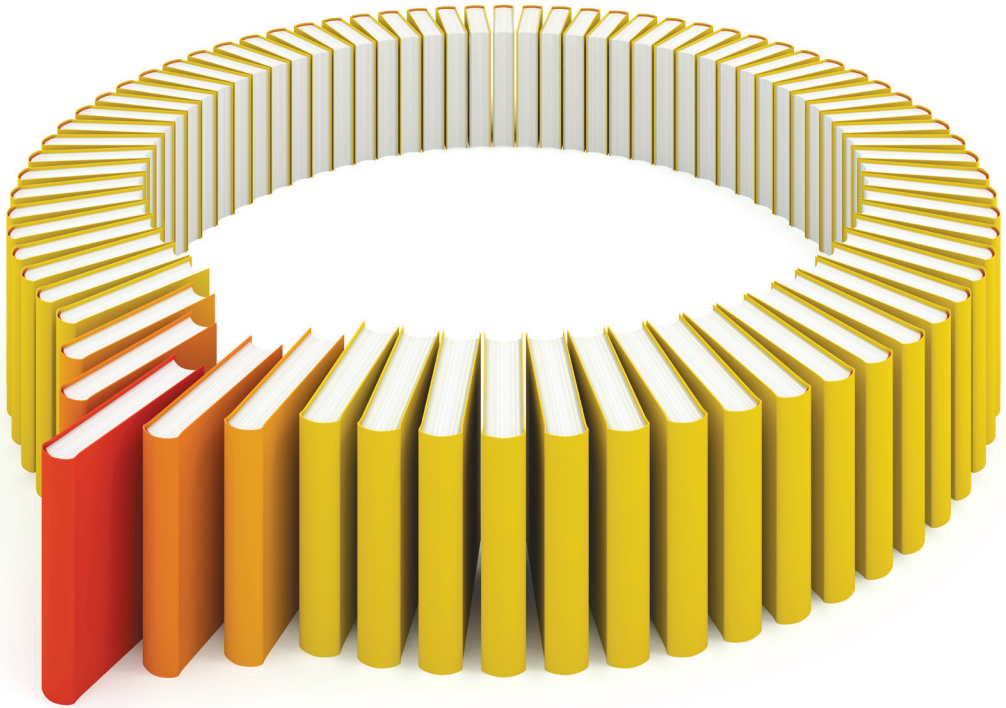


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