Research Article

Quality Improvement and Robust Design Methods to a Pharmaceutical Research and Development

Byung Rae Cho and Sangmun Shin

1 Department of Industrial Engineering, Clemson University, Clemson, SC 29634, USA
2 Department of Systems Management & Engineering, Inje University, Gyeongnam Gimhae 621-749, Republic of Korea

Correspondence should be addressed to Sangmun Shin, sshin@inje.ac.kr

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1. Introduction

Continuous quality improvement has become widely recognized by many industries as a critical concept in maintaining a competitive advantage in the marketplace. It is also recognized that quality improvement activities are efficient and cost-effective when implemented during the design stage. Based on this awareness, Taguchi [1] introduced a systematic method for applying experimental design, which has become known as robust design which is often referred to as robust parameter design. The primary goal of this method is to determine the best design factor settings by minimizing performance variability and product bias, that is, the deviation from the target value of a product. Because of the practicability in reducing
the inherent uncertainty associated with system performance, the widespread application
of robust design techniques has resulted in significant improvements in product quality,
manufacturability, and reliability at low cost. Although the main robust design principles
have been implemented in a number of different industrial settings, our literature study
indicates that robust design has been rarely addressed in the pharmaceutical design process.

In the pharmaceutical industry, the development of a new drug is a lengthy process
involving laboratory experiments. When a new drug is discovered, it is important to design
an appropriate pharmaceutical dosage or formulation for the drug so that it can be delivered
efficiently to the site of action in the body for the optimal therapeutic effect on the intended
patient population. The Food and Drug Administration (FDA) requires that an appropriate
assay methodology for the active ingredients of the designed formulation be developed and
validated before it can be applied to animal or human subjects. Given this fact, one of the
main challenges faced by many researchers during the past decades is the optimal design
of pharmaceutical formulations to identify better approaches to various unmet clinical
needs. Consequently, the pharmaceutical industry’s large investment in the research and
development (R&D) of new drugs provides a great opportunity for research in the areas of
experimentation and design of pharmaceutical formulations. By definition, pharmaceutical
formulation studies are mixture problems. These types of problems take into account the
proportions within the mixture, not the amount of the ingredient; thus, the ingredients in such
formulations are inherently dependent upon one another, and consequently experimental
design methodologies commonly used in many manufacturing settings may not be effective.
Instead, for mixture problems, a special kind of experimental design, referred to as a mixture
experiment, is needed. In mixture experiments, typical factors in question are the ingredients
of a mixture, and the quality characteristic of interest is often based on the proportionality of
each of those ingredients. Hence, the quality of the pharmaceutical product is influenced by
such designs when they are applied in the early stages of drug development.

In this paper, we propose a new robust design model in the context of pharmaceutical
production R&D. The main contribution of this paper is twofold. First, traditional experi-
mental design methods have often applied to situations in which the quality characteristics
of interest are typically time-insensitive. In pharmaceutical manufacturing processes, time-
oriented quality characteristics, such as the degradation of a drug, are often of interest,
and these time-oriented data often follow a Weibull distribution. Since it may take a long
time to observe the degradation of a drug product, the concept of censored samples can be
integrated in designing optimal pharmaceutical formulations. In this paper, we develop a
censored sample-based experimental design model for optimal pharmaceutical formulations
by integrating the main robust design principles. Second, we then show how the response
surface methodology, which is a well-established statistical tool, can be integrated with the
proposed censored sample-based robust design model. Finally, we show how the maximum
likelihood method is implemented in estimating mean and variance of censored Weibull data.
A numerical example is given, and comparison studies for the two estimation methods are
discussed for model verification. This paper is organized as follows. In the next section, we
present a literature review on mixture design and robust design. In Section 3, we describe
our proposed censored robust design model for the optimal design of pharmaceutical
formulations in detail. The maximum likelihood method is then studied, and optimization
models are proposed. In Section 4, we demonstrate our proposed methods using a numerical
example and compare the results under the two different optimization models. In the last
section, we conclude the paper with a discussion of our findings.
2. Literature Study

In this section, the literature of robust design and mixture designs is discussed.

2.1. Robust Design

Because product performance is directly related to product quality, Taguchi’s techniques [1, 2] of robust design (RD) have become increasingly popular in industry since the mid-1980s. RD is a powerful and cost-effective quality improvement methodology for products and processes, which results in higher customer satisfaction and operational performance. There is little disagreement among researchers and practitioners about Taguchi’s basic philosophy. Steinberg and Bursztyn [3] provided a comprehensive discussion on Taguchi’s off-line quality control and showed that the use of noise factors can significantly increase the capability for detecting factors with dispersion effects, when noise factors are explicitly modeled in the analysis. However, the ad hoc robust design methods suggested by Taguchi remain controversial due to various mathematical flaws. The controversy surrounding Taguchi’s assumptions, experimental design, and statistical analysis has been well addressed by Leon et al. [4], Box [5], Box et al. [6], Nair [7], and Tsui [8]. Consequently, researchers have closely examined alternative approaches using well-established statistical and optimization tools. Vining and Myers [9] introduced the dual response approach based on response surface methodology (RSM) as an alternative for modeling process relationships by separately estimating the response functions of process mean and variance, thereby achieving the primary goal of robust design by minimizing the process variance while adjusting the process mean at the target. Del Castillo and Montgomery [10] and Copeland and Nelson [11] showed that the optimization technique used by Vining and Myers [9] does not always guarantee optimal robust design solutions and proposed standard nonlinear programming techniques, such as the generalized reduced gradient method and the Nelder-Mead simplex method, which can provide better robust design solutions. The modified dual response approaches using fuzzy theory were further developed by Khattree [12] and Kim and Lin [13]. However, Lin and Tu [14], pointing out that the robust design solutions obtained from the dual response model may not necessarily be optimal since this model forces the process mean to be located at the target value, proposed the mean-squared error model, relaxing the zero-bias assumption. While allowing some process bias, the resulting process variance is less than or at most equal to the variance obtained from the Vining and Myers model [9]; hence, the mean-squared error model may provide better (or at least equal) robust design solutions unless the zero-bias assumption must be met. Further modifications to the mean-squared error model have been discussed by Jayaram and Ibrahim [15], Cho et al. [16], Kim and Cho [17, 18], Yue [19], Park and Cho [20], Miro-Quesada and Del Castillo [21], Cho and Park [22], Govindaluri and Cho [23], Shin and Cho [24, 25], and Lee et al. [26]. Along this line, Myers et al. [27], Park and Cho [22], and Robinson et al. [28] developed modified dual-response models using generalized linear model, a robust design model using the weighted-least-square method for unbalanced data, and a robust design model using a generalized linear mixed model for nonnormal quality characteristics, respectively. As for an experimental strategy, Kovach and Cho [29–31] and Kovach et al. [32] studied D-optimal robust design problems by minimizing the variance of the regression coefficients. Ginsburg and Ben-Gal [33] then developed a new optimality criterion, called the Vs optimality, which minimizes the variance of the optimal solution by prioritizing the estimation of various model coefficients, thereby, estimating coefficients more accurately at each experimental stage. It is well known
that estimated empirical models are often subject to random error. In order to obtain a more precise robust design solution in the presence of the error, Xu and Albin [34] developed a model which can be resistant to the error by considering all points in the confidence intervals associated with the estimated model. When multiple quality characteristics are considered, those characteristics are often correlated. Govindaluri and Cho [23], investigated the effect of correlations of quality characteristics on robust design solutions, while Egorov et al. [35] and Kovach et al. [32] studied optimal robust design solutions using the indirect optimization algorithm and physical programming, respectively. Finally, Shin and Cho [25] studied trade-off studies on minimizing variance and achieving the predetermined target value.

2.2. Mixture Designs

Schéffe [36] first introduced his theory on the prediction of the responses of mixture experiments based on their proportions. The theory defines \( x_i \) as the proportion of ingredient \( i \) in the mixture. Furthermore, the proportionality idea of this theory provides the experiment with a property in which the proportions of the \( k \) ingredients within the mixture must equal 100 percent, as illustrated by the equation \( \sum_{i=1}^{k} x_i = x_1 + x_2 + \ldots + x_k = 1 \), where \( x_i \geq 0 \) for all \( i = 1, 2, \ldots, k \). Schéffe [36] employed a simplex lattice design to represent the design points of the feasible experimental region of the ingredients. The simplex lattice design is defined by the notation \((k, m)\), where \( m + 1 \) defines the number of equally spaced proportion values from 0 to 1 for each experiment and those proportions are determined by the equation \( x_i = 0, 1/m, 2/m, \ldots, 1 \). All possible combinations of the proportions are used to determine the design points within the simplex lattice design. In general, the number of design points in a \((k, m)\) simplex lattice design is defined \( n = (k + m - 1)!/m!(k-1)! \). Schéffe [37] also modified this simplex lattice design to introduce the simplex centroid design for experiments that include the overall centroid of the region at the coordinate \((1/k, 1/k, \ldots, 1/k)\).

Augmented designs of both the simplex lattice and simplex centroid designs exist. Cornell [38] analyzed both an augmented simplex lattice design and an augmented simplex centroid design with ten design points each. Applications of mixture experiments revealed other design possibilities. The most natural obstacle is the limitation on the proportion of a certain ingredient within a mixture. The limitation could be found in the form of lower, upper, and both lower and upper bounds or constraints. This led researchers to develop other ways to obtain design points that are within the feasible region given the constraints. An example of such models is the extreme vertices design for mixture experiments. First introduced by Mclean and Anderson [39], extreme vertices designs for mixture problems consider the extreme points of the irregular polyhedron, formed by constraints in experimental runs, in addition to the centroids of each facet. The major disadvantage with this design is the possible large number of design points that can be obtained with the given constraints, specifically as the number of ingredients increases and the feasible region becomes more complex. Snee and Marquart [40] presented an algorithm to determine the appropriate subset of design points when the vertices of the feasible region are too many to handle. They compare the efficiency of their approach to G- and D-optimal designs, both of which are common techniques used for determining the appropriate points at which to take observations. Bayesian D-optimal designs shown by DuMouchel and Jones [41] are a modification of D-optimal designs, which reduces the dependency of the design on the assumed model. Using such models as a leverage point, Andere-Rendon et al. [42] investigated the Bayesian D-optimal design specifically for mixture experiments which include both potential and primary model terms.
in order to form the Bayesian slack variable model. The results favored the Bayesian D-optimal design with smaller bias errors and better-fitted models. Along the same lines, Goos and Donev [43] extended the work of Donev [44] with the implementation of D-optimal designs for blocked mixture experiments. Unlike other research that used orthogonally blocked experiments (see [45, 46]), they employed mixture designs that are not orthogonally blocked and used an algorithm that provided a simpler methodology to construct blocked mixture designs.

The simplified polynomials, also referred to as canonical polynomials, are widely used throughout the literature and are embedded in software packages for mixture experiments. However, these designs have been scrutinized, especially because of their lack of squared terms. Piepel et al. [47] proposed a partial quadratic mixture model that includes the linear Scheffé terms but augments them with the appropriate squared or quadratic cross product terms. Extending from alternative models proposed by Snee and Rayner [48], Cornell and Gorman [49] explained how highly constrained regions, such as those in mixture experiments having components with considerably smaller ranges than others, result in skewed responses, thus creating fitted models that have inherent collinearity. Both models attempt to modify the scale on the feasible region that results in the experiment’s constraints in an effort to eliminate the collinearity between components. For other collinearity research and discussions, refer to the publications of Sengupta et al. [50] and Prescott et al. [51]. Other research publications have employed robust design methodologies for mixture experiments. Steiner and Hamada [52] modeled a mixture experiment to include the coefficient and terms that account for the interactions of mixture and controllable process variables and the interactions of the mixture and noise variables. This model utilizes the Taguchi loss function [1, 2] to reduce the noise variables. The practicality of the design may be questionable as it does not account for constraints within the system, which opens the opportunity for further research. A different approach to dealing with noise factors can be studied in Goldfarb et al. [53]. Continuing in similar research, Goldfarb et al. [54] introduced a three-dimensional variance dispersion graph with the purpose of comparing competing mixture experimental designs based on their prediction variance properties. Goldfarb et al. [55] proposed an interesting addition to this research by implementing genetic algorithms within an objective function to minimize the maximum scaled prediction variance in the mixture design region. This investigation showed that with a few runs of the genetic algorithm, the scaled prediction variance can be significantly reduced, allowing the experimenter to control noise variables inherent in the experiment.

### 3. Proposed Censored Robust Design Model

In this section, we describe the proposed model in three phases—experimental phase, estimation phase, and optimization phase.

#### 3.1. Notations

Notations associated with parameters and variables used in paper are defined as follows:

- \( \mathbf{x} = [x_1, x_2, \ldots, x_k] \) vector of \( k \) control factors,
- \( \mathbf{y} \) vector of output observations,
- \( y_i \) \( i \) output observations,
- \( T \) censored observations,
Table 1: General layout of the proposed methodology.

| Design points | Control factors | Experimental observations | Estimate |
|---------------|-----------------|---------------------------|----------|
|               | $x_1, x_2, \ldots, x_f$ | $y_{i(1)}, \ldots, y_{i(n)}, T_{i(1)}, \ldots, T_{i(m)}$ | $\hat{\mu}_i$, $\hat{\sigma}_i$ |
| $1$           |                 |                           |          |
| $2$           |                 |                           |          |
| $i$           |                 |                           |          |
| $d$           |                 |                           |          |

$T_i$ $i$ censored observations,

$\theta$ vector of parameter $\theta$,

$\theta_k$ the component of vector parameter $\theta$,

$F(y; \theta)$ cumulative distribution function associated with parameters $y$ and $\theta$,

$f(y; \theta)$ probability density function associated with parameters $y$ and $\theta$,

$L(y, T; \theta)$ maximum likelihood function associated with parameters $y$, $T$, and $\theta$,

$l(y, T; \theta)$ loglikelihood function of $L(y, T; \theta)$,

$\Gamma(x)$ gamma function,

$\hat{\mu}(x)$ estimated function of process mean,

$\hat{\sigma}(x)$ estimated function of process variance.

### 3.2. Experimental Phase

Table 1 displays the general framework of the RD methodology, where the $y_i$’s are the observed pharmaceutical quality characteristic values and the $T_i$’s are the censored times. The mean and variance for each design point are estimated using the observations.

### 3.3. Estimation Phase

Observations are of two kinds—actual and censored observations. Assume that the observations follow a distribution with underlying cumulative distribution function $F(y; \theta)$ and probability density function $f(y; \theta)$, where $\theta$ is a vector of parameters and $y$ is a vector of observations. Suppose that for each design point, we have $n$ actual observations $y_{i(1)}, y_{i(2)}, \ldots, y_{i(n)}$ and $m$ censored observations $T_{i(1)}, T_{i(2)}, \ldots, T_{i(m)}$. Then the maximum likelihood function is

$$L(y, T; \theta) = \prod_{i=1}^{n} f(y_{i}; \theta) \prod_{j=1}^{m} [1 - F(T_{j}; \theta)],$$

(3.1)
and the loglikelihood function is

\[ l(y, T; \theta) = \sum_{i=1}^{n} \ln f(y_i; \theta) + \sum_{j=1}^{m} \ln [1 - F(T_j; \theta)]. \]  

(3.2)

If the censoring time is fixed at \( T \), say, then

\[ \prod_{j=1}^{m} [1 - F(T_j; \theta)] = [1 - F(T; \theta)]^m. \]

In that case, the loglikelihood function is

\[ l(y, T; \theta) = \sum_{i=1}^{n} \ln f(y_i; \theta) + m \ln [1 - F(T; \theta)]. \]  

(3.3)

The values of the components of \( \theta \) that maximize the loglikelihood function will constitute the maximum likelihood estimates. These are computed as the solutions to the system of equations:

\[ \frac{\partial}{\partial \theta_k} l(y, T; \theta) = 0, \]  

(3.4)

where the \( \theta_k \)'s are the components of the vector of parameters \( \theta \). If the underlying distribution follows a Weibull distribution with parameters \( \alpha \) and \( \beta \), then \( \theta = [\alpha, \beta] \), and for the \( n \) actual observations \( y_1, y_2, \ldots, y_n \), and \( m \) censored observations \( T_1, T_2, \ldots, T_m \), the loglikelihood function is

\[ l(y, T; \mu, \sigma) = n (\ln \alpha + \ln \beta) + \sum_{i=1}^{n} (\beta - 1) \ln y_i - \alpha \sum_{i=1}^{n} y_i^\beta - \alpha \sum_{j=1}^{m} T_j^\beta. \]  

(3.5)

For a fixed censoring time \( T \),

\[ l(y, T; \mu, \sigma) = n (\ln \alpha + \ln \beta) + \sum_{i=1}^{n} (\beta - 1) \ln y_i - \alpha \sum_{i=1}^{n} y_i^\beta - \alpha m T. \]  

(3.6)

The maximum likelihood estimates of \( \alpha \) and \( \beta \) are the solutions to the system of equations:

\[ \sum_{i=1}^{n} y_i^\beta - m T^\beta = 0, \]

\[ \sum_{i=1}^{n} \ln y_i + \alpha \sum_{i=1}^{n} y_i^\beta \ln y_i - \alpha m T^\beta \ln T = 0. \]  

(3.7)

Equation (3.7) is obtained by taking the derivatives of the loglikelihood function with respect to \( \alpha \) and \( \beta \). Similarly, a system of equations can be derived using (3.6) for varying censoring.
times. The solutions to (3.7), namely, $\hat{\alpha}$ and $\hat{\beta}$, are the maximum likelihood estimates of $\alpha$ and $\beta$, and we use them in estimating the mean and standard deviation as follows:

$$
\hat{\mu} = \hat{\alpha}^{1/\hat{\beta}} \left( 1 + \frac{1}{\hat{\beta}} \right)
$$

$$
\hat{\alpha} = \left[ \frac{\hat{\mu}^2}{\hat{\beta}} \right] = \hat{\mu}^2.
$$

### 3.4. Optimization Phase

The main objective of the proposed robust design is to obtain the optimal pharmaceutical formulation settings by maximizing mean response while minimizing variability. Thus, in order to meet this goal, we seek to maximize the mean response while minimizing the variability. To achieve this objective, we propose the following optimization model (Model 1):

$$
\min_{x \in \Omega} \left\{ -\mu^2(x) + \sigma^2(x) \right\}
$$

s.t. $\sum_{i=1}^k x_k = 1.$

It is noted that the sum of pharmaceutical component proportion is one. By considering the usual approximation of the Taguchi’s loss function [1], we can also find the solution to the following optimization model (Model 2):

$$
\min_{x \in \Omega} \left\{ \frac{1}{\mu^2(x)} \left( 1 + \frac{\hat{\sigma}^2(x)}{\mu^2(x)} \right) \right\}
$$

s.t. $\sum_{i=1}^k x_k = 1.$

By inspection, we notice that this function decreases as $\mu(x)$ increases and as $\hat{\sigma}(x)$ decreases. Also, a part of the feasibility requirements for these proposed objective functions is that the mean response is nonzero, that is, $\mu(x) \neq 0$, which is the case for censored samples where the objective is to get $\mu(x)$ as large as possible. We will demonstrate that both proposed optimization models yield optimal solutions in the next section.

### 4. Numerical Example and Comparison Study

Consider an experiment on the degradation of a drug where the factors of concern are corn starch ($x_1$), saccharin sodium ($x_2$), and dextrose ($x_3$). Thus, the vector of the control factors is $x = [x_1, x_2, x_3]$. The objective of the experiment is to determine the settings of the control factors, $x^* = [x^*_1, x^*_2, x^*_3]$, that give the longest possible degradation and the smallest possible variability. The chosen design is a mixture design for three control factors. Suppose
future study includes the development of optimal designs, known as computerized designs, for the case in which physical experimental constraints are imposed.

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