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RESEARCH AND DEVELOPMENT EFFORT IN DEVELOPING THE OPTIMAL FORMULATIONS FOR NEW TABLET DRUGS

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RESEARCH AND DEVELOPMENT EFFORT IN DEVELOPING THE OPTIMAL FORMULATIONS FOR NEW TABLET DRUGS

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ABSTRACT

Seeking the optimal pharmaceutical formulation is considered one of the most critical research components during the drug development stage. It is also an R&D effort incorporating design of experiments and optimization techniques, prior to scaling up a manufacturing process, to determine the optimal settings of ingredients so that the desirable performance of related pharmaceutical quality characteristics (QCs) specified by the Food and Drug Administration (FDA) can be achieved. It is widely believed that process scale-up potentially results in changes in ingredients and other pharmaceutical manufacturing aspects, including site, equipment, batch size and process, with the purpose of satisfying the clinical and market demand. Nevertheless, there has not been any single comprehensive research work on how to model and optimize the pharmaceutical formulation when scale-up changes occur. Based upon the FDA guidance, the documentation tests for scale-up changes generally include dissolution comparisons and bioequivalence studies. Hence, this research proposes optimization models to ensure the equivalent performance in terms of dissolution and bioequivalence for the pre-change and post-change formulations by extending the existing knowledge of formulation optimization. First, drug professionals traditionally consider the mean of a QC only; however, the variability of the QC of interest is essential because large variability may result in unpredictable safety and efficacy issues. In order to simultaneously take into account the mean and variability of the QC, the Taguchi quality loss concept is applied to the optimization procedure. Second, the standard 2×2 crossover

design, which is extensively conducted to evaluate bioequivalence, is incorporated into the ordinary experimental scheme so as to investigate the functional relationships between the characteristics relevant to bioequivalence and ingredient amounts. Third, as many associated FDA and United States Pharmacopeia regulations as possible, regarding formulation characteristics, such as disintegration, uniformity, friability, hardness, and stability, are included as constraints in the proposed optimization models to enable the QCs to satisfy all the related requirements in an efficient manner. Fourth, when dealing with multiple characteristics to be optimized, the desirability function (DF) approach is frequently incorporated into the optimization. Although the weight-based overall DF is usually treated as an objective function to be maximized, this approach has a potential shortcoming: the optimal solutions are extremely sensitive to the weights assigned and these weights are subjective in nature. Moreover, since the existing DF methods consider mean responses only, variability is not captured despite the fact that individuals may differ widely in their responses to a drug. Therefore, in order to overcome these limitations when applying the DF method to a formulation optimization problem, a priority-based goal programming scheme is proposed that incorporates modified DF approaches to account for variability.

The successful completion of this research will establish a theoretically sound foundation and statistically rigorous base for the optimal pharmaceutical formulation without loss of generality. It is believed that the results from this research will have the potential to impact a wide range of tasks in the pharmaceutical manufacturing industry.

DEDICATION

This work is dedicated to my parents, Huifen Yu and Weimin Li, for their continued support of me during my doctoral research at Clemson University. Without their constant encouragement and support, this study would not have been completed.

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NOMENCLATURE

ABE	Average Bioequivalence
ANN	Artificial Neural Network
API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutics Classification System
CCD	Central Composite Design
CV	Coefficient of Variation
DE	Dissolution Efficiency
DF	Desriability Funtion
DOE	Design of Experiments
EMEA	European Medicines Agency
FDA	Food and Drug Administration
IR	Immediate-Release
IVIVC	*In Vitro*/*In Vivo* Correlation
MRS	Multi-Response Surface
MDT	Mean Dissolution Time
NDA	New Drug Application
PE	Prediction Error
QC	Quality Characteristic
RSD	Relative Standard Deviation

RSM	Response Surface Methodology
SD	Standard Deviation
USP	The United States Pharmacopeia
WHO	World Health Organization
C_{max}	Maximum Plasma Concentration
t_{max}	Time to Reach C_{max}
AUC	Area under Plasma Concentration-Time Curve
r	total number of runs in the experiment
$\mathbb{X}$	experimental design matrix
$\mathbf{X}$	matrix of data for least squares regression containing predictor variables
τ_i	pre-identified weight of the i^{th} excipient in the reference formulation ($i = 1, 2, \ldots, 6$)
a_i	pre-identified weight of the i^{th} active ingredient ($i = 1, 2, ..., p$)
p	number of active pharmaceutical ingredients in the formulation
subscripts R and T	related terms for the reference and test formulations, respectively
$A(t_i)$	average cumulative amount dissolved at time t_i
n	number of time points
$\mathbf{x}$	vector of input factors
$A_i(t,\mathbf{x})$	response function of the average dissolution over time t for the i^{th} active pharmaceutical ingredient
τ	target value for f_2

$s[\bullet]$ and $s^2[\bullet]$	sample standard deviation and variance of the characteristic of interest
W_R	pre-identified weight of the total reference dosage form
Q	amount of dissolved active ingredient, expressed as a percentage of the labeled content
a_{Ui} and a_{Li}	upper and lower bounds of a dissolution range for the i^{th} active pharmaceutical ingredient, respectively
t_α and t_β	predefined earlier and later time points for the dissolution specification, respectively
λ_1	upper bound of the relative standard deviation of dissolution data
K	acceptability constant for uniformity tests
T_c	target content per dosage expressed as a percentage
χ_j	individual active pharmaceutical ingredients of the units tested expressed as a percentage of the label claim ($j = 1, 2, \ldots, q$)
q	number of samples for uniformity tests
$\bar{\chi}$ and s	sample mean and standard deviation of χ_j, respectively
χ_{ij}	χ_j for the i^{th} active ingredient
G	upper limit of the acceptance value for uniformity tests
a_{ij}	weight of the i^{th} active pharmaceutical ingredient for the j^{th} replication
$\bar{\chi}_i(\mathbf{x})$ and $s_i(\mathbf{x})$	response functions of the mean and standard deviation of ($\chi_{i1}, \chi_{i2}, \ldots, \chi_{iq}$) for the i^{th} active pharmaceutical ingredient
$W_T(\mathbf{x})$	response function of the weight of the total test dosage form
$D(\mathbf{x})$	response function of the average disintegration time
d_U and d_L	upper and lower disintegration time limits, respectively

λ_2	upper bound of the relative standard deviation for disintegration time
$F(\mathbf{x})$	response function of the average mass loss
CI($\mathbf{x}$)	response function of the compressibility index
H	upper limit of the compressibility index
$N_i(\mathbf{x})$	response functions for hardness, thickness, and degradation time, respectively (i = 1, 2, 3)
η_{Ui} and η_{Li}	upper and lower limits for hardness, thickness, and degradation time, respectively (i = 1, 2, 3)
n_1 and n_2	number of subjects within Sequences 1 and 2, respectively
γ_A and γ_C	upper limits of intra-subject variations for AUC and $C_{\max}$, respectively
t_z	critical time point at which the absorption ends
$\hat{\sigma}$	pooled sample standard deviation of period differences from both sequences
s_{in}^2	intra-subject variation
ψ	total number of parameters in a full regression model
$\mathbf{X}_F$	matrix of data for the predicator variables in the full model
$\mathbf{X}_{R,v}$	matrix of data for the predicator variables in the reduced model with $v - 1$ ($1 \le v \le \psi$) predictors
$\hat{d}_{M,\omega}(\mathbf{x})$ and $\hat{d}_{M,\omega}(\mathbf{x})$	ω^{th} estimated mechanistic and empirical individual DFs, respectively
$\widehat{D}_M(\mathbf{x})$ and $\widehat{D}_E(\mathbf{x})$	estimated mechanistic and empirical overall DFs, respectively
$\mathbf{H}_v$	hat matrix for the esimated desirability model with $v - 1$ predictors

Δ_{ω}^{-}	deficiency variables associated with the underachievement of the ω^{th} desirability
h	total number of response variables
$\hat{\pi}_{\omega}$	ω^{th} response variable concerning the response mean, variance, and covariance ($\omega = 1, 2, \ldots, h$)
$\hat{\mu}_{is}$	mean of the i^{th} response at the s^{th} run
σ_{is}^2	variance of the i^{th} response at the s^{th} run
$\sigma_{wg,s}^2$	covariance between the w^{th} and g^{th} responses at the s^{th} run
$\hat{\mu}_i(\mathbf{x})$	estimated response surface function for the i^{th} response mean
$\sigma_i^2(\mathbf{x})$	estimated response surface function for the i^{th} response variance
$\sigma_{wg,s}^2(\mathbf{x})$	estimated response surface function for the covariance between the w^{th} and g^{th} responses

CHAPTER 1

INTRODUCTION

Pharmaceutical optimization has been defined as the implementation of systematic approach to establish the best possible settings of material and process variables under a given set of conditions that will result in the production of a pharmaceutical product with predetermined and specified characteristics each time it is manufactured (Singh *et al.*, 2005). First, formulation development, which is the process to produce a final drug product by combining active pharmaceutical ingredients (APIs) and inactive ingredients, makes a significant contribution to the delivery of a drug to the body. Formulation designers seek optimal formulations in order to maximize the clinical benefit of drug ingredients by means of delivering the right amount, at the right rate, to the right site, at the right time (Gibson, 2001). Second, sponsors are dedicated to optimizing the manufacturing process by taking into account both ingredients and process parameters, so that the manufacturability and scale-up ability of drugs can be ensured. This dissertation focuses on the formulation optimization and aims at developing comprehensive optimization models incorporating design of experiments (DOE) and response surface methodology (RSM) for new tablets while all related regulatory requirements are satisfied. Hence, an overview of the development process of new drugs is presented in Section 1.1. Research motivations and significance are provided in Section 1.2. Along with these motivations, research tasks to be conducted in this work are

introduced in Section 1.3. Finally, the organization of this dissertation is described in the last section.

1.1 An Overview of Development Process of New Drugs

The drug can be categorized into the new and generic drugs. Developing a new drug is an extremely expensive, time-consuming, and risky proposition. Based on a U.S. government publication titled "Focus on: Intellectual Property Rights" (Field *et al.*, 2006), it is estimated that the annual cost of developing a new drug varies widely from a low of $800 million to nearly $2 billion. Moreover, drug companies usually spend 12 to 15 years to discover and develop a new drug and have to take the risk of a low probability of getting a payoff. It is known that only about 30 percent of new drugs actually earn enough revenue during their product lifecycle to recover the cost of development. The good news is that the new drug approval rate is relatively high in the United States. According to Tsuji and Tsutani (2010), 325 out of the 398 (81.7%) new drugs were approved from 1999 to 2007. Once a new drug is developed, the drug company receives a drug patent which provides protection related to rights and benefits for selling the new drug lasting around 20 years. When the patent expires, other drug companies are allowed to start developing, manufacturing, and selling a generic version of the novel drug. Since generic drug makers do not develop a drug from scratch but copy the content of APIs of the new drug, the costs to bring the generic drug to market are less; therefore, generic drugs are less expensive.

Unfortunately, the relatively higher price of new drugs alone cannot ensure their desirable quality. Based on the report about drug recalls published weekly by the Food and Drug Administration (FDA) (2009-2010), 58 new drugs out of 190 were recalled because of their various quality issues from January 2009 to February 2010. Furthermore, drug recalls usually lead to substantial economy loss. For example, the J&J's recalling its new children's medicines in 2010 would "shave J&J's sales by $300 million this year", a JP Morgan analyst Weinstein said in 2010. Therefore, in order to decrease these negative effects on developing new drugs, the reduction of development time and costs specifically, and continual improvement of quality in general, have recently gained more interest in pharmaceutical industry. Formulation development significantly impacts these costs, time and related pharmaceutical quality characteristics (QCs) throughout the development of new drugs (Hwang & Noack, 2011).

The entire development process of new drugs can be broken into several key stages: drug discovery, preclinical phase, investigational new drug application, clinical phase (I, II, III), new drug application (NDA), FDA review, NDA approval, manufacturing, and post-marketing surveillance. Each stage must meet the regulatory standards regarding safety, efficacy and quality. Figure 1.1 shows the framework of developing a new drug from Phase I to manufacture. Phase I trials are designed to learn more about the safety of a new drug, and they may also collect some information concerning efficacy. The purposes of these studies are the rapid elimination of potential failures from the pipeline, definition of biological markers for efficacy or toxicity, and demonstration of early evidence of efficacy. Phase II studies are designed to determine

whether the new drug is effective in treating, disease or condition for which it is intended, short-term side effects, and risks in patients. Phase III trials, which are conducted on larger patient populations under conditions that more closely approximate medical practices, provide the scientific evidence required for the approval of a new drug. With the completion of Phase III trials, sponsors submit NDA to the FDA for marketing approval. Once FDA accepts NDA, FDA starts the review program. The NDA review generally involves medical, biopharmaceutical, pharmacology, statistical, chemistry, microbiology, labeling, and inspection of sites reviews. Drugs must be manufactured in accordance with standards called good manufacturing practices, and the FDA inspects manufacturing facilities before a drug can be approved. Marketing approval, when received, the drug company is able to manufacture and market the new drug.

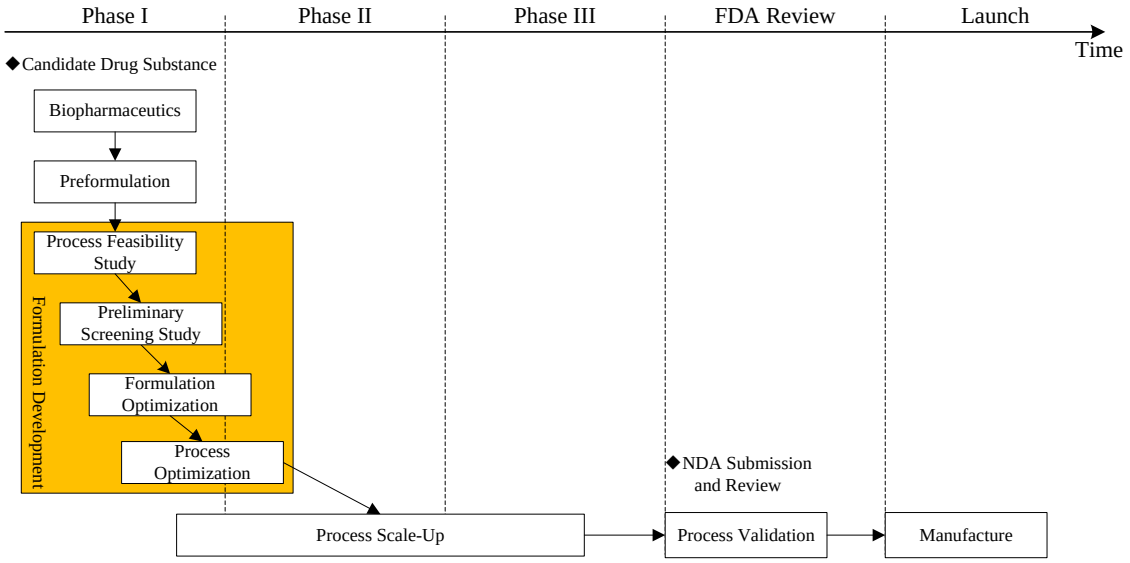

Figure 1.1 Framework for New Drug Development

During the period of discovery and preclinical phase, it is important to consider the biopharmaceutical properties of the drug substance including *in vivo* and *in vitro*

dissolution performance and bioavailability profiles (Gibson, 2001). Note that dissolution testing is a key analytical study used for characterizing how an API is extracted out of a dosage form, while the bioavailability is associated with the rate and extent to which the API is absorbed from a drug product and becomes available at the site of action (FDA, 2003). For the development of robust formulation and process, critical formulation issues must be first identified from the preformulation work, such as dissolution rate, stability, stabilization, and processing difficulties due to poor powder properties of the API (Smith & O'Donnell, 2006). Once the critical formulation issues are identified, the target product profile of the new drug, including the route of administration, maximum and minimum dose, delivery requirement and appearance, is needed to be established. The target profile serves as a guide for formulation designers to set up formulation strategies and keep formulation effort focused and efficient (Hwang & Kowalski, 2005). The formulation strategy is associated with a systematic approach to identifying the optimal composition and process during the period of formulation development which includes four studies: process feasibility, preliminary screening, formulation optimization, and process optimization. Based on the results of preliminary screening studies, formulation scientists seek optimal levels of selected excipients, also known as inactive ingredients, in order to achieve the target profile of the formulation, while meeting various requirements related to time, costs, ingredient amounts, and manufacturing feasibility. Note that excipients are added to a formulation to enhance certain performance of a drug. After the final formulation is determined during the stage of formulation optimization, the manufacturing process, such as granulation, milling, drying and blending, will be

optimized by evaluating critical process parameters. Commonly, with the completion of formulation development, the manufacturing process is scaled up from the laboratory, through the pilot, and to the commercial production scale.

1.2 Research Motivation and Significance

In the real world, process scale-up during the development of new drugs often results in modifications concerning ingredients, site, batch size, and manufacturing. The FDA guidance (1995) for immediate-release (IR) solid oral dosage forms requires that drug developers provide documentation tests so as to exclude the need for reestablishing the drug safety and efficacy by means of submitting duplicate data to the FDA. It should be mentioned that the pre-change formulation is chosen as a reference standard against the test post-change one for the related tests. Documentation tests usually include *in vitro* dissolution comparisons and *in vivo* bioequivalence studies. The former is an analytical study that investigates the similarity of the dissolution performance between the reference and test formulations, while the latter is conducted to compare the bioavailability between the two formulations of a drug product with respect to the rate and extent of absorption. It should be mentioned that the crossover design is widely utilized to determine bioequivalence. An example template of a single-dose, two-treatment, two-period, two-sequence (2×2) crossover design is shown in Figure 1.2. An equal number of subjects is randomly assigned to each of the two sequences (FDA, 1995). Within the first sequence, the reference formulation is administered to subjects first, while the test

formulation is administered first within the second one. The 2×2 crossover design is discussed in greater detail in Chapter 4.

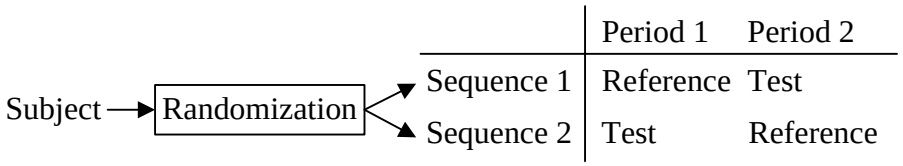

Figure 1.2 2×2 Crossover Design Scheme

The basic motivation of this work is twofold. First, the formulation optimization issue arises when scale-up changes occur, which has not been adequately addressed in the previous investigations. Second, when dealing with multiple QCs to be optimized, the desirability function (DF) approach can be incorporated into formulation optimization. However, this approach has several weaknesses that affect the accuracy of optimal solutions. The following subsections provide the research significance derived from this motivation. Note that the oral administration route is the one most often used, and tablets are the most popular oral dosage forms. Hence, this dissertation focuses on the tablet formulation optimization problem.

1.2.1 Significance I: Formulation Optimization for Scale-Up Changes

As discussed earlier, formulation optimization is conducted to determine the optimal excipient amounts of the formulation so that the target profile can be achieved. It is also believed that formulation optimization plays a critical role during the formulation developing process (Hwang & Kowalski, 2005; Hwang & Noack, 2011). Therefore, it is necessary to propose a methodology that extends the application of current formulation

optimization when the excipient amounts need to be modified. That is, after the period of formulation development, formulation optimization can be conducted so as to ensure the equivalent performance in documentation tests between the reference and test formulations when scale-up changes in excipients occur. Figure 1.3 describes the extension of formulation development.

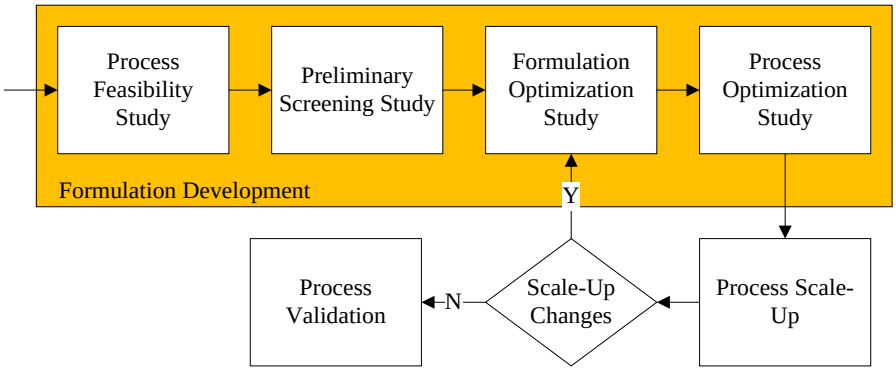

Figure 1.3 A Simplified Extended Pharmaceutical Formulation Development

Similar to the current formulation optimization study, many formulation factors and responses need to be evaluated in the extended study. The factors are the excipient amounts, while the responses are relevant to the critical pharmaceutical QCs generally selected based on the target product profile and documentation tests, such as uniformity, hardness, disintegration, stability, dissolution, and bioavailability performance. The DOE technique is one of the most efficient and effective approaches to evaluate the relationship between the response and factors. Once the relationship is identified, the formulation can be mathematically optimized by choosing the best combination of excipient amounts to achieve the specific goals. It is critical to mention that

1) the input factors of DOE remain the same as the decision variables of the optimization procedure;

2) the optimization constraints are developed according to the regulatory requirements on the responses of DOE;
3) the objective function of the current formulation optimization is to minimize or maximize specific characteristic associated with the target profile, while the extended optimization is to ensure the equivalent performance in documentation tests required by the FDA.

Moreover, the extended formulation optimization procedure is able to provide continuous improvement of product quality from the period of formulation development to the scale-up stage. During the formulation development, formulation optimization is performed to obtain the desirable ingredient amounts of a formulation so as to achieve the target profile. Within the scale-up phase, scale-up changes in the ingredient amounts potentially challenge the safety and efficacy of the changed formulation. In this case, formulation optimization is useful to determine the optimal amounts of ingredients for guaranteeing the equivalence with respect to safety and efficacy between the original and new formulations.

1.2.2 Significance II: Assessment of Similarity in Dissolution and Bioequivalence

It is necessary to integrate the regular assessment methods for the two documentation tests into the proposed formulation optimization models. Several approaches are available for evaluating the similarity in dissolution and bioequivalence between formulations; however, different numerical results can be obtained depending on

the methods used. Despite the recommendations of FDA on some of these methods, there remains no agreement over which is the best method.

- Dissolution comparisons

According to the FDA guideline (2000), the two factors f_1 and f_2 are useful to determine if the dissolution profiles of two formulations are similar (see section titled "Assessment of *In Vitro* Dissolution" of the Chapter 2). The main drawback of the recommended evaluation methods is that they are applicable to the dissolution data with low variability only. The variance is generally considered essential to the safety and efficacy issues because individual subjects may differ widely in their responses to a drug. If the variance of the test formulation is comparatively large, the safety and efficacy of the test formulation may be questionable. In order to overcome this shortcoming, a rigorous technique should be developed for simultaneously comparing both the mean and variance related to the dissolution data for the reference and test formulations (see Chapter 3).

- Bioequivalence Assessment

First, as stated earlier, the crossover design is widely conducted during the bioequivalence study, since its main advantage is that it excludes the inter-subject variability from the comparison between formulations. Under the proposed optimization scheme, it is essential to incorporate this special type of experimental design into the ordinary DOE technique so as to evaluate the relationships between the factors and

responses associated with the characteristics of bioequivalence studies. In order words, a crossover design is performed at each experimental run within the DOE format. Second, a discretization method, specifically the linear trapezoidal technique, is most frequently used to approximate the bioequivalence characteristics (FDA, 2006a) because of its simplicity. However, the continuous methods, which involve curve fitting and more mathematical calculations, are also applicable to the bioequivalence evaluation. Both methods are discussed and compared in greater detail in Chapter 4.

1.2.3 Significance III: Taguchi Quality Loss Concept and Regulatory Constraints

When optimizing a formulation, the drug designer is typically dedicated to optimizing the performance regarding the mean of a QC. However, the variance of a QC is considered essential because large variance may result in safety and efficacy issues. Based on the Taguchi quality loss concept, any deviation from target values will result in costs and consequently quality loss. This concept appears to be appealing to drug developers because it evaluates the deviations from target profiles of both the mean and variance. On the other hand, although multiple regulatory constraints in the formulation optimization problem are acknowledged, there is little formal research on integrating the quality loss concept as well as all the related FDA requirements with scientific formulation optimization techniques. Therefore, comprehensive optimization models taking into consideration the Taguchi quality loss concept and as many associated constraints as possible need to be developed in order (1) to optimize both the mean and

variance of the QC of interest and (2) to ensure that the related QCs of the tablet formulation satisfy all the requirements in an efficient manner.

1.2.4 Significance IV: Modified Desirability Approach and Goal Programming

When applying RSM to the optimization of a new drug formulation, drug designers are usually faced with multiple QCs of interest, namely, multi-response surface (MRS) optimization problems. In this case, the DF approach can be incorporated into the optimization where the weight-based overall DF is usually considered an objective function to be maximized. However, this approach has a potential shortcoming: the optimal solutions are extremely sensitive to the weights assigned and assigning these weights is a very subjective process. Since the goal programming technique is one of the most popular approaches to finding good solutions in a multi-objective problem (Rardin, 1998), a priority-based optimization scheme can be a more effective alternative that is performed based upon the priority instead of the numerical weight for each individual characteristic. Moreover, since the existing DF methods only consider the mean of a QC, variability is not captured despite the fact that individuals may differ widely in their responses to a drug. Finally, the commonly used RSM, which calls for the development of linear or quadratic response surface designs in estimating the QC of interest, may be less effective for the estimation than a higher-order model (Shaibu & Cho, 2009). Considering that the estimation accuracy heavily impacts the effectiveness in seeking optimal solutions, the traditional low-order response surface functions may not always be suitable. Therefore, in order to improve the effectiveness of the traditional approach to

formulation optimization for multiple characteristics, (1) the conventional DF method is modified to take into consideration both the mean and variability of a QC by proposing two separate DFs- *empirical* and *mechanistic* (see Chapter 5), (2) a priority-based goal programming model is proposed to optimize individual desirability of the multiple characteristics with the purpose of determining the best compromise among the characteristics, and (3) as one of the few research attempts integrating higher-order response surface functions into the formulation optimization procedure, the use of higher-order (up to fourth-order) regression functions is proposed in Chapter 5 in order to improve the estimation accuracy of response surfaces and thereby the effectiveness of the optimization.

1.3 Research Tasks

In order to achieve the research goal, which is to develop optimization models for the extended tablet formulation development, some of the fundamental questions should be answered. The fundamental research questions of this work include:

Question 1: *What types of DOE and assessment methods for documentation tests should be applied to the evalution of the response mean and varability related to dissolution comparisons and bioequivalence studies?*

Question 2: *How can we develop an optimization scheme that allows a drug designer to minimize both deviations from the target values and variability of the related QCs?*

Question 3: *What regulatory requirements are involved in an extended tablet formulation optimization problem?*

Question 4: *How can we validate the optimization results?*

Based on the research questions above, the major research tasks to be accomplished are presented as follows:

Task 1: *The investigations of the existing assessment methods for dissolution comparisons and bioequivalence studies, various DOE techniques used in formulation optimization procedure, and enhanced optimization methods which take into consideration multiple QCs concerning the mean and variability of the related QCs.*

Task 2: *The study of all the possible related regulatory constraints for the tablet optimization problem; the development of extended formulation optimization models.*

Task 3: *The comparisons of the existing and proposed approaches.*

Task 4: *The validation of the results of the proposed optimization methodologies.*

The first task is implemented in Chapter 2. The second and third tasks are accomplished by integrating appropriate DOE, RSM, and associated assessment methods for the documentation tests into the optimization procedure while taking into account necessary constraints. Finally, validation studies are conducted by means of sensitivity analysis in this work.

1.4 Outline of Dissertation

The overall structure of the research is shown in Table 1.1. Chapter 1 mainly introduces research significance and tasks. In Chapter 2, a review of the relevant research in the literature and pertinent technological basis for the formulation optimization are provided, including mathematical models of dissolution and bioequivalence studies, fundamental definitions of scale-up changes, various DOE techniques, and several widely used optimization methodologies. Chapters 3, 4 and 5 present the proposed formulation optimization models for dissolution comparisons, bioequivalence studies, and MRS problems, respectively. Finally, Chapter 6 includes a description of the research achievements and scope for future study.

Table 1.1 Dissertation Structure

Chapter	Feature
1	Overview of the development process of new drugs, research motivations, significance and tasks
2	Literature reivew of assessment methods for dissolution and bioequivalence testing, DOE techniques, and optimization methodologies
3	A formulation optimization model for dissolution comparisons with several proposed objective functions
4	A formulation optimization model for bioequivalence studies with two assessment methods
5	An MRS formulation optimization model incorporating modified DF and priority-based goal programming methods
6	Summary of research findings, contributions, and further work

CHAPTER 2

LITERATURE REVIEW AND KNOWLEDGE BACKGROUND

In this chapter, an overview of the literature and knowledge basis for the formulation modeling and optimization is presented and divided into separate sections, namely, biopharmaceutical tests, scale-up changes for IR solid orally administered drugs, DOE approaches, and common optimization methodologies. Section 2.1 provides a brief review of the existing mathematical models employed to implement biopharmaceutical supports for the formulation development. Sections 2.1.1, 2.1.2, and 2.1.3 introduce the assessment of *in vitro* dissolution tests, the evaluation of *in vivo* bioavailability studies, and the establishment of *in vitro*/*in vivo* correlation (IVIVC), respectively. Scale-up changes and requirements on related documentation tests for IR oral formulations are outlined in Section 2.2. In Section 2.3, diverse types of DOE techniques applied to the formulation optimization problem are discussed. Several popular optimization methodologies are presented in detail in Section 2.4. Finally, Section 2.5 is the summary of this chapter.

2.1 Typical Biopharmaceutical Tests for Formulation Development

To investigate the clinical benefits of drug ingredients, biopharmaceutical tests are rigorously performed from the stage of preformulation, through formulation development, to filling FDA applications. The biopharmaceutical tests for the formulation development, which typically include *in vitro* dissolution testing, *in vivo*

bioavailability evaluation, and IVIC studies, are conducted to assess the *in vitro* impact of physicochemical properties of drugs on the bioavailability of drugs (Shargel *et al.*, 2004). Following sections introduce the assessment of these studies for oral drug profiles.

2.1.1 Assessment of *In Vitro* Dissolution

In vitro dissolution testing of solid dosage forms is the most frequently used biopharmaceutical test in the drug development. It is conducted from the start of dosage form development and in all subsequent processes. Standard *in vitro* dissolution tests measure the rate and extent of dissolution or release of the drug substance from a drug product. Drug release is often determined by formulation factors such as excipients. Excipients are inactive pharmaceutical ingredients that enhance certain performance of the drug. According to Shargel *et al.* (2004), Hwang *et al.* (2011), and the United States Pharmacopeia (USP) document (2009a), common excipients used in solid drugs are summarized in Table 2.1.

Moreover, one of the most common responses measured to analyze the dissolution performance of a formulation is the ingredient amount dissolved at a certain point in time. Both linear and nonlinear regression models (Yuksel *et al.*, 2000; Berry & Likar, 2007) that evaluate the response over time can be applied to *in vitro* dissolution tests, as shown in Table 2.2.

In Table 2.2, $A(t)$ is the percent dissolved after time t, k_d is the dissolution rate constant, and τ_r is a rate parameter which is a scale factor of the time axis, α is scale factor, and β is a parameter that characterizes the shape of the curve. Dave *et al.* (2004) indicated that the

method developed by Bamba *et al.* (1979) could be adopted for selecting the most appropriate model based on the results of *F*-statistics.

Table 2.1 Common Excipients Used in Solid Drug Products

Ingredient	Functional Properties	Examples
Binder	To provide the adhesion for holding the ingredients in a tablet together.	Carboxymethylcellulose (CMC) Sodium, Hydroxypropyl Methylcellulose (HPMC)
Diluent	To provide the bonding strength and to fill out the additional volume/weight.	Lactose, Dicalcium Phosphate, Microcrystalline Cellulose (MMC)
Disintegrant	To help break apart the tablet.	Sodium Starch Glycolate, Crospovidone, Starch
Lubricant	To increase the lubricity for manufacturing.	Magnesium Stearate, Stearic Acid, Talc
Gildant	To enhance the flowability.	Silicon Dioxide, Talc
Coating Agent	To stabilize the drug against degradation and to make tablets easier to swallow.	HPMC

Table 2.2 Regression Models for *In Vitro* Dissolution Tests

Function	Equation
First-order (Gibaldi & Feldman, 1967)	$A(t) = 100\left(1 - e^{-k_d t}\right)$
Hixson-Crowell (Hixson & Crowell, 1931)	$A(t) = 100\left[1 - \left(1 - \frac{k_d t}{4.6416}\right)^3\right]$
Higuchi (Higuchi, 1963)	$A(t) = k_d t^{0.5}$
Weibull (Langenbucher, 1976)	$A(t) = 100\left[1 - e^{-(t/\tau_r)^\beta}\right]$
Logistic (Romero *et al.*, 1991)	$A(t) = 100\left[\frac{e^{(\alpha+\beta\log t)}}{1+e^{(\alpha+\beta\log t)}}\right]$
Gompertz (Dawoodbhai *et al.*, 1991)	$A(t) = 100e^{\left[-\alpha^{\left(e^{-\beta\log t}\right)}\right]}$

Another approach to obtain the parameter that describes the dissolution rate is to use the statistical moment technique to determine the mean dissolution time (MDT) (Von

Hattingberg, 1984). This method has the advantage of being applicable to all types of dissolution profiles, and it does not require fitting to any regression model. However, lack of data points close to the final plateau level will potentially affect the evaluation accuracy of MDT (Gibson, 2001). The MDT can be computed by (Brockmeier, 1986)

$$\mathrm{MDT} = \frac{\sum_i \bar{t}_i \times \Delta M_i}{\sum_i \Delta M_i},$$

where $\bar{t}_i$ is the midpoint of the i^{th} time period during which the fraction, ΔM_i, has been released from the drug. Note that the length of each time period is given by the sampling intervals.

Issues arise when two dissolution performances are compared. According to the FDA guidance (1997b), for major changes concerning scale-up and post-approval changes, a dissolution profile comparison performed under identical conditions for the product before and after the change(s) is recommended. Dissolution profiles may be considered similar by virtue of overall profile similarity (Moore & Flanner, 1996)

$$f_1 = \left(\sum_{t=1}^{n} |R_t - T_t| \Big/ \sum_{t=1}^{n} R_t \right) \times 100,$$

and similarity at each point in time

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right]^{-1/2} \times 100 \right\}, \qquad (2.1)$$

where n is the number of points in time, and R_t and T_t are the cumulative amounts dissolved at time t for the reference and test formulations, respectively. Curves can be considered similar when f_1 and f_2 values are respectively on the intervals (0, 15) and (50,

100). Once the similarity of dissolution curves is established, the equivalent performance with respect to safety and efficacy of the test and reference products is ensured (FDA, 1997b). The main advantages of this method are that the f_1 and f_2 are easy to compute and they both provide a single value to describe the extent of difference/similarity of two dissolution profiles. Since f_1 and f_2 are mentioned for use in a number of FDA guidance, they are considered the most popular method to compare dissolution profiles. In practice, formulation researchers are more interested in evaluating the dissolution similarity at each point in time with the f_2.

However, Chow *et al.* (1997) and Polli *et al*. (1997) pointed out that the values of f_1 and f_2 were sensitive to the number of points in time used. O'Hara *et al.* (1998) also summarized the disadvantages of this method that the f_1 and f_2 equations did not take into account the variability or correlation structure in the data, and the basis of criteria used to decided on difference or similarity was unclear. Shah *et al.* (1998) discussed the statistical properities of the estimate of f_2, $\hat{f}_2$, based on sample means and concluded that the commonly used $\hat{f}_2$ was a biased and conservative estimate of f_2.

Chow *et al.* (1997), Polli *et al.* (1997), and Yuksel *et al.* (2000) made significant efforts to summarize and examine the general approaches for describing and comparing dissolution profiles: ANOVA-based, model-dependent, and model-independent methods. (1) The ANOVA-based method uses repeated measures designs to detect differences between dissolution profiles. The percents dissolved are dependent variables and time is the repeated factor. (2) For the model-dependent method, the linear or nonlinear dissolution models presented in Table 2.2 are fitted to the test and reference dissolution

profiles. The estimated parameters for both profiles are then employed for the pairwise comparison using *t*-test (Bolton & Bon, 2009). (3) In addtion to the f_1 and f_2 method, Rescigno (1992) introduced the Rescigno index as an alternative model-independent method. The indices are originally used to compare blood plasma concentration profiles; however, they do not take into account the variability or correlation related to the dissolution data, and there are no criteria for judging difference or similarity between dissolution profiles (O'Hara *et al.*, 1998). The indices are denoted by ξ_i (i = 1, 2) and can be calculated by

$$\xi_i = \left(\frac{\int_0^{t_n} \left| R_t - T_t \right|^i dt}{\int_0^{t_n} \left| R_t + T_t \right|^i dt} \right)^{1/i},$$

where R_t and T_t are the mean values of percent dissolved for the reference and test formulations at time t, and t_n is the last point in time. When the value of ξ_i (i = 1, 2) approaches zero, the similarity between dissolution profiles can be ensured. According to O'Hara *et al.* (1998), the denominator of ξ_i can be considered a scaling factor, and the indices ξ_i (i = 1, 2) can then be reviewed as a function of the weigthed average of the veritical distances between the test and reference mean profiles at each point in time. Moreover, Chow *et al.* (1997) proposed a method for the comparison of dissolution profiles that can be regarded as being similar to that used in the assessment of the average bioequivalence (ABE) for two formualtions. This method uses the concept of 'local' and 'global' similarity to assess the closeness between the test and reference dissolution profiles. The assessment of global similiarity assumes that the true relative dissolution

rate at each location is the same for all the time, while local similarity presuppose that each location has the same relative dissolution rate. O'Hara *et al.* (1998), however, revealed that the main drawbacks of this method were that its power and Type I error were unknown. Finally, Anderson *et al.* (1998) indicated that Dissolution Efficiency (DE) (Khan, 1975) could also be used to evaluate the similarity of dissolution profiles. In Equation (2.2), DE, defined as the area under the dissolution curve between time t_1 and t_2, is expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period.

$$\mathrm{DE} = \frac{\int_{t_1}^{t_2} y\mathrm{d}t}{y_{100}(t_2 - t_1)} \times 100\%, \tag{2.2}$$

where y is the percentage of dissolved.

2.1.2 Evaluation of Bioavailability Studies

Bioavailability studies are widely performed during the formulation development to evaluate the absorption properties of a drug, establish bioequivalence between formulations, and develop IVIVCs. In a bioavailability study, the drug plasma concentrations after administration are followed over an appropriate time interval. The standard bioavailability characteristics after a single-dose administration are the maximum plasma concentration ($C_{\max}$), the time to reach $C_{\max}$ ($t_{\max}$), and the area under the plasma concentration-time curve (AUC). Figure 2.1 illustrates a typical plasma concentration profile. It should be noted that sampling is generally more frequent at time

intervals in the ascent to the peak concentration and around the peak in order to detect the C_{max} and t_{max} as accurately as possible under the experimental condition.

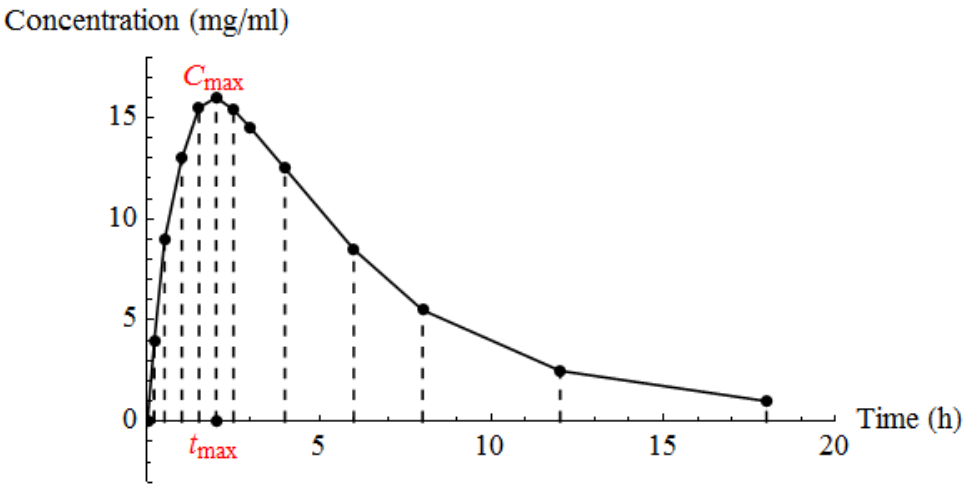

Figure 2.1 A Typical Plasma Concentration-Time Curve

C_{max} and t_{max} are influenced by several pharmacokinetic properties such as the absorption rate (K_a) and the elimination rate (K_e). If a drug exhibits first-order absorption, the drug concentration (C) in the plasma at any time t can be calculated based on the following equation (Shargel *et al.*, 2004):

$$C = \frac{FD}{V_d}\frac{K_a}{K_a - K_e}\left(e^{-K_e t} - e^{-K_a t}\right). \tag{2.3}$$

Correspondingly, C_{max} and t_{max} can be obtained by (Shargel *et al.*, 2004):

$$C_{max} = \frac{FD}{V_d}\frac{K_a}{K_a - K_e}\left(e^{-K_e t_{max}} - e^{-K_a t_{max}}\right) \tag{2.4}$$

and

$$t_{max} = \frac{\ln(K_a/K_e)}{K_a - K_e} = \frac{\ln 10 \times \log\left(K_a/K_e\right)}{K_a - K_e}, \tag{2.5}$$

where F is the extent of oral drug bioavailability expressed as a fraction, D is the administered dose, K_e is the first-order elimination rate constant, and V_d is the apparent volume in the body in which the drug is dissolved. However, C_{max} and t_{max} are single-point characteristics, which do not take into account all data sampled during the absorption process. According to Gibson (2001), C_{max} and t_{max} are not useful as pure measures of the absorption rate but can be utilized in comparisons of the test and reference plasma concentration profiles. In addition, they cannot accurately identify the maximum in the case of rapid dissolution processes.

AUC, on the hand, is used to evaluate the extent of absorption. Similar to C_{max} and t_{max}, it is only of interest as a relative characteristic for comparisons of between different profiles. Several methods exist for evaluating the *AUC* from time 0 to t which is denote by $AUC_{0\text{-}t}$. These methods include the interpolation using the trapezoidal rule, the Lagrange and spline methods, the use of a planimeter, the use of digital computers, and the physical method that compares the weight of a paper corresponding to the area under the experimental curve to the weight of a paper of known area (Chow & Liu, 2009). The calculation of *AUC* is commonly determined by the linear trapezoidal rule. Yeh *et al.* (1978) discussed the strengths and weaknesses of using the Lagrange and spline methods against the trapezoidal rule in the aspect of interpolation. According to the linear trapezoidal rule, the summation of the areas of a series of trapezoids, which are formed between the data for two contiguous points in time, is computed. This approximate method requires that blood sampling be frequent enough so that the curvature of the

plasma concentrations between two data points is negligible. The area under each segment between two data points for the linear trapezoidal is determined by

$$AUC\left(t_i, t_{i+1}\right) = \left(\frac{C_i + C_{i+1}}{2}\right) \times \left(t_{i+1} - t_i\right), \tag{2.6}$$

where C_i is the plasma concentration for the sample obtained at time t_i. The *AUC*, however, should be calculated from zero to infinity, not just to the time of the last blood sample, as is so often done. The $AUC_{0\text{-}\infty}$ can be estimated by (Tozer & Rowland, 1980):

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_n}{K_e}, \tag{2.7}$$

where C_n is the concentration at the last measured sample after drug administration, and K_e is the elimination rate constant, which can be estimated as the slope of the terminal portion of the log concentration-time (Shargel *et al.*, 2004), as shown in Figure 2.2.

As stated in the FDA guidance (2003), it is recommended to perform a natural log-transformation of $C_{\max}$ and *AUC* before analysis, since the transformed data are believed to be normally distributed. No assumption checking or verification of the log-transformation data is encouraged. On the basis of log-transformed data, the FDA (2003) requires that both *AUC* and $C_{\max}$ of the test formulation be within 80% to 125% of those of the reference formulation at the 90% significance level for the establishment of ABE. However, Liu *et al.* (1992) studied the distribution of log-transformed pharmacokinetic data assuming that the hourly concentrations were normally distributed. The results indicated that the log-transformed data over time were not normally distributed under certain conditions.

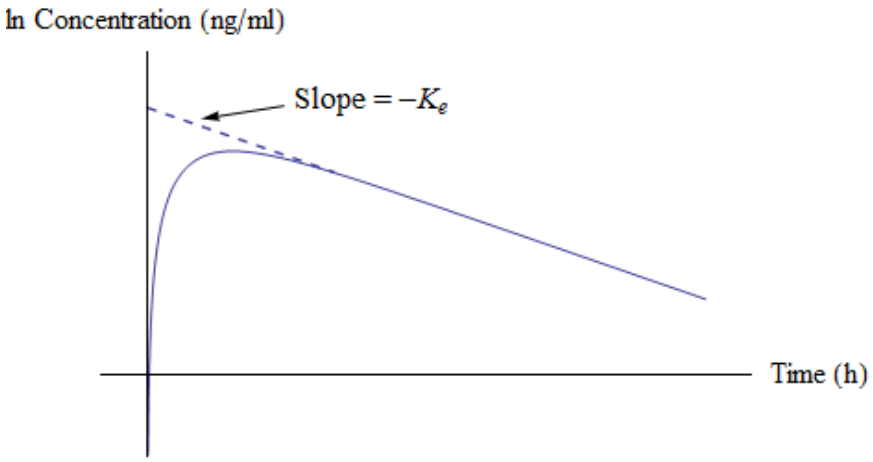

Figure 2.2 Logarithmic Drug Plasma Concentration-Time Curve for an Oral Administration

Moreover, it is not uncommon to pass *AUC* but fail C_{max}. In this case, ABE cannot be claimed according to the FDA guidance on bioequivalence. According to Hauck *et al.* (2001), some regulatory agencies consider a wider bioequivalence limit for C_{max}, because of the typically higher variability of C_{max} compared to *AUC*. The European Medicines Agency (EMEA) and World Health Organization (WHO) guidelines use a wider equivalence standard of (70%, 133%) for C_{max}. Endrenyi *et al.* (1991) indicated that C_{max}/AUC could be used as another bioequivalence measure between formulations. It was also revealed that the variability of C_{max}/AUC was substantially decreased compared with C_{max} under most conditions (Endrenyi & Yan, 1993). However, C_{max}/AUC is not currently selected as the required pharmacokinetic responses for approval of drug products by any of the regulatory authorities in the world. On the other hand, it is very likely that we may pass C_{max} but fail *AUC*. In this case, it is suggested that we may look at partial *AUC* as an alternative measure of bioequivalence (Chen *et al.*,

2001). One of the possible reasons is that the incremental area under the plasma concentration-time curve representing 10-30% of the total *AUC* may be more sensitive than either C_{max} or t_{max} in detecting the difference of absorption rates between formulations (Rosenbaum *et al.*, 1990).

2.1.3 Establishment of IVIVC

Increasing clinical or market demand for tablet drugs necessitates the expansion of the production scale. Scale-up may encompass modifications concerning ingredients, site, batch size and manufacturing. When any of these changes occurs, *in vivo* bioequivalence studies need to be performed to prove the equivalent efficacy and safety of the new formulation. Bioequivalence studies are generally time-consuming and costly procedures. However, the establishment of IVIVC may minimize the need for conducting the expensive *in vivo* studies. According to the FDA guidance (FDA, 1997a), IVIVC is a predictive mathematical model describing the relationship between an *in vitro* property of a formulation and a relevant *in vivo* characteristic. Four different types of correlation are defined in FDA guidance (FDA, 1997a), namely, Level A, B, C, and Multiple-Level C. It should be mentioned that the Level A correlation is the most commonly developed type of correlation in NDAs submitted to the FDA, and Gibson (2001) pointed out that only the Level A correlation was accepted by FDA as an evidence for eliminating *in vivo* bioequivalence studies. Therefore, the focus of the following review is primarily centered on the Level A correlation.

A Level A correlation can be developed by a two-stage approach: (1) the *in vivo* dissolution profile is estimated from the plasma concentration profiles for the test formulation and an oral solution that is considered a reference formulation in the IVIVC bioavailability study, and (2) the estimated *in vivo* data is correlated with the *in vitro* dissolution profile. This type of correlation is generally linear in which the *in vitro* and *in vivo* dissolution-time curves may be directly superimposable or may be made to be superimposable by the use of a scaling factor (e.g., time scaling and a scaling of the amount dissolved). Figure 2.3 illustrates a general Level A correlation. Once a Level A correlation is established, the *in vivo* plasma concentration profile of the test formulation can be predicted from the *in vitro* dissolution data and the bioavailability performance of the oral solution and thereby the *in vivo* bioequivalence study for the test and reference formulations can be substituted by the comparison of their *in vitro* dissolution profiles.

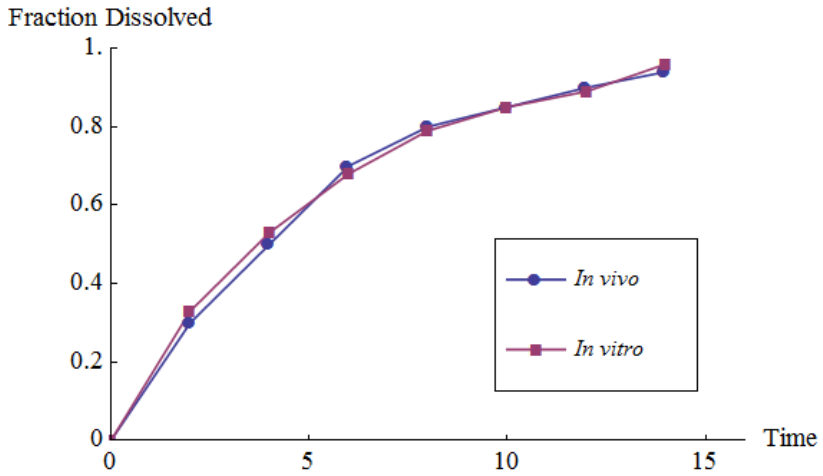

Figure 2.3 A Level A Correlation of Drug Dissolution

A Level B correlation is developed according to the principle of statistical moment analysis. It can be utilized when a Level A correlation is not possible. A Level C

correlation establishes a single-point relationship between a characteristic of the *in vitro* dissolution profile (e.g., amount dissolved at 1h) and a bioavailability characteristic (e.g., C_{max}, t_{max} and *AUC*). A multiple Level C correlation takes into account multiple measures related to the dissolution and bioavailability profiles. Since a Level B or C correlation does not establish a point-to-point relationship, its likelihood of predicting the entire *in vivo* plasma concentration profile from the *in vitro* dissolution data is relatively lower, compared to a Level A correlation (Gibson, 2001; Emami, 2006). Level B or Level C correlations, therefore, have a limited use for regulatory purpose.

2.2 Scale-Up Changes and Related Documentation Tests for IR Oral Drugs

When an oral drug undergoes scale-up changes, the documentation tests, including the dissolution comparison and bioequivalence study, are conducted to exclude the need for reestablishing the drug safety and efficacy by retesting the patients administrating each formulation. Based on the FDA guidance (1995) for IR orally administered drugs, levels of change and involved documentation tests are summarized in Table 2.3. Under some circumstances, *in vivo* bioequivalence studies can be substituted by comparing *in vitro* dissolution profiles of the test and reference formulations. In addition to the establishment of IVIVC, depending on the Biopharmaceutics Classification System (BCS), bioequivalence studies can be eliminated if the following requirements are met: (1) APIs are classified as Class 1, (2) the test and reference formulations have rapid dissolution profiles, and (3) the coefficient of variation (CV) of dissolution data for the test and reference formulations should not be more than 20% at

Table 2.3 Scale-Up Changes and Related Tests for IR Orally Administered Drugs

	Level	Classification	Dissolution Documentation	Bioequivalence Documentation
Changes in the Amount of Inactive Ingredients	I	The total additive effect of all excipient changes should not change by more than 5%.	None beyond application requirements.	None.
	II	The total additive effect of all excipient changes should not be more than 10%.	The dissolution profiles of the reference and test formulations should be similar.	None: if the similarity of two dissolution profiles cannot be ensured, refer to Level III.
	III	Level III changes are those that are likely to have a significant impact on formulation quality.	The dissolution profiles of the reference and test formulations should be similar.	*In vivo* bioequivalence study or acceptable IVIVC.
Site Changes	I	Changes within a single facility.	None beyond application requirements.	None.
	II	Changes within a contiguous campus or between facilities in adjacent city blocks.	None beyond application requirements.	None.
	III	Changes in manufacturing site to a different campus.	The dissolution profiles of the reference and test formulations should be similar.	None.
Batch Size Changes	I	Changes up to and including a factor of 10 times the size of the pilot batch.	None beyond application requirements.	None.
	II	Changes beyond a factor of 10 times the size of the pilot batch.	The dissolution profiles of the reference and test formulations should be similar.	None.
Equipment Changes	I	A change to alternative equipment of the same design and operating principles.	None beyond application requirements.	None.
	II	A change in equipment to a different design and operating principles.	The dissolution profiles of the reference and test formulations should be similar.	None.
Process Changes	I	Such changes as mixing times and operating speeds within application limits.	None beyond application requirements.	None.
	II	Such changes as mixing times and operating speeds beyond application limits.	The dissolution profiles of the reference and test formulations should be similar.	None.
	III	Changes in the type of process used in the manufacture of the product.	The dissolution profiles of the reference and test formulations should be similar.	*In vivo* bioequivalence study or acceptable IVIVC.

the earlier points in time (e.g., 10 min) and should not be more than 10% at other points in time. Note that the BCS classifies APIs into four types: high solubility and high permeability (Class 1), low solubility and high permeability (Class 2), high solubility and low permeability (Class 3), and low solubility and low permeability (Class 4) (FDA, 2000).

2.3 DOE Supports in Formulation Optimization

DOE was first applied to the agricultural industry. With the spread of DOE, the first publication for the pharmaceutical industry appeared in 1952 (Hwang, 1998). Over the years, it has been widely acknowledged that DOE is one of the most efficient methods for identifying the effects of ingredient amounts on critical QCs related to a pharmaceutical formulation, such as dissolution, friability, disintegration, and hardness. Estimated response functions can then be obtained by performing a regression analysis based on the DOE results. In order to determine the optimal formulation, the estimated functions are finally employed to implement the optimization procedure where they are minimized, maximized, or ensured to be within the criteria specified by the FDA. Additionally, suitable user-friendly software packages, such as Minitab, SAS, JMP, NEMROD, and Design-Expert, also contribute to a quick uptake of DOE, since the computing environments help drug designers reduce the time and materials as well as mitigate the risk of failure (Gupta & Kaisheva, 2003).

In practice, various DOE methods, such as full or fractional factorial experimental designs, response surface designs including central composite designs (CCDs) and Box-

Behnken designs (Box & Behnken, 1960), mixture designs, and Taguchi designs, are extensively applied to the formulation optimization:

- Factorial designs. Ragonese *et al.* (2002) and Hwang *et al.* (2011) indicated that factorial designs were frequently used during the phase of preliminary screening studies which were designed to select the excipients for the initial formulation. Factorial designs can be divided into full factorial designs and fractional factorial designs. In a full factorial design, each possible combination of factors is evaluated. Hwang *et al.* (2001b) and Hwang *et al.* (2001a) used full factorial experimental designs to evaluate the effects of diluents-related and lubricant-related factors on the tablet characteristics, such as compression. Gohel *et al*. (2004) and Patel *et al.* (2007) also conducted a two-factor, three-level full factorial design to prepare and evaluate a drug formulation. The fractional factorial design allows a large number of factors to be evaluated using a relatively small number of experimental runs. Kincl *et al.* (2004) conducted a tablet formulation optimization study in which a fractional factorial design was used to investigate the effects of the physicochemical factors on the release performance of a tablet drug.
- Response surface designs. Response surface designs mainly include CCDs and Box–Behnken designs, which usually use quadratic polynomial regression functions instead of linear equations to investigate the response surface. CCDs combined with the RSM have been widely used in response surface modeling and optimization, since they are systematic and efficient methods to study the effects

of multiple factors on formulation characteristics (Abu-Izz*a et al.*, 1996). Gupt*a et al.* (2001) performed a CCD to study the effects of three factors of a colonic drug delivery system on two formulation responses. Ibr*i et al.* (2002) and Sing*h et al.* (2006) conducted a CCD with two factors and several responses to optimize the release performace of a tablet formulation. On the other hand, the main advantage of Box–Behnken designs over CCDs is that they ensure that all factors are never simultanenously set at their high levels and therefore all design points are more likely to remain within their safe operation zones (Kinc*l et al.*, 2005). In the literature, Sastr*y et al.* (1997), Nazza*l et al.* (2002), and Kinc*l et al.* (2005) conducted three-factor, three-level Box-Behnken designs based on the RSM to investigate, characterize, and optimize critical characteristics associated with pharmaceutical formulations.

- Mixture designs. Mixture designs are useful in situations where the amounts of individual components in a formulation require optimization, but where each individual amount is constrained by a maximum value for the overall formulation (Gorman & Hinman, 1962). The weight percentages of ingredients are considered input factors. In the literature, RSM-based mixture designs like simplex lattice designs were conducted to prepare systematic formulations (Huang, Tsai, Yang, Chang, Wu, *et al.*, 2004; Patel *et al.*, 2007). Campisi *et al.* (1998) utilized a D-optimal mixture design to analyze the theophylline solubility in a four-component formulation optimization problem; meanwhile, El-Malah *et al.* (2006) demonstrated that a D-optimal mixture design was effective to evaluate the effects

of three pharmaceutical ingredients on the release profile of a formulation. Hariharan *et al.* (1997) applied a four-component mixture design to optimize a tablet formulation with the most desirable properties; however, Piepel (1999) pointed out that they ignored the fixed components by working in terms of the relative proportions. In order to overcome this weakness, Piepel (1999) proposed an enhanced mixture-of-mixture design. In reality, input factors are not constrained to the contents of a drug, because extra manufacturing processing parameters, such as stirring speed (Bhavsar *et al.,* 2006), may be involved. In this case, it is difficult to apply mixture designs to the formulation optimization.

- Taguchi designs. As one of the popular DOE methods, Taguchi methods can help formulators extract much critical information from only a few experimental trials. Wang *et al.*(1996) utilized a seven-factor, three-level orthogonal Taguchi experimental design (L_{27}) to find the optimal formation of chitosan. The L and the subscript, 27, represent the Latin square and the number of experimental runs, respectively. Varshosaz *et al.* (2009) applied an L_8 orthogonal array design to obtaining the optimal release system of an oral tablet with chitosan beads. Moreover, Taguchi designs together with the overall desriability funtion (DF) can be conducted to deal with a multi-objective formulation optimization problem (Wang *et al.,* 1996).

The wide application of DOE to the formulation optimization is summarized in Table 2.4, where DCP, RSD, and TPP stand for Dibasic Calcium Phosphate, relative standard

deviation (the ratio of the standard deviation to the mean, expressed as a percentage), and Tripolyphosphate, respectively.

2.4 Opitmization Methodologies for Selecting Pharmaceutical Formulations

Using prospectively planned and appropriately designed DOE techniques, the formulation comprising of several input factors and output responses can be effectively evaluated. Generally, since the relationship between the factors and response is unknown, enhanced estimation techniques are applied to predicting the response quantitatively from the combination of the factors. In the literature, a twofold tendency for investigating the relationship can be found, which includes artificial neural network (ANN) techniques and ordinary regression approaches employing either first- or higher-order polynomial equations. On the basis of the prediction results, optimization techniques are then applied to determining the optimal input factor settings under a set of specified constraints. Several optimization algorithms, including modified computer optimization methodology (Takayama & Nagai, 1989; Takayama *et al.*, 1999), Taguchi quadratic loss function (Taguchi, 1985), and DF (Derringer & Suich, 1980) approaches, are typically applied in the literature. Following subsections discuss the ANN prediction methods and three common optimization methodologies in greater detail.

2.4.1 ANN Prediction Techniques

An ANN, as a learning system based on a computational technique, is increasingly applied to describing the nonlinear relationship between pharmaceutical

Table 2.4 Summary of the DOE Application in Formulation Development and Optimization

Year	Author	Optimization Target	DOE Method	Inactive Ingredients	Factors	Responses
1996	Aub-Izza *et al.*	Optimizing the overall properties of a sustained-release formulation	CCDs	N/A	Emulsifier concentration, drug to polymer ratio, composition of the internal phase of emulsion	The time for 85% release, loading efficiency, yield, percentage of loose surface crystals, overall desirability
1996	Wang *et al.*	Optimizing the formulation of Cisplatin-loaded Chitosan microspheres	Taguchi designs	Disintegrant: Chitosan	Concentration of Chitosan, volume ratio of water and oil phase, stirring rate, percentage of Cisplatin, oil phase type, Chitosan type, stabilization time	Percentage of particle numbers, drug content, drug trapping efficiency, overall desirability
1997	Hariharan *et al.*	Optimizing a sustained-release tablet formulation with the most desirable properties	Mixture designs	Suspending agent: γ-carrageenan, CMC Sodium Diluent: DCP, Lactose	The amounts of γ-carrageenan, CMC Sodium, Lactose, and DCP	The time taken to release 80% drug, the release exponent, the crushing strength
1997	Sastry *et al.*	Optimizing an osmotically controlled formulation	Box-Behnken designs	Suspending agent: Carbopol 934P	Orifice size, coating level, the amount of Carbopol 934P	The cumulative percent of the drug release on time for 10%, 25%, 50% and 75% release
1998	Campisi *et al.*	Evaluating the evolution of theophylline solubility	Mixture designs	Humectant: Propylene Glycol Lubricant: Polyethylene Glycol Solvent: Ethanol	The amounts of Polyethylene Glycol, water, Propylene Glycol, and Ethanol	The evolution of theophylline solubility
1998	Hwang *et al.*	Optimizing a tablet formulation	Fractional factorial designs	Diluents: Lactose Binder: Avicel Disintegrant: Starch 1500, Na Starch Glycolate Lubricant: Magnesium Stearate Glidant: Talc	Active ingredients particle size, percentage of active ingredients, Lactose/Avicel ratio, Avicel particle size, Avicel density, disintegrant type, percentage of disintegrant,	Percentage of blend uniformity, compression force RSD, ejection force, tablet weight RSD, tablet hardness, disintegration time, percent of dissolved at 5min

					percentage of Talc, percentage of Magnesium Stearate	
1999	Piepel	Optimizing a sustained-release tablet formulation with the most desirable properties	Mixture-of-mixture designs	Suspending agent: γ-carrageenan, CMC Sodium Diluent: DCP, Lactose	The amounts of γ-carrageenan, CMC Sodium, Lactose, and DCP	The time taken to release 80% drug, the release exponent, the crushing strength
2001a	Hwang *et al.*	Evaluating the compression characteristics of a tablet	Full factorial designs	Diluent: MCC Lubricant: Magnesium Stearate	Lubricant level, lubrication time, compression speed, particle size, particle density	Compression force RSD, ejection force, tablet weight RSD, hardness, friability
2001b	Hwang *et al.*	Evaluating the compression characteristics of a tablet	Full factorial designs	Diluent: DCP, Lactose Lubricant: Magnesium Stearate	Lubricant level, lubrication time, compression speed,	Compression force RSD, ejection force, tablet weight RSD, hardness, friability
2002	Nazzal *et al.*	Characterizing and optimizing a tablet dosage	Box-Behnken designs	Diluent: Maltodextrin, MMC Coating agent: Copolyvidone	The amounts of Copolyvidone, Maltodextrin, and MMC	Tablet weight, flowability index, tensile strength, percentage of friability, disintegration time, the cumulative percent of the drug release after 45min
2002	Ibri *et al.*	Optimizing aspirin extended release tablets	CCDs	Coating agent: Eudragit® RS PO	The amount of Eudragit® RS PO, tablet hardness	*In vitro* dissolution profiles at 1h, 2h, 4h, and 8h, release order, release constant
2003	Gupta *et al.*	Identifying optimal preservatives for a formulation	I-optimal designs	Persevative: Benzyl Alcohol, Chlorobutanol, Methylparaben, Propylparaben, Phenol, M-Cresol	Amounts of Benzyl Alcohol, Chlorobutanol, Methylparaben, Propylparaben	Formulation stability and antimicrobial efficacy (i.e., the bacterial and fungal count)
2004	Gohel *et al.*	Evaluating the effect of the amounts of camphor and Crospovidone on the disintegration time,	Full factorial designs	Disintegrant: Crospovidone	Amounts of Camphor and Crospovidone	Disintegration time, percentage friability

		and percentage friability				
2004	Huang *et al.*	Developing and optimizing a extended-release formulation	Mixture designs	Diluent: MCC, and Lactose Binder: HPMC	The amounts of HPMC, MCC, and Lactose	The drug release percent at 1.5, 4, 8, 14, and 24h
2004	Kincl *et al.*	Evaluating and characterizing critical parameters which have a significant effect on the drug release	Fractional factorial designs	N/A	Apparatus, rotation speeds, pH, relative ionic strength, salt, producer of the on-line dissolution system	The percentage of the released drug product in 2h, 4h, 6h, 8h, 10h, 12h, and 24h
2005	Kincl *et al.*	Characterizing and optimizing the drug release performance	Box-Behnken designs	N/A	Rotation speeds, pH, and ionic strengths of the dissolution medium	The Cumulative percentage of the dissolved drug in 2, 6,12,and 24h
2006	El-Malah *et al.*	Evaluating the effect of three matrix ingredients on thephylline release rates for a tablet formulation	D-optimal mixture designs	Suspending agent: Polyethylene Oxide, Carbopol Diluent: Lactose	The amounts of Polyethylene Oxide, Carbopol, and Lactose	Percent thephylline released in 2h, and 4h, percent amount release in 6h, 8h, and 12h, similarity factor (f_2)
2006	Singh *et al.*	Optimizing the drug release profile and bioadhesion for controlled release tablets	CCDs	Suspending agent: CMC Sodium, Carbopol 934P	The amounts of Carbopol 934P and CMC Sodium	Release exponent, bioadhesive strength, the percentage of the released drug product at 18h, 24h, time taken to lease 50% of the drug
2007a	Patel *et al.*	Developing an optimum drug delivery system containing Carbamazepine	Simplex lattice designs	Alkalizing agent: Sodium Bicarbonate Binder: Ethylcellulose, HPMC K4 M	The amounts of HPMC K4 M, Sodium Bicarbonate, and Ethylcellulose	The floating lag time, the time required for 50% and 80% drug dissolution
2007b	Patel *et al.*	Developing and optimizing a controlled-release multiunit floating system with	Full factorial designs	Binder: Ethylcellulose	The amounts of Gelucire 43/01 and Ethylcellulose	The percentage drug released in 1, 5, and 10 hours

		desirable release performance				
2009	Varshosaz *et al.*	Optimizing a sustained-release formulation	Taguchi designs	Disintegrant: Chitosan	Chitosan weight, concentration of Chitosan and Sodium TPP, pH of TPP, cross-linking time after addition of Chitosan	The rate of drug release, mean release time, release efficiency, particle size of the beads

factors and response by means of iterative training of data obtained from a designed experiment (Takayama *et al.*, 2000). Figure 2.4 shows a typical structure of hierarchical ANN which is composed of three input units (I_1, I_2, I_3), three hidden units (H_1, H_2, H_3), and two output units (O_1, O_2). The units in neighboring layers are fully interconnected with links corresponding to synapses. Processing takes place in each hidden layer and output layer, and the processing unit sums its input from the previous layer and then utilities the sigmoidal function to compute its output to the following layer according to the equations (Takayama *et al.*, 1999):

$$y_q = \sum w_{pq} x_p \text{ and } f\left(y_q\right) = \frac{1}{1+e^{-\alpha_s y_q}},$$

where w_{pq} is the weight of the connection from unit p to unit q, and x_p is the output value from the previous layer. Once y_q is computed, $f(y_q)$ is conducted to the following layer as an output value varying continuously between 0 and 1. Finally, α_s is a parameter related to the shape of the sigmoidal function.

Based on Armstrong (2006), iterative training should be applied to the network in order to identify a set of weight values that minimizes the differences between the outputs of the network and the measured response values. The weight of each transmission is initially set as a low randomly chosen value, and then it is changed after comparing the computed output values with the measured ones. This process will be repeated until the differences fall in the predetermined interval.

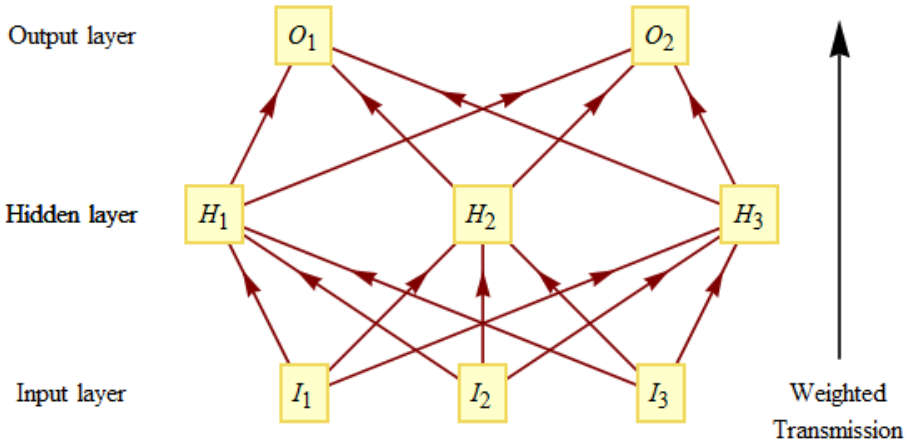

Figure 2.4 A Typical Structure of ANN

ANN has successful been applied to solving various problems in pharmaceutical research such as drug product development (Hussain *et al.*, 1991; Takahara *et al.*, 1997a; Takahara *et al.*, 1997b), estimating diffusion coefficients (Jha *et al.*, 1995), characterizing crushing and disintegration effects (Rocksloh *et al.*, 1999), forecasting the mechanism of drug action (Weinstein *et al.*, 1992), and predicting certain pharmacokinetic parameters (Hussain *et al.*, 1993; Smith & Brier, 1996). Fan *et al.* (2004) conducted a formulation optimization procedure incorporating the RSM and compared the solutions resulting from the ANN and second-order regression techniques. In their study, ANN was found to be more suitable for formulating paclitaxel emulsions. Moreover, it was concluded that the second-order polynomial equation could be less effective in expressing a nonlinear relationship between the factors and response than ANN (Takahara *et al.*, 1997a; Takayama *et al.*, 1999; Takayama *et al.*, 2000). However, it is of importance to mention that the RSM incorporating regression approaches may show superiority in the estimation

of responses compared to the ANN approach, considering the robustness of the prediction model against outliers (Bourquin *et al.*, 1998).

2.4.2 Common Optimization Methodologies

The pharmaceutical formulation optimization can be considered a mathematical process of minimization (or maximization) of an objective function while satisfying various constraints. Generally, the ingredient amounts of a formulation compose the input factor vector, which is denoted by **x**, and the constraints are associated with the regulatory requirements on certain drug performance, for instance, dissolution, friability, and stability. In the review of recent literature, the objective function is generally set up using three methodologies including modified computer optimization techniques, Taguchi quality loss concept, and DF approaches.

- Modified computer optimization methodology

The modified computer-based optimization approach can be divided into single-objective and multiple-objective. Based on Takayama and Nagai (1989), the single-objective optimization for pharmaceutical formulations can be viewed in terms of minimization (or maximization) of the objective function, $F(\mathbf{x})$, under the following inequality and equality constraints:

$$\begin{cases} G_i(\mathbf{x}) \geq 0, & i = 1, 2, 3, \ldots \\ H_j(\mathbf{x}) = 0, & j = 1, 2, 3, \ldots \end{cases}.$$

As it is difficult to solve the constrained optimization problem described above without any mathematical modifications, the constrained optimization problem can be transformed to one that is unconstrained by adding a penalty function as follows:

$$T(\mathbf{x}, r) = F(\mathbf{x}) + r^{-1}\sum \Phi_i \left\{G_i(\mathbf{x})\right\}^2 + r^{-1}\sum \left\{H_i(\mathbf{x})\right\}^2,$$

$$\text{when } G_i(\mathbf{x}) < 0,\ \Phi_i = 1;\ \text{when } Gi(\mathbf{x}) \geq 0,\ \Phi_i = 0,$$

where $T(\mathbf{x},r)$ is the transformed unconstrained objective function, r is a perturbation parameter ($r > 0$), and Φ_i is a step function by which the objective function is penalized.

On the other hand, when the optimization problem includes several objectives, related multiple responses should be incorporated into a single function. Based on Takayma *et al.* (1999), the generilized distance between the predicted value of each repsonse and the optimum one that was individually calcualted using Khuri and Conlon methods (1981) is given by

$$S(\mathbf{x}) = \left\{\sum_k \left[\frac{FD_k(\mathbf{x}) - FO_k(\mathbf{x})}{SD_k}\right]^2\right\}^{1/2},$$

where $S(\mathbf{x})$ is the distance function generalized by the standard deviation (SD), SD_k, of the observed values for each response, $FD_k(\mathbf{x})$ is the optimum value of each response, and $FO_k(\mathbf{x})$ is the estimated value of each response. Similarly, the transformed function, $T(\mathbf{x},r)$, is expressed as

$$T(\mathbf{x}, r) = \left\{\sum \left[\frac{FD_k(\mathbf{x}) - FO_k(\mathbf{x})}{SD_k}\right]^2\right\}^{1/2} + r^{-1}\sum \Phi_i \left\{G_i(\mathbf{x})\right\}^2 + r^{-1}\sum \left\{H_i(\mathbf{x})\right\}^2,$$

$$\text{when } G_i(\mathbf{x}) < 0,\ \Phi_i = 1;\ \text{when } G_i(\mathbf{x}) \geq 0,\ \Phi_i = 0.$$

The optimum solution is estimated as the point, $\mathbf{x}^*(r)$, which results in a minimum value of $T(\mathbf{x},r)$. Based on the modified computer methodology, Takayama and Nagai (1989) and Takayama *et al.* (1999) conducted formulation optimization procedures using the regression and ANN approaches, respectively.

- Taguchi quadratic loss function

Taguchi quality philosophy emphasizes the need for concurrently investigating the mean and variability of QCs of interest, and three categories of characteristics were set up, namely, nominal-the-best (NTB), smaller-the-better (STB), and larger-the-better (LTB). Any deviation from target values of the mean and variance will result in costs and consequently quality loss. Hence, a number of quality loss functions have been developed to relate a key characteristic of a product to its performance in terms of quality. Kailash and Cho (1994) proposed the Laurent series expansion of the quality loss function for LTB characteristics. Cho and Leonard (1997) presented a class of quasi-convex quality loss functions for use in target problem research. Shaibu and Cho (2006) provided exponential-type quality loss functions for proper applications to real-world issues.

In particular, the quadratic quality loss function for a QC proposed by Taguchi (1985) took the form $L(y) = k(y - \tau)^2$, where $L(y)$ is a measure of the loss in quality related to the QC, y and τ are respectively the observed and target values, and k is a positive loss coefficient based on the magnitude of estimated losses. Moreover, it is well known that the expected value of the univariate squared-error loss function for NTB characteristics can be expressed as

$$E(L) = (\mu - \tau)^2 + \sigma^2, \tag{2.8}$$

where $E(L)$, μ and σ^2 denote the expected quality loss, the actual mean of the QC and the variance of the QC, respectively. Therefore, in order to minimize the expected loss, the mean squared error and variance need to be reduced. In the literature, however, no formal research work integrating Taguchi loss function with scientific formulation optimization techniques has been found.

- DF approaches

As discussed earlier, it is common that drug designers are faced with an MRS formulation optimization problem. In the literature, researchers proposed various scientific techniques for solving MRS problems in the past thirty years. The usage of Taguchi's method (1986) for designing robust products or processes prevailed among earlier research work. Pignatiello (1993), Elsayed and Chen (1993), Vining (1998), and Ko *et al*. (2005) employed the expected Taguchi quality loss function approach to determine the optimal settings of input factors for products with multiple QCs. Some extensions to Taguchi's method were also made by researchers such as Chen (1997), Wu (2002), Fung and Kang (2005), and Kovach and Cho (2008). In practice, in addition to the approaches to MRS optimization problems mentioned above, some formulation scientists have demonstrated the effectiveness of the DF method in MRS formulation optimization problems (Abu-Izza *et al.*, 1996; Paterakis *et al.*, 2002; Rosas *et al.*, 2011).

The DF technique is useful to convert multiple characteristics with different units of measurement into a single commensurable objective by means of normalizing each

estimated response variable to individual desirability, whose value varies between 0 and 1, and the response becomes desirable as its desirability approaches 1. If $\hat{y}_i$ (i = 1, 2, …, m) is the i^{th} estimated response variable, the individual desirability for an LTB or STB characteristic is computed by

$$d(\hat{y}_i)=\begin{cases} 0 & \hat{y}_i < L_i \\ \left[\dfrac{\hat{y}_i - L_i}{T_i - L_i}\right]^{\rho_i} & L_i \le \hat{y}_i \le T_i \\ 1 & \hat{y}_i > T_i \end{cases} \quad \text{or} \quad d(\hat{y}_i)=\begin{cases} 1 & \hat{y}_i < T_i \\ \left[\dfrac{U_i - \hat{y}_i}{U_i - T_i}\right]^{\rho_i} & T_i \le \hat{y}_i \le U_i \\ 0 & \hat{y}_i > U_i \end{cases}, \quad (2.9)$$

where L_i and U_i respectively represent acceptable minimum and maximum values, T_i is an allowable maximum or minimum value for the LTB or STB characteristic, and ρ_i is the shape parameter for the DF, which is determined based on how important to hit the value T_i. Similarly, if $\hat{y}_i$ is an NTB characteristic, its individual desirability is given by

$$d(\hat{y}_i)=\begin{cases} 0 & \hat{y}_i < L_i \\ \left[\dfrac{\hat{y}_i - L_i}{T_i - L_i}\right]^{\rho_{i1}} & L_i \le \hat{y}_i \le T_i \\ \left[\dfrac{U_i - \hat{y}_i}{U_i - T_i}\right]^{\rho_{i2}} & T_i \le \hat{y}_i \le U_i \\ 0 & \hat{y}_i > U_i \end{cases}, \quad (2.10)$$

where T_i is the target value, and the shape parameters are denoted by ρ_{i1} and ρ_{i2}. Derringer (1994) also suggested using a weighted geometric mean function to convert the multiple individual desirability into a single measure of characteristic performance known as the overall desirability, D. Let W_i (i = 1, 2, …, m) be the pre-defined weight for the $\hat{y}_i$, D can be expressed as

$$D=\left\{\prod_{i=1}^{m}\left[d(\hat{y}_i)\right]^{W_i}\right\}^{1/\sum_{i=1}^{m} W_i}. \quad (2.11)$$

Hence, when applying the DF approach to optimizing a formulation, the overall DF value is always maximized so that the optimal settings of the ingredient amounts can ensure the best compromise among multiple characteristics of interest (Wang *et al.*, 1996; Ficarra *et al.*, 2002; Candioti *et al.*, 2006; Holm *et al.*, 2006; Zidan *et al.*, 2007; Li *et al.*, 2011). In this traditional way, the estimated individual and overall DF can be obtained by fitting polynomial regression functions of **x** to the calculated desirability for the responses and therefore one may estimate the desirability for the formulation determined by the responses which in turn are at the same time determined by the factors.

Furthermore, several innovative attempts have been made to improve the traditional DF approach. Del Castillo et al. (1996) proposed a differentiable DF method which allowed researchers to use more efficient gradient-based optimization methods for maximizing the overall desirability. Wu and Hamada (2000) suggested using the double-exponential function as an alternative DF, and Wu (2004) extended the double exponential DF based on the Taguchi's loss function in order to optimize correlated multiple QCs. Moreover, Bashiri and Salmasnia (2009) and Goethals and Cho (2011) also presented new optimization procedures based on the DF method for correlated characteristics. However, the conventional DF method does not consider the variability of QCs, which is not adequately addressed in the literature and may affect its effectiveness of optimizing a formulation with multiple QCs. Several researchers also revealed additional shortcomings of the DF approach. Takayama *et al*. (1999) argued that one of the weaknesses of the DF was the subjectivity in the selection of acceptable interval for

each response. Kim and Lin (2000) pointed out that the DF value did not provide a clear interpretation except the basic principle that a higher value of desirability is preferred.

2.5 Summary

In Chapter 2, assessment of biopharmaceutical tests, including *in vitro* dissolution tests, *in vivo* bioavailability studies, and IVIVC, are discussed as a basis for understanding the development of pharmaceutical formulations. The levels of scale-up changes and required documentation tests for IR oral formulations are succinctly summarized. Various DOE techniques and common optimization methodologies applied to the formulation optimization are provided in detail. These investigations establish essential foundation for assessing dissolution and bioavailability of IR oral drugs and for developing a rigorous formulation optimization model when scale-up changes occur. The following chapters will cover the proposed models to achieve the equivalent performance in dissolution and bioequivalence between the pre-change and post-change formulations while all regulatory requirements are satisfied.

CHAPTER 3

DEVELOPING THE OPTIMAL FORMULATIONS FOR NEW TABLET DRUGS (DISSOLUTION COMPARISONS)

3.1 Introduction

Growth in clinical or market demand for tablet drugs often provides the impetus for increasing the scale of production. Pharmaceutical formulation optimization is conducted initially to find the optimal combination of inactive ingredients, but changes of formulations may occur as consequence of scale-up. In this case, *in vitro* dissolution comparisons may need to be performed so as to demonstrate the equivalent safety and efficacy of pre-change and post-change formulations. Therefore, the extended formulation optimization is necessary to determine the levels of composition aimed at ensuring the equivalent safety and efficacy for the changed formulation, while meeting all related regulatory constraints. This chapter is an attempt to propose formulation optimization models for the test formulation by incorporating all necessary FDA requirements and USP-National Formulary (USP-NF) specifications. In Section 3.2, the proposed optimization model is developed. Based on the FDA and USP-NF guidance, DOE, estimation, and optimization stages are discussed in Sections 3.2.1, 3.2.2, and 3.2.3, respectively. In Section 3.3, the proposed optimization methodology is introduced. Numerical examples and analysis are presented in Section 3.4 in order to investigate the feasibility of the proposed methodology in solving the formulation optimization problem for scale-up changes in composition. Moreover, possible effects of constraints boundaries

on the behavior of the optimal input settings are studied by carrying out a sensitivity analysis in Section 3.4. Finally, conclusions are provided in Section 3.5.

3.2 Development of Proposed Model

An optimization procedure is used to seek the best combination of excipient levels of the test formulation in order to assure the closeness of dissolution characteristics between the test and reference formulations, while meeting various constraints. The following subsections are primarily centered on the development of the proposed optimization model consisting of three phases: experimental phase, estimation phase, and optimization phase. Furthermore, the input factors, output responses of interest, and related specifications have been identified and serve as a prior knowledge base for the proposed methodology. Figure 3.1 illustrates the development sequence of the proposed model.

3.2.1 Experimental Phase

Based on the FDA guidance (1995) associated with IR solid oral dosage forms, scale-up modifications to pharmaceutical formulations include changes in excipients rather than active ingredients. It is indicated by the FDA guidance (1995) that the APIs for the reference and test formulations remain the same. Consequently, for an extended formulation optimization problem, the input factors are the excipient amounts for the test formulation (typically measured in mg). The commonly used excipients for formulating an IR tablet include (1) filler, (2) starch (as a disintegrant), (3) binder, (4) magnesium

stearate (as a lubricant), (5) talc (as a glidant) and (6) film coat. Let x_i (i = 1, 2, …, 6) denote the weight of each excipient in the test formulation. Moreover, the output responses are associated with the constraints in the optimization procedure. In the proposed procedure, they include dissolution, uniformity, disintegration, friability, compressibility, hardness, thickness and stability.

Replicated observations can be taken for these characteristics in the experimental phase in order not only to evaluate the mean and variance of data in the estimation phase, but also to comply with the FDA or USP-NF regulations. A general DOE with r experimental runs for extended formulation optimization problems is illustrated in Table 3.1, where Y^R represents the replicated response, and the sample mean $\bar{Y}_i^R$ and variance $s^2(Y_i^R)$ of Y_i^R can be calculated from the corresponding replicated observations at the i^{th} run for i = 1, 2, …, r.

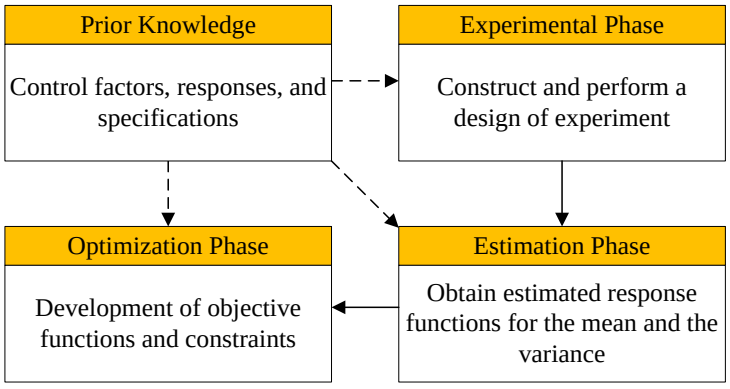

Figure 3.1 Development of Proposed Methodology

3.2.2 Estimation Phase

During the estimation phase, response functions that relate the levels of excipients

(**x**) and responses (Y^R), including the sample averages and variances for the measures of interest, are obtained using linear or nonlinear regression techniques in order to implement the optimization phase. Generally, these experimental responses can be divided into two classes: time-sensitive and non-time-sensitive responses. In this chapter, the former includes dissolution data, which are related to the cumulative amounts dissolved at predetermined points in time, while the latter refers to the other responses. The following part focuses on the development of second-order models for time-sensitive responses.

Table 3.1 General DOE Format

Run	Factors (**x**)	Replicated Responses (Y^R)						Mean of Y^R	Variance of Y^R
1	Input Factor Settings ($\mathbb{X}$)	Y_{11}^R	Y_{12}^R	…	Y_{1v}^R	…	Y_{1m}^R	$\bar{Y}_1^R$	$s^2(Y_1^R)$
2		Y_{21}^R	Y_{22}^R	…	Y_{2v}^R	…	Y_{2m}^R	$\bar{Y}_2^R$	$s^2(Y_2^R)$
⋮		⋮	⋮	⋱	⋮	⋮	⋮	⋮	⋮
u		Y_{u1}^R	Y_{u2}^R	…	Y_{uv}^R	…	Y_{um}^R	$\bar{Y}_u^R$	$s^2(Y_u^R)$
⋮		⋮	⋮	…	⋮	⋱	⋮	⋮	⋮
r		Y_{r1}^R	Y_{r2}^R	…	Y_{rv}^R	…	Y_{rm}^R	$\bar{Y}_r^R$	$s^2(Y_r^R)$

Referring to Table 3.1, let $\mathbf{M} = [\,\mathbf{M}_{t_1}\ \mathbf{M}_{t_2}\ \ldots\ \mathbf{M}_{t_k}\,]$ be the matrix of the means of the dissolution data, in which $\mathbf{M}_{t_1}$, $\mathbf{M}_{t_2}$, …, and $\mathbf{M}_{t_k}$ denote the mean vectors, $(\bar{Y}_1^R, \bar{Y}_2^R, \ldots, \bar{Y}_r^R)_k$, at the k^{th} time point. Also let $\mathbf{V} = [\,\mathbf{V}_{t_1}\ \mathbf{V}_{t_2}\ \ldots\ \mathbf{V}_{t_k}\,]$ represent the matrix of the variances of the dissolution responses, where $\mathbf{V}_{t_1}$, $\mathbf{V}_{t_2}$, …, and $\mathbf{V}_{t_k}$ denote the variance vectors, $[\,s^2(Y_1^R), s^2(Y_2^R), \ldots, s^2(Y_r^R)\,]_k$, at the k^{th} time point. It is reasonable to consider the estimated response matrices $\hat{\mathbf{M}}_t$ and $\hat{\mathbf{V}}_t$ ($t = t_1, t_2, \ldots, t_k$) as functions of

the input factors, **x**. Additionally, the second-order polynomial model for the 6-factor case is known to be

$$Y = \beta_0 + \sum_{i=1}^{6} \beta_i x_i + \sum_{i=1}^{5} \sum_{j=i+1}^{6} \beta_{ij} x_i x_j + \sum_{i=1}^{6} \beta_{ii} x_i^2 + \varepsilon . \qquad (3.1)$$

Hereafter, this equation will be referred to as Model (3.1). Hence, the predicted values at **x** can be obtained by the following equations:

$$\hat{\mathbf{M}}_t(\mathbf{x}) = \omega(\mathbf{x})\beta_{\mathbf{M}} \text{ and } \hat{\mathbf{V}}_t(\mathbf{x}) = \omega(\mathbf{x})\beta_{\mathbf{V}} ,$$

where $\omega(\mathbf{x}) = [1\ x_1 \ldots x_6\ x_1x_2 \ldots x_5x_6\ x_1^2 \ldots x_6^2]$ is the vector corresponding to the Model (3.1), and $\beta_{\mathbf{M}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{M}_t$ and $\beta_{\mathbf{V}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{V}_t$ are the ordinary least squares estimators of the parameters for the mean and variance matrices, respectively. Note that **X** is a matrix of data for the predictor variables; it is derived from the experimental design matrix $\mathbb{X}$. The design matrix $\mathbb{X}$ is the $r \times 6$ matrix whose rows and columns correspond to the r experimental runs and 6 factors, respectively. Finally, the functions describing the correlations of the means and variances with **x** over time t can be developed as follows:

$$\hat{\mathbf{M}}(t,\mathbf{x}) = \left[1\ x_1 \ldots x_6\ x_1x_2 \ldots x_5x_6\ x_1^2 \ldots x_6^2\right] \times \left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^T\mathbf{M}_t \text{ and}$$

$$\hat{\mathbf{V}}(t,\mathbf{x}) = \left[1\ x_1 \ldots x_6\ x_1x_2 \ldots x_5x_6\ x_1^2 \ldots x_6^2\right] \times \left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^T\mathbf{V}_t .$$

3.2.3 Optimization Phase

3.2.3.1 Definitions of Variables

The decision variables in the extended formulation optimization problem are the

input factors mentioned in Section 3.2.1. In addition, the pre-identified weight of each excipient in the reference formulation can be expressed as τ_i (i = 1, 2, …, 6), and a_i (i = 1, 2, ..., p) is defined as the pre-identified weight of each active ingredient, where p is the number of APIs.

3.2.3.2 Development of Objective Function

According to the FDA (1995, 2000), the equivalent safety and efficacy of the test and reference formulations can be evaluated by conducting *in vivo* bioequivalence studies or *in vitro* dissolution comparisons when process scale-up changes occur. It is necessary to establish equivalence with respect to the average and variance of bioequivalence or dissolution characteristics for the test and reference formulations. In this chapter, the objective functions are set up based on Equation (2.8).

Assume that multiple dissolution data are observed at the same point in time for each formulation, and let $A_T(t_i)$ and $A_R(t_i)$ denote the average cumulative amounts dissolved at time t_i for the test and reference formulations, respectively, where i = 1, 2, …, n. As stated in Chapter 2, dissolution-time curves can be considered similar when f_2 values are on the interval (50,100) according to the FDA guideline. Therefore, as proposed below, the objective function associated with dissolution comparisons minimizes the summation of squared deviations of f_2 from the target value τ for each API:

$$\text{Minimize } \sum_{i=1}^{p}\left\{50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{j=1}^{n}\left[A_{Ti}\left(t_j,\mathbf{x}\right)-A_{Ri}\left(t_j,\mathbf{x}\right)\right]^2\right]^{-1/2}\times 100\right\}-\tau\right\}^2,$$

where $A_{Ti}(t,\mathbf{x})$ and $A_{Ri}(t,\mathbf{x})$ are the average dissolution functions over time t for the i^{th} API in the test and reference formulations, respectively. Note that τ is typically set as 100, since two dissolution profiles become similar as τ approaches 100.

However, the main shortcoming of the f_2 method is that it is applicable to the dissolution data with low SDs only. In practice, because individual subjects may differ widely in their response to the drug release, it is essential to ensure the low variability of dissolution data. If the variability of the test formulation is relatively large, then the safety of the test formulation may be questionable. Incorporating $E(L)$, an alternative objective function can be formulated to minimize the sum of the squared difference between $A_T(t,\mathbf{x})$ and $A_R(t,\mathbf{x})$ and the variance of $A_T(t,\mathbf{x})$ at each point in time. When the formulation contains p APIs, our objective function becomes:

$$\text{Minimize } \sum_{i=1}^{p}\sum_{j=1}^{n}\left\{\left[A_{Ti}\left(t_j,\mathbf{x}\right)-A_{Ri}\left(t_j,\mathbf{x}\right)\right]^2+s^2\left[A_{Ti}\left(t_j,\mathbf{x}\right)\right]\right\}.$$

3.2.3.3 Development of Constraints

In this chapter, the constraints for the extended formulation optimization procedure can be divided into two classes: specific and common. The former is related to categories of scale-up changes, dissolution comparisons, bioequivalence studies and BCS, since a different objective function is selected, depending on the types of changes and the category of BCS. The latter refers to process knowledge and release characteristics. The constraints, associated with excipient changes, dissolution testing, uniformity, disintegration, friability, hardness, thickness, stability and design space, are

included. Recall that the BCS classifies APIs into four types: high solubility and high permeability (Class 1), low solubility and high permeability (Class 2), high solubility and low permeability (Class 3), and low solubility and low permeability (Class 4) (FDA, 2000).

- Constraints associated with excipient changes

The FDA guidance (1995) defined different types of scale-up changes and different levels within each type. When a Level 1 change of any type occurs, neither *in vitro* dissolution comparisons nor *in vivo* bioequivalence studies are required. When a Level 2 change in excipients occurs, investigators should provide the documentation tests related to dissolution comparisons based on the BCS. Thus, it is of importance to develop the constraints related to excipient changes at Level 2. According to the limits on the percentage change in excipient amounts for Level 2 (FDA, 1995), the constraints for the test formulation are formulated in Table 3.2, where W_R represents the pre-identified weight of the total reference dosage form, and (θ_1, θ_2, θ_3, θ_4, θ_5, θ_6) = (10%, 6%, 1%, 0.5%, 2%, 2%).

Table 3.2 Proposed Constraints on Excipient Changes at Level 2

1.	$\left\|\frac{x_i - \tau_i}{W_R}\right\| \le \theta_i, \quad i = 1,2,...,6$
2.	$\sum_{i=1}^{6}\left\|\frac{x_i - \tau_i}{W_R}\right\| \le 10\%$

- Constraints associated with *in vitro* dissolution tests and comparisons

The dissolution test is designed to determine compliance with the specific

dissolution requirements for a tablet or capsule dosage form (USP-NF, 2009b). The dissolution specification contains the three stages shown in Table 3.3, where the quantity, Q, is the amount of dissolved active ingredient, expressed as a percentage of the labeled content; the 5%, 15%, and 25% values also represent such percentages.

Table 3.3 Acceptance Table for Dissolution

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit $\geq Q + 5\%$
S_2	6	Average of 12 units $(S_1 + S_2) \geq Q$, and no unit $< Q - 15\%$
S_3	12	Average of 24 units $(S_1 + S_2 + S_3) \geq Q$, not more than 2 units $< Q - 15\%$, and no unit $< Q - 25\%$

When setting dissolution specifications for a new drug, the FDA (1997b) recommended establishing a single-point specification for Class 1 and 3 APIs and a two-point specification for Class 2 based on the BCS. Moreover, it is appropriate to set an upper limit on the RSD of dissolution data to substitute for the three-stage acceptance procedure in order to ensure the small variability of dissolution data, because the RSD is used extensively as a universal yardstick of variability (Torbeck, 2010). Therefore, the single- and two-point specifications for the i^{th} API ($i = 1, 2, \ldots, p$) are modeled in Table 3.4, where a_{Ui} and a_{Li} are defined as the upper and lower bounds of a dissolution range for the i^{th} API, respectively, $s[\bullet]$ denotes the sample SD of the characteristic of interest, λ_1 is the upper bound of the RSD of dissolution data, and Q is generally set as 80%.

When applying the f_2 to comparing dissolution profiles, the FDA (2000) specified several requirements on the use of mean values. Accordingly, the constraint on the usage of f_2 for each API can be expressed in Table 3.5 ($i = 1, 2, \ldots, p$), where $\alpha = 1, 2, \ldots, l$ and $\beta = l + 1, l + 2, \ldots, n$. Note that t_α and t_β represent the predefined earlier and later time

points, respectively, l is the demarcation point that distinguishes what is considered early and late, and t_l is usually set as 10 minutes.

Table 3.4 Proposed Constraints for Single- and Two-Point Specifications

Single-point	Two-point	RSD
$\frac{A_{Ti}(t_a,\mathbf{x})}{a_i} \geq Q+5\%$ $(t_a = 60\,\text{min})$	$a_{Li} \leq \frac{A_{Ti}(t_b,\mathbf{x})}{a_i} \leq a_{Ui}$ $\frac{A_{Ti}(t_c,\mathbf{x})}{a_i} \geq Q+5\%$ $(t_b = 15\,\text{min},\ t_c = 30, 45, \text{or } 60\,\text{min})$	$\frac{s\left[A_{Ti}(t_j,\mathbf{x})\right]}{A_{Ti}(t_j,\mathbf{x})} \leq \lambda_1$ $(i = 1,2,...,p;\ j = a,b,c)$

Table 3.5 Proposed Constraints for the f_2 Method

1.	$\frac{s\left[A_{Ti}(t_\alpha,\mathbf{x})\right]}{A_{Ti}(t_\alpha,\mathbf{x})} \leq 20\%$
2.	$\frac{s\left[A_{Ti}(t_\beta,\mathbf{x})\right]}{A_{Ti}(t_\beta,\mathbf{x})} \leq 10\%$
3.	$\frac{A_{Ti}(t_b,\mathbf{x})}{a_i} < 85\%$
4.	$50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{j=1}^{n}\left[A_{Ti}(t_j,\mathbf{x}) - A_{Ri}(t_j,\mathbf{x})\right]^2\right]^{-\frac{1}{2}} \times 100\right\} \geq 50$

- Constraints associated with uniformity acceptance criteria

Generally, two methods, content uniformity and weight variation (WV), can be applied to testing uniformity. Since the input factors are associated with the weights of inactive ingredients, the following part focuses on the WV tests.

The USP-NF (2009c) presents the approach to calculate acceptance value (AV) for WV by the following equation:

$$\text{AV} = \begin{cases} \begin{cases} ks & \text{if } 98.5\% \le \bar{X} \le 101.5\% \\ 98.5\% - \bar{\chi} + ks & \text{if } \bar{X} < 98.5\% \\ \bar{\chi} - 101.5\% + ks & \text{if } \bar{X} > 101.5\% \end{cases} & \text{when } T_c \le 101.5\% \\ \begin{cases} ks & \text{if } 98.5\% \le \bar{X} \le T_c \\ 98.5\% - \bar{\chi} + ks & \text{if } \bar{X} < 98.5\% \\ \bar{\chi} - T + ks & \text{if } \bar{X} > T_c \end{cases} & \text{when } T_c > 101.5\% \end{cases}, \quad (3.2)$$

where k is the acceptability constant, and T_c is the target content per dosage expressed as a percentage, which is usually set as 100%. Let χ_i (i = 1, 2, …, q) denote the individual APIs of the units tested expressed as a percentage of the label claim, where q is the sample size. $\bar{\chi}$ and s are the sample mean and SD of χ_i, respectively. Note that k is set as 2.4 (2.0) when the sample size equals 10 (30) based on the USP-NF guidance. The uniformity requirements are met if the AV of the first 10 (q = 10) dosage units is no more than G%, which is the upper limit of the AV. If the AV is greater than G%, an additional 20 units should be tested. The RSD should be no more than 2% based on the USP-NF guideline (2009c). Moreover, the requirements usually apply individually to each active ingredient. In our proposed optimization model, χ_{ij} for the i^{th} active ingredient is estimated by:

$$\chi_{ij}(\mathbf{x}) = a_{ij}\left(\sum_{j=1}^{6} x_j + a_i\right) \Big/ a_i\left(\sum_{j=1}^{6} x_j + \frac{1}{q}\sum_{j=1}^{q} a_{ij}\right), \; i = 1, 2, ..., \; p,$$

where a_{ij} is the weight of the i^{th} API for the j^{th} replication. Based on the USP-NF requirement, the constraints for the i^{th} active ingredient are proposed in Table 3.6. $\bar{\chi}_i(\mathbf{x})$ and $s_i(\mathbf{x})$ represent the response functions for the mean and SD of (χ_{i1}, χ_{i2}, …, χ_{iq}) for the i^{th} API, and W_T is the weight of the total test dosage form comprising the active and

inactive ingredients. They can be calculated by the respective equations for the i^{th} active ingredient presented in Table 3.7.

Table 3.6 Proposed Constraints on WV Tests

1. Weight of API ≥ 25mg	$a_i \geq 25$ (mg)
2. Ratio of API ≥ 25%	$\frac{a_i}{W_T(\mathbf{x})} \geq 25\%$
3. RSD ≤ 2%	$\frac{s_i(\mathbf{x})}{\bar{\chi}_i(\mathbf{x})} \leq 2\%$
4. $AV \leq G\%$ (Referring to Equation (3.2))	$\begin{cases} AV_i(\mathbf{x}) \leq G\% \quad (q=10, k=2.4) \\ AV_i(\mathbf{x}) \leq G\% \quad (q=30, k=2) \quad \text{if} \quad AV_i(\mathbf{x}) > G\% \quad (q=10, k=2.4) \end{cases}$

Table 3.7 Proposed Estimating Equations for WV Tests

1.	$\bar{\chi}_i(\mathbf{x}) = \frac{1}{q}\sum_{j=1}^{q}\chi_{ij} = \sum_{j=1}^{q} a_{ij}\left(\sum_{j=1}^{6} x_j + a_i\right) \Big/ qa_i\left(\sum_{j=1}^{6} x_j + \frac{1}{q}\sum_{j=1}^{q} a_{ij}\right)$	(3.3)
2.	$s_i(\mathbf{x}) = \left[\frac{1}{q-1}\sum_{j=1}^{q}\left(\chi_{ij} - \bar{\chi}_i\right)^2\right]^{\frac{1}{2}}$	(3.4)
3.	$W_T(\mathbf{x}) = \sum_{i=1}^{6} x_i + \sum_{i=1}^{p} a_i$	

- Constraints associated with disintegration acceptance criteria

The disintegration time is the time taken for all six tablets to disintegrate completely. If one or two tablets out of the six fail to disintegrate sufficiently, 12 additional tablets are tested (USP-NF, 2009a). The proposed constraints for disintegration time are described as:

$$d_L \leq D(\mathbf{x}) \leq d_U \text{ and } \text{RSD} = \frac{s\left[D(\mathbf{x})\right]}{D(\mathbf{x})} \leq \lambda_2,$$

where $D(\mathbf{x})$ is the response function that relates the average disintegration time to the set of factors, $\mathbf{x}$. d_U and d_L are the upper and lower disintegration time limits, respectively. Finally, $s[D(\mathbf{x})]$ and λ_2 denote the standard deviation of $D(\mathbf{x})$ and the upper bound of the RSD, respectively.

- Constraints associated with friability acceptance criteria

Tablet friability is measured by evaluating the loss of mass for a tablet. According to USP-NF (2009e), the loss of mass for a single tablet should be no more than 1%. If the weight loss is greater than 1%, the test should be repeated twice and the mean loss of mass for the three tablets should be no more than 1%. Therefore, the constraints on friability, under two scenarios (1.1 and 1.2), are proposed in Table 3.8, in which $F(\mathbf{x})$ is the response function that relates the average mass loss to the set of factors, $\mathbf{x}$, and the subscript i (i = 1, 2, 3) represents the individual measure for the i^{th} sample.

Table 3.8 Proposed Constraints on Friability

Scenario 1.1	$\frac{F_1(\mathbf{x})}{W_T(\mathbf{x})} \le 1\%$
Scenario 1.2	$\frac{\sum_{i=1}^{3} F_i(\mathbf{x})}{3W_T(\mathbf{x})} \le 1\%$ if $\frac{F_1(\mathbf{x})}{W_T(\mathbf{x})} > 1\%$

- Constraints associated with compressibility acceptance criteria

The compressibility index (CI) is determined by $CI = 100\times(V_0 - V_f)/V_0$, where V_0 is the unsettled apparent volume and V_f is the final tapped volume (USP-NF, 2009d). Based on the USP-NF guideline (2009d), a CI value less than 25 is considered to be

acceptable; further, a value less than 10 is regarded as excellent. Therefore, the related constraint is developed as follows:

$$\mathrm{CI}(\mathbf{x}) = 100 \times \left[1 - \frac{V_f(\mathbf{x})}{V_0(\mathbf{x})} \right] \leq H ,$$

where $V_0(\mathbf{x})$ and $V_f(\mathbf{x})$ are the response functions that relate the average volumes to the set of factors, **x**, and H denotes the upper limit of CI.

- Constraints associated with hardness, thickness, and stability acceptance criteria

Hwang *et al.* (2011) indicated that the hardness, thickness, and stability of a tablet were essential responses when conducting formulation optimization. Tablet hardness and thickness are usually measured in kilopascals (kp) and millimeters (mm), respectively. Stability usually refers to the degradation time of a tablet under certain environmental conditions. Let $N_i(\mathbf{x})$ (i = 1, 2, 3) represent the related DOE response functions and η_{Li} and η_{Ui} (i = 1, 2, 3) define the corresponding lower and upper limits for hardness, thickness, and degradation time. Therefore, the constraints can be described as:

$$\eta_{Li} \leq N_i(\mathbf{x}) \leq \eta_{Ui}, \quad i = 1, 2, 3 .$$

- Constraints associated with design space

Based on the type of DOE methods applied in the optimization procedure, the input factors should remain within the corresponding design space. The design space is the region explored by DOE that determines the levels of a formulation that are both optimal and feasible. For a factorial design or a Taguchi design, the design space for each

factor should be within the interval between the minimum and maximum coded values. That is, $-1 \leq x_i \leq 1$ for $i = 1, 2, \ldots, 6$. For a CCD, $\mathbf{x}^T\mathbf{x} \leq \rho^2$ where ρ is the distance in any direction from the center point and is analogous to the radius of a sphere. A CCD will be employed here since it is one of the most effective DOE methods for capturing the quadratic effects of input factors.

3.3 Proposed Optimization Model

In this section, the formulation optimization procedure is developed on the premises that (1) the factors, responses, and specifications of interest have been identified prior to the optimization study; (2) 12 individual units of the test and reference formulations, based on FDA requirements, are used in dissolution tests.

The acceptance criteria of Level 2 excipient changes for different biopharmaceutics classes are presented in Table 3.9 (FDA, 1995). The proposed formulation optimization involves Level 2 excipient changes for three classes of drugs. Taking into consideration all the related acceptance criteria and constraints, the proposed optimization procedure is described in Table 3.10. It should be mentioned that the objective functions for Class 1 drugs exclude the term associated with the deviation from the target value because no target values for the mean can be identified based on Table 3.9. In other words, the objective function for Class 1 drugs is established to minimize the summation of either the variance or SD of dissolution data for each API. Ensuring either the minimum variance or SD depends on which of the two is chosen as the response.

Note that the second-order response functions, which estimate the correlations of the variance and SD with the input factors, are different.

3.4 Examples for Level 2 Excipient Changes

Few formal numerical examples for the extended formulation optimization problem can be found in the literature; therefore, simulated data are used in this section. The data are obtained randomly using Microsoft® Excel. The statistical software used to evaluate the experimental design results is Minitab® 16. The optimization procedure is conducted using Wolfram Mathematica® 8. The formulation optimization procedure is performed to seek the optimal weights (mg) of five input factors including the amounts of filler (x_1), disintegrant (x_2), binder (x_3), lubricant (x_4) and glidant (x_5). A five-factor CCD with a total of 32 ($r = 32$) experimental runs is used to evaluate the effects of these factors on the responses and to optimize the formulation. The uncoded values of five levels (−2, −1, 0, +1, +2) for each factor are provided in Table 3.11. In addition, the pre-identified weight of each excipient in the reference formulation is (τ_1, τ_2, τ_3, τ_4, τ_5) = (190, 10.5, 20, 15, 2.5), measured in mgs. The number of APIs is $p = 1$, and the pre-identified weight of the API is a_1 = 80mg. Thus, the total weight of the reference formulation turns out to be W_R = 318mg. As for the parameters related to the USP-NF acceptance criteria, let Q = 80%, $\lambda_1 = \lambda_2$ = 10%, G = 15,T_c = 100%, d_L = 10min, d_U = 11.8min, η_{L1} = 9.5kp, η_{U1} = 10.5kp, a_U = 50%, a_L = 65% and H = 25.

Table 3.9 Acceptance Criteria of Level 2 Excipient Changes Based on the BCS

Classification	Acceptance Criteria		
	Class 1	Class 2	Class 3
Level 2 Excipient Changes	Single point dissolution of 85% within 15 minutes.	Multi-point dissolution profile should be similar to the reference one.	Multi-point dissolution profile should be similar to the reference one.

Table 3.10 Proposed Optimization Scheme for the Formulation Optimization Problem

Minimize

1. For Class 1 drugs

(1) $\sum_{i=1}^{p} s^2\left[A_{Ti}\left(t_b, \mathbf{x}\right)\right]$

(2) $\sum_{i=1}^{p} s\left[A_{Ti}\left(t_b, \mathbf{x}\right)\right]$

2. For Class 2 and 3 drugs

(1) $\sum_{i=1}^{p}\left\{50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{j=1}^{n}\left[A_{Ti}\left(t_j, \mathbf{x}\right)-A_{Ri}\left(t_j, \mathbf{x}\right)\right]^2\right]^{-\frac{1}{2}}\times 100\right\}-\tau\right\}^2$

(2) $\sum_{i=1}^{p}\sum_{j=1}^{n}\left\{\left[A_{Ti}\left(t_j, \mathbf{x}\right)-A_{Ri}\left(t_j, \mathbf{x}\right)\right]^2+s^2\left[A_{Ti}\left(t_j, \mathbf{x}\right)\right]\right\}$

Subject to

Specific constraints:

1. For Class 1 drugs ($i=1,2,...,p$)

$$\frac{A_{Ti}\left(t_b, \mathbf{x}\right)}{a_i} \geq 85\%$$

2. For Class 2 and 3 drugs ($i=1,2,...,p$)

$$(1)\frac{s\left[A_{Ti}\left(t_\alpha, \mathbf{x}\right)\right]}{A_{Ti}\left(t_\alpha, X\right)} \leq 20\%$$

$$(2)\frac{s\left[A_{Ti}\left(t_\beta, \mathbf{x}\right)\right]}{A_{Ti}\left(t_\beta, X\right)} \leq 10\%$$

$$(3)\frac{A_{Ti}\left(t_b, \mathbf{x}\right)}{a_i} < 85\%$$

$$(4)\,50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{j=1}^{n}\left[A_{Ti}\left(t_j, \mathbf{x}\right)-A_{Ri}\left(t_j, \mathbf{x}\right)\right]^2\right]^{-\frac{1}{2}}\times 100\right\} \geq 50$$

3. For Class 1,2, and 3 drugs

$$(1)\left|\frac{x_i-\tau_i}{W_R}\right|\le\theta_i,\quad i=1,2,...,6\quad (2)\sum_{i=1}^{6}\left|\frac{x_i-\tau_i}{W_R}\right|\le 10\%$$

Common constraints:

1. Disintegration time criteria

$$(1)\,d_L\le D(\mathbf{x})\le d_U\quad (2)\frac{s\left[D(\mathbf{x})\right]}{D(\mathbf{x})}\le\lambda_2$$

2. Dissolution criteria ($i=1,2,...,p$)

(1) For Class 1 and 3 drugs

$$\frac{A_{Ti}(t_a,\mathbf{x})}{a_i}\ge Q+5\%$$

(2) For Class 2 drugs

$$1)\,a_{Li}\le\frac{A_{Ti}(t_b,\mathbf{x})}{a_i}\le a_{Ui}\quad 2)\frac{A_{Ti}(t_c,\mathbf{x})}{a_i}\ge Q+5\%$$

(3) For Class 1, 2, and 3 drugs

$$\frac{s\left[A_{Ti}(t_j,\mathbf{x})\right]}{A_{Ti}(t_j,\mathbf{x})}\le\lambda_1\quad (j=a,b,c)$$

3. Uniformity criteria

$$(1)\,a_i\ge 25\ (\text{mg})\quad (2)\frac{a_i}{W_T(\mathbf{x})}\ge 25\%\quad (3)\frac{s_i(\mathbf{x})}{\bar{\chi}_i(\mathbf{x})}\le 2\%$$

$$(4)\begin{cases} AV_i(\mathbf{x})\le G\% \quad (q=10,k=2.4) \\ AV_i(\mathbf{x})\le G\% \quad (q=30,k=2) \end{cases}\ \text{if}\ AV_i(\mathbf{x})>G\%\quad (q=10,k=2.4)$$

4. Friability criteria

$$(1)\frac{F_1(\mathbf{x})}{W_T(\mathbf{x})}\le 1\%\quad (2)\frac{\sum_{i=1}^{3}F_i(\mathbf{x})}{3W_T(\mathbf{x})}\le 1\%\ \text{ if }\ \frac{F_1(\mathbf{x})}{W_T(\mathbf{x})}>1\%$$

5. Compressibility criteria

$$CI(\mathbf{x})\le H$$

6. Hardness, thickness and stability criteria

$$\eta_{Li}\le N_i(\mathbf{x})\le\eta_{Ui},\quad i=1,2,3$$

7. Nonnegativity of regression functions

$$\Delta(\mathbf{x})\ge 0$$

where Δ stands for all derived response regression equations.

8. Design space

(1) For a factorial design or a Taguchi design

$$-1\le x_i\le 1,\quad i=1,2,...,6$$

(2) For a CCD

$$\mathbf{x}^T\mathbf{x}\le\rho^2$$

Find Optimal solutions $\mathbf{x}^*\left(x_1^*,x_2^*,x_3^*,x_4^*,x_5^*,x_6^*\right)$

Table 3.11 The Uncoded Values of Factors

Factors	Levels				
	−2	−1	0	+1	+2
x_1	160	170	180	190	200
x_2	4.8	7.8	10.8	13.8	16.8
x_3	15	20	25	30	35
x_4	1	5	9	13	17
x_5	2	6	10	14	18

3.4.1 Class 1 Drugs with Level 2 Changes

Within each experimental run, 12, 10, and 6 formulations are prepared for single-point dissolution tests, uniformity tests, and disintegration tests, respectively, and 3 formulations for friability, compressibility and hardness tests. The means and variances of the responses of interest are provided in Table 3.12. Moreover, in order to calculate the responses associated with uniformity tests, replicated observations on the amount of the API are presented in Table 3.13. Note that the responses $\bar{\chi}_1$ and s_1 can be obtained using Equations (3.3) and (3.4).

The optimization procedures for minimizing the variance and SD of the dissolution data are performed; the composition and predicted responses for both scenarios (1.3 and 1.4) are listed in Table 3.14. It is concluded that the optimal solution in the second scenario provides a smaller $s(A_T)$ than that in the first one. Therefore, in terms of reducing the variability of dissolution data for the test formulation, the second scenario optimization procedure is preferred.

Table 3.12 Response Sets for Class 1 Drugs

Run	$A_T(t_b)$	$s^2[A_T(t_b)]$	$s[A_T(t_b)]$	D	$s(D)$	CI	N_1	F_1	F_2	$F3$
1	67.06	28.78	5.37	10.5	0.94	34.3	10.3	2.7	1.9	2.0
2	64.09	14.79	3.85	11.2	1.06	15.1	10.7	2.6	1.8	2.7
3	68.13	37.60	6.13	9.8	1.07	20.9	9.9	2.1	2.0	2.0
4	65.88	52.52	7.25	11.9	0.96	23.1	10.9	3.7	1.9	2.2
5	69.68	69.92	8.36	9.4	0.86	28.3	9.0	2.9	2.3	3.2
6	64.62	50.52	7.11	11.5	1.23	28.5	11.6	2.6	2.9	3.4
7	71.95	101.47	10.07	9.9	1.06	34.4	10.1	3.5	2.9	1.6
8	69.94	110.05	10.49	11.8	1.17	20.2	10.5	2.5	2.8	2.9
9	68.69	16.98	4.12	10.8	1.15	14.5	8.2	2.7	1.9	2.9
10	68.16	16.72	4.09	10.0	0.86	27.7	10.2	2.9	3.1	1.9
11	70.82	12.54	3.54	9.2	0.83	14.1	8.1	2.6	2.1	3.0
12	65.98	15.67	3.96	12.0	0.98	24.0	9.7	2.5	3.7	2.9
13	64.34	20.28	4.50	9.0	0.90	17.5	11.1	1.7	1.8	2.3
14	71.90	101.34	10.07	11.0	1.03	25.9	9.7	3.5	1.9	2.5
15	70.91	32.18	5.67	10.5	0.89	10.4	11.7	2.1	2.7	2.2
16	69.87	48.82	6.99	10.6	0.94	32.1	10.9	2.5	2.5	2.2
17	64.74	60.36	7.77	10.8	1.17	27.2	12.0	1.9	1.6	3.0
18	66.06	15.71	3.96	9.1	0.84	18.0	10.8	2.4	2.7	1.8
19	71.23	41.10	6.41	9.1	0.75	14.8	9.2	3.2	1.8	1.7
20	64.49	50.32	7.09	9.3	0.96	33.6	8.2	2.9	2.3	3.2
21	67.29	54.78	7.40	9.3	0.79	30.6	11.3	2.9	3.1	3.3
22	66.90	54.15	7.36	10.9	0.93	27.8	11.9	3.7	2.9	2.6
23	67.12	101.36	10.07	12.4	1.00	34.8	9.4	2.5	2.7	3.4
24	68.80	38.34	6.19	10.9	1.17	30.8	8.7	2.4	1.6	1.9
25	70.27	96.79	9.84	10.3	1.09	23.2	11.8	1.6	3.1	3.2
26	71.38	32.61	5.71	10.7	0.99	14.9	8.8	2.4	3.6	2.9
27	69.38	30.81	5.55	10.4	0.95	18.1	8.7	2.4	3.5	2.2
28	66.59	99.78	9.99	12.0	1.22	16.5	11.3	2.4	2.9	2.9
29	66.70	11.12	3.33	9.4	1.00	24.8	8.5	3.2	2.2	3.5
30	68.08	29.66	5.45	10.2	1.07	13.9	9.6	2.2	2.1	1.7
31	64.22	69.71	8.35	10.2	1.07	24.3	8.5	2.0	2.4	2.8
32	65.98	10.88	3.30	11.4	1.21	25.3	10.6	2.9	2.9	1.6

3.4.2 Class 2 and 3 Drugs with Level 2 Changes

Similar to Section 3.4.1, the amounts of the input factors are considered as decision variables. Assume that the observations associated with disintegration, uniformity, friability, compressibility and hardness tests are still valid in this section. The dissolution means and SDs derived from the 12 replicated formulations at 8 time points are provided in Table 3.15. The output responses are simulated from 5 min to 60 min. Further, 5 min, 8 min, and 10 min are defined as earlier time points, and the two-point specification for dissolution performance is established at 15 min and 45 min. The amount (mg) dissolved for the reference formulation at each time point is set as follows:

$A_R(t_1 = 5\text{min}) = 22$	$A_R(t_2 = 8\text{min}) = 33$	$A_R(t_3 = 10\text{min}) = 38$	$A_R(t_4 = 15\text{min}) = 48$
$A_R(t_5 = 30\text{min}) = 65$	$A_R(t_6 = 45\text{min}) = 74$	$A_R(t_7 = 55\text{min}) = 77$	$A_R(t_8 = 60\text{min}) = 78$

The proposed optimization procedures are performed for the two scenarios (1.5 and 1.6). In the first one, similarity factor f_2 with its related constraints are used. However, the second scenario does not take f_2 into consideration. The optimal amounts of ingredients in both scenarios are achieved and summarized in Table 3.16. Note that within each scenario, there is no significant difference in the optimal settings between Class 2 and 3 drugs. The f_2 value in Scenario 1.5 is greater than that in Scenario 1.6; thus, the optimal formulation in the former scenario is better than that in the latter, with respect to the FDA suggestion on the use of f_2. However, for the test formulation, the mean of the dissolution data at each time point in Scenario 1.6 is generally closer to the reference value, except for $A_T(t_6)$ and $A_T(t_7)$. The dissolution rates at t_6 and t_7 decrease most sharply, which probably leads to these relatively large deviations from the corresponding reference values. Further investigations may be needed to penalize the dissolution data at certain points in time that have most sharp dissolution rates by assigning weights to the corresponding terms in the objective function. Additionally, the variability of dissolution data at each time point in the second scenario is generally smaller, except for $s(t_1)$, $s(t_4)$ and $s(t_8)$. It is important to mention that the differences of $s(t_1)$, $s(t_4)$ and $s(t_8)$ between both scenarios are insignificant with p-values of 0.919, 0.859 and 0.896 greater than α = 0.05 based on the following two-sample F-test for the variance ratio for i = 1, 4, 8.

$$H_0: \hat{s}(t_i, \mathbf{x}^*) \text{ under Scenario 1.5} = \hat{s}(t_i, \mathbf{x}^*) \text{ under Scenario 1.6}$$

versus

$$H_1: \hat{s}(t_i, \mathbf{x}^*) \text{ under Scenario 1.5} \neq \hat{s}(t_i, \mathbf{x}^*) \text{ under Scenario 1.6.}$$

Table 3.13 API Levels and Responses Associated with Uniformity Tests

Run	API Levels										Mean		
	a_{11}	a_{12}	a_{13}	a_{14}	a_{15}	a_{16}	a_{17}	a_{18}	a_{19}	a_{110}	$\bar{a}_{1j}$	$\bar{\chi}_1$	s_1
1	79.63	79.38	79.92	80.37	79.43	80.58	79.66	80.85	78.93	79.91	79.87	0.9989	0.010
2	80.28	79.24	79.95	79.17	79.33	80.83	80.46	80.05	80.02	79.16	79.85	0.9987	0.013
3	80.98	79.67	79.01	80.24	79.46	79.27	80.36	80.63	79.15	80.88	79.96	0.9997	0.012
4	79.61	79.95	79.89	79.12	80.22	80.90	79.57	79.42	79.20	79.12	79.70	0.9973	0.013
5	80.74	79.99	80.51	79.32	80.68	79.77	80.93	80.33	79.60	80.26	80.21	1.0019	0.022
6	80.21	80.98	79.19	79.23	80.77	80.33	80.82	80.37	79.74	79.10	80.07	1.0007	0.014
7	80.72	78.98	80.56	80.92	79.10	79.02	79.01	80.65	79.50	80.01	79.85	0.9987	0.018
8	80.43	79.36	79.91	80.93	79.42	80.14	79.84	80.50	79.08	79.93	79.95	0.9996	0.013
9	79.13	79.50	80.71	79.45	79.53	79.33	79.31	80.72	79.40	80.37	79.74	0.9977	0.020
10	80.54	80.79	78.95	79.88	80.98	80.03	79.51	80.85	79.09	80.37	80.10	1.0009	0.021
11	80.07	80.20	79.27	80.23	79.29	80.65	79.50	79.77	80.28	80.77	80.00	1.0000	0.021
12	80.56	78.92	79.94	80.32	80.90	79.89	80.44	80.54	80.84	79.30	80.16	1.0015	0.012
13	79.72	79.37	80.90	80.74	78.96	80.08	80.75	79.98	79.66	80.75	80.09	1.0008	0.017
14	80.19	79.66	80.24	79.33	79.94	80.79	80.73	79.26	79.40	79.06	79.86	0.9987	0.012
15	80.98	80.91	79.20	78.95	80.71	80.83	80.12	79.76	80.08	79.68	80.12	1.0011	0.011
16	80.50	79.23	80.89	79.51	79.93	80.17	79.08	80.62	79.61	79.28	79.88	0.9989	0.021
17	79.06	80.16	80.41	80.07	80.24	79.66	78.97	80.49	79.23	79.35	79.76	0.9979	0.022
18	80.37	80.93	80.54	80.62	79.34	79.96	80.50	80.86	79.87	80.49	80.35	1.0032	0.019
19	79.93	79.35	79.99	80.08	80.10	79.63	80.64	79.46	79.36	80.22	79.88	0.9989	0.018
20	79.36	80.70	80.28	79.89	80.20	79.19	79.43	79.44	80.90	80.73	80.01	1.0001	0.014
21	79.39	80.64	79.38	80.41	80.58	80.10	80.36	80.05	80.70	79.99	80.16	1.0015	0.012
22	80.36	79.01	80.75	80.77	80.53	79.17	79.36	78.99	80.43	79.69	79.90	0.9991	0.011
23	79.27	79.09	80.66	80.40	80.11	79.71	79.45	79.80	79.52	79.43	79.74	0.9976	0.014
24	79.70	80.15	79.95	79.81	80.00	80.09	80.46	79.25	80.34	79.10	79.88	0.9989	0.017
25	79.55	79.40	79.73	80.19	80.39	79.11	80.94	80.40	78.92	79.79	79.84	0.9985	0.022
26	80.66	80.73	80.26	80.27	79.64	79.51	80.54	79.42	80.68	80.56	80.23	1.0021	0.013
27	79.91	79.52	79.65	80.20	80.53	79.01	79.67	80.77	79.94	80.52	79.97	0.9997	0.022
28	80.35	80.71	79.18	79.02	79.93	80.35	80.25	80.01	80.53	80.62	80.09	1.0009	0.020
29	78.94	79.15	79.39	79.46	80.04	79.38	80.81	78.94	79.85	80.43	79.64	0.9966	0.012
30	79.85	79.65	79.50	80.89	79.90	79.35	80.21	79.38	80.69	79.68	79.91	0.9991	0.012
31	80.54	80.86	79.90	80.18	80.91	80.64	79.17	79.22	79.85	79.94	80.12	1.0011	0.018
32	79.05	78.92	80.33	80.75	80.19	79.64	80.94	80.33	79.13	79.24	79.85	0.9986	0.018

Therefore, the optimization model in Scenario 1.6 generally works better in terms of minimizing both deviations from the target values and variances.

The three-dimensional response surfaces, shown in Figure 3.2, are drawn to estimate the effects of the input factors on the expected quality loss. x_1, x_2, and the values of the objective function in each scenario are included for each diagram. Additionally, the contour plots illustrating the simultaneous effect of x_1 and x_2 on the objective functions are provided in Figure 3.3. Note that in both Figures 3.2 and 3.3, x_3, x_4, and x_5 are set at their optimal levels.

Table 3.14 The Factors and Responses of the Optimal Formulation

Scenario	x_1^*	x_2^*	x_3^*	x_4^*	x_5^*	A_T	$s(A_T)$	D	$s(D)$	CI	N_1	F_1	AV_1
1.3	173.61	13.38	18.48	15.24	7.06	68.30	4.19	11.49	1.11	21.60	9.76	2.16	0.03
1.4	169.10	12.45	20.18	16.51	8.77	68.79	3.97	11.56	1.15	17.30	9.50	1.91	0.04

3.4.3 Sensitivity Analysis

The behavior of the optimal solutions is further examined by varying associated constraint boundaries in order to validate the optimization results. The boundaries which are associated with dissolution performance, including the lower bounds of λ_1 and f_2, are respectively altered for the sensitivity analysis on the models in Sections 3.4.1 and 3.4.2, while additional boundaries remain the same. The results for Class 1 drugs with Level 2 changes are summarized in Table 3.17. As λ_1 increases from 0.2 to 0.4 with an increment of 0.1, the optimal input settings provided by the model in Scenario 1.4 always produce a smaller $s(A_T)$. In other words, the conclusion that the optimization model in Scenario 1.4 is superior in terms of minimizing the variability is consistent with that stated in Section 3.4.1. Similarly, a sensitivity analysis of the constraint boundary to the optimal solution is performed by varying the lower bound of f_2 from 60 to 70 with an increment of 5, which is shown in Table 3.18. Note that no change occurs in the optimal solutions for Scenario 1.5. Based on Table 3.18, it can be observed that (1) the means of the amounts dissolved at t_6 and t_7 in Scenario 1.6 deviate more significantly from the corresponding reference values, and (2) $s(t_1)$, $s(t_4)$ and $s(t_8)$ are smaller in the first scenario, while the differences of them between both scenarios are statistically insignificant. Hence again, the optimal solutions in the second scenario provide overall preferred outputs.

Table 3.15 Multi-Point Dissolution Data

Run	t_1		t_2		t_3		$t_4 = t_b$		t_5		$t_6 = t_c$		t_7		t_8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	22.75	3.62	33.05	5.94	36.34	3.85	48.55	4.41	66.01	6.09	75.41	7.38	76.89	7.66	78.50	7.58
2	22.07	3.93	32.99	5.65	38.04	3.70	46.34	4.48	63.55	6.08	72.72	7.31	76.84	7.62	78.09	7.76
3	22.14	3.71	31.97	5.91	37.21	3.89	48.98	4.39	66.96	6.08	73.49	7.37	76.82	7.80	78.06	7.53
4	20.24	3.97	33.67	5.67	37.48	3.86	47.30	4.57	66.43	6.06	75.04	7.21	77.70	7.61	78.00	7.60
5	20.40	3.77	34.55	5.91	38.97	3.50	48.98	4.31	63.80	6.10	72.80	7.34	77.85	7.78	78.12	7.55
6	20.77	3.97	31.64	5.97	37.26	3.60	46.03	4.44	63.79	6.14	75.06	7.39	76.66	7.60	78.89	7.70
7	20.46	3.60	33.37	5.76	36.51	3.71	48.50	4.48	63.71	6.13	74.78	7.40	77.73	7.64	78.96	7.34
8	21.26	4.01	31.74	5.71	36.89	3.80	46.30	4.44	63.27	6.09	74.52	7.22	77.85	7.62	78.93	7.71
9	21.47	3.98	33.75	5.74	36.21	3.79	48.86	4.44	63.71	6.02	74.89	7.22	77.74	7.71	77.90	7.59
10	22.43	3.90	34.34	5.69	37.79	3.75	48.96	4.47	64.49	6.03	74.50	7.21	77.58	7.70	78.77	7.74
11	20.92	3.79	31.64	5.73	36.26	3.84	46.66	4.44	63.00	6.18	74.96	7.39	77.38	7.65	78.90	7.45
12	20.98	3.76	33.59	5.86	37.71	3.87	48.23	4.40	65.51	6.16	72.70	7.26	76.94	7.61	78.70	7.27
13	22.39	3.83	34.25	5.86	37.22	3.78	46.02	4.59	63.37	6.09	75.44	7.29	76.91	7.72	77.90	7.56
14	22.68	4.04	34.74	5.75	38.65	3.64	46.89	4.56	65.47	6.02	75.82	7.25	77.57	7.78	78.87	7.78
15	20.80	3.90	33.99	5.69	36.69	3.78	46.78	4.43	63.90	6.19	74.29	7.20	76.98	7.78	78.16	7.60
16	20.95	4.05	31.84	5.97	36.89	3.58	48.29	4.49	66.62	6.05	73.59	7.22	77.62	7.73	78.71	7.60
17	22.63	4.07	34.12	5.87	36.67	3.56	47.96	4.40	66.80	6.07	73.49	7.39	77.45	7.61	78.09	7.55
18	20.34	3.97	34.81	5.77	36.25	3.72	46.13	4.44	65.63	6.06	73.93	7.25	77.83	7.64	78.72	7.27
19	22.07	3.81	33.82	5.93	37.21	3.80	48.80	4.44	63.31	6.00	72.43	7.23	76.67	7.60	77.90	7.31
20	22.37	3.72	34.65	5.63	36.14	3.55	48.45	4.60	65.87	6.08	75.42	7.37	77.90	7.77	78.66	7.64
21	22.33	3.96	31.95	5.65	36.86	3.90	48.28	4.48	63.88	6.02	74.52	7.21	77.57	7.66	78.87	7.46
22	20.06	4.01	32.38	6.00	38.99	3.71	48.41	4.36	64.64	6.18	74.10	7.40	77.55	7.61	78.30	7.75
23	22.45	3.97	31.39	5.63	36.39	3.90	46.65	4.55	64.33	6.11	72.79	7.36	76.74	7.75	78.89	7.76
24	20.30	3.74	33.09	5.83	36.73	3.81	48.22	4.49	64.10	6.16	75.05	7.27	76.53	7.60	78.11	7.38
25	22.81	3.85	34.05	5.64	38.08	3.52	47.58	4.35	63.52	6.03	75.44	7.25	77.58	7.71	78.21	7.56
26	22.62	3.71	32.45	5.65	38.02	3.69	48.99	4.37	64.79	6.20	73.07	7.30	77.44	7.61	77.96	7.53
27	20.89	3.71	31.72	5.64	38.16	3.52	46.58	4.57	63.45	6.14	74.15	7.27	76.74	7.65	78.77	7.65
28	21.41	3.75	32.18	5.87	36.58	3.58	47.18	4.32	65.47	6.21	74.25	7.32	76.88	7.59	78.26	7.78
29	21.33	3.81	31.67	5.97	37.72	3.64	48.98	4.47	66.34	6.12	74.80	7.34	77.12	7.58	78.66	7.39
30	21.67	3.98	33.02	5.85	36.13	3.50	47.81	4.53	65.87	6.18	74.11	7.10	77.64	7.68	78.76	7.51
31	20.75	3.74	34.84	5.69	38.63	3.87	47.46	4.51	65.48	6.27	75.55	7.40	76.99	7.71	78.36	7.50
32	21.28	3.94	33.06	5.65	38.12	3.56	48.81	4.60	65.87	6.25	75.41	7.39	76.89	7.68	78.54	7.20

Table 3.16 Summary of Optimal Formulations in Two Scenarios

	Scenario 1.5	Scenario 1.6
x_1^*	178.02	190.05
x_2^*	14.88	9.60
x_3^*	16.82	22.16
x_4^*	13.41	13.73
x_5^*	8.86	4.15
f_2	84.28	63.34
$A_R(t_1) : A_T(t_1) \pm s(t_1)$	22 : 19.95 ± 3.82	21.85 ± 3.84
$A_R(t_2) : A_T(t_2) \pm s(t_2)$	33 : 30.49 ± 5.72	33.35 ± 5.51
$A_R(t_3) : A_T(t_3) \pm s(t_3)$	38 : 36.20 ± 3.90	37.26 ± 3.73
$A_R(t_4) : A_T(t_4) \pm s(t_4)$	48 : 48.57 ± 4.39	48.51 ± 4.43
$A_R(t_5) : A_T(t_5) \pm s(t_5)$	65 : 63.46 ± 6.22	63.92 ± 6.13
$A_R(t_6) : A_T(t_6) \pm s(t_6)$	74 : 73.94 ± 7.35	74.51 ± 7.22
$A_R(t_7) : A_T(t_7) \pm s(t_7)$	77 : 77.28 ± 7.66	77.63 ± 7.66
$A_R(t_8) : A_T(t_8) \pm s(t_8)$	78 : 78.90 ± 7.43	78.71 ± 7.48

Table 3.17 Sensitivity Analysis for Class 1 Drugs with Level 2 Changes

λ_1	Scenario	x_1^*	x_2^*	x_3^*	x_4^*	x_5^*	$s(A_T)$
0.2	1.3	173.71	13.39	18.44	15.22	7.04	4.19
	1.4	168.50	12.29	20.40	16.66	8.90	3.95
0.3	1.3	173.70	13.39	18.44	15.22	7.04	4.19
	1.4	168.69	12.34	20.25	16.60	8.90	3.95
0.4	1.3	173.73	13.39	18.44	15.22	7.04	4.19
	1.4	169.51	12.32	16.82	16.27	8.08	3.98

3.5 Conclusion

Throughout the development of a new drug, it is frequent for a new product to encounter changes in composition due to scaling up production. In order to smooth the scale-up and to ensure the equivalent safety and efficacy of the product, the traditional pharmaceutical formulation optimization procedure can be extended to determine the

Table 3.18 Sensitivity Analysis for Class 2 and 3 Drugs with Level 2 Changes

Optimal settings		$f_2 \geq 60$	$f_2 \geq 65$	$f_2 \geq 70$
	Scenario 1.5	Scenario 1.6	Scenario 1.6	Scenario 1.6
x_1^*	178.02	190.05	190.12	186.67
x_2^*	14.88	9.60	9.58	11.62
x_3^*	16.82	22.16	21.82	20.58
x_4^*	13.41	13.73	13.50	13.41
x_5^*	8.86	4.15	4.89	5.80
f_2	84.28	63.34	65.00	70.00
$A_R(t_1) : A_T(t_1) \pm s(t_1)$	22 : 19.95 ± 3.82	21.85 ± 3.85	21.67 ± 3.86	21.04 ± 3.83
$A_R(t_2) : A_T(t_2) \pm s(t_2)$	33 : 30.49 ± 5.72	33.35 ± 5.51	33.20 ± 5.53	32.16 ± 5.60
$A_R(t_3) : A_T(t_3) \pm s(t_3)$	38 : 36.20 ± 3.90	37.26 ± 3.73	37.21 ± 3.72	36.86 ± 3.76
$A_R(t_4) : A_T(t_4) \pm s(t_4)$	48 : 48.57 ± 4.39	48.51 ± 4.43	48.56 ± 4.44	48.68 ± 4.42
$A_R(t_5) : A_T(t_5) \pm s(t_5)$	65 : 63.46 ± 6.22	63.92 ± 6.13	64.04 ± 6.13	64.26 ± 6.20
$A_R(t_6) : A_T(t_6) \pm s(t_6)$	74 : 73.94 ± 7.35	74.51 ± 7.22	74.37 ± 7.22	74.11 ± 7.24
$A_R(t_7) : A_T(t_7) \pm s(t_7)$	77 : 77.28 ± 7.66	77.63 ± 7.66	77.61 ± 7.65	77.33 ± 7.64
$A_R(t_8) : A_T(t_8) \pm s(t_8)$	78 : 78.90 ± 7.43	78.71 ± 7.48	78.73 ± 7.48	78.71 ± 7.43

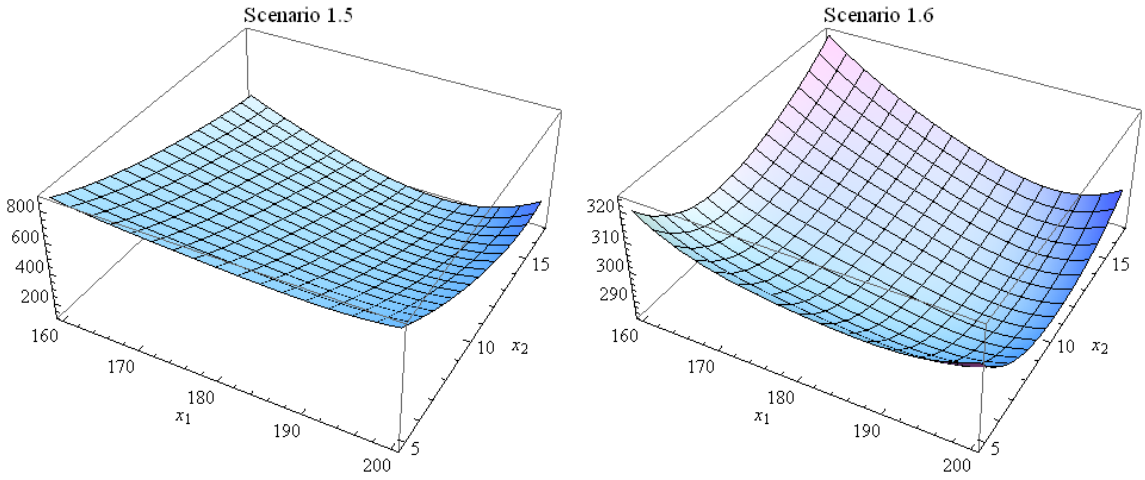

Figure 3.2 Response Surface Plots Showing the Effects of x_1 and x_2 on the Objective Function

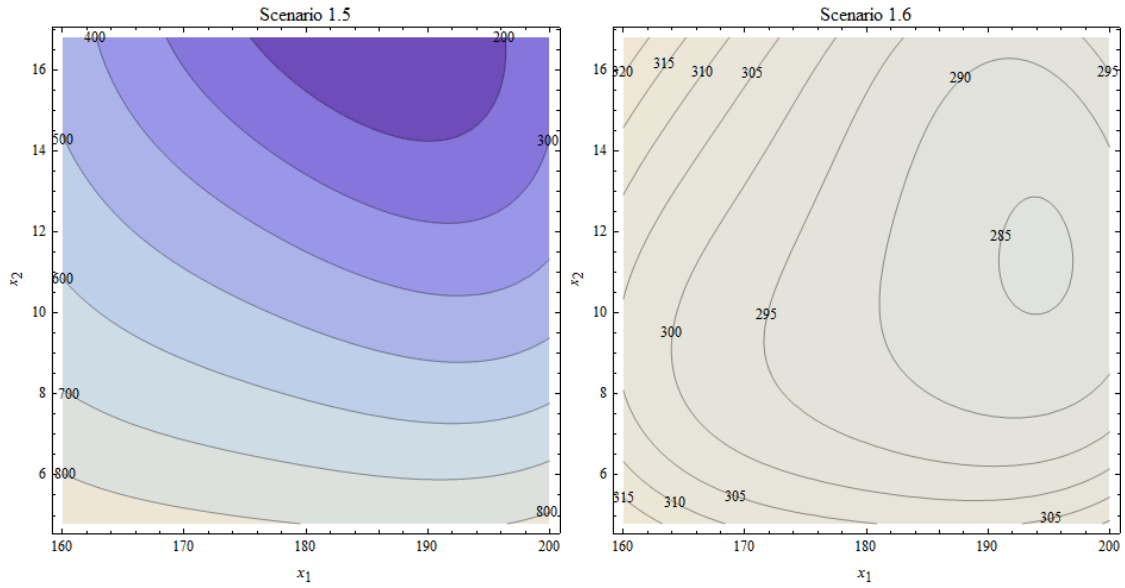

Figure 3.3 Contour Plots of x1 and x2 for the Dissolution Comparison Problem

optimal settings of inactive ingredients when ingredient changes occur. The proposed optimization model can also be used to avoid duplicate submission of data to the FDA for excipient changes. Incorporating the quality loss concept, more comprehensive quality loss functions are developed and used as the objective functions in this chapter. The concept of quality loss is attractive because it evaluates the deviations from target profiles of both the mean and variance, while traditional methods only consider the mean. The variance is generally considered essential because large variability in the dissolution performance of the formulation may result in unpredictable safety and efficacy issues. Furthermore, the extended formulation optimization procedure is developed by investigating all related regulatory regulations and incorporating modern DOE and regression techniques into the optimization methodology. The numerical examples under different scenarios examine the feasibility of introducing the proposed approach to the practical optimization problem. Finally, a sensitivity analysis is conducted to study the

behavior of optimal input factor settings for varying associated constraint boundaries. In summary, implementing the extended formulation optimization methodology not only minimizes the quality loss, but also potentially achieves cost savings.

CHAPTER 4

DEVELOPING THE OPTIMAL FORMULATIONS FOR NEW TABLET DRUGS (BIOEQUIVALENCE STUDIES)

4.1 Introduction

In the previous chapter, the extended formulation optimization procedure associated with dissolution comparisons was developed. This chapter is a continuous effort on optimizing pharmaceutical formulations for scale-up changes in excipients when bioequivalence studies are carried out. If a Level 3 change in excipients for Class 4 drugs (containing APIs with low solubility and low permeability) is detected, the FDA guidance (1995) for IR solid oral dosage forms requires establishing bioequivalence between the pre-change reference and post-change test formulations so as to avoid resubmission of data for excipient changes to the FDA. Note that Level 3 changes refer to those that are likely to have a significant impact on formulation quality. In that case, the *in vivo* bioequivalence study is generally performed to compare the critical bioavailability attributes for the two formulations. Bioavailability is a measurement of the rate and extent of the active ingredient which is absorbed and becomes available at the site of action (Shargel *et al.*, 2004). Furthermore, ABE is concluded if the average bioavailability attributes of the test formulation is within 80% to 125% of those of the reference formulation at the 90% significance level (FDA, 2001). Additionally, bioequivalence studies may be excluded by establishing an IVIVC.

In order to determine the optimal setting of excipients and to ensure the bioequivalence of the test formulation, DOE and regression techniques can be incorporated into the optimization model. However, no formal research incorporating bioequivalence studies into DOE techniques has been found. However, several methods for evaluating the bioavailability characteristics for an individual profile exist in the literature (Shargel *et al.*, 2004; Chow & Liu, 2009). The question remains as to which method is most appropriate for the integration of bioequivalence and DOE methodologies. In this chapter, we shall perform the following studies:

- Describe the integration of bioequivalence studies into DOE methods, and develop assessment methods for the bioavailability characteristics of interest, when replicated profiles are sampled under the DOE framework.
- Propose a formulation optimization procedure to identify the optimal levels of excipients for the test formulation, while satisfying bioequivalence criteria.

The next section incorporates the bioequivalence study into DOE methodologies and introduces the associated methods for bioequivalence assessment. In Section 4.3, the optimization procedure is proposed. Sections 4.4 and 4.5 respectively present a numerical example and a sensitivity analysis for validation, and Section 4.6 finally provides conclusions.

4.2 Integration of the *In Vivo* Bioequivalence Study into Experimental Designs

The *in vivo* bioequivalence study is conducted in order to compare a test and its reference formulation with respect to critical bioavailability characteristics. On the other

hand, the DOE technique requires establishing the input factor settings related to the ingredient amounts of the test formulation. Therefore, a bioequivalence study should be performed under each input setting when integrated into DOE. This section introduces the bioequivalence assessment under both the standard and DOE format.

4.2.1 Regular Bioequivalence Assessment

The *in vivo* bioequivalence study generally utilizes a single-dose, two-treatment, two-period, two-sequence (2×2) crossover design to compare critical bioavailability attributes of the test and reference formulations. An equal number of subjects is randomly assigned to each of the two sequences (FDA, 1995). Within the first sequence, the reference formulation is administered to subjects first, while the test formulation is administered first within the second one. The general framework of the study design is shown in Table 4.1 (Chow & Liu, 2009), in which Y_{ijk} denotes the bioavailability characteristic, i, j and k are the numbers of subjects, periods, and sequences, respectively, for $i = 1, 2, \ldots, n_k$, j and $k = 1, 2$, with n_k defined as the number of subjects within sequence k. Also note that n_1 is always equal to n_2, since both sequences have the same number of subjects. The main advantage of crossover designs is that they exclude the inter-subject variability from the comparison between formulations.

Table 4.1 2×2 Crossover Design Format for the Bioequivalence Study

Sequence	Period 1	Period 2
1	Reference formulation: Y_{i11}	Test formulation: Y_{i21}
2	Test formulation: Y_{i12}	Reference formulation: Y_{i22}

The standard bioavailability responses after a single-dose administration are the maximum plasma concentration (C_{max}), the time to reach C_{max} (t_{max}), and the area under the plasma concentration-time curve ($AUC_{0\text{-}t}$) from time 0 to time t (FDA, 2003). In order to assess the means and variances of these responses for the test and reference formulations, while at the same time complying with the USP and FDA regulations, an unreplicated experiment should be conducted. In other words, a single-dose 2×2 crossover design is performed at each experimental run.

4.2.1.1 Continuous Computational Method for Assessment

The continuous method refers to fitting a smooth curve to the discrete concentration data. When drug absorption has been completed, Equation (2.3) reduces to the following expression (Shargel *et al.*, 2004):

$$C_{reduced}(t) = \frac{FD}{V_d}\frac{K_a}{K_a - K_e}e^{-K_e t},\ \ t \in [t_z, \infty) \tag{4.1}$$

where t_z is the critical time point at which absorption ends. $AUC_{0\text{-}t}$ can be derived by $AUC_{0-t} = \int_0^t C(t)\mathrm{d}t$, which is clearly dependent on time t. Generally, t is set to a specific value (denoted by t_0), or infinity during the bioequivalence study. Since it has been widely accepted that the function in Equation (2.3) is always concave with $K_a > K_e$, C_{max} and t_{max} exist and can be obtained by setting the rate of concentration change to zero. Moreover, the rate of concentration change can be achieved by differentiating Equation (2.3) with respect to t. Note that Equations (2.4) and (2.5) can be used to calculate C_{max} and t_{max}; neither C_{max} nor t_{max} are functions of t. $AUC_{0\text{-}t}$ is given by

$$AUC_{0-t} = -\frac{K}{K_e}\left(e^{-K_e t} - 1\right) + \frac{K}{K_a}\left(e^{-K_a t} - 1\right),$$

where $K = \dfrac{FDK_a}{V_d\left(K_a - K_e\right)}$.

It is important to note that the estimators of K and K_e, denoted respectively by $\hat{K}$ and $\hat{K}_e$, can be obtained by performing an ordinary linear regression analysis with the natural logarithm transformation of Equation (4.1). The method of residuals for fitting a curve to the experimental data of a drug can be used to estimate K_a (Gibaldi & Perrier, 1982). Instead of plotting a fitted curve, we propose a method to estimate K_a using regression techniques. First, $\hat{K}$ and $\hat{K}_e$ are substituted into Equation (2.3) as follows:

$$C(t) = \hat{K}\left(e^{-\hat{K}_e t} - e^{-K_a t}\right), \quad t \in [0, \infty) \tag{4.2}$$

which has only one unknown parameter, K_a. Subsequently, Equation (4.2) can be simplified to

$$C^*(t) = e^{-K_a t},$$

in which $C^*(t) = e^{-\hat{K}_e t} - C(t)/\hat{K}$. Let $[C^*(t_i), t_i]$ denote the observed value of $[C^*(t), t]$ on the i^{th} trial, where $i = 1, 2, \ldots, n$, and n is the number of time points. Thus, the estimator for K_a, $\hat{K}_a$ can be derived by minimizing the following equation:

$$Q(K_a) = \sum_{i=1}^{n}\left[C^*(t_i) - e^{-K_a t_i}\right]^2. \tag{4.3}$$

By differentiating Equation (4.3) with respect to K_a and then setting the derivative equal to zero, we obtain

$$Q'(K_a) = \sum_{i=1}^{n} t_i e^{-K_a t_i} \left[C^*(t_i) - e^{-K_a t_i} \right] = 0. \qquad (4.4)$$

$Q'(K_a)$ can be considered a linear combination of n bi-exponential functions, so the shape of its function curve is similar to the one shown in Figure 4.1. Additionally,

$$\lim_{K_a \to \hat{K}_e} Q'(K_a) = \sum_{i=1}^{n} t_i e^{-\hat{K}_e t_i} \left[C^*(t_i) - e^{-\hat{K}_e t_i} \right] = \sum_{i=1}^{n} t_i e^{-\hat{K}_e t_i} \left[-\frac{C(t_i)}{\hat{K}} \right] < 0,$$

and

$$\lim_{K_a \to \infty} Q'(K_a) = 0.$$

Therefore, it is concluded that Equation (4.4) has a unique solution on the interval $(\hat{K}_e, \infty)$; the general shape of the function $Q'(K_a)$ curve is illustrated in Figure 4.1.

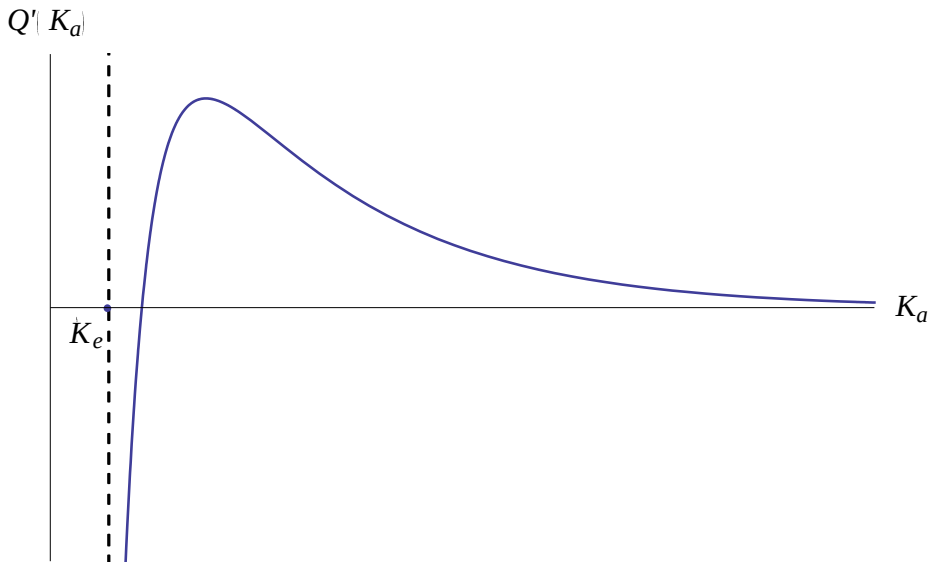

Figure 4.1 General Shape of $Q'(K_a)$ Curve

Let $\mathbf{C} = [C(t_1), C(t_2), \ldots, C(t_n)]'$ and $\mathbf{T} = [t_1, t_2, \ldots, t_n]'$ be the $n \times 1$ vectors for the concentration levels and time points. The matrix exponential of **T,** exp(**T**), is given by

$\exp(\mathbf{T}) = [\, e^{t_1}, e^{t_2}, \ldots, e^{t_n} \,]'$. Furthermore, $\mathbf{T}^{\mathrm{d}}$ denotes a diagonal matrix with dimension $n \times n$ for the time points, where

$$\mathbf{T}^{\mathrm{d}} = \begin{bmatrix} t_1 & 0 & \cdots & 0 \\ 0 & t_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & t_n \end{bmatrix}.$$

Hence, Equation (4.4) can be rewritten in matrix notation as

$$\exp\left(-\hat{K}_a \mathbf{T}\right)' \mathbf{T}^{\mathrm{d}} \left[\exp\left(-\hat{K}_e \mathbf{T}\right) - \frac{1}{\hat{K}} \mathbf{C} - \exp\left(-\hat{K}_a \mathbf{T}\right) \right] = 0 . \tag{4.5}$$

In order to solve for $\hat{K}_a$ in Equation (4.5), the bisection procedure can be applied to iteratively converge on the solution which lies inside the interval $[\, \hat{K}_e, \mathcal{K}]$. Note that $\mathcal{K}$ denotes the pre-determined upper bound of the interval. Alternatively, a numerical computing environment, such as MATLAB® 2009, can be used to solve for $\hat{K}_a$.

4.2.1.2 Discrete Computational Method for Assessment

In addition to the continuous method above, the FDA recommends the use of a discretization method, specifically the linear trapezoidal technique, to approximate the *AUC*. In this method, the *AUC* can be estimated based on Equations (2.6) and (2.7); K_e can be obtained by using regression analysis based on Equation (4.1). Note that $C_{\max} = \max\{C_1, C_2, \ldots, C_n\}$, and the estimate of $t_{\max}$ is established as the corresponding point in time at which $C_{\max}$ occurs.

4.2.2 Bioequivalence Assessment under the Experimental Design Structure

The input factors are the amounts of excipients in the test formulation. Let **x** and $\mathbb{X}$ denote the vector of input factors and design matrix, respectively. An unreplicated DOE format with r experimental runs for the bioequivalence study is illustrated in Table 4.2, where Y^U represents the unreplicated response, and C_{ijkhu} denotes the plasma concentration level at time point h of the u^{th} run, with j and k = 1, 2, h = 1, 2, …, n and u =1, 2, …, r. Note that the subscript u denotes the characteristic of interest for the u^{th} design point and $s^2[\bullet]$ is the sample variance of the characteristic of interest. Log-transformations of $C_{\max}$ and $AUC_{0\text{-}t}$ are recommended by the FDA, since the transformed data appear to be approximately normally distributed and achieve a relatively homogeneous variance (Chow *et al.*, 1991). Hence, let $\overline{\ln C_{\max u}}$ and $\overline{\ln AUC_{0-t,u}}$ denote the means of log-transformed $C_{\max}$ and $AUC_{0\text{-}t}$ at the u^{th} run, respectively. The pooled sample SD of period differences from both sequences, denoted by $\hat{\sigma}$, is useful to evaluate the 90% confidence interval (CI) of the bioavailability characteristics differences. According to (Chow & Liu, 2009), $\hat{\sigma}_u$ is calculated by

$$\hat{\sigma}_u = \sqrt{\frac{1}{n_1 + n_2 - 2} \sum_{k=1}^{2} \sum_{i=1}^{n_k} \left(d_{iku} - \bar{d}_{\bullet ku} \right)^2},$$

where $d_{iku} = (Y_{i2ku} - Y_{i1ku})/2$ and $\bar{d}_{\bullet ku} = \frac{1}{n_k} \sum_{i=1}^{n_k} d_{iku}$ for i = 1, 2, …, n_k and k = 1, 2. Note that no specific CI related to $t_{\max}$ is provided in the FDA guidance, as $t_{\max}$ is not often used because of its high inter-individual variability (Qiu *et al.*, 2009). Therefore, Y denotes

either $\ln AUC_{0\text{-}t}$ or $\ln C_{\max}$. Moreover, the intra-subject variability between the test and reference formulations at the u^{th} run, denoted by s_{inu}^2, can be estimated by

$$s_{inu}^2 = \frac{1}{n_1 + n_2 - 2}\left(\sum_{k=1}^{2}\sum_{j=1}^{2}\sum_{i=1}^{n_k} Y_{ijku}^2 - \sum_{k=1}^{2}\sum_{i=1}^{n_k} \frac{Y_{i\bullet ku}^2}{2} - \sum_{k=1}^{2}\sum_{j=1}^{2} \frac{Y_{\bullet jku}^2}{n_k} + \sum_{k=1}^{2} \frac{Y_{\bullet\bullet ku}^2}{2n_k} \right), \qquad (4.6)$$

where $Y_{i\bullet ku} = \sum_{j=1}^{2} Y_{ijku}$, $Y_{\bullet jku} = \sum_{i=1}^{n_k} Y_{ijku}$, and $Y_{\bullet\bullet ku} = \sum_{i=1}^{n_k}\sum_{j=1}^{2} Y_{ijku}$. Again, Y is either $\ln AUC_{0\text{-}t}$ or $\ln C_{\max}$ in Equation (4.6).

When multiple concentration profiles are collected at each design point under the framework of a 2×2 crossover design, equations for calculating the sample means and variances of $AUC_{0\text{-}t}$, $C_{\max}$, and $t_{\max}$ for the test formulation at the u^{th} experimental run must be developed; theses equations are listed in Table 4.3, where $AUC_{0\text{-}t,ijku}$, $C_{\max ijku}$, and $t_{\max ijku}$ denote the corresponding bioavailability characteristic at the u^{th} run with i concentration profiles, j periods, and k sequences. Moreover, $u = 1, 2, \ldots, r$, $\begin{cases} j = 1, k = 2 \\ j = 2, k = 1 \end{cases}$, and the subscript T represents the test formulation. It should be mentioned that characteristic variances for the reference formulation are not chosen as responses under the DOE format, because they are not considered the target values of the variances for the test formulation when applying the Taguchi quality loss concept to the optimization procedure. Similarly, the mean estimators for the reference formulation at the u^{th} design point are found using the formulas in Table 4.4, where the subscript R represents the reference formulation.

Table 4.2 DOE Format for the Bioequivalence Study

Run	Factors (**x**)	Observations	Unreplicated Responses (Y^U)							
		Concentration data	C_{max}	Variance of C_{max}	t_{max}	Variance of t_{max}	$AUC_{0\text{-}t}$	Variance of $AUC_{0\text{-}t}$	Pooled SD of period differences	Intra-subject variance
1	Input Factor Settings ($\mathbb{X}$)	C_{ijkh1}	$\overline{\ln C_{max1}}$	$s^2(\ln C_{max1})$	t_{max1}	$s^2(t_{max1})$	$\overline{\ln AUC_{0-t,1}}$	$s^2(\ln AUC_{0\text{-}t,1})$	$\hat{\sigma}_1$	s^2_{in1}
2		C_{ijkh2}	$\overline{\ln C_{max2}}$	$s^2(\ln C_{max2})$	t_{max2}	$s^2(t_{max2})$	$\overline{\ln AUC_{0-t,2}}$	$s^2(\ln AUC_{0\text{-}t,2})$	$\hat{\sigma}_2$	s^2_{in2}
⋮		⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
u		C_{ijkhu}	$\overline{\ln C_{maxu}}$	$s^2(\ln C_{maxu})$	t_{maxu}	$s^2(t_{maxu})$	$\overline{\ln AUC_{0-t,u}}$	$s^2(\ln AUC_{0\text{-}t,u})$	$\hat{\sigma}_u$	s^2_{inu}
⋮		⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
r		C_{ijkhr}	$\overline{\ln C_{maxr}}$	$s^2(\ln C_{maxr})$	t_{maxr}	$s^2(t_{maxr})$	$\overline{\ln AUC_{0-t,r}}$	$s^2(\ln AUC_{0\text{-}t,r})$	$\hat{\sigma}_r$	s^2_{inr}

Table 4.3 Mean and Variance of Characteristics for the Test Formulation

Mean	Variance
$\overline{\ln AUC_{0-t,Tu}} = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1}\ln AUC_{0-t,i12u} + \sum_{i=1}^{n_2}\ln AUC_{0-t,i21u}\right)$	$s^2\left(\ln AUC_{0-t,Tu}\right) = \frac{1}{n_1+n_2-1}\sum_{i=1}^{n_1+n_2}\left(\ln AUC_{0-t,ijku} - \overline{\ln AUC_{0-t,Tu}}\right)^2$
$\overline{\ln C_{maxTu}} = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1}\ln C_{maxi12u} + \sum_{i=1}^{n_2}\ln C_{maxi21u}\right)$	$s^2\left(\ln C_{maxTu}\right) = \frac{1}{n_1+n_2-1}\sum_{i=1}^{n_1+n_2}\left(\ln C_{maxijku} - \overline{\ln C_{maxTu}}\right)^2$
$\overline{t_{maxTu}} = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1}t_{maxi12u} + \sum_{i=1}^{n_2}t_{maxi21u}\right)$	$s^2\left(t_{maxTu}\right) = \frac{1}{n_1+n_2-1}\sum_{i=1}^{n_1+n_2}\left(t_{maxijku} - \overline{t_{maxTu}}\right)^2$

Table 4.4 Mean of Characteristics for the Reference Formulation

$$\overline{\ln AUC_{0-t,Ru}} = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1}\ln AUC_{0-t,i11u} + \sum_{i=1}^{n_2}\ln AUC_{0-t,i22u}\right)$$

$$\overline{\ln C_{\max Ru}} = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1}\ln C_{\max i11u} + \sum_{i=1}^{n_2}\ln C_{\max i22u}\right)$$

$$\overline{t_{\max Ru}} = \frac{1}{n_1+n_2}\left(\sum_{i=1}^{n_1} t_{\max i11u} + \sum_{i=1}^{n_2} t_{\max i22u}\right)$$

Additionally, for the continuous computational method, the estimation of K, K_a, and K_e can be achieved by extending the dimension of the matrix presented in Section 2.1.1. Let us define vectors $\tilde{\mathbf{T}}$, $\mathbf{K}$, $\mathbf{K}_e$, $\mathbf{K}_a$, and $\boldsymbol{\beta}$ as follows:

$$\underset{n\times 2}{\tilde{\mathbf{T}}} = [\mathbf{1}, \mathbf{T}],$$

$$\underset{1\times 2ir}{\mathbf{K}} = [\hat{K}_{1111}, \hat{K}_{2111}, \hat{K}_{3111}, \ldots, \hat{K}_{1211}, \hat{K}_{2211}, \hat{K}_{3211}, \ldots, \hat{K}_{(i/2+1)121}, \hat{K}_{(i/2+2)121}, \hat{K}_{(i/2+3)121},$$

$$\ldots, \hat{K}_{(i/2+1)221}, \hat{K}_{(i/2+2)221}, \hat{K}_{(i/2+3)221}, \ldots, \hat{K}_{ijkr}],$$

$$\underset{1\times 2ir}{\mathbf{K}_e} = [\hat{K}_{e1111}, \hat{K}_{e2111}, \hat{K}_{e3111}, \ldots, \hat{K}_{e1211}, \hat{K}_{e2211}, \hat{K}_{e3211}, \ldots, \hat{K}_{e(i/2+1)121}, \hat{K}_{e(i/2+2)121},$$

$$\hat{K}_{e(i/2+3)121}, \ldots, \hat{K}_{e(i/2+1)221}, \hat{K}_{e(i/2+2)221}, \hat{K}_{e(i/2+3)221}, \ldots, \hat{K}_{eijkr}],$$

$$\underset{1\times 2ir}{\mathbf{K}_a} = [\hat{K}_{a1111}, \hat{K}_{a2111}, \hat{K}_{a3111}, \ldots, \hat{K}_{a1211}, \hat{K}_{a2211}, \hat{K}_{a3211}, \ldots, \hat{K}_{a(i/2+1)121}, \hat{K}_{a(i/2+2)121},$$

$$\hat{K}_{a(i/2+3)121}, \ldots, \hat{K}_{a(i/2+1)221}, \hat{K}_{a(i/2+2)221}, \hat{K}_{a(i/2+3)221}, \ldots, \hat{K}_{aijkr}],$$

and

$$\underset{2\times 2ir}{\boldsymbol{\beta}} = [\ln\mathbf{K}, -\mathbf{K}_e]',$$

where the subscripts i, j, k and r denote the related parameter for the i^{th} subject, during the j^{th} period, within the k^{th} sequence, at the r^{th} design point, and $\ln\mathbf{K}$ denotes the vector that

is obtained after taking the natural logarithm of each element of **K**. Moreover, the matrix containing the concentration data from time t_z to t_n, denoted by $\mathbf{C}_{reduce}$, is defined as

$$\underset{n\times 2ir}{\mathbf{C}_{reduce}} = \begin{bmatrix} C_{111p1} & C_{211p1} & C_{311z1} & \cdots & C_{(i/2+1)22z1} & C_{(i/2+2)22z1} & C_{(i/2+3)22z1} & \cdots & C_{ijkzr} \\ C_{111(p+1)1} & C_{211(p+1)1} & C_{311(z+1)1} & \cdots & C_{(i/2+1)22(z+1)1} & C_{(i/2+2)22(z+1)1} & C_{(i/2+3)22(z+1)1} & \cdots & C_{ijk(z+1)r} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ C_{111n1} & C_{211n1} & C_{311n1} & \cdots & C_{(i/2+1)22n1} & C_{(i/2+2)22n1} & C_{(i/2+3)22n1} & \cdots & C_{ijknr} \end{bmatrix}'.$$

The regression coefficient vector, **β**, for the natural logarithm transformation of Equation (4.1) can be calculated by

$$\boldsymbol{\beta} = \left(\tilde{\mathbf{T}}'\tilde{\mathbf{T}}\right)^{-1}\tilde{\mathbf{T}}'\mathbf{C}_{reduce}.$$

Based on the equations above, the values of **K** and $\mathbf{K}_e$ can now be determined. Moreover, each element of the vector $\mathbf{K}_a$ can be obtained by solving Equation (4.5), and MATLAB code has been provided in Appendix 2.1 for this purpose.

Finally, the estimated second-order response function, shown below, can be obtained by using the ordinary least squares method.

$$\hat{Y}^U(\mathbf{x}) = \left[1\ x_1\ \ldots\ x_6\ x_1x_2\ \ldots\ x_5x_6\ x_1^2\ \ldots\ x_6^2\right]\times\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^TY^U,$$

where **X** is a matrix for the predictor variables. Moreover, when the Y^U includes $AUC_{0\text{-}t}$, the estimated response function becomes

$$\hat{Y}^U(t,\mathbf{x}) = \left[1\ x_1\ \ldots\ x_6\ x_1x_2\ \ldots\ x_5x_6\ x_1^2\ \ldots\ x_6^2\right]\times\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{X}^TY^U(t).$$

4.3 Proposed Optimization Model

4.3.1 Objective Function

The Taguchi quality loss concept is the basis for the objective function, which

ensures that the optimal solution provides minimum deviations from the target values of bioavailability characteristics for the test formulation, including $AUC_{0\text{-}t}$, $C_{\max}$ and $t_{\max}$. Referring to the univariate squared-error loss function (Taguchi, 1985), the objective of the optimization procedure is to minimize the summation of squared differences between characteristics of interest for the test formulation and their target values. The target values for the mean and variance are chosen as the means for the reference formulation and zero, respectively. Although $t_{\max}$ is not a common measurement when assessing bioequivalence, Shargel et al. (2004) indicated that drug products were generally tested in chemically equivalent doses in bioequivalence studies, and $t_{\max}$ could be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products. Hence, in order to capture the performance of $t_{\max}$ in addition to $AUC_{0\text{-}t}$ and $C_{\max}$, we propose the following objective function:

$$\text{Minimize } \left[\overline{\ln C_{\max T}(\mathbf{x})} - \overline{\ln C_{\max R}(\mathbf{x})}\right]^2 + s^2\left[\ln C_{\max T}(\mathbf{x})\right] + \left[\overline{t_{\max T}(\mathbf{x})} - \overline{t_{\max R}(\mathbf{x})}\right]^2 + s^2\left[t_{\max T}(\mathbf{x})\right] + \left[\overline{\ln AUC_{0-t,T}(t,\mathbf{x})} - \overline{\ln AUC_{0-t,R}(t,\mathbf{x})}\right]^2 + s^2\left[\ln AUC_{0-t,T}(t,\mathbf{x})\right],$$

in which a function of **x** denotes the estimated response surface function for either the mean or variance, and a function of t and **x** is the response function over time t.

4.3.2 Constraints on Excipient Changes

According to the FDA (1995), the ranges of Level 3 changes in the excipient are beyond those of Level 2. Hence, the constraints on Level 3 excipient changes are proposed by incorporating all possible combinations of the following seven inequalities, where (θ_1, θ_2, θ_3, θ_4, θ_5, θ_6) = (10%, 6%, 1%, 0.5%, 2%, 2%).

$$\left|\frac{x_i-\tau_i}{W_R}\right|>\theta_i \quad (i=1,2,...,6) \text{ and } \sum_{i=1}^{6}\left|\frac{x_i-\tau_i}{W_R}\right|>10\% .$$

4.3.3 Constraints Associated with *In Vivo* Bioequivalence Studies

Based on the FDA (2006a) and Chow and Liu (2009), the 90% CI for the difference in means of log-transformed data is provided in Table 4.5, where Y denotes either $C_{\max}$ or $AUC_{0\text{-}t}$. Then, constraints on the CIs for $C_{\max}$ and $AUC_{0\text{-}t}$ are developed, which are shown in Table 4.6.

Table 4.5 90% Confidence Interval for Assessing Bioequivalence

Upper bound	$\left(\overline{\ln Y_T}-\overline{\ln Y_R}\right)+t_{n_1+n_2-2,0.05}\hat{\sigma}\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}$
Lower bound	$\left(\overline{\ln Y_T}-\overline{\ln Y_R}\right)-t_{n_1+n_2-2,0.05}\hat{\sigma}\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}$

Table 4.6 Proposed Constraints for the Bioequivalence Study

$Y = C_{\max}$	Upper bound	$\left[\overline{\ln Y_T(\mathbf{x})}-\overline{\ln Y_R(\mathbf{x})}\right]+t_{n_1+n_2-2,0.05}\hat{\sigma}(\mathbf{x})\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}\le 25\%\overline{\ln Y_R(\mathbf{x})}$
	Lower bound	$\left[\overline{\ln Y_T(\mathbf{x})}-\overline{\ln Y_R(\mathbf{x})}\right]-t_{n_1+n_2-2,0.05}\hat{\sigma}(\mathbf{x})\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}\ge -20\%\overline{\ln Y_R(\mathbf{x})}$
$Y = AUC_{0\text{-}t}$	Upper bound	$\left[\overline{\ln Y_T(t,\mathbf{x})}-\overline{\ln Y_R(t,\mathbf{x})}\right]+t_{n_1+n_2-2,0.05}\hat{\sigma}(t,\mathbf{x})\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}\le 25\%\overline{\ln Y_R(t,\mathbf{x})}$
	Lower bound	$\left[\overline{\ln Y_T(t,\mathbf{x})}-\overline{\ln Y_R(t,\mathbf{x})}\right]-t_{n_1+n_2-2,0.05}\hat{\sigma}(t,\mathbf{x})\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}\ge -20\%\overline{\ln Y_R(t,\mathbf{x})}$

4.3.4 Intra-Subject Variability Constraints

For a standard 2×2 crossover design, Chow and Liu (2009) pointed out that the difference in total variability between test and reference formulations is the difference in

intra-subject variability between the two formulations, since the crossover design removes the inter-subject variability. However, there is no universal agreement on how much difference in variability would be considered to be of clinically meaningful significance. Let γ_A and γ_C be the upper limits of intra-subject variations (s_{in}^2) for $AUC_{0\text{-}t}$ and $C_{\max}$, respectively. Therefore, the constraints on s_{in}^2 are proposed as

$$s_{in}^2(t,\mathbf{x}) \le \gamma_A \text{ and } s_{in}^2(\mathbf{x}) \le \gamma_C .$$

4.3.5 Other Constraints

Additional constraints that were developed (in Chapter 3) for disintegration time, uniformity, friability, compressibility, hardness, thickness, stability, nonnegativity and design space, also need to be taken into consideration in this optimization model.

4.4 Numerical Examples

The formulation optimization is performed for Class 4 Drugs with Level 3 excipient changes. Plasma concentration profiles for the bioequivalence study are simulated under a standard 2×2 crossover design framework. The number of subjects within each sequence for the crossover study is $n_1 = n_2 = 3$. The vector of points in time, measured in hours, is set as $\mathbf{T}$ = [0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12]′. The input factors (treated as decision variables) include x_1 and x_2 in this case; therefore, a two-factor CCD with 13 experimental runs (i.e., r = 13) is analyzed using Minitab® 16. Table 4.7 provides the plasma concentration data under a DOE format. The uncoded values of two

levels (−1, +1) for x_1 and x_2 are set as (170, 190) and (7.8, 13.8), respectively. The design format with coded factor values is described in Table 4.8.

We will adopt the estimated response functions associated with disintegration, uniformity, friability, compressibility, and hardness tests from Chapter 3, and let the weights of x_3, x_4, and x_5 be 20mg, 15mg, and 2.5mg, respectively. The target weight of each excipient in the reference formulation is $(\tau_1, \tau_2) = (150, 10.5)$ measured in mg. The pre-identified average weight of the API is 80mg. Therefore, the total weight of the reference formulation is W_R = 278mg. In addition, let the upper bounds of intra-subject variability be $\gamma_A = \gamma_C = 0.1$.

We compare the *AUC*s from time 0 to infinity, $AUC_{0\text{-}\infty}$, for the test and reference formulations in this numerical example. The bioavailability characteristics, $t_{\max}$, $C_{\max}$, and $AUC_{0\text{-}\infty}$, can be derived by the discrete (Scenario 2.1) and continuous (Scenario 2.2) methods; the results for the two scenarios are listed in Table 4.9. Note that the data calculated by the continuous method are presented in bold in the table. Referring to Equation (4.1), the regression coefficients of the concentration-time function were estimated under the condition that t_z = 4h.

Running a regression analysis with Minitab, we obtain the estimated response surface functions for both scenarios, which are then used to implement the optimization procedure with respect to the objective function and constraints. The optimal solutions and critical characteristics which are associated with assessing bioequivalence for both

Table 4.7 Plasma Concentration Data Set under a 2-Factor CCD Structure

Run	Sequence	Period	Subject	Time point										
				0	0.5	1	1.5	2	3	4	6	8	10	12
1	1	1	1	0	8.60	12.91	16.00	16.08	14.31	12.36	8.15	5.63	3.87	2.41
			2	0	9.48	12.96	15.73	16.42	14.58	12.79	8.53	5.10	4.02	2.69
			3	0	9.10	12.79	15.27	15.94	14.56	12.55	8.50	5.44	3.87	2.47
	1	2	1	0	9.23	12.96	15.95	15.61	14.27	12.23	8.19	5.22	3.75	2.28
			2	0	9.13	12.76	15.32	16.23	14.87	12.32	8.08	5.04	3.87	2.84
			3	0	9.17	12.55	15.56	15.54	14.18	12.74	8.86	5.63	4.46	3.00
	2	1	1	0	9.32	12.91	15.56	16.24	14.30	12.89	8.88	5.28	4.00	2.43
			2	0	9.24	12.78	15.04	16.31	14.60	12.77	8.80	5.37	4.03	3.00
			3	0	8.57	12.96	15.16	15.77	14.49	12.88	8.61	5.20	3.93	2.27
	2	2	1	0	8.84	12.89	15.16	16.27	14.84	12.45	8.95	5.85	3.86	2.46
			2	0	8.51	12.90	15.49	16.34	14.03	12.54	8.23	5.10	3.85	2.79
			3	0	8.66	12.92	15.86	15.88	14.28	12.59	8.48	5.08	4.05	2.17
2	1	1	1	0	9.43	12.59	15.46	16.35	14.73	12.81	8.94	5.57	4.43	2.57
			2	0	8.77	12.97	15.40	15.89	14.07	12.03	8.38	5.08	3.88	2.76
			3	0	8.75	12.79	15.12	16.47	14.64	12.68	8.20	5.12	3.60	2.95
	1	2	1	0	9.04	12.96	15.66	15.68	14.88	12.30	8.71	5.62	4.44	2.87
			2	0	9.48	12.80	15.01	15.69	14.06	12.75	8.50	5.16	4.13	2.02
			3	0	9.11	12.81	15.88	15.97	14.18	12.12	8.24	5.63	3.94	2.23
	2	1	1	0	9.06	12.98	15.08	15.93	14.58	12.26	8.40	5.64	4.26	2.41
			2	0	9.01	12.78	15.57	16.31	14.99	12.31	8.52	5.50	4.15	2.36
			3	0	9.00	12.81	15.78	16.31	14.77	12.84	8.99	5.96	4.03	2.34
	2	2	1	0	8.62	12.95	15.17	16.04	14.66	12.00	8.10	5.41	4.20	2.74
			2	0	9.11	12.57	15.26	16.31	14.57	12.41	8.64	5.00	3.96	2.61
			3	0	9.05	12.84	15.99	15.85	14.92	12.93	8.23	5.63	4.12	2.03
3	1	1	1	0	9.11	12.63	15.67	15.63	14.43	12.29	8.00	5.70	4.25	2.04
			2	0	8.87	13.00	15.85	15.75	14.96	12.83	8.11	5.36	4.15	2.23
			3	0	9.26	13.00	15.32	15.54	14.30	12.20	8.69	5.07	4.47	2.67
	1	2	1	0	8.90	12.72	15.20	15.51	14.85	12.68	8.18	5.70	3.79	2.28
			2	0	9.33	12.56	15.31	15.54	14.01	12.51	8.18	5.68	4.04	2.08

			3	0	9.30	12.55	15.74	16.37	14.95	12.74	8.00	5.88	3.92	2.63
	2	1	1	0	8.80	12.83	15.96	16.47	14.87	12.26	8.37	5.21	4.31	2.31
			2	0	8.66	12.86	15.18	16.38	14.12	12.50	8.12	5.19	4.42	2.94
			3	0	8.61	12.64	15.08	16.17	14.52	12.78	8.87	5.00	3.97	2.66
	2	2	1	0	8.76	12.67	15.13	16.01	14.04	12.33	8.37	5.12	4.49	2.69
			2	0	8.86	12.83	15.81	16.32	14.66	12.46	8.43	5.94	3.50	2.62
			3	0	9.11	12.76	15.88	16.09	14.77	12.79	8.69	5.37	3.75	2.87
4	1	1	1	0	8.82	12.95	15.51	16.43	14.70	12.51	8.24	5.63	4.15	2.08
			2	0	8.50	12.97	15.15	16.09	14.89	12.22	8.59	5.74	4.05	2.99
			3	0	9.05	12.55	15.09	16.40	14.65	12.94	8.25	5.41	4.31	2.59
	1	2	1	0	9.18	12.95	15.02	16.42	14.11	12.92	8.90	5.09	4.25	2.65
			2	0	9.11	12.70	15.22	15.85	14.97	12.02	8.97	5.27	3.77	2.68
			3	0	9.24	12.58	15.78	16.02	14.61	12.12	8.71	5.45	3.51	2.78
	2	1	1	0	8.64	12.79	15.88	16.03	14.85	12.99	8.22	5.08	4.32	2.96
			2	0	8.61	12.55	15.18	16.14	14.49	12.81	8.55	5.84	4.46	2.20
			3	0	9.27	12.96	15.03	16.19	14.35	12.27	8.30	5.63	3.76	2.19
	2	2	1	0	9.42	12.99	15.12	15.60	14.95	12.88	8.66	5.30	3.51	2.89
			2	0	8.90	12.79	15.76	15.98	14.21	12.48	8.44	5.59	3.84	2.10
			3	0	8.74	12.71	15.29	16.49	14.82	12.47	8.12	5.37	4.47	2.11
5	1	1	1	0	8.98	12.81	15.23	16.42	14.42	12.13	8.51	5.72	4.41	2.98
			2	0	8.65	12.71	15.79	15.59	14.64	12.20	8.97	5.58	3.97	2.79
			3	0	8.77	12.57	15.25	15.78	14.94	12.57	8.06	5.31	3.61	2.62
	1	2	1	0	9.24	12.95	15.19	16.21	14.76	12.38	8.93	5.56	3.66	2.12
			2	0	8.61	12.78	15.57	16.47	14.12	12.03	8.72	5.42	4.16	2.16
			3	0	8.72	12.76	15.52	16.34	14.27	12.09	8.21	5.87	4.24	2.98
	2	1	1	0	9.33	12.62	15.26	15.54	14.34	12.68	8.26	5.22	3.65	2.91
			2	0	8.58	12.70	15.48	16.05	14.27	12.01	8.50	5.71	3.61	2.32
			3	0	8.96	12.71	15.76	15.92	14.35	12.19	8.60	5.99	3.72	2.62
	2	2	1	0	9.02	12.71	15.08	15.65	14.02	12.99	8.90	5.09	3.79	2.40
			2	0	8.77	12.91	15.15	16.46	14.34	12.72	8.16	5.28	4.10	2.88
			3	0	9.12	12.83	15.46	15.51	14.17	12.15	8.75	5.83	4.37	2.15
6	1	1	1	0	8.55	12.70	15.03	16.37	14.21	12.48	8.07	5.18	3.93	2.10
			2	0	9.43	12.57	15.60	16.43	14.24	12.40	8.47	5.28	4.33	2.66

			3	0	8.66	12.74	15.24	16.06	14.06	12.32	8.88	5.81	3.58	2.06
	1	2	1	0	8.69	12.66	15.55	15.59	14.41	12.73	8.09	5.69	4.28	2.94
			2	0	9.15	12.76	15.85	16.16	14.90	12.92	8.13	5.69	3.57	2.99
			3	0	8.91	12.66	15.33	16.35	14.48	12.17	8.36	5.82	3.51	2.25
	2	1	1	0	8.93	12.76	15.44	16.24	14.01	12.09	8.02	5.83	4.41	2.44
			2	0	9.05	12.98	15.78	15.72	14.58	12.95	8.80	5.70	4.22	2.06
			3	0	8.90	12.90	15.16	15.95	14.12	12.53	8.09	5.36	4.50	2.17
	2	2	1	0	8.75	12.87	16.00	16.23	14.93	12.52	8.51	5.68	3.77	2.27
			2	0	8.76	12.75	15.97	16.38	14.88	12.92	8.02	5.64	3.77	2.26
			3	0	9.09	12.95	15.86	15.78	14.54	12.05	8.94	5.68	4.25	2.64
7	1	1	1	0	9.45	12.89	15.56	15.69	14.54	12.80	9.00	5.69	4.15	2.54
			2	0	9.28	12.50	15.70	15.81	14.83	12.38	8.90	5.24	3.94	2.61
			3	0	9.01	12.56	15.69	16.04	14.16	12.68	8.76	5.94	4.20	2.80
	1	2	1	0	8.87	12.76	15.54	15.61	14.93	12.92	8.54	5.48	3.83	2.98
			2	0	8.84	12.88	15.92	15.64	14.88	12.83	8.26	5.81	3.76	2.76
			3	0	8.59	12.72	15.28	16.02	14.83	12.03	8.20	5.39	4.34	2.00
	2	1	1	0	9.33	12.54	15.96	16.44	14.86	12.96	8.95	5.90	4.27	2.30
			2	0	9.02	12.51	15.61	15.72	14.18	12.47	8.53	5.24	4.10	2.93
			3	0	8.79	12.52	15.47	15.90	14.02	12.04	8.14	5.09	4.33	2.25
	2	2	1	0	8.95	12.95	15.20	15.68	14.44	12.46	8.11	5.77	3.50	2.00
			2	0	9.33	12.59	15.03	16.28	14.12	12.66	8.79	5.27	3.78	2.24
			3	0	9.50	12.81	15.70	16.47	14.69	12.65	8.91	5.74	4.26	2.33
8	1	1	1	0	9.44	12.90	15.02	15.57	14.01	12.61	8.78	5.79	4.23	2.07
			2	0	8.98	12.96	15.93	15.76	14.97	12.66	8.60	5.40	4.08	2.90
			3	0	9.12	12.77	15.83	15.66	14.77	12.57	8.84	5.02	3.76	2.35
	1	2	1	0	9.34	12.58	15.11	16.27	14.97	12.21	8.05	5.39	3.85	2.09
			2	0	9.36	12.67	15.26	15.95	14.45	12.81	8.24	5.66	4.49	2.44
			3	0	8.64	12.67	15.05	16.44	14.18	12.36	8.22	5.11	3.57	2.31
	2	1	1	0	8.69	12.96	15.49	16.22	14.85	12.63	8.64	5.88	4.43	2.98
			2	0	9.06	12.84	15.10	16.27	14.04	12.34	8.78	5.63	3.94	2.05
			3	0	8.55	12.74	15.61	15.66	14.10	12.94	8.08	5.61	3.67	2.48
	2	2	1	0	8.54	12.83	15.04	16.45	14.71	12.56	8.73	5.21	4.45	2.79
			2	0	9.15	12.66	15.86	15.52	14.55	12.43	8.16	5.59	4.26	2.52

			3	0	8.60	12.87	15.60	16.24	15.00	12.42	8.23	5.03	4.33	2.90
9	1	1	1	0	9.09	12.98	15.43	16.27	14.44	12.23	8.15	5.14	4.50	2.79
			2	0	8.93	12.82	15.22	15.80	14.84	12.10	8.92	6.00	3.86	2.09
			3	0	8.56	12.77	15.76	16.41	14.44	12.74	8.83	5.21	4.09	2.88
	1	2	1	0	8.79	12.71	15.13	16.22	14.87	12.50	8.30	5.52	3.72	2.06
			2	0	9.10	12.64	15.60	15.51	14.08	12.34	8.78	5.85	4.12	2.02
			3	0	8.91	12.82	15.74	15.62	14.91	12.04	8.36	5.22	4.27	2.88
	2	1	1	0	9.05	12.64	15.16	15.79	14.80	12.28	8.98	5.35	3.96	2.04
			2	0	8.54	12.61	15.94	16.19	14.78	12.38	8.02	5.95	4.01	2.62
			3	0	9.27	12.96	15.15	15.52	14.56	12.64	8.31	5.87	3.87	2.53
	2	2	1	0	9.21	12.96	15.74	16.33	14.38	13.00	8.44	5.42	3.62	3.00
			2	0	8.71	12.79	15.70	16.46	14.74	12.18	9.00	5.95	4.09	2.32
			3	0	9.43	12.54	15.10	16.10	14.34	12.82	8.11	5.92	3.92	2.85
10	1	1	1	0	9.29	12.84	15.06	15.50	14.84	12.76	8.69	5.77	3.50	2.63
			2	0	9.07	12.89	15.31	16.46	14.94	12.38	8.06	5.13	4.36	2.03
			3	0	9.21	12.50	15.34	15.74	14.03	12.05	8.31	5.86	3.56	2.31
	1	2	1	0	9.26	12.86	15.06	15.91	14.08	13.00	8.21	5.91	4.39	2.62
			2	0	8.64	12.70	15.82	16.24	14.27	12.90	8.41	5.48	4.30	2.16
			3	0	9.35	12.89	15.00	16.34	14.12	12.30	8.91	5.34	4.46	2.06
	2	1	1	0	9.15	12.88	15.13	16.07	14.53	12.51	8.48	5.36	4.44	2.37
			2	0	8.84	12.96	15.53	15.78	14.85	12.57	8.34	5.88	3.69	2.91
			3	0	9.02	12.98	15.47	15.97	14.97	12.84	8.12	5.10	3.72	2.77
	2	2	1	0	8.55	12.77	15.80	16.19	14.39	12.89	8.52	5.12	3.78	2.08
			2	0	8.63	12.78	15.89	16.24	14.65	12.27	8.48	5.03	3.96	2.49
			3	0	8.81	12.67	15.56	15.78	15.00	12.15	8.41	5.71	4.01	2.22
11	1	1	1	0	8.66	12.87	15.82	15.70	14.37	12.83	8.28	5.45	4.36	2.08
			2	0	8.54	12.63	16.00	15.98	14.81	12.55	8.13	5.85	3.60	2.20
			3	0	9.16	12.65	15.80	15.74	14.20	12.01	8.32	5.00	3.89	2.36
	1	2	1	0	9.21	12.50	15.99	15.93	14.60	12.59	8.61	5.40	3.85	2.16
			2	0	8.52	12.85	15.16	15.67	14.79	12.65	8.29	5.31	4.44	2.08
			3	0	8.97	12.68	15.69	16.09	14.73	12.69	8.68	5.43	4.14	2.01
	2	1	1	0	9.24	12.61	15.47	16.08	14.36	12.26	8.42	5.94	3.95	2.58
			2	0	8.55	12.97	15.64	15.72	14.21	12.07	8.89	5.71	3.74	2.83

			3	0	8.50	12.76	15.44	15.61	14.20	12.85	8.11	5.14	4.24	2.25
	2	2	1	0	9.31	12.52	15.13	16.32	14.75	12.17	8.91	5.62	3.90	2.89
			2	0	8.64	12.70	15.41	16.15	14.52	12.56	8.31	5.67	3.55	2.51
			3	0	9.28	12.69	15.35	15.58	14.02	13.00	8.16	5.77	3.86	2.05
12	1	1	1	0	9.22	12.67	15.87	15.72	14.11	12.88	8.11	5.03	3.63	2.97
			2	0	9.45	12.72	15.14	16.28	14.02	12.54	8.15	5.31	3.69	2.60
			3	0	9.09	12.72	15.66	15.50	14.29	12.67	8.56	5.40	3.50	2.17
	1	2	1	0	9.44	12.74	15.31	15.57	14.61	12.16	8.90	5.14	4.24	2.31
			2	0	9.17	12.98	15.54	15.63	14.77	12.67	8.09	5.38	3.71	2.57
			3	0	8.65	12.62	15.42	16.12	14.07	12.03	8.16	5.84	3.92	2.95
	2	1	1	0	8.74	13.00	15.02	15.74	14.58	12.84	8.35	5.32	4.16	2.45
			2	0	8.70	12.94	15.55	15.87	14.33	12.97	8.88	5.27	4.19	2.43
			3	0	9.10	12.51	15.21	16.16	14.09	12.36	8.97	5.95	4.04	2.04
	2	2	1	0	9.46	12.66	15.53	15.51	14.98	12.28	8.55	5.28	4.03	2.25
			2	0	8.89	12.71	15.11	16.12	14.34	12.71	8.74	5.00	3.93	2.37
			3	0	8.95	12.75	15.94	16.50	14.14	12.03	8.25	5.25	4.08	2.54
13	1	1	1	0	9.47	12.82	15.70	16.28	14.13	12.29	8.12	5.18	4.44	2.81
			2	0	9.08	12.94	15.85	15.69	14.14	12.09	8.06	5.83	3.79	2.48
			3	0	9.50	12.54	15.02	16.12	14.87	12.47	8.90	5.99	3.70	2.33
	1	2	1	0	8.69	12.94	15.20	15.95	14.03	12.06	8.36	5.85	3.73	2.61
			2	0	9.39	12.61	15.28	16.29	14.31	12.95	8.91	5.67	3.77	2.45
			3	0	9.04	12.81	15.74	16.50	14.21	12.55	8.81	5.32	4.01	2.99
	2	1	1	0	9.46	12.92	15.32	15.58	14.97	12.81	8.03	5.66	4.21	2.85
			2	0	9.39	12.55	15.69	16.21	14.74	12.39	8.53	5.00	4.01	2.35
			3	0	9.16	12.58	15.78	15.68	14.64	12.27	8.04	5.18	4.18	2.43
	2	2	1	0	8.97	12.81	15.64	15.99	14.70	12.30	8.74	5.56	3.73	2.66
			2	0	9.30	12.76	15.77	15.77	14.21	12.50	8.85	5.06	4.07	2.96
			3	0	8.67	12.97	15.79	16.44	14.48	12.03	8.44	5.30	3.99	2.96

Table 4.8 The Coded CCD Design Format

Run	Factors	
	x_1	x_2
1	170.000	7.8000
2	190.000	7.8000
3	170.000	13.8000
4	190.000	13.8000
5	165.858	10.8000
6	194.142	10.8000
7	180.000	6.5574
8	180.000	15.0426
9	180.000	10.8000
10	180.000	10.8000
11	180.000	10.8000
12	180.000	10.8000
13	180.000	10.8000

scenarios are found using Mathematica; they are summarized in Table 4.10. According to the objective function values in Table 4.10, the optimal levels of excipients in the second scenario result in less quality loss. Based on the following two-sample *t*-test with unknown population variances, the ln*AUC* values in both scenarios are statistically equivalent with a p-value of 0.75 (greater than $\alpha = 0.05$).

H_0: $\ln\widehat{AUC}_T(\infty, \mathbf{x}^*)$ under Scenario 2.1 = $\ln\widehat{AUC}_T(\infty, \mathbf{x}^*)$ under Scenario 2.2

versus

H_1: $\ln\widehat{AUC}_T(\infty, \mathbf{x}^*)$ under Scenario 2.1 $\neq$ $\ln\widehat{AUC}_T(\infty, \mathbf{x}^*)$ under Scenario 2.2.

Hence, it can be concluded that the *AUC* is not particularly sensitive to the method used (discrete or continuous) during the estimation phase. However, the deviations of C_{max} and t_{max} between both scenarios are significant. There are two main reasons underlying causes. First, it is observed that in Scenario 2.1 (which uses the discrete method), C_{max} and t_{max} are sensitive to the time at which the observation is taken. The true C_{max} and t_{max} can be overlooked due to a long observation interval. Second, the major advantage of the

Table 4.9 Parameters and Responses Related to the Bioequivalence Study

Run	Reference			Test						$s_{in}^2(AUC)$	$s_{in}^2(C_{\max})$	$\hat{\sigma}(AUC)$	$\hat{\sigma}(C_{\max})$
	$\overline{\ln C_{\max R}}$	$t_{\max R}$	$\overline{\ln AUC_{0-\infty R}}$	$\overline{\ln C_{\max T}}$	$s^2(\ln C_{\max T})$	$t_{\max T}$	$s^2(t_{\max T})$	$\overline{\ln AUC_{0-\infty T}}$	$s^2(\ln AUC_{0-\infty T})$				
1	2.782151	2	4.741269	2.773065	0.000358	1.833333	0.066667	4.753819	0.001247	0.0005988	0.0000199	0.02261	0.003633
	2.744712	**1.893755**	**4.733302**	**2.739993**	**0.000231**	**1.887438**	**0.006731**	**4.74422**	**0.001134**				
2	2.783381	1.916667	4.750856	2.771314	0.000308	2	0	4.742571	0.000928	0.0004463	0.0001023	0.029875	0.014303
	2.734822	**1.862566**	**4.73917**	**2.749241**	**0.000167**	**1.924573**	**0.004165**	**4.73923**	**0.000779**				
3	2.767023	1.833333	4.745939	2.776852	0.000747	2	0	4.742459	0.000684	0.0002493	0.0004283	0.02233	0.029268
	2.740561	**1.88373**	**4.739395**	**2.737923**	**0.000227**	**1.897756**	**0.005612**	**4.734738**	**0.000461**				
4	2.782659	2	4.744578	2.779277	0.000142	2	0	4.75147	0.000565	0.0004735	0.0001656	0.030772	0.018198
	2.744083	**1.912908**	**4.736324**	**2.740232**	**0.000093**	**1.900239**	**0.006397**	**4.741138**	**0.000397**				
5	2.768252	1.916667	4.754009	2.777915	0.000433	2	0	4.742185	0.000796	0.0016708	0.0003927	0.056322	0.026031
	2.731869	**1.896427**	**4.744763**	**2.737605**	**0.000319**	**1.895376**	**0.005261**	**4.733489**	**0.000661**				
6	2.786269	1.916667	4.732484	2.773179	0.000332	1.916667	0.041667	4.744774	0.000832	0.0006898	0.0004163	0.037142	0.028854
	2.749011	**1.923233**	**4.726806**	**2.741245**	**0.000309**	**1.907178**	**0.00595**	**4.739313**	**0.000575**				
7	2.772103	2	4.745118	2.768383	0.000323	1.916667	0.041667	4.749261	0.001085	0.0016925	0.0005759	0.058181	0.033937
	2.753132	**1.953868**	**4.739915**	**2.739653**	**0.000421**	**1.903634**	**0.003714**	**4.741486**	**0.000757**				
8	2.771177	1.75	4.755942	2.780863	0.000309	2	0	4.734519	0.001545	0.0004325	0.0003790	0.029412	0.02753
	2.738077	**1.887436**	**4.746859**	**2.742229**	**0.000068**	**1.925901**	**0.002097**	**4.72888**	**0.001588**				
9	2.786663	2	4.76211	2.762604	0.000348	1.833333	0.066667	4.735141	0.000764	0.0005943	0.0001304	0.034477	0.016148
	2.741727	**1.887007**	**4.751459**	**2.740857**	**0.000228**	**1.926366**	**0.010238**	**4.727862**	**0.000626**				
10	2.771432	2	4.723731	2.775742	0.00017	2	0	4.748185	0.000414	0.0000107	0.0002820	0.004613	0.023277
	2.746066	**1.92329**	**4.716238**	**2.745198**	**0.000096**	**1.919142**	**0.004561**	**4.74271**	**0.000297**				
11	2.769029	1.75	4.728223	2.763722	0.000188	1.916667	0.041667	4.731403	0.000464	0.0002061	0.0001599	0.020302	0.017883
	2.744255	**1.928227**	**4.721642**	**2.74523**	**0.000199**	**1.944836**	**0.002282**	**4.726819**	**0.000351**				
12	2.771945	1.75	4.731515	2.762962	0.000245	2	0	4.741492	0.000273	0.0006430	0.0004033	0.03586	0.0284
	2.739869	**1.879108**	**4.721926**	**2.739748**	**0.000283**	**1.925679**	**0.007764**	**4.735026**	**0.000187**				
13	2.77716	1.916667	4.758695	2.775622	0.000459	1.916667	0.041667	4.752271	0.000605	0.0007606	0.0005001	0.039001	0.031625
	2.735566	**1.839498**	**4.747834**	**2.739958**	**0.000156**	**1.873638**	**0.004121**	**4.74353**	**0.000491**				

Table 4.10 Optimal Settings in Both Scenarios for Bioequivalence Assessment

Scenario	x_1^*	x_2^*	Objective value	$\ln AUC_R$	$\ln AUC_T$	$\ln C_{\max R}$	$\ln C_{\max T}$	$t_{\max R}$	$t_{\max T}$
2.1	184.05	10.31	0.066	4.738	4.742	2.779	2.765	1.892	1.935
2.2	177.80	8.06	0.025	4.730	4.738	2.748	2.735	1.921	1.919

continuous method over the discrete one is the complete smoothness of the fitted curve. Theoretically, the existence of experimental errors will result in the discontinuity of data. Since errors are experimentally inevitable, it is believed that the continuous method may become less effective. Also, the estimation of K, K_e and K_a in Scenario 2.2 only utilizes the concentration data at the later time intervals, which potentially causes biases in these regression coefficients and consequently in the estimated characteristics. Furthermore, the values of x_1^* and x_2^* in Scenario 2.1 are greater than those in Scenario 2.2, which potentially results in more input material costs.

Table 4.11 Comparisons of Scenarios 2.1 and 2.2

Scenario	CI		Variance			$t_{\max T}/t_{\max R}$
	ratio of AUC	ratio of $C_{\max}$	AUC_T	$C_{\max T}$	$t_{\max T}$	
2.1	[99.65%, 100.50%]	[98.33%, 100.70%]	0.000	0.013	0.050	102.3%
2.2	[99.46%, 100.88%]	[98.50%, 100.50%]	0.012	0.000	0.013	99.86%

Additionally, Table 4.11 compares the bioavailability characteristics for the test and reference formulations within both scenarios and presents the related variances for the test formulation. Based on Table 4.11, the CIs for the ratios of AUC and $C_{\max}$ stay strictly within the regulatory limit [80%, 125%] in both scenarios. Further, the $t_{\max}$ for the test formulation in the second scenario is much closer to the reference value than that in the first. Finally, characteristic variances for the test formulation in both scenarios are close to zero. Note that the summation of these variances in Scenario 2.2 is even less than that in Scenario 2.1. Figure 4.2 illustrates the response surfaces of the objective functions in both scenarios. The contour plots depicting the effect of x_1 and x_2 on the objective functions in the two scenarios are presented in Figure 4.3.

In summary, the continuous computational method generally works better for this formulation optimization problem. It turns out that the continuous method is superior in assessing C_{max} and t_{max}, since it results in (1) a smaller CI for the ratio of C_{max}, (2) a smaller deviation of t_{max}, and (3) smaller variances of C_{max} and t_{max} for the test formulation. By comparison, the discrete method produces a smaller CI for the ratio of *AUC* and a reduced *AUC* variance for the test formulation. Additionally, the optimal input factor amounts are less in Scenario 2.2 (which uses the continuous method), leading to lower input costs.

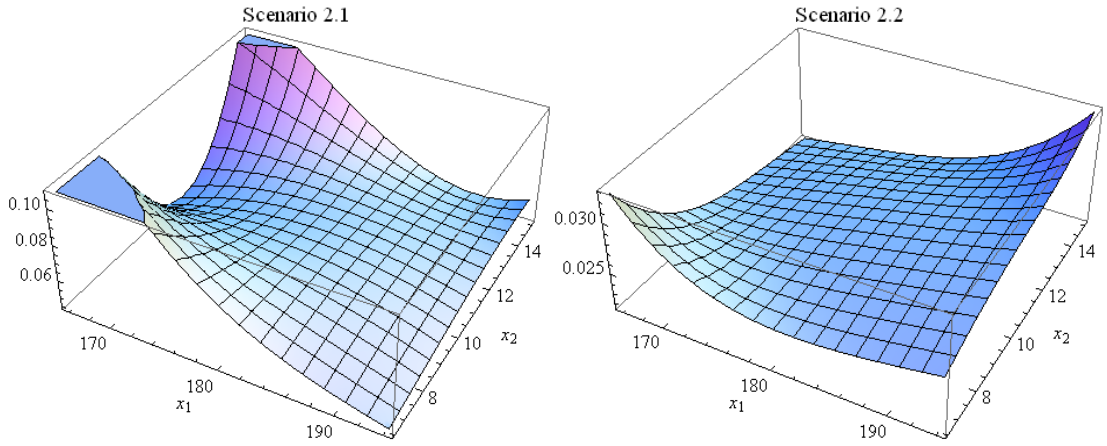

Figure 4.2 Response Surface Plots of the Two Scenarios

4.5 Sensitivity Analysis

As presented in the previous section, the proposed approach in Scenario 2.2 is not preferred for evaluating *AUC*. In order to validate this result, a sensitivity analysis of the constraint boundary to the optimal ingredient amounts is performed by varying η_{L1} from 9.7 to 10.1 with an increment of 0.2. The results are provided in Table 4.12. The same

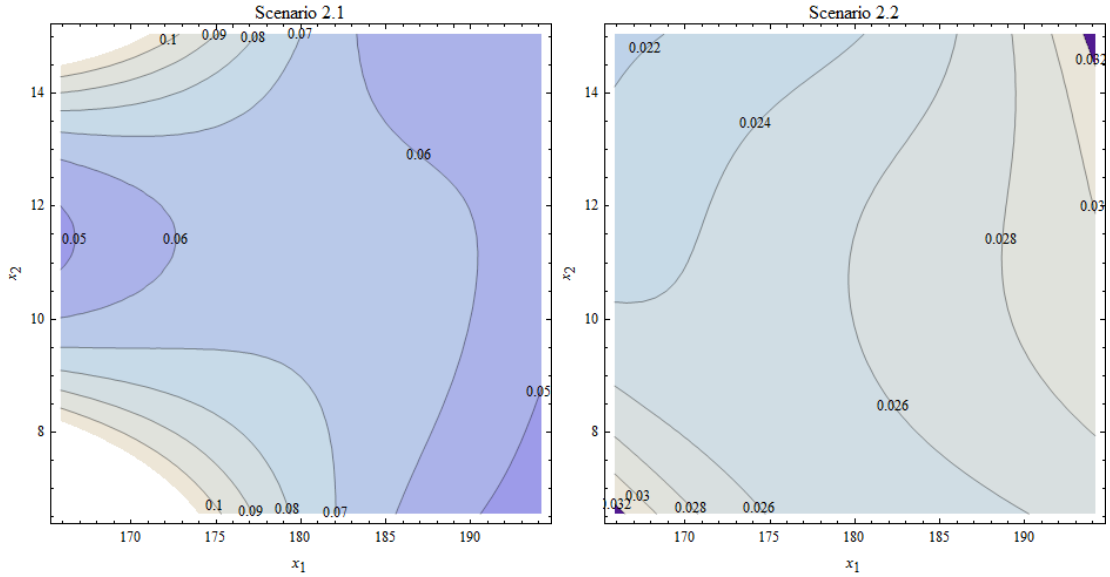

Figure 4.3 Contour Plots of x_1 and x_2 for the Bioequivalence Studies Problem

Table 4.12 Sensitivity Analysis for the Bioequivalence Studies Problem

η_{L1}	Scenario	(x_1^*, x_2^*)	CI		Variance			$t_{\max T}/t_{\max R}$
			ratio of AUC	ratio of $C_{\max}$	AUC_T	$C_{\max T}$	$t_{\max T}$	
9.7	2.1	(184.06, 10.28)	[99.65%, 100.50%]	[98.32%, 100.70%]	0.000	0.013	0.050	102.24%
	2.2	(177.80, 8.26)	[99.49%, 100.85%]	[98.50%, 100.53%]	0.012	0.000	0.013	99.98%
9.9	2.1	(184.05, 10.32)	[99.65%, 100.50%]	[98.33%, 100.70%]	0.000	0.013	0.050	102.31%
	2.2	(177.80, 8.77)	[99.55%, 100.79%]	[98.49%, 100.59%]	0.011	0.000	0.013	100.26%
10.1	2.1	(184.00, 10.45)	[99.66%, 100.49%]	[98.34%, 100.71%]	0.000	0.013	0.050	102.42%
	2.2	(177.80, 9.33)	[99.61%, 100.72%]	[98.48%, 100.66%]	0.011	0.000	0.013	100.53%

conclusion as that in Section 4.4 can be reached. That is, the discrete computational method works better for assessing *AUC*, while the continuous method results in lower input costs and more desirable performance related to C_{max} and t_{max}.

4.6 Conclusion and Future Study

In this chapter, we propose an experimental design integrating *in vivo* bioequivalence studies and the formulation optimization procedure in order to seek the optimal levels of excipients that ensure bioequivalence between formulations when Level 3 excipient changes are detected. Two bioequivalence assessment methods, designated as continuous and discrete, are developed for this research. Furthermore, a numerical example shows that the continuous methodology generally performs better than the discrete one.

Finally, recall that if IVIVC is not established, then an *in vivo* bioequivalence study is mandated; otherwise, a dissolution test may serve as the surrogate for this comparatively expensive study. While the former was the subject of this chapter, the latter has yet to be considered (to the same extent). The motivation for a future investigation of the dissolution test is identical to that of the current study. That is, the objective would be to determine a test formulation whose performance is deemed equivalent to that of the reference drug, while at the same time minimizing the associated costs.

CHAPTER 5

QUALITY BY DESIGN STUDIES ON MULTI-RESPONSE PHARMACEUTICAL FORMULATION MODELING AND OPTIMIZATION

5.1 Introduction

Pharmaceutical formulation is the process that combines active and inactive ingredients to produce a final drug product. Formulation designers seek optimal ingredient amounts in order to maximize the clinical benefit of ingredients. Beyond its significant role in drug delivery, formulation optimization has gained increasing attention over the years because of the desirable benefits of building drug quality in early design phases, in contrast to the traditional quality control philosophy of inspecting finished products (FDA, 2006b).

It is widely acknowledged that the formulation optimization can be implemented by the use of a combination of analytical approaches, such as DOE, RSM, and optimization (Holm *et al.*, 2006; Huang *et al.*, 2009; Rosas *et al.*, 2011). DOE combined with RSM permits the mathematical modeling of a QC associated with the clinical benefit, such as friability, hardness, thickness, and dissolution performance, as a function of the ingredient amounts. Based upon the established response surface function, optimization techniques are then utilized to determine optimal settings of the ingredients so that the desirable performance of the characteristic can be achieved. In practice, during the formulation optimization, designers are usually faced with multiple pharmaceutical QCs, namely an MRS problem. In this case, it is difficult to determine the optimal factor

settings for all the responses, because (1) these characteristics may have different scales of measurement and different types of optimality, and (2) as one characteristic is optimized, it is usually at the expense of one or more others (Derringer, 1994; Xu *et al.*, 2004). Therefore, it is necessary to develop an optimization model for pharmaceutical formulation that simultaneously considers multiple characteristics in order to find the best compromise among them.

Despite the existing research efforts on solving an MRS optimization problem for formulation optimization, there remain several issues which have not been comprehensively studied in the literature. First, in addition to the response mean, formulation researchers need to take into account the variance, since individual subjects may differ widely in their responses to a drug and variability may potentially lead to safety and efficacy issues. The correlation between responses is frequently overlooked when multiple QCs are evaluated. For instance, the optimization of the dissolution profile is a usual routine for developing a new formulation, where the associated responses, including the amounts dissolved at multiple points in time, are believed to be correlated over time. Their covariance is most likely to influence the dissolution performance over time; hence, additional response variables regarding the variance and covariance are considered in our proposed model. Second, one of the most popular methods for solving MRS problems is the DF approach, originally developed by Harrington (1965) and later improved by Derringer and Suich (1980). In this chapter, the conventional DF method is modified and incorporated into the formulation optimization as enhanced *empirical* and *mechanistic* DF approaches. Third, the commonly-used RSM, which calls for fitting the

response desirability or response variable to a first- or second-order polynomial regression function to predict the response surface, may be less effective for estimation than a higher-order model (Shaibu & Cho, 2009). Since the precision in the model fit heavily influences the effectiveness in finding optimal factor settings, the solution resulting from the traditional low-order response surface functions may be less accurate. In order to improve the accuracy of the estimated response surface, we propose the use of higher-order (up to fourth order) models, incorporating the best subsets regression method. Finally, despite the fact that the weight-based overall DF is extensively treated as an objective function for simultaneously optimizing multiple QCs, there are potential shortcomings, which include the high sensitivity of the optimal solution resulting from the weights assigned and the subjectivity in determining the weights of subjects. A priority-based optimization scheme that is based upon a priority, rather than a numerical weight for each individual characteristic, can be a more effective alternative. Since goal programming is one of the most popular approaches to finding good solutions to a multi-objective problem (Rardin, 1998), a priority-based goal programming model is proposed to optimize individual desirability of the multiple characteristics with the purpose of determining the best formulation.

The rest of this chapter is organized as follows. Section 5.2 provides modified DFs as a basis of the proposed DF methods. The development of the proposed multi-response formulation optimization model, integrated with two modified DF methods and the well-investigated goal programming technique, is given in Section 5.3. A numerical example to demonstrate the effectiveness of the proposed model in optimizing a

dissolution profile and comparative conclusions are presented in Sections 5.4 and 5.5, respectively.

5.2 Analysis of DF

In the literature, researchers proposed various scientific techniques for solving MRS problems in the past thirty years. The usage of Taguchi's method (1986) for designing robust products or processes prevailed among earlier research work. Pignatiello (1993), Elsayed and Chen (1993), Vining (1998), and Ko *et al*. (2005) employed the Taguchi quality loss function approach to determine the optimal settings of input factors for products with multiple QCs. Some extensions to Taguchi's method were also made by researchers such as Chen (1997), Wu (2002), Fung and Kang (2005), and Kovach and Cho (2008). In practice, in addition to the approaches mentioned above, some formulation scientists applied the DF method to formulation optimization for optimizing multiple characteristics simultaneously (Abu-Izza *et al.*, 1996; Paterakis *et al.*, 2002; Rosas *et al.*, 2011).

The DF technique is useful to convert multiple characteristics with different units of measurement into a single commensurable objective by means of normalizing each estimated response variable to individual desirability. Its value varies between 0 and 1, and the response becomes desirable as its desirability approaches 1. Derringer (1994) also suggested using a weighted geometric mean function to convert multiple individual desirability into a single measure of characteristic performance known as the overall desirability, *D*. Hence, when applying the DF approach to formulation optimization, the

overall DF value is always maximized so that the optimal settings of the ingredient amounts can ensure the best compromise among multiple characteristics of interest (Wang *et al.*, 1996; Ficarra *et al.*, 2002; Candioti *et al.*, 2006; Holm *et al.*, 2006; Zidan *et al.*, 2007; Li *et al.*, 2011). Adopting this traditional approach, the estimated DF can be obtained by fitting polynomial regression functions of **x** to the calculated desirability for the responses. As a result, one may estimate the desirability for the formulation determined by the *h* responses which in turn are at the same time determined by the *k* factors.

Furthermore, several innovative attempts have been made to improve the traditional DF approach. Del Castillo et al. (1996) proposed a differentiable DF method which allowed researchers to use more efficient gradient-based optimization methods for maximizing the overall desirability. Wu and Hamada (2000) suggested using the double-exponential function as an alternative DF, and Wu (2004) extended the double exponential DF based on the Taguchi's loss function in order to optimize correlated multiple QCs. Moreover, Bashiri and Salmasnia (2009) and Goethals and Cho (2011) also presented new optimization procedures based on the DF method for correlated characteristics. However, several researchers also revealed some shortcomings of the DF approach. Takayama *et al*. (1999) argued that one of the weaknesses of DF was the subjectivity associated with the selection of an acceptable interval for each response. Kim and Lin (2000) pointed out that it was difficult to assign meaning to a DF value, beyond the basic principle that a higher value of desirability is preferred.

In this chapter, we propose a modified DF which allows the formulation designer to incorporate correlations between QCs. Suppose that h QCs of interest concerning the mean, variance, and covariance, denoted by $\hat{\pi}_\omega$ for $\omega = 1, 2, \ldots, h$, are determined by a set of k factors, $\mathbf{x} = [x_1, x_2, \ldots, x_k]'$. Referring to Equations (2.9) and (2.10), if the ω^{th} response is a LTB or STB characteristic, the individual desirability is computed by the transformation

$$d(\hat{\pi}_\omega) = \begin{cases} 0 & \hat{\pi}_\omega < L_\omega \\ \left[\dfrac{\hat{\pi}_\omega - L_\omega}{T_\omega - L_\omega}\right]^{\rho_\omega} & L_\omega \le \hat{\pi}_\omega \le T_\omega \\ 1 & \hat{\pi}_\omega > T_\omega \end{cases} \quad \text{or} \quad d(\hat{\pi}_\omega) = \begin{cases} 1 & \hat{\pi}_\omega < T_\omega \\ \left[\dfrac{U_\omega - \hat{\pi}_\omega}{U_\omega - T_\omega}\right]^{\rho_\omega} & T_\omega \le \hat{\pi}_\omega \le U_\omega \\ 0 & \hat{\pi}_\omega > U_\omega \end{cases}, \quad (5.1)$$

where L_ω and U_ω respectively represent acceptable minimum and maximum values, T_ω is an allowable maximum or minimum value for the LTB or STB response, and ρ_ω is the shape parameter for the DF. ρ_ω is determined by the importance of hitting the value T_ω. If $\hat{\pi}_\omega$ is a NTB response, its individual desirability is given by the transformation

$$d(\hat{\pi}_\omega) = \begin{cases} 0 & \hat{\pi}_\omega < L_\omega \\ \left[\dfrac{\hat{\pi}_\omega - L_\omega}{T_\omega - L_\omega}\right]^{\rho_{\omega 1}} & L_\omega \le \hat{\pi}_\omega \le T_\omega \\ \left[\dfrac{U_\omega - \hat{\pi}_\omega}{U_\omega - T_\omega}\right]^{\rho_{\omega 2}} & T_\omega \le \hat{\pi}_\omega \le U_\omega \\ 0 & \hat{\pi}_\omega > U_\omega \end{cases}, \quad (5.2)$$

where T_ω is the target value, and the shape parameters are denoted by $\rho_{\omega 1}$ and $\rho_{\omega 2}$. Based upon Equation (2.11), let W_ω ($\omega = 1, 2, \ldots, h$) be the predefined weight for the π_ω; then, D can be expressed as

$$D = \left\{ \prod_{\omega=1}^{h} \left[d\left(\hat{\pi}_{\omega}\right) \right]^{W_{\omega}} \right\}^{1/\sum_{\omega=1}^{h} W_{\omega}} . \quad (5.3)$$

This modified DF will be the basis of the proposed mechanistic and empirical DF models developed in the next section.

5.3 Proposed Model Development

Figure 5.1 illustrates the phases of model development. During the first phase, DOE is performed based upon the prior knowledge of the factors, responses, and experimental space of interest. The second phase, which incorporates higher-order polynomial functions, least squares regression, and best subsets model selection method, is designed to obtain estimated DFs by proposing two separate DF methods- mechanistic and empirical. First, we develop the estimated mechanistic DF, which employs the piecewise form of the traditional DF method utilizing the higher-order estimated response surface function for each response variable. Second, we propose the use of least squares method to develop estimated empirical DFs that take the higher-order polynomial form for evaluating the response variance and covariance in addition to the mean. Finally, by means of incorporating goal programming techniques and related constraints into the optimization procedure, the optimal settings of ingredient amounts that minimize the deviations of responses from their respective goals can be determined. Each phase is discussed in greater detail in the following sections.

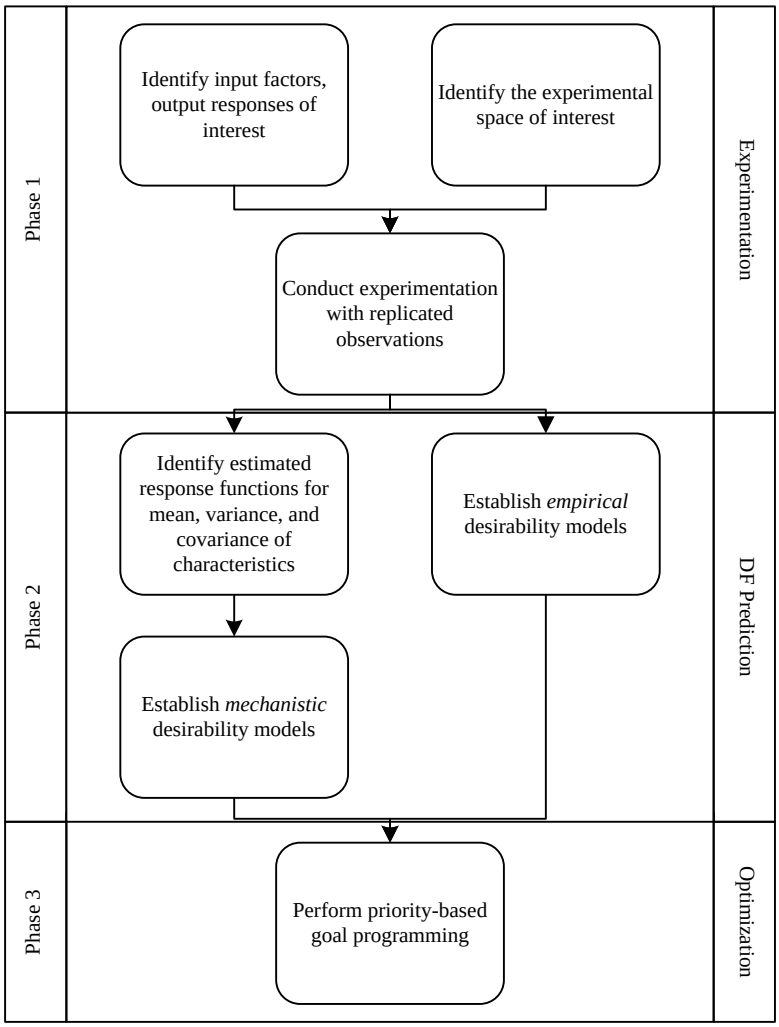

Figure 5.1 Development of Proposed Optimization Scheme

5.3.1 Experimentation Phase

In this chapter, the ingredient amounts, **x**, are chosen as input factors, and the QCs of interest, **y**, are the amounts or percentages dissolved at multiple points in time. Since the dissolution data are classified as time series data, the responses are correlated over time; the behavior of the covariance between responses is considered in the proposed

model. Commonly, factorial designs, CCDs, and mixture designs with replications can be performed in order to evaluate the response surfaces of related characteristics in terms of the mean, variance, and covariance. Let y_{ijs} be the j^{th} (j = 1, 2, …, m) observation for the i^{th} (i = 1, 2, ..., n) characteristic (i.e., i^{th} point in time) on the s^{th} (s = 1, 2, …, r) experimental run, then the mean and variance of the i^{th} response as well as the covariance between the w^{th} and g^{th} ($1 \le w < g \le n$) responses on the s^{th} run are respectively given by

$$\hat{\mu}_{is} = \frac{1}{m}\sum_{j=1}^{m} y_{ijs},\ \sigma_{is}^2 = \frac{1}{m-1}\sum_{j=1}^{m}\left(y_{ijs} - \hat{\mu}_{is}\right)^2, \text{ and } \sigma_{wg,s}^2 = \frac{1}{m-1}\sum_{j=1}^{m}\left(y_{wjs} - \hat{\mu}_{ws}\right)\left(y_{gjs} - \hat{\mu}_{gs}\right).$$

It should be mentioned that (1) since a small response variance is always desired, we consider $\widehat{\sigma_{is}^2}$ to be a STB characteristic, and (2) it is also reasonable to treat $\widehat{\sigma_{wg,s}^2}$ as a NTB characteristic since the covariance to be optimized should be close to its target value. A general experimental format with r runs and m replications for each run is provided in Table 5.1, where $\mathbb{X}$ is the factor settings for k factors. It can be easily shown that the total number of response variables, h, is equal to $2n + {}_nC_2$.

Table 5.1 A General Experimental Format

Run	Factors (**x**)	y_1	$\hat{\mu}_1$	$\widehat{\sigma_1^2}$	...	y_n	$\hat{\mu}_n$	$\widehat{\sigma_n^2}$	...	$\widehat{\sigma_{12}^2}$	...	$\widehat{\sigma_{(n-1)n}^2}$
1	Input factor settings ($\mathbb{X}$)	$y_{111} \cdots y_{1m1}$	$\hat{\mu}_{11}$	$\widehat{\sigma_{11}^2}$	…	$y_{n11} \cdots y_{nm1}$	$\hat{\mu}_{n1}$	$\widehat{\sigma_{n1}^2}$	…	$\widehat{\sigma_{12,1}^2}$	...	$\widehat{\sigma_{(n-1)n,1}^2}$
2		$y_{112} \cdots y_{1m2}$	$\hat{\mu}_{12}$	$\widehat{\sigma_{12}^2}$	…	$y_{n12} \cdots y_{nm2}$	$\hat{\mu}_{n2}$	$\widehat{\sigma_{n2}^2}$	…	$\widehat{\sigma_{12,2}^2}$	...	$\widehat{\sigma_{(n-1)n,2}^2}$
⋮		⋮	⋮	⋮	…	⋮	⋮	⋮	…	⋮	...	⋮
s		$y_{11s} \cdots y_{1ms}$	$\hat{\mu}_{1s}$	$\widehat{\sigma_{1s}^2}$	…	$y_{n1s} \cdots y_{nms}$	$\hat{\mu}_{ns}$	$\widehat{\sigma_{ns}^2}$	…	$\widehat{\sigma_{12,s}^2}$	...	$\widehat{\sigma_{(n-1)n,s}^2}$
⋮		⋮	⋮	⋮	…	⋮	⋮	⋮	…	⋮	...	⋮
r		$y_{11r} \cdots y_{1mr}$	$\hat{\mu}_{1r}$	$\widehat{\sigma_{1r}^2}$	…	$y_{n1r} \cdots y_{nmr}$	$\hat{\mu}_{nr}$	$\widehat{\sigma_{nr}^2}$	…	$\widehat{\sigma_{12,r}^2}$	...	$\widehat{\sigma_{(n-1)n,r}^2}$

5.3.2 DF Prediction Phase

As discussed earlier, the traditional DF is implemented by plugging the response mean into Equations (5.1) – (5.3). Alternatively, the mechanistic model can be established by utilizing the estimated response surface function based upon the underlying mechanism of the DF approach. Moreover, the empirical desirability model can be developed by modifying the traditional method, which employs the variance, covariance, and mean of the individual desirability for m observations on each of the experimental runs. The use of higher-order regression functions is proposed for modeling the responses and desirability; then, the best subsets model selection method is extended to identify the estimated functions that most precisely approximate both the proposed mechanistic and empirical desirability. Hereafter, we use the subscripts M and E to differentiate their related terms.

5.3.2.1 Proposed Mechanistic Desiraiblity Model

In order to obtain the estimated mechanistic DFs, ordinary least squares regression techniques are initially utilized to develop the estimated response surface functions in terms of the mean, variance, and covariance. Hereafter, a regression function with ψ parameters or $\psi - 1$ predictor variables is considered a full model; correspondingly, a reduced model is regarded as a regrssion function containing less than $\psi - 1$ predictors. Let $\hat{\mu}_i(\mathbf{x})$ and $\widehat{\sigma_i^2}(\mathbf{x})$ be the higher-order (up to fourth-order) regression functions for the mean and variance of the i^{th} ($i = 1, 2, \ldots, h$) response, respectively. Their full models can be expressed by the following equations:

$$\hat{\mu}_i(\mathbf{x}) = \left[1\ x_1\ \ldots\ x_1x_2\ \ldots\ x_1^2\ \ldots\ x_1^2x_2\ \ldots\ x_1^3\ \ldots\ x_1^3x_2\ \ldots\ x_1^4\ \ldots\ x_k^4\right] \times \left(\mathbf{X}_F^T\mathbf{X}_F\right)^{-1}\mathbf{X}_F^T\mathbf{Y}_i \quad (5.4)$$

and

$$\sigma_i^2(\mathbf{x}) = \left[1\ x_1\ \ldots\ x_1x_2\ \ldots\ x_1^2\ \ldots\ x_1^2x_2\ \ldots\ x_1^3\ \ldots\ x_1^3x_2\ \ldots\ x_1^4\ \ldots\ x_k^4\right] \times \left(\mathbf{X}_F^T\mathbf{X}_F\right)^{-1}\mathbf{X}_F^T\boldsymbol{\Sigma}_i, \quad (5.5)$$

where $\mathbf{Y}_i = [\hat{\mu}_{i1}, \hat{\mu}_{i2}, \ldots, \hat{\mu}_{ir}]'$ is the vector of the i^{th} response means, and $\boldsymbol{\Sigma}_i = [\widehat{\sigma_{i1}^2}, \widehat{\sigma_{i2}^2}, \ldots, \widehat{\sigma_{ir}^2}]'$ is the vector of the i^{th} response variances. Additionally, $\mathbf{X}_F$ is an $r \times \psi$ matrix of data for the predicator variables in the full model:

$$\mathbf{X}_F = \begin{bmatrix} 1 & X_{11} & X_{12} & \cdots & X_{1,\psi-1} \\ 1 & X_{21} & X_{22} & \cdots & X_{2,\psi-1} \\ \vdots & \vdots & \vdots & & \vdots \\ 1 & X_{r1} & X_{r2} & \cdots & X_{r,\psi-1} \end{bmatrix} = \begin{bmatrix} \mathbf{X}_{F,1} \\ \mathbf{X}_{F,2} \\ \vdots \\ \mathbf{X}_{F,r} \end{bmatrix},$$

in which $\mathbf{X}_{F,s}$ ($s = 1, 2, \ldots, r$) is the data vector for the full model on the s^{th} experimental run. In a reduced model with $v - 1$ ($1 \le v \le \psi$) predictors, the $r \times v$ data matrix for the predictors is denoted by $\mathbf{X}_{R,v} = [\mathbf{X}_{R,1,v}\ \mathbf{X}_{R,2,v}, \ldots, \mathbf{X}_{R,r,v}]'$ in which $\mathbf{X}_{R,s,v}$ is the data vector for the reduced model on the s^{th} experimental run; especially, $\mathbf{X}_F = \mathbf{X}_{R,\psi}$. Subsequently, the full model for the covariance between the w^{th} and g^{th} ($1 \le w < g \le n$) repsonses is given by

$$\sigma_{wg}^2(\mathbf{x}) = \left[1\ x_1\ \ldots\ x_1x_2\ \ldots\ x_1^2\ \ldots\ x_1^2x_2\ \ldots\ x_1^3\ \ldots\ x_1^3x_2\ \ldots\ x_1^4\ \ldots\ x_k^4\right] \times \left(\mathbf{X}_F^T\mathbf{X}_F\right)^{-1}\mathbf{X}_F^T\boldsymbol{\Sigma}_{wg}, \quad (5.6)$$

where $\boldsymbol{\Sigma}_{wg} = [\widehat{\sigma_{wg,1}^2}, \widehat{\sigma_{wg,2}^2}, \ldots, \widehat{\sigma_{wg,r}^2}]'$ is the vector of the covariances between the w^{th} and g^{th} responses. When employing a higher-order regression model, an increase in the number of predictors may result in multicollinearity between predictors. Variance Inflation Factor (VIF) is widely used to diagnose the multicollinearity. The VIF is defined as $\text{VIF}_f = 1/(1 - R_f^2)$, where R_f^2 is the coefficient of multiple determination when

the f^{th} predictor is regressed on the $v - 1$ other predictors in the model (Kutner *et al.*, 2004). A maximum of these VIF values greater than 10 indicates that the multicollinearity may impact the least squares estimates. In this case, the correlated predictors can be removed from the estimated function.

If $\hat{\pi}_{\omega}(\mathbf{x})$ denotes any estimated response surface function for $\omega = 1, 2, \ldots, h$ whose predictors are considered appropriate for the estimation of the related response variable based upon the best subsets critieria, the estimated mechanistic individual DF, $d[\hat{\pi}_{\omega}(\mathbf{x})]$, and overall DF, $\widehat{D}_M(\mathbf{x})$, can be finally expressed using Equations (5.4) – (5.6) under the traditional DF mechanism. Hereafter, we use $\hat{d}_{M,\omega}(\mathbf{x})$ instead of $d[\hat{\pi}_{\omega}(\mathbf{x})]$ for the sake of simplicity; more specifically, we have

$$\hat{d}_{M,\omega}(\mathbf{x}) = \begin{cases} d\left[\hat{\mu}_{\omega}(\mathbf{x})\right] & \omega = i \\ d\left[\sigma^2_{(\omega-n)}(\mathbf{x})\right] & \omega = n+i \\ d\left[\sigma^2_{wg}(\mathbf{x})\right] & \omega = 2n+1, 2n+2, \ldots, h \end{cases} . \quad (5.7)$$

5.3.2.2 Proposed Empirical Desiraiblity Model

If $d(y_{ijs})$ is the individual DF value for y_{ijs}, its formulas categorized by the characteristic type are developed in Table 5.2. The estimated empirical individual DF for the response mean can be derived from the raw observations by using the ordinary least squares method. Let $\hat{d}_{E,\omega}(\mathbf{x})$ ($\omega = i$) be the esimated empirical fourth-order individual DF of $\mathbf{x}$ for the the ω^{th} response mean. Then its full model can be expressed as

$$\hat{d}_{E,\omega}(\mathbf{x}) = \left[1\ x_1\ \ldots\ x_1x_2\ \ldots\ x_1^2\ \ldots\ x_1^2x_2\ \ldots\ x_1^3\ \ldots\ x_1^3x_2\ \ldots\ x_1^4\ \ldots\ x_k^4\right] \times \left(\mathbf{X}_F^T\mathbf{X}_F\right)^{-1}\mathbf{X}_F^T\mathbf{d}_{\omega}, \quad (5.8)$$

where $\mathbf{d}_\omega = [d_{\omega 1}, d_{\omega 2}, \ldots, d_{\omega r}]'$ is the vector of the mean values for the ω^{th} individual desiraiblity and $d_{\omega s}$ can be calculated by $d_{\omega s} = \frac{1}{m}\sum_{j=1}^{m} d(y_{ijs})$ for $s = 1, 2, \ldots, r$. Efforts are also made to extend the application of Equation (5.8) for expressing the full model of the estimated individual DFs for the response variance and covariance. If $\omega = n + i$, the $d_{\omega s}$ represents the desiraiblity of $\widehat{\sigma_{is}^2}$ that is calculated by $d(\widehat{\sigma_{is}^2})$; otherwise, it is the desiraiblity of $\widehat{\sigma_{wg,s}^2}$ that is calculated by $d(\widehat{\sigma_{wg,s}^2})$. In a similar fashion, the full model of the estimated empirical fourth-order overall DFs of $\mathbf{x}$, denoted by $\widehat{D}_E(\mathbf{x})$, is given by

$$\hat{D}_E(\mathbf{x}) = \left[1\ x_1\ \ldots\ x_1x_2\ \ldots\ x_1^2\ \ldots\ x_1^2x_2\ \ldots\ x_1^3\ \ldots\ x_1^3x_2\ \ldots\ x_1^4\ \ldots\ x_k^4\right] \times \left(\mathbf{X}_F^T\mathbf{X}_F\right)^{-1}\mathbf{X}_F^T\mathbf{D}, \quad (5.9)$$

where $\mathbf{D} = [D_1, D_2, \ldots, D_r]'$ is the vector of overall DF values. Note that D_s ($s = 1, 2, \ldots, r$) is defined as the overall desirability value on the s^{th} run. It is the weighted geometric mean of $d_{\omega s}$ and can be computed by

$$D_s = \left\{\prod_{\omega=1}^{h} d_{\omega s}^{W_\omega}\right\}^{1/\sum_{\omega=1}^{h} W_\omega}. \quad (5.10)$$

However, some of the y_{ijs} may go beyond the allowable maximum or minimum value of desirability potentially resulting in that the proposed $d_{\omega s}$ and consequently the overall desirability on the corresponding experimental run becomes zero. If the overall desiraiblity for many of the runs appears to be zero, the appropriateness of using the least squares method to obtain the estimated overall DF can be questionable. As a supplement to Table 5.1, Table 5.3 shows an extended experimental format from the perspective of desirability concerning the mean, variance, and covaraince of each response, in which $\hat{d}_\omega(\mathbf{x})$ denotes either the mechanistic or empirical desirability model.

Table 5.2 Formulas for Calculating $d(y_{ijs})$

Characteristic Type	Formula
LTB	$d(y_{ijs}) = \begin{cases} 0 & y_{ijs} < L_i \\ \left[\dfrac{y_{ijs} - L_i}{T_i - L_i}\right]^{\rho_i} & L_i \le y_{ijs} \le T_i \\ 1 & y_{ijs} > T_i \end{cases}$
STB	$d(y_{ijs}) = \begin{cases} 1 & y_{ijs} < T_i \\ \left[\dfrac{U_i - y_{ijs}}{U_i - T_i}\right]^{\rho_i} & T_i \le y_{ijs} \le U_i \\ 0 & y_{ijs} > U_i \end{cases}$
NTB	$d(y_{ijs}) = \begin{cases} 0 & y_{ijs} < L_i \\ \left[\dfrac{y_{ijs} - L_i}{T_s - L_s}\right]^{\rho_{i1}} & L_i \le y_{ijs} \le T_i \\ \left[\dfrac{U_i - y_{ijs}}{U_i - T_i}\right]^{\rho_{i2}} & T_i \le y_{ijs} \le U_i \\ 0 & y_{ijs} > U_i \end{cases}$

Table 5.3 An Extended Experimental Format Concerning Desirability

Run	y_1	$\hat{\mu}_1$	$\widehat{\sigma_1^2}$	...	y_n	$\hat{\mu}_n$	$\widehat{\sigma_n^2}$	$\widehat{\sigma_{12}^2}$	$\widehat{\sigma_{13}^2}$	...	$\widehat{\sigma_{(n-1)n}^2}$
1	$d(y_{111}) \dots d(y_{1m1})$			…	$d(y_{n11}) \dots d(y_{nm1})$					...	
2	$d(y_{112}) \dots d(y_{1m2})$			…	$d(y_{n12}) \dots d(y_{nm2})$					...	
⋮	⋮	$\hat{d}_1(\mathbf{x})$	$\hat{d}_{n+1}(\mathbf{x})$	…	⋮	$\hat{d}_n(\mathbf{x})$	$\hat{d}_{2n}(\mathbf{x})$	$\hat{d}_{2n+1}(\mathbf{x})$	$\hat{d}_{2n+2}(\mathbf{x})$	...	$\hat{d}_n(\mathbf{x})$
s	$d(y_{11s}) \dots d(y_{1ms})$			…	$d(y_{n1s}) \dots d(y_{nms})$					...	
⋮	⋮			…	⋮					...	
r	$d(y_{11r}) \dots d(y_{1mr})$			…	$d(y_{n1r}) \dots d(y_{nmr})$					...	

5.3.2.3 Model Selection of Estimated Empirical DFs

In addtion to seeking the appropriate subset of predictor variables for $\hat{\pi}_{\omega}(\mathbf{x})$, which has been well studied in the literature, we focus on the identification of the proper subsets of predictors under the empirical models for estimating DF values which necessitates the development of different subset selection criteria. Cruz-Monteagudo *et*

al. (2008) proposed the desirability's determination coefficient, R_d^2, and adjusted R_d^2 (adj. R_d^2) for the traditional desiraiblity method to measure the effect of a specific set of predictors on reducing the uncertainty when predicting desirability. The both critiera as well as three alternative criteria, including Akaike information criterion (AIC), Bayesian information criterion (BIC), and prediction sum of squares (PRESS), need to be further investigated for examining the estimated empirical individual and overall DFs with different sizes of predictors. Each subset selection criterion is delineated in terms of desirability in Table 5.4, where the subscripts d and v ($1 \leq v \leq \psi$) indicate that the statistic is related to desirability and there are $v - 1$ predictor variables in the model. The following paragraphs provide the development of these statistics.

Table 5.4 Subset Selection Criteria for Desirability Models with $v - 1$ Predictors

Criterion	Fomula	Description
$R_{d,v}^2$	$\frac{\text{SSR}_{d,v}}{\text{SSTO}_d}$	$\text{SSR}_{d,v}$ and SSTO_d denote regression sum of squares (SSR) and total sums of sqaures (SSTO) for the DF with $v - 1$ predictors. Large $R_{d,v}^2$ values are preferred. $R_{d,v}^2$ always increases as v increases, so it is not appropriate to compare desirability models with different sizes.
adj. $R_{d,v}^2$	$1-\left(\frac{r-1}{r-v}\right)\frac{\text{SSE}_{d,v}}{\text{SSTO}_d}$	$\text{SSE}_{d,v}$ denotes error sum of squares (SSE) for the DF with $v - 1$ predictors. Large adj. $R_{d,v}^2$ values are preferred. This criterion can be used to compare desirability models with different sizes, since this criteria provides penalty for adding predictors.
$\text{AIC}_{d,v}$	$r\ln(\text{SSE}_{d,v}) - r\ln(r) + 2v$	Small values of $\text{AIC}_{d,v}$ are preferred. Similar to adj. $R_{d,v}^2$, this criteria penalizes desirability models have large numbers of predictors and can be used to compare desirability models with different sizes.
$\text{BIC}_{d,v}$	$r\ln(\text{SSE}_{d,v}) - r\ln(r) + v\ln(r)$	By analogy with $\text{AIC}_{d,v}$, small values of $\text{BIC}_{d,v}$ are sought. However, the $\text{BIC}_{d,v}$ gives more penalty for over-fitting than $\text{AIC}_{d,v}$ when $r \geq 8$. This indicates that the $\text{BIC}_{d,v}$ tends to favor more simple models.
$\text{PRESS}_{d,v}$	$\sum_{s=1}^{r}\left(\frac{\hat{\varepsilon}_{d,s,v}}{1-h_{ss,v}}\right)^2$	$\hat{\varepsilon}_{d,s,v}$ is the s^{th} residual term and $h_{ss,v}$ is the s^{th} diagnal element of the $r \times r$ hat matrix $\mathbf{H}_v = \mathbf{X}_{R,v}(\mathbf{X}_{R,v}^T\mathbf{X}_{R,v})^{-1}\mathbf{X}_{R,v}^T$ for the esimated desirability model with $v - 1$ predictors. Desirability models with small $\text{PRESS}_{d,v}$ values fit well in the sense of having small prediction errors (also known as residuals).

- **Analysis of variance for estimated empirical DFs**

Let $\text{SSTO}_{d,\omega}$ be the SSTO of the ω^{th} individual desirability model, which can be

written as Equation (5.11) incorporating the unity matrix, $\mathbf{J} = \mathbf{1}\mathbf{1}'$, and the identity matrix, $\mathbf{I}$.

$$\text{SSTO}_{d,\omega} = \sum_{s=1}^{r}\left(d_{\omega s} - \bar{d}_{\omega}\right)^2 = \mathbf{d}'_{\omega}\mathbf{d}_{\omega} - \frac{1}{r}\mathbf{d}'_{\omega}\mathbf{J}\mathbf{d}_{\omega} = \mathbf{d}'_{\omega}\left[\mathbf{I} - \frac{1}{r}\mathbf{J}\right]\mathbf{d}_{\omega}, \tag{5.11}$$

where $\bar{d}_{\omega}$ is the mean of $d_{\omega s}$ for $s = 1, 2, \ldots, r$. Similarly, if the SSTO for the overall desirability model is denoted by SSTO_D and $\bar{D}$ is the mean of D_s, SSTO_D can be computed by

$$\text{SSTO}_D = \sum_{s=1}^{r}\left(D_s - \bar{D}\right)^2 = \mathbf{D}'\mathbf{D} - \frac{1}{r}\mathbf{D}'\mathbf{J}\mathbf{D} = \mathbf{D}'\left[\mathbf{I} - \frac{1}{r}\mathbf{J}\right]\mathbf{D}. \tag{5.12}$$

Using the fact that $\hat{\mathbf{d}}_{v,\omega} = \mathbf{X}_{R,v}(\mathbf{X}_{R,v}^T\mathbf{X}_{R,v})^{-1}\mathbf{X}_{R,v}^T\mathbf{d}_{\omega} = \mathbf{H}_v\mathbf{d}_{\omega}$, in which $\hat{\mathbf{d}}_{v,\omega} = [\hat{d}_{E,\omega}(\mathbf{X}_{R,1,v}), \hat{d}_{E,\omega}(\mathbf{X}_{R,2,v}), \ldots, \hat{d}_{E,\omega}(\mathbf{X}_{R,r,v})]'$ is the vector of the ω^{th} estimated empirical DF values at $\mathbf{X}_{R,s,v}$ ($s = 1, 2, \ldots, r$), it can be shown that the SSE and SSR of the ω^{th} empirical individual desirability model with $v - 1$ predictors, denoted by $\text{SSE}_{d,v,\omega}$ and $\text{SSR}_{d,v,\omega}$, are given by

$$\text{SSE}_{d,v,\omega} = \sum_{s=1}^{r}\left[d_{\omega s} - \hat{d}_{E,\omega}\left(\mathbf{X}_{R,s,v}\right)\right]^2 = \left[\mathbf{d}_{\omega} - \mathbf{H}_v\mathbf{d}_{\omega}\right]'\left[\mathbf{d}_{\omega} - \mathbf{H}_v\mathbf{d}_{\omega}\right] = \mathbf{d}'_{\omega}\left[\mathbf{I} - \mathbf{H}_v\right]\mathbf{d}_{\omega} \tag{5.13}$$

and

$$\text{SSR}_{d,v,\omega} = \text{SSTO}_{d,\omega} - \text{SSE}_{d,v,\omega} = \mathbf{d}'_{\omega}\left[\mathbf{H}_v - \frac{1}{r}\mathbf{J}\right]\mathbf{d}_{\omega}. \tag{5.14}$$

In the same manner as in Equations (5.13) and (5.14), the formulas of the SSE and SSR for the empirical overall desirability with $v - 1$ predictors, denoted by $\text{SSE}_{DE,v}$ and $\text{SSR}_{DE,v}$, are given by

$$\text{SSE}_{D,v} = \left[\mathbf{D} - \mathbf{H}_v\mathbf{D}\right]'\left[\mathbf{D} - \mathbf{H}_v\mathbf{D}\right] = \mathbf{D}'\left[\mathbf{I} - \mathbf{H}_v\right]\mathbf{D} \tag{5.15}$$

and

$$\mathrm{SSR}_{D,v} = \mathrm{SSTO}_D - \mathrm{SSE}_{D,v} = \mathbf{D}'\left[\mathbf{H}_v - \frac{1}{r}\mathbf{J}\right]\mathbf{D}. \tag{5.16}$$

Furthermore, let $\mathbf{e}_{v,\omega}$ and $\mathbf{e}_v$ denote the residual vectors for the ω^{th} empirical individual and overall desirability, then they can be developed as linear combinations of $\mathbf{d}_\omega$ and $\mathbf{D}$, respectively:

$$\mathbf{e}_{v,\omega} = \left[\hat{\varepsilon}_{d,1,v,\omega}, \hat{\varepsilon}_{d,2,v,\omega}, \ldots, \hat{\varepsilon}_{d,r,v,\omega}\right]' = \left(\mathbf{I} - \mathbf{H}_v\right)\mathbf{d}_\omega \tag{5.17}$$

and

$$\mathbf{e}_v = \left[\hat{\varepsilon}_{D,1,v}, \hat{\varepsilon}_{D,2,v}, \ldots, \hat{\varepsilon}_{D,r,v}\right]' = \left(\mathbf{I} - \mathbf{H}_v\right)\mathbf{D}, \tag{5.18}$$

where $\hat{\varepsilon}_{d,s,v,\omega}$ and $\hat{\varepsilon}_{D,s,v}$ correspond to the residual terms of the ω^{th} individual DF and overall DF with $v - 1$ predictors on the s^{th} experimental run.

- **Subset selection criteria development**

As shown in Table 5.5, the selection criteria for the individual and overall DFs under empirical models can be obtained based upon Equations (5.11) – (5.18). In our proposed model, one may need to consider more than one criterion when selecting the ideal estimated function. Since the number of possible regression functions, 2^{v-1}, increases dramatically as v increases, it is an overwhelming task for a data analyst to examine all possible subsets of predictors. Commonly, we use the best subsets regression technique to simply the task. This technique requires the calculation of only a small fraction of all the possible regression models, so that a small group of regression functions that are considered desirable candidates according to these criteria can be

identified. A detail examination can then be made, leading to the selection of the final estimated DF to be employed in the optimization phase.

Table 5.5 Subset Selection Criteria for the Individual and Overall Desirability

Criterion	Formula with $v-1$ predictors	
	ω^{th} Individual DF	Overall DF
R_d^2	$\dfrac{\mathbf{d}_\omega'\left[\mathbf{H}_v-\frac{1}{r}\mathbf{J}\right]\mathbf{d}_\omega}{\mathbf{d}_\omega'\left[\mathbf{I}-\frac{1}{r}\mathbf{J}\right]\mathbf{d}_\omega}$	$\dfrac{\mathbf{D}'\left[\mathbf{H}_v-\frac{1}{r}\mathbf{J}\right]\mathbf{D}}{\mathbf{D}'\left[\mathbf{I}-\frac{1}{r}\mathbf{J}\right]\mathbf{D}}$
adj. R_d^2	$1-\left(\dfrac{r-1}{r-v}\right)\dfrac{\mathbf{d}_\omega'\left[\mathbf{I}-\mathbf{H}_v\right]\mathbf{d}_\omega}{\mathbf{d}_\omega'\left[\mathbf{I}-\frac{1}{r}\mathbf{J}\right]\mathbf{d}_\omega}$	$1-\left(\dfrac{r-1}{r-v}\right)\dfrac{\mathbf{D}'\left[\mathbf{I}-\mathbf{H}_v\right]\mathbf{D}}{\mathbf{D}'\left[\mathbf{I}-\frac{1}{r}\mathbf{J}\right]\mathbf{D}}$
AIC_d	$r\ln\left(\mathbf{d}_\omega'\left[\mathbf{I}-\mathbf{H}_v\right]\mathbf{d}_\omega\right)-r\ln(r)+2v$	$r\ln\left(\mathbf{D}'\left[\mathbf{I}-\mathbf{H}_v\right]\mathbf{D}\right)-r\ln(r)+2v$
BIC_d	$r\ln\left(\mathbf{d}_\omega'\left[\mathbf{I}-\mathbf{H}_v\right]\mathbf{d}_\omega\right)-r\ln(r)+v\ln(r)$	$r\ln\left(\mathbf{D}'\left[\mathbf{I}-\mathbf{H}_v\right]\mathbf{D}\right)-r\ln(r)+v\ln(r)$
PRESS_d	$\sum_{s=1}^{r}\left(\dfrac{\hat{\varepsilon}_{Md,s,v,\omega}}{1-h_{ss,v}}\right)^2$	$\sum_{s=1}^{r}\left(\dfrac{\hat{\varepsilon}_{MD,s,v}}{1-h_{ss,v}}\right)^2$

5.3.3 Optimization Phase

At this stage, we need to solve an MRS optimization problem; namely, the optimal settings of ingredient amounts of a pharmaceutical formulation need to be determined in order to ensure that the dissolution data at multiple points in time have most desirable performance referencing the target profile. Traditionally, the MRS optimization problem can be simplified into a single-objective optimization problem in which the overall DF is maximized subject to a rigid set of constraints. It can alternatively be viewed as a multi-objective optimization problem.

5.3.3.1 Proposed Optimization Model

Goal programming, as one of the most widely applied tools of multi-objective optimization, is constructed in terms of specific goals to be achieved rather than quantities to be maximized or minimized (Rardin, 1998). According to the basic thread of goal programming, prior to formulating an objective function for each of the individual DFs by means of introducing nonnegative deficiency variables to model the extent of violation in their respective goals that need not to be rigidly enforced, a specific numerical target is established for each of them. Since the response performance becomes more desirable as its DF value approaches 1, the numerical target of the individual DF is usually set to 1. Subsequently, each of the individual DFs can be expressed in an equality-form mathematical format with the target value and deficiency variables: $\hat{d}_{\omega}(\mathbf{x}) - \Delta_{\omega}^{+} + \Delta_{\omega}^{-} = 1$, in which Δ_{ω}^{-} and Δ_{ω}^{+} are the nonnegative deficiency variables associated with the underachievement and overachievement of the ω^{th} desirability. Since the allowable maximum of desirability is 1, Δ_{ω}^{+} does not exist in this case and therefore the equality reduces to

$$\hat{d}_{\omega}(\mathbf{x}) + \Delta_{\omega}^{-} = 1. \tag{5.19}$$

In order to ensure that all desirability values are as close as possible to 1, involved deficiency variables should be minimized. Generally, non-preemptive and preemptive optimization schemes can be utilized to facilitate the minimization of the deficiency variables (Hillier & Lieberman, 2001). The objective of the former is to satisfy all goals by minimizing a weighted sum of the deficiency variables. However, it is believed that the subjectivity in assigning the weights of subjects may impact the resulting optimal

solution which is highly sensitive to the different weights. In the latter scheme, there is hierarchy of priority levels for the goals, so that deficiency in the DF of primary importance is minimized, deficiency in the DF of secondary importance is minimized subject to an additional constraint that the first achieve its minimum, and so forth. Therefore, with the purpose of overcoming the weaknesses of weight-based goal programming, we propose a priority-based approach for optimizing multiple individual DFs.

Based on the pre-identified shape parameters for the DFs, the procedural steps for the algorithm of our proposed optimization model are illustrated in Figure 5.2 and described below in greater detail:

(1) Determine the priority hierarchy of the ω individual DFs based on importance levels of the dissolved amounts or percentages at different points in time. For example, the half-life of dissolution is critical to a dissolution profile because it establishes the time to promote the dissolution of 50% of the drug (Chazel *et al.*, 1998); hence, the half-life dissolution performance in terms of the mean and variance can be the highest ranked responses in the priority hierarchy. Suppose that b_ξ individual DFs are categorized as the ξ^{th}-priority goals to be achieved with $\sum_{\xi=1} b_\xi = \omega$, and ξ is initially set to 1.

(2) Formulate the objective function of the ξ^{th} optimization model by minimizing the summation of b_ξ deficiency variables in the ξ^{th}–priority individual DFs while satisfying the following constraints:

a) Let Ω_ω be the specification region of $\hat{\pi}_\omega(\mathbf{x})$ for $\omega = 1, 2, \ldots, h$. For an estimated function in terms of either the mean or covariance (NTB), the lower and upper bounds of its specification region are the corresponding acceptable minimum and maximum values; meanwhile, for an estimated function related to the variance (STB), the target and acceptable maximum values are considered the lower and upper bounds.

b) The input factors should remain within the design space which is explored by DOE and ensures the optimality and feasibility of a pharmaceutical formulation. The design space for each of the k factors should be within the interval between the minimum and maximum coded values. That is, $-1 \leq x_1, \ x_2, \ldots, x_k \leq 1$ for a factorial design, Taguchi design, or mixture design; $\mathbf{x}^T\mathbf{x} \leq \rho^2$ for a CCD, where ρ is the distance in any direction from the center point and is analogous to the radius of a sphere.

c) Nonnegativity of deficiency variables involved in the ξ^{th} optimization model should be satisfied. It is introduced by the constraint form: $\boldsymbol{\Delta}_\xi^- \geq 0$, where $\boldsymbol{\Delta}_\xi^-$ denotes any of the involved underachievement deficiency variables.

d) Referring to Equation (5.19), the constraints associated with the goals of involved individual DFs needs to be included. For the sake of simplicity, these constraints are established in an equality form: $\hat{\mathbf{d}}_\xi(\mathbf{x}) + \boldsymbol{\Delta}_\xi^- = 1$, where $\hat{\mathbf{d}}_\xi(\mathbf{x})$ represents any of the ξ^{th}–priority individual DFs in the ξ^{th} optimization model.

e) If $\xi > 1$ and the resulting optimal solution of deficiency variables in the $(\xi - O)^{\text{th}}$ optimization model is denoted by $\boldsymbol{\Delta}^{*}_{(\xi-O)}$, extra constraints with the expression of $\hat{\mathbf{d}}_{(\xi-O)}(\mathbf{x}) + \boldsymbol{\Delta}^{*}_{(\xi-O)} = 1$ for $O = 1, 2, \ldots, \xi - 1$ are added to the ξ^{th} optimization model, which guarantees that all the preceding goals are achieved in the ξ^{th} optimization model.

f) The values of all the estimated DFs should vary from 0 to 1, so that the validity of these DFs can be ensured at each iteration of the proposed optimization model.

g) Additional constraints specified by the FDA may be added to the optimization model as appropriate, such as hardness, thickness, and stability requirements for the formulation. Any of these estimated response functions, denoted by $\widehat{\mathbf{A}}(\mathbf{x})$, can be obtained by the RSM discussed in the previous subsections. In a similar fashion to Step (a), $\widehat{\mathbf{A}}(\mathbf{x})$ should remain within the associated regulatory region, $\boldsymbol{\Omega}_{\mathbf{A}}$.

(3) If the ξ^{th} optimization model yields a unique solution, the routine is terminated and this optimal solution vector $(\mathbf{x}^{*}_{\xi}, \boldsymbol{\Delta}^{*}_{\xi})'$ is finalized as the most desirable settings of both the factors and deficiency variables without considering any lower-priority goals. Note that $\mathbf{x}^{*}_{\xi}$ is the vector of optimal factor settings for the ξ^{th} optimization model. Otherwise, Step (4) is executed.

(4) If $(\xi + 1)^{\text{th}}$-priority goals exist, ξ is increased by one and the procedure returns to Step (2). Otherwise, we adopt the $(\mathbf{x}^{*}_{\xi}, \boldsymbol{\Delta}^{*}_{\xi})'$ immediately.

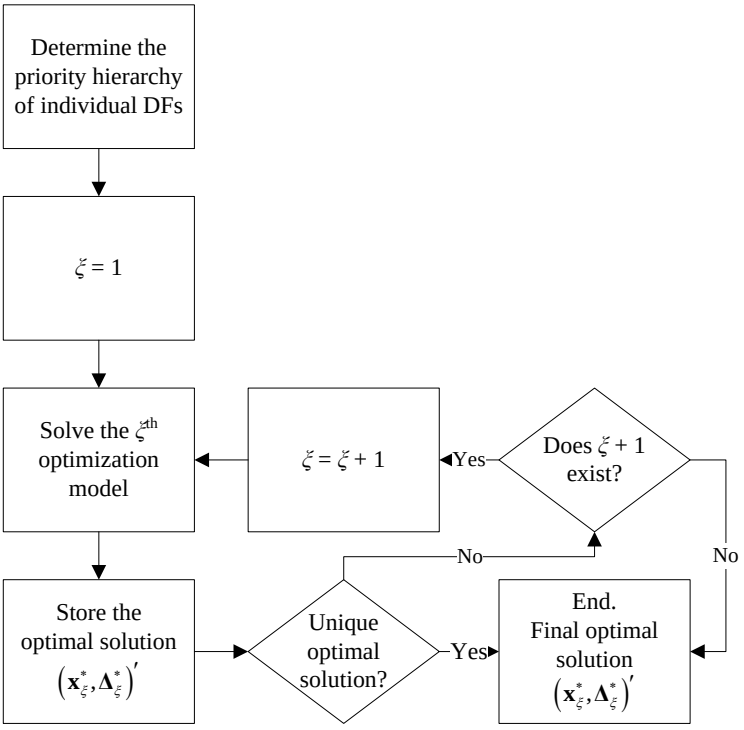

Figure 5.2 Flowchart for the Algorithm of the Proposed Optimization Model

Moreover, based upon Step (2), Table 5.6 outlines the proposed ξ^{th} optimization scheme for the priority-based goal programming methodology to the formulation optimization problem.

5.3.3.2 Comparative models

As references for comparison with the proposed model, optimization models that maximize the overall DF under both mechanistic and empirical models are developed in Table 5.7, in which the optimal settings of deficiency variables under both models are expressed as: $\mathbf{\Delta}_{M}^{*}$ and $\mathbf{\Delta}_{E}^{*}$.

Table 5.6 Proposed Optimization Scheme for the ξ^{th}-Priority Individual DFs

Minimize	$\sum \boldsymbol{\Delta}_{\xi}^{-}$
Subject to	Constraints: 1. Specification region of estimated response surface functions ($\omega = 1, 2, \ldots, h$): $\hat{\pi}_{\omega}(\mathbf{x}) \in \Omega_{\omega}$ 2. Design space of factors: $-1 \le x_1, x_2, \ldots, x_k \le 1$ (for a factorial design, Taguchi design, or mixture design) or $\mathbf{x}^T\mathbf{x} \le \rho^2$ (for a CCD) 3. Nonnegativity of deficiency variables: $\boldsymbol{\Delta}_{\xi} \ge 0$ 4. Goals of present individual DFs: $\hat{\mathbf{d}}_{\xi}(\mathbf{x}) + \boldsymbol{\Delta}_{\xi}^{-} = 1$ 5. Goals of preceding individual DFs (applicable if $\xi > 1$): $\hat{\mathbf{d}}_{(\xi-O)}(\mathbf{x}) + \boldsymbol{\Delta}_{(\xi-O)}^{*} = 1$ for $O = 1, 2, \ldots, \xi - 1$ 6. Individual DF ($\omega = 1, 2, \ldots, h$): $0 \le \hat{\mathbf{d}}_{\omega}(\mathbf{x}) \le 1$ 7. Additional constraints specified by the FDA: $\hat{\mathbf{A}}(\mathbf{x}) \in \boldsymbol{\Omega}_{\mathbf{A}}$
Find	Optimal solution $(\mathbf{x}_{\xi}^{*}, \boldsymbol{\Delta}_{\xi}^{*})'$

Table 5.7 Comparative Optimization Schemes Using the Overall DF

	Mechanistic Model	Empirical Model
Maximize	$\hat{D}_M(\mathbf{x})$	$\hat{D}_E(\mathbf{x})$
Given	Predefined weights for each individual DF	
Subject to	**Common constraints:** 1. Specification region of estimated response surface functions ($\omega = 1, 2, \ldots, h$): $\hat{\pi}_{\omega}(\mathbf{x}) \in \Omega_{\omega}$ 2. Design space of factors: $-1 \le x_1, x_2, \ldots, x_k \le 1$ (for a factorial design, Taguchi design, or mixture design) or $\mathbf{x}^T\mathbf{x} \le \rho^2$ (for a CCD) 3. Additional constraints specified by the FDA: $\hat{\mathbf{A}}(\mathbf{x}) \in \boldsymbol{\Omega}_{\mathbf{A}}$	
	Specific constraints: 1. Individual DF ($\omega = 1, 2, \ldots, h$): $0 \le \hat{d}_{M,\omega}(\mathbf{x}) \le 1$ 2. Overall DF: $0 \le \hat{D}_M(\mathbf{x}) \le 1$	1. Overall DF: $0 \le \hat{D}_E(\mathbf{x}) \le 1$
Find	Optimal solution $\mathbf{x}^*$	Optimal solution $\mathbf{x}^*$

5.4 Numerical Example

To demonstrate the effectiveness of the proposed optimization scheme and compare its resulting performance with that of the comparative scheme using the mechanistic and empirical desirability models, a numerical example is studied in the following paragraphs. Employing second-order estimated response surface functions, Huang *et al*. (2004) conducted a formulation optimization study to develop propranolol extended release formulations containing two inactive ingredients: HPMC and avicel. HPMC as a pH-independent material is widely used to prepare extended release dosage forms while avicel incorporating with HPMC can modify the dissolution performance of a drug. A randomized 3^2 full factorial design with additional two center point runs (r = 11) was performed in their experiment where two factors, including the HPMC/drug ratio (x_1) and content percentage of avicel (x_2), were measured on the five output responses: drug dissolution percentages (y_1, y_2, y_3, y_4, and y_5) at 1.5, 4, 8, 14, and 24h. Note that the center runs were primarily used to provide a measure of pure error. Furthermore, FDA (2000) recommends the use of the equally-weighted similarity factor, f_2, to evaluate the equivalence between two dissolution profiles if the following requirements are satisfied: (1) at least 12 units should be used for both profile determination; (2) the RSD at the earlier point of time should not be more than 20% and at other points should not be more than 10%; and (3) no more than 85% dissolved in 15 minutes. The f_2 can be calculated by Equation (2.1). Dissolution-time curves are considered similar when f_2 is greater than 50, and they become similar when f_2 approaches 100. The f_2 method is utilized as an

additional reference for model comparison in order to validate our comparative conclusions from the perspective of FDA suggestions.

Therefore, given the experimental data set in terms of the mean and variance provided by Huang *et al*. (2004), we initially regard y_1 as the dissolution data at the earlier point of time and the other four responses as those at the later points. In other words, these response variances should meet their respective requirements on RSD mentioned earlier. Subsequently, it is feasible and necessary to simulate normally distributed observations with 12 replicates (m = 12) on each experimental run using Microsoft® Excel, so that $\hat{\mu}_i(\mathbf{x})$ (i = 1, 2, …, h) represents the estimated mean dissolution of 12 units at each point of time in accordance with one of the f_2 requirements. The factor settings, target dissolution profile against priority, and specifications of each variance and covariance measures are summarized in Table 5.8. The highest priority pertaining to the individual DFs is given to $\hat{\mu}_2$ and $\hat{\mu}_3$ along with their variances, since both points in time are adjacent to the half-life of the dissolution; meanwhile, the second priority is assigned for the other response means and variances and the third for the covariance terms. The corresponding weights in the overall DF are also identified in Table 5.8 so as to implement the comparative optimization study, and the shape parameters of the DFs are all set to 1. Moreover, in order to obtain the best regression functions for estimating the mean, variance, covariance, and desirability, all possible combinations of predictors up to fourth order are examined by using the software program Minitab® 16, and only those contributing to the regression analysis are kept for further study. In Table 5.9, a comparison of estimated functions related to the response means is displayed, and the

fourth-order regression functions concerning response variance, covariance, and empirical individual desirability with the highest R^2 (or R_a^2) and adj. R^2 (or adj. R_a^2) are selected out of the results of the best subsets screening. Finally, these candidate functions are evaluated against the various selection criteria developed in the previous section. Since the adj. R^2 is generally utilized to compare the regression function with different sizes of predictors, the best models that achieve desirable values for most of the criteria and maintain higher adj. R^2 or adj. R_a^2 values are identified and given in bold in Table 5.9. It should be noted that because the majority of D_s for s = 1, 2, …, r are equal to zero, the $\widehat{D}_E(\mathbf{x})$ cannot be obtained in this particular example and thereby we perform the comparative optimization scheme using the mechanistic overall desirability model. The differences in the estimation of the response means under the second- and proposed fourth-order models can be illustrated by the contour plots for x_1 and x_2 with corresponding contour labels (see Figure 5.3). The contour plots, shown in Figure 5.4, are drawn to compare the resulting estimated fourth-order DFs related to the response mean by using the traditional and proposed empirical desirability models.

Using the results of Table 5.9, the proposed priority- and comparative overall DF-based optimization procedures can be performed. The resulting optimal settings under the different models along with the weighted overall desirability and f_2 are obtained by Mathematica® 8.0 and summarized in Table 5.10, in which the ideal desirability and f_2 values are highlighted in bold. Note that because both of the solutions to the achievement of the 1st-priority goals using the empirical and mechanistic DF methods are unique, their respective priority-based optimization procedures are then terminated, with (x_1^*, x_2^*) =

(0.138, 1.000) and (x_1^*, x_2^*) = (0.589, –0.968) as the corresponding optimal factor settings. The Mathematica programming code is provided in Appendix 3. Moreover, Figure 5.5 describes a comparison of the resulting optimal desirability against ω. The impact of the assigned weights or priorities on the optimal desirability under the associated optimization models can be observed in Figure 5.6, which shows a comparison of the optimal individual desirability under each of the models in Table 5.10 (solid line) and that under the respective equally-weighted optimization model (dashed line). In Figure 5.5 and 5.6, the lines marked with ●, ▲, and ■ describe the resulting desirability under the empirical, mechanistic, and overall DF models, respectively.

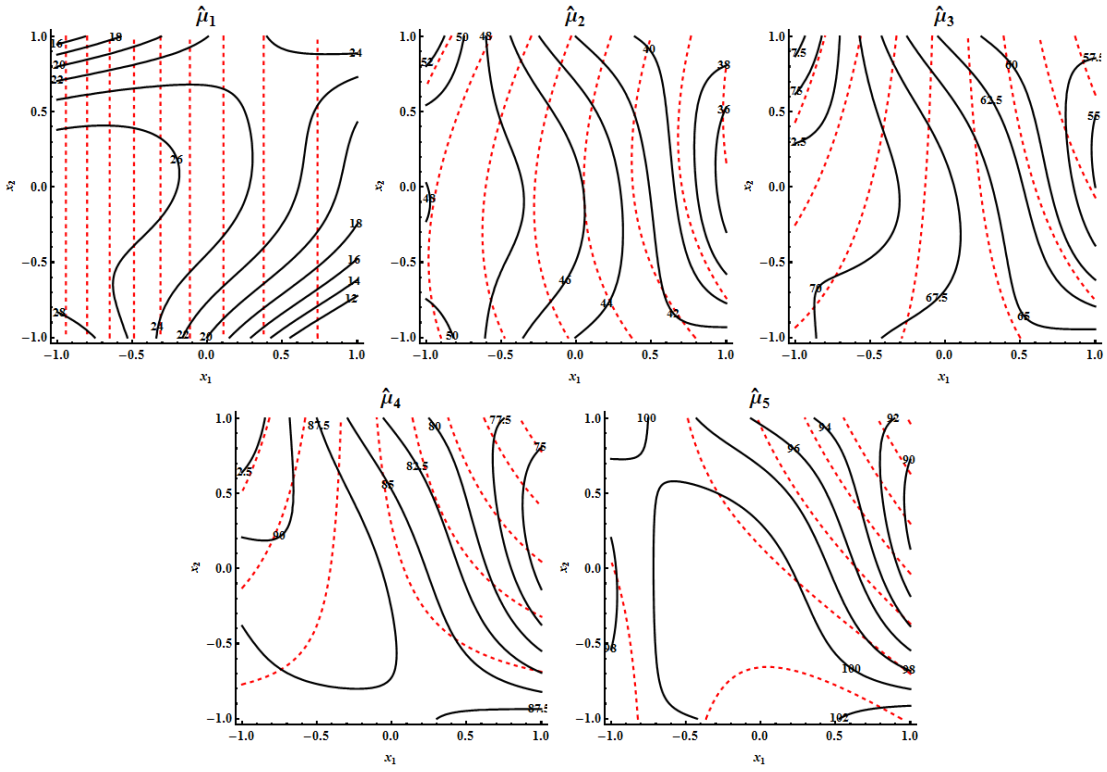

Figure 5.3 Comparison of Contour Plots between Second- (---) and Fourth-Order (—) Models for the Response Means

Table 5.8 Experimental Factor Settings and Target Dissolution Profile

Factors	Actual values under coded levels				
	−1	0	+1		
x_1	1 : 1	1.5 : 1	2 : 1		
x_2	8%	14%	20%		
Characteristic	Acceptable minimum (%)	Target (%)	Acceptable maximum (%)	Priority	Weight
$\hat{\mu}_1$	0	12.5	25	2nd	10
$\hat{\mu}_2$	35	42.5	50	1st	100
$\hat{\mu}_3$	55	62.5	70	1st	100
$\hat{\mu}_4$	75	82.5	90	2nd	10
$\hat{\mu}_5$	95	102.5	110	2nd	10
$\widehat{\sigma_1^2}$	−	0	25	2nd	10
$\widehat{\sigma_2^2}$	−	0	25	1st	100
$\widehat{\sigma_3^2}$	−	0	49	1st	100
$\widehat{\sigma_4^2}$	−	0	81	2nd	10
$\widehat{\sigma_5^2}$	−	0	121	2nd	10
Covariance	−5	0	+5	3rd	1

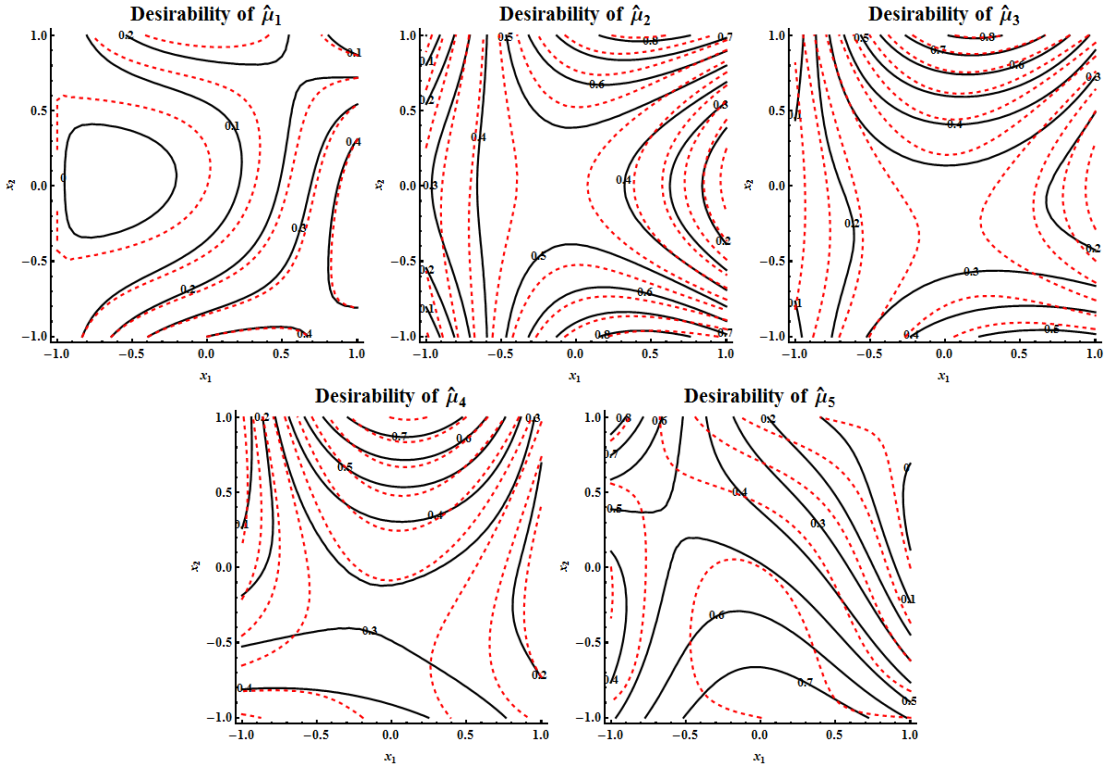

Figure 5.4 Comparison of Contour Plots between Estimated Traditional (---) and Proposed Empirical (—) Desirability Models for the Response Means

Table 5.9 Model Selection for the Mean, Variance, Covariance, and Individual Desirability

	Estimated Response Surface Function								Estimated Empirical Individual Desirability						
	Characteristic	v	R^2	adj. R^2	AIC	BIC	PRESS	ω	v	R_d^2	adj. R_d^2	AIC_d	BIC_d	$PRESS_d$
Second-order	$\hat{\mu}_1$	3	0.607	0.508	24.64	25.83	117.38	1	3	0.382	0.228	−36.34	−35.14	0.45
	$\hat{\mu}_2$	4	0.770	0.672	26.62	28.21	143.11	2	4	0.349	0.070	−23.88	−22.89	1.83
	$\hat{\mu}_3$	3	0.789	0.736	29.14	30.33	183.45	3	3	0.246	0.057	−28.92	−27.73	0.68
	$\hat{\mu}_4$	4	0.764	0.662	30.34	31.92	248.26	4	4	0.112	0	−27.80	−26.21	1.18
	$\hat{\mu}_5$	5	0.710	0.517	27.29	29.27	291.94	5	5	0.653	0.422	−31.09	−29.10	1.60
Proposed fourth-order	$\hat{\mu}_1$	**9**	**0.996**	**0.978**	**−14.83**	**−12.44**	**0**	1	8	0.994	**0.980**	−78.80	−75.62	**0**
									9	**0.996**	0.978	**−80.34**	**−76.75**	**0**
	$\hat{\mu}_2$	6	0.973	**0.947**	13.33	15.72	58.38	2	**6**	0.936	**0.873**	**−45.47**	**−43.08**	**0**
		9	**0.984**	0.919	**8.57**	**12.15**	**0**		9	**0.953**	0.763	−42.70	−39.12	**0**
	$\hat{\mu}_3$	6	0.938	**0.877**	21.60	**23.99**	102.5	3	**7**	0.871	**0.677**	**−40.34**	**−37.55**	**0**
		9	**0.967**	0.836	**20.65**	24.23	**0**		9	**0.880**	0.401	−37.15	−33.57	**0**
	$\hat{\mu}_4$	8	0.949	**0.830**	21.47	24.65	**0**	4	**7**	0.871	**0.678**	**−42.96**	**−40.17**	**0**
		9	**0.961**	0.803	**20.65**	**24.23**	**0**		9	**0.877**	0.383	−35.86	−39.44	**0**
	$\hat{\mu}_5$	**8**	**0.974**	**0.915**	**6.57**	**9.75**	**0**	5	**7**	0.946	**0.864**	**−47.49**	**−44.71**	0.19
		9	**0.974**	0.872	8.57	12.15	0		9	**0.953**	0.767	−45.21	−41.63	**0**
	$\widehat{\sigma_1^2}$	**7**	0.970	**0.926**	**8.44**	**11.23**	**0**	6	**7**	0.970	**0.926**	**−62.38**	**−59.59**	**0**
		9	**0.973**	0.865	11.33	14.91	**0**		9	**0.973**	0.865	−59.48	−55.90	**0**
	$\widehat{\sigma_2^2}$	**4**	0.373	**0.105**	**43.74**	**45.33**	617.5	7	**4**	0.373	**0.105**	**−27.08**	**−25.48**	0.988
		7	**0.468**	0	47.94	50.73	**0**		7	**0.468**	0	−22.87	−20.09	**0**
	$\widehat{\sigma_3^2}$	**2**	0.137	**0.041**	**57.63**	**58.43**	2243.9	8	**2**	0.137	**0.041**	**−28.00**	**−27.20**	0.93
		8	**0.272**	0	67.77	70.95	**0**		8	**0.271**	0	−17.86	−14.68	**0**
	$\widehat{\sigma_4^2}$	**3**	0.260	**0.076**	**59.37**	**60.56**	2259.4	9	**2**	0.237	**0.152**	**−38.95**	**−38.15**	0.28
		9	**0.440**	0	68.32	70.90	**0**		9	**0.440**	0	−28.35	−24.77	**0**
	$\widehat{\sigma_5^2}$	**7**	0.828	**0.569**	**68.80**	**71.59**	496.5	10	**7**	0.828	**0.569**	**−61.08**	**−58.30**	0.03
		8	**0.830**	0.433	70.90	74.08	**0**		8	**0.830**	0.433	−59.22	−56.04	**0**
	$\widehat{\sigma_{12}^2}$	**5**	0.600	**0.333**	0.44	**2.43**	**0**	11	**4**	0.612	**0.446**	**−41.72**	**−40.13**	0.21
		9	**0.670**	0	**0.63**	4.21	**0**		9	**0.630**	0	−32.24	−28.66	**0**
	$\widehat{\sigma_{13}^2}$	8	0.965	**0.884**	−1.96	1.22	**0**	12	**7**	0.959	**0.898**	**−45.75**	**−42.96**	0.15
		9	**0.974**	0.871	**−3.22**	**0.36**	**0**		9	**0.961**	0.807	−42.37	−38.79	**0**
	$\widehat{\sigma_{14}^2}$	**4**	0.739	**0.627**	**3.68**	**5.27**	15.75	13	**6**	0.803	**0.607**	**−41.84**	**−39.46**	**0**
		9	**0.818**	0.008	9.72	13.30	**0**		9	**0.842**	0.210	−38.25	−34.67	**0**
	$\widehat{\sigma_{15}^2}$	**5**	0.891	**0.818**	**3.20**	**5.19**	48.76	14	**7**	0.929	**0.822**	**−42.89**	**−40.11**	**0**
		7	**0.923**	0.807	3.40	6.19	**0**		9	**0.930**	0.648	−39.03	−35.44	**0**
	$\widehat{\sigma_{23}^2}$	7	0.937	**0.843**	−6.24	−3.45	**0**	15	**7**	0.783	**0.458**	**−46.36**	**−43.58**	0.14
		9	**0.964**	0.819	**−8.27**	**−4.69**	**0**		9	**0.807**	0.037	−43.68	−40.09	**0**
	$\widehat{\sigma_{24}^2}$	**4**	0.386	**0.123**	**23.26**	**24.85**	118.39	16	**3**	0.526	**0.408**	**−29.99**	**−28.80**	0.60
		9	**0.722**	0	24.52	28.11	**0**		9	**0.651**	0	−21.37	−17.79	**0**
	$\widehat{\sigma_{25}^2}$	**4**	0.537	**0.338**	**18.27**	**19.86**	69.87	17	**4**	0.484	**0.262**	**−23.52**	**−21.92**	0.88
		9	**0.635**	0	25.65	29.24	**0**		9	**0.603**	0	−16.41	−12.83	**0**
	$\widehat{\sigma_{34}^2}$	**5**	0.700	**0.501**	**19.46**	**21.45**	44.71	18	**5**	0.663	**0.438**	**−26.54**	**−24.55**	0.75
		9	**0.748**	0	25.56	29.146	**0**		9	**0.721**	0	−20.63	−17.05	**0**
	$\widehat{\sigma_{35}^2}$	**4**	0.602	**0.432**	**19.27**	**20.86**	54.61	19	**6**	0.911	**0.821**	**−41.11**	**−38.72**	0.31
		9	**0.674**	0	27.08	30.66	**0**		9	**0.937**	0.683	−38.87	−35.29	**0**
	$\widehat{\sigma_{45}^2}$	**7**	**0.934**	**0.835**	**6.17**	**8.95**	10.88	20	**5**	0.672	**0.453**	**−27.55**	**−25.56**	0.67
		8	**0.934**	0.782	8.08	11.27	**0**		9	**0.806**	0.028	−25.31	−21.73	**0**

Table 5.10 Comparison of Optimal Settings

Optimal Settings			Proposed Priority-Based Optimization		Comparative Model
			Proposed Empirical DF	Proposed Mechanistic DF	Overall DF
$\mathbf{x}^*$			(0.138, 1.000)	(0.589, –0.968)	(1.000, –0.799)
f_2			62.71	68.88	**70.63**
Desirability	$\omega = 1$	$\hat{\mu}_1$	0.277	**0.449**	0.410
	2	$\hat{\mu}_2$	0.796	**1.000**	0.714
	3	$\hat{\mu}_3$	0.815	0.632	**0.988**
	4	$\hat{\mu}_4$	0.795	0.300	0.727
	5	$\hat{\mu}_5$	0.168	**0.931**	0. 659
	6	$\widehat{\sigma_1^2}$	0.370	**0.997**	0.956
	7	$\widehat{\sigma_2^2}$	0.840	0.833	**0.853**
	8	$\widehat{\sigma_3^2}$	0.861	**0.999**	0.978
	9	$\widehat{\sigma_4^2}$	**0.920**	0.729	0.732
	10	$\widehat{\sigma_5^2}$	**0.952**	0.939	0.864
	11	$\widehat{\sigma_{12}^2}$	0.563	**0.993**	0.990
	12	$\widehat{\sigma_{13}^2}$	0.047	0.660	**0.721**
	13	$\widehat{\sigma_{14}^2}$	0.305	**0.763**	0.759
	14	$\widehat{\sigma_{15}^2}$	0.600	**0.995**	0.990
	15	$\widehat{\sigma_{23}^2}$	**0.805**	0.687	0.687
	16	$\widehat{\sigma_{24}^2}$	0.506	**0.897**	0.653
	17	$\widehat{\sigma_{25}^2}$	0.618	**0.847**	0.492
	18	$\widehat{\sigma_{34}^2}$	0.655	**0.966**	0.859
	19	$\widehat{\sigma_{35}^2}$	**0.873**	0.801	0.428
	20	$\widehat{\sigma_{45}^2}$	**0.569**	0.388	0.457
	Overall		0.762	0.822	**0.847**

5.5 Conclusion

One of the strengths of the proposed optimization model is that higher-order (up to fourth-order) rather than second-order regression functions are combined with the best subset approach to provide a more precise approximation to the characteristics of interest, which is considered critical to a pharmaceutical formulation optimization problem, because the error in estimating these characteristics may result in the additional error in the optimal settings of ingredient amounts. In Table 5.9, the proposed higher-order

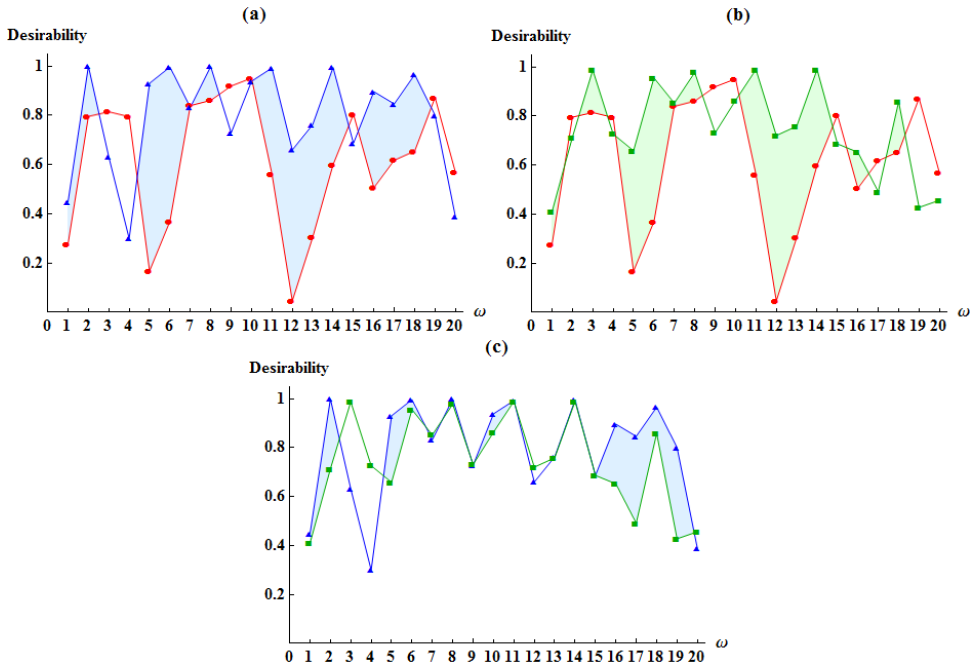

Figure 5.5 Comparison of Resulting Individual Desirability

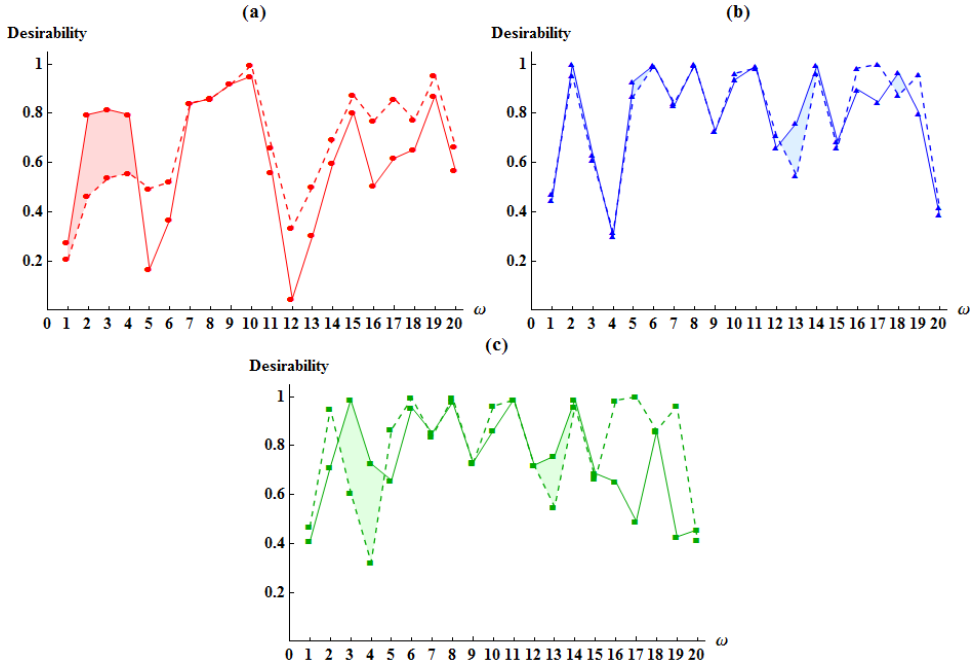

Figure 5.6 Impacts of Assigned Weights or Priorities on the Optimal Desirability Settings under Different Models

functions fit the observation data better than the second-order since they achieve more desirable values for the model selection criteria, including R^2, adj. R^2, AIC, BIC, and PRESS; meanwhile, these higher-order estimated response surface functions with different subsets of predictors are evaluated against the criteria in order to identify the ideal regression models that most appropriately estimate the true response mean, variance, and covariance. Moreover, in order to solve an MRS formulation optimization problem where multiple QCs are correlated over time, efforts are made to develop DFs under the empirical and mechanistic models that evaluate the desirability of the response covariance in addition to the mean and variance. It is essential to ensure small variability of these responses, since large variability may lead to the safety and efficacy issue of the formulation. By analogy with the ordinary model selection criteria for responses, we propose the desirability-related criteria for screening the higher-order estimated DFs under the empirical model with different sizes of predictors. The appropriate estimated desirability models, which most accurately approximate the associated desirability, are finally determined according to the proposed criteria. However, it is not necessary that the ideal higher-order estimated function contains higher-order terms, for instance $\widehat{\sigma_3^2}(\mathbf{x})$ and $\hat{d}_{E,8}(\mathbf{x})$, both of which are the functions of x^2. Considering the large number of the candidate regression functions, the extent of enhanced accuracy in the estimation of the response and desirability is considerably significant.

Another insight of applying our model to the formulation optimization with multiple QCs is that we propose a priority-based optimization procedure incorporated with the modified DF approaches. As shown in Table 5.10 and Figure 5.5, it can be

observed that (1) the optimal factor settings of the comparative optimization model using the mechanistic overall DF approach results in the highest weighted overall desirability value and the highest f_2 value that demonstrates that the resulting equally-weighted optimal dissolution profile is the most similar to the target profile according to the FDA regulation; and (2) for the priority-based model using the mechanistic DF approach, the majority of its resulting individual desirability values are larger than those of the other models. Moreover, in Figure 5.6, the optimal solution resulting from the optimization model using the empirical approaches significantly improves the performance of the 1st-priority response variables compared with its equally-weighted model, which can observed by examining the overlapping plot of desirability against ω. Therefore, first, the optimal desirability settings of the optimization model using the empirical DFs are comparatively sensitive to the assigned priorities and less desirable than those using the mechanistic and overall DF approaches. Despite the fact that one main advantage of the empirical model over the others is the complete smoothness of the fitted curve, it may lead to errors as a consequence of the discontinuity of DF that is mechanistically expressed in a piecewise form. Recall that it may be infeasible to obtain an empirical overall DF by using the least squares method; hence, it is believed that the empirical model may become less effective in the optimization procedure. Second, although the comparative model produces the most desirable f_2 and overall desirability, its optimal solution appears to be sensitive to the numerical weight assigned to each of the individual DFs (see Figure 5.6 (c)), which may also result in further errors of the solution. Third, in this numerical example, the optimal solution of the comparative model fails to provide a

desirable value of $\hat{\mu}_2$ although the heaviest weight is assigned for it in the objective function. Finally, the priority-based optimization model integrated with the mechanistic DF approach works best among all the models when simultaneously taking into account the performance related to the f_2, overall desirability, and sensitivity to the assigned priorities.

In summary, the proposed priority-based optimization model is a competitive alternative to solve an MRS problem in the formulation optimization. Higher-order regression models combined with the best subsets technique are utilized to improve the estimation of the response and desirability in terms of the mean, variance, and covariance. Identified priorities can significantly reduce the potential sensitivity and undesirable subjectivity associated with the weight-based optimization method. Based upon the numerical example, it is concluded that by comparison the mechanistic desirability model is the most effective method to implement the proposed priority-based optimization procedure. Finally, a future investigation of more rigorous multi-objective optimization techniques, such as Tchebycheff method, may be needed to develop alternative multi-response formulation optimization models.

CHAPTER 6

CONCLUSIONS AND FUTURE RESEARCH

Pharmaceutical formulation optimization is the area in which the optimal settings of ingredient amounts are determined prior to scaling up a manufacturing process. The optimal formulation is able to fulfill the desirable performance of QCs specified by the FDA. Process scale-up always results in various modifications, such as ingredients, in order to meet the mounting clinical and market demand. In this case, the current formulation optimization approaches need to be extended to determine the optimal post-change formulation which achieves the desirable performance in regulatory documentation tests including dissolution comparisons and bioequivalence studies. The establishment of similarity in dissolution profiles and bioequivalence for the pre-change and post-change formulations can not only ensure the equivalent safety and efficacy of the two formulations, but also eliminate the need for submitting the duplicate data to the FDA for approval after the scale-up changes occur. Nevertheless, the formulation optimization for scale-up changes is not adequately documented in the previous investigations. Hence, the objective of this research is to improve the existing formulation optimization techniques by expanding their ability to solve the optimization problem when scale-up changes occur. Following a review of current formulation optimization methods in Chapter 2, the proposed models are developed in Chapters 3, 4, and 5 with focus on dissolution comparisons, bioequivalence studies, and MRS problems, respectively.

6.1 Contributions

Several academic contributions as a result of this research are summarized as follows:

1. Traditionally, drug designers only consider the mean of a QC; however, the variability of the QC of interest can be essential, since individual subjects may differ widely in their responses to a drug, which may result in large variability of the QC and thereby unpredictable safety and efficacy issue. In the proposed models, both the mean and variability of the QCs are taken into account. The Taguchi quality loss concept appears to be attractive because it describes the deviations from target profiles of the mean as well as variance. In Chapters 3 and 4, the Taguchi quality loss functions for the dissolution comparison and bioequivalence study are developed and then incorporated into the proposed optimization models, while the current methods, such as the f_2 equation for comparing dissolution profiles, do not consider the variance. Further, in Chapter 5, the traditional DF method is modified to evaluate the desirability associated with the variance and correlation of the QCs rather than solely the mean.
2. The standard 2×2 crossover design, which is a special type of DOE and typically performed for the evaluation of bioequivalence between formulations, is integrated into the ordinary experimental scheme in order to estimate the functional relationship between the ingredient amounts and the characteristic related to bioequivalence (see Chapter 4). In addition, the traditional evaluation method for bioequivalence is compared with the proposed method in Chapter 4,

and it turns out that the proposed one generally performs better based upon the numerical example and sensitivity analysis.

3. No formal research work for solving formulation optimization problems, where all related FDA and USP requirements are included, can be found in the literature. Therefore, as many regulatory regulations associated with the formulation optimization as possible are considered and mathematically formulated as constraints in the proposed optimization models, in an effort to enable the QCs to satisfy all the related requirements in an efficient manner. The development of various constraints, including disintegration, dissolution, friability, hardness, thickness, stability, and uniformity, are offered in Chapters 3 and 4.
4. It is common that formulation professionals are faced with multiple characteristics to be optimized. In the literature, the DF approach is extensively combined with the optimization technique to seek the best compromise among multiple characteristics. Traditionally, the weight-based overall DF is considered as an objective function to solve the MRS problems. However, this approach has a potential shortcoming: the optimal solutions are extremely sensitive to the weights assigned and these weights are subjective in nature. In order to overcome this weakness, two proposed DF approaches- mechanistic and empirical, which consider the mean as well as the variability of a QC, are incorporated into the priority-based goal programming procedure to solve MRS formulation optimization problems. Moreover, efforts are made to extend the traditional second-order estimators to higher-order in Chapter 5 as a way to reduce the error

in the characteristic prediction and therefore improve the precision of the resulting optimal solutions.

In summary, it is believed that the methodologies proposed in this dissertation can provide a significant support for modeling and optimizing pharmaceutical formulations.

6.2 Future Research

As stated in Chapter 4, the proposed formulation optimization model for bioequivalence studies relies on the assumption that the IVIVC is not established. However, the establishment of IVIVC may minimize the need for conducting costly and time-consuming bioequivalence studies. One of the motivations for a future investigation is to relax this assumption when conducting formulation optimization. Hence, a more comprehensive optimization procedure can be developed based upon the identified critical characteristics relevant to the IVIVC and associated constraints. The objective would be to seek an optimal post-change formulation whose bioequivalence studies can be substituted by dissolution comparisons as a consequence of an acceptable IVIVC.

Moreover, although the establishment of IVIVC can save considerable costs of developing a new drug for a drug company, it is not necessarily desirable for customers who are exposed to the potential risk of unpredictable safety and efficacy issue due to the relatively simple testing conducted during the R&D stage. Finding the best trade-off regarding the costs between the drug company and customers may deserve further considerations.

Finally, further research into the extended formulation optimization problem when multiple scale-up changes occur would be of great value. However, the FDA guidance does not adequately address associated requirements for this situation. It would be possible that dissolution comparisons and bioequivalence studies need to be performed simultaneously as required documentation tests for multiple changes. In this case, the existing formulation optimization methods should be further improved by expanding their ability to solve more realistic problems.

APPENDICES

APPENDIX 1

Mathematica Codes for the Examples in Chapter 3

1.1 Estimated Response Functions

```
vara[x1_,x2_,x3_,x4_,x5_]=-644+8.6x1+8.2x2-12.9x3-22.3x4+21.6x5-
    0.009x1*x2+0.104x1*x3+0.173x1*x4-0.124x1*x5+0.039x2*x3-
    0.957x2*x4+0.555x2*x5-0.18x3*x4-0.368x3*x5-0.269x4*x5-0.0318x1*x1-
    0.14x2*x2+0.037x3*x3+0.298x4*x4+0.218x5*x5

sa[x1_,x2_,x3_,x4_,x5_]=-26+0.56x1+0.18x2-1.12x3-
    1.97x4+0.62x5+0.0011x1*x2+0.0076x1*x3+0.0133x1*x4-0.0033x1*x5-0.0011x2*x3-
    0.0619x2*x4+0.0361x2*x5-0.006x3*x4-0.0253x3*x5-0.0221x4*x5-0.00237x1*x1-
    0.0018x2*x2+0.0056x3*x3+0.0205x4*x4+0.015x5*x5

a[x1_,x2_,x3_,x4_,x5_]=28+0.84x1+1.34x2-2.02x3-3x4-0.7x5-
    0.019x1*x2+0.0126x1*x3+0.021x1*x4-0.0002x1*x5+0.0389x2*x3-
    0.031x2*x4+0.0716x2*x5-0.0239x3*x4-0.0522x3*x5-0.0077x4*x5-
    0.00324x1*x1+0.0322x2*x2+0.0039x3*x3+0.0197x4*x4+0.0645x5*x5

w[x1_,x2_,x3_,x4_,x5_]=x1+x2+x3+x4+x5+80

d[x1_,x2_,x3_,x4_,x5_]=-17.9+0.309x1-0.5x2-
    0.24x3+0.57x4+0.22x5+0.00604x1*x2+0.00162x1*x3-0.00422x1*x4-
    0.00016x1*x5+0.0063x2*x3+0.0036x2*x4-0.0057x2*x5-0.0003x3*x4+0.0016x3*x5-
    0.0277x4*x5-0.00095x1*x1-0.0314x2*x2-0.00232x3*x3+0.0206x4*x4+0.0026x5*x5

sd[x1_,x2_,x3_,x4_,x5_]=-1.03+0.021x1+0.175x2-0.107x3+0.186x4-0.041x5-
    0.00027x1*x2+0.000987x1*x3-0.000703x1*x4-0.000016x1*x5+0.00087x2*x3-
    0.00245x2*x4-0.00078x2*x5-0.00109x3*x4+0.00266x3*x5-0.00215x4*x5-
    0.000102x1*x1-0.0053x2*x2-0.00186x3*x3+0.00061x4*x4-0.00009x5*x5

xbar[x1_,x2_,x3_,x4_,x5_]=1.04-0.00075x1+0.00157x2+0.00162x3-0.00064x4-0.00003x5-
    0.000004x1*x2-0.000008x1*x3+0.000005*x1*x4+0.000002x1*x5-
    0.000026x2*x3+0.000042x2*x4-0.000058x2*x5-0.000021x3*x4-
    0.000005x3*x5+0.000023x4*x5+0.000003x1*x1-0.000001x2*x2+0.000008x3*x3-
    0.000019x4*x4+0.000013x5*x5

s[x1_,x2_,x3_,x4_,x5_]=0.328-0.00336x1-0.00359x2+0.00441x3+0.00052x4-
    0.00817x5+0.000013x1*x2-
    0.000005x1*x3+0.000009x1*x4+0.000028x1*x5+0.000017x2*x3-
    0.00001x2*x4+0.000156x2*x5-
    0.0001x3*x4+0.000013x3*x5+0.000117x4*x5+0.000008x1*x1-0.000035x2*x2-
    0.000058x3*x3-0.000028x4*x4+0.000004x5*x5
```

av1[x1_,x2_,x3_,x4_,x5_]=2.4*s[x1,x2,x3,x4,x5]

av2[x1_,x2_,x3_,x4_,x5_]=0.985-xbar[x1,x2,x3,x4,x5]+2.4*s[x1,x2,x3,x4,x5]

av3[x1_,x2_,x3_,x4_,x5_]=xbar[x1,x2,x3,x4,x5]-1.015+2.4*s[x1,x2,x3,x4,x5]

f1[x1_,x2_,x3_,x4_,x5_]=-22.9+0.298x1-0.251x2-0.131x3-0.257x4+0.259x5-0.00146x1*x2-
0.00087x1*x3+0.00328x1*x4-0.00016x1*x5-0.00042x2*x3-0.0109x2*x4+0.0255x2*x5-
0.00406x3*x4-0.00844x3*x5-0.0137x4*x5-
0.000761x1*x1+0.0165x2*x2+0.00845x3*x3-0.00007x4*x4-0.0071x5*x5

f2[x1_,x2_,x3_,x4_,x5_]=-62.8+0.608x1+0.712x2+0.457x3-0.144x4-0.099x5-0.00125x1*x2-
0.00275x1*x3+0.00375x1*x4+0.00063x1*x5+0.00417x2*x3+0.00833x2*x4-
0.0188x2*x5-0.0163x3*x4+0.0025x3*x5-0.00547x4*x5-0.00151x1*x1-
0.0196x2*x2+0.00245x3*x3-0.00945x4*x4+0.0093x5*x5

f3[x1_,x2_,x3_,x4_,x5_]=-10.1+0.173x1-0.22x2-0.345x3+0.978x4-
0.254x5+0.00271x1*x2+0.00237x1*x3-0.00516x1*x4+0.00016x1*x5-
0.0129x2*x3+0.0172x2*x4+0.0036x2*x5-0.0116x3*x4+0.00031x3*x5+0.002x4*x5-
0.00061x1*x1-0.0054x2*x2+0.00305x3*x3+0.00007x4*x4+0.00632x5*x5

ci[x1_,x2_,x3_,x4_,x5_]=351-1.38x1-7.7x2-5.16x3-
25.3x4+1.87x5+0.0354x1*x2+0.0125x1*x3+0.132x1*x4+0.027x2*x3+0.014x2*x4+0.02
1x2*x5-0.0387x3*x4+0.0094x3*x5-0.075x4*x5-
0.0014x1*x1+0.029x2*x2+0.0606x3*x3+0.151*x4*x4-0.0639x5*x5

n[x1_,x2_,x3_,x4_,x5_]=129-1.35x1+1.15x2-0.34x3+0.36x4-0.49x5-0.00292x1*x2-
0.00525x1*x3-0.00469x1*x4+0.00344x1*x5+0.0108x2*x3+0.0073x2*x4-
0.0385x2*x5+0.0244x3*x4+0.0056x3*x5-0.007x4*x5+0.00427x1*x1-
0.0275x2*x2+0.0191x3*x3-0.01x4*x4+0.0095x5*x5

a1[x1_,x2_,x3_,x4_,x5_]=26.8+0.055x1+0.44x2-0.792x3-1.08x4+1.03x5-
0.00381x1*x2+0.00396x1*x3+0.00448x1*x4-0.00673x1*x5+0.007x2*x3-0.0179x2*x4-
0.0266x2*x5+0.0167x3*x4-0.0008x3*x5+0.0094x4*x5-0.00029x1*x1+0.0172x2*x2-
0.00407x3*x3-0.0035x4*x4+0.0174x5*x5

s1[x1_,x2_,x3_,x4_,x5_]=21-0.169x1-0.041x2-0.189x3+0.248x4-
0.191x5+0.00031x1*x2+0.000637x1*x3-0.00145x1*x4+0.00105x1*x5+0.00062x2*x3-
0.0013x2*x4+0.00224x2*x5+0.00084x3*x4-
0.00053x3*x5+0.00059x4*x5+0.000439x1*x1-
0.00221x2*x2+0.0014x3*x3+0.00016x4*x4-0.00101x5*x5

a2[x1_,x2_,x3_,x4_,x5_]=113-1.19x1-1.33x2+2.82x3-0.51x4+0.1x5+0.00367x1*x2-
0.013x1*x3+0.00591x1*x4+0.00059x1*x5-0.0041x2*x3-
0.0236x2*x4+0.0103x2*x5+0.0059x3*x4-0.0135x3*x5-
0.0175x4*x5+0.00392x1*x1+0.0371x2*x2-0.00734x3*x3-0.0103x4*x4+0.0055x5*x5

s2[x1_,x2_,x3_,x4_,x5_]=20.8-0.116x1-0.176x2-0.171x3-0.253x4-
0.072x5+0.00106x1*x2+0.000788x1*x3+0.0012x1*x4+0.000453x1*x5-
0.00213x2*x3+0.00328x2*x4-
0.00234x2*x5+0.00022x3*x4+0.00197x3*x5+0.0002x4*x5+0.000186x1*x1+0.00096x2
*x2+0.000795x3*x3-0.00024x4*x4-0.00157x5*x5

a3[x1_,x2_,x3_,x4_,x5_]=-61.5+0.948x1+1.05x2+1.12x3-1.08x4-0.54x5-0.00146x1*x2-
0.00587x1*x3+0.00628x1*x4+0.00138x1*x5-
0.0255x2*x3+0.001x2*x4+0.0099x2*x5+0.0029x3*x4-0.0063x3*x5+0.0095x4*x5-
0.00232x1*x1-0.0199x2*x2+0.00535x3*x3-0.013x4*x4+0.0103x5*x5

s3[x1_,x2_,x3_,x4_,x5_]=6.05-0.0203x1-0.02x2-
0.122x3+0.052x4+0.185x5+0.00025x1*x2+0.00005x1*x3-0.000563x1*x4-
0.000687x1*x5-0.00008x2*x3-0.0026x2*x4-0.00365x2*x5+0.00069x3*x4-
0.00031x3*x5-
0.00102x4*x5+0.000078x1*x1+0.00184x2*x2+0.00196x3*x3+0.00385x4*x4-
0.00006x5*x5

a4[x1_,x2_,x3_,x4_,x5_]=39.1+0.547x1-1.98x2-0.146x3-3.07x4-2.08x5+0.00706x1*x2-
0.00069x1*x3+0.0205x1*x4+0.0105x1*x5+0.0145x2*x3-0.0102x2*x4+0.0103x2*x5-
0.0105x3*x4+0.0026x3*x5-0.0024x4*x5-0.00258x1*x1+0.0152x2*x2+0.00266x3*x3-
0.0101x4*x4+0.00322x5*x5

s4[x1_,x2_,x3_,x4_,x5_]=-3.65+0.0715x1+0.017x2+0.0437x3+0.077x4+0.103x5-
0.000083x1*x2-0.00015x1*x3-0.0005x1*x4-0.000406x1*x5-0.00025x2*x3-
0.00281x2*x4+0.00104x2*x5+0.00156x3*x4+0.00025x3*x5-0.00047x4*x5-
0.000157x1*x1+0.00104x2*x2-0.000627x3*x3+0.000582x4*x4-0.00192x5*x5

a5[x1_,x2_,x3_,x4_,x5_]=207-1.24x1-0.42x2-0.607x3-3.61x4-
1.11x5+0.00802x1*x2+0.00509x1*x3+0.018x1*x4+0.00908x1*x5-0.0128x2*x3-
0.0064x2*x4-0.0053x2*x5+0.0345x3*x4+0.0027x3*x5-0.0136x4*x5+0.00218x1*x1-
0.021x2*x2-0.0108x3*x3-0.0177x4*x4-0.0186x5*x5

s5[x1_,x2_,x3_,x4_,x5_]=-6.58+0.112x1+0.164x2+0.0911x3+0.0577x4+0.0876x5-
0.000396x1*x2-0.000213x1*x3-0.000297x1*x4-0.000266x1*x5-
0.000625x2*x3+0.00245x2*x4-0.0012x2*x5-0.000594x3*x4-0.000031x3*x5-
0.00043x4*x5-0.000272x1*x1-0.00371x2*x2-0.000736x3*x3-0.000604x4*x4-
0.000916x5*x5

a6[x1_,x2_,x3_,x4_,x5_]=20.7+0.506x1+1.17x2-1.08x3+1.76x4+1.43x5-
0.00256x1*x2+0.00684x1*x3-0.00598x1*x4-0.0042x1*x5-0.0025x2*x3-0.0362x2*x4-
0.0042x2*x5+0.005x3*x4-0.0146x3*x5-0.0233x4*x5-0.00155x1*x1-0.0113x2*x2-
0.00021x3*x3-0.0064x4*x4-0.0012x5*x5

s6[x1_,x2_,x3_,x4_,x5_]=7.48-0.0065x1+0.171x2-0.0305x3-0.069x4+0.089x5-
0.000792x1*x2+0.000275x1*x3+0.000312x1*x4-0.000531x1*x5-
0.00142x2*x3+0.00167x2*x4+0.0001x2*x5-
0.00062x3*x4+0.00081x3*x5+0.00016x4*x5+0.00002x1*x1-0.00033x2*x2-

0.000068x3*x3+0.00005x4*x4-0.00058x5*x5

a7[x1_,x2_,x3_,x4_,x5_]=134-0.549x1-x2-0.135x3+0.183x4-
0.406x5+0.00404x1*x2+0.00147x1*x4+0.00131x1*x5+0.00583x2*x3-
0.0143x2*x4+0.0198x2*x5-0.0075x3*x4-
0.00794x3*x5+0.0025x4*x5+0.00135x1*x1+0.00509x2*x2+0.00458x3*x3-
0.00729x4*x4+0.00638x5*x5

s7[x1_,x2_,x3_,x4_,x5_]=10.4-0.0123x1+0.031x2-0.0252x3-0.154x4-0.13x5-
0.000271x1*x2+0.000112x1*x3+0.000609x1*x4+0.000641x1*x5-0.00038x2*x3-
0.00078x2*x4+0.00016x2*x5+0.00122x3*x4-0.000469x3*x5+0.0009x4*x5-
0.000003x1*x1+0.00163x2*x2+0.000086x3*x3+0.00076x4*x4+0.000526x5*x5

a8[x1_,x2_,x3_,x4_,x5_]=70.9+0.048x1+0.799x2-0.437x3-0.359x4+0.878x5-
0.00404x1*x2+0.00257x1*x3+0.003x1*x4-0.0035x1*x5+0.00242x2*x3+0.00354x2*x4-
0.00188x2*x5-0.009x3*x4-0.00325x3*x5-0.00195x4*x5-0.000125x1*x1-
0.00486x2*x2+0.0013x3*x3+0.0007x4*x4-0.00578x5*x5

s8[x1_,x2_,x3_,x4_,x5_]=5.7+0.043x1+0.117x2-0.201x3+0.073x4-0.121x5-
0.00092x1*x2+0.00065x1*x3-0.00091x1*x4+0.00072x1*x5+0.002x2*x3-
0.00177x2*x4-0.0001x2*x5+0.00206x3*x4-0.00206x3*x5+0.00172x4*x5-
0.000128x1*x1+0.00038x2*x2+0.00144x3*x3+0.0017x4*x4+0.00131x5*x5

v1[x1_,x2_,x3_,x4_,x5_]=150-1.33x1-0.33x2-1.49x3+1.87x4-
1.45x5+0.00244x1*x2+0.00504x1*x3-0.011x1*x4+0.00794x1*x5+0.0053x2*x3-
0.0103x2*x4+0.0176x2*x5+0.0066x3*x4-0.004x3*x5+0.0041x4*x5+0.00343x1*x1-
0.017x2*x2+0.0109x3*x3+0.0013x4*x4-0.0078x5*x5

v2[x1_,x2_,x3_,x4_,x5_]=207-1.32x1-2.05x2-1.99x3-2.94x4-
0.85x5+0.0123x1*x2+0.00917x1*x3+0.0139x1*x4+0.00535x1*x5-
0.0246x2*x3+0.0384x2*x4-
0.0272x2*x5+0.0027x3*x4+0.0229x3*x5+0.0023x4*x5+0.00211x1*x1+0.0112x2*x2+0
.0093x3*x3-0.0029x4*x4-0.0182x5*x5

v3[x1_,x2_,x3_,x4_,x5_]=30.6-0.142x1-0.16x2-
0.901x3+0.37x4+1.36x5+0.00201x1*x2+0.00039x1*x3-0.00407x1*x4-0.00501x1*x5-
0.0011x2*x3-0.019x2*x4-0.027x2*x5+0.0051x3*x4-0.0024x3*x5-
0.0074x4*x5+0.00054x1*x1+0.0134x2*x2+0.0145x3*x3+0.0285x4*x4-0.0005x5*x5

v4[x1_,x2_,x3_,x4_,x5_]=-53.2+0.645x1+0.15x2+0.404x3+0.687x4+0.918x5-0.00066x1*x2-
0.00138x1*x3-0.00444x1*x4-0.00361x1*x5-0.0025x2*x3-
0.0252x2*x4+0.0094x2*x5+0.014x3*x4+0.00216x3*x5-0.0041x4*x5-
0.00142x1*x1+0.0092x2*x2-

v5[x1_,x2_,x3_,x4_,x5_]=-118+1.37x1+2.01x2+1.11x3+0.71x4+1.07x5-0.00486x1*x2-
0.00259x1*x3-0.00363x1*x4-0.00323x1*x5-0.0076x2*x3+0.0299x2*x4-0.0146x2*x5-
0.00726x3*x4-0.00042x3*x5-0.0053x4*x5-0.00334x1*x1-0.0455x2*x2-0.00904x3*x3-
0.00752x4*x4-0.0112x5*x5

v6[x1_,x2_,x3_,x4_,x5_]=55.7-0.093x1+2.51x2-0.45x3-x4+1.29x5-
0.0116x1*x2+0.00403x1*x3+0.00455x1*x4-0.00773x1*x5-
0.0206x2*x3+0.0243x2*x4+0.0015x2*x5-
0.0092x3*x4+0.0118x3*x5+0.0022x4*x5+0.00029x1*x1-0.0049x2*x2-
0.00099x3*x3+0.0006x4*x4-0.0085x5*x5

v7[x1_,x2_,x3_,x4_,x5_]=101-0.189x1+0.49x2-0.39x3-2.37x4-2x5-
0.0042x1*x2+0.00173x1*x3+0.00938x1*x4+0.00988x1*x5-0.0059x2*x3-
0.012x2*x4+0.0024x2*x5+0.0188x3*x4-0.0072x3*x5+0.0138x4*x5-
0.00005x1*x1+0.0251x2*x2+0.00132x3*x3+0.0117x4*x4+0.0081x5*x5

v8[x1_,x2_,x3_,x4_,x5_]=27+0.65x1+1.81x2-3x3+1.09x4-1.77x5-0.0141x1*x2+0.0097x1*x3-
0.0135x1*x4+0.0106x1*x5+0.0302x2*x3-0.0268x2*x4-0.0016x2*x5+0.0308x3*x4-
0.0309x3*x5+0.0256x4*x5-
0.00194x1*x1+0.0056x2*x2+0.0215x3*x3+0.0256x4*x4+0.0191x5*x5

1.2 Optimization Models for Class 1 Drugs with Level 2 Changes

Minimize[{sa[x1,x2,x3,x4,x5],a[x1,x2,x3,x4,x5]/80>=0.85,10<=d[x1,x2,x3,x4,x5]<=11.8,Abs[(x
1-190)/318]<=0.1,Abs[(x2-10.5)/318]<=0.06,Abs[(x3-20)/318]<=0.01,Abs[(x4-
15)/318]<=0.005,Abs[(x5-2.5)/318]<=0.02,Abs[(x1-190)/318]+Abs[(x2-
10.5)/318]+Abs[(x3-20)/318]+Abs[(x4-17)/318]+Abs[(x5-
2.5)/318]<=0.1,sd[x1,x2,x3,x4,x5]/d[x1,x2,x3,x4,x5]<=0.1,sa[x1,x2,x3,x4,x5]/a[x1,x2,x
3,x4,x5]<=0.1,80/w[x1,x2,x3,x4,x5]>=0.25,s[x1,x2,x3,x4,x5]/xbar[x1,x2,x3,x4,x5]<=0.0
2,f1[x1,x2,x3,x4,x5]/w[x1,x2,x3,x4,x5]<=0.01,ci[x1,x2,x3,x4,x5]<=25,sd[x1,x2,x3,x4,x
5]>=0,d[x1,x2,x3,x4,x5]>=0,vara[x1,x2,x3,x4,x5]>=0,a[x1,x2,x3,x4,x5]>=0,w[x1,x2,x3,
x4,x5]>=0,0.985<=xbar[x1,x2,x3,x4,x5]<=1.105,0<=av1[x1,x2,x3,x4,x5]<=0.15,s[x1,x2,
x3,x4,x5]>=0,f1[x1,x2,x3,x4,x5]>=0,ci[x1,x2,x3,x4,x5]>=0,9.5<=n[x1,x2,x3,x4,x5]<=1
0.5,sa[x1,x2,x3,x4,x5]>=0,160<=x1<=200,4.8<=x2<=16.8,15<=x3<=35,1<=x4<=17,2<
=x5<=18},{x1,x2,x3,x4,x5}]

Minimize[{vara[x1,x2,x3,x4,x5],a[x1,x2,x3,x4,x5]/80>=0.85,10<=d[x1,x2,x3,x4,x5]<=11.8,Abs[
(x1-190)/318]<=0.1,Abs[(x2-10.5)/318]<=0.06,Abs[(x3-20)/318]<=0.01,Abs[(x4-
15)/318]<=0.005,Abs[(x5-2.5)/318]<=0.02,Abs[(x1-190)/318]+Abs[(x2-
10.5)/318]+Abs[(x3-20)/318]+Abs[(x4-17)/318]+Abs[(x5-
2.5)/318]<=0.1,sd[x1,x2,x3,x4,x5]/d[x1,x2,x3,x4,x5]<=0.1,sa[x1,x2,x3,x4,x5]/a[x1,x2,x
3,x4,x5]<=0.1,80/w[x1,x2,x3,x4,x5]>=0.25,s[x1,x2,x3,x4,x5]/xbar[x1,x2,x3,x4,x5]<=0.0
2,f1[x1,x2,x3,x4,x5]/w[x1,x2,x3,x4,x5]<=0.01,ci[x1,x2,x3,x4,x5]<=25,sd[x1,x2,x3,x4,x
5]>=0,d[x1,x2,x3,x4,x5]>=0,vara[x1,x2,x3,x4,x5]>=0,a[x1,x2,x3,x4,x5]>=0,w[x1,x2,x3,
x4,x5]>=0,0.985<=xbar[x1,x2,x3,x4,x5]<=1.105,0<=av1[x1,x2,x3,x4,x5]<=0.15,s[x1,x2,
x3,x4,x5]>=0,f1[x1,x2,x3,x4,x5]>=0,ci[x1,x2,x3,x4,x5]>=0,9.5<=n[x1,x2,x3,x4,x5]<=1
0.5,sa[x1,x2,x3,x4,x5]>=0,160<=x1<=200,4.8<=x2<=16.8,15<=x3<=35,1<=x4<=17,2<
=x5<=18},{x1,x2,x3,x4,x5}]

1.3 Optimization Models for Class 2 and 3 Drugs with Level 2 Changes

```
obj1[x1_,x2_,x3_,x4_,x5_]=(50*(Log[10,(1+1/8*((a1[x2,x2,x3,x4,x5]-
    22)^2+(a2[x1,x2,x3,x4,x5]-33)^2+(a3[x1,x2,x3,x4,x5]-38)^2+(a4[x1,x2,x3,x4,x5]-
    48)^2+(a5[x1,x2,x3,x4,x5]-65)^2+(a6[x1,x2,x3,x4,x5]-74)^2+(a7[x1,x2,x3,x4,x5]-
    77)^2+(a8[x1,x2,x3,x4,x5]-78)^2))^(-0.5)*100])-100)^2

Minimize[{obj1[x1,x2,x3,x4,x5],s1[x1,x2,x3,x4,x5]/a1[x1,x2,x3,x4,x5]<=0.2,s1[x1,x2,x3,x4,x5]
    >=0,a1[x1,x2,x3,x4,x5]>=0,s2[x1,x2,x3,x4,x5]/a2[x1,x2,x3,x4,x5]<=0.2,a2[x1,x2,x3,x4,
    x5]>=0,s2[x1,x2,x3,x4,x5]>=0,s3[x1,x2,x3,x4,x5]/a3[x1,x2,x3,x4,x5]<=0.2,a3[x1,x2,x3,
    x4,x5]>=0,s3[x1,x2,x3,x4,x5 >=0,s4[x1,x2,x3,x4,x5]/a4[x1,x2,x3,x4,x5]<=0.1,s4[x1,x2,
    x3,x4,x5]>=0,a4[x1,x2,x3,x4,x5]>=0,s5[x1,x2,x3,x4,x5]/a5[x1,x2,x3,x4,x5]<=0.1,s5[x1,
    x2,x3,x4,x5]>=0,a5[x1,x2,x3,x4,x5]>=0,s6[x1,x2,x3,x4,x5]/a6[x1,x2,x3,x4,x5]<=0.1,s6[
    x1,x2,x3,x4,x5]>=0,a6[x1,x2,x3,x4,x5]>=0,s7[x1,x2,x3,x4,x5]/a7[x1,x2,x3,x4,x5]<=0.1,
    s7[x1,x2,x3,x4,x5]>=0,a7[x1,x2,x3,x4,x5]>=0,s8[x1,x2,x3,x4,x5]/a8[x1,x2,x3,x4,x5]<=0
    .1,s8[x1,x2,x3,x4,x5]>=0,a8[x1,x2,x3,x4,x5]>=0,a4[x1,x2,x3,x4,x5]/80<=0.85,sd[x1,x2,
    x3,x4,x5]/d[x1,x2,x3,x4,x5]<=0.1,Abs[(x4-15)/318]<=0.005,Abs[(x1-
    190)/318]<=0.1,Abs[(x2-10.5)/318]<=0.06,Abs[(x3-20)/318]<=0.01,Abs[(x5-
    2.5)/318]<=0.02,Abs[(x1-190)/318]+Abs[(x2-10.5)/318]+Abs[(x3-20)/318]+Abs[(x4-
    15)/318]+Abs[(x5-
    2.5)/318]<=0.1,a4[x1,x2,x3,x4,x5]/80<=0.85,sd[x1,x2,x3,x4,x5]/d[x1,x2,x3,x4,x5]<=0.1,
    10<=d[x1,x2,x3,x4,x5]<=11.8,sd[x1,x2,x3,x4,x5]>=0,a6[x1,x2,x3,x4,x5]/80>=0.85,80/w
    [x1,x2,x3,x4,x5]<=0.25,w[x1,x2,x3,x4,x5]>=0,s[x1,x2,x3,x4,x5]/xbar[x1,x2,x3,x4,x5]<=
    0.02,0.985<=xbar[x1,x2,x3,x4,x5]<=1.105,s[x1,x2,x3,x4,x5]>=0,0<=av1[x1,x2,x3,x4,x5
    ]<=0.15,f1[x1,x2,x3,x4,x5]>=0,ci[x1,x2,x3,x4,x5]>=0,9.5<=n[x1,x2,x3,x4,x5]<=10.5,f1[
    x1,x2,x3,x4,x5]/w[x1,x2,x3,x4,x5]<=0.01,ci[x1,x2,x3,x4,x5]<=25,d[x1,x2,x3,x4,x5]>=0,
    160<=x1<=200,4.8<=x2<=16.8,15<=x3<=35,1<=x4<=17,2<=x5<=18,0.50<=a4[x1,x2,x
    3,x4,x5]/80<=0.65,factor[x1,x2,x3,x4,x5]>=50},{x1,x2,x3,x4,x5}]

obj2[x1_,x2_,x3_,x4_,x5_]=(a1[x1,x2,x3,x4,x5]-22)^2+v1[x1,x2,x3,x4,x5]+(a2[x1,x2,x3,x4,x5]-
    33)^2+v2[x1,x2,x3,x4,x5]+(a3[x1,x2,x3,x4,x5]-
    38)^2+v3[x1,x2,x3,x4,x5]+(a4[x1,x2,x3,x4,x5]-
    48)^2+v4[x1,x2,x3,x4,x5]+(a5[x1,x2,x3,x4,x5]-
    65)^2+v5[x1,x2,x3,x4,x5]+(a6[x1,x2,x3,x4,x5]-
    74)^2+v6[x1,x2,x3,x4,x5]+(a7[x1,x2,x3,x4,x5]-
    77)^2+v7[x1,x2,x3,x4,x5]+(a8[x1,x2,x3,x4,x5]-78)^2+v8[x1,x2,x3,x4,x5]

Minimize[{obj2[x1,x2,x3,x4,x5],s4[x1,x2,x3,x4,x5]/a4[x1,x2,x3,x4,x5]<=0.1,s4[x1,x2,x3,x4,x5]
    >=0,a4[x1,x2,x3,x4,x5]>=0,s6[x1,x2,x3,x4,x5]/a6[x1,x2,x3,x4,x5]<=0.1,s6[x1,x2,x3,x4,
    x5]>=0,a6[x1,x2,x3,x4,x5]>=0,Abs[(x1-190)/318]<=0.1,Abs[(x2-
    10.5)/318]<=0.06,Abs[(x3-20)/318]<=0.01,Abs[(x4-15)/318]<=0.005,Abs[(x5-
    2.5)/318]<=0.02,Abs[(x1-190)/318]+Abs[(x2-10.5)/318]+Abs[(x3-20)/318]+Abs[(x4-
    7)/318]+Abs[(x5-
    2.5)/318]<=0.1,sd[x1,x2,x3,x4,x5]/d[x1,x2,x3,x4,x5]<=0.1,10<=d[x1,x2,x3,x4,x5]<=11.
    8,sd[x1,x2,x3,x4,x5]>=0,0.50<=a4[x1,x2,x3,x4,x5]/80<=0.65,a6[x1,x2,x3,x4,x5]/80>=0.
    85,80/w[x1,x2,x3,x4,x5]>=0.25,w[x1,x2,x3,x4,x5]>=0,s[x1,x2,x3,x4,x5]/xbar[x1,x2,x3,
    x4,x5]<=0.02,0.985<=xbar[x1,x2,x3,x4,x5]<=1.105,s[x1,x2,x3,x4,x5]>=0,0<=av1[x1,x2,
    x3,x4,x5]<=0.15,f1[x1,x2,x3,x4,x5]>=0,ci[x1,x2,x3,x4,x5]>=0,9.5<=n[x1,x2,x3,x4,x5]<
```

=10.5,f1[x1,x2,x3,x4,x5]/w[x1,x2,x3,x4,x5]<=0.01,ci[x1,x2,x3,x4,x5]<=25,d[x1,x2,x3,x4,x5]>=0,160<=x1<=200,4.8<=x2<=16.8,15<=x3<=35,1<=x4<=17,2<=x5<=18,factor[x1,x2,x3,x4,x5]>=50},{x1,x2,x3,x4,x5}]

APPENDIX 2

MATLAB and Mathematica Codes for the Example in Chapter 4

2.1 MATLAB Code for Estimating $\mathbf{K}_a$

```
C=xlsread('filename',sheet,'range');
T=xlsread('filename',sheet,'range');
TD=xlsread('filename',sheet,'range');
Ke=xlsread('filename',sheet,'range');
K=xlsread('filename',sheet,'range');
%Read vectors C, T, TD, Ke and K from a Microsoft® Excel file.

syms Ka
KA=[];
for m=1:1:x  %x=2*i*r.
   C_temp=[];
   for o=1:1:y  %y=n.
      C_temp(o)=C(m,o);
   end
   C_vector=C_temp';
   f1=exp((-Ka*T).')*TD;
   f2=exp(-Ke(m)*T)-C_vector/K(m)-exp(-Ka*T);
   f=f1*f2;
   KA(m)=solve(f,Ka);
end
KA=KA'
xlswrite('filename',KA,sheet,'range');  %output vector KA into an Excel file.
```

2.2 Estimated Response Functions

rauc[x1_,x2_]=4.95-0.0025x1+0.0061x2-0.000091x1*x2+0.000009x1*x1+0.000503x2*x2

rauc1[x1_,x2_]=5.14-0.0043x1+0.0016x2-0.000074x1*x2+0.000013x1*x1+0.000572x2*x2

tauc[x1_,x2_]=5.78-0.0094x1-0.0345x2+0.000169x1*x2+0.000021x1*x1+0.000147x2*x2

tauc1[x1_,x2_]=5.45-0.00672x1-0.0206x2+0.000095x1*x2+0.000016x1*x1+0.000112x2*x2

rtmax[x1_,x2_]=14.8-0.119x1-0.408x2+0.00208x1*x2+0.000271x1*x1+0.00069x2*x2

rtmax1[x1_,x2_]=3.71-0.0138x1-0.112x2+0.000503x1*x2+0.000025x1*x1+0.00087x2*x2

ttmax[x1_,x2_]=3.21-0.0294x1+0.232x2-0.00139x1*x2+0.000125x1*x1+0.00139x2*x2

ttmax1[x1_,x2_]=-1.96+0.0388x1+0.0598x2-0.000289x1*x2-0.000097x1*x1-0.000329x2*x2

rcmax[x1_,x2_]=3.59-0.00831x1-0.0206x2+0.00012x1*x2+0.000021x1*x1-0.000079x2*x2

rcmax1[x1_,x2_]=2.61+0.0027x1-0.0245x2+0.000112x1*x2-0.00001x1*x1+0.000173x2*x2

tcmax[x1_,x2_]=4.08-0.0138x1-0.0129x2+0.000035x1*x2+0.000037x1*x1+0.000362x2*x2

tcmax1[x1_,x2_]=2.28+0.00433x1+0.0106x2-0.000058x1*x2-0.00001x1*x1-0.000024x2*x2

dauc[x1_,x2_]=1.83-0.0191x1-0.0124x2+0.00001x1*x2+0.000052x1*x1+0.000417x2*x2

dcmax[x1_,x2_]=-0.73+0.0063x1+0.0324x2-0.000181x1*x2-0.000012x1*x1+0.00005x2*x2

lauc[x1_,x2_]=(tauc[x1,x2]-rauc[x1,x2])-2.132*dauc[x1,x2]*Sqrt[1/3+1/3]

lauc1[x1_,x2_]=(tauc1[x1,x2]-rauc1[x1,x2])-2.132*dauc[x1,x2]*Sqrt[1/3+1/3]

uauc[x1_,x2_]=(tauc[x1,x2]-rauc[x1,x2])+2.132*dauc[x1,x2]*Sqrt[1/3+1/3]

uauc1[x1_,x2_]=(tauc1[x1,x2]-rauc1[x1,x2])+2.132*dauc[x1,x2]*Sqrt[1/3+1/3]

lcmax[x1_,x2_]=(tcmax[x1,x2]-rcmax[x1,x2])-2.132*dcmax[x1,x2]*Sqrt[1/3+1/3]

lcmax1[x1_,x2_]=(tcmax1[x1,x2]-rcmax1[x1,x2])-2.132*dcmax[x1,x2]*Sqrt[1/3+1/3]

ucmax[x1_,x2_]=(tcmax[x1,x2]-rcmax[x1,x2])+2.132*dcmax[x1,x2]*Sqrt[1/3+1/3]

ucmax1[x1_,x2_]=(tcmax1[x1,x2]-rcmax1[x1,x2])+2.132*dcmax[x1,x2]*Sqrt[1/3+1/3]

s2auc[x1_,x2_]=0.0767-0.000766x1-
    0.00099x2+0.000003x1*x2+0.000002x1*x1+0.000016x2*x2

s2cmax[x1_,x2_]=-0.0082+0.000068x1+0.000464x2-0.000003x1*x2-
    0.00000011x1*x1+0.000003x2*x2

varauc[x1_,x2_]=0.0426-0.000392x1-
    0.00116x2+0.000002x1*x2+0.000001x1*x1+0.000039x2*x2

varauc1[x1_,x2_]=0.0312-0.000261x1-
    0.00125x2+0.000002x1*x2+0.000001x1*x1+0.000038x2*x2

vartmax[x1_,x2_]=-0.71+0.0142x1-0.0917x2+0.000556x1*x2-0.000056x1*x1-0.00062x2*x2

vartmax1[x1_,x2_]=0.137-0.0013x1-0.00249x2+0.000028x1*x2+0.000003x1*x1-0.00012x2*x2

varcmax[x1_,x2_]=0.0129-0.000177x1+0.000776x2-

0.000005x1*x2+0.000001x1*x1+0.000003x2*x2

varcmax1[x1_,x2_]=0.0114-0.000125x1+0.0000773x2-
0.00000058x1*x2+0.00000036x1*x1+0.00000013x2*x2

2.3 Optimization Models for Class 4 Drugs with Level 3 Changes

obj1[x1_,x2_]=(tcmax[x1,x2]-rcmax[x1,x2])^2+varcmax[x1,x2]+(ttmax[x1,x2]-
rtmax[x1,x2])^2+vartmax[x1,x2]+(tauc[x1,x2]-rauc[x1,x2])^2+varauc[x1,x2]

Minimize[{obj1[x1,x2],Abs[(x1-150)/278]>0.1,Abs[(x2-10.5)/278]<=0.06,Abs[(x1-
190)/278]+Abs[(x2-10.5)/278]<=0.1,lauc[x1,x2]>=-
0.2*rauc[x1,x2],uauc[x1,x2]<=0.25*rauc[x1,x2],lcmax[x1,x2]>=-
0.20*rcmax[x1,x2],ucmax[x1,x2]<=0.25*rcmax[x1,x2],0<=s2auc[x1,x2]<=0.1,0<=s2cm
ax[x1,x2]<=0.1,165.858<=x1<=194.142,6.5574<=x2<=15.0426,s[x1,x2,20,15,2.5]/xbar[
x1,x2,20,15,2.5]<=0.02,f1[x1,x2,20,15,2.5]/w[x1,x2,20,15,2.5]<=0.01,ci[x1,x2,20,15,2.5
]<=25,sd[x1,x2,20,15,2.5]>=0,d[x1,x2,20,15,2.5]>=0,w[x1,x2,20,15,2.5]>=0,0.985 xba
r[x1,x2,20,15,2.5]<=1.105,0<=av1[x1,x2,20,15,2.5]<=0.15,s[x1,x2,20,15,2.5]>=0,f1[x1,
x2,20,15,2.5]>=0,ci[x1,x2,20,15,2.5]>=0,9.5<=n[x1,x2,20,15,2.5]<=10.5,tcmax[x1,x2]>
=0,rcmax[x1,x2]>=0,varcmax[x1,x2]>=0,ttmax[x1,x2]>=0,rtmax[x1,x2]>=0,vartmax[x1,
x2]>=0,tauc[x1,x2]>=0,rauc[x1,x2]>=0,varauc[x1,x2]>=0},{x1,x2}]

obj2[x1_,x2_]=(tcmax1[x1,x2]-rcmax1[x1,x2])^2+varcmax1[x1,x2]+(ttmax1[x1,x2]-
rtmax1[x1,x2])^2+vartmax1[x1,x2]+(tauc1[x1,x2]-rauc1[x1,x2])^2+varauc1[x1,x2]

Minimize[{obj2[x1,x2],Abs[(x1-150)/278]>0.1,Abs[(x2-10.5)/278]<=0.06,Abs[(x1-
190)/278]+Abs[(x2-10.5)/278]<=0.1,lauc1[x1,x2]>=-
0.2*rauc1[x1,x2],uauc1[x1,x2]<=0.25*rauc1[x1,x2],lcmax1[x1,x2]>=-
0.20*rcmax1[x1,x2],ucmax1[x1,x2]<=0.25*rcmax1[x1,x2],0<=s2auc[x1,x2]<=0.1,0<=s
2cmax[x1,x2]<=0.1,165.858<=x1<=194.142,6.5574<=x2<=15.0426,s[x1,x2,20,15,2.5]/x
bar[x1,x2,20,15,2.5]<=0.02,f1[x1,x2,20,15,2.5]/w[x1,x2,20,15,2.5]<=0.01,ci[x1,x2,20,15
,2.5]<=25,sd[x1,x2,20,15,2.5]>=0,d[x1,x2,20,15,2.5]>=0,w[x1,x2,20,15,2.5]>=0,0.985<
=xbar[x1,x2,20,15,2.5]<=1.105,0<=av1[x1,x2,20,15,2.5]<=0.15,s[x1,x2,20,15,2.5]>=0,f
1[x1,x2,20,15,2.5]>=0,ci[x1,x2,20,15,2.5]>=0,9.5<=n[x1,x2,20,15,2.5]<=10.5,tcmax1[x
1,x2]>=0,rcmax1[x1,x2]>=0,varcmax1[x1,x2]>=0,ttmax1[x1,x2]>=0,rtmax1[x1,x2]>=0,
vartmax1[x1,x2]>=0,tauc1[x1,x2]>=0,rauc1[x1,x2]>=0,varauc1[x1,x2]>=0},{x1,x2}]

APPENDIX 3

Mathematica Codes for the Example in Chapter 5

3.1 Estimated Response Functions

```
y1[x1_,x2_]=25.33-4x1+x2+x1*x2-2.33x1*x1-
        4.33x2*x2+0.5x1*x1*x2+0.5x1*x2*x2+8.33x1*x2*x2*x1

y2[x1_,x2_]=46.33-6.5x1-x2-1.25x1*x2-4.833x1*x1-
        3.33x2*x2+0.75x1*x1*x2+0.75x1*x2*x2+9.083x1*x1*x2*x2

y3[x1_,x2_]=68-8x1-2x2-3.75x1*x2-5x1*x1-
        4x2*x2+2.25x1*x1*x2+1.75x1*x2*x2+9.75x1*x1*x2*x2

y4[x1_,x2_]=87-7.5x1-2.5x2-5.25x1*x2-5.5x1*x1-
        2.5x2*x2+1.75x1*x1*x2+3.75x1*x2*x2+7.75x1*x1*x2*x2

y5[x1_,x2_]=101-3.5x1-2.5x2-3.5x1*x2-6.83x1*x1-2.83x2*x2+2x1*x2*x2+7.83x1*x1*x2*x2

s1[x1_,x2_]=2.8-1.83x1+7.5x2+2x1*x2+5.7x2*x2-9.5x1*x1*x2-5.5x1*x1*x2*x2

s2[x1_,x2_]=12.667-8.667x1*x1-8.667x2*x2+8.147x1*x1*x2*x2

s3[x1_,x2_]=16-9.167x2*x2

s4[x1_,x2_]=17.4-8.667x2-4.067x2*x2

s5[x1_,x2_]=19.667+3.333x1+8.25x1*x2-13.167x1*x1-15.667x2*x2-
        3.75x1*x1*x2+25.917x1*x1*x2*x2

s13[x1_,x2_]=0.9083+2.1596x2-2.1464x1*x2-1.1335x1*x1+1.6509x2*x2-
        1.7137x1*x1*x2+1.4781x1*x2*x2-2.724x1*x1*x2*x2

s14[x1_,x2_]=0.2912+2.6292x2-1.5448x1*x1*x2-0.9812x1*x1*x2*x2

s15[x1_,x2_]=0.5241+1.5428x2-1.6603x1*x2+1.4837x1*x2*x2-2.3758x1*x1*x2*x2

s23[x1_,x2_]=1.1798-2.3364x1-1.4173x1*x1-2.6574x2*x2-
        0.4314x1*x1*x2+1.1681x1*x2*x2+2.5304x1*x1*x2*x2

s24[x1_,x2_]=0.5331-2.462x1+1.951x1*x2+2.744x1*x2*x2

s25[x1_,x2_]=-1.4572+1.2974x1*x2+2.17x2*x2+1.793x1*x1*x2
```

s34[x1_,x2_]=2.3125+2.104x1+0.9361x2-2.608x1*x2*x2-4.233x1*x1*x2*x2

s35[x1_,x2_]=-0.064-2.672x1*x1*x2-1.056x1*x2*x2+2.29x1*x1*x2*x2

s45[x1_,x2_]=3.0493+1.8775x1-1.5451x2-2.0523x1*x2-1.5968x1*x1-
2.6055x2*x2+2.281x1*x1*x2

3.2 Estimated Empirical DFs

d1[x1_,x2_]=0.04123+0.23612x1-0.05889x2-0.07924x1*x2+0.20266x1*x1+0.29988x2*x2-
0.02035x1*x1*x2-0.15536x1*x2*x2-0.463x1*x1*x2*x2

d2[x1_,x2_]=0.45476-0.08741x1-0.25742x1*x1+0.29891x2*x2+0.4471x1*x2*x2-
0.1366x1*x1*x2*x2

d3[x1_,x2_]=0.27038+0.16835x2-0.1465x1*x1+0.357x2*x2-
0.1917x1*x1*x2+0.21794x1*x2*x2-0.21x1*x1*x2*x2

d4[x1_,x2_]=0.31675+0.17898x2+0.1168x1*x2-0.1625x1*x1+0.2956x2*x2-0.2923x1*x1*x2-
0.206x1*x1*x2*x2

d5[x1_,x2_]=0.50795-0.17436x1-0.28947x2-0.22744x1*x2-
0.30795x1*x1+0.26476x1*x1*x2+0.3101x1*x1*x2*x2

ds1[x1_,x2_]=0.888+0.0733x1-0.3x2-0.08x1*x2-
0.228x2*x2+0.38x1*x1*x2+0.22*x1*x2*x1*x2

ds2[x1_,x2_]=0.4933+0.3467x1*x1+0.3467x2*x2-0.3367x1*x1*x2*x2

ds3[x1_,x2_]=0.6735+0.1871x2*x2

ds4[x1_,x2_]=0.81257+0.107x2

ds5[x1_,x2_]=0.83747-0.02755x1-
0.06818x1*x2+0.10882x1*x1+0.12948x2*x2+0.03099x1*x1*x2-0.21419x1*x1*x2*x2

d12[x1_,x2_]=0.78905-0.23362x2+0.17063x1*x1+0.2248x1*x1*x2

d13[x1_,x2_]=0.80472+0.07446x1-0.43191x2-0.22277x1*x2+0.08768x1*x1-
0.31997x2*x2+0.6907x1*x1*x2

d14[x1_,x2_]=0.82298-0.17008x2-0.3488x2*x2+0.3058x1*x1*x2-
0.07486x1*x2*x2+0.3067x1*x1*x2*x2

d15[x1_,x2_]=0.79688-0.20242x2-
0.22856x1*x2+0.127x1*x1+0.4605x1*x1*x2+0.21986x1*x2*x2-0.2174x1*x1*x2*x2

d23[x1_,x2_]=0.74022-0.06442x1+0.08802x2-0.08628x1*x2-0.20751x1*x1-
0.14719x1*x1*x2+0.23363x1*x1*x2*x2

d24[x1_,x2_]=0.5617-0.24458x1-0.1614x1*x2

d25[x1_,x2_]=0.68037-0.2417x1-0.1879x1*x2-0.1543x1*x1*x2

d34[x1_,x2_]=0.3923-0.4162x1+0.2722x2*x2+0.2186x1*x1*x2+0.3154x1*x2*x2

d35[x1_,x2_]=0.436-0.12602x1*x2+0.3085x1*x1+0.4549x2*x2+0.35997x1*x1*x2-
0.6766x1*x1*x2*x2

d45[x1_,x2_]=0.5682-0.3064x1-0.1675x1*x2+0.3044x1*x1*x2+0.4389x1*x2*x2

3.3 Estimated Mechanistic DFs

dd1[x1_,x2_]=Piecewise[{{0,y1[x1,x2]<0|| y1[x1,x2]>25},{(y1[x1,x2]-0)/(12.5-
0),0<=y1[x1,x2]<=12.5},{(25-y1[x1,x2])/(25-12.5),12.5<y1[x1,x2]<=25}}]

dd2[x1_,x2_]=Piecewise[{{0,y2[x1,x2]<35|| y2[x1,x2]>50},{(y2[x1,x2]-35)/(42.5-
35),35=y2[x1,x2]<=42.5},{(50-y2[x1,x2])/(50-42.5),42.5<=y2[x1,x2]<=50}}]

dd3[x1_,x2_]=Piecewise[{{0,y3[x1,x2]<55|| y3[x1,x2]>70},{(y3[x1,x2]-55)/(62.5-
55),55<=y3[x1,x2]<=62.5},{(70-y3[x1,x2])/(70-62.5),62.5<=y3[x1,x2]<=70}}]

dd4[x1_,x2_]=Piecewise[{{0,y4[x1,x2]<75|| y4[x1,x2]>90},{(y4[x1,x2]-75)/(82.5-
75),75<=y4[x1,x2]<=82.5},{(90-y4[x1,x2])/(90-82.5),82.5<=y4[x1,x2]<=90}}]

dd5[x1_,x2_]=Piecewise[{{0,y5[x1,x2]<95|| y5[x1,x2]>110},{(y5[x1,x2]-95)/(102.5-
95),95<=y5[x1,x2]<=102.5},{(110-y5[x1,x2])/(110-102.5),102.5<=y5[x1,x2] <=110}}]

dds1[x1_,x2_]=Piecewise[{{1,s1[x1,x2]<=0},{(25-s1[x1,x2])/(25-
0),0<s1[x1,x2]<=25},{0,s1[x1,x2]>25}}]

dds2[x1_,x2_]=Piecewise[{{1,s2[x1,x2] <=0},{(25-s2[x1,x2])/(25-
0),0<s2[x1,x2]<=25},{0,s2[x1,x2]>25}}]

dds3[x1_,x2_]=Piecewise[{{1,s3[x1,x2] <=0},{(49-s1[x1,x2])/(49-
0),0<s3[x1,x2]<=49},{0,s3[x1,x2]>49}}]

dds4[x1_,x2_]=Piecewise[{{1,s4[x1,x2] <=0},{(81-s4[x1,x2])/(81-
0),0<s4[x1,x2]<=81},{0,s4[x1,x2]>81}}]

dds5[x1_,x2_]=Piecewise[{{1,s5[x1,x2] <=0},{(121-s5[x1,x2])/(121-
0),0<s5[x1,x2]<=121},{0,s5[x1,x2]>121}}]

```
dd12[x1_,x2_]=Piecewise[{{0,s12[x1,x2]<-5|| s12[x1,x2]>5},{(s12[x1,x2]+5)/5,-
        5<=s12[x1,x2]<=0},{(5-s12[x1,x2])/5,0<=s12[x1,x2] <=5}}]

dd13[x1_,x2_]=Piecewise[{{0,s13[x1,x2]<-5|| s13[x1,x2]>5},{(s13[x1,x2]+5)/5,-
        5<=s13[x1,x2]<=0},{(5-s13[x1,x2])/5,0<=s13[x1,x2] <=5}}]

dd14[x1_,x2_]=Piecewise[{{0,s14[x1,x2]<-5|| s14[x1,x2]>5},{(s14[x1,x2]+5)/5,-
        5<=s14[x1,x2]<=0},{(5-s14[x1,x2])/5,0<=s14[x1,x2] <=5}}]

dd15[x1_,x2_]=Piecewise[{{0,s15[x1,x2]<-5|| s15[x1,x2]>5},{(s15[x1,x2]+5)/5,-
        5<=s15[x1,x2]<=0},{(5-s15[x1,x2])/5,0<=s15[x1,x2] <=5}}]

dd23[x1_,x2_]=Piecewise[{{0,s23[x1,x2]<-5|| s23[x1,x2]>5},{(s23[x1,x2]+5)/5,-
        5<=s23[x1,x2]<=0},{(5-s23[x1,x2])/5,0<=s23[x1,x2] <=5}}]

dd24[x1_,x2_]=Piecewise[{{0,s24[x1,x2]<-5|| s24[x1,x2]>5},{(s24[x1,x2]+5)/5,-
        5<=s24[x1,x2]<=0},{(5-s24[x1,x2])/5,0<=s24[x1,x2] <=5}}]

dd25[x1_,x2_]=Piecewise[{{0,s25[x1,x2]<-5|| s25[x1,x2]>5},{(s25[x1,x2]+5)/5,-
        5<=s25[x1,x2]<=0},{(5-s25[x1,x2])/5,0<=s25[x1,x2] <=5}}]

dd34[x1_,x2_]=Piecewise[{{0,s34[x1,x2]<-5|| s34[x1,x2]>5},{(s34[x1,x2]+5)/5,-
        5<=s34[x1,x2]<=0},{(5-s34[x1,x2])/5,0<=s34[x1,x2] <=5}}]

dd35[x1_,x2_]=Piecewise[{{0,s35[x1,x2]<-5|| s35[x1,x2]>5},{(s35[x1,x2]+5)/5,-
        5<=s35[x1,x2]<=0},{(5-s35[x1,x2])/5,0<=s35[x1,x2] <=5}}]

dd45[x1_,x2_]=Piecewise[{{0,s45[x1,x2]<-5|| s45[x1,x2]>5},{(s45[x1,x2]+5)/5,-
        5<=s45[x1,x2]<=0},{(5-s45[x1,x2])/5,0<=s45[x1,x2] <=5}}]
```

3.4 Optimization Models

- Model using proposed empirical DFs

```
FindMinimum[{k21+k31+ks21+ks31,d2[x1,x2]+k21==1,d3[x1,x2]+k31==1,ds2[x1,x2]+ks21==
        1,ds3[x1,x2]+ks31==1,0<=y1[x1,x2]<=25,35<=y2[x1,x2]<=50,55<=y3[x1,x2]<=70,75<
        =y4[x1,x2]<=90,95<=y5[x1,x2]<=110,0<=s1[x1,x2]<=25,0<=s2[x1,x2]<=25,0<=s3[x1,
        x2]<=49,0<=s4[x1,x2]<=81,0<=s5[x1,x2]<=121,-5<=s12[x1,x2]<=5,-
        5<=s13[x1,x2]<=5,-5<=s14[x1,x2]<=5,-5<=s15[x1,x2]<=5,-5<=s23[x1,x2]<=5,-
        5<=s24[x1,x2]<=5,-5<=s25[x1,x2]<=5,-5<=s34[x1,x2]<=5,-5<=s35[x1,x2]<=5,-
        5<=s45[x1,x2]<=5,k21>=0,k31>=0,ks21>0,ks31>=0,-1<=x1<=1,-
        1<=x2<=1,0<=d1[x1,x2]<=1,0<=d2[x1,x2]<=1,0<=d3[x1,x2]<=1,0<=d4[x1,x2]<=1,0<=
        d5[x1,x2]<=1,0<=ds1[x1,x2]<=1,0<=ds2[x1,x2]<=1,0<=ds3[x1,x2]<=1,0<=ds4[x1,x2]<
        =1,0<=ds5[x1,x2]<=1,0<=d12[x1,x2]<=1,0<=d12[x1,x2]<=1,0<=d13[x1,x2]<=1,0<=d1
        4[x1,x2]<=1,0<=d15[x1,x2]<=1,0<=d23[x1,x2]<=1,0<=d24[x1,x2]<=1,0<=d25[x1,x2]<
```

=1,0<=d34[x1,x2]<=1,0<=d35[x1,x2]<=1,0<=d45[x1,x2]<=1},{x1,x2,k21,k31,ks21,ks31},MaxIterations->1000]

- Model using proposed mechanistic DFs

Minimize[{k21+k31+ks21+ks31,dd2[x1,x2]+k21==1,dd3[x1,x2]+k31==1,dds2[x1,x2]+ks21==1,dds3[x1,x2]+ks31==1,0<=y1[x1,x2]<=25,35<=y2[x1,x2]<=50,55<=y3[x1,x2]<=70,75<=y4[x1,x2]<=90,95<=y5[x1,x2]<=110,0<=s1[x1,x2]<=25,0<=s2[x1,x2]<=25,0<=s3[x1,x2]<=49,0<=s4[x1,x2]<=81,0<=s5[x1,x2]<=121,-5<=s12[x1,x2]<=5,-5<=s13[x1,x2]<=5,-5<=s14[x1,x2]<=5,-5<=s15[x1,x2]<=5,-5<=s23[x1,x2]<=5,-5<=s24[x1,x2]<=5,-5<=s25[x1,x2]<=5,-5<=s34[x1,x2]<=5,-5<=s35[x1,x2]<=5,-5<=s45[x1,x2]<=5,k21>=0,k31>=0,ks21>0,ks31>=0,-1<=x1<=1,-1<=x2<=1,0<=dd1[x1,x2]<=1,0<=dd2[x1,x2]<=1,0<=dd3[x1,x2]<=1,0<=dd4[x1,x2]<=1,0<=dd5[x1,x2]<=1,0<=dds1[x1,x2]<=1,0<=dds2[x1,x2]<=1,0<=dds3[x1,x2]<=1,0<=dds4[x1,x2]<=1,0<=dds5[x1,x2]<=1,0<=dd12[x1,x2]<=1,0<=dd13[x1,x2]<=1,0<=dd14[x1,x2]<=1,0<=dd15[x1,x2]<=1,0<=dd23[x1,x2]<=1,0<=dd24[x1,x2]<=1,0<=dd25[x1,x2]<=1,0<=dd34[x1,x2]<=1,0<=dd35[x1,x2]<=1,0<=dd45[x1,x2]<=1},{x1,x2,k21,k31,ks21,ks31}]

- Model using the weighted overall DF

objd[x1_,x2_]=(dd1[x1,x2]^10*dd2[x1,x2]^100*dd3[x1,x2]^100*dd4[x1,x2]^10*dd5[x1,x2]^10*dds1[x1,x2]^10*dds2[x1,x2]^100*dds3[x1,x2]^100*dds4[x1,x2]^10*dds5[x1,x2]^10*dd12[x1,x2]*dd13[x1,x2]*dd14[x1,x2]*dd15[x1,x2]*dd23[x1,x2]*dd24[x1,x2]*dd25[x1,x2]*dd34[x1,x2]*dd35[x1,x2]*dd45[x1,x2])^(1/470)

Maximize[{objd[x1,x2],0<=y1[x1,x2]<=25,35<=y2[x1,x2]<=50,55<=y3[x1,x2]<=70,75<=y4[x1,x2]<=90,95<=y5[x1,x2]<=110,0<=s1[x1,x2]<=25,0<=s2[x1,x2]<=25,0<=s3[x1,x2]<=49,0<=s4[x1,x2]<=81,0<=s5[x1,x2]<=121,-5<=s12[x1,x2]<=5,-5<=s13[x1,x2]<=5,-5<=s14[x1,x2]<=5,-5<=s15[x1,x2]<=5,-5<=s23[x1,x2]<=5,-5<=s24[x1,x2]<=5,-5<=s25[x1,x2]<=5,-5<=s34[x1,x2]<=5,-5<=s35[x1,x2]<=5,-5<=s45[x1,x2]<=5,-1<=x1<=1,-1<=x2<=1,0<=d1[x1,x2]<=1,0<=d2[x1,x2]<=1,0<=dd3[x1,x2]<=1,0<=dd4[x1,x2]<=1,0<=dd5[x1,x2]<=1,0<=dds1[x1,x2]<=1,0<=dds2[x1,x2]<=1,0<=dds3[x1,x2]<=1,0<=dds4[x1,x2]<=1,0<=dds5[x1,x2]<=1,0<=dd12[x1,x2]<=1,0<=dd13[x1,x2]<=1,0<=dd14[x1,x2]<=1,0<=dd15[x1,x2]<=1,0<=dd23[x1,x2]<=1,0<=dd24[x1,x2]<=1,0<=dd25[x1,x2]<=1,0<=dd34[x1,x2]<=1,0<=dd35[x1,x2]<=1,0<=dd45[x1,x2]<=1,0<=objd[x1,x2]<=1},{x1,x2}]

REFERENCES

Abu-Izza, K., Garcia-Contreras, L., & Lu, D. R. (1996). Preparation and evaluation of zidovudine-loaded sustained-release microspheres. 2. Optimization of multiple response variables. *Journal of Pharmaceutical Sciences, 85*(6), 572-576.

Anderson, N. H., Bauer, M., Boussac, N., Khan-Malek, R., Munden, P., & Sardaro, M. (1998). An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. *Journal of Pharmaceutical and Biomedical Analysis, 17*(4-5), 811-822.

Armstrong, N. A. (2006). *Pharmaceutical Experimental Design and Interpretation*. Boca Raton: CRC Press.

Bamba, M., Puisieux, F., Marty, J. P., & Carstensen, J. T. (1979). Physical model for release of drug from gelforming sustained release preparations. *International Journal of Pharmaceutics, 3*(2-3), 87-92.

Bashiri, M., & Salmasnia, A. (2009). *Decision making for interactive optimization of correlated desirability functions.* Paper presented at the IEEE International Conference, Hong Kong.

Berry, M. R., & Likar, M. D. (2007). Statistical assessment of dissolution and drug release profile similarity using a model-dependent approach. *Journal of Pharmaceutical and Biomedical Analysis, 45*(2), 194-200.

Bhavsar, M. D., Tiwari, S. B., & Amiji, M. M. (2006). Formulation optimization for the nanoparticles-in-microsphere hybrid oral delivery system using factorial design. *Journal of Controlled Release, 110*(2), 422-430.

Bolton, S., & Bon, C. (2009). *Pharmaceutical Statistics: Practical and Clinical Applications* (5th ed.). New York: Informa Healthcare USA, Inc.

Bourquin, J., Schmidli, H., van Hoogevest, P., & Leuenberger, H. (1998). Pitfalls of artificial neural networks (ANN) modelling technique for data sets containing outlier measurements using a study on mixture properties of a direct compressed dosage form. *European Journal of Pharmaceutical Sciences, 7*(1), 17-28.

Box, G. E. P., & Behnken, D. W. (1960). Some new three level designs for the study of quantitative variables. *Technometrics, 2*(4), 455-475.

Brockmeier, D. (1986). In vitro/in vivo correlation of dissolution using moments of dissolution and transit times. *Acta Pharmaceutica Technologica, 32*(4), 164-174.

Campisi, B., Chicco, D., Vojnovic, D., & Phan-Tan-Luu, R. (1998). Experimental design for a pharmaceutical formulation: optimisation and robustness. *Journal of Pharmaceutical and Biomedical Analysis, 18*(1-2), 57-65.

Candioti, L. V., Robles, J. C., Mantovani, V. E., & Goicoechea, H. C. (2006). Multiple response optimization applied to the development of a capillary electrophoretic method for pharmaceutical analysis. *Talanta, 69*(1), 140-147.

Chazel, V., Houpert, P., & Ansoborlo, E. (1998). Effect of U3O8 specific surface area on in vitro dissolution, biokinetics, and dose coefficients. *Radiation Protection Dosimetry, 79*(1-4), 39-42.

Chen, L. H. (1997). Designing robust products with multiple quality characteristics. *Computers & Operations Research, 24*(10), 937-944.

Chen, M. L., Lesko, L. J., & Williams, R. L. (2001). Measures of exposure versus measures of rate and extent of absorption. *Clinical Pharmacokinetics, 40*(8), 565-572.

Cho, B. R., & Leonard, M. S. (1997). Identification and extensions of quasiconvex quality loss functions. *International Journal of Reliability Quality and Safety Engineering, 4*, 191-204.

Chow, S. C., Peace, K. E., & Shao, J. (1991). Assessment of bioequivalence using a multiplicative model. *Journal of Biopharmaceutical Statistics, 1*(2), 193-203.

Chow, S. C., & Fanny, Y. K. (1997). Statistical comparison between dissolution profiles of drug products. *Journal of Biopharmaceutical Statistics, 7*(2), 241-258.

Chow, S. C., & Liu, J. P. (2009). *Design and Analysis of Bioavailability and Bioequivalence Studies* (3rd ed.). Boca Raton: Chapman & Hall/CRC.

Cruz-Monteagudo, M., Borges, F., & Cordeiro, M. (2008). Desirability-based multiobjective optimization for global QSAR studies: Application to the design of novel NSAIDs with improved analgesic, antiinflammatory, and ulcerogenic profiles. *Journal of Computational Chemistry, 29*(14), 2445-2459.

Dave, B. S., Amin, A. F., & Patel, M. M. (2004). Gastroretentive drug delivery system of ranitidine hydrochloride: Formulation and in vitro evaluation. *AAPS PharmSciTech, 5*(2), 77-82.

Dawoodbhai, T. S., Suryanarayan, E. R., Woodruff, C. W., & Rhodes, C. T. (1991). Optimization of tablet formulations containing. *Drug Development and Industrial Pharmacy, 17*(10), 1343-1371.

Del Castillo, E., Montgomery, D. C., & McCarville, D. R. (1996). Modified desirability functions for multiple response optimization. *Journal of Quality Technology, 28*(3), 337-337.

Derringer, G., & Suich, R. (1980). Simultaneous optimization of several response variables. *Journal of quality technology, 12*(4), 214-219.

Derringer, G. C. (1994). A balancing act: optimizing a product's properties. *Quality Progress, 27*(6), 51-60.

El-Malah, Y., Nazzal, S., & Khanfar, N. M. (2006). D-optimal mixture design: optimization of ternary matrix blends for controlled zero-order drug release from oral dosage forms. *Drug Development and Industrial Pharmacy, 32*(10), 1207-1218.

Elsayed, E. A., & Chen, A. (1993). Optimal levels of process parameters for products with multiple characteristics. *International Journal of Production Research, 31*(5), 1117-1132.

Emami, J. (2006). In vitro-in vivo correlation: from theory to applications. *Journal of Pharmacy and Pharmaceutical Sciences, 9*(2), 169-189.

Endrenyi, L., Fritsch, S., & Yan, W. (1991). Cmax/AUC is a clearer measure than Cmax for absorption rates in investigations of bioequivalence. *International Journal of Clinical Pharmacology, Therapy, and Toxicology, 29*(10), 394-399.

Endrenyi, L., & Yan, W. (1993). Variation of Cmax and Cmax/AUC in investigations of bioequivalence. *International Journal of Clinical Pharmacology, Therapy, and Toxicology, 31*(4), 184-189.

Fan, T., Takayama, K., Hattori, Y., & Maitani, Y. (2004). Formulation optimization of paclitaxel carried by PEGylated emulsions based on artificial neural network. *Pharmaceutical Research, 21*(9), 1692-1697.

FDA. (1995). *Guidance for industry: immediate release solid oral dosage forms: scale-up and postapproval changes: chemistry, manufacturing, and controls, in vitro dissolution testing, and in vivo bioequivalence documentation*. USA: FDA.

FDA. (1997a). *Guidance for industry: extended release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations*. USA: FDA.

FDA. (1997b). *Guidance for industry: dissolution testing of immediate release solid oral dosage forms*. USA: FDA.

FDA. (2000). *Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system*. USA: FDA.

FDA. (2001). *Guidance for industry: statistical approaches to establishing bioequivalence*. USA: FDA.

FDA. (2003). *Guidance for industry: bioavailability and bioequivalence studies for orally administered drug products - general considerations*. USA: FDA.

FDA. (2006a). *Guidance for industry: bioequivalence guidance*. USA: FDA.

FDA. (2006b). *Guidance for Industry: quality systems approach to pharmaceutical CGMP regulations*. USA: FDA.

FDA. (2009-2010). Enforcement Report Retrieved Oct. 5th, 2010, from http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm

Ficarra, R., Cutroneo, P., Aturki, Z., Tommasini, S., Calabrņ, M., Phan-Tan-Luu, R., Fanali, S., & Ficarra, P. (2002). An experimental design methodology applied to the enantioseparation of a non-steroidal anti-inflammatory drug candidate. *Journal of Pharmaceutical and Biomedical Analysis, 29*(6), 989-997.

Field, T. J., Clack, G., & Neely, M. S. (2006). *Focus on: Intellectual Property Rights* (1st ed.). Washington, D.C.: U.S. Department of State, Bureau of International Information Programs.

Fung, C. P., & Kang, P. C. (2005). Multi-response optimization in friction properties of PBT composites using Taguchi method and principle component analysis. *Journal of Materials Processing Technology, 170*(3), 602-610.

Gibaldi, M., & Feldman, S. (1967). Establishment of sink conditions in dissolution rate determinations. Theoretical considerations and application to nondisintegrating dosage forms. *Journal of Pharmaceutical Sciences, 56*(10), 1238-1242.

Gibaldi, M., & Perrier, D. (1982). *Pharmacokinetics* (2nd ed.). New York: Marcel Dekker.

Gibson, M. (2001). *Pharmaceutical Preformulation and Formulation: a practical guide from candidate drug selection to commercial dosage form* (2nd ed.). New York: Informa Healthcare USA, Inc.

Goethals, P. L., & Cho, B. R. (2011). Extending the desirability function to account for variability measures in univariate and multivariate response experiments. *Computers & Industrial Engineering, 62*(2), 457-468.

Gohel, M., Patel, M., Amin, A., Agrawal, R., Dave, R., & Bariya, N. (2004). Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPS PharmSciTech, 5*(3), 10-15.

Gorman, J. W., & Hinman, J. E. (1962). Simplex lattice designs for multicomponent systems. *Technometrics, 4*(4), 463-487.

Gupta, S., & Kaisheva, E. (2003). Development of a multidose formulation for a humanized monoclonal antibody using experimental design techniques. *The AAPS Journal, 5*(2), 1-9.

Gupta, V., Assmus, M., Beckert, T., & Price, J. (2001). A novel pH-and time-based multi-unit potential colonic drug delivery system. II. Optimization of multiple response variables. *International Journal of Pharmaceutics, 213*(1-2), 93-102.

Hariharan, M., Gupta, V., & Price, J. C. (1997). Optimization of sustained-release tablet formulations: a four-component mixture experiment. *Pharmaceutical Development and Technology, 2*(4), 365-371.

Harrington, E. C. (1965). The desirability function. *Industrial Quality Control, 21*(10), 494-498.

Hauck, W. W., Parekh, A., Lesko, L. J., Chen, M. L., & Williams, R. L. (2001). Limits of 80%-125% for AUC and 70%-143% for Cmax: What is the impact on bioequivalence studies? *International Journal of Clinical Pharmacology and Therapeutics, 39*(8), 350-355.

Higuchi, T. (1963). Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *Journal of pharmaceutical sciences, 52*(12), 1145-1149.

Hillier, F. S., & Lieberman, G. J. (2001). *Introduction to Operations Research* (7th ed.). Boston, USA: McGraw Hill.

Hixson, A. W., & Crowell, J. H. (1931). Dependence of reaction velocity upon surface and agitation. *Industrial & Engineering Chemistry, 23*(8), 923-931.

Holm, R., Jensen, I. H. M., & Sonnergaard, J. (2006). Optimization of self-microemulsifying drug delivery systems (SMEDDS) using a D-optimal design and the desirability function. *Drug Development and Industrial Pharmacy, 32*(9), 1025-1032.

Huang, J., Kaul, G., Cai, C. S., Chatlapalli, R., Hernandez-Abad, P., Ghosh, K., & Nagi, A. (2009). Quality by design case study: An integrated multivariate approach to drug product and process development. *International Journal of Pharmaceutics, 382*(1-2), 23-32.

Huang, Y. B., Tsai, Y. H., Yang, W. C., Chang, J. S., & Wu, P. C. (2004). Optimization of sustained-release propranolol dosage form using factorial design and response surface methodology. *Biological and Pharmaceutical Bulletin, 27*(10), 1626-1629.

Huang, Y. B., Tsai, Y. H., Yang, W. C., Chang, J. S., Wu, P. C., & Takayama, K. (2004). Once-daily propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation. *European Journal of Pharmaceutics and Biopharmaceutics, 58*(3), 607-614.

Hussain, A., Johnson, R., Vachharajani, N., & Ritschel, W. (1993). Feasibility of developing a neural network for prediction of human pharmacokinetic parameters from animal data. *Pharmaceutical Research, 10*(3), 466-469.

Hussain, A. S., Yu, X., & Johnson, R. D. (1991). Application of neural computing in pharmaceutical product development. *Pharmaceutical Research, 8*(10), 1248-1252.

Hwang, R. (1998). *Formulation/process optimization using design of experiments*. Paper presented at the WorldPHARM 98, Philadelphia, PA.

Hwang, R., & Peck, G. R. (2001a). A systematic evaluation of the compression and tablet characteristics of various types of lactose and dibasic calcium phosphate. *Pharmaceutical Technology, 25*, 54-68.

Hwang, R., & Peck, G. R. (2001b). A systematic evaluation of the compression and tablet characteristics of various types of microcrystalline cellulose. *Pharmaceutical Technology, 25*(3), 112-132.

Hwang, R., & Kowalski, D. L. (2005). Design of experiments for formulation development Retrieved Mar. 2nd, 2011, from http://pharmtech.findpharma.com/pharmtech/Formulation+Article/Design-of-Experiments-for-Formulation-Development/ArticleStandard/Article/detail/283907

Hwang, R., & Noack, R. M. (2011). Application of design of experiments to pharmaceutical formulation development. *International Journal of Experimental Design and Process Optimisation, 2*(1), 58-65.

Ibri, S., Jovanovi, M., Djuri, Z., Paroji, J., & Solomun, L. (2002). The application of generalized regression neural network in the modeling and optimization of aspirin extended release tablets with Eudragit® RS PO as matrix substance. *Journal of Controlled Release, 82*(2-3), 213-222.

Jha, B. K., Tambe, S. S., & Kulkarni, B. D. (1995). Estimating diffusion coefficients of a micellar system using an artificial neural network. *Journal of Colloid and Interface Science, 170*(2), 392-398.

Kailash, C. K., & Cho, B. R. (1994). Economic design and development of specifications. *Quality Engineering, 6*(3), 401-417.

Khan, K. A. (1975). The concept of dissolution efficiency. *The Journal of Pharmacy and Pharmacology, 27*(1), 48-49.

Khuri, A. I., & Conlon, M. (1981). Simultaneous optimization of multiple responses represented by polynomial regression functions. *Technometrics, 23*(4), 363-375.

Kim, K. J., & Lin, D. K. J. (2000). Simultaneous optimization of mechanical properties of steel by maximizing exponential desirability functions. *Journal of the Royal Statistical Society: Series C (Applied Statistics), 49*(3), 311-325.

Kincl, M., Vreer, F., & Veber, M. (2004). Characterization of factors affecting the release of low-solubility drug from prolonged release tablets. *Analytica Chimica Acta, 502*(1), 107-113.

Kincl, M., Turk, S., & Vrecer, F. (2005). Application of experimental design methodology in development and optimization of drug release method. *International Journal of Pharmaceutics, 291*(1-2), 39-49.

Ko, Y. H., Kim, K. J., & Jun, C. H. (2005). A new loss function-based method for multiresponse optimization. *Journal of Quality Technology, 37*(1), 50-59.

Kovach, J., & Cho, B. R. (2008). Solving multiresponse optimization problems using quality function–based robust design. *Quality Engineering, 20*(3), 346-360.

Kutner, M. H., Nachtsheim, C., & Neter, J. (2004). *Applied Linear Regression Models* (4 ed.). New York, USA: McGraw Hill.

Langenbucher, F. (1976). Parametric representation of dissolution-rate curves by the RRSBW distribution. *Pharmazeutische Industrie, 38*(5), 472-477.

Li, G., Zhong, M., Zhou, Z., Zhong, Y., Ding, P., & Huang, Y. (2011). Formulation optimization of chelerythrine loaded O-carboxymethylchitosan microspheres using response surface methodology. *International Journal of Biological Macromolecules, 49*(5), 970-978.

Liu, J. P., & Weng, C. S. (1992). Estimation of direct formulation effect under log-normal distribution in bioavailability/bioequivalence studies. *Statistics in Medicine, 11*(7), 881-896.

Moore, J. W., & Flanner, H. H. (1996). Mathematical comparison of dissolution profiles. *Pharmaceutical Technology, 20*(6), 64-74.

Nazzal, S., Nutan, M., Palamakula, A., Shah, R., Zaghloul, A. A., & Khan, M. A. (2002). Optimization of a self-nanoemulsified tablet dosage form of Ubiquinone using response surface methodology: effect of formulation ingredients. *International Journal of Pharmaceutics, 240*(1-2), 103-114.

O'Hara, T., Dunne, A., Butler, J., & Devane, J. (1998). A review of methods used to compare dissolution profile data. *Pharmaceutical Science & Technology Today, 1*(5), 214-223.

Patel, D. M., Patel, N. M., Patel, V. F., & Bhatt, D. A. (2007). Floating granules of ranitidine hydrochloride-gelucire 43/01: Formulation optimization using factorial design. *AAPS PharmSciTech, 8*(2), 25-31.

Paterakis, P. G., Korakianiti, E. S., Dallas, P. P., & Rekkas, D. M. (2002). Evaluation and simultaneous optimization of some pellets characteristics using a 3^3 factorial design and the desirability function. *International Journal of Pharmaceutics, 248*(1-2), 51-60.

Piepel, G. F. (1999). Modeling methods for mixture-of-mixtures experiments applied to a tablet formulation problem. *Pharmaceutical Development and Technology, 4*(4), 593-606.

Pignatiello, J. J. (1993). Strategies for robust multiresponse quality engineering. *IIE Transactions, 25*(3), 5-15.

Polli, J. E., Rekhi, G. S., Augsburger, L. L., & Shah, V. P. (1997). Methods to compare dissolution profiles and a rationale for wide dissolution specifications for metoprolol tartrate tablets. *Journal of Pharmaceutical Sciences, 86*(6), 690-700.

Qiu, Y., Chen, Y., Liu, L., & Zhang, G. G. Z. (2009). *Developing solid oral dosage forms: pharmaceutical theory and practice*. London: Academic Press.

Ragonese, R., Macka, M., Hughes, J., & Petocz, P. (2002). The use of the Box-Behnken experimental design in the optimisation and robustness testing of a capillary electrophoresis method for the analysis of ethambutol hydrochloride in a pharmaceutical formulation. *Journal of Pharmaceutical and Biomedical Analysis, 27*(6), 995-1007.

Rardin, R. L. (1998). *Optimization in Operations Research* (1st ed.). Upper Saddle River, USA: Prentice Hall.

Rescigno, A. (1992). Bioequivalence. *Pharmaceutical Research, 9*(7), 925-928.

Rocksloh, K., Rapp, F. R., Abed, S. A., Müller, W., Reher, M., Gauglitz, G., & Schmidt, P. C. (1999). Optimization of crushing strength and disintegration time of a high-dose plant extract tablet by neural networks. *Drug Development and Industrial Pharmacy, 25*(9), 1015-1025.

Romero, A. P., Caramella, C., Ronchi, M., Ferrari, F., & Chulia, D. (1991). Water-uptake and force development in an optimized prolonged release formulation. *International Journal of Pharmaceutics, 73*(3), 239-248.

Rosas, J. G., Blanco, M., González, J. M., & Alcalá, M. (2011). Quality by design approach of a pharmaceutical gel manufacturing process, part 1: Determination of the design space. *Journal of Pharmaceutical Sciences, 100*(10), 4432-4441.

Rosenbaum, S. E., Rhodes, C. T., & Bon, C. (1990). Area under the curve estimation in bioequivalence studies. *Drug Development and Industrial Pharmacy, 16*(1), 157-163.

Sastry, S. V., Reddy, I. K., & Khan, M. A. (1997). Atenolol gastrointestinal therapeutic system: optimization of formulation variables using response surface methodology. *Journal of Controlled Release, 45*(2), 121-130.

Shah, V. P., Tsong, Y., Sathe, P., & Liu, J. P. (1998). In vitro dissolution profile comparison - statistics and analysis of the similarity factor, f_2. *Pharmaceutical Research, 15*(6), 889-896.

Shaibu, A., & Cho, B. R. (2009). Another view of dual response surface modeling and optimization in robust parameter design. *The International Journal of Advanced Manufacturing Technology, 41*(7), 631-641.

Shaibu, A. B., & Cho, B. R. (2006). Development of realistic quality loss functions for industrial applications. *Journal of Systems Science and Systems Engineering, 15*(4), 385-398.

Shargel, L., Wu-Pong, S., & Yu, A. B. C. (2004). *Applied Biopharmaceutics and Pharmacokinetics* (5th ed. Vol. 32). New York: McGraw-Hill Medical.

Singh, B., Kumar, R., & Abuja, N. (2005). Optimizing drug delivery systems using systematic design of experiments. Part I: Fundamental aspects. *Critical Reviews in Therapeutic Drug Carrier Systems, 22*(1), 27-105.

Singh, B., Chakkal, S. K., & Ahuja, N. (2006). Formulation and optimization of controlled release mucoadhesive tablets of atenolol using response surface methodology. *AAPS PharmSciTech, 7*(1), 19-28.

Smith, B. P., & Brier, M. E. (1996). Statistical approach to neural network model building for gentamicin peak predictions. *Journal of Pharmaceutical Sciences, 85*(1), 65-69.

Smith, C. G., & O'Donnell, J. T. (2006). *The Process of New Drug Discovery and Development* (2nd ed.). New York: Informa Healthcare USA, Inc.

Taguchi, G. (1985). *A tutorial on quality control and assurance - the Taguchi methods*. Paper presented at the ASA Annual Meeting, Las Vegas, Nevada, USA.

Taguchi, G. (1986). *Introduction to Quality Engineering*. Tokyo, Japan: Asian Productibity Organization.

Takahara, J., Takayama, K., & Nagai, T. (1997a). Multi-objective simultaneous optimization technique based on an artificial neural network in sustained release formulations. *Journal of Controlled Release, 49*(1), 11-20.

Takahara, J., Takayama, K., Isowa, K., & Nagai, T. (1997b). Multi-objective simultaneous optimization based on artificial neural network in a ketoprofen hydrogel formula containing O-ethylmenthol as a percutaneous absorption enhancer. *International Journal of Pharmaceutics, 158*(2), 203-210.

Takayama, K., & Nagai, T. (1989). Novel computer optimization methodology for pharmaceutical formulations investigated by using sustained-release granules of indomethacin. *Chemical & pharmaceutical Bulletin, 37*(1), 160-167.

Takayama, K., Fujikawa, M., & Nagai, T. (1999). Artificial neural network as a novel method to optimize pharmaceutical formulations. *Pharmaceutical Research, 16*(1), 1-6.

Takayama, K., Morva, A., Fujikawa, M., Hattori, Y., Obata, Y., & Nagai, T. (2000). Formula optimization of theophylline controlled-release tablet based on artificial neural networks. *Journal of Controlled Release, 68*(2), 175-186.

Torbeck, L. D. (2010). %RSD: friend or foe? When to use percent relative standard deviation - and how to do so correctly. [Article]. *Pharmaceutical Technology, 34*(1), 37-38.

Tozer, T. N., & Rowland, M. (1980). *Clinical pharmacokinetics: concepts and applications* (1st ed.). Philadelphia: Lea & Febiger.

Tsuji, K., & Tsutani, K. (2010). Approval of new drugs 1999–2007: comparison of the US, the EU and Japan situations. *Journal of Clinical Pharmacy and Therapeutics, 35*(3), 289-301.

USP-NF. (2009a). *Excipients*. USA: U.S. Pharmacopeial Convention, Inc.

USP-NF. (2009b). *Dissolution*. USA: U.S. Pharmacopeial Convention, Inc.

USP-NF. (2009c). *Uniformity of Dosage Units*. USA: U.S. Pharmacopeial Convention, Inc.

USP-NF. (2009d). *Powder Flow*. USA: U.S. Pharmacopeial Convention, Inc.

USP-NF. (2009e). *Friability*. USA: U.S. Pharmacopeial Convention, Inc.

Varshosaz, J., Tavakoli, N., Minayian, M., & Rahdari, N. (2009). Applying the taguchi design for optimized formulation of sustained release gliclazide chitosan beads: an in vitro/in vivo study. *AAPS PharmSciTech, 10*(1), 158-165.

Vining, G. G. (1998). A compromise approach to multiresponse optimization. *Journal of Quality Technology, 30*(4), 309-313.

Von Hattingberg, H. M. (1984). Moment analysis in vivo and in vitro. *Methods and Findings in Experimental and Clinical Pharmacology, 6*(10), 589-595.

Wang, Y. M., Sato, H., Adachi, I., & Horikoshi, I. (1996). Optimization of the formulation design of chitosan microspheres containing cisplatin. *Journal of Pharmaceutical Sciences, 85*(11), 1204-1210.

Weinstein, J. N., Kohn, K. W., Grever, M. R., Viswanadhan, V. N., Rubinstein, L. V., Monks, A. P., Scudiero, D. A., Welch, L., Koutsoukos, A. D., & Chiausa, A. J. (1992). Neural computing in cancer drug development: predicting mechanism of action. *Science, 258*(5081), 447-451.

Wu, C. F. J., & Hamada, M. (2000). *Experiments: Planning, Analysis, and Parameter Design Optimization*. New York, USA: Wiley Interscience.

Wu, F. C. (2002). Optimisation of multiple quality characteristics based on percentage reduction of Taguchi's quality loss. *International Journal of Advanced Manufacturing Technology*, *20*(10), 749-753.

Wu, F. C. (2004). Optimization of correlated multiple quality characteristics using desirability function. *Quality Engineering, 17*(1), 119-126.

Xu, K., Lin, D. K. J., Tang, L., & Xie, M. (2004). Multiresponse systems optimization using a goal attainment approach. *IIE Transactions*, *36*(5), 433-445.

Yeh, K. C., & Kwan, K. C. (1978). A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximation. *Journal of Pharmacokinetics and Pharmacodynamics*, *6*(1), 79-98.

Yuksel, N., KanIk, A. E., & Baykara, T. (2000). Comparison of in vitro dissolution profiles by ANOVA-based, model-dependent and-independent methods. International Journal of Pharmaceutics, 209(1-2), 57-67.

Zidan, A. S., Sammour, O. A., Hammad, M. A., Megrab, N. A., Habib, M. J., & Khan, M. A. (2007). Quality by design: Understanding the formulation variables of a cyclosporine A self-nanoemulsified drug delivery systems by Box-Behnken design and desirability function. International Journal of Pharmaceutics, 332(1-2), 55-63.