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Research Article

Optimal Tolerance Design and Optimization for a Pharmaceutical Quality Characteristic

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A number of pharmaceutical quality characteristics are destructive or too costly to inspect. However, most quality improvement tools developed in the pharmaceutical research community typically assume that quality characteristics are nondestructive. This paper proposes a new design system for quality improvement by incorporating the concept of surrogate variables with the concepts of robust design (RD) and tolerance design (TD). The proposed robust-tolerance design paradigm determines the optimal factor setting and specification limits simultaneously, thereby improving quality of pharmaceutical products. In addition, the proposed methodology can provide the optimal tolerance as a mathematical closed-form solution. Finally, a numerical example and its associated sensitivity analysis for a pharmaceutical case are conducted for verification purposes. Based on the numerical example results, the proposed approach could provide robust factor settings with significant tradeoffs between quality and cost.

1. Introduction

Effectively considering product quality in the early stage of product/process design could reduce production cost, which is one of the key issues in quality engineering. It has been more than twenty years that enterprises integrate product quality into their business strategies. In off-line quality improvement inspired by Taguchi [1, 2], there are three major phases as follows:

(i) system design: a design phase for an activity of proceeding and functional prototyping from an identified set of requirements,

(ii) robust design (RD): a design phase for determining the optimal factor setting which minimizes product/process variability and bias,

(iii) tolerance design (TD): a design phase for determining optimal specification limits in order to improve product quality by reducing the variability of quality characteristics.

RD directly reflects a design for an optimal factor setting [3] with the aims of minimizing process bias and variability of a quality characteristic. Because of its practicability in reducing inherent uncertainty associated with design factors and system performance, the applications of RD techniques have resulted in significant improvements of product quality, manufacturability, and reliability at low cost. Even though the *ad hoc* robust design methods suggested by Taguchi remain controversial due to various mathematical flaws, there is little disagreement among researchers and practitioners about his basic philosophy. The controversy surrounding Taguchi's assumptions, experimental design, and statistical analysis has been well addressed by Box [4], Box et al. [5], León et al. [6], Nair [7], and Tsui [8]. Consequently, researchers have closely examined alternative approaches using well-established statistical and optimization tools. As an alternative for modeling process relationships, Vining and Myers [9] introduced a dual response approach based on response surface methodology (RSM) by separately estimating the response functions of process mean and variance, thereby achieving the primary goal of robust design by minimizing

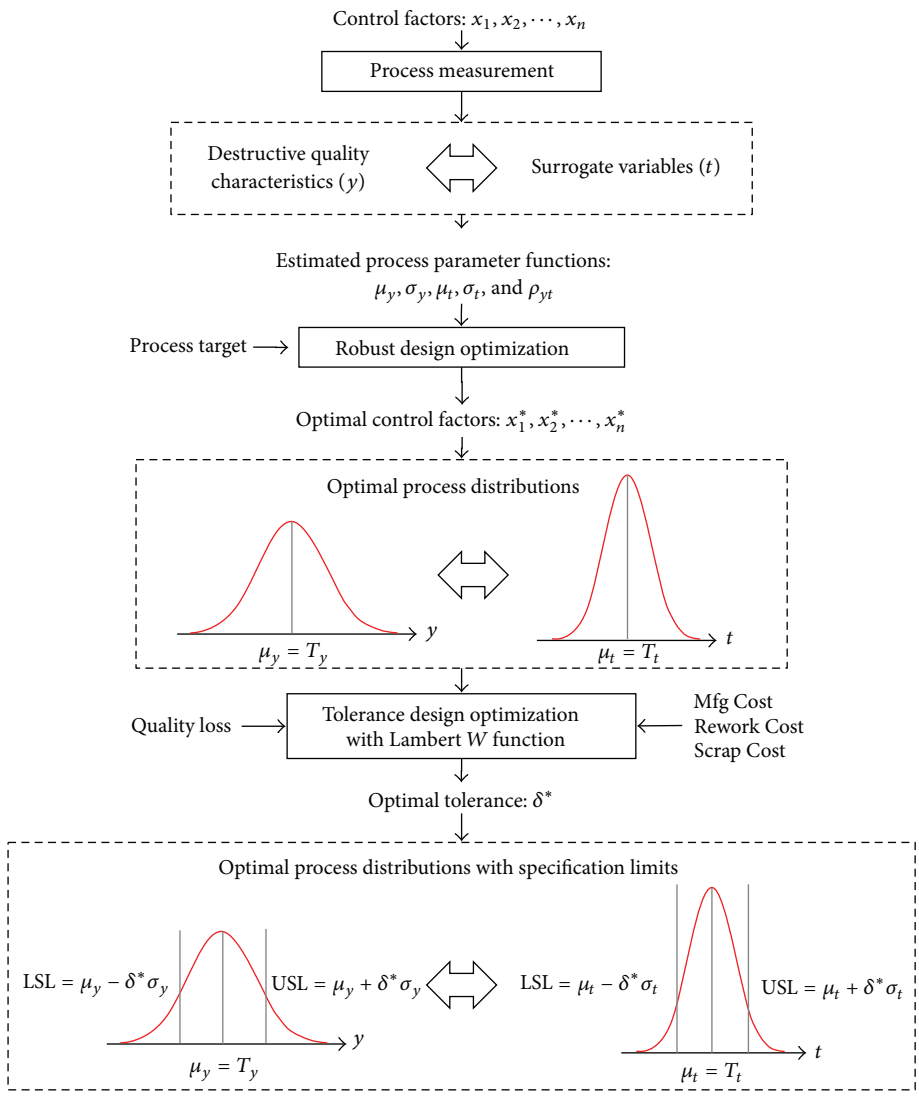

Figure 1: An overview of the proposed robust-tolerance design approach.

the process variance while adjusting the process mean at the target. Many extensions of the dual response approach are reported in the literature, such as in [3, 10–16].

As advanced types of automated inspection equipment become an integral part of modern manufacturing systems, the implementation of a tolerance on every product item has increased in recent years and become an attractive means of manufacturing high quality products. Automated equipment can perform rigorous inspection procedures and provide a consistent performance. When the nature of a performance variable is destructive, a surrogate variable, which is correlated to the performance variable, can be used effectively for the TD optimization under 100% inspections in many industrial applications. K. Tang and J. Tang [17] provided an excellent discussion of the overall concept for determining the optimal product specification limits under various screening inspection environments including the Deming's all-or-none rules, Taguchi's tolerance design, economic models for correlated variables, burn-in, and group testing.

Pharmaceutical applications of RD and TD during granulation process, tablet pressing process, and coating process require a careful implementation because the primary characteristics of interest are often destructive. The primary purpose of this paper is to propose a new design modeling and optimization framework for the optimal factor setting and specification limits by incorporating the concept of surrogate variables with RD and TD. An overview of the proposed robust-tolerance design approach is presented in Figure 1.

2. Development of a Robust Design Method for Destructive Characteristics

2.1. Modification of Response Surface Methodology. Researchers have sought to combine Taguchi's robust design

principles with conventional response surface methodology (RSM) to model the response directly as a function of design variables. a second-order polynomial model is adequate to accommodate the curvature of the process mean and variance functions, as evidenced by [3, 9, 11, 13, 14, 16–19]. When the nature of a quality characteristic is destructive, a surrogate variable which is correlated to the quality characteristic is applied in many industrial applications. The response surface model associates control factors x with the correlation between destructive variables y and surrogate variables t. y and t are treated as random variables whose means depend upon the fixed values of x. Based on the dual response approach [9], the following models are recommended for destructive and surrogate variables:

$$\begin{aligned} y(x) &= \alpha_0 + a_1 x + a_2 x^2 + \varepsilon_y, \\ t(x) &= b_0 + b_1 x + b_2 x^2 + \varepsilon_t, \end{aligned} \tag{1}$$

where ε_y and ε_t are normal random variables with mean zero and variances $\sigma^2_{y\varepsilon}$ and $\sigma^2_{t\varepsilon}$, respectively; and α_0, a_1, a_2, b_0, b_1, and b_2 are model parameters. Based on the experimental results, the relationships between destructive quality characteristics and surrogate variables can be found as functional forms. Expanding the dual response approach, the estimated process mean functions of the performance variable $\widehat{\mu}_y$, and that of the surrogate variable $\widehat{\mu}_t$, the estimated variance function of the performance variable $\widehat{\sigma}^2_y$ and that of the surrogate variable $\widehat{\sigma}^2_t$, and the estimated correlation coefficient function between the performance variable and the surrogate variable $\widehat{\rho}_{yt}$ are given as follows:

$$\begin{aligned} \widehat{\mu}_y(x) &= \alpha_{y0} + \alpha_{y1} x + \alpha_{y2} x^2, \\ \widehat{\mu}_t(x) &= \alpha_{t0} + \alpha_{t1} x + \alpha_{t2} x^2, \\ \widehat{\sigma}^2_y(x) &= \beta_{y0} + \beta_{y1} x + \beta_{y1} x^2, \\ \widehat{\sigma}^2_t(x) &= \beta_{t0} + \beta_{t1} x + \beta_{t1} x^2, \\ \widehat{\rho}_{yt}(x) &= \gamma_0 + \gamma_1 x + \gamma_2 x^2, \end{aligned} \tag{2}$$

where x is a design factor (or a control factor); α_{y0}, α_{y1}, and α_{y2} are estimated regression coefficients of $\widehat{\mu}_y$; α_{t0}, α_{t1}, and α_{t2} are estimated regression coefficients of $\widehat{\mu}_t$; β_{y0}, β_{y1}, and β_{y2} are estimated regression coefficients of $\widehat{\sigma}^2_y$; β_{t0}, β_{t1}, and β_{t2} are estimated regression coefficients of $\widehat{\sigma}^2_t$; and γ_0, γ_1, and γ_2 are estimated regression coefficients of $\widehat{\rho}_{yt}$. To determine the regression coefficients, ordinary methods, such as least square method, could be used. An experimental format for destructive quality characteristics and their associated surrogate variables is shown in Table 1. $\overline{y}$ and s^2_y are the sample mean and the sample variance of destructive quality characteristic y; $\overline{t}$ and s^2_t are the sample mean and the sample variance of surrogate variable t; and ρ_{yt} is the sample correlation coefficient associated with the destructive quality characteristic y and the surrogate variable t.

2.2. Variability Reduction of Destructive Characteristics. From the experimental data, the functions of process mean $\widehat{\mu}(x)$ and variance $\widehat{\sigma}(x)$ are separately estimated by using the dual response approach. This model implies that the process mean is adjusted to the target τ_y first and then the variability is minimized. Because the primarily role of the RD approach in this paper is to reduce the variability of destructive quality characteristics, these destructive quality characteristics are considered in the RD stage, and their associated surrogate variables are considered in the TD stage for cost reduction. The RD optimization model associated with destructive quality characteristics y is formulated as follows:

$$\begin{aligned} &\text{Minimize} && \widehat{\sigma}^2_y(\mathbf{x}) \\ &\text{Subject to} && \mu_y(\mathbf{x}) = \tau_y \\ & && x \in \Omega, \end{aligned} \tag{3}$$

where τ_y is a process target of destructive quality characteristic y, Ω is $\{x \in S : g_i(x) \leq 0, i = 1, 2, \ldots, n\}$, S is a convex set in R^n, and $g_i(\mathbf{x})$ is the ith constraint associated with the destructive quality characteristic.

3. Development of an Economic Tolerance Design Method for Destructive Characteristics

Functional performance and cost are two factors primarily affecting the design of tolerances [20]. Thus, the determination of optimal tolerance involves a tradeoff between the level of quality (based on functional performance) and costs (associated with the tolerance). In manufacturing processes, the following tolerances could be specified on quality characteristics:

(i) a tight tolerance which causes slow processing rates and high manufacturing costs due to additional manufacturing operations, additional care on part of operators, and need of expensive measuring and processing equipments,

(ii) a loose tolerance which causes low manufacturing costs while decreasing product/process quality.

In order to facilitate the economic tradeoff, researchers typically express quality in monetary terms using quality loss functions. As a result, proper implementation of the TD optimization under 100% inspections might lead to a substantial cost savings in scrap and rework costs and provide consistently high product quality throughout the manufacturing process. Ultimately, the selection of specification limits for a product is particularly important, since it directly affects the process defective rate, rejection cost, and loss to the customer due to the variability of product performance.

TD involves the problem of determining optimal specification limits from the viewpoint of cost reduction and functional performance. For example, Chase et al. [21], Kim and Cho [22], Speckhart [23], and Spotts [24] considered

Table 1: Experimental format.

Run No.	Control factors (x)				Quality characteristics (y)						Surrogate variables (t)						ρ_{yt}
	x_1	x_2	$\cdots$	x_p	y_1	y_2	$\cdots$	y_q	μ_y	s_y^2	t_1	t_2	$\cdots$	t_q	μ_t	s_t^2	
1	x_{11}	x_{21}	$\cdots$	x_{p1}	y_{11}	y_{21}	$\cdots$	y_{q1}	μ_{y1}	s_{y1}^2	t_{11}	t_{21}	$\cdots$	t_{q1}	μ_{t1}	s_{t1}^2	ρ_{yt1}
2	x_{12}	x_{22}	$\cdots$	x_{p2}	y_{12}	y_{22}	$\cdots$	y_{q2}	μ_{y2}	s_{y2}^2	t_{12}	t_{22}	$\cdots$	t_{q2}	μ_{t2}	s_{t2}^2	ρ_{yt2}
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n	x_{1n}	x_{2n}	$\cdots$	x_{pn}	y_{1n}	y_{2n}	$\cdots$	y_{qn}	μ_{yn}	s_{yn}^2	t_{1n}	t_{2n}	$\cdots$	t_{qn}	μ_{tn}	s_{tn}^2	ρ_{ytn}

the reduction of manufacturing cost in tolerance allocation problems whereas Fathi [25], Kim and Cho [26], and Phillips and Cho [27] studied the issue of TD from the viewpoint of functional performance and expressing it in monetary terms by using Taguchi quality loss concept. In an integrated study considering the effect of both cost reduction and functional performance, Tang [28] developed an economic model for selecting the most profitable tolerance in situations where inspection cost is a linear function. When two viewpoints, such as cost and functional performance, are integrated, a tradeoff is often necessary. Along this line, Jeang [29] considered the simultaneous optimization of manufacturing cost, rejection cost, and quality loss by using a process capability index to establish a relationship between tolerance and standard deviation. When historical data of losses are available, a regression analysis could be applied, as exemplified by Phillips and Cho [27], who studied the minimization of the quality loss and the rejection cost. They developed optimization models using the first-order and second-order empirical loss functions. Wang and Liang [30] studied a tolerance optimization problem in the context of machining processes, such as milling, turning, drilling, reaming, boring, and grinding. Recently, Shin and Cho [31] studied two separate process parameters, such as process mean and variability, in the biobjective framework. Peng et al. [32] and Prabhaharan et al. [33] considered optimal process tolerances and stack-up conditions for mechanical assemblies as a combinatorial optimization problem. Destructive characteristics are often required in many situations, for instance, glass industry. Thus, an implementation of surrogate variables might be more practical. For surrogate variable-based TD optimization procedures, readers could refer to [17, 34–46].

3.1. Tolerance Design and Surrogate Variables. If the nature of major quality characteristics involves destructive testing, it is impossible to inspect all major quality characteristics themselves. In this case, it is more economical to use surrogate variables highly correlated with the major quality characteristics and relatively inexpensive to measure as screening variables. Let $h(y,t)$ denoting the joint distribution of major quality characteristic y and surrogate variable t. Then, $h(y,t)$ assumed to be a bivariate normal distribution with means μ_y and μ_t, variances σ_y^2 and σ_t^2, and correlation coefficient $\rho_{yt}(=\sigma_{yt}/\sigma_y\sigma_t)$. In the RD stage, the optimal setting of control factors is determined by setting all the major characteristics to their target values. Therefore, the values of these parameters μ_y, μ_t, σ_y^2, σ_t^2, and ρ_{yt} are already known [47]. Note that $h(y,t) = g(y \mid t)f(t)$ where $f(t)$ is the marginal density function of T and $g(y \mid t)$ is the conditional density function of y, given $T = t$. It can be shown that $f(t)$ is a normal density function with mean μ_t and variance σ_t^2, and $g(y \mid t)$ is a normal density function with mean $\mu = \mu_y + \rho_{yt}(\sigma_y/\sigma_t)(t-\mu_t)$ and variance $\sigma^2 = \sigma_y^2(1-\rho_{yt}^2)$.

TD determines the tolerance limit of surrogate variables by minimizing cost incurred by both customer and manufacturer sides [47]. In the side of customers, it has been assumed that if the performance of a product falls within a tolerance limit, the product is acceptable to customers and its quality loss is zero. However, it is more reasonable to assume that quality loss occurs when a product performance deviates from its target although it is in the tolerance limit. Within the tolerance limit, the expected quality loss is evaluated by integrating a quality loss function and a probability density function over a region of interest. In this paper, the following quadratic quality loss function is applied:

$$\text{Quality Loss}(y) = \theta\,(y-\tau)^2, \tag{4}$$

where θ is a positive loss coefficient. Let LSL and USL be lower and upper bounds of a tolerance limit for surrogate variable T, respectively. By integrating the loss function defined in (4) and the product performance $h(y,t)$, the expected quality loss within a tolerance limit can be formulated as follows:

$$\begin{aligned} E[\text{Quality Loss}(y)] &= \int_{\text{LSL}}^{\text{USL}} \int_{-\infty}^{\infty} \theta(y-\tau)^2 h(y,t)\,dy\,dt \\ &= \int_{\text{LSL}}^{\text{USL}} \theta\left(\sigma^2 + (\mu-\tau)^2\right) f(t)\,dt. \end{aligned} \tag{5}$$

From the definition of $g(y \mid t)$, after replacing μ with $\mu_y + \rho_{yt}(\sigma_y/\sigma_t)(t-\mu_t)$ and σ with $\sigma_y^2(1-\rho_{yt}^2)$, (5) becomes

$$\begin{aligned} &E[\text{Quality Loss}(y)] \\ &\quad = \theta \int_{\text{LSL}}^{\text{USL}} \left(\sigma_y^2\left(1-\rho_{yt}^2\right) \right. \\ &\qquad \left. + \left[\mu_y + \frac{\rho_{yt}^2 \sigma_y (t-\mu_t)}{\sigma_t} - \tau \right]^2 \right) f(t)\,dt. \end{aligned} \tag{6}$$

The rejection cost includes unit rework cost C_{rework} and unit scrap cost C_{scrab}, which incur when a product performance falls above the upper specification limit and below the lower specification limit, respectively. The expected rework cost $E[\text{Rework Cost}]$ and the expected scrap cost $E[\text{Scrap Cost}]$ are given as follows:

$$\begin{aligned} E[\text{Rework Cost}] &= C_{\text{rework}}(P[\text{USL} \le T]) \\ &= C_{\text{rework}} \int_{\text{USL}}^{\infty} f(t)\,dt, \\ E[\text{Scrap Cost}] &= C_{\text{scrap}}(P[T \le \text{LSL}]) \\ &= C_{\text{scrap}} \int_{-\infty}^{\text{LSL}} f(t)\,dt. \end{aligned} \tag{7}$$

To achieve tight tolerance, additional manufacturing operations and trainings, which probably decrease manufacturing processing rates and increase manufacturing cost, are usually required. The manufacturing cost contributes to a significant portion of the product unit cost, and its exclusion from the TD optimization model might result in a suboptimal tolerance. A tolerance range is defined in terms of δ, μ_t, and σ_t as follows:

$$\begin{aligned} \text{Tolerance Range} &= \text{USL} - \text{LSL} \\ &= (\mu_t + \delta\sigma_t) - (\mu_t - \delta\sigma_t) = 2\delta\sigma_t. \end{aligned} \tag{8}$$

For simplicity, the manufacturing cost is assumed to have a linear relationship with the tolerance range as described below:

$$\text{Mfg Cost} = a_0 + a_1 \text{Tolerance Range} + \varepsilon_{\text{mfg}}, \tag{9}$$

where ε_{mfg} represents the least-squares regression error. This linear manufacturing cost-tolerance model is also implemented in [48, 49]. The expected manufacturing cost could then be written as:

$$E[\text{Mfg Cost}] = a_0 + a_1 \text{Tolerance Range}. \tag{10}$$

Substituting Tolerance Range $= 2\delta\sigma_t$ in (10), the expected manufacturing cost becomes

$$E[\text{Mfg Cost}] = a_0 + 2a_1\delta\sigma_t. \tag{11}$$

3.2. The Proposed Optimization Model for Tolerance Design. The objective of economic TD is to find the tolerance limit which minimizes the expected total cost including expected quality loss, expected rework cost, expected scrap cost, and expected manufacturing cost. Thus, the expected total cost is mathematically expressed as

$$\begin{aligned} E[\text{Total Cost}] &= E[\text{Quality Loss}(y)] \\ &\quad + E[\text{Rework Cost}] + E[\text{Scrap Cost}] \\ &\quad + E[\text{Mfg Cost}]. \end{aligned} \tag{12}$$

By replacing (6), (7), and (11) into (12), the expected total cost is reformulated as:

$$\begin{aligned} &E[\text{Total Cost}] \\ &= \theta \int_{\text{LSL}}^{\text{USL}} \left(\sigma_y^2 \left(1 - \rho_{yt}^2\right) \right. \\ &\qquad \left. + \left[\mu_y + \frac{\rho_{yt}^2 \sigma_y (t - \mu_t)}{\sigma_t} - \tau \right]^2 \right) f(t)\,dt \\ &\quad + C_{\text{rework}} \int_{\text{USL}}^{\infty} f(t)\,dt \\ &\quad + C_{\text{scrap}} \int_{-\infty}^{\text{LSL}} f(t)\,dt \\ &\quad + a_0 + 2a_1\delta\sigma_t. \end{aligned} \tag{13}$$

To simplify (13), the marginal density function of t is converted from normal distribution function $f(t)$ to standard normal distribution $\phi(z)$ by using

$$z = \frac{(t - \mu_t)}{\sigma_t}. \tag{14}$$

Thus, (13) could be rewritten as

$$\begin{aligned} E[\text{Total Cost}] &= \theta \int_{-\delta}^{\delta} \left(\sigma_y^2 \left(1 - \rho_{yt}^2\right) \right. \\ &\qquad \left. + \left(\mu_y + \rho_{yt}\sigma_y z - \tau\right)^2 \right) \phi(z)\,dz \\ &\quad + C_{\text{rework}} \int_{\delta}^{\infty} \phi(z)\,dz \\ &\quad + C_{\text{scrap}} \int_{-\infty}^{-\delta} \phi(z)\,dz + a_0 + 2a_1\sigma_t\delta, \end{aligned} \tag{15}$$

where $\text{USL} = \mu_y + \delta\sigma_y$, $\text{LSL} = \mu_y - \delta\sigma_y$, and $\delta > 0$. Based on the dual response approach used in the RD stage, terms μ_y and τ are removed from (15). Also, after applying the following properties of normal probability density functions:

$$\begin{aligned} &\int_{-\infty}^{r} \phi(z)\,dz = \Phi(r), \qquad \int_{-\infty}^{r} z\phi(z)\,dz = -\phi(r), \\ &\int_{-\infty}^{r} z^2\phi(z)\,dz = \Phi(r) - r\phi(r), \end{aligned} \tag{16}$$

the expected total cost becomes

$$\begin{aligned} E[\text{Total Cost}] &= 2a_1\sigma_t\delta - 2\rho_{yt}^2\sigma_y^2\theta\delta\phi(\delta) \\ &\quad + \left\{ 2\sigma_y^2\left(1 - \rho_{yt}^2\right)\theta + 2\rho_{yt}^2\sigma_y^2\theta \right. \\ &\qquad \left. - C_{\text{rework}} - C_{\text{scrap}} \right\} \Phi(\delta) \\ &\quad + C_{\text{rework}} + C_{\text{scrap}} - \theta\sigma_y^2 + a_0. \end{aligned} \tag{17}$$

3.3. Determination of the Closed-Form Solution for Tolerance Optimization. To investigate the optimal solution of tolerance design, the first derivative with respect to δ is as follows:

$$\frac{\partial E\,[\text{Total Cost}]}{\partial \delta} = 2a_1\sigma_t + \phi(\delta) \times \left[2\sigma_y^2\left(1-\rho_{yt}^2\right)\theta - C_{\text{rework}} - C_{\text{scrap}}\right] + 2\rho_{yt}^2\sigma_y^2\theta\delta^2\phi(\delta). \tag{18}$$

Equating $\partial E[\text{Total Cost}]/\partial\delta$ to zero and substituting $\phi(\delta)$ with $e^{(-1/2)\delta^2}/\sqrt{2\pi}$, (18) becomes

$$2a_1\sigma_t + \left(2\sigma_y^2\left(1-\rho_{yt}^2\right)\theta - C_{\text{rework}} - C_{\text{scrap}} + 2\rho_{yt}^2\sigma_y^2\theta\delta^2\right) \times \left(\frac{e^{-\delta^2/2}}{\sqrt{2\pi}}\right) = 0. \tag{19}$$

Since it is nearly impossible to obtain a closed-form solution from this complex equation, Lambert W function is introduced to effectively obtain such a solution for δ as discussed in Appendix B. According to the property of Lambert W function ([20, 50]) such that

$$\xi_1\left(\delta^2+\xi_2\right)e^{\xi_3\,\delta^2} = \xi_4, \tag{20}$$

where ξ_1, ξ_2, ξ_3, and ξ_4 are not functions of δ, the optimal tolerance δ^* can be derived from the following relationship:

$$\delta = \pm\sqrt{\frac{\text{Lambert}\ \ W\left(\xi_3\xi_4\ e^{\xi_2\,\xi_3}/\xi_1\right)}{\xi_3} - \xi_2}. \tag{21}$$

According to (20), (19) after formatting becomes

$$\left(\delta^2 + \frac{2\sigma_y^2\left(1-\rho_{yt}^2\right)\theta - C_{\text{rework}} - C_{\text{scrap}}}{2\rho_{yt}^2\sigma_y^2\theta}\right)e^{-\delta^2/2} = \frac{-a_1\sigma_t\sqrt{2\pi}}{\rho_{yt}^2\sigma_y^2\theta}. \tag{22}$$

ξ_1, ξ_2, ξ_3, and ξ_4 in (21) can be replaced with 1, $[2\sigma_y^2(1-\rho_{yt}^2)\theta - C_{\text{rework}} - C_{\text{scrap}}]/2\rho_{yt}^2\sigma_y^2\theta$, $-1/2$, and $-a_1\sigma_t\sqrt{2\pi}/\rho_{yt}^2\sigma_y^2\theta$, respectively. Then, the closed-form solution of δ^* is formulated and provided as follows:

$$\delta^* = \pm\left(-2\ \text{Lambert}\ W\left(\frac{a_1\sigma_1\sqrt{2\pi}e^{((C_{\text{rework}}+C_{\text{scrap}}-2\sigma_y^2(1-\rho_{yt}^2)\theta)/(4\rho_{yt}^2\sigma_y^2\theta))}}{2\rho_{yt}^2\sigma_y^2\theta}\right) + \left(\frac{C_{\text{rework}} + C_{\text{scrap}} - 2\sigma_y^2\left(1-\rho_{yt}^2\right)\theta}{2\rho_{yt}^2\sigma_y^2\theta}\right)\right)^{1/2}, \tag{23}$$

where σ_y^2, σ_t^2, ρ_{yt}, θ, C_{rework} and C_{scrap}; are the optimal variance of the destructive quality characteristic y, the optimal variance of the surrogate variable t, the correlation coefficient associated with the destructive quality characteristic y and the surrogate variable t, the positive loss coefficient, unit rework cost, and unit scrap cost, respectively. Although the closed-form solution shown in (23) consists of the Lambert W function, its computation is remarkably simple. After δ^* is obtained, the optimal LSL and USL can be derived from $\mu_t^* - \delta^*\sigma_t^*$ and $\mu_t^* + \delta^*\sigma_t^*$, respectively.

3.4. Determination of the Conditions for Convexity. To verify the validity of the optimal solution, the second derivative is computed and the conditions for obtaining the minimum value of E[Total Cost] are investigated. The second derivative of E[Total Cost] with respect to δ is as follows:

$$\frac{\partial^2 E\,[\text{Total Cost}]}{\partial \delta^2} = \delta\phi(\delta) \times \left[C_{\text{rework}} + C_{\text{scrap}} - 2\sigma_y^2\theta \times \left(1 - 3\rho_{yt}^2 + \rho_{yt}^2\delta^2\right)\right]. \tag{24}$$

The value of E[Total Cost] at the stationary points will be minimum if the second derivative is greater than or equal to zero. Therefore, the interval for a minimum value of δ could be written as

$$0 \le \delta \le \sqrt{\frac{C_{\text{rework}} + C_{\text{scrap}} - 2\sigma_y^2\theta}{2\rho_{yt}^2\sigma_y^2\theta} + 3}. \tag{25}$$

In order to avoid imaginary values, the following condition needs to be satisfied:

$$\frac{C_{\text{rework}} + C_{\text{scrap}} - 2\sigma_y^2\theta}{2\rho_{yt}^2\sigma_y^2\theta} \ge -3. \tag{26}$$

If both conditions in (25) and (26) are satisfied, the closed-form solution of δ^* defined in (23) represents the global minimum of E[Total Cost]. The overall framework of TD optimization and its associated key elements are provided as follows.

Given Parameters

f(t): the normal probability density function of surrogate variable *t*,

τ: the target of the process mean of destructive quality characteristic *y*,

μ_y: the optimal process mean of destructive quality characteristic y, derived from the RD stage,

σ_y^2: the optimal variance of destructive quality characteristic y, derived from the RD stage,

μ_t: the optimal process mean of surrogate variable t, derived from the RD stage,

σ_t^2: the optimal variance of surrogate variable t, derived from the RD stage,

ρ_{yt}: the optimal correlation coefficient between destructive quality characteristic y and surrogate variable t, derived from the RD stage.

System Parameters

$$\begin{aligned} E[\text{Total Cost}] &= E[\text{Quality Loss}] \\ &\quad + E[\text{Mfg Cost}] \\ &\quad + E[\text{Rework Cost}] \\ &\quad + E[\text{Scrap Cost}], \end{aligned}$$

$$\begin{aligned} &E[\text{Quality Loss } (y)] \\ &= \theta \int_{\text{LSL}}^{\text{USL}} \left(\sigma_y^2 \left(1 - \rho_{yt}^2\right) + \left\{ \mu_y + \frac{\rho_{yt}^2 \sigma_y (t - \mu_t)}{\sigma_t} - \tau \right\}^2 \right) f(t)\, dt, \\ &E[\text{Mfg Cost}] = a_0 + 2a_1 \delta \sigma_t, \\ &E[\text{Rework Cost}] = C_{\text{rework}} \int_{\text{USL}}^{\infty} f(t)\, dt, \\ &E[\text{Scrap Cost}] = C_{\text{scrap}} \int_{-\infty}^{\text{LSL}} f(t)\, dt. \end{aligned} \tag{27}$$

Find

δ^*: the optimal tolerance, which leads to the derivation of USL and LSL as follows:

$$\text{USL} = \mu_t + \delta^* \sigma_t, \qquad \text{LSL} = \mu_t - \delta^* \sigma_t. \tag{28}$$

Minimize

$$\begin{aligned} E[\text{Total Cost}] &= 2a_1 \sigma_t \delta - 2\rho_{yt}^2 \sigma_y^2 \theta \delta \phi(\delta) \\ &\quad + \left\{ 2\sigma_y^2 \left(1 - \rho_{yt}^2\right) \theta + 2\rho_{yt}^2 \sigma_y^2 \theta \right. \\ &\quad \left. - C_{\text{rework}} - C_{\text{scrap}} \right\} \Phi(\delta) \\ &\quad + C_{\text{rework}} + C_{\text{scrap}} - \theta \sigma_y^2 + a_0. \end{aligned} \tag{29}$$

Closed-Form Solution

$$\begin{aligned} \delta^* = \pm \Bigg(&-2 \text{ Lambert } W \\ &\times \left(\frac{a_1 \sigma_1 \sqrt{2\pi} e^{((C_{\text{rework}} + C_{\text{scrap}} - 2\sigma_y^2 (1 - \rho_{yt}^2)\theta)/4\rho_{yt}^2 \sigma_y^2 \theta)}}{2\rho_{yt}^2 \sigma_y^2 \theta} \right) \\ &+ \left(\frac{C_{\text{rework}} + C_{\text{scrap}} - 2\sigma_y^2 \left(1 - \rho_{yt}^2\right) \theta}{2\rho_{yt}^2 \sigma_y^2 \theta} \right) \Bigg)^{1/2} \end{aligned} \tag{30}$$

4. Numerical Example

To illustrate the application of the proposed approach, a problem of measuring tablet hardness in pharmaceutical manufacturing process is provided. Three factors, which are pressure (x_1, MPa), humidity (x_2, %), and compression speed (x_3, mm/min), were in control. The hardness (y, kg), required at five [18, 51], was considered as a destructive quality characteristic because the tablet could be easily destroyed during the measurement. Process Analytical Technology (PAT) tools such as Raman, Near-Infrared (NIR), and Focused Beam Reflectance Measurement (FBRM) were used to understand and control the pharmaceutical process. In addition, Terahertz Pulsed Spectroscopy (TPS) and Terahertz Pulsed Imaging (TPI) techniques were used and terahertz refractive index (t) was introduced as a surrogate variable for the tablet hardness (y) [18, 51].

From the overview of the proposed robust-tolerance approach, provided in Figure 1, there are three main steps: process measurement, RD optimization, and TD optimization with Lambert W function. Central composite design (CCD) with three replications was applied to collect the experimental data of the destructive quality characteristic y and its associated surrogate variable t. Then, the sample mean of $y(\mu_y)$, the sample variance of $y(s_y^2)$, the sample mean of $t(\mu_t)$, the sample variance of $t(s_t^2)$, and the correlation coefficient of y and $t(\rho_{yt})$ were calculated. Table 2 shows all the experimental data obtained from step one. The other two steps are explained in Sections 4.1 and 4.2, respectively.

4.1. Stage I: Robust Design Optimization. By applying RSM to the experimental data shown in Table 2, fitted functions of the mean and the variance of y, the mean and the variance of

Table 2: Experimental data for a pharmaceutical manufacturing process.

Control factors (x)			Destructive quality characteristic hardness (y)					Surrogate variable terahertz refractive index (t)					ρ_{yt}
x_1	x_2	x_3	y_1	y_2	y_3	μ_y	s_y^2	t_1	t_2	t_3	μ_t	s_t^2	
−1	−1	−1	6.478	7.518	6.281	6.759	0.442	1.477	1.560	1.407	1.481	0.006	0.948
−1	−1	1	2.000	3.004	2.345	2.450	0.260	1.043	1.180	1.000	1.074	0.009	0.840
−1	1	−1	8.839	10.220	9.088	9.382	0.542	1.670	1.787	1.641	1.699	0.006	0.937
−1	1	1	5.699	6.750	5.581	6.010	0.414	1.403	1.460	1.284	1.382	0.008	0.807
1	−1	−1	5.495	6.817	6.280	6.197	0.443	1.351	1.505	1.343	1.400	0.008	0.779
1	−1	1	9.600	10.570	9.103	9.757	0.554	1.753	1.801	1.648	1.734	0.006	0.922
1	1	−1	4.987	5.985	4.807	5.260	0.403	1.327	1.362	1.205	1.298	0.007	0.774
1	1	1	10.756	11.940	10.510	11.070	0.586	1.903	2.000	1.866	1.923	0.005	0.994
−1.68	0	0	7.113	7.848	6.443	7.135	0.494	1.480	1.523	1.380	1.461	0.005	0.968
1.68	0	0	7.473	8.470	7.143	7.695	0.477	1.570	1.626	1.466	1.554	0.007	0.900
0	−1.68	0	8.657	9.609	8.195	8.820	0.520	1.655	1.718	1.567	1.647	0.006	0.957
0	1.68	0	10.647	12.000	10.557	11.070	0.653	1.828	1.936	1.804	1.856	0.005	0.993
0	0	−1.68	2.705	3.804	3.089	3.199	0.312	1.082	1.213	1.050	1.115	0.007	0.858
0	0	1.68	7.779	8.888	7.546	8.071	0.514	1.610	1.657	1.490	1.586	0.007	0.820
0	0	0	8.431	8.511	7.271	8.071	0.482	1.651	1.561	1.475	1.563	0.008	0.828
0	0	0	7.379	7.286	6.173	6.946	0.451	1.475	1.551	1.383	1.470	0.007	0.858
0	0	0	6.993	7.887	6.521	7.134	0.481	1.519	1.549	1.392	1.487	0.007	0.868
0	0	0	8.856	8.856	7.623	8.445	0.507	1.700	1.609	1.527	1.612	0.008	0.849
0	0	0	7.299	8.657	7.694	7.883	0.488	1.537	1.654	1.480	1.557	0.008	0.818
0	0	0	10.443	10.300	9.092	9.945	0.550	1.739	1.788	1.631	1.720	0.006	0.918

t, and the correlation coefficient of y and, t are obtained and respectively, provided as follows:

$$\begin{aligned}
\widehat{\mu}_y &= 8.09 + 0.631x_1 + 0.757x_2 + 0.724x_3 \\
&\quad - 0.726x_1x_2 + 2.13x_1x_3 + 0.398x_2x_3 \\
&\quad - 0.344x_1^2 + 0.551x_2^2 - 0.973x_3^2; \\
\widehat{\sigma}_y^2 &= 0.494 + 0.0219x_1 + 0.0344x_2 + 0.0237x_3 \\
&\quad - 0.0328x_1x_2 + 0.0755x_1x_3 + 0.0157x_2x_3 \\
&\quad - 0.0111x_1^2 + 0.0246x_2^2 - 0.0367x_3^2; \\
\widehat{\mu}_t &= 1.57 + 0.0641x_1 + 0.0706x_2 + 0.0752x_3 \\
&\quad - 0.0549x_1x_2 + 0.210x_1x_3 + 0.0476x_2x_3 \\
&\quad - 0.0290x_1^2 + 0.0573x_2^2 - 0.0845x_3^2; \\
\widehat{\sigma}_t^2 &= 0.00731 + 0.000027x_1 - 0.000343x_2 + 0.000073x_3 \\
&\quad - 0.000125x_1x_2 - 0.00112x_1x_3 - 0.000125x_2x_3 \\
&\quad - 0.000307x_1^2 - 0.000484x_2^2 + 0.000046x_3^2, \\
\widehat{\rho}_{yt} &= 0.858 - 0.0130x_1 + 0.0061x_2 + 0.0045x_3 \\
&\quad + 0.0139x_1x_2 + 0.0751x_1x_3 + 0.0069x_2x_3 \\
&\quad + 0.0180x_1^2 + 0.0325x_2^2 - 0.0156x_3^2.
\end{aligned} \tag{31}$$

To demonstrate the statistical analysis, ANOVA for the five responses based on significant level α at 0.05 was conducted as shown in Tables 3, 4, 5, 6, and 7. The result could be summarized as follows. For $\widehat{\mu}_y$, two main effects (i.e. x_2 and x_3), the interaction between x_1 and x_3, and the quadratic effect of x_3 are significant; for $\widehat{\sigma}_y^2$, x_2, the interaction between x_1 and x_3, and the quadratic effect of x_3 are significant; for $\widehat{\mu}_t$, all the main effects (i.e. x_1, x_2, and x_3), the interaction between x_1 and x_3, and the quadratic effect of x_3 are significant; for $\widehat{\sigma}_t^2$, only the interaction between x_1 and x_3 is significant; and for $\widehat{\rho}_{yt}$, the interaction between x_1 and x_3 and the quadratic effect of x_2 are significant.

The variability of destructive quality characteristic y could be reduced by applying the RD model shown in (3) with $\tau_y = 5$. The optimal solutions (i.e. $x_1^* = -0.3000$, $x_2^* = -0.6219$, and $x_3^* = -1.6810$) and then the optimal parameters associated with y and t (i.e. $\mu_y^* = 5.0000$, $\sigma_y^{2*} = 0.3792$, $\mu_t^* = 1.3061$, $\sigma_t^{2*} = 0.0070$, and $\rho_{yt}^* = 0.8684$) were obtained and provided in Table 8. Figures 2, 3, and 4 present the graphical representations of all the fitted response functions (i.e. $\widehat{\mu}_y$, $\widehat{\sigma}_y^2$, $\widehat{\mu}_t$, $\widehat{\sigma}_t^2$, and $\widehat{\rho}_{yt}$) with respect to the optimal setting of each input factor (i.e. x_1^*, x_2^*, and x_3^*, resp.).

4.2. Stage II: Tolerance Design Optimization. After the variability was reduced in the RD stage and the optimal setting for the hardness (y) and the Terahertz Refractive Index (t) were obtained, the proposed economic TD framework was

Table 3: ANOVA of the mean of y ($\hat{\mu}_y$).

Predictor	Coef	SE Coef	T		P
Constant	8.0877	0.4857	16.65		0.000
$x1$	0.6315	0.3222	1.96		0.078
$x2$	0.7573	0.3222	2.35		0.041
$x3$	0.7236	0.3222	2.25		0.049
$x1x2$	−0.7259	0.4210	−1.72		0.115
$x1x3$	2.1314	0.4210	5.06		0.000
$x2x3$	0.3984	0.4210	0.95		0.366
$x1x1$	−0.3435	0.3136	−1.10		0.299
$x2x2$	0.5507	0.3136	1.76		0.110
$x3x3$	−0.9727	0.3136	−3.10		0.011
S = 1.1908	R^2 = 85.5%			R^2 (adj) = 72.4%	
		Analysis of variance			
Source	DF	SS	MS	F	P
Regression	9	83.371	9.263	6.53	0.004
Residual error	10	14.18	1.418		
Total	19	97.55			

Table 4: ANOVA of the variance of y ($\hat{\sigma}_y^2$).

Predictor	Coef	SE Coef	T		P
Constant	0.4944	0.0225	21.92		0.000
$x1$	0.0219	0.0149	1.46		0.174
$x2$	0.0343	0.0149	2.30		0.044
$x3$	0.0237	0.0149	1.58		0.144
$x1x2$	−0.0327	0.0195	−1.67		0.125
$x1x3$	0.0755	0.0195	3.86		0.003
$x2x3$	0.0157	0.0195	0.81		0.439
$x1x1$	−0.0110	0.0145	−0.76		0.465
$x2x2$	0.0246	0.0145	1.69		0.122
$x3x3$	−0.0366	0.0145	−2.52		0.030
S = 0.0553138	R^2 = 79.6%			R^2 (adj) = 61.2%	
		Analysis of variance			
Source	DF	SS	MS	F	P
Regression	9	0.119074	0.01323	4.32	0.016
Residual error	10	0.030596	0.00306		
Total	19	0.149671			

conducted with respect to t in order to find the optimal tolerance δ^*, which could be easily found by the closed-form solution shown in (23) and then lead to the derivation of the optimal lower and upper specification limits (i.e., LSL* and USL*), respectively. When the inspection was implemented, the expected quality loss (E[Quality Loss (y)]) occurred as shown in (6) where the positive loss coefficient θ was 250. The expected manufacturing cost (E[Mfg Cost]) presented in (11) was described as a polynomial model where a_0 and a_1 were 100 and −0.2, respectively. Also, when the product performance fell above the upper limit or below the lower limit of the production specification, the expected rework cost (E[Rework Cost]) and the expected scrap cost (E[Scrap Cost]) were calculated as, respectively, defined in (7) where both C_{rework} and C_{scrap} were set to an arbitrary value such as 80. All the parameters, objectives, and optimal solutions involved in this TD stage are provided as follows.

Given Conditions

$f(t)$ $\quad e^{-((t-\mu_t)^2/2\sigma_t^2)}/\sqrt{2\pi\sigma_t^2}$

τ $\quad$ 5.0000

μ_y $\quad$ 5.0000

σ_y^2 $\quad$ 0.3792

μ_t $\quad$ 1.3061

σ_t^2 $\quad$ 0.0070

ρ_{yt} $\quad$ 0.8684.

Table 5: ANOVA of the mean of t ($\widehat{\mu}_t$).

Predictor	Coef	SE Coef	T	P
Constant	1.5693	0.0417	37.63	0.000
$x1$	0.0641	0.0276	2.32	0.043
$x2$	0.0706	0.0276	2.55	0.029
$x3$	0.0752	0.0276	2.72	0.022
$x1x2$	−0.0548	0.0361	−1.52	0.160
$x1x3$	0.2103	0.0361	5.82	0.000
$x2x3$	0.0476	0.0361	1.32	0.217
$x1x1$	−0.0289	0.0269	−1.08	0.307
$x2x2$	0.0572	0.0269	2.13	0.059
$x3x3$	−0.0844	0.0269	−3.14	0.011
$S = 0.102261$	$R^2 = 88.1\%$		R^2 (adj) = 77.4%	

Analysis of variance

Source	DF	SS	MS	F	P
Regression	9	0.77375	0.08597	8.22	0.001
Residual error	10	0.10457	0.01046		
Total	19	0.87833			

Table 6: ANOVA of the variance of t ($\widehat{\sigma}_t^2$).

Predictor	Coef	SE Coef	T	P
Constant	0.0073	0.0003	19.34	0.000
$x1$	0.0000	0.0002	0.11	0.917
$x2$	−0.0003	0.0002	−1.37	0.201
$x3$	0.0000	0.0002	0.29	0.776
$x1x2$	−0.0001	0.0003	−0.38	0.711
$x1x3$	−0.0011	0.0003	−3.43	0.006
$x2x3$	−0.0001	0.0003	−0.38	0.711
$x1x1$	−0.0003	0.0002	−1.26	0.237
$x2x2$	−0.0004	0.0002	−1.98	0.076
$x3x3$	0.0000	0.0002	0.19	0.853
$S = 0.000926452$	$R^2 = 65.9\%$		R^2 (adj) = 35.3%	

Analysis of variance

Source	DF	SS	MS	F	P
Regression	9	$1.66169E-05$	$1.84632E-06$	2.15	0.124
Residual error	10	$8.58313E-06$	$8.58313E-07$		
Total	19	0.0000252			

System Parameters

$$\begin{aligned} &E[\text{Total Cost}] \\ &\quad = E[\text{Quality Loss}] + E[\text{Mfg Cost}] \\ &\qquad + E[\text{Rework Cost}] \\ &\qquad + E[\text{Scrap Cost}], \\ &E[\text{Quality Loss}(y)] \\ &\quad = 250 \\ &\quad \times \int_{\text{LSL}}^{\text{USL}} \left(\sigma_y^2 \left(1 - \rho_{yt}^2\right) \right. \\ &\qquad \left. + \left\{ \mu_y + \frac{\rho_{yt}^2 \sigma_y (t - \mu_t)}{\sigma_t} - 5 \right\}^2 \right) \\ &\quad \times f(t)\, dt, \\ &E[\text{Mfg Cost}] = 100 - 0.4\delta\sigma_t. \\ &E[\text{Rework Cost}] = 80 \int_{\text{USL}}^{\infty} f(t)\, dt, \\ &E[\text{Scrap Cost}] = 80 \int_{-\infty}^{\text{LSL}} f(t)\, dt, \end{aligned} \tag{32}$$

Find

δ^*: the optimal tolerance, which leads to the derivation of USL and LSL as follows:

$$\text{USL} = \mu_t + \delta^* \sigma_t, \qquad \text{LSL} = \mu_t - \delta^* \sigma_t. \tag{33}$$

Table 7: ANOVA of the correlation coefficient of y and t ($\widehat{\rho}_{yt}$).

Predictor	Coef	SE Coef	T	P
Constant	0.8579	0.0167	51.14	0.000
$x1$	−0.0129	0.0111	−1.17	0.270
$x2$	0.0061	0.0111	0.55	0.595
$x3$	0.0044	0.0111	0.40	0.696
$x1x2$	0.0138	0.0145	0.95	0.363
$x1x3$	0.0751	0.0145	5.17	0.000
$x2x3$	0.0068	0.0145	0.47	0.647
$x1x1$	0.0180	0.0108	1.66	0.127
$x2x2$	0.0325	0.0108	3.00	0.013
$x3x3$	−0.0155	0.0108	−1.44	0.181
S = 0.0411335	R^2 = 81.5%		R^2 (adj) = 64.8%	

Analysis of variance

Source	DF	SS	MS	F	P
Regression	9	0.074522	0.00828	4.89	0.01
Residual error	10	0.01692	0.001692		
Total	19	0.091441			

Table 8: Optimal solutions from the RD stage.

Control factors (x)			Hardness (y)		Terahertz refractive index (t)		ρ^*_{yt}
x^*_1	x^*_2	x^*_3	μ^*_y	σ^{2*}_y	μ^*_t	σ^{2*}_t	
−0.2999	−0.6219	−1.6810	5.0000	0.3792	1.3061	0.0070	0.8684

Minimize

$$E\,[\text{Total Cost}] = -0.4\sigma_t\delta - 500\rho^2_{yt}\sigma^2_y\delta\varphi(\delta) + \left\{500\sigma^2_y\left(1-\rho^2_{yt}\right) + 500\rho^2_{yt}\sigma^2_y - 160\right\} \times \Phi(\delta) + 260 - 250\sigma^2_y. \tag{34}$$

Closed-Form Solution

$$\delta^* = \pm\left(-2\,\text{Lambert}\,W \times \left(\frac{-0.2\sigma_1\sqrt{2\pi}e^{((160-500\sigma^2_y(1-\rho^2_{yt}))/1000\rho^2_{yt}\sigma^2_y)}}{500\rho^2_{yt}\sigma^2_y}\right) + \left(\frac{160-500\sigma^2_y\left(1-\rho^2_{yt}\right)}{500\rho^2_{yt}\sigma^2_y}\right)\right)^{1/2} = 0.8910 \tag{35}$$

$\text{USL}^* = 1.3806$ and $\text{LSL}^* = 1.2317$.

The optimal tolerance δ^* is 0.8910 and then USL^* and LSL^* are 1.3806 and 1.2317, respectively. Figure 5 illustrates the relationship between δ and all relevant costs which are expected total cost, expected manufacturing cost, cost incurred by the expected quality loss, and expected rejection cost including expected rework cost and expected scrap cost.

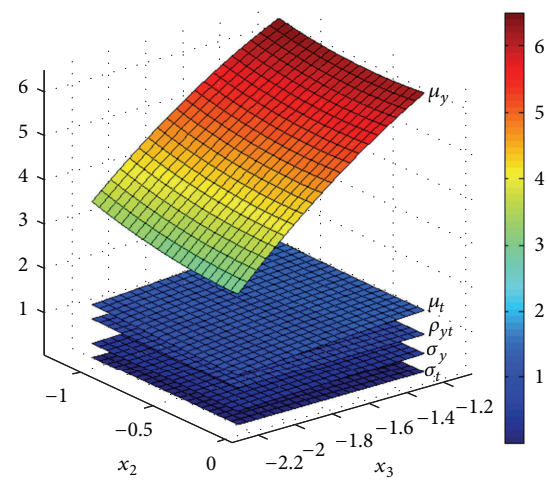

Figure 2: Plot of $\widehat{\mu}_y$, $\widehat{\sigma}^2_y$, $\widehat{\mu}_t$, $\widehat{\sigma}^2_t$, and $\widehat{\rho}_{yt}$ with respect to x^*_1.

In order to verify the optimality conditions of δ^*, the plots of the first and the second derivatives of the expected total cost function with respect to δ are provided in Figures 6 and 7, respectively. The former shows that, at δ^*, the value of $\partial E[\text{Total Cost}]/\partial\delta$ is zero; while the latter shows that, at δ^*, the expected total cost is minimum because the value of $\partial^2 E[\text{Total Cost}]/\partial\delta^2$ is greater than zero. Also, the value of δ^* is between 0 and 1.6712, which is relevant to the interval defined in (25).

Three sensitivity analyses were conducted in order to determine the impact of θ, C_{rework}, and C_{scrap} on

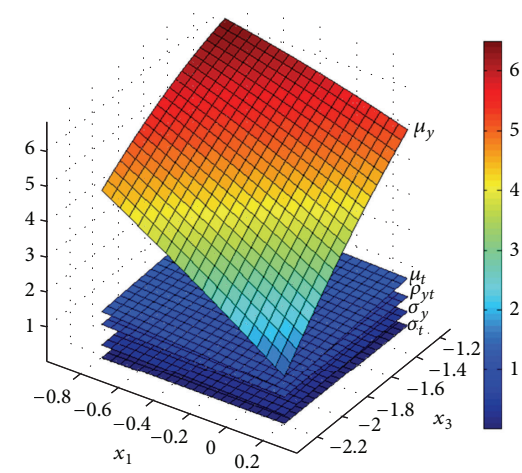

FIGURE 3: Plot of $\widehat{\mu}_y$, $\widehat{\sigma}_y^2$, $\widehat{\mu}_t$, $\widehat{\sigma}_t^2$, and $\widehat{\rho}_{yt}$ with respect to x_2^*.

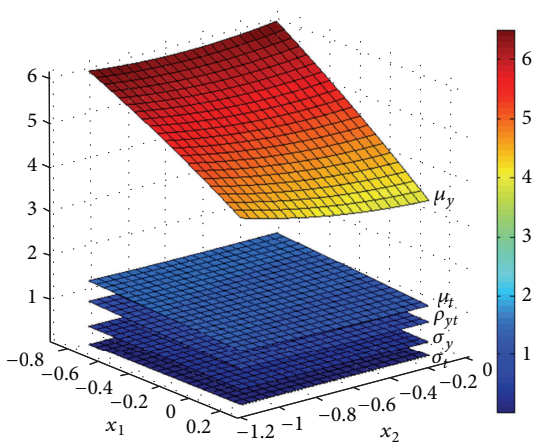

FIGURE 4: Plot of $\widehat{\mu}_y$, $\widehat{\sigma}_y^2$, $\widehat{\mu}_t$, $\widehat{\sigma}_t^2$, and $\widehat{\rho}_{yt}$ with respect to x_3^*.

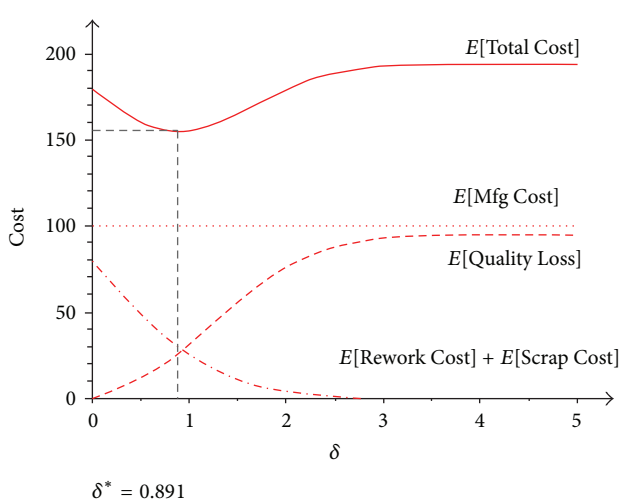

FIGURE 5: Plots of E[Total Cost], E[Mfg Cost], E[Quality Loss], and E[Rework Cost] + E [Scrap Cost] with respect to δ.

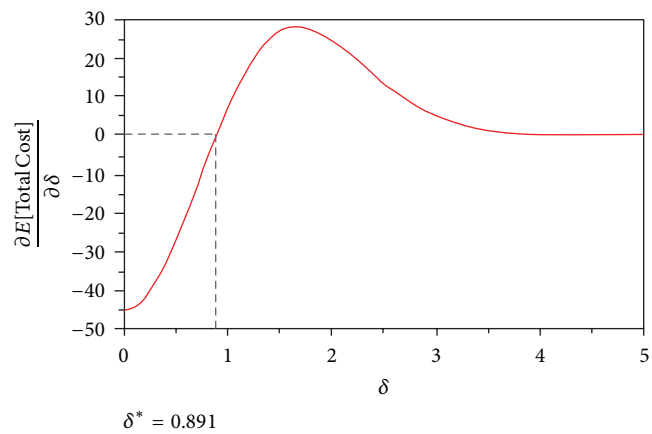

FIGURE 6: Plot of ∂E[Total Cost]/$\partial\delta$ with respect to δ.

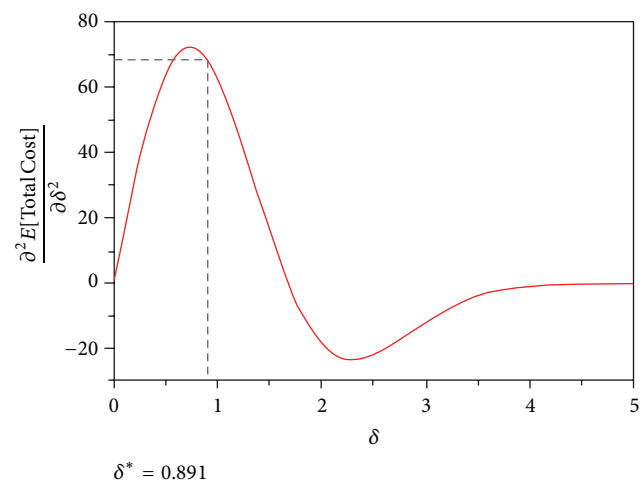

FIGURE 7: Plot of $\partial^2 E$[Total Cost]/$\partial\delta^2$ with respect to δ.

E[Rework Cost] around δ^* A full data set of each sensitivity analysis is provided in Tables 9, 10, and 11, respectively. First is the effect of θ while C_{rework} and C_{scrap} are held at 80. Figure 8 identifies that while the value of θ changes from 100 to 400 with an increment of 25, the values of E[Rework Cost], E[Scrap Cost], E[Mfg Cost], and E[Total Cost] increase; and while the value of δ decreases, E[Quality Loss] has a concave pattern.

Second is the effect of C_{rework} while θ and C_{scrap} are held at 250 and 80, respectively. Figure 9 demonstrates that while the value of C_{rework} changes from 40 to 160 with an increment of 8, the values of δ^*, E[Rework Cost], E[Quality Loss], and E[Total Cost] increase; and while the values of E[Scrap Cost] and E[Mfg Cost] decrease, the rejection cost (which is a summation of E[Rework Cost] and E[Scrap Cost]) has a concave pattern.

Last is the effect of C_{scrap} while θ and C_{rework} are held at 250 and 80, respectively. Figure 10 represents that while the value of C_{scrap} changes from 40 to 160 with an increment of 8, the values of, E[Scrap Cost], E[Quality Loss], and

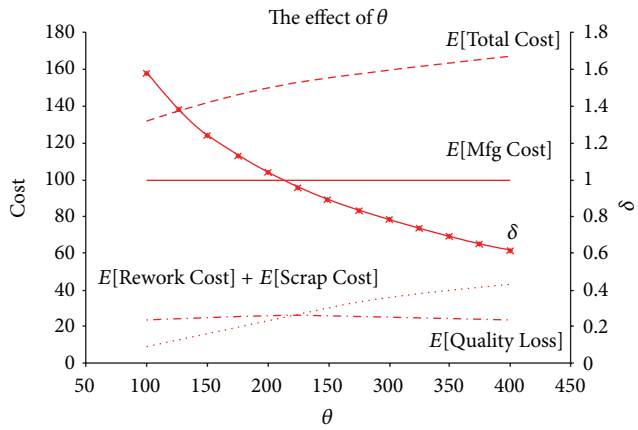

FIGURE 8: The effect of θ on minimum costs ($C_{\text{rework}} = 80$ and $C_{\text{scrap}} = 80$).

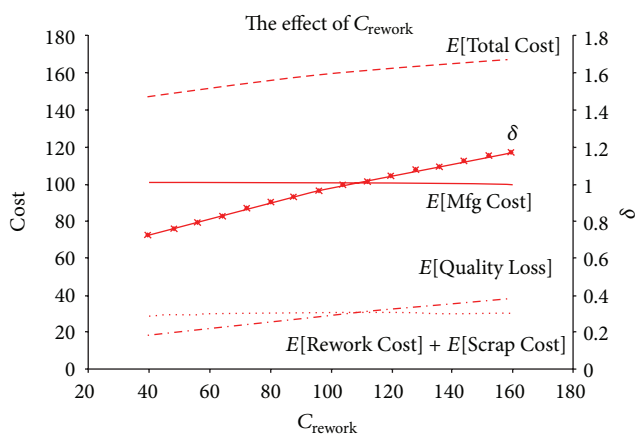

FIGURE 9: The effect of C_{rework} on minimum costs ($\theta = 250$ and $C_{\text{scrap}} = 80$).

E[Total Cost] increase. Similar to the second sensitivity analysis, while the values of E[Rework Cost] and E[Mfg Cost] decrease, the rejection cost has a concave pattern.

5. Conclusions and Future Research

This paper proposed the optimization schemes for determining an optimal factor setting and tolerances for a destructive pharmaceutical characteristic. In reality, there are a number of destructive quality characteristics in pharmaceutical processes. Conceptualizing destructive pharmaceutical characteristics for the purpose of optimizing such pharmaceutical parameters, to our best knowledge, might be the first attempt in this field. To find the optimal factor setting with minimal variability, RD is an effective method. It is more effective when applied in the early stage of process design. Then, to remove possible variability, TD based on the concept of Taguchi's offline quality management is applied. With the result from RD stage, optimal tolerance and specification limits are obtained.

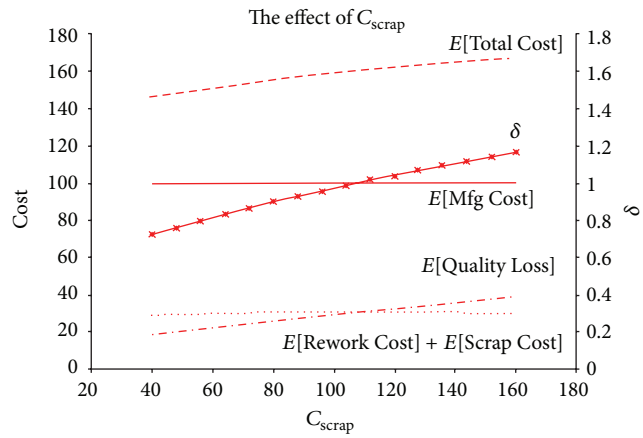

FIGURE 10: The effect of C_{scrap} on minimum costs ($\theta = 250$ and $C_{\text{rework}} = 80$).

The proposed approach integrated the RD and TD concepts with the use of RSM and surrogate variables within the framework of destructive characteristics in order to achieve the target requirement with minimal variability and handle the destructive quality characteristic under 100% inspection. The experimental design format to find the relationship between a destructive quality characteristic and its associated surrogate variable was also proposed. Moreover, mathematical procedures for finding optimal tolerance and its closed-form solution by applying the Lambert W function principle were provided. The numerical example showed that the proposed approach not only delivered a robust factor setting but also considered tradeoff between the level of quality and cost.

Based on the results of this paper, a significant extension to support multiple quality characteristics can be a potential future research topic. In addition, current interesting issues, related to fractals associated with fractal dimension and Hurst parameter [52–58] in the field of pharmaceutical science and technology, can be incorporated into the proposed robust-tolerance design optimization method. By observing the fractal phenomena, these possible further approaches may achieve the realization of process understanding (PU) and process analysis technology (PAT) in pharmaceutical processes.

Appendices

A. Sensitivity Analysis

This section provides a result of the sensitivity analyses conducted for the numerical example in Section 4. Table 9 shows effects of θ while holding C_{rework} and C_{scrap} at 80 and while changing values of θ from 100 to 400 with an increment of 25. Table 10 shows effects of C_{rework} while holding θ and C_{scrap} at 250 and 80, respectively and while changing values of C_{rework} from 40 to 160 with an increment of 8. Table 11 shows effects of C_{scrap} while holding θ and C_{rework} at 250 and 80, respectively and while changing values of C_{scrap} from 40 to 160 with an increment of 8.

Table 9: Effects of θ on minimum costs ($C_{\text{rework}} = 80$ and $C_{\text{scrap}} = 80$).

θ	δ^*	E [Rework Cost]	E [Scrap Cost]	E [Quality Loss]	E [Mfg Cost]	E [Total Cost]
100	1.5737	4.6227	4.6227	23.1282	99.9474	132.3210
125	1.3838	6.6567	6.6567	24.3612	99.9537	137.6283
150	1.2414	8.5787	8.5787	25.0187	99.9585	142.1345
175	1.1288	10.3601	10.3601	25.3359	99.9623	146.0184
200	1.0363	12.0022	12.0022	25.4404	99.9653	149.4102
225	0.9583	13.5167	13.5167	25.4044	99.9680	152.4057
250	0.8910	14.9177	14.9177	25.2706	99.9702	155.0762
275	0.8319	16.2194	16.2194	25.0646	99.9722	157.4755
300	0.7792	17.4346	17.4346	24.8024	99.9739	159.6456
325	0.7317	18.5747	18.5747	24.4940	99.9755	161.6189
350	0.6883	19.6496	19.6496	24.1454	99.9770	163.4216
375	0.6484	20.6679	20.6679	23.7604	99.9783	165.0745
400	0.6114	21.6372	21.6372	23.3408	99.9796	166.5948

Table 10: Effects of C_{rework} on minimum costs ($\theta = 250$ and $C_{\text{scrap}} = 80$).

C_{rework}	δ^*	E [Rework Cost]	E [Scrap Cost]	E [Quality Loss]	E [Mfg Cost]	E [Total Cost]
40	0.7169	9.4683	18.9365	18.2914	99.9760	146.6723
48	0.7550	10.8066	18.0109	19.7268	99.9748	148.5190
56	0.7912	12.0078	17.1541	21.1413	99.9735	150.2767
64	0.8258	13.0859	16.3573	22.5362	99.9724	151.9518
72	0.8590	14.0524	15.6138	23.9125	99.9713	153.5500
80	0.8910	14.9177	14.9177	25.2706	99.9702	155.0762
88	0.9219	15.6907	14.2643	26.6108	99.9692	156.5349
96	0.9517	16.3794	13.6495	27.9333	99.9682	157.9303
104	0.9807	16.9908	13.0699	29.2381	99.9672	159.2660
112	1.0088	17.5314	12.5224	30.5253	99.9663	160.5454
120	1.0362	18.0068	12.0045	31.7949	99.9653	161.7715
128	1.0629	18.4222	11.5139	33.0467	99.9645	162.9472
136	1.0889	18.7823	11.0484	34.2808	99.9636	164.0751
144	1.1143	19.0915	10.6064	35.4970	99.9627	165.1576
152	1.1391	19.3537	10.1861	36.6954	99.9619	166.1971
160	1.1634	19.5724	9.7862	37.8758	99.9611	167.1955

B. The Lambert W Function

Since the Lambert W function is defined as $f(\Psi) = \Psi e^{\Psi}$, Lambert W (Ψ) allows solving such functional equation as $g(\Psi)\, e^{g(\Psi)} = \Psi$ and $g(\Psi) = e^{\text{Lambert}\, W\, (\ln(\Psi))}$, and $\Psi e^{\Psi} = \omega$ and $\Psi = \text{Lambert}\ \ W(\omega)$ ([20, 53]). As shown in Section 3.3, this functional equation is encountered in the tolerance optimization models involving normally distributed random variables and use of the Lambert W function facilitates obtaining a closed-form solution for the optimal specification limits. Based on Lambert W principle [52], Shin et al. [20] consider the equation as follows:

$$\Delta_4 = \Delta_1 (x + \Delta_2)\, e^{\Delta_3 x}. \tag{B.1}$$

By dividing Δ_1, multiplying Δ_3, and denoting $\Psi = \Delta_3(x + \Delta_2)$, (B.1) becomes

$$\frac{\Delta_3 \Delta_4\ e^{\Delta_2 \Delta_3}}{\Delta_1} = \Psi\, e^{\Psi_1}. \tag{B.2}$$

Replacing $\Delta_3 \Delta_4\ e^{\Delta_2 \Delta_3}/\Delta_1$ by ω, (B.2) then becomes

$$\Psi = \text{Lambert}\ \ W(\omega). \tag{B.3}$$

Denoting $\omega = \Delta_3 \Delta_4\ e^{\Delta_2 \Delta_3}/\Delta_1$, (B.3) can then be

$$\Psi = \text{Lambert}\ \ W\left(\frac{\Delta_3 \Delta_4\ e^{\Delta_2 \Delta_3}}{\Delta_1}\right). \tag{B.4}$$

Table 11: Effects of C_{scrap} on minimum costs ($\theta = 250$ and $C_{\text{rework}} = 80$).

C_{scrap}	δ^*	E [Rework Cost]	E [Scrap Cost]	E [Quality Loss]	E [Mfg Cost]	E [Total Cost]
40	0.7169	18.9365	9.4683	18.2914	99.9760	146.6723
48	0.7550	18.0109	10.8066	19.7268	99.9748	148.5190
56	0.7912	17.1541	12.0078	21.1413	99.9735	150.2767
64	0.8258	16.3573	13.0859	22.5362	99.9724	151.9518
72	0.8590	15.6138	14.0524	23.9125	99.9713	153.5500
80	0.8910	14.9177	14.9177	25.2706	99.9702	155.0762
88	0.9219	14.2643	15.6907	26.6108	99.9692	156.5349
96	0.9517	13.6495	16.3794	27.9333	99.9682	157.9303
104	0.9807	13.0699	16.9908	29.2381	99.9672	159.2660
112	1.0088	12.5224	17.5314	30.5253	99.9663	160.5454
120	1.0362	12.0045	18.0068	31.7949	99.9653	161.7715
128	1.0629	11.5139	18.4222	33.0467	99.9645	162.9472
136	1.0889	11.0484	18.7823	34.2808	99.9636	164.0751
144	1.1143	10.6064	19.0915	35.4970	99.9627	165.1576
152	1.1391	10.1861	19.3537	36.6954	99.9619	166.1971
160	1.1634	9.7862	19.5724	37.8758	99.9611	167.1955

Substituting Ψ to $\Delta_3(x + \Delta_2)$, the solution in terms of x can then be obtained as follows:

$$x = \pm\sqrt{\left\{\frac{\text{Lambert } W\left(\Delta_3\Delta_4\, e^{\Delta_2\Delta_3}/\Delta_1\right)}{\Delta_3}\right\} - \Delta_2}. \quad \text{(B.5)}$$

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