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The t-Distribution Approach to the Second-Order Multiresponse Surface Model of Paracetamol Tablets Quality Characteristics

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Abstract: The normal distribution approach is often used in regression analysis at the Response Surface Methodology (RSM) modeling stage. Several studies have shown that the normal distribution approach has drawbacks compared to the more robust t-distribution approach. The t-distribution approach is found to control size much more successfully in small samples compared to existing methods in the presence of moderately heavy tails. In many RSM applications, there is more than one response (multiresponse), which is usually correlated with each other (multivariate). On the other hand, the actual response surface habitually indicates the curve by the optimal value, so the second-order model is used. This paper aims to develop the second-order multiresponse surface model using a multivariate t-distribution approach. This work also provides the parameter estimation procedure and hypothesis testing for the significance of the parameter. First, the parameter estimation is performed using the Maximum Likelihood Estimation (MLE), followed by the Expectation–Maximization algorithm as an iterative method to find (local) maximum likelihood. Next, the Likelihood Ratio Test (LRT) method is used to test the parameters simultaneously. The model obtained uses this approach to determine the conditions of input variables that optimize the Paracetamol tablets' physical quality characteristics.

Keywords: response surface methodology; t-distribution; maximum likelihood estimation; likelihood ratio test; Paracetamol tablets

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1. Introduction

The classical theory of statistical analysis is predicated on the assumption that model errors have a normal distribution. When the error has a normal distribution, the Ordinary Least Squares (OLS) method can be used to estimate a linear regression model. However, minor differences in the distribution of model errors could significantly affect the resulting inferences [1].

The multivariate t-distribution approach is more suitable than the multivariate Pareto distribution approach when the data has heavy tails and is not bounded below. The multivariate t-distribution can handle such data, while the multivariate Pareto distribution is only suitable for non-negative variables [2].

Furthermore, the multivariate t-distribution can be utilized for a robust estimate of means, regression coefficients, and variance-covariance matrices in multivariate linear models, even in missing data [3]. The multivariate t-distribution approach matches various data conditions examined in several studies [4–6]. Although these studies use the t-distribution approach, they do not use data obtained from the experimental design or for the second-order model.

The Maximum Likelihood Estimation (MLE) method with the Expectation Maximization (EM) algorithm can be used to estimate the linear regression model parameters with the t-distribution approach [7]. It is recommended to treat the t-distribution's degrees of freedom as a known parameter if the sample size is small. If the sample size is large, estimating the degree of freedom is recommended. It is demonstrated that the EM algorithm has a relatively high computing efficiency and that, from an analytical standpoint, it is pretty straightforward and converges monotonically to an approximated local maximum [3].

The multivariate t-distribution approach matches various data conditions, and utilizing the EM algorithm makes this approach a simple and decent alternative in practice to get robust results [5]. These previous studies show that the estimator obtained using the t-distribution approach is more efficient than that obtained under the normality assumption when the data is in the form of a heavy tail.

After obtaining the estimator parameter MLE, the next step is using the Likelihood Ratio Test (LRT) method to test the parameters simultaneously. These methods have also been used in several other studies related to modeling using a non-normal distribution approach [8,9].

The Response Surface Methodology (RSM) was first introduced by Box and Wilson [10]. RSM includes experimental strategies to explore experimental regions, empirical statistical modeling to obtain an approach to the relationship between responses and input variables (factor levels), then optimization methods to find the level of factors that optimize response values [11]. In this paper, data collection used a Central Composite Design (CCD) for the second-order model strategy. Then, the main objective is to develop a Second-Order Multiresponse Surface (SOMRS) model with a multivariate t-distribution approach and the tools for statistical inference, including parameter estimation and hypothesis testing.

Since the RSM is intended to determine the optimal conditions of the system, the optimization technique used in this paper is the Dual Response System (DRS). In the DRS technique, one of the responses (considered the most important) is determined as a primary response, while other responses are secondary. Furthermore, this primary response is optimized, subject to conditions that have been determined from the secondary response [12,13] and using the mean squared error (MSE) criterion [14].

RSM has been used in several studies in the pharmaceutical industry, especially in optimizing the product's quality characteristics. These studies, among others, are to find the best conditions for the adsorption of methylthioninium chloride on a low-cost adsorbent prepared from sunflower seed shells [15], to improve the quality of natural pharmaceutical complex products by integrating robust design and optimization methodologies [16], and as an approach for modeling and optimization tasks of tablet compression process [17, 18].

Tablets are the most common form of dosage/consumable, containing one or more types of medicinal material (active ingredients) and any required additives. Active ingredients are the medicines' properties, which have been determined through tests by the pharmacist to cure the disease. Other substances of the tablet are the binder to provide adhesion to the mass of powders during granulation, disintegrant to aid the destruction of the tablet after ingestion, lubricant to reduce friction during the compression process and prevent the tablets from sticking to the mold, and diluent to fill the tablets to achieve a predetermined weight.

This paper aims to develop the second-order multiresponse surface model using a multivariate t-distribution strategy. This work also includes a procedure for parameter estimation and a test of the significance of the parameter's hypotheses. One of the studies related to Paracetamol was conducted to monitor its quality characteristics [19]. Applying the SOMRS model with a multivariate t-distribution approach, this research aims to determine optimal conditions of the physical quality characteristics (friability, hardness, and disintegration time) of Paracetamol tablets.

2. Materials and Methods

2.1. Multivariate *t*-Distribution

The multivariate *t*-distribution is a generalized version of the univariate *t*-distribution for two or more variables. Let Y has a univariate *t*-distribution with a location parameter μ , scale parameter ψ , and degrees of freedom v , or written down as $Y \sim t(\mu, \psi, v)$, then the probability density function is

$$f(y) = \frac{\Gamma\left(\frac{v+1}{2}\right)}{(\pi v)^{\frac{1}{2}} \Gamma\left(\frac{v}{2}\right) \psi^{\frac{1}{2}}} \cdot \left(1 + \frac{(y-\mu)^2}{v\psi}\right)^{-\frac{v+1}{2}}, -\infty < y < \infty \quad (1)$$

with $E(Y) = \mu$, $\text{Var}(Y) = \left(\frac{v}{v-2}\right)\psi$, $v > 2$.

Suppose there are q random variables Y_i , $i = 1, 2, \dots, q$, correlated with each other, so that $\mathbf{Y} = [Y_1 \ Y_2 \ \dots \ Y_q]^T$ has a q -variate (multivariate) *t*-distribution with a

location parameter $\boldsymbol{\mu} = [\mu_1 \ \mu_2 \ \dots \ \mu_q]^T$, scale parameter $\boldsymbol{\psi} = \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \dots & \sigma_{1q} \\ \sigma_{12} & \sigma_2^2 & \dots & \sigma_{2q} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{1q} & \sigma_{2q} & \dots & \sigma_q^2 \end{bmatrix}$,

and degrees of freedom v , or written down as $\mathbf{Y} \sim t_q(\boldsymbol{\mu}, \boldsymbol{\psi}, v)$. Next, the probability density function is

$$f(\mathbf{y}) = \frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\boldsymbol{\psi}|^{\frac{1}{2}}} \cdot \left(1 + \frac{(\mathbf{y}-\boldsymbol{\mu})' \boldsymbol{\psi}^{-1} (\mathbf{y}-\boldsymbol{\mu})}{v}\right)^{-\frac{v+q}{2}}, \quad (2)$$

$$-\infty < y_i < \infty, i = 1, 2, \dots, q, |\boldsymbol{\psi}| > 0, v > 0$$

with $E(\mathbf{Y}) = \boldsymbol{\mu}$, $\text{Var}(\mathbf{Y}) = \left(\frac{v}{v-2}\right)\boldsymbol{\psi}$, $v > 2$.

2.2. Second-Order Multiresponse Surface (SOMRS) Model with Multivariate *t*-Distribution

A first-order response surface model illustrates the relationship between the response variable Y and k input variables (levels of factors) x_j , $j = 1, 2, \dots, k$. If a series of observations are made as much as n ($n \geq k+1$), which produces a response value of y_u , $u = 1, 2, \dots, n$, then the first-order response surface model will have $p = k+1$ parameters and can be written as

$$E(Y_u) = \beta_0 + \beta_1 x_{u1} + \beta_2 x_{u2} + \dots + \beta_k x_{uk}, u = 1, 2, \dots, n \quad (3)$$

For a second-order response surface model, there are $m = 1 + 2k + \frac{1}{2}k(k-1)$ parameters and can be written as

$$E(Y_u) = \mathbf{g}'(\mathbf{x}_u) \boldsymbol{\beta}, u = 1, 2, \dots, n \quad (4)$$

with $\mathbf{g}'(\mathbf{x}_u) = [1 \ x_{u1} \ x_{u2} \ \dots \ x_{uk} \ x_{u1}^2 \ x_{u2}^2 \ \dots \ x_{uk}^2 \ x_{u1}x_{u2} \ x_{u1}x_{u3} \ \dots \ x_{u(k-1)}x_{uk}]$ and

$$\boldsymbol{\beta} = [\beta_0 \ \beta_1 \ \beta_2 \ \dots \ \beta_k \ \beta_{11} \ \beta_{22} \ \dots \ \beta_{kk} \ \beta_{12} \ \beta_{13} \ \dots \ \beta_{(k-1)k}]^T.$$

If there are q response variables $\mathbf{Y}_u = [Y_{u1} \ Y_{u2} \ \dots \ Y_{uq}]'$, then a second-order multiresponse surface model can be written as

$$E(\mathbf{Y}_u) = \mathbf{B}'\mathbf{g}(\mathbf{x}_u), \quad u = 1, 2, \dots, n \quad (5)$$

with $\mathbf{B} = [\boldsymbol{\beta}_1 \ \boldsymbol{\beta}_2 \ \dots \ \boldsymbol{\beta}_q]'$,

$\boldsymbol{\beta}_i = [\beta_{0i} \ \beta_{1i} \ \beta_{2i} \ \dots \ \beta_{ki} \ \beta_{11i} \ \beta_{22i} \ \dots \ \beta_{kki} \ \beta_{12i} \ \beta_{13i} \ \dots \ \beta_{(k-1)ki}]'$, and

$\mathbf{g}'(\mathbf{x}_u) = [1 \ x_{u1} \ x_{u2} \ \dots \ x_{uk} \ x_{u1}^2 \ x_{u2}^2 \ \dots \ x_{uk}^2 \ x_{u1}x_{u2} \ x_{u1}x_{u3} \ \dots \ x_{u(k-1)}x_{uk}]$

2.3. Estimation and Hypothesis Testing for Parameters of the SOMRS Model with a Multivariate t -Distribution

Parameters estimation of the SOMRS Model with a Multivariate t -Distribution using the Maximum Likelihood Estimation (MLE) method is shown in Figure 1.

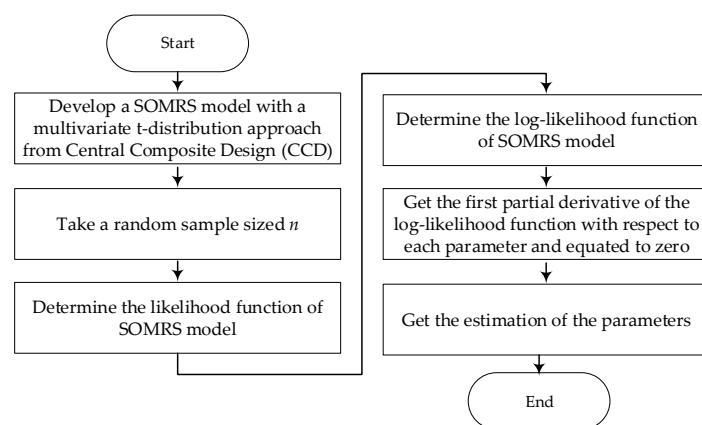


Figure 1. Parameters Estimation Flowchart.

The Likelihood Ratio Test (LRT) method to test the SOMRS model parameters simultaneously is shown in Figure 2.

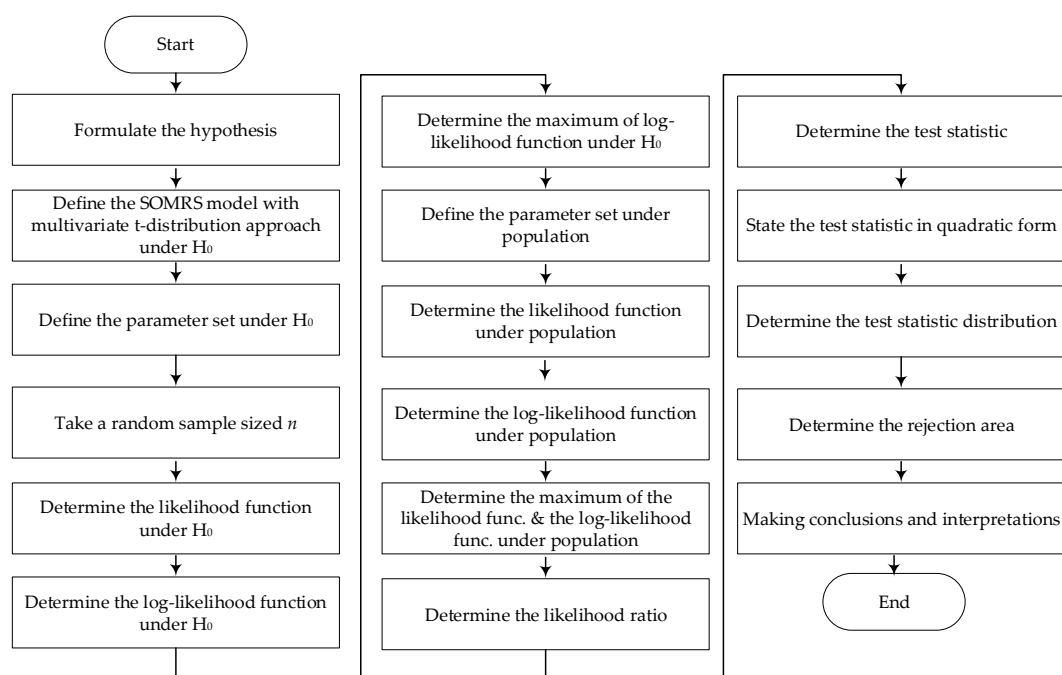


Figure 2. Model Parameter Test Flowchart.

2.4. Paracetamol Tablets

The making of Paracetamol tablets was done by wet granulation, with material Paracetamol (active substance), Polyvinylpyrrolidone/PVP K-30 (binder), Primogel (disintegrant), Mg Stearate (lubricant), and Lactose (filler).

Based on research from the process of making Paracetamol tablets with wet granulation, the quality characteristics of the tablet include the level of friability, the level of hardness, and the disintegration time of the tablet [19]. Next, the three input variables are the level of binder (PVP K-30), the level of disintegrant (Primogel), and the compression force level on the hydraulic press. Table 1 shows the response variables and their specifications as the tablet's quality characteristics. Table 2 shows the input variables and their levels.

Table 1. Response Variables (Tablet's Quality Characteristics).

Response Variable	Label	Characteristic	Specifications
Y_1	Tablet's Friability	Smaller the better	$\leq 1\%$
Y_2	Tablet's Hardness	Nominal the best	39.23–98.07 N
Y_3	Tablet's Disintegration Time	Smaller the better	≤ 15 min (≤ 900 s)

Table 2. Input Variables (Factor's Level).

Input Variable	Label	Natural Level	Coded Level
X_1	Level of Binder	4.68%	+1.682
		4%	+1.000
		3%	0.000
		2%	−1.000
		1.32%	−1.682
X_2	Level of Disintegrant	5.68%	+1.682
		5%	+1.000
		4%	0.000

X_3	Compression Force Level	3%	−1.000
		2.32%	−1.682
		19,991.49 N	+1.682
		17,650.80 N	+1.000
		14,218.70 N	0.000
		10,786.60 N	−1.000
		8445.91 N	−1.682

Tablets were prepared with combinations of levels of PVP K-30, Primogel, and compression force. Experiments were carried out as many as 20 runs using a CCD, then the tablet's physical quality characteristics (friability, hardness, and disintegration time) were evaluated. The experimental data obtained using this design is shown in Table 3.

Table 3. Experiment Data Result using CCD.

No	Input Variable			Response		
	X_1	X_2	X_3	Y_1 (%)	Y_2 (N)	Y_3 (sec)
1	−1	−1	−1	0.67	95.33	161.83
2	+1	−1	−1	0.93	67.00	246.00
3	−1	+1	−1	0.52	68.00	202.83
4	+1	+1	−1	0.83	66.83	279.67
5	−1	−1	+1	0.22	117.67	147.00
6	+1	−1	+1	0.32	113.33	367.50
7	−1	+1	+1	0.44	103.50	201.50
8	+1	+1	+1	0.54	94.33	242.98
9	−1.682	0	0	0.57	96.83	194.17
10	+1.682	0	0	0.66	83.50	340.83
11	0	−1.682	0	0.47	96.17	261.00
12	0	+1.682	0	0.59	84.33	336.83
13	0	0	−1.682	0.45	60.00	196.33
14	0	0	+1.682	0.12	134.17	217.17
15	0	0	0	0.27	111.50	279.83
16	0	0	0	0.40	82.33	211.00
17	0	0	0	0.47	82.00	159.33
18	0	0	0	0.63	84.00	254.67
19	0	0	0	0.50	78.00	257.83
20	0	0	0	0.89	87.83	301.33

3. Results

3.1. Parameter Estimation of SOMRS Model with a Multivariate t -Distribution Approach

Maximum likelihood estimation for the parameters of the SOMRS model with the EM algorithm is given in Theorem 1.

Theorem 1. Suppose it is known that the expected value of a SOMRS model with a multivariate t -distribution is $E(\mathbf{Y}_u) = \mathbf{B}'\mathbf{g}(\mathbf{x}_u)$ for $u = 1, 2, \dots, n$, with $\mathbf{Y}_u$ is $q \times 1$ response variable, $\mathbf{B}$ is $p \times q$ model parameter matrix, and $\mathbf{g}(\mathbf{x}_u)$ is a known vector function of the factor levels (according to the polynomial model order). If $\mathbf{Y}_u$ has multivariate t -distribution with a scale parameter $\boldsymbol{\psi}$ and the degrees of freedom v , then the maximum likelihood estimator for each parameter $\mathbf{B}$ and $\boldsymbol{\psi}$, i.e.,

$$\hat{\mathbf{B}}^{(h+1)} = \left(\mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \mathbf{X} \right)^{-1} \mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \hat{\mathbf{Y}}^{(h)}$$

$$\hat{\boldsymbol{\Psi}}^{(h+1)} = \frac{1}{n} \left(\hat{\mathbf{Y}}^{(h+1)} - \mathbf{X} \hat{\mathbf{B}}^{(h+1)} \right)' \boldsymbol{\Omega}^{(h+1)} \left(\hat{\mathbf{Y}}^{(h+1)} - \mathbf{X} \hat{\mathbf{B}}^{(h+1)} \right) + \frac{1}{n} \sum_{u=1}^n \boldsymbol{\Psi}^{(h)}$$

Proof of Theorem 1. The development of a SOMRS model with a multivariate t-distribution is based on the probability density function of the multivariate t-distribution. As Equation (5) shows that this model is $E(\mathbf{Y}_u) = \mathbf{B}'\mathbf{g}(\mathbf{x}_u)$ for $u=1, 2, \dots, n$, with $\mathbf{B}$, and $\boldsymbol{\Psi}$ respectively according to that Equation. If a random variable $\mathbf{Y} = [Y_1 \ Y_2 \ \dots \ Y_q]'$ has a multivariate t-distribution, then n random samples $\mathbf{y}_u = [y_{u1} \ y_{u2} \ \dots \ y_{uq}]'$ for $u=1, 2, \dots, n$ are taken that are mutually independent and identical to the $t_q(\mathbf{B}'\mathbf{g}(\mathbf{x}), \boldsymbol{\Psi}, v)$ distribution. The joint probability density function of $\mathbf{y}_u$ is

$$f(\mathbf{y}_u) = \frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\boldsymbol{\Psi}|^{\frac{1}{2}}} \cdot \left(1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \boldsymbol{\Psi}^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right)^{-\frac{v+q}{2}} \quad (6)$$

for $u=1, 2, \dots, n$.

The likelihood function of the Equation (6) is

$$L(\mathbf{B}, \boldsymbol{\Psi}, v) = \prod_{u=1}^n f(\mathbf{y}_u | \mathbf{B}, \boldsymbol{\Psi}, v) = \prod_{u=1}^n f(\mathbf{y}_u)$$

$$= \frac{\left[\Gamma\left(\frac{v+q}{2}\right) \right]^n}{(\pi v)^{\frac{qn}{2}} \left[\Gamma\left(\frac{v}{2}\right) \right]^n |\boldsymbol{\Psi}|^{\frac{n}{2}}} \cdot \prod_{u=1}^n \left(1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \boldsymbol{\Psi}^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right)^{-\frac{v+q}{2}} \quad (7)$$

The log-likelihood function from Equation (7) is

$$\ell(\mathbf{B}, \boldsymbol{\Psi}, v) = \ln L(\mathbf{B}, \boldsymbol{\Psi}, v) =$$

$$= n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\boldsymbol{\Psi}|^{\frac{1}{2}}} \right] - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \boldsymbol{\Psi}^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right] \quad (8)$$

The first partial derivative of the log-likelihood function with respect to each parameter (assumed v to be known) and equated to zero, i.e., $\frac{\partial \ell(\mathbf{B}, \boldsymbol{\Psi})}{\partial \mathbf{B}} = \mathbf{0}$ and

$$\frac{\partial \ell(\mathbf{B}, \boldsymbol{\Psi})}{\partial \boldsymbol{\Psi}} = \mathbf{0}.$$

$$\frac{\partial \ell(\mathbf{B}, \boldsymbol{\Psi})}{\partial \mathbf{B}} =$$

$$\frac{\partial}{\partial \mathbf{B}} \left(n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\boldsymbol{\Psi}|^{\frac{1}{2}}} \right] - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \boldsymbol{\Psi}^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right] \right) \quad (9)$$

$$\begin{aligned}
&= -\frac{v+q}{2} \sum_{u=1}^n \frac{-2(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} \mathbf{g}(\mathbf{x}_u)/v}{\left[1 + (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))/v\right]} \\
&= v + q \sum_{u=1}^n \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} \mathbf{g}(\mathbf{x}_u)}{\left[v + (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))/v\right]} \\
&= v + q \sum_{u=1}^n \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} \mathbf{g}(\mathbf{x}_u)}{[v + D_i(\mathbf{B}, \psi)]} \\
&= \sum_{u=1}^n \frac{(v+q)(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} \mathbf{g}(\mathbf{x}_u)}{[v + D_i(\mathbf{B}, \psi)]} \\
&= \sum_{u=1}^n \omega_u (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} \mathbf{g}(\mathbf{x}_u)
\end{aligned}$$

with $\omega_u = \frac{v+q}{v + D_u(\mathbf{B}, \psi)}$ and $D_u(\mathbf{B}, \psi) = (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))$ as

Mahalanobis distance. Then

$$\begin{aligned}
\frac{\partial \ell(\mathbf{B}, \psi)}{\partial \psi} &= \frac{\partial \left(n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\psi|^{\frac{1}{2}}} \right] - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right] \right)}{\partial \psi} \\
&= -\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{v+q}{2} \sum_{u=1}^n \frac{\frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \left[-\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \psi^{-1} \right] (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v}}{\left[1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right]} \\
&= -\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{v+q}{2} \sum_{u=1}^n \frac{\frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \left[-\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \psi^{-1} \right] (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v}}{\left[1 + \frac{D_u(\mathbf{B}, \psi)}{v} \right]} \\
&= -\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{1}{2} \sum_{u=1}^n (v+q) \frac{\frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \left[-\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \psi^{-1} \right] (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v}}{\left[1 + \frac{D_u(\mathbf{B}, \psi)}{v} \right]} \\
&= -\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{1}{2} \sum_{u=1}^n (v+q) \frac{\frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \left[-\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \psi^{-1} \right] (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v}}{\left[\frac{v + D_u(\mathbf{B}, \psi)}{v} \right]} \\
&= -\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{1}{2} \sum_{u=1}^n (v+q) \frac{\frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \left[-\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \psi^{-1} \right] (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v + D_u(\mathbf{B}, \psi)}}{\frac{v + D_u(\mathbf{B}, \psi)}{v}} \\
&= -\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{1}{2} \sum_{u=1}^n \omega_u (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \left[-\psi^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \psi^{-1} \right] (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))
\end{aligned} \tag{10}$$

where $\frac{\partial \psi}{\partial \sigma_{ui}}$ is a $q \times q$ symmetric matrix with the value “1” for the u -th row and i -th column and the value “0” for the others, i.e.,

$$\begin{aligned}
\frac{\partial \psi}{\partial \sigma_{11}} &= \begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 \end{bmatrix}_{q \times q} & \frac{\partial \psi}{\partial \sigma_{12}} &= \begin{bmatrix} 0 & 1 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 \end{bmatrix}_{q \times q} \\
\frac{\partial \psi}{\partial \sigma_{21}} &= \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 1 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 \end{bmatrix}_{q \times q} & \frac{\partial \psi}{\partial \sigma_{22}} &= \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 \end{bmatrix}_{q \times q} \\
u = q, i = 1 & & u = q, i = q & \\
\frac{\partial \psi}{\partial \sigma_{q1}} &= \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 0 & 0 & 0 \end{bmatrix}_{q \times q} & \frac{\partial \psi}{\partial \sigma_{qq}} &= \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 1 \end{bmatrix}_{q \times q} .
\end{aligned}$$

If the two partial derivatives of the two Equations (9) and (10) are equated with zero, then the following is obtained:

$$\sum_{u=1}^n \omega_u \mathbf{g}(\mathbf{x}_u) (\mathbf{y}_u - \mathbf{B}' \mathbf{g}(\mathbf{x}_u))' \boldsymbol{\psi}^{-1} = \mathbf{0} \quad (11)$$

$$-\frac{1}{2} \sum_{u=1}^n \text{tr} \left(\boldsymbol{\psi}^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \right) - \frac{1}{2} \sum_{u=1}^n \omega_u (\mathbf{y}_u - \mathbf{B}' \mathbf{g}(\mathbf{x}_u))' \left[-\boldsymbol{\psi}^{-1} \frac{\partial \psi}{\partial \sigma_{ui}} \boldsymbol{\psi}^{-1} \right] (\mathbf{y}_u - \mathbf{B}' \mathbf{g}(\mathbf{x}_u)) = 0 \quad (12)$$

However, because the solution is not closed form, it must be completed by an iterative process. Then, the EM algorithm used to obtain estimators $\mathbf{B}$ and $\boldsymbol{\psi}$ is as follows. In the $(h+1)$ -th iteration $h=0,1,2,\dots$, determine the initial value of each parameter, namely $\hat{\mathbf{B}}^{(0)}$ and $\hat{\boldsymbol{\psi}}^{(0)}$. Expectation (E) Step is done by calculating the value of the auxiliary variable, i.e.,

$$\omega_u^{(h+1)} = \frac{v+q}{v+D_u^{(h)}(\mathbf{B}, \boldsymbol{\psi})} \quad \text{and} \quad \hat{\mathbf{Y}}^{(h)} = \mathbf{X} \hat{\mathbf{B}}^{(h)}$$

with

$$D_u^{(h)}(\mathbf{B}, \boldsymbol{\psi}) = (\mathbf{y}_u - \hat{\mathbf{B}}^{(h)} \mathbf{g}(\mathbf{x}_u))' (\hat{\boldsymbol{\psi}}^{(h)})^{-1} (\mathbf{y}_u - \hat{\mathbf{B}}^{(h)} \mathbf{g}(\mathbf{x}_u))$$

$$\boldsymbol{\Omega} = \text{diag}(\omega_1, \omega_2, \dots, \omega_n)$$

Besides that, it also calculates sufficient statistics:

$$S_{\omega XX}^{(h+1)} = \sum_{u=1}^n \omega_u^{(h+1)} \mathbf{g}(\mathbf{x}_u) \mathbf{g}'(\mathbf{x}_u) = \mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \mathbf{X}$$

$$S_{\omega XY}^{(h+1)} = \sum_{u=1}^n \omega_u^{(h+1)} \mathbf{g}(\mathbf{x}_u) (\hat{\mathbf{y}}_u^{(h)})' = \mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \hat{\mathbf{Y}}^{(h)}$$

$$S_{\omega YY}^{(h+1)} = \sum_{u=1}^n \omega_u^{(h+1)} (\hat{\mathbf{y}}_u^{(h)}) (\hat{\mathbf{y}}_u^{(h)})' + \frac{1}{n} \sum_{u=1}^n \hat{\boldsymbol{\psi}}_u^{(h)} = (\hat{\mathbf{Y}}^{(h)})' \boldsymbol{\Omega}^{(h+1)} (\hat{\mathbf{Y}}^{(h)}) + \frac{1}{n} \sum_{u=1}^n \hat{\boldsymbol{\psi}}_u^{(h)}$$

Furthermore, Maximization (M) Step is done to get the estimator value of $\mathbf{B}$ and $\boldsymbol{\psi}$, namely:

$$\begin{aligned}
\hat{\mathbf{B}}^{(h+1)} &= \left(S_{\omega XX}^{(h+1)} \right)^{-1} S_{\omega XY}^{(h+1)} = \left(\mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \mathbf{X} \right)^{-1} \mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \hat{\mathbf{Y}}^{(h)} \\
\hat{\boldsymbol{\Psi}}^{(h+1)} &= \frac{1}{n} \left[S_{\omega YY}^{(h+1)} - \left(S_{\omega XY}^{(h+1)} \right)' \left(S_{\omega XX}^{(h+1)} \right)^{-1} S_{\omega XY}^{(h+1)} \right] \\
&= \frac{1}{n} \left(\hat{\mathbf{Y}}^{(h+1)} - \mathbf{X} \hat{\mathbf{B}}^{(h+1)} \right)' \boldsymbol{\Omega}^{(h+1)} \left(\hat{\mathbf{Y}}^{(h+1)} - \mathbf{X} \hat{\mathbf{B}}^{(h+1)} \right) + \frac{1}{n} \sum_{u=1}^n \psi_u^{(h)}
\end{aligned} \quad (13)$$

Variance-covariance matrix for B can be obtained through a fisher information matrix for B [20], i.e.,

$$\mathbf{K}(\mathbf{B}) = \sum_{u=1}^n \left(\frac{v+q}{v+q+2} \right) \mathbf{g}(\mathbf{x}_u) \boldsymbol{\psi}^{-1} \mathbf{g}'(\mathbf{x}_u) \quad (14)$$

The consistent asymptotic estimator of the variance-covariance matrix for B is:

$$\text{Cov}(\hat{\mathbf{B}}) = \left[n \mathbf{K}(\hat{\mathbf{B}}) \right]^{-1} = \left[n \sum_{u=1}^n \left(\frac{v+q}{v+q+2} \right) \mathbf{g}(\mathbf{x}_u) \hat{\boldsymbol{\psi}}^{-1} \mathbf{g}'(\mathbf{x}_u) \right]^{-1} \quad (15)$$

Because the MLE method produces an estimated value that approaches the actual value of the estimated parameter, the $\hat{\mathbf{B}}$ is consistent, so that $(\hat{\mathbf{B}} - \mathbf{B})$ can be approached with a multivariate normal distribution, i.e.,

$$\begin{pmatrix} \hat{\mathbf{B}} - \mathbf{B} \\ (k+1) \times q \quad (k+1) \times q \end{pmatrix} \sim N_{q(k+1)} \left(\mathbf{0}, \text{Cov}(\hat{\mathbf{B}}) \right) \quad (16)$$

Then, the algorithm for model parameter estimation using EM is as follows:

Step-1: Determine the initial value for each parameter using the OLS method, i.e.,

$$\hat{\mathbf{B}}^{(0)} = (X'X)^{-1} X'Y \text{ and } \hat{\boldsymbol{\psi}}^{(0)} = \frac{1}{n} (Y - X\hat{\mathbf{B}}^{(0)})'$$

Step-2: Determine the value $D_u^{(h)}(\mathbf{B}, \boldsymbol{\psi}) = (\mathbf{y}_u - \hat{\mathbf{B}}^{(h)} \mathbf{g}(\mathbf{x}_u))' (\hat{\boldsymbol{\psi}}^{(h)})^{-1} (\mathbf{y}_u - \hat{\mathbf{B}}^{(h)} \mathbf{g}(\mathbf{x}_u))$

$$\text{with } \boldsymbol{\Omega} = \text{diag}(\omega_1, \omega_2, \dots, \omega_n) \text{ and } \omega_u^{(h+1)} = \frac{v+q}{v+D_u^{(h)}(\mathbf{B}, \boldsymbol{\psi})}$$

Step-3: Determine sufficient statistics for parameters $(\mathbf{B}, \boldsymbol{\psi})$, i.e.;

$$S_{\omega XX}^{(h+1)} = \sum_{u=1}^n \omega_u^{(h+1)} \mathbf{g}(\mathbf{x}_u) \mathbf{g}'(\mathbf{x}_u) = \mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \mathbf{X}$$

$$S_{\omega XY}^{(h+1)} = \sum_{u=1}^n \omega_u^{(h+1)} \mathbf{g}(\mathbf{x}_u) (\hat{\mathbf{y}}_u^{(h)})' = \mathbf{X}' \boldsymbol{\Omega}^{(h+1)} \hat{\mathbf{Y}}^{(h)}$$

$$S_{\omega YY}^{(h+1)} = \sum_{u=1}^n \omega_u^{(h+1)} (\hat{\mathbf{y}}_u^{(h)}) (\hat{\mathbf{y}}_u^{(h)})' + \frac{1}{n} \sum_{u=1}^n \hat{\boldsymbol{\psi}}_u^{(h)} = (\hat{\mathbf{Y}}^{(h)})' \boldsymbol{\Omega}^{(h+1)} (\hat{\mathbf{Y}}^{(h)}) + \frac{1}{n} \sum_{u=1}^n \hat{\boldsymbol{\psi}}_u^{(h)}$$

Step-4: Calculate $\hat{\mathbf{B}}^{(h+1)}$ and $\hat{\boldsymbol{\psi}}^{(h+1)}$ according to the Equation (13);

Step-5: Determine the tolerance limit ε ;

Step-6: Calculate $\|\hat{\boldsymbol{\Theta}}^{(h+1)} - \hat{\boldsymbol{\Theta}}^{(h)}\|$ with $\hat{\boldsymbol{\Theta}}^h = \begin{bmatrix} \hat{\mathbf{B}}^{(h)} & \hat{\boldsymbol{\psi}}^{(h)} \end{bmatrix}'$

Step-7: If $\|\hat{\boldsymbol{\Theta}}^{(h+1)} - \hat{\boldsymbol{\Theta}}^{(h)}\| < \varepsilon$ then $\hat{\mathbf{B}} = \hat{\mathbf{B}}^{(h+1)}$ and $\hat{\boldsymbol{\psi}} = \hat{\boldsymbol{\psi}}^{(h+1)}$

Step-8: If $\|\hat{\boldsymbol{\Theta}}^{(h+1)} - \hat{\boldsymbol{\Theta}}^{(h)}\| < \varepsilon$ Then, repeat steps 2 to 8. $\square$

3.2. Hypothesis Testing for Parameters of the SOMRS Model with a Multivariate t-Distribution Approach

After conducting parameter estimation, the next step is to test the SOMRS model parameters simultaneously. In this testing, the first step is to formulate a hypothesis, i.e.,

$$\begin{aligned} H_0 : \beta_{1i} = \dots = \beta_{ki} = \beta_{11i} = \dots = \beta_{kki} = \beta_{12i} = \dots = \beta_{(k-1)ki} = 0 \\ H_1 : \text{At least one of } \beta_{ji} \neq 0 \text{ atau } \beta_{jji} \neq 0 \text{ or } \beta_{(j-1)ji} \neq 0, i = 1, 2, \dots, q, \\ j = 1, 2, \dots, k \end{aligned} \quad (17)$$

Thus, the SOMRS model with a multivariate t-distribution approach under H_0 is:

$$E(\mathbf{Y}_u) = \mathbf{B}'_0 \mathbf{g}(\mathbf{x}_u) = \boldsymbol{\beta}'_0 = [\beta_{001} \quad \beta_{002} \quad \dots \quad \beta_{00q}]', \quad u = 1, 2, \dots, n \quad (18)$$

Simultaneous test statistics using the LRT method can be determined as follows. Define the parameter set under H_0 and under the population, namely $\boldsymbol{\Theta}_0 = \{\boldsymbol{\beta}_0, \boldsymbol{\psi}_0\}$ and $\boldsymbol{\Theta} = \{\mathbf{B}, \boldsymbol{\psi}\}$. Next, take a random sample sized n , namely $\mathbf{y}_u = [y_{u1} \quad y_{u2} \quad \dots \quad y_{uq}]'$, $u = 1, 2, \dots, n$, and determine the function of likelihood below H_0 , i.e.,

$$\begin{aligned} L(\boldsymbol{\Theta}_0) &= \prod_{u=1}^n f(\mathbf{y}_u | \mathbf{B}_0, \boldsymbol{\psi}_0) \\ &= \frac{\left[\Gamma\left(\frac{v+q}{2}\right) \right]^n}{(\pi v)^{\frac{qn}{2}} \left[\Gamma\left(\frac{v}{2}\right) \right]^n |\boldsymbol{\psi}_0|^{\frac{n}{2}}} \cdot \prod_{u=1}^n \left[1 + \frac{(\mathbf{y}_u - \boldsymbol{\beta}'_0)' \boldsymbol{\psi}_0^{-1} (\mathbf{y}_u - \boldsymbol{\beta}'_0)}{v} \right]^{-\frac{v+q}{2}} \end{aligned} \quad (19)$$

The log-likelihood function, i.e.,

$$\begin{aligned} \ell(\boldsymbol{\Theta}_0) &= \ln L(\boldsymbol{\Theta}_0) = \sum_{u=1}^n f(\mathbf{y}_u | \mathbf{B}_0, \boldsymbol{\psi}_0) \\ &= n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\boldsymbol{\psi}_0|^{\frac{1}{2}}} \right] - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \boldsymbol{\beta}'_0)' \boldsymbol{\psi}_0^{-1} (\mathbf{y}_u - \boldsymbol{\beta}'_0)}{v} \right]; \end{aligned} \quad (20)$$

So that the maximum likelihood function under H_0 is

$$L(\hat{\boldsymbol{\Theta}}_0) = \frac{\left[\Gamma\left(\frac{v+q}{2}\right) \right]^n}{(\pi v)^{\frac{qn}{2}} \left[\Gamma\left(\frac{v}{2}\right) \right]^n} \cdot \prod_{u=1}^n |\hat{\boldsymbol{\psi}}_0|^{-\frac{1}{2}} \left[1 + \frac{(\mathbf{y}_u - \hat{\boldsymbol{\beta}}'_0)' \boldsymbol{\psi}_0^{-1} (\mathbf{y}_u - \hat{\boldsymbol{\beta}}'_0)}{v} \right]^{-\frac{v+q}{2}} \quad (21)$$

and the maximum of log-likelihood function under H_0 is

$$\ell(\hat{\boldsymbol{\Theta}}_0) = n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right)} \right] - \frac{1}{2} \sum_{u=1}^n \ln |\hat{\boldsymbol{\psi}}_0| - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \hat{\boldsymbol{\beta}}'_0)' \boldsymbol{\psi}_0^{-1} (\mathbf{y}_u - \hat{\boldsymbol{\beta}}'_0)}{v} \right] \quad (22)$$

where $(\hat{\boldsymbol{\beta}}_0, \hat{\boldsymbol{\psi}}_0)$ is an estimator for $(\boldsymbol{\beta}_0, \boldsymbol{\psi}_0)$ on the SOMRS model with a multivariate t-distribution approach as stated in Equation (5). Next is to determine the likelihood function under the population, i.e.,

$$L(\Theta) = \frac{\left[\Gamma\left(\frac{v+q}{2}\right)\right]^n}{(\pi v)^{\frac{qn}{2}} \left[\Gamma\left(\frac{v}{2}\right)\right]^n |\Psi|^{\frac{n}{2}}} \cdot \prod_{u=1}^n \left[1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \Psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right]^{-\frac{v+q}{2}} \quad (23)$$

Then, the log-likelihood function under the population is

$$\ell(\Theta) = n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right) |\Psi|^{\frac{1}{2}}} \right] - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))' \Psi^{-1} (\mathbf{y}_u - \mathbf{B}'\mathbf{g}(\mathbf{x}_u))}{v} \right] \quad (24)$$

So, the maximum of likelihood function under the population is

$$L(\hat{\Theta}) = \frac{\left[\Gamma\left(\frac{v+q}{2}\right)\right]^n}{(\pi v)^{\frac{qn}{2}} \left[\Gamma\left(\frac{v}{2}\right)\right]^n} \cdot \prod_{u=1}^n |\hat{\Psi}|^{-\frac{1}{2}} \left[1 + \frac{(\mathbf{y}_u - \hat{\mathbf{B}}'\mathbf{g}(\mathbf{x}_u))' \hat{\Psi}^{-1} (\mathbf{y}_u - \hat{\mathbf{B}}'\mathbf{g}(\mathbf{x}_u))}{v} \right]^{-\frac{v+q}{2}} \quad (25)$$

Moreover, the maximum of log-likelihood function under the population is

$$\begin{aligned} \ell(\hat{\Theta}) = n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right)} \right] - \frac{1}{2} \sum_{u=1}^n \ln |\hat{\Psi}| + \\ - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \hat{\mathbf{B}}'\mathbf{g}(\mathbf{x}_u))' \hat{\Psi}_0^{-1} (\mathbf{y}_u - \hat{\mathbf{B}}'\mathbf{g}(\mathbf{x}_u))}{v} \right] \end{aligned} \quad (26)$$

where $(\hat{\beta}, \hat{\psi})$ is an estimator for (β, ψ) on the SOMRS model with multivariate t-distribution as stated in Equation (5).

Theorem 2. If $\hat{\Theta}$ is the parameter set under the population, $\hat{\Theta}_0$ is the parameter set under H_0 , and a hypothesis is given by Equation (17), then the test statistic for the hypothesis testing in that Equation is $\zeta = 2(\ell(\hat{\Theta}) - \ell(\hat{\Theta}_0))$

Proof of Theorem 2. The likelihood ratio for hypothesis testing Equation (17):

$$R = \frac{L(\hat{\Theta}_0)}{L(\hat{\Theta})} < R_0 \quad (27)$$

where R_0 is a constant whose value lies between 0 and 1.

$$R = \frac{\prod_{u=1}^n |\hat{\Psi}_0|^{-\frac{1}{2}} \left[1 + \frac{(\mathbf{y}_u - \hat{\beta}'_0)' \Psi_0^{-1} (\mathbf{y}_u - \hat{\beta}'_0)}{v} \right]^{-\frac{v+q}{2}}}{\prod_{u=1}^n |\hat{\Psi}|^{-\frac{1}{2}} \left[1 + \frac{(\mathbf{y}_u - \hat{\mathbf{B}}'\mathbf{g}(\mathbf{x}_u))' \hat{\Psi}^{-1} (\mathbf{y}_u - \hat{\mathbf{B}}'\mathbf{g}(\mathbf{x}_u))}{v} \right]^{-\frac{v+q}{2}}} \quad (28)$$

Based on Equation (27), the R-value is difficult to simplify, so to simplify calculations, the likelihood ratio in Equation (27) is expressed in an equivalent form, namely

$$R^2 = \left[\frac{L(\hat{\Theta}_0)}{L(\hat{\Theta})} \right]^{-2} = \left[\frac{L(\hat{\Theta})}{L(\hat{\Theta}_0)} \right]^2 \quad (29)$$

Applying the natural logarithm to the Equation (29) yields the test statistic

$$\begin{aligned} \zeta &= \ln(R^{-2}) = -2 \ln(R) = -2 \ln \left[\frac{L(\hat{\Theta}_0)}{L(\hat{\Theta})} \right] = 2 \ln \left[\frac{L(\hat{\Theta})}{L(\hat{\Theta}_0)} \right] \\ &= 2 \left(\ell(\hat{\Theta}) - \ell(\hat{\Theta}_0) \right) \end{aligned} \quad (30)$$

with $\ell(\hat{\Theta})$ according to Equation (26) and $\ell(\hat{\Theta}_0)$ according to Equation (22). $\square$

Theorem 3. Based on Theorem 2, the distribution of test statistics ζ is Chi-square with the degrees of freedom kq , which can be written as follows:

$$\zeta = 2 \left(\ell(\hat{\Theta}) - \ell(\hat{\Theta}_0) \right) \xrightarrow{d} \chi_{kq}^2, k \rightarrow \infty \quad (31)$$

Proof of Theorem 3. The distribution of test statistics ζ will be determined based on the definition of the parameter set under H_0 and under the population.

$$\begin{aligned} \zeta &= 2 \left(\ell(\hat{\Theta}) - \ell(\hat{\Theta}_0) \right) \\ &= 2 \left(\ell(\hat{\Theta}) - \ell(\Theta_0) + \ell(\Theta_0) - \ell(\hat{\Theta}_0) \right) \\ &= 2 \left(\ell(\hat{\Theta}) - \ell(\Theta_0) \right) - 2 \left(\ell(\hat{\Theta}_0) - \ell(\Theta_0) \right) \end{aligned} \quad (32)$$

The function $\ell(\Theta_0)$ can be approached by the second degree of Taylor expansion around $\hat{\Theta}$ as follows.

$$\ell(\Theta_0) \approx \ell(\hat{\Theta}) + g(\hat{\Theta})(\Theta_0 - \hat{\Theta}) - \frac{1}{2}(\Theta_0 - \hat{\Theta})' [K(\hat{\Theta})](\Theta_0 - \hat{\Theta}) \quad (33)$$

with $g(\hat{\Theta}) = \frac{\partial \ell(\Theta)}{\partial(\Theta)} \Big|_{\Theta=\hat{\Theta}}$ and $K(\hat{\Theta}) = -\frac{\partial^2 \ell(\Theta)}{\partial(\Theta)\partial(\Theta)} \Big|_{\Theta=\hat{\Theta}}$. Because $\hat{\Theta}$ is an estimated parameter that maximizes $\ell(\Theta)$, so $g(\hat{\Theta}) = 0$, then

$$\begin{aligned} \ell(\Theta_0) &\approx \ell(\hat{\Theta}) - \frac{1}{2}(\Theta_0 - \hat{\Theta})' [K(\hat{\Theta})](\Theta_0 - \hat{\Theta}) \\ \ell(\Theta_0) - \ell(\hat{\Theta}) &\approx -\frac{1}{2}(\Theta_0 - \hat{\Theta})' [K(\hat{\Theta})](\Theta_0 - \hat{\Theta}) \\ -2 \left(\ell(\Theta_0) - \ell(\hat{\Theta}) \right) &\approx \left(-(\Theta_0 - \hat{\Theta})' \right) [K(\hat{\Theta})] \left(-(\Theta_0 - \hat{\Theta}) \right) \\ 2 \left(\ell(\hat{\Theta}) - \ell(\Theta_0) \right) &\approx (\hat{\Theta} - \Theta_0)' [K(\hat{\Theta})](\hat{\Theta} - \Theta_0) \end{aligned} \quad (34)$$

In the same way, the function $\ell(\hat{\Theta}_0)$ can be approached by the second degree of Taylor expansion around $\hat{\Theta}_0$ as follows:

$$\ell(\Theta_0) \approx \ell(\hat{\Theta}_0) + g(\hat{\Theta}_0)(\Theta_0 - \hat{\Theta}_0) - \frac{1}{2}(\Theta_0 - \hat{\Theta}_0)' [K(\hat{\Theta}_0)](\Theta_0 - \hat{\Theta}_0) \quad (35)$$

Because $g(\hat{\Theta}) = 0$, it is obtained

$$\begin{aligned}
 \ell(\Theta_0) &\approx \ell(\hat{\Theta}_0) - \frac{1}{2}(\Theta_0 - \hat{\Theta}_0)' [\mathbf{K}(\hat{\Theta})] (\Theta_0 - \hat{\Theta}_0) \\
 \ell(\Theta_0) - \ell(\hat{\Theta}_0) &\approx -\frac{1}{2}(\Theta_0 - \hat{\Theta}_0)' [\mathbf{K}(\hat{\Theta})] (\Theta_0 - \hat{\Theta}_0) \\
 -2(\ell(\Theta_0) - \ell(\hat{\Theta}_0)) &\approx -(\Theta_0 - \hat{\Theta}_0)' [\mathbf{K}(\hat{\Theta})] (\Theta_0 - \hat{\Theta}_0) \\
 2(\ell(\hat{\Theta}_0) - \ell(\Theta_0)) &\approx (\hat{\Theta}_0 - \Theta_0)' [\mathbf{K}(\hat{\Theta})] (\hat{\Theta}_0 - \Theta_0)
 \end{aligned} \tag{36}$$

By substituting the Equation **Error! Reference source not found.** to Equation (32) obtained

$$\begin{aligned}
 \zeta &= (\hat{\Theta} - \Theta_0)' [\mathbf{K}(\hat{\Theta})] (\hat{\Theta} - \Theta_0) - (\hat{\Theta}_0 - \Theta_0)' [\mathbf{K}(\hat{\Theta})] (\hat{\Theta}_0 - \Theta_0) \\
 &= (\hat{\Theta} - \hat{\Theta}_0)' [\mathbf{K}(\hat{\Theta})] (\hat{\Theta} - \hat{\Theta}_0)
 \end{aligned} \tag{37}$$

The Fisher Information matrix and its inverse in the Equation **Error! Reference source not found.** can be stated as follows

$$[\mathbf{K}(\hat{\Theta})] = \begin{bmatrix} [\mathbf{K}_{11}] & [\mathbf{K}_{12}] \\ [\mathbf{K}_{21}] & [\mathbf{K}_{22}] \end{bmatrix} \tag{38}$$

and

$$[\mathbf{K}(\hat{\Theta})]^{-1} = \begin{bmatrix} [\mathbf{K}^{11}] & [\mathbf{K}^{12}] \\ [\mathbf{K}^{21}] & [\mathbf{K}^{22}] \end{bmatrix} \tag{39}$$

The inverse of the Fisher Information Matrix in the Equation **Error! Reference source not found.** can be declared to be

$$[\mathbf{K}(\hat{\Theta})]^{-1} = \begin{bmatrix} [\mathbf{K}_{11.2}^{-1}] & -[\mathbf{K}_{11.2}^{-1}][\mathbf{K}_{12}][\mathbf{K}_{22}^{-1}] \\ -[\mathbf{K}_{22}^{-1}][\mathbf{K}_{21}][\mathbf{K}_{11.2}^{-1}] & [\mathbf{K}_{22.1}^{-1}] \end{bmatrix} \tag{40}$$

with $[\mathbf{K}_{11.2}] = [\mathbf{K}_{11}] - [\mathbf{K}_{12}][\mathbf{K}_{22}^{-1}][\mathbf{K}_{21}]$ and $[\mathbf{K}_{11}]^{-1} = [\mathbf{K}_{11.2}]$. (41)

$[\mathbf{K}_{11}]$, $[\mathbf{K}_{22}]$, $[\mathbf{K}_{11.2}]$, and $[\mathbf{K}_{22.1}]$ are non-singular matrices [21]. Based on Equations **Error! Reference source not found.** and **Error! Reference source not found.** the following Equation can be obtained:

$$[\mathbf{K}^{21}][\mathbf{K}^{11}]^{-1} = -[\mathbf{K}_{22}]^{-1}[\mathbf{K}_{21}] \tag{42}$$

The maximum likelihood estimator of the SOMRS model in the population is partitioned to be

$$\hat{\Theta} = [\hat{\beta}^* \quad \hat{\Theta}_1]' \tag{43}$$

with dengan $\beta^* = [\beta'_1 \quad \beta'_2 \quad \dots \quad \beta'_i \quad \dots \quad \beta'_n]'$ for $i = 1, 2, \dots, n$, dan

$$\hat{\Theta}_1 = [\hat{\psi}_1 \quad \dots \quad \hat{\psi}_n \quad \hat{\beta}'_0]'.$$

The maximum likelihood estimator of the SOMRS model on H_0 is partitioned to be

$$\hat{\Theta}_0 = [0 \quad \hat{\Theta}'_{10}]' \tag{44}$$

with $\hat{\Theta}_{10} = [\hat{\psi}_1 \quad \dots \quad \hat{\psi}_n \quad \hat{\beta}'_{00}]'$. If $(\hat{\Theta} - \Theta) \xrightarrow{d} N(0, [K(\hat{\Theta})]^{-1}), k \rightarrow \infty$ is known [22], and pays attention to the Equation (47), then

$$\begin{bmatrix} \hat{\beta}^* - \beta^* \\ \hat{\Theta}_1 - \Theta_1 \end{bmatrix} \xrightarrow{d} N \left(\begin{bmatrix} 0_{(kq \times 1)} \\ 0_{(kq \times 1)} \end{bmatrix}, [K(\hat{\Theta})]^{-1} \right), k \rightarrow \infty \quad (45)$$

Based on the theory of multivariate normal distribution, the conditional distribution of y if given x is multivariate normal, i.e.,

$$y|x \sim N(E(y|x), \text{cov}(y|x)) \quad (46)$$

With $E(y|x) = \mu_y + \Sigma_{yx}\Sigma_{xx}^{-1}(x - \mu_x)$ and $\text{cov}(y|x) = \Sigma_{yy} - \Sigma_{yx}\Sigma_{xx}^{-1}(x - \mu_x)$.

Based on the Equation **Error! Reference source not found.**, the maximum likelihood estimator for μ_x if given y, x, μ_x [22,23] are:

$$\mu_x = y - \Sigma_{yx}\Sigma_{xx}^{-1}(x - \mu_x) \quad (47)$$

Based on Equations **Error! Reference source not found.** and **Error! Reference source not found.**, in the same way, the maximum likelihood estimator $\hat{\Theta}_{01}$ can be expressed in the component vector $\hat{\Theta}$ if given $\beta^* = 0_{(kq \times 1)}$, $\hat{\beta}^*$, and $\hat{\Theta}_1$ is

$$\hat{\Theta}_{10} = \hat{\Theta}_1 - [K^{21}][K^{11}]^{-1}(\hat{\beta}^* - 0_{(kq \times 1)}) = \hat{\Theta}_1 - [K^{21}][K^{11}]^{-1}\hat{\beta}^* \quad (48)$$

and based on the Equation (42) obtained

$$\hat{\Theta}_{10} = \hat{\Theta}_1 + [K_{22}]^{-1}[K_{21}]\hat{\beta}^* \quad (49)$$

Based on Equations **Error! Reference source not found.** and (46), the following can be obtained:

$$(\hat{\Theta}_0 - \Theta_0) = \begin{bmatrix} 0_{(kq \times 1)} - 0_{(kq \times 1)} \\ \hat{\Theta}_{01} - \Theta_1 \end{bmatrix} = \begin{bmatrix} 0_{(kq \times 1)} \\ \hat{\Theta}_1 - \Theta_1 + [K_{22}]^{-1}[K_{21}]\hat{\beta}^* \end{bmatrix}$$

and

$$\begin{aligned} (\hat{\Theta}_0 - \Theta_0)' [K(\hat{\Theta})] (\hat{\Theta}_0 - \Theta_0) &= \begin{bmatrix} 0_{(kq \times 1)} \\ \hat{\Theta}_{10} - \Theta_1 \end{bmatrix}' \begin{bmatrix} [K_{11}] & [K_{12}] \\ [K_{21}] & [K_{22}] \end{bmatrix} \begin{bmatrix} 0_{(kq \times 1)} \\ \hat{\Theta}_{10} - \Theta_1 \end{bmatrix} \\ &= (\hat{\Theta}_{10} - \Theta_1)' [K_{22}] (\hat{\Theta}_{10} - \Theta_1) \\ &= (\hat{\Theta}_1 - \Theta_1 + [K_{22}]^{-1}[K_{21}]\hat{\beta}^*)' [K_{22}] (\hat{\Theta}_1 - \Theta_1 + [K_{22}]^{-1}[K_{21}]\hat{\beta}^*) \\ &= \begin{bmatrix} \hat{\beta}^* \\ \hat{\Theta}_1 - \Theta_1 \end{bmatrix}' \begin{bmatrix} [K_{12}][K_{22}]^{-1}[K_{21}] & [K_{12}] \\ [K_{21}] & [K_{22}] \end{bmatrix} \begin{bmatrix} \hat{\beta}^* \\ \hat{\Theta}_1 - \Theta_1 \end{bmatrix} \end{aligned} \quad (50)$$

Equation (37) can be simplified by describing the square form of $(\hat{\Theta} - \Theta_0)' [K(\hat{\Theta})] (\hat{\Theta} - \Theta_0)$ and square form of Equation (50) so that the following is obtained:

$$\begin{aligned}
\zeta &= 2 \left(\ell(\hat{\Theta}) - \ell(\hat{\Theta}_0) \right) \\
&= (\hat{\Theta}_1 - \hat{\Theta}_{10})' \left[\mathbf{K}^{11}(\hat{\Theta}) \right]^{-1} (\hat{\Theta}_1 - \hat{\Theta}_{10}) \\
&= \beta^{*'} \left[\mathbf{K}^{11}(\hat{\Theta}) \right]^{-1} \beta^* \\
&= \left[\left[\mathbf{K}^{11}(\hat{\Theta}) \right]^{-1/2} \beta^{*'} \right]' \left[\left[\mathbf{K}^{11}(\hat{\Theta}) \right]^{-1/2} \beta^* \right] \\
&= \mathbf{z}' \mathbf{z} \xrightarrow{d} \chi_{(kq)}^2, k \rightarrow \infty
\end{aligned} \tag{51}$$

□

The critical area for the hypothesis testing of the model parameters simultaneously is

$$\begin{aligned}
\alpha &= P(R < R_0) \\
&= P(-2 \ln R > -2 \ln R_0) \\
&= P(\zeta > c)
\end{aligned}$$

where $c = -2 \ln R_0$, so that the following is obtained:

$$\alpha = P(\zeta > \chi_{\alpha, kq}^2) \tag{52}$$

Based on Equation **Error! Reference source not found.**, the critical area for the simultaneous hypothesis testing of the SOMRS model with multivariate t-distribution is to reject H_0 if the value is $\zeta > \chi_{\alpha, kq}^2$.

Then, the algorithm for hypothesis testing of the SOMRS model is as follows:

Step-1: Determine the estimator value for the set of model parameters under H_0 and under the population by running the EM algorithm;

Step-2: Determine the null hypothesis (H_0) and alternative hypotheses (H_1)

$$\begin{aligned}
H_0 : \beta_{1i} = \dots = \beta_{ki} = \beta_{11i} = \dots = \beta_{kki} = \beta_{12i} = \dots = \beta_{(k-1)ki} &= 0 \\
H_1 : \text{At least one of } \beta_{ji} \neq 0 \text{ atau } \beta_{jji} \neq 0 \text{ or } \beta_{(j-1)ji} \neq 0, i = 1, 2, \dots, q, \\
& j = 1, 2, \dots, k
\end{aligned}$$

Step-3: Calculate the value of $\ell(\hat{\Theta}_0)$, i.e.,

$$\ell(\hat{\Theta}_0) = n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right)} \right] - \frac{1}{2} \sum_{u=1}^n \ln |\hat{\Psi}_0| - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \hat{\beta}'_0)' \Psi_0^{-1} (\mathbf{y}_u - \hat{\beta}'_0)}{v} \right]$$

Step-4: Calculate the value of $\ell(\hat{\Theta})$, i.e.,

$$\begin{aligned}
\ell(\hat{\Theta}) &= n \ln \left[\frac{\Gamma\left(\frac{v+q}{2}\right)}{(\pi v)^{\frac{q}{2}} \Gamma\left(\frac{v}{2}\right)} \right] - \frac{1}{2} \sum_{u=1}^n \ln |\hat{\Psi}| + \\
&\quad - \frac{v+q}{2} \sum_{u=1}^n \ln \left[1 + \frac{(\mathbf{y}_u - \hat{\mathbf{B}}' \mathbf{g}(\mathbf{x}_u))' \Psi_0^{-1} (\mathbf{y}_u - \hat{\mathbf{B}}' \mathbf{g}(\mathbf{x}_u))}{v} \right]
\end{aligned}$$

- Step-5: Calculate the value of the statistical test $\zeta = 2 \left(\ell(\hat{\Theta}) - \ell(\hat{\Theta}_0) \right)$;
- Step-6: Determine the level of significance α and critical value $\chi^2_{\alpha, kq}$;
- Step-7: Determine the rejection area, i.e., reject H_0 if $\zeta > \chi^2_{\alpha, kq}$;
- Step-8: Make conclusions and interpretations.

3.3. Application of SOMRS Model with a Multivariate t-Distribution Approach

Based on the experimental result using CCD, it is obtained the mean of the Paracetamol tablet's friability is 0.52% (according to specifications, which is less than 1%), the mean of the tablet's hardness is 90.33 Newtons (according to specifications, which is 39.23–98.07 Newtons), and the mean of tablet's disintegration time is 242.98 s or 4.05 min (according to specifications, which is less than 15 min). A complete data description is presented in Table 4.

Table 4. Descriptive Statistics of Paracetamol Tablets Quality Characteristics.

Quality Characteristics	Mean	Std. Dev.	Min.	Q ₁	Med	Q ₃	Maks.	Skewness	Kurtosis
Tablet's Friability (Y_1)	0.52	0.21	0.12	0.41	0.51	0.65	0.93	0.18	−0.04
Tablet's Hardness (Y_2)	90.33	19.01	60.00	79.00	86.08	101.83	134.17	0.52	0.06
Tablet's Disintegration Time (Y_3)	242.98	62.01	147.00	197.62	244.49	279.79	367.50	0.39	−0.51

With the help of R Language version 4.1.0 and RStudio 2021.09.0, the SOMRS model with a multivariate t-distribution approach is obtained as follows:

$$\hat{y}_1 = 0.5239 + 0.0675 x_1 + 0.0287 x_2 - 0.1453 x_3 + 0.0492 x_1^2 + 0.0191 x_2^2 - 0.0675 x_3^2 + 0.0063 x_1 x_2 - 0.0462 x_1 x_3 + 0.0862 x_2 x_3 \quad (53)$$

$$\hat{y}_2 = 87.6758 - 4.7906 x_1 - 5.9001 x_2 + 18.7743 x_3 + 0.4714 x_1^2 + 0.5014 x_2^2 + 2.9174 x_3^2 + 2.7912 x_1 x_2 + 1.9987 x_1 x_3 - 0.7088 x_2 x_3 \quad (54)$$

$$\hat{y}_3 = 244.8791 + 49.0306 x_1 + 9.6788 x_2 + 7.5927 x_3 + 2.5301 x_1^2 + 13.6342 x_2^2 - 18.9430 x_3^2 - 23.2938 x_1 x_2 + 12.6212 x_1 x_3 - 18.0863 x_2 x_3 \quad (55)$$

The Equation in the coded level can be used to predict the response value based on each factor's levels and to identify each factor's relative impact by observing the corresponding parameters (models).

Furthermore, the R-square values for the model in Equations (53)–(55) are 0.6572, 0.8483, and 0.7109, respectively. Based on R-square values, it is possible to conclude that the model adequately describes the relationship between the input and response variables.

By using the DRS technique, the tablet's disintegration time (Y_3) is considered the most important among the three responses, while the tablet's friability (Y_1) and the tablet's hardness (Y_2) are considered the same level of importance. The three response variables, optimal characteristics, and specifications are presented in Table 1. Thus, the optimal level set obtained is 1.32% binder, 2.32% disintegrant, and 8445.91 N compression force. In this setting, Paracetamol tablets have a friability of 0.73%, a hardness of 96.63 N, and a disintegration time of 44.14 s, with a minimum MSE of 1988.21. The three response values obtained are in accordance with the desired specifications.

4. Discussion

In some experiments, the data obtained did not meet the normality assumptions, such as having a heavy tail distribution. This condition can cause unreliable or even

misleading results for practitioners in the field of quality improvement [1]. However, some studies have proven that the multivariate t-distribution can handle such data [3–5,7,20]. Therefore, the multivariate t-distribution approach is to be developed for Response Surface Methodology (RSM), especially for the modeling stage.

The Second-Order Multiresponse Surface (SOMRS) model with multivariate t-distribution approach developed in this research differs from other development carried out in several previous studies [4,6–8]. The differences are in the type of input variable (a setting of experimental conditions) and the order model (second-order model).

The proposed SOMRS model with a multivariate t-distribution approach has been developed along with its parameter estimation and hypothesis testing. The solution of parameter estimation using the Maximum Likelihood Estimation (MLE) is not closed-form such that it is optimized numerically using the Expectation–Maximization (EM) algorithm. Afterward, the Likelihood Ratio Test (LRT) is employed for testing simultaneously the parameters model.

The use of the MLE method to get the parameter estimation and LRT parameter estimation for testing the parameter hypothesis of the model obtained in this study is the same as the research conducted for the multivariate t-distribution approach [6], and the multivariate Gamma distribution approach [8]. Therefore, the results obtained also do not differ from these two studies.

This paper has applied this approach to determine the SOMRS model and optimal conditions of the physical quality characteristics (friability, hardness, and disintegration time) of Paracetamol tablets. All of these quality characteristics are in accordance with the desired specifications [19].

The model's goodness of fit is based on the R-square values; further research can use other methods to be more convincing. At the optimization stage, the Dual Response Systems (DRS) technique is used to set conditions to achieve the desired quality characteristics. Other optimization methods can also be used for further research.

5. Conclusions

The proposed Second-Order Multiresponse Surface (SOMRS) model with a multivariate t-distribution approach has been developed along with its parameter estimation and hypothesis testing. The solution of parameter estimation using the Maximum Likelihood Estimation (MLE) is not closed-form such that it is optimized numerically using the Expectation–Maximization (EM) algorithm. Afterward, the Likelihood Ratio Test (LRT) is employed for testing simultaneously the model parameters.

The application of this approach shows appropriate results in the modeling stage and determining optimal conditions of the physical quality characteristics (friability, hardness, and disintegration time) of Paracetamol tablets. All of these quality characteristics are under the desired specifications.

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