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Original Research Article

Application of Matrices, Regression, and ANOVA in the Design and Analysis of Experimental Data Using Statistical Software for Pharmaceutical Formulation Optimization

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Abstract: ***Background:*** In the early twentieth century, we were analyzing the experimental data after performing the experiment, but in the meantime the idea of using statistical analysis in the planning stages of research, as opposed to the conclusion of experimentation, was first presented by Sir Ronald Fisher. This concept of planning, designing, performing and analyzing the experimental results was used in the field of Engineering and Agriculture Science. In over time the pharmaceutical industries started applying these new paradigms extensively in the formulation development to optimize the product, to measure the main effect and interaction effect of factors or ingredients selected in preparing a formulation and to verify the level of significance between the experimental values which are obtained after performing and predicted values which are computed after obtaining the mathematical model or mathematical equation. The objective of this study was to help the investigator understand the application of matrix techniques, Standard Deviation, Coefficient of Variance, Regression and ANOVA for analyzing the data of different formulations prepared using different ingredients at different quantity or levels. To perform these types of studies in pharmaceutical research, the Design of Experiments (DoE) is a main statistical tool, that can be used for analyzing the data and to verify the level of significance $\alpha = 0.05$ or 0.01 by determining F-ratio. This statistical analysis shows that the model which is developed is more appropriate to perform experiments and analyze the resulting data.

Keywords: Design of Experiments, Application of Matrices, Regression and ANOVA

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INTRODUCTION

The primary goal is to demonstrate how Mathematical and Statistical methods are more appropriate to analyze the response variable using DOE (Design of Experiments) [1]. It can be applied for Matrices & Determinants, Standard Deviation, Coefficient of Variation, Regression and ANOVA. To perform this type of study, DOE is the only statistical software which can be used to Design, Perform the experiment and analyzing the result to verify the level of significance [2]. Before the existence or development of DOE, investigators were using the traditional method of changing one factor at time among the input variable within an appropriate levels by retaining the range of remaining factors as constant. But the traditional method OFAT (Integrated Factory Acceptance Test) approach fails to explain the measure of interaction between the factors, which may lead to an inadequate conduction of the development and optimization. To overcome these types of problems, DoE has been considered as a better approach to get accurate results with few numbers of experiments [3]. DoE has become one of the main components of pharmaceutical and analytical QbD. In this paper we are providing the theoretical and practical aspect of DoE in pharmaceuticals [4]. There are different software's such as GraphPad Prism, SPSS, R, and MATLAB are utilized for conducting statistical analyses These software packages are often found to be costly, and their utility extends beyond statistical analyses to encompass curve fitting, modeling, and graphing functionalities, which are more expensive if the user's only objective is to perform the statistical analysis [5].

2. Materials and Methods

Computational methods and theory

To prepare pharmaceutical formulation, investigators may consider n-ingredients as input variables and they perform an experiment to obtain one response variable or formulation. In general, the input variables which are selected for study will be designated as low and high level and the designations of the variables will be noted as -1 for low level and +1 for high level of any one variable. But for the response variables, one cannot assign the coded values, here one has to consider actual value of the resultant [6]. If the investigator considers the three input variables, namely A, B and C, their designated levels can be tabulated as.

Table 1: Coded Levels of Ingredients A, B, and C

Ingredients	Designated Levels in Coded Form	
	Low level	High Level
A	-1	+1
B	-1	+1
C	-1	+1

If the investigator considers the factorial design in DOE to design and analyze the data of a formulation, then 2^3 – Factorial design has to be chosen to perform experiments [7].

Table 2: Design of experiment without interaction and response variable.

Runs	Combinations of ingredients with different levels	Ingredients		
		A	B	C
1	1	-1	-1	-1
2	a	1	-1	-1
3	b	-1	1	-1
4	ab	1	1	-1
5	c	-1	-1	-1
6	ac	1	-1	1
7	bc	-1	1	1
8	abc	1	1	1

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Table 3: Design of experiment table with response variable.

Runs	Combinations of ingredients with different levels	Ingredients			
		A	B	C	Response Variable – Y1
1	1	-1	-1	-1	Y1
2	a	1	-1	-1	Y2
3	b	-1	1	-1	Y3
4	ab	1	1	-1	Y4
5	c	-1	-1	-1	Y5
6	ac	1	-1	1	Y6
7	bc	-1	1	1	Y7
8	abc	1	1	1	Y8

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RESULTS AND DISCUSSION

Mathematical and statistical methods to obtain a Model to analyze the data in DOE

To analyze the experimental results, investigators should follow the matrix method to obtain the mathematical or regression model. To obtain regression model, one has to proceed as per the steps listed [8].

Step 1: Construct three matrices as per ingredients or input variables selected, response variables and regression coefficients need to be computed.

$$X = \begin{bmatrix} 1 & -1 & -1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & 1 & -1 \\ 1 & -1 & -1 & 1 \\ 1 & 1 & -1 & 1 \\ 1 & -1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{bmatrix} = \begin{bmatrix} x11 & x21 & x31 & x41 \\ x12 & x22 & x32 & x42 \\ x13 & x23 & x33 & x43 \\ x14 & x24 & x34 & x44 \\ x15 & x25 & x35 & x45 \\ x16 & x26 & x36 & x46 \\ x17 & x27 & x37 & x47 \\ x18 & x28 & x38 & x48 \end{bmatrix} \quad Y = \begin{bmatrix} Y1 \\ Y2 \\ Y3 \\ Y4 \\ Y5 \\ Y6 \\ Y7 \\ Y8 \end{bmatrix} \quad \beta = \begin{bmatrix} \beta 0 \\ \beta 1 \\ \beta 2 \\ \beta 3 \end{bmatrix}$$

Step 2: Obtaining the transpose Matrix of X

$$X^T = \begin{bmatrix} x11 & x12 & x13 & x14 & x15 & x16 & x17 & x18 \\ x21 & x22 & x23 & x24 & x25 & x26 & x27 & x28 \\ x31 & x32 & x33 & x34 & x35 & x36 & x37 & x38 \\ x41 & x42 & x43 & x44 & x45 & x46 & x47 & x48 \end{bmatrix}$$

Step 3: Obtaining the product of X^TX

$$X^TX = \begin{bmatrix} x11 & x12 & x13 & x14 & x15 & x16 & x17 & x18 \\ x21 & x22 & x23 & x24 & x25 & x26 & x27 & x28 \\ x31 & x32 & x33 & x34 & x35 & x36 & x37 & x38 \\ x41 & x42 & x43 & x44 & x45 & x46 & x47 & x48 \end{bmatrix} * \begin{bmatrix} x11 & x21 & x31 & x41 \\ x12 & x22 & x32 & x42 \\ x13 & x23 & x33 & x43 \\ x14 & x24 & x34 & x44 \\ x15 & x25 & x35 & x45 \\ x16 & x26 & x36 & x46 \\ x17 & x27 & x37 & x47 \\ x18 & x28 & x38 & x48 \end{bmatrix}$$

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Model example of multiplication of matrices

$$A=\begin{bmatrix}1 & 2 & -3\\ 5 & 0 & 2\\ 1 & -1 & 1\end{bmatrix},\ B=\begin{bmatrix}3 & -1 & 2\\ 4 & 2 & 5\\ 2 & 0 & 3\end{bmatrix},\ \text{and}\ C=\begin{bmatrix}4 & 1 & 2\\ 0 & 3 & 2\\ 0 & -2 & 3\end{bmatrix}$$

$$AB=\begin{bmatrix}1 & 2 & -3\\ 5 & 0 & 2\\ 1 & -1 & 1\end{bmatrix}\begin{bmatrix}3 & -1 & 2\\ 4 & 2 & 5\\ 2 & 0 & 3\end{bmatrix}$$

$$=\begin{bmatrix}3+8-6 & -1+4+0 & 2+10-9\\ 15+0+4 & -5+0+0 & 10+0+6\\ 3-4+2 & -1-2+0 & 2-5+3\end{bmatrix}=\begin{bmatrix}5 & 3 & 3\\ 19 & -5 & 16\\ 1 & -3 & 0\end{bmatrix} \quad \text{.....(1)}$$

$$AC=\begin{bmatrix}1 & 2 & -3\\ 5 & 0 & 2\\ 1 & -1 & 1\end{bmatrix}\begin{bmatrix}4 & 1 & 2\\ 0 & 3 & 2\\ 0 & -2 & 3\end{bmatrix}$$

$$=\begin{bmatrix}4+0+0 & 1+6+6 & 2+4-9\\ 20+0+0 & 5+0-4 & 10+0+6\\ 4+0+0 & 1-3-2 & 2-2+3\end{bmatrix}=\begin{bmatrix}4 & 13 & -3\\ 20 & 1 & 16\\ 4 & -4 & 3\end{bmatrix}$$

$$AB=\begin{bmatrix}1 & 2 & -3\\ 5 & 0 & 2\\ 1 & -1 & 1\end{bmatrix}\begin{bmatrix}3 & -1 & 2\\ 4 & 2 & 5\\ 2 & 0 & 3\end{bmatrix}$$

$$=\begin{bmatrix}3+8-6 & -1+4+0 & 2+10-9\\ 15+0+4 & -5+0+0 & 10+0+6\\ 3-4+2 & -1-2+0 & 2-5+3\end{bmatrix}=\begin{bmatrix}5 & 3 & 3\\ 19 & -5 & 16\\ 1 & -3 & 0\end{bmatrix} \quad \text{..... (2)}$$

$$AC=\begin{bmatrix}1 & 2 & -3\\ 5 & 0 & 2\\ 1 & -1 & 1\end{bmatrix}\begin{bmatrix}4 & 1 & 2\\ 0 & 3 & 2\\ 0 & -2 & 3\end{bmatrix}$$

$$=\begin{bmatrix}4+0+0 & 1+6+6 & 2+4-9\\ 20+0+0 & 5+0-4 & 10+0+6\\ 4+0+0 & 1-3-2 & 2-2+3\end{bmatrix}=\begin{bmatrix}4 & 13 & -3\\ 20 & 1 & 16\\ 4 & -4 & 3\end{bmatrix}$$

$$X^TX=\begin{bmatrix}1 & 1 & 1 & 1 & 1 & 1 & 1 & 1\\ -1 & 1 & -1 & 1 & -1 & 1 & -1 & 1\\ -1 & -1 & 1 & 1 & -1 & -1 & 1 & 1\\ -1 & -1 & -1 & -1 & -1 & 1 & 1 & 1\end{bmatrix}\begin{bmatrix}1 & -1 & -1 & -1\\ 1 & 1 & -1 & -1\\ 1 & -1 & 1 & -1\\ 1 & 1 & 1 & -1\\ 1 & -1 & -1 & 1\\ 1 & 1 & -1 & 1\\ 1 & -1 & 1 & 1\\ 1 & 1 & 1 & 1\end{bmatrix}$$

$$X^TX=\begin{bmatrix}8 & 0 & 0 & 0\\ 0 & 8 & 0 & 0\\ 0 & 0 & 8 & 0\\ 0 & 0 & 0 & 8\end{bmatrix}$$

Step 4: Obtaining the co-factor matrix of X^TX

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$$A = \begin{bmatrix} a11 & a12 & a13 \\ a21 & a22 & a23 \\ a31 & a32 & a33 \end{bmatrix}$$

$$\text{Let } A = \begin{bmatrix} 1 & 4 & -2 \\ -2 & -5 & 4 \\ 1 & -2 & 1 \end{bmatrix}$$

$$|A| = \begin{vmatrix} 1 & 4 & -2 \\ -2 & -5 & 4 \\ 1 & -2 & 1 \end{vmatrix}$$

Co-factors are

$$A_{11} = +\begin{vmatrix} -5 & 4 \\ -2 & 1 \end{vmatrix} = 3 \quad A_{12} = -\begin{vmatrix} -2 & 4 \\ 1 & 1 \end{vmatrix} = 6 \quad A_{13} = +\begin{vmatrix} -2 & -5 \\ 1 & -2 \end{vmatrix} = 9$$

,

$$A_{21} = +\begin{vmatrix} 4 & -2 \\ -2 & 1 \end{vmatrix} = 0 \quad A_{22} = +\begin{vmatrix} 1 & -2 \\ 1 & 1 \end{vmatrix} = 3 \quad A_{23} = +\begin{vmatrix} 1 & 4 \\ 1 & -2 \end{vmatrix} = 6$$

, ,

$$A_{31} = +\begin{vmatrix} 4 & -2 \\ -5 & 4 \end{vmatrix} = 6 \quad A_{32} = +\begin{vmatrix} 1 & -2 \\ -2 & 4 \end{vmatrix} = 0 \quad A_{33} = +\begin{vmatrix} 1 & 4 \\ -2 & -5 \end{vmatrix} = 3$$

, ,

$$\text{The C.F matrix } A = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} = \begin{vmatrix} 3 & 6 & 9 \\ 0 & 3 & 6 \\ 6 & 0 & 3 \end{vmatrix}$$

Step 5: Obtaining the adjoint of X^TX matrix as explained in the

$$\text{The C.F matrix } A = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} = \begin{vmatrix} 3 & 6 & 9 \\ 0 & 3 & 6 \\ 6 & 0 & 3 \end{vmatrix}$$

$$\text{adj } A = \begin{bmatrix} A_{11} & A_{21} & A_{31} \\ A_{12} & A_{22} & A_{32} \\ A_{13} & A_{23} & A_{33} \end{bmatrix} = \begin{bmatrix} 3 & 0 & 6 \\ 6 & 3 & 0 \\ 9 & 6 & 3 \end{bmatrix}$$

Step 6: Obtaining the value of determinant A

According to the property of determinant

| |( )

$a_{11}A_{11} + a_{12}A_{12} + a_{13}A_{13} = |A|$

$$|X^TX| = \begin{vmatrix} 8 & 0 & 0 & 0 \\ 0 & 8 & 0 & 0 \\ 0 & 0 & 8 & 0 \\ 0 & 0 & 0 & 8 \end{vmatrix}$$

Step 7: Obtaining the inverse of $X^TX = (X^TX)^{-1}$

$$A = \begin{bmatrix} a11 & a12 & a13 \\ a21 & a22 & a23 \\ a31 & a32 & a33 \end{bmatrix}$$

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$$A = \begin{bmatrix} 1 & 4 & -2 \\ -2 & -5 & 4 \\ 1 & -2 & 1 \end{bmatrix}$$

The C.F matrix $A = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} = \begin{vmatrix} 3 & 6 & 9 \\ 0 & 3 & 6 \\ 6 & 0 & 3 \end{vmatrix}$

$a_{11}A_{11} + a_{12}A_{12} + a_{13}A_{13} = |A|$
$1*3 + 4*6 + (-2)*9 = 9$

In the given example $A^{-1} = \frac{1}{|A|} \text{adj}A = \frac{1}{9} \begin{bmatrix} 3 & 0 & 6 \\ 6 & 3 & 0 \\ 9 & 6 & 6 \end{bmatrix}$

Step 8: Obtaining the inverse of X^TY

Step 9: Obtaining the product of $(X^TX)^{-1}X^TY = \beta = \begin{bmatrix} \beta 0 \\ \beta 1 \\ \beta 2 \\ \beta 3 \end{bmatrix}$

Then the regression equation can be written as $Y^1 = \beta 0 + \beta 1 * X1 + \beta 2 * X2 + \beta 3 * X3$

Step 10: Obtaining the sum of the squares due to regression, due to error and Total sum square

Runs	**Y**	$\mathbf{Y^1 = \beta 0 + \beta 1 * X1\ \beta 2 * X2 + \beta 3 * X3}$	$\mathbf{(Y - Y^1)^2}$	$\mathbf{(Y^1 - \bar{Y})^2}$	$\mathbf{(Y - \bar{Y})^2}$
1	Y1	Y_1^1	$(Y1 - Y_1^1)^2$	$(Y_1^1 - \bar{Y})^2$	$(Y1 - \bar{Y})^2$
2	Y2	Y_2^1	$(Y2 - Y_2^1)^2$	$(Y_2^1 - \bar{Y})^2$	$(Y2 - \bar{Y})^2$
3	Y3	Y_3^1	$(Y3 - Y_3^1)^2$	$(Y_3^1 - \bar{Y})^2$	$(Y3 - \bar{Y})^2$
4	Y4	Y_4^1	$(Y4 - Y_4^1)^2$	$(Y_4^1 - \bar{Y})^2$	$(Y4 - \bar{Y})^2$
5	Y5	Y_5^1	$(Y5 - Y_5^1)^2$	$(Y_5^1 - \bar{Y})^2$	$(Y5 - \bar{Y})^2$
6	Y6	Y_6^1	$(Y6 - Y_6^1)^2$	$(Y_6^1 - \bar{Y})^2$	$(Y6 - \bar{Y})^2$
7	Y7	Y_7^1	$(Y7 - Y_7^1)^2$	$(Y_7^1 - \bar{Y})^2$	$(Y7 - \bar{Y})^2$
8	Y8	Y_8^1	$(Y8 - Y_8^1)^2$	$(Y_8^1 - \bar{Y})^2$	$(Y8 - \bar{Y})^2$
			$\sum (Y - Y1)^2$ = Sum of squares due to residual error SSE	$\sum (Y1 - \bar{Y})^2$ = Sum of squares due to regression SSR	$\sum (Y - \bar{Y})^2$ = Total sum squares SST

$\sum Y = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8$

$\bar{Y} = \frac{\sum Y}{N}$

N= Number of run

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Step 11: Developing of ANOVA table

Table 4: Construction of ANOVA table to verify the level of significance of Regress

Sources of variation		Sum of squares	Degree of freedom	Mean squares	F – Distribution value (F-Ratio)
Variation due to regression		SSR = Sum of squares due to regression	λ1 = 3 (Degree of freedom is equal to number of independent variables chosen for the study)	MSR = Mean square due to regression MSR = $\frac{SSR}{\lambda_1}$	F= $\frac{MSR}{MSE}$
Variation due to error		SSE = Sum of squares due to error	λ2 = n- 1+3 λ2 = 8 – 1+ 3 λ2 = 4	MSE = Mean square due to error	
Total		SST	λ3 = n - 1 = 8 - 1 = 7		

Step 12: **Analyzing the main and interaction effect of factors**:

Investigator has to verify main effect and interaction effect of the ingredients which are chosen for preparing the formulation [9]. The regression equation which is obtained by applying the matrix method is taken as $Y^1 = \beta 0 + \beta 1 * X1 + \beta 2 * X2 + \beta 3 * X3$, here $\beta 1$, $\beta 2$ and $\beta 3$ are regression coefficients of input variables. Here we have taken the regression equation *without* an interaction [10].

If the interaction term is statistically significant and $p<0.05$ the interaction term has to be considered to analyze the response variables and also if the coefficient interaction term is very high, then the investigator has to consider the interaction effect and the model will be $Y^1 = \beta 0 + \beta 1 * X1 + \beta 2 * X2 + \beta 3 * X3 + \beta 12 * X1 * X2 + \beta 13 * X1 * X3 + \beta 23 * X2 * X3$, If $P > 0.05$, then the interaction effect has to be removed from the model equation [11,12].

Table 5: Combinations of ingredients with interaction

Runs	Combinations of ingredients with different levels	Ingredients with interaction							
		A	B	C	AB	AC	BC	ABC	Response Variable is Y^1
1	1	-1	-1	-1	1	1	1	-1	Y1
2	a	1	-1	-1	-1	-1	1	1	Y2
3	b	-1	1	-1	-1	1	-1	1	Y3
4	ab	1	1	-1	1	-1	-1	-1	Y4
5	c	-1	-1	1	1	-1	-1	1	Y5
6	ac	1	-1	1	-1	1	-1	-1	Y6
7	bc	-1	1	1	-1	-1	1	-1	Y7
8	abc	1	1	1	1	1	1	1	Y8

The main (Average) effect of each of the factors can be obtained using the mathematical equations

$$A = \left(\frac{-1+a-b+ab-c+ac-bc+abc}{4n}\right) = \left(\frac{-Y1+Y2-Y3+Y4-Y5+Y6-Y7+Y8}{4n}\right)$$

$$B = \left(\frac{-1-a+b+ab-c-ac+bc+abc}{4n}\right) \left(\frac{-Y1-Y2+Y3+Y4-Y5-Y6+Y7+Y8}{4n}\right)$$

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C= $\left(\frac{-1-a-b-ab+c+ac+bc+abc}{4n}\right) = \left(\frac{-Y1-Y2-Y3+Y4-Y5+Y6+Y7+Y8}{4n}\right)$

Here n = number taken as replication.

The interaction effects can be obtained as

AB = $\left(\frac{+1-a-b+ab+c-\ ac-bc+abc}{4n}\right) = \left(\frac{+Y1-Y2-Y3+Y4+Y5-\ Y6-Y7+Y8}{4n}\right)$

BC = $\left(\frac{+1+a-b-ab-c-\ ac+bc+abc}{4n}\right) = \left(\frac{+Y1+Y2-Y3-Y4-Y5-\ Y6+Y7+Y8}{4n}\right)$

AC = $\left(\frac{+1-a\ +b-ab-c+\ ac-bc+abc}{4n}\right) = \left(\frac{+Y1-Y2+Y3-Y4-Y5+\ Y6-Y7+Y8}{4n}\right)$

ABC = $\left(\frac{-1+a\ +b-ab+c-\ ac-bc+abc}{4n}\right) = \left(\frac{-Y1+Y2+Y3-Y4+Y5-\ Y6-Y7+Y8}{4n}\right)$

Step 13: The contrast is an important part of the experimental design. It describes the key differences that are being compared within an experiment.

The contrast of the first factor or variable A is obtained using the equation $(-1 + a - b + ab - c + ac - bc + abc)$

Usually, this contrast in DOE is called as total effect. Similarly, investigators can obtain the contrast for factor B, C, AB, AC, BC and ABC.

The sum of the squares for each effect are computed, because each effect will have a single degree of freedom contrast [13 -16].

The sum of squares of the factor A = $\frac{(-1+a-b+ab-c+ac-bc+abc)^2}{8n}$

$= \frac{(-Y1+Y2-Y3+Y4-Y5+Y6-Y7+Y8)^2}{8n}$

The sum of squares of the factor B= $\frac{(-1-\ a+b+ab-c-ac+\ bc+abc)^2}{8n}$

$= \frac{(-Y1-Y2+Y3+Y4-Y5-Y6+Y7+Y8)^2}{8n}$

The sum of squares of the factor C= $\frac{(\ -1-a-b-ab+c+ac+bc+abc)^2}{8n}$

$= \frac{(-Y1-Y2-Y3-Y4+Y5+Y6+Y7+Y8)^2}{8n}$

The sum of squares of the factor AB= $\frac{(\ +1-a-b+ab+c-\ ac-bc+abc)^2}{8n}$

$= \frac{(+Y1-Y2-Y3+Y4+Y5-Y6-Y7+Y8)^2}{8n}$

The sum of squares of the factor BC= $\frac{(+1+a-b-ab-c-\ ac+bc+abc\ )^2}{8n}$

$= \frac{(+Y1+Y2-Y3-Y4-Y5-Y6+Y7+Y8)^2}{8n}$

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The sum of squares of the factor AC= $\frac{(+1-a+b-ab-c+ac-bc+abc)^2}{8n}$

$$= \frac{(+Y1-Y2+Y3-Y4-Y5+Y6-Y7+Y8)^2}{8n}$$

The sum of squares of the factor ABC= $\frac{(-1+a+b-ab+c-ac-bc+abc)^2}{8n}$

$$= \frac{(-Y1+Y2+Y3-Y4+Y5+Y6-Y7+Y8)^2}{8n}$$

Table 6: 2^3 - Factorial Design

		Factor 1	Factor 2	Factor 3	Response 1
Std	Run	A: Stearate	B: Drug	C: Starc	Thickness (Mg)
4	1	1.5	120	30	420
5	2	0.5	60	50	500
1	3	0.5	60	30	350
3	4	0.5	120	30	210
6	5	1.5	60	50	530
2	6	1.5	60	30	428
8	7	1.5	120	50	505
7	8	0.5	120	50	455

Table 7: The ANOVA table for the Statistical model of thickness of the response variable.

Source	Sum of Squares	df	Mean Square	F-value	p-value
Model	65209.00	3	21736.33	8.18	0.0350
A-Stearate	16928.00	1	16928.00	6.37	0.0650
B-Drug	5940.50	1	5940.50	2.24	0.2091
C-Starc	42340.50	1	42340.50	15.94	0.0162
Residual	10624.50	4	2656.13		
Cor Total	75833.50	7			

The model is significant, as indicated by the F-value of 8.18. The probability of an F-value of this magnitude by random chance is only 3.50%. Model terms are considered significant when their p-values are less than 0.0500. In this specific instance, "C" emerges as a significant model term, while "B" does not achieve significance, as its p-value exceeds 0.1000.

Table 8: Fit Statistics

Standard Deviation	51.54
Mean	424.75
C.V.% - Coefficient of Variation	12.13
R^2	0.8599

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The coefficient of variation is obtained as C.V.% = $\frac{Standard\ deviation\ of\ reponse\ variable}{Mean\ of\ the\ response\ variable}$

$$= (51.54/424.75) = 12.13\%$$

The coefficient of variation is 12.13%, indicating the degree of variation of the of response variables of a particular series. If the investigators observe, the coefficient of variation is very high, indicates that the design of experiment need to be modified or not appropriate [17,18].

After doing the analysis, model was found significant. Final Equation in Terms of Actual Factors. Y = 123. 50 + 92.00X1 – 0.908X2 +7.2750X3.

The equation, expressed in terms of actual factors, enables predictions about the response for given levels of each factor. In this case, each factor levels ought to be stated in their original units. However, this equation should not be utilized to assess the relative impact of each factor due to the coefficients being scaled to accommodate the units of each factor, and the intercept not being positioned at the center of the design space [19 - 23].

Report of Actual and Predicted value are obtained using the model equation Y = 123. 50 + 92.00X_1 – 0.908X_2 +7.2750X_3.

Table 9: Regression Model Residuals

Run Order	Actual Value	Predicted Value	Residual
1	420.00	370.75	49.25
2	500.00	478.75	21.25
3	350.00	333.25	16.75
4	210.00	278.75	-68.75
5	530.00	570.75	-40.75
6	428.00	425.25	2.75
7	505.00	516.25	-11.25
8	455.00	424.25	30.75

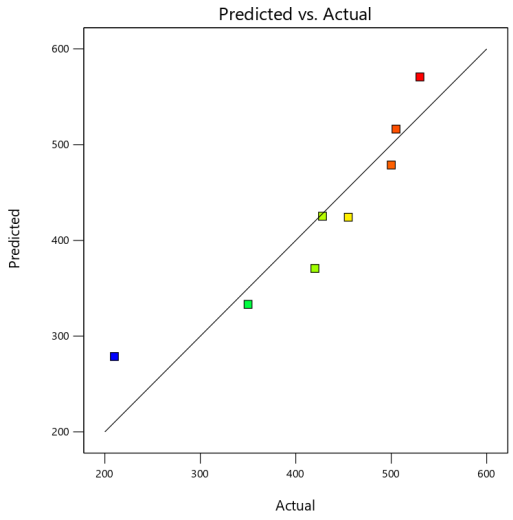

Figure 1: Graph to how observed values scattered around the predicted values in DOE.

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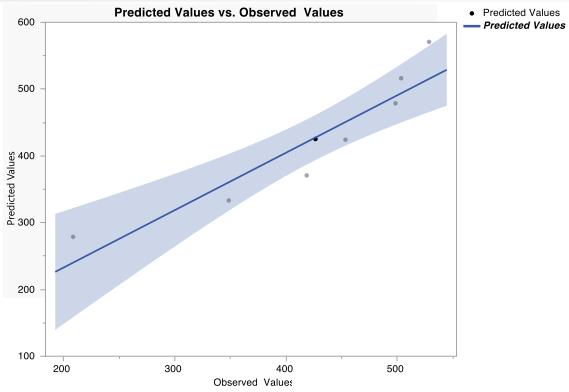

Figure 2: Graph to how observed values scattered around the predicted values (around the straight line) in JMP software.

The graph which is constructed taking the observed values on X-axis and Predicted Values on Y-Axis indicated the observed /experimental values are very close to the straight line of predicted values. This is an indication to show that model is significant [24]. Distributions of response variables is normal.

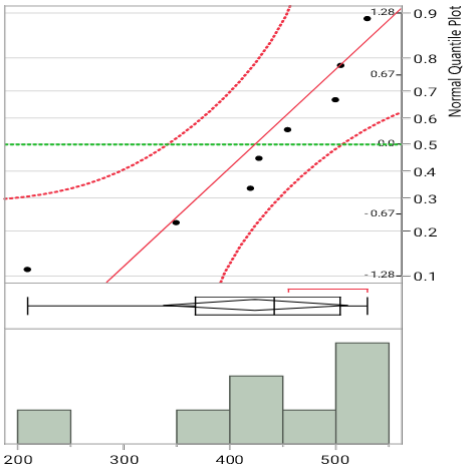

Figure 3: Graph to show the normality of the distribution.

CONCLUSION

The following conclusion was based on the above study was to explain the important applications of Matrices in developing Regression model or forming the regression equation in establishing the functional the relationship between the input variables (Ingredients which are used with different levels to prepare a formulation) & response variable (Output Variable). After developing the regression model, it is explained how we can verify the effect of each variable, the interaction effects of between the variables or ingredients and explained the importance of ANOVA to verify the level of significance of the mathematical model.

Competing Interests

The authors declare no competing interests

Authors' Contributions

All authors made contributions to the writing of this article and have approved the final manuscript.

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