Application of design mixture and desirability function in the optimization of pharmaco-technical parameters of macrogols-based suppositories

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ABSTRACT
The objective of this work is to (i) study the effect of variations in the proportions of four Macrogols on the pharmaco-technical characteristics of suppositories, (ii) define the optimal formula for a suppository with immediate effect; maximum disintegration and a minimum of hardness as defined in the European Pharmacopoeia. The lattice design mixture has been proposed as an optimization technique, the formulation factors are presented by the proportions of PEG 400 (X1), PEG 600 (X2), PEG 4000 (X3) and PEG 6000 (X4) and the response variables are (i) the disintegration time (Y1) (ii) the hardness (Y2). The second-degree empirical model was postulated to model the variations of the two response variables using the least-squares method. The selected model explained about 67% and 84% of the variation for Y1 and Y2, respectively. All four factors had significant effects on the properties of the suppository. Interactions negatively affected both responses. The numerical desirability method gave the following optimal formula: PEG400 (28.71334 %); PEG600 (24.23773%), PEG4000 (35.00944%) and PEG6000 (12.03949%) for a disintegration of 25.839 (+/- 2.3) min and hardness =2147.321 (+/- 50) g.

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use and well-established safety profile (D’Souza and Shegokar, 2016; Ham and Buckheit, 2017a). For the development of controlled release suppositories based on Polys Ethylene Glycol (Yvonne and V’iain, 2015; Jannin et al., 2014; Berkó, 2002), it is important to design an optimal formulation (based on the proportions of different PEGs) with a reasonable time of action; the shortest possible or longest possible depending on whether the immediate or prolonged effect is sought (Yvonne and V’iain, 2015; Ham and Buckheit, 2017a; Ela et al., 2016), and a better bioavailability (Jannin et al., 2014; Ham and Buckheit, 2017a).

Nowadays, most of the experimentation in the development of Macrogol suppository formulations is done randomly without being able to discuss the contribution of each internal component at the formula level; these are generally empirical formulations (Ela et al., 2016), without proceeding to optimization (Ham and Buckheit, 2017b). The formulation involves taking into account the complexity of systems in which physicochemical phenomena are involved for all stages of the drug’s life (Yvonne and V’iain, 2015; Jannin et al., 2014). As such, the development of suppositories has focused on improving the existing conventional design to improve active ingredient delivery.

Our study aims to understand the effect of different individual excipients on the bio pharmacy and pharmacokinetics of suppositories, develop predictive models of their pharmaco-technical characteristics as a function of PEG proportions and estimate by absolute desirability functions the optimal formulas based on their Physico-chemical characteristics, for immediate effect, before adding additives such as surfactants and cyclo-dextrins.

MATERIALS AND METHODS

Raw materials

Four types of Macrogols were selected in this study for the preparation (formulation) of suppositories; PEG 400 D, PEG 600 D, PEG 4000 D and PEG 6000 D (Shanghai Yayu Biomedical Shanghai, China). The four Macrogols are characterized by different Physico-chemical properties: molecular weight, melting temperature and hydroxyl number, hence the interest of the association to have hard, but not brittle suppositories (D’Souza and Shegokar, 2016; Raymond et al., 2006). The characteristics of the suppository, including the rate and speed of dissolution, are directly influenced by the exact combination and composition of Macrogols (Yvonne and V’iain, 2015; Ham and Buckheit, 2017a; Berkó, 2002).

Design of experiment (DOE)

Emerging research on suppository development includes the use of experimental designs to better understand the effect of different individual excipients on the dissolution and pharmacokinetics of suppositories and to optimize their composition. The simplex design mixing study was used in this research (Sahin et al., 2016; Cafaggi et al., 2003) to statistically optimize suppository formulation parameters for maximum delay and disaggregation. It delimits an experimental domain in the form of a regular tetrahedron without upper or lower limits of its four components (Satish and ., 2012). The factors studied were Macrogol 400 ($X_1$), Macrogol 600 ($X_2$), Macrogol 4000 ($X_3$) and Macrogol 6000 ($X_4$) (Wang et al., 2010). For each formula, the sum of the proportions of the four components is 100% (Sahin et al., 2016; Wang et al., 2010; Dabbas et al., 2003).

Table A summarizes the proportions of the 4 components and the responses recorded for the 15 trials (Wang et al., 2010).

Preparation of suppositories: fusion method

A mixture 20 g of four Macrogols; taking into account the losses when filling the metal molds (sufficient quantity for 6 suppositories), was prepared, the weight of the suppositories was designed to reach about 3 g for each unit by manually feeding the six cells of the metal molds with stainless steel (Yvonne and V’iain, 2015; Jannin et al., 2014). For each test, the required quantities of PEGs were loaded into a stainless-steel capsule, then heated to 42 °C (Yvonne and V’iain, 2015; Raymond et al., 2006), mixed until the mixture was homogeneous and cooled to a temperature below 40 °C. The liquid mixture obtained was poured into the metal mold previously lubricated by petroleum jelly oil and then allowed to cool in the refrigerator for a few minutes. Once cooled and de-molded, the suppositories were stored in vials until later use (Ela et al., 2016).

Evaluation of manufactured suppositories

Table 1 show the hardness and disintegration time of the prepared suppositories, 15 tests with two replicates.

Determination of Mechanical Strength (Hardness)

This test was performed with the Erweka AR 400 hardness tester (Erweka, Langen, Germany). The suppository was placed in the holding device with the tip up and the test chamber was then closed with a glass plate. The temperature inside the test chamber was maintained at 25°C by means of circulating
Table 1: Experimental design and observed responses

| Run | PEG 400 | PEG 600 | PEG 4000 | PEG 6000 |
|-----|---------|---------|----------|---------|
| 1   | 6       | 6       | 6        | 2       |
| 2   | 1.4     | 6       | 1.4      | 11.2    |
| 3   | 1.4     | 1.4     | 1.4      | 16.8    |
| 4   | 6       | 1.4     | 1.4      | 6.6     |
| 5   | 6       | 6       | 1.4      | 6.6     |
| 6   | 6       | 1.4     | 1.4      | 6.6     |
| 7   | 5       | 5       | 5        | 5       |
| 8   | 2       | 6       | 6        | 6       |
| 9   | 4       | 4       | 6        | 6       |
| 10  | 3       | 10      | 4        | 3       |
| 11  | 4       | 3       | 10       | 3       |
| 12  | 11      | 3       | 3        | 3       |
| 13  | 11.2    | 1.4     | 6        | 1.4     |
| 14  | 16.4    | 1.2     | 1.2      | 1.2     |
| 15  | 6.6     | 1.4     | 6        | 6       |

Legend: X₁ = Macrogol 400, X₂ = Macrogol 600, X₃ = Macrogol 4000 and X₄ = Macrogol 6000 g/mol.

Table 2: Experimental design and observed responses

| Run | PEG 400 | PEG 600 | PEG 4000 | PEG 6000 | Désintégration time (min): Y₁ | Hardness (g): Y₂ |
|-----|---------|---------|----------|----------|------------------------------|-----------------|
|     |         |         |          |          | Y₁ (1) | Y₁ (2) | Y₂ (1) | Y₂ (2) |
| 1   | 6       | 6       | 6        | 2        | 26.66  | 19.33  | 4532   | 3666   |
| 2   | 1.4     | 6       | 1.4      | 11.2     | 40.66  | 27.66  | 3532   | 3933   |
| 3   | 1.4     | 1.4     | 1.4      | 16.8     | 36.66  | 35.33  | 3266   | 3333   |
| 4   | 6       | 1.4     | 1.4      | 6.6      | 34     | 36.831 | 2720   | 2333   |
| 5   | 6       | 6       | 1.4      | 6.6      | 29     | 21.66  | 3933   | 4333   |
| 6   | 6       | 1.4     | 6        | 6.6      | 46.5   | 28     | 2100   | 2400   |
| 7   | 5       | 5       | 5        | 5        | 28     | 21.66  | 1733   | 2266   |
| 8   | 2       | 6       | 6        | 6        | 32.33  | 25     | 2666   | 2261   |
| 9   | 4       | 4       | 6        | 6        | 31.16  | 23.66  | 2200   | 3066   |
| 10  | 3       | 10      | 4        | 3        | 19     | 19.66  | 3533   | 3533   |
| 11  | 4       | 3       | 10       | 3        | 27.66  | 25.66  | 2533   | 2133   |
| 12  | 11      | 3       | 3        | 3        | 20.66  | 18.33  | 2600   | 1466   |
| 13  | 11.2    | 1.4     | 6        | 1.4      | 18.66  | 18.00  | 2666   | 2550   |
| 14  | 16.4    | 1.2     | 1.2      | 1.2      | 14     | 12.5   | 200    | 200    |
| 15  | 6.6     | 1.4     | 6        | 6        | 29     | 19.3   | 2600   | 2450   |

Legend: X₁ = Macrogol 400, X₂ = Macrogol 600, X₃ = Macrogol 4000 and X₄ = Macrogol 6000 g/mol.

Water from the thermostat connected to the tester. An initial load (600 g) was applied and at regular one-minute intervals, a 200 g disc was added until the suppository was crushed. The mass required to crush the suppository was then calculated as the sum of the initial charge and the added masses until the suppository collapsed (Yvonne and Viain, 2015; Nürnberg, 1986; Onyeji et al., 1999; Hasian, 2015).

**Determination of the disintegration time**

The test was performed in a 6.8 pH buffer solution at 37°C (+/- 0.5) using the U.S.P tablet disintegration apparatus (SOTAX DT 3, Heusenstamm, Germany). The disintegration time was recorded as soon as the suppositories placed in the basket were completely dissolved. (Lloyd et al., 2013; Belniak et al., 2017; Onyeji et al., 1999; Hargoli et al., 2013).

**Development of mathematical models**

The variations of the two responses are modelled...
### Table 3: Effects and Estimated Coefficients for Modeling

| Name | Coefficient | Standard Deviation | Sig % |
|------|-------------|--------------------|-------|
| (a)  |             |                    |       |
| b1   | 35.5976     | 3.5256937          | < 0.01 *** |
| b2   | 34.2126     | 3.5256937          | < 0.01 *** |
| b3   | 39.2137     | 3.5256937          | < 0.01 *** |
| b4   | 46.3775     | 3.5256937          | < 0.01 *** |
| b1-2 | -12.5678    | 15.21507           | 42.3  |
| b1-3 | -9.4300     | 15.21507           | 54.5  |
| b2-3 | -30.4213    | 15.21507           | 6.5   |
| b1-4 | -80.1436    | 15.21507           | 0.0119 *** |
| b2-4 | -65.0504    | 15.21507           | 0.0769 *** |
| b3-4 | -69.1346    | 15.21507           | 0.0459 *** |
| (b)  |             |                    |       |
| b1   | 3864.1975   | 257.44597          | < 0.01 *** |
| b2   | 4014.4827   | 255.19091          | < 0.01 *** |
| b3   | 3462.4841   | 254.00011          | < 0.01 *** |
| b4   | 3277.7652   | 267.53083          | < 0.01 *** |
| b1-2 | -3020.1088  | 1088.0028          | 1.80 * |
| b1-3 | -4985.2649  | 1139.6026          | 0.111 ** |
| b2-3 | -4526.3601  | 1087.9251          | 0.159 ** |
| b1-4 | -3140.1518  | 1370.0661          | 4.26 * |
| b2-4 | -9808.0218  | 1281.7597          | < 0.01 *** |
| b3-4 | 1264.9601   | 1179.261           | 2.16  |

(a) time disintegration, (b) Hardness

**Figure 1: Plot of adequacy between calculated and experimental responses for the two responses: a(Y1) and b(Y2)**
### Table 4: Statistical analysis.

| Source of variation | Sum of squares | Degrees of freedom | Middle Square | F value | value |
|---------------------|----------------|-------------------|---------------|---------|-------|
| Regression          | 8.76747E+002   | 9                 | 9.74163E+001  | 6.2361  | 0.131 ** |
| Residues            | 2.18700E+002   | 14                | 1.56214E+001  |         |       |
| Total               | 1.09545E+003   | 23                |               |         |       |

(a) Analysis of Variance for Disintegration time, (b) Coefficient Estimates and Statistics: Y1 Response, (c) Analysis of Variance for Hardness response, (d) Coefficient Estimates and Statistics: Y2 Response

### Table 5: Optimization of formulation parameters

| Property               | Requirement          | Goal             | Minimum threshold | Maximum threshold |
|------------------------|----------------------|------------------|-------------------|-------------------|
| Disintegration time    | Below 1h             | Minimization     | 12.21             | 40.66             |
| (min)                  |                       |                  |                   |                   |
| Hardness ((g))         | Greater than 1800 - 2000 g | Minimum value | 200               | 4532              |

### Table 6: Maximum Characteristics

| Response | Response       | Value | di % |
|----------|----------------|-------|------|
| Y1       | Disintegration time | 25.839 | 100.00 |
| Y2       | Hardness        | 2147.321 | 83.18 |
|          | Désirabilité    |       | 91.20 |
Table 7: The Response Variables of the Optimal suppository

| Response | Constraint sets | Predicted optimal Value | Experimental optimal Value | Bias (%) |
|----------|----------------|-------------------------|---------------------------|---------|
| Y1 (min) | Minimal        | 21.61                   | 20 + -2                   | 8%      |
| Y2 (g)   | Minimal        | 2146                    | 2100 + -50                | 2.23%   |

*The bias was calculated as ((predicted value - experimental value) / experimental value) × 100

Figure 2: Residue distribution curves (a): Residual values based on adjusted values for Y1, (b) Henry’s residual values right for Y2, (c) Residual values based on adjusted values for Y1, (d) Henry’s entitlement to residual values for Y2.
according to the fractions of the four Macrogols using the mathematical quadratic model (Cornell, 2011; Tinsson, 2010) according to Equation (1),

\[ Y = b_1 X_1 + b_2 X_2 + b_3 X_3 + b_4 X_4 + b_1 X_2 + b_1 X_3 + b_2 X_3 + b_3 X_4 \]

where \( Y \) is the dependent variable (hardness or disintegration) and \( b_1 b_2 ... b_3-4 \) are the parameters of the model to be estimated. The main effects (\( X_1, X_2, X_3 \) and \( X_4 \)) represent the average result of modifying a factor. The interaction terms (\( X_1 X_4, X_2 X_3, X_2 X_4, X_2 X_4 \) and \( X_3 X_4 \)) show how the response changes when two or more factors are modified simultaneously (Cornell, 2011; Tinsson, 2010; Tabandeh and Erfan, 2013; Bello et al., 2011).

The selection of the most parsimonious model for each of the two response variables was carried out by the step-by-step method (Khusainova et al., 2016) by (Chodankar and Dev, 2016).

To determine whether the association between the response and each of the model terms is statistically significant, the p-value of the term is compared to the significance level (noted alpha or \( \alpha \)) of 0.05 to assess the null hypothesis that there is no association between the term and the response.
Figure 5: The Three-Dimensional (3D) Response Surface Plot of Desirability at the Prediction

The model was selected on the basis of the adjusted determination coefficient (R²) and PRESS. The normality of the residues and the homo-scedasticity of the model were verified for the global model and re-verified for the selected model (Patel et al., 2017; Preece and Cornell, 1982). A test for lack of model fit was also performed to test the adequacy of the model (Tinsson, 2010; Tabandeh and Erfan, 2013; Tauler et al., 2009).

Optimization of multiple quality characteristics (desirability function)

The use of the notion of absolute desirability, introduced by Derringer and Suich (Sahin et al., 2016; Şimşek et al., 2013; Preece and Cornell, 1982; Pal and Gauri, 2018), makes it possible to optimize the choice of mixture parameters on the basis of the Physico-chemical characteristics of Macrogols. In this way; for each answer Yi(x), the desirability function di(Yi) varies between 0 and 1 di(Yi) = 0 representing a totally undesirable value of Yi and di(Yi) = 1 representing the desirable or ideal response value. The desirability (di) of a response variable (Yi) may increase or decrease with the increase of (Yi); under certain conditions, the relationship between di and Yi may be parabolic in nature. In the case of Y1, our objective is to minimize the response. The desirability function of Y1 is Equation (2),

\[
di(\hat{Y}_1) = \hat{Y}_1(x) - U_i Si - U_i
\]

With Ui and Si, the upper and lower values observed for the response Y1.
In the case of Y2, our objective is to target a minimum hardness value of 1800 to 2000 g knowing that the values of Y2 are between the target value (Ti) and the maximum value (Ui), the desirability function for Y2 (hardness) is given by the following Equation (3):

\[ di(Y2) = \frac{\tilde{Y}2(X) - Ui}{Ti - Ui} \] (3)

With Ui and Ti, the desired upper and target values for the answer Y2 and Li ≤ Ti ≤ Ui.

The individual desirability are then combined to obtain the overall desirability D (Wu, 2004) as follows Equation (4),

\[ D = (d1(Y1)d2(Y2))^{1/2} \] (4)

RESULTS AND DISCUSSION

In Table 2, columns 2 to 5 represent the four control factors and their proportions and columns 6 and 7 correspond to the results of the two controls Y1 and Y2.

The experimental results are analyzed by ANOVA (Analysis of Variance) procedures and the results are given in Table 3.

Statistical modeling

The experimental results are analyzed by ANOVA procedures (Analysis of Variance) and the results (the ANOVA table) are given as following. The coefficients with \( p \leq \alpha \) will be retained in the model equation. On the contrary, if \( p > \alpha \), the coefficient will not be retained in the model equation (see Table 3 below) (Preece and Cornell, 1982). The regression model equations obtained with NemrodW® were given in the following Equation (5) and Equation (6), (Cornell, 2011).

Equation of Disintegration time (5)

\[ Y = 35.59X1 + 34.21X2 + 39.21X3 + 46.37X4 - 80.14X1X2 - 65X2X4 - 69.13X3X4 \] (5)

Equation of Hardness (6)

\[ Y = 3930.11X1 + 3814.62X2 + 3669X3 + 3929.67X4 - 6356.61X1X3 - 6937.95X2X4 \] (6)

All four factors had positive effects on the properties of the suppository. The interactions had a negative effect on both responses. The disintegration time equation suggests that X4 (PEG 6000) had a more dominant effect than X3 (PEG4000), X2 (PEG 600) and X1 (PEG 400) with an antagonistic effect between X1 and X4. Equation of hardness shows the importance of PEG low molecular weight 400, as well as the antagonism between X1 and X3 (Satish and , 2012; Tabandeh and Erfan, 2013).

Table 4 (a) shows that the variables selected for the modeling of the response as a whole have a significant effect at a confidence level of 95% (F exp (9.14) = 6.2361) is higher than theoretical (F0.05 (9.14) = 2.65. So, the model allows a better fit of the data. Table 4 (c) shows that the variables selected for the modeling of the response as a whole have a significant effect at a confidence level of 95% (F exp (9.11) = 11.8265) is higher than theoretical (F0.05 (9.11) = 2.90). So, the model allows a better fit of the data (Tauler et al., 2009). The selected model was significant with P < 0.05 (Sahin et al., 2016; Şimşek et al., 2013) and explained approximately 84% (R square (adjust) = 0.84) and 67% (R square (adjust) = 0.67) of the variation for suppository hardness and disintegration time respectively (Table 4 (b) and Table 4 (d)).

Validation of the model (Validation of model)

Figure 1 represent the degree of reconciliation of the experimental data with the data predicted by the model. The model allowed a better adjustment of the data (Dabbas et al., 2003; Bello et al., 2011).

The linear correlation coefficient is a statistical parameter used to define the linear relationship between the predicted and actual value, indicating the reliability and stability of the response surface. The linear correlation coefficient results for time disintegration (0.894), while for the hardness, it is quite low (0.695). The reliability of these results was confirmed by the corresponding residual plot between the run number and internally studentized residuals for various response variables, as shown in Figure 2 (Cornell, 2011; Preece and Cornell, 1982). Based on the completely randomized analysis, the dispersion of residues studied internally was not off the line, from bottom to top, indicating that most of the points are within limits (at the level of confidence 95%). Our results indicate that NemrodW® has successfully estimated the response surface showing the relationship between the composition and the characteristics of the suppositories (Cornell, 2011).

From these data, it can be said that the model is adequate and allows for better data adjustment (Cornell, 2011; Bello et al., 2011).

Determination of the optimal formula by maximizing the multi-response desirability

At this stage, and in Table 5, the target of our responses is guided by the specifications of the sup-
**CONCLUSIONS**

The study showed that the proportions of different Macrogols have a significant influence on the disintegration time and hardness of suppositories. The reduction in disintegration time has compromised the hardness of suppository, a key parameter for measuring the performance of these pharmaceutical forms. It can be attributed to an increase in the proportion of low molecular weight Macrogols and a decrease in the proportion of high molecular weight Macrogol, which allows for an improvement in biopharmaceuticals while maintaining the minimum hardness required by regulation. Finally, in addition to the composition in excipients, other factors should be studied in the presence of an active ingredient to control its release from the mass of Macrogol; namely its solubility in the mass of excipients, additives (TA and Cyclodextrin) and Physico-chemical interactions PA-excipients.

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**REFERENCES**

Bello, L. H. A. D., Vieira, A. F., De, C. 2011. Tutorial for mixture-process experiments with an industrial application. *Pesquisa Operacional*, 31(3):543–564.

Belniak, P., Świader, K., Szumiolo, M., Hyla, A., Poleszak, E. 2017. Comparison of physico-chemical properties of suppositories containing starch hydrolysates. *Saudi Pharmaceutical Journal*, 25(3):365–369.

Berkó, S. 2002. Formulation of rectal suppositories containing diuretic drugs and their biopharmaceutical studies, in Pharmacy Department of Pharmaceutical Technology. pages 51–51.

Cafaggi, S., Leardi, R., Parodi, B., Caviglioli, G., Bignardi, G. 2003. An example of application of a mixture design with constraints to a pharmaceutical formulation. 65:139–147.

Chatterjee, A., Mohan, S., Varshney, H. M., Jaimini, M., Sharma, S. K. 2014. Formulation and in vitro characterization of Zaltoprofen suppositories using bases and different concentration of plasticizer. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 5:359–70.

Chodankar, R. S., Dev, A. 2016. Optimisation techniques: a futuristic approach for formulating and processing of pharmaceuticals. *Indian J. Pharm.*
Biol. Res, 4(2):32–32.

Cornell, J. A. 2011. A Primer on Experiments with Mixtures. A Primer on Experiments with Mixtures.

Şimşek, B., Iç, Y. T., Şimşek, E. H. 2013. A full factorial design based desirability function approach for optimization of properties of C 40/50 concrete class. *Mathematical and Computational Applications*, 18(3):330–339.

Dabbas, R. M., Fowler, J. W., Rollier, D. A., McCarville, D. 2003. Multiple response optimization using mixture-designed experiments and desirability functions in semiconductor scheduling. *International Journal of Production Research*, 41(5):939–961.

Dalavi, V. V., Patil, J. S. 2009. Optimization techniques: An introductory overview. *Journal of Pharmacy Research*, 2(2):144–1275.

D'souza, A. A., Shegokar, R. 2016. Polyethylene glycol (PEG): a versatile polymer for pharmaceutical applications. *Expert Opinion on Drug Delivery*, 13(9):1257–1275.

Ham, A. S., Buckheit, R. W. 2017a. Designing and developing suppository formulations for anti-HIV drug delivery. *Therapeutic Delivery*, 8(9):805–817.

Hargoli, S., Farid, J., Azarmi, S. H., Ghanbarzadeh, S., Zakeri-Milani, P. 2013. Preparation and in vitro evaluation of naproxen suppositories. *Indian Journal of Pharmaceutical Sciences*, 75(2):143–151.

Hasian, J. A. 2015. Formulation and in vitro evaluation of adults levodropropizine suppositories using various excipients. *Journal of Chemical and Pharmaceutical Research*, 7:673–772.

Jannin, V., Lemagnen, G., Guerout, P., Larrouette, D., Tuleu, C. 2014. Rectal route in the 21st Century to treat children. *Advanced Drug Delivery Reviews*, 73:34–49.

Kellaway, I. W., Marriott, C. 1975. Correlations between Physical and Drug Release Characteristics of Polyethylene Glycol Suppositories. *Journal of Pharmaceutical Sciences*, 64(7):1162–1166.

Khusainova, R. M., Shilova, Z. V., Curteva, O. V. 2016. Selection of appropriate statistical methods for research results processing. *Mathematics Education*, 11(1):303–315.

Kumar, R., Kumar, G. S., Satyanarayana, J. N., Rani, V. S., Prasad, G. S., B. 2016. Formulation development and evaluation of clidogrel fast dissolving tablets. *Iranian Journal of Pharmaceutical Sciences*, 12(2):61–74.

Loyd, A., Howard, C., A. 2013. Ansel’s pharmaceutical dosage forms and drug delivery systems.

Nürnberg, E. 1986. Suppositorien; Pharmakologie, Biopharmazie und Galenik rektal und vaginale Arzneiformen; Monographie der Arbeitsgemeinschaft für Pharmaz. *Archiv der Pharmazie*, 132(8):767–768. Unter Mitarbeit von acht weiteren Autoren. 209 Seiten, 122 Abb., 35 Tabellen, Kst. geb. DM.

Onyeji, C. O., Adebayo, A. S., Babalola, C. P. 1999. Effects of absorption enhancers in chloroquine suppository formulations: I. *European Journal of Pharmaceutical Sciences*, 9(2):53–59.

Pal, S., Gauri, S. K. 2018. A desirability functions-based approach for simultaneous optimization of quantitative and ordinal response variables in industrial processes. *International Journal of Engineering, Science and Technology*, 10(1):76–76.

Patel, M. B., Shaikh, F., Patel, V., Surti, N. I. 2017. Application of simplex centroid design in formulation and optimization of floating matrix tablets of metformin. *Journal of Applied Pharmaceutical Science*, 7(04):23–030.

Preece, D. A., Cornell, J. A. 1982. Experiments with Mixtures: Designs, Models, and the Analysis of Mixture Data. *Biometrics*, 38(1).

Raymond, C., Rowe, Paul, J., Sheskey 2006. Handbook of Pharmaceutical Excipients Fifth edition. *Pharmaceutical press and American Pharmacists Association*.

Sachdeva, V., Alam, M. S., Kumar, R., Kataria, M. K. 2013. Oral multiunit pellet extended release dosage form: A review. *International Current Pharmaceutical Journal*, 2(10):177–184.

Sahin, Y. B., Demirtaş, E. A., Burnak, N. 2016. Mixture design: A review of recent applications in the food industry. *Pamukkale University Journal of Engineering Sciences*, 22(4):297–304.

Satish, M., K. 2012. Application of Simplex Lattice Design in Formulation and Development of Buoyant Matrices of Dipyridamole. *Journal of Applied
Pharmaceutical Science, 2(12):107–111.

Shargel, L., Yu, B. C., , A. 2015. Applied Biopharmaceutics & Pharmacokinetics, Seventh Edition. 928 Seiten.

Shivakumar, H. N., Desai, B. G., Patel, M. 2007. Optimización del sistema gastroretentivo para la administración oral controlada de cinarizina mediante la metodología de superficie de respuesta.

Tabandeh, H., Erfan, M. 2013. Development and optimization of ferrous fumarate chewable tablets by simplex experimental design. *Iranian Journal of Pharmaceutical Sciences*, 9(2):49–66.

Tauler, R., Walczak, B., Brown, S. D. 2009. Comprehensive chemometrics: chemical and biochemical data analysis2009.

Tinsson, W. 2010. Plans d’expérience: constructions et analyses statistiques. *Plans d’expérience: constructions et analyses statistiques*.

Touitou, E., Barry, B. W. 2006. Enhancement in drug delivery. *Enhancement in Drug Delivery*.

Ummadi, S. 2013. Overview on Controlled Release Dosage Form. *Int J Pharma Sci*, 3(4):258–269.

Wang, P., Sen, Fang, J. J. 2010. The optimization of medicine formulation using mixture experiments. *Proceedings of the International MultiConference of Engineers and Computer Scientists*, 2010.

Wu, F. C. 2004. Optimization of Correlated Multiple Quality Characteristics Using Desirability Function. *Quality Engineering*, 17(1):119–126.

Yvonne, B. B., Viain, F. M. 2015. Practical Pharmaceutics: An International Guideline for the Preparation, Care and Use of Medicinal Products. pages 1–6.