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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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INTRODUCTION

The modern pharmaceutical industry has different routes of administration and pharmaceutical forms in order to deliver the active ingredients to the site of action (Ummadi, 2013; Shargel *et al.*, 2015; Loyd and Howard, 2013; Yvonne and V'iain, 2015). Among these routes, the oral route is the most commonly used, with the use of tablet and capsule forms in particular (Shargel *et al.*, 2015; Loyd and Howard, 2013; Sachdeva *et al.*, 2013). Next to it are the topical, parenteral, and rectal pathways (Yvonne and V'iain, 2015; Sachdeva *et al.*, 2013). The latter is one of the oldest routes of administration (Shargel *et al.*, 2015; Loyd and Howard, 2013; Touitou and Barry, 2006) and can be considered a good alternative to the oral route for children in an emergency with loss of consciousness, elderly subjects and in case of vomiting (Yvonne and V'iain, 2015; Jannin *et al.*, 2014). Recent studies have shown that this pathway is equivalent to others (Loyd and Howard, 2013; Touitou and Barry, 2006; Jannin *et al.*, 2014).

Suppositories are the main representatives of this pathway with a renewed interest in the use of Macrogols (Yvonne and V'iain, 2015; Jannin *et al.*, 2014; Rowe *et al.*, 2006). This polymer approved by the United States Food and Drug Administration (UFDA) is popular because of its safe 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 Macrogols 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; Rowe *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 design was used in this study (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 *et al.*, 2012). The factors studied were Macrogol 400 (X_1), Macrogol 600 (X_2), Macrogol 4000 (X_3) and Macrogol 6000 (X_4) (Wang and Fang, 2010). For each formula, the sum of the proportions of the four components is 100% (Sahin *et al.*, 2016; Wang and Fang, 2010; Dabbas *et al.*, 2003).

Table 1 summarizes the proportions of the 4 components and the responses recorded for the 15 trials (Wang and Fang, 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; Rowe *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 water from the thermostat connected to the tester.

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	6	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 : X_1 = Macrogol 400, X_2 = Macrogol 600, X_3 = Macrogol 4000 and X_4 = Macrogol 6000g/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 6000g/mol.

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 V'iain, 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 (Loyd and Howard, 2013; Belniak *et al.*, 2017; Onyeji *et al.*, 1999; Hargoli *et al.*, 2013).

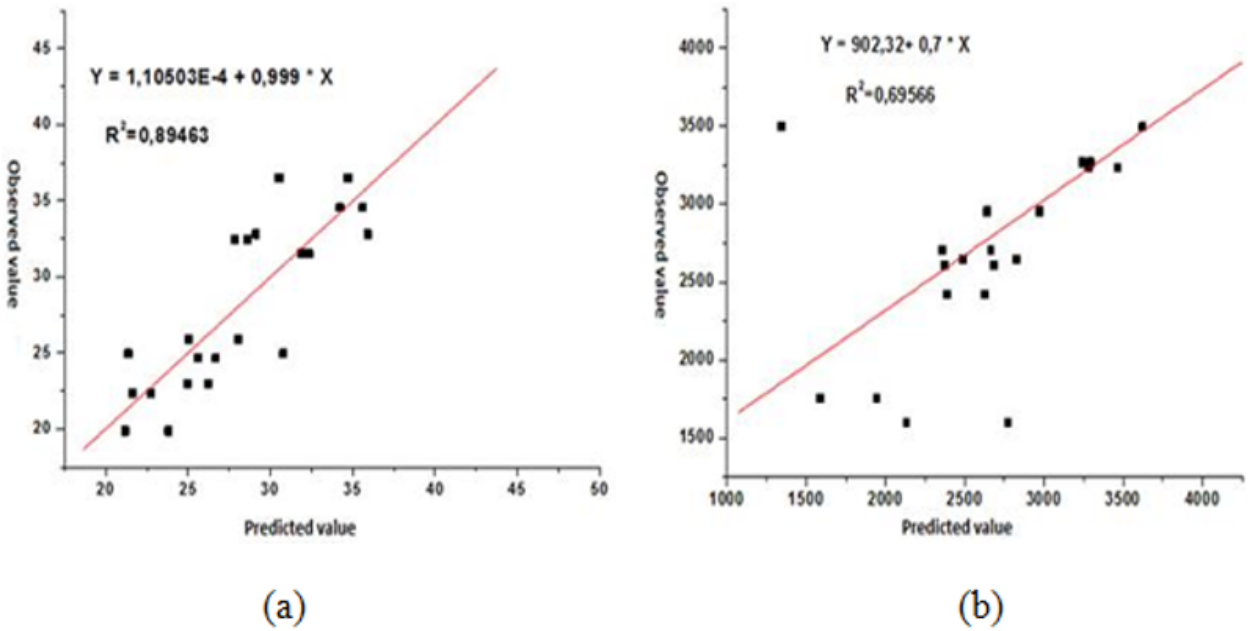
Development of mathematical models

The variations of the two responses are modelled according to the fractions of the four Macrogols

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)	
Name	Coefficient	Standard deviation	Sig. %
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



(a) (b)

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
			(a)		
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			
			(b)		
Deviation Type of the answer				3.9523949	
R2				0.800	
R2A				0.672	
R2 pre				N.D.	
PRESS				1224.9277	
Number of degrees of freedom				14	
			(c)		
Source of variation	Sum of squares	Degrees of freedom	Middle square	F value	value
Regression	8.48708E+0006	9	9.43009E+0005	11.8265	0.0179 ***
Residues	8.77108E+0005	11	7.97371E+0004		
Total	9.36419E+ 0006	20			
			(d)		
Deviation Type of the answer				282.3775	
R^2				0.906	
R^2A				0.830	
R^2 pred				0.543	
PRESS				4277656.4	
Number of degrees of freedom				11	

(a) Analysis of Variance for Disintegration time, (b) Coefficient Estimatesand 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 (min)	Below 1h	Minimiza-tion	12.21	40.66
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
	Désirability		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

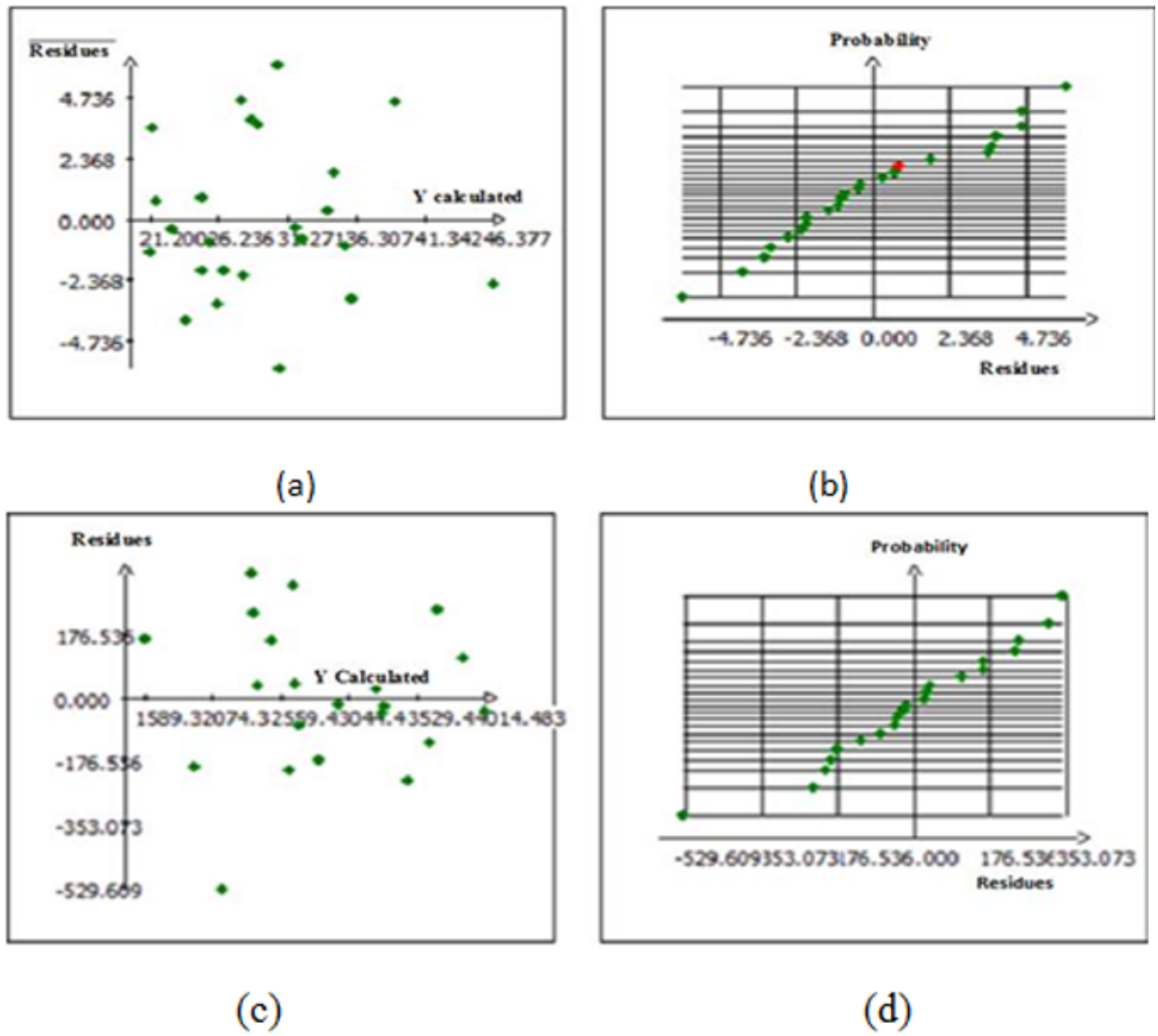


Figure 2: Residue distribution curves (a): Residual values based on adjusted values for Y1, (b) Henry's residual values right for Y2, (c) Residual values based on adjusted values for Y1, (d) Henry's entitlement to residual values for Y2

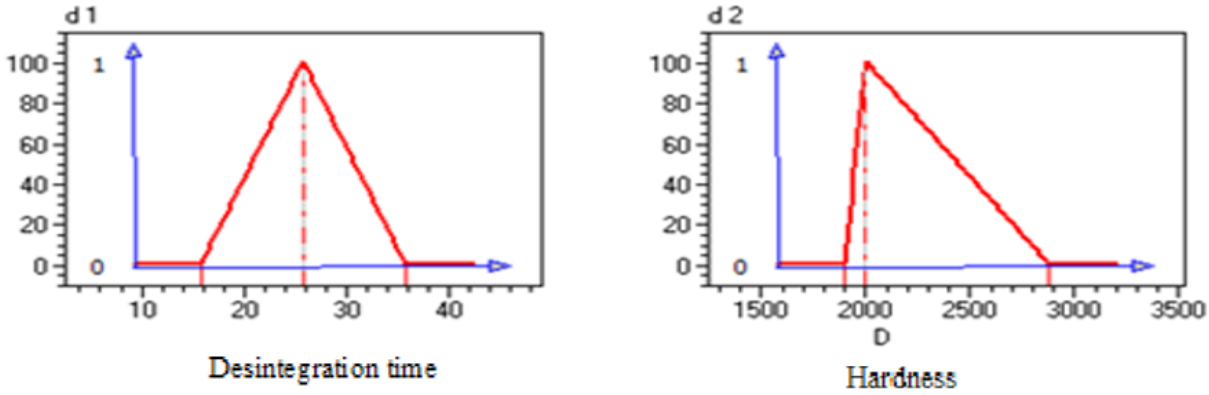


Figure 3: Desirability Functions Graph

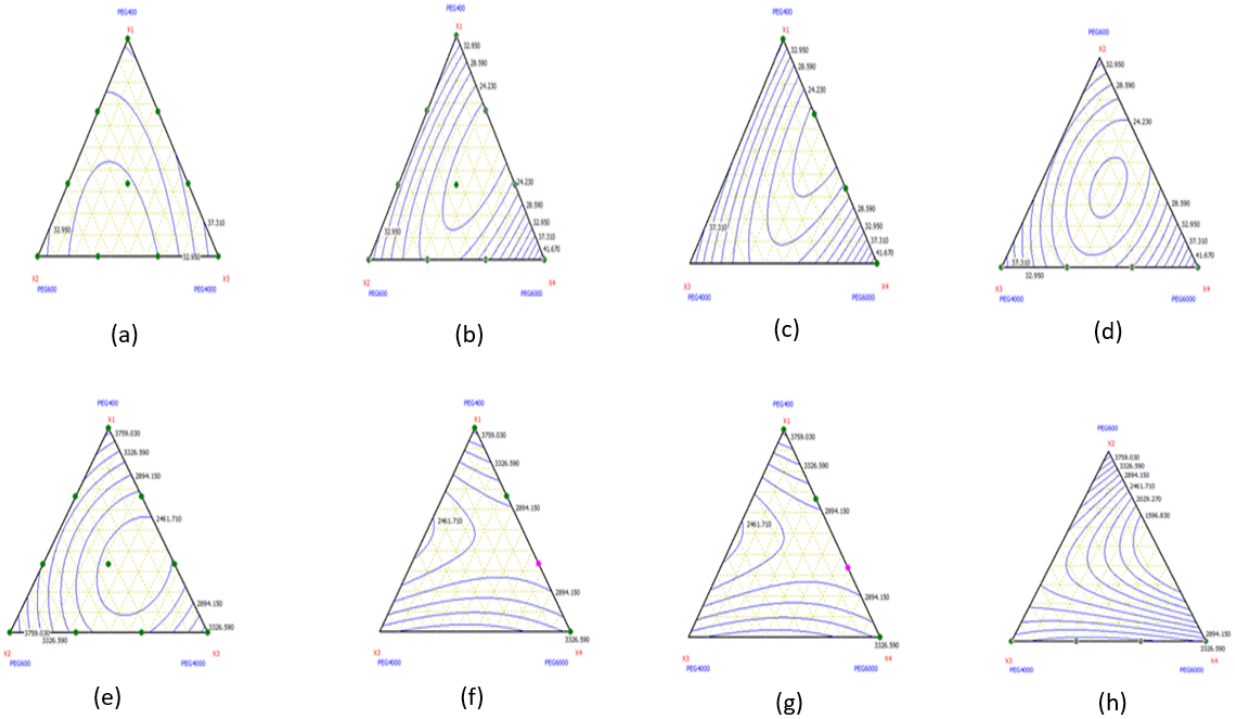


Figure 4: Response surfaces of suppository characteristics by Nemrod® software as a function of the percentage of Macrogols 400, 600, 4000 and 6000 g / mol. (a, b, c, d) ; Disintegration time (Y1), (e, f, g, h) : Hardness (Y2)

using the mathematical quadratic model (Cornell, 2011; Tinsson, 2010) according to Equation (1),

$$Y = b1X1 + b2X2 + b3X3 + b4X4 + b1 - 2X1X2 + b1 - 3X1X3 + b1 - 4X1X4 + b2 - 3X2X3 + b2 - 4X2X4 + b3 - 4X3X4 \quad (1)$$

Where Y is the dependent variable (hardness or disintegration) and b1 b2 ...b3-4 are the parameters of the model to be estimated. The main effects (X1, X2, X3 and X4) represent the average result of modifying a factor. The interaction terms (X1X4, X2X3, X2X4, X2X4 and X3X4) 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 α) of 0.05 to assess the null hypothesis that there is no association between the term and the response.

The model was selected on the basis of the adjusted

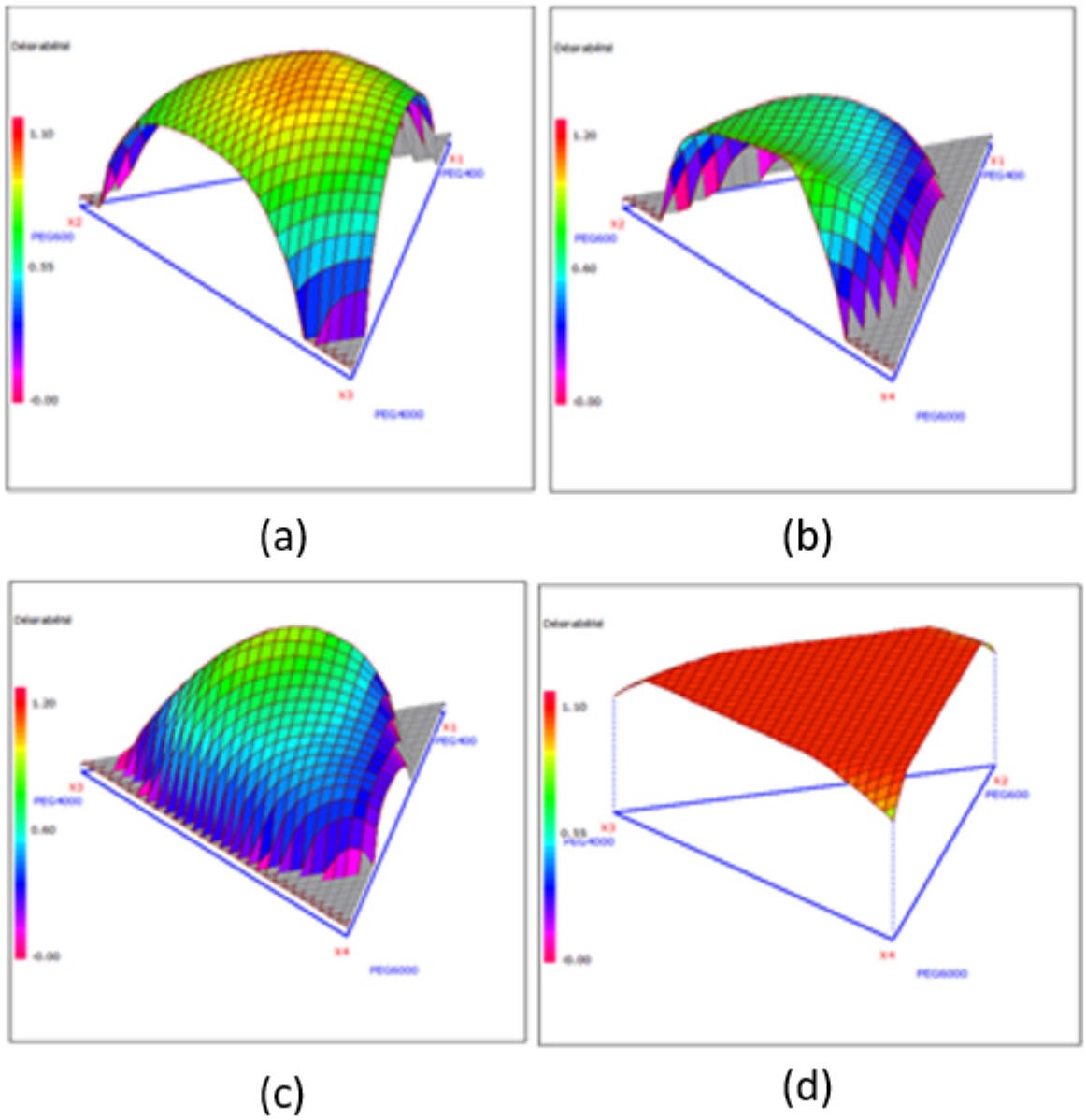


Figure 5: The Three-Dimensional (3D) Response Surface Plot of Desirability at the Prediction

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),

$$di(\widehat{Y}1) = \widehat{Y}1(X) - Ui \div Si - Ui \qquad (2)$$

With Ui and Si, the upper and lower values observed for the response Y1.

In the case of Y 2, our objective is to target a min-

imum 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),

$$di(\widehat{Y}2) = \widehat{Y}2(X) - Ui \div Ti - Ui \quad (3)$$

With Ui and Ti, the desired upper and target values for the answer Y2 and Li $\leq$ Ti $\leq \leq$ Ui.

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

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

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 Y_1 and Y_2.

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)

$$\begin{aligned} Y = {} & 35.59X1 + 34.21X2 + \\ & 39.21X3 + 46.37X4 - 80.14X1X2 - \\ & 65X2X4 - 69.13X3X4 \end{aligned} \quad (5)$$

Equation of Hardness (6)

$$\begin{aligned} Y = {} & 3930.11X1 + 3814.62X2 + \\ & 3669X3 + 3929.67X4 - \\ & 6356.61X1X3 - 6937.95X2X4 \end{aligned} \quad (6)$$

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 *et al.*, 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 suppository.

The factors obtained at the minimum points of Y1 and Y2 (target: Y1 = 25.839 min and Y2 = 2147.321 g, respectively, see the figure below) were obtained by numerical desirability method as follows: PEG400 (28.71334%); PEG600 (24.23773%), PEG4000 (35.00944%) and PEG6000 (12.03949%) (Dabbas *et al.*, 2003; Cornell, 2011; Dalavi and Patil, 2009).

Table 6 shows the overall desirability that is the order of 91.20 %.

The effect of four Macrogols on the pharmaco-technical characteristics of the suppository is shown in Figure 3. (Bello *et al.*, 2011; Preece and Cornell, 1982).

The formulations generally use both categories of Macrogols, for compensatory purposes, mixed in various proportions as required to obtain a finished product of satisfactory hardness and dissolution time (Rowe *et al.*, 2006; Berkó, 2002; Kellaway and Marriott, 1975). Different PEG ratios of low and high molecular weight can be used to alter the time to disintegrate the hardness of the suppository (Rowe *et al.*, 2006; Kellaway and Marriott, 1975; Chatterjee *et al.*, 2014).

Figure 4 shows the iso-résponses curves of the different combinations of Macrogol for both responses each taken alone. The PEG 6000, which has a higher molecular weight, will be tougher than the PEG 4000, but both can break and delay disintegration, whereas the addition of PEG 400 and 600 makes the suppositories hard, elastic and In view of drug incompatibilities, it is advantageous to minimize the proportions of low molecular weight PEGs because they have higher OH-values (Kellaway and Marriott, 1975; Chatterjee *et al.*, 2014; Duangjit *et al.*, 2014).

Checking the optimal parameters

Figure 5 shows the three-dimensional representation (3D) of the response surface of the desirability of the suppository. (Shivakumar *et al.*, 2007; Kumar *et al.*, 2016). The opportunity of the prediction was 91.20%. To evaluate the accuracy of the optimal formulation predicted by NemrodW ®, the optimal formulation was prepared and studied experimentally. The ideal characteristics estimated by the software and the experimental characteristics measured are shown in Table 5. The results showed that the optimal characteristics demonstrated by the experiment were more or less close to the estimated predicted values. The reliability of this study was judged by the calculation of the bias (See Table 7) (Duangjit *et al.*, 2014).

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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