

## MATHEMATICAL MODELING OF 4-[(2-ISOPROPOXYETHOXY)METHYL]PHENOL SYNTHESIS

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### Abstract

The most difficult step in the industrial manufacturing of bisoprolol fumarate, an important beta-blocker agent, is the synthesis of 4-[(2-isopropoxyethoxy)methyl]phenol, which is influenced by three main parameters: 2-isopropoxy ethanol/4-hydroxybenzyl alcohol molar ratio, reaction time and temperature. In order to establish the optimum reaction conditions, an experimental factorial design was accomplished, in which the real values of the parameters and their limits of variation were randomly chosen. The mathematical modeling of 4-[(2-isopropoxyethoxy)methyl]phenol obtaining process enabled to settle the optimum values of the parameters for a maximum yield in 4-[(2-isopropoxyethoxy)methyl]phenol synthesis.

### Rezumat

Cea mai importantă etapă în sinteza bisoprololului fumarat, un important medicament beta-blocant, este obținerea 4-[(2-isopropoxietoxi)metil]fenolului, prin reacția de eterificare a alcoolului 4-hidroxibenzilic cu 2-isopropoxietanol. Această reacție este influențată de trei parametri: raportul molar al celor doi reactanți, timpul necesar desfășurării reacției și temperatura reacției. Pentru a stabili condițiile optime de reacție, s-a dezvoltat un program de experimentare, în cadrul căruia valorile parametrilor și limitele lor de variație au fost alese în mod arbitrar. Modelarea matematică a sintezei 4-[(2-isopropoxietoxi)metil]fenolului a condus la obținerea valorilor optime ale parametrilor aleși, pentru valoarea maximă a randamentului de reacție.

**Keywords:** 4-[(2-isopropoxiethoxy)methyl]-phenol, mathematical modeling, regression equations.

### Introduction

Bisoprolol, 1-{4-[(2-isopropoxyethoxy) methyl] phenoxy}-3-(isopropylamino) propan-2-ol, is a beta-adrenoreceptor blocking drug which was first synthesised and developed by E. Merck [1] and was first

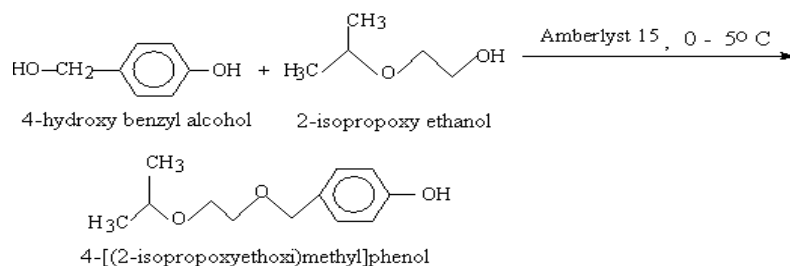
introduced on the German market in 1986. Bisoprolol is indicated for therapeutic use for the following effects: the control of arterial hypertension, the management of ischaemic heart disease, the control of some forms of cardiac arrhythmias and in the adjunctive management of hyperthyroidism [2].

Because of the special therapeutical effects of bisoprolol, the research regarding finding new economical and ecological methods of synthesis has reached a high level of interest. The wide variety of procedures of synthesis of bisoprolol can be resumed into the following two groups: the synthesis of bisoprolol from 4-hydroxybenzyl alcohol and the synthesis of bisoprolol from phenol [3].

The synthesis of bisoprolol fumarate from 4-hydroxybenzyl alcohol means going through the following sequence of steps: the synthesis of the intermediate 4-[(2-isopropoxyethoxy)methyl]phenol by using 4-hydroxybenzyl alcohol and 2-isopropoxy ethanol, the condensation of the phenolic intermediate with epichlorohydrin to give 2-[[4-(2-isopropoxyethoxy)methyl]-phenoxy]methyl]oxirane which is further reacted with isopropyl amine to give bisoprolol base and then the step of obtaining bisoprolol fumarate by treating bisoprolol base with fumaric acid [4].

The most important step in the synthesis of bisoprolol fumarate from 4-hydroxybenzyl alcohol consist of obtaining the intermediate 4-[(2-isopropoxyethoxy)methyl]phenol, out of the etherification reaction between 4-hydroxybenzyl alcohol and 2-isopropoxy ethanol. The data from literature indicate that the following conditions of etherification reaction are possible [5]: the homogenous acid catalysis in the presence of the sulphuric acid; the heterogenous catalysis in the presence of aluminium oxyde at high temperatures; the heterogenous acid catalysis in the presence of sulphonic resins and, especially, Amberlyst15, at low temperatures.

The present paper provides a process for the preparation of pure 4-[(2-isopropoxyethoxy)methyl]phenol, which is economical and easy to carry out at industrial scale. This way, in order to obtain 4-[(2-isopropoxyethoxy)methyl]phenol, we made our option of using Amberlyst 15, in accordance with figure 1 [6]. This is a highly acid exchanging ions resin obtained by the crossed combination of divinyl benzenstiren copolymers, on which are grafted sulphonic groups.

**Figure 1**

The chemical reaction applied for the synthesis of 4-[(2-isopropoxyethoxy)methyl]phenol

The advance of the chemical process will be checked by detecting the concentration of 4-hydroxybenzyl alcohol in the reaction mass. For this purpose, it has been elaborated a HPLC method with UV detection.

In order to establish the optimum conditions to achieve this chemical reaction, we suggested a mathematical model based on statistical analysis and regression equations. This way, a series of experiments, in which the values of the independent parameters and their variation limits were arbitrarily chosen, were accomplished. The mathematical modeling of the chemical reaction enabled to settle the most propitious values of the parameters for the maximum yield of reaction.

### Materials and methods

#### *Equipment and chromatographic conditions*

The LC system, HPLC Agilent 1100 device was employed during this study. The output signal was monitored using HP Chemstation software. The separation was performed using a reverse phase column Zorbax Extend C18, 150mmx4.6, 5 $\mu$ m packing (Agilent) [7]. The flow rate of the mobile phase (a mixture from acid acetic 0.2% solution and acetonitrile) was of 1.2 mL/min. The chromatography was performed at 35°C temperature, automatically injecting 75  $\mu$ L into the chromatographic system.

#### *Materials*

All solvents and other chemicals (acetonitrile, Amberlyst 15, 2-isopropoxy ethanol, water, acetic acid, potassium carbonate, toluene, sodium hydroxide) were HPLC grade provided by Merck, Germany. The reference substance of 4-hydroxybenzyl alcohol was supplied from Sigma-Aldrich.

*General procedure for the 4-[(2-isopropoxyethoxy) methyl] phenol synthesis*

To the mixture containing 4-hydroxybenzyl alcohol and 2-isopropoxy ethanol, in variable molar ratios (table I), Amberlyst 15 was added on an ice bath (0-5°C), firmly stirring it. The reaction mixture was stirred at a temperature of 0-5°C for two hours (the initiation phase), and then it was brought to room temperature (15-20°C) and it was firmly stirred for another ten hours (the concluding phase). After the time of reaction expired, the reaction mixture was filtered, the recovered catalyst was washed on the filter with 10 mL 2-isopropoxy ethanol, and the organic phase was HPLC analysed aiming to detect the concentration of 4-hydroxybenzyl alcohol which hasn't reacted chemically. The yield of the chemical reaction has been estimated according to the quantity of 4-hydroxybenzyl alcohol which has reacted. The filtrate was treated with 0.67g potassium carbonate and was firmly stirred for 30 minutes. After this time has expired, the excess of potassium carbonate was filtered and the reaction mixture was distilled allowing the recovery of the 2-isopropoxy ethanol excess.

The 4-[(2-isopropoxyethoxy)methyl]phenol obtained was placed in a separation funnel with 96 mL toluene and was washed three times with a volume of 96 mL water per wash. The toluenic extract was separated and then treated with a sodium hydroxide solution (previously prepared by the solubilization of 4.8 g of sodium hydroxide in 72 mL water) obtaining 4-[(2-isopropoxyethoxy)methyl]phenolate of sodium.

### **Results and discussion**

The etherification reaction of 4-hydroxybenzyl alcohol with 2-isopropoxy ethanol takes place in two phases: the initiation phase, which lasts about two hours and the concluding phase which lasts about ten hours. In the following, the mathematical modeling of the two phases of reaction will be described. For the calculation of the regression coefficients and dispersion, the software Matlab and Mathcad were used.

#### **1. The mathematical modeling in the initiation phase**

For the mathematical modeling of 4-[(2-isopropoxyethoxy)methyl]phenol synthesis, in the initiation phase, a rotary centered factorial experiment of second-degree order with an extension in the range  $(-a-1)$ , 0,  $(+1+a)$ , has been used. The mathematical model quantifies the influence of the independent variables (2-isopropoxy ethanol /4-hydroxy benzyl alcohol molar ratio ( $x_1$ ), time( $x_2$ ) and temperature ( $x_3$ )) on the reaction yield ( $y$ ), and it was established by a statistical analysis. The real values of the process

variables were chosen arbitrarily, their limits of variation and coding being given in table I.

**Table I**  
The limits and coding of independent variables that influence the 4-[(2-isopropoxyethoxy)methyl]phenol obtaining process

| Variable                                                   | Cod   | Real values of coded levels |    |     | Step |
|------------------------------------------------------------|-------|-----------------------------|----|-----|------|
|                                                            |       | -1                          | 0  | +1  |      |
| 2-isopropoxy ethanol /4-hydroxy benzyl alcohol molar ratio | $x_1$ | 9                           | 12 | 15  | 3    |
| Time (hours)                                               | $x_2$ | 0.5                         | 2  | 3.5 | 1.5  |
| Temperature, °C                                            | $x_3$ | 0                           | 5  | 10  | 5    |

The experimental matrix followed for the mathematical modeling along with experimental yields  $y_E$  (%), as the real answer of the system and calculated yields  $y_{calc}$  (%), are given in table II.

**Table II**  
The experimental matrix and the real answers

| No. | $x_1$  | $x_2$  | $x_3$  | $x_1^2$ | $x_2^2$ | $x_3^2$ | $x_1x_2$ | $x_1x_3$ | $x_2x_3$ | $y_E$ | $y_{calc}$ |
|-----|--------|--------|--------|---------|---------|---------|----------|----------|----------|-------|------------|
| 1.  | -1     | -1     | -1     | +1      | +1      | 1       | +1       | +1       | +1       | 24.4  | 24.4       |
| 2.  | +1     | -1     | -1     | +1      | +1      | 1       | -1       | -1       | +1       | 40.2  | 40.6       |
| 3.  | -1     | +1     | -1     | +1      | +1      | 1       | -1       | +1       | -1       | 36.1  | 35.6       |
| 4.  | +1     | +1     | -1     | +1      | +1      | 1       | +1       | -1       | -1       | 64.7  | 64.7       |
| 5.  | -1     | -1     | +1     | +1      | 1       | 1       | +1       | -1       | -1       | 16.4  | 16.7       |
| 6.  | +1     | -1     | +1     | +1      | 1       | 1       | -1       | +1       | -1       | 29.7  | 30.2       |
| 7.  | -1     | +1     | +1     | +1      | 1       | 1       | -1       | -1       | +1       | 27.7  | 27.6       |
| 8.  | +1     | +1     | +1     | +1      | 1       | 1       | +1       | +1       | +1       | 53.6  | 53.9       |
| 9.  | -1.682 | 0      | 0      | 2.828   | 0       | 0       | 0        | 0        | 0        | 18.4  | 18.4       |
| 10. | +1.682 | 0      | 0      | 2.828   | 0       | 0       | 0        | 0        | 0        | 54.7  | 54.0       |
| 11. | 0      | -1.682 | 0      | 0       | 2.828   | 0       | 0        | 0        | 0        | 19.7  | 19.0       |
| 12. | 0      | +1.682 | 0      | 0       | 2.828   | 0       | 0        | 0        | 0        | 48.1  | 48.5       |
| 13. | 0      | 0      | -1.682 | 0       | 0       | 2.828   | 0        | 0        | 0        | 53.2  | 53.7       |
| 14. | 0      | 0      | +1.682 | 0       | 0       | 2.828   | 0        | 0        | 0        | 38.2  | 38.1       |
| 15. | 0      | 0      | 0      | 0       | 0       | 0       | 0        | 0        | 0        | 70.9  | 69.6       |
| 16. | 0      | 0      | 0      | 0       | 0       | 0       | 0        | 0        | 0        | 68.8  | 69.6       |
| 17. | 0      | 0      | 0      | 0       | 0       | 0       | 0        | 0        | 0        | 69.5  | 69.6       |
| 18. | 0      | 0      | 0      | 0       | 0       | 0       | 0        | 0        | 0        | 68.6  | 69.6       |
| 19. | 0      | 0      | 0      | 0       | 0       | 0       | 0        | 0        | 0        | 69.3  | 69.6       |
| 20. | 0      | 0      | 0      | 0       | 0       | 0       | 0        | 0        | 0        | 70.2  | 69.6       |

In order to settle the correlation between the reaction yield,  $y$  and the above mentioned parameters (independent variables), the following model of polynomial equation type has been proposed:

$$y = b_0 + b_1x_1 + b_2x_2 + b_3x_3 + b_{11}x_1^2 + b_{22}x_2^2 + b_{33}x_3^2 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3 \quad (1)$$

where  $b_0, \dots, b_{23}$  are the regression coefficients.

The regression coefficients were calculated using the equations (2)-(11) [8], their calculated values being given in table III.

$$b_{00} = 69.67 \quad (2)$$

$$b_{11} = 10.59 \quad (3); \quad b_2 = 0.073224 \sum_{i=1}^{20} X_2 Y_{ei} \quad (4)$$

$$b_{33} = 0.073224 \sum_{i=1}^{20} X_3 Y_{ei} \quad (5); \quad b_{12} = 0.125 \sum_{i=1}^{20} X_2 Y_{ei} \quad (6)$$

$$b_{13} = 0.125 \sum_{i=1}^{20} X_3 Y_{ei} \quad (7); \quad b_{23} = 0.125 \sum_{i=1}^{20} X_3 Y_{ei} \quad (8)$$

$$b_{111} = 0.0025 \sum_{i=1}^{20} X_1^2 Y_{ei} - 0.056791 \quad (9)$$

$$b_{112} = 0.0025 \sum_{i=1}^{20} X_1 X_2 Y_{ei} - 0.056791 \quad (10)$$

$$b_{113} = 0.0025 \sum_{i=1}^{20} X_1 X_3 Y_{ei} - 0.056791 \quad (11)$$

**Table III**

The calculated values for the regression coefficients

| $b_0$ | $b_1$ | $b_2$ | $b_3$ | $b_{11}$ | $b_{22}$ | $b_{33}$ | $b_{12}$ | $b_{13}$ | $b_{23}$ |
|-------|-------|-------|-------|----------|----------|----------|----------|----------|----------|
| 69.67 | 10.59 | 8.77  | -4.64 | -11.81   | -12.68   | -8.38    | 3.175    | -0.65    | -0.125   |

The regression equation which permits the yield calculation for the 4-[(2-isopropoxyethoxy)methyl]phenol obtaining process, in the initiation phase, depending on each individual parameter has the following expression:

$$y = 69.67 + 10.59x_1 + 8.77x_2 - 4.64x_3 - 11.81x_1^2 - 12.68x_2^2 - 8.38x_3^2 + 3.175x_1x_2 - 0.65x_1x_3 - 0.125x_2x_3 \quad (12)$$

Analyzing the values of the regression coefficients, one can conclude that the process performance is noticeably influenced by all three parameters, the order of influence being: 2-isopropoxy ethanol /4-hydroxy benzyl alcohol molar ratio > process duration > temperature. In order to establish the maximum value of this function and to determine the reaction conditions that allow a maximum yield respectively, the equation (12) was derived in function of  $x_1$ ,  $x_2$  and  $x_3$  successively. After the nullification of the derivatives of first-degree order a system of three linear, non-homogeneous equations (13)-(15) was obtained:

$$dy/dx_1 = 10.59 - 23.62x_1 + 3.175x_2 - 0.65x_3 = 0 \quad (13)$$

$$dy/dx_2 = 8.77 - 25.36x_2 + 3.175x_1 - 0.125x_3 = 0 \quad (14)$$

$$dy/dx_3 = -4.64 - 16.76x_3 - 0.65x_1 - 0.125x_2 = 0 \quad (15)$$

By solving this equations system, the coded values of the independent variables that permit a maximum value for the function  $y$ , are as follows:

$$x_1^0 = 0.51171; x_2^0 = 0.41017; x_3^0 = -0.298$$

After decoding, the following values for the independent variables are obtained:

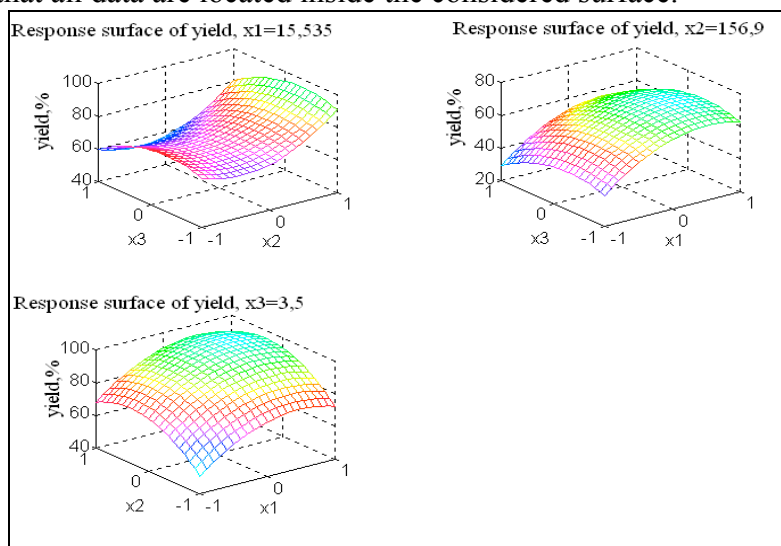
$$x_1 = 15.535 \text{ mols 2-isopropoxy ethanol / mols 4-hydroxy benzyl alcohol};$$

$$x_2 = 156.9 \text{ minutes};$$

$$x_3 = 3.5^\circ\text{C}$$

Using these values, the obtained maximum yield was 74.88%.

For the validation of the adequacy of the mathematical model, the Fischer test was calculated using the dispersion of the experimental data for which the value 0.582 was obtained. This value was compared with the tabulated critical value for Fischer test,  $F=5.93$ , for a confidence level of  $\alpha=0.05$ . Since  $F$  critical is lower than  $F$  calculated, one can conclude that the proposed regression equation is adequate. The spacial representations of the response surfaces ( $y$ ) (figure 2) for a constant value of coded variables reveal that all data are located inside the considered surface.



**Figure 2**

Spatial representations of the regression equation for  $x_1, x_2$  and  $x_3 = \text{optimum}$

## 2. The mathematical modeling in the concluding phase

For the mathematical modeling of 4-[(2-isopropoxyethoxy)methyl]phenol synthesis (concluding phase), a rotary centered factorial

experiment of second-degree order with an extension in the range  $(-a-1)$ ,  $0$ ,  $(+1+a)$ , has been used. The mathematical model quantifies the influence of the independent variables (2-isopropoxy ethanol /4-hydroxy benzyl alcohol molar ratio ( $x_1$ ), time( $x_2$ ) and temperature( $x_3$ )) on the reaction yield ( $y$ ), and it was established by a statistical analysis. The real values of the process variables were chosen arbitrarily, their limits of variation and coding being given in table IV.

**Table IV**

The limits and coding of independent variables that influence the 4-[(2-isopropoxyethoxy)methyl]phenol obtaining process

| Variable        | Cod   | Real values of coded levels |    |    | Step |
|-----------------|-------|-----------------------------|----|----|------|
|                 |       | -1                          | 0  | +1 |      |
| Time (hours)    | $x_1$ | 5                           | 10 | 15 | 5    |
| Temperature, °C | $x_2$ | 15                          | 20 | 25 | 5    |

The experimental matrix followed for the mathematical modeling along with experimental yields  $y_E$  (%), as the real answer of the system and calculated yields  $y_{calc.}$  (%), are given in table V.

**Table V**

The experimental matrix and the real answers

| No. | $x_0$ | $x_1$  | $x_2$  | $x_1^2$ | $x_2^2$ | $x_1x_2$ | $y_{exp.}$ | $y_{calc.}$ |
|-----|-------|--------|--------|---------|---------|----------|------------|-------------|
| 1.  | +1    | -1     | -1     | 1       | 1       | +1       | 88.7       | 88.4        |
| 2.  | +1    | +1     | -1     | 1       | 1       | -1       | 95.6       | 96.9        |
| 3.  | +1    | -1     | +1     | 1       | 1       | -1       | 89.3       | 87.6        |
| 4.  | +1    | +1     | +1     | 1       | 1       | +1       | 92.4       | 92.3        |
| 5.  | +1    | -1.414 | 0      | 2       | 0       | 0        | 83.2       | 85.5        |
| 6.  | +1    | +1.414 | 0      | 2       | 0       | 0        | 94.6       | 94.8        |
| 7.  | +1    | 0      | -1.414 | 0       | 2       | 0        | 94.8       | 94.3        |
| 8.  | +1    | 0      | +1.414 | 0       | 2       | 0        | 88.3       | 90.5        |
| 9.  | +1    | 0      | 0      | 0       | 0       | 0        | 93.8       | 95.0        |
| 10. | +1    | 0      | 0      | 0       | 0       | 0        | 94.4       | 95.0        |
| 11. | +1    | 0      | 0      | 0       | 0       | 0        | 93.6       | 95.0        |
| 12. | +1    | 0      | 0      | 0       | 0       | 0        | 94.8       | 95.0        |
| 13. | +1    | 0      | 0      | 0       | 0       | 0        | 94.2       | 95.0        |

In order to settle the correlation between the reaction yield,  $y$ , and the above mentioned parameters (independent variables), the following model of polynomial equation type (16) has been proposed:

$$y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2 \quad (16)$$

where  $b_0, \dots, b_{12}$  are the regression coefficients.

The regression coefficients were calculated using the equations (2)-(11), their calculated values being given in table VI.

**Table VI**  
The calculated values for the regression coefficients

| $b_0$ | $b_1$ | $b_2$  | $b_{11}$ | $b_{22}$ | $b_{12}$ |
|-------|-------|--------|----------|----------|----------|
| 95.06 | 3.26  | - 1.35 | - 2.437  | - 1.287  | - 0.95   |

The regression equation which allows the yield calculation for the 4-[(2-isopropoxyethoxy)methyl]phenol obtaining process, in the concluding phase, depending on each individual parameter has the following expression (17):

$$y = 95.06 + 3.265x_1 - 1.35x_2 - 2.437x_1^2 - 1.287x_2^2 - 0.95x_1x_2 \quad (17)$$

Analyzing the values of regression coefficients, one can conclude that the process performance is noticeably influenced by both parameters, the order of influence being: process duration > temperature. In order to establish the maximum value of this function and to determine the reaction conditions that permit a maximum yield respectively, the equation (17) was derived in function of  $x_1$  and  $x_2$ , successively. After the nullification of the derivatives of first-degree order a system of three linear, non-homogeneous equations (18)-(19) was obtained:

$$dy/dx_1 = 3.265 - 2 \times 2.437x_1 - 0.95x_2 = 0 \quad (18)$$

$$dy/dx_2 = -1.35 - 2 \times 1.287x_2 - 0.95x_1 = 0 \quad (19)$$

By solving this equations system, the coded values of the independent variables that permit a maximum value for the function  $y$ , are as follows:

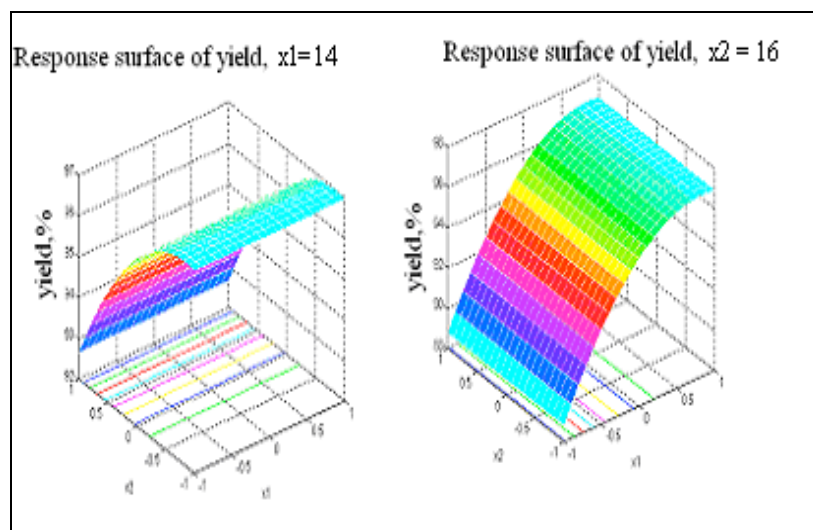
$$x_1^0 = 0.832; \quad x_2^0 = -0.831$$

After decoding, the following values for the independent variables are obtained:

$$x_1 = 14 \text{ hours}; \quad x_2 = 16^\circ\text{C}$$

Using these values, the obtained maximum yield was 96.98%.

For the validation of the adequacy of the mathematical model, the Fischer test was calculated using the dispersion of the experimental data for which the value 0.0538 was obtained. This value was compared with the tabulated critical value for Fischer test,  $F=6.93$ , for a confidence level of  $\alpha=0.05$ . Since  $F$  critical is lower than  $F$  calculated, one can conclude that the proposed regression equation is adequate. The special representations of the response surfaces ( $y$ ) (figure 3) for a constant value of the coded variables reveal that all data are located inside the considered surface.

**Figure 3**

Spatial representations of the regression equation for  $x_1$  and  $x_2$  = optimum

### Conclusions

Bisoprolol is an important exponent of the beta-blocker class of drugs, which is successfully administered in the treatment of cardiovascular diseases. The most important phase in the synthesis of bisoprolol is represented by the etherification reaction of this compound with 2-isopropoxy ethanol, resulting 4-[(2-isopropoxyethoxy)methyl]phenol, which takes place in two phases: the initiation phase, with an approximate duration of three hours and the concluding phase, with an approximate duration of fourteen hours.

With the purpose of providing the most propitious conditions for the chemical reaction in order to obtain the maximum yield in 4-[(2-isopropoxyethoxy)methyl]phenol, a rotary centered factorial experiment of second-degree order with an extension in the range  $(-a-1)$ , 0,  $(+1+a)$  has been used, in which the values of the independent parameters and their variation limits have been arbitrarily chosen. This way, for a maximum value of the reaction yield of 74.88%, in the initiation phase, the next values of the independent parameters have been obtained: 2-isopropoxy ethanol /4-hydroxy benzyl alcohol molar ratio = 13.535, time of reaction = 156.9 minutes and the temperature of reaction = 3.5°C. In the concluding phase of the chemical reaction, for a maximum value of the yield of 96.98%, the next values of the independent parameters have been obtained: time = 14 hours and temperature of reaction = 16°C. We can conclude that the results obtained in the mathematical modelling are consistent and offer valuable

information in order to obtain the 4-[(2-isopropoxyethoxy)methyl]phenol with a maximum yield.

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