Study and modeling of the estherification process of m-nitrobenzoic acid with ethanol

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Abstract

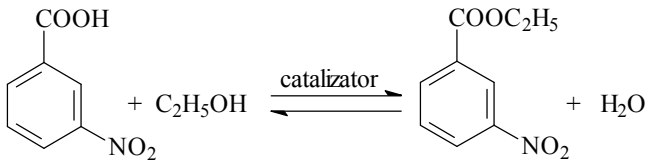
In order to obtain new pesticides having antifungal activity, the estherification of m-nitrobenzoic acid with ethanol was studied. A comparative study was carried out for homogeneous and heterogeneous catalysis. Because the heterogeneous catalysis was proved to be better both by global yield and by separation of the esther from the reaction mixture, the studies were continued to establish the effects of the catalyst amount or the reaction time and temperature on the yield of esther. An empirical model was elaborated by a factorial experiment of first order 2^3 type, considering reaction time, temperature, and gr.catalyst/gr.m-nitrobenzoic acid mass ratio as independent variables, while the yield was chosen as optimization criteria. The empirical model was found adequate for the estherification process of m-nitrobenzoic acid with ethanol. Also, an analysis of the model was performed to find the optimal operating conditions, in order to apply this process for an efficient estherification of m-nitrobenzoic acid with ethanol. The optimal values correspond to a temperature of 80^0C, a reaction time of 7.2 h and a mass ratio gr.catalyst/gr.m-nitrobenzoic acid of 0.6 for an optimal yield of 94%.

Keywords: estherification, ethylic esther of m-nitrobenzoic acid, experiment design, mathematical modeling, optimization.

Introduction

Ethylic esther of m-nitrobenzoic acid is a basic intermediate for the synthesis of some pesticides with antifungal activity, having an aromatic structure with nitro and sulfonamide groups, substituted with triazoles, aminopyridyl, pyrimidyl, morpholine, pyperazine, aromatic amines moieties [1-5].

Thus, a study of the estherification process of m-nitrobenzoic acid with ethanol is required, using m-nitrobenzoic acid 98,5% purity and ethanol 95.45%.



The main reaction that describes the estherification process is showed above, and, depending on the catalyst nature the reaction occurs in homogeneous catalysis (using H_2SO_4 or p-toluene sulfonic acid) or in heterogeneous catalysis (using Dowex-50 as catalyst) [2, 4].

This paper will discuss the influence of the reaction time, temperature, and gr. catalyst/ gr. m-

nitrobenzoic acid mass ratio on estherification process of m-nitrobenzoic acid with ethanol as applied to synthesis of pesticides with antifungal activity. Variables concerning the reaction time, temperature, and gr.catalyst/gr.m-nitrobenzoic acid mass ratio were considered in order to appreciate the process efficiency. Process modeling and optimization were also performed in order to find the optimal operating conditions using a complete factorial design, 2^3 type [6-8]. All experiments were performed on a laboratory scale.

Materials and methods

The study of the estherification process of m-nitrobenzoic acid with ethanol was carried out by the following method:
Into the reaction flask with 3 necks, the prescribed quantities of reactants (3.46 mols ethanol and 0.072 mols m-nitrobenzoic acid) were added.
The equipment was provided with a mechanical stirring system in order to assure the homogeneity of the reaction mixture and with a thermostat for strictly controlling the reaction temperature.
After the reactants and the catalyst were added to the reaction flask, the reaction mixture was brought at the regime temperature and maintained, under reflux, for different periods of time (between 1 and 13 hours).
The estherification in homogeneous system occurred in the presence of sulphuric acid monohydrate, next to prescribed amounts of reactants, and the reaction mixture was heated at various temperatures and reaction times.
The heterogeneous estherification used a Dowex-50 catalyst.
The reaction progress was followed by harvesting samples of 2-3 cm^3, that were fast cooled to 5-6°C, diluted in 15-20 l ethanol and then the organic acid was titrated with NaOH 0.1 N solutions.
The ethyl m-nitrobenzoate is a white, crystalline substance, having a melting point of 39.7°C.
IR spectrum of the ethylic esther of m-nitrobenzoic acid is given in Fig.1.

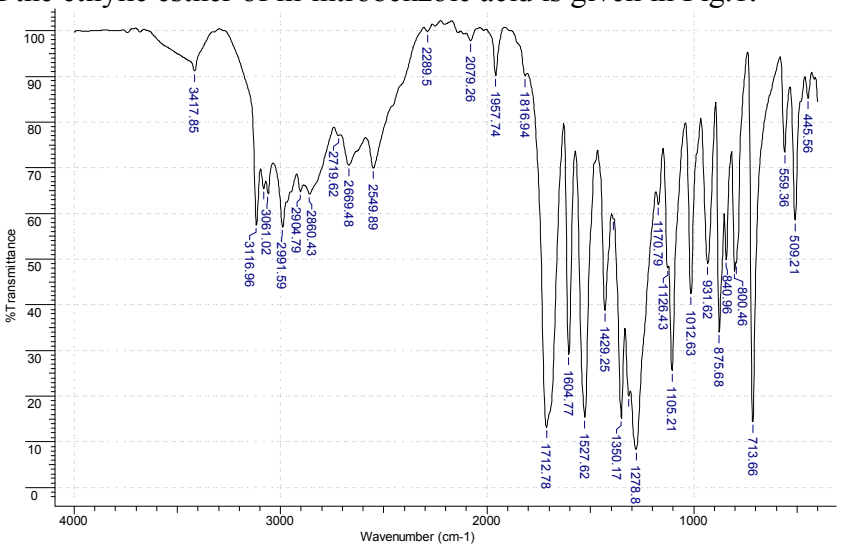


Figure 1. IR spectra of the ethylic esther of m-nitrobenzoic acid

The structure of the ethylic esther has been confirmed through FT-IR spectra.
The compound exhibits a characteristic absorption at 1527 cm^{-1}, corresponding to νC-C aromatic stretching vibrations.
The benzene ring is identified by the stretching vibration bands ν=CH, at 3061 cm^{-1}. The methyl group gives the band 2904 cm^{-1}, corresponding to νC-H stretching vibrations and at 1388 and 1429

cm^{-1}, due to deformation vibrations δCH_3 sym. and asym. The deformation vibrations for δCH_2 sym. and asym. are registered at 713 and 1315 cm^{-1}, respectively. The stretching vibration bands for CH_3 and CH_2 groups appear at 3061, and 3080 cm^{-1}, respectively.
Another characteristic signal is at 1012 cm^{-1}, corresponding to $\nu_{C\text{-}O\text{-}C}$, the stretching vibration band for the estheric oxygen. The carbonylic group of the esther has been seen at 1126 and 1712 cm^{-1}.
The substituent in the benzene ring (the p-NO_2 group) produces characteristic absorptions at 1278 cm^{-1} due to stretching vibration ν_{NO2} sym. and 1604 cm^{-1} for ν_{NO2} asym. In the spectrum appears the band for the stretching vibration $\nu_{C\text{-}N}$ at 1170 cm^{-1}.

Results and discussions

Preliminary estherification experiments

During this study we follow the yields obtained according to the catalyst nature (H_2SO_4 or Dowex-50), reaction temperature and time, considering the fact that the esther separation method varied with the nature of the catalyst.
In all of the experiments, samples were gathered from the reaction mixture that were fast cooled and then titrated with NaOH solution 0.1N.
a) Influence of the catalyst nature on the estherification yield
The study of the catalyst nature influence was made at 78°C, using the following data:

- for homogeneous catalysis:
  - catalyst H_2SO_4 0.02 g H_2SO_4/gr. m-nitrobenzoic acid;
  - ethanol p.a. 3.46 mol/l;
  - m-nitrobenzoic acid 0.072 mol/l.
- for heterogeneous catalysis:
  - catalyst Dowex-50 0.5 g Dowex 50/gr. m-nitrobenzoic acid;
  - ethanol p.a. 3.46 molls/l;
  - m-nitrobenzoic acid 0.072 mol/l.

Studies recorded the yield variation according to catalyst nature and reaction time, the results being showed in table 1 and figure 2.

Table 1. Variation of the esther yield with time, in homogeneous and heterogeneous catalysis

τ, h	**η %, cat. Dowex-50**	**η%, cat. H_2SO_4**
1	58	36
2	78	50
3	83	58
4	87	65
5	90	69
6	92	75
7	92	77
8	92	79
9	92	0
11	92	83
13	92	84

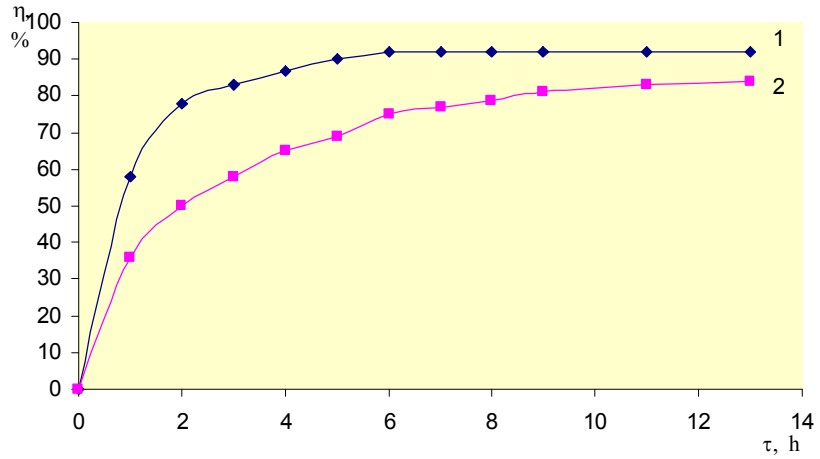


Figure 2. Variation of the esther yield with time, in homogeneous and heterogeneous catalysis: 1 – homogeneous catalysis: H_2SO_4, 2- heterogeneous catalysis: Dowex-50

The data from table 1 and figure 2 showed the yields of heterogeneous catalysis to be higher than those of homogeneous catalysis. It should also be considered the fact that the separation method of the esther from the reaction mixture in heterogeneous catalysis can be more simple, easily attainable and non-polluting.

According to these results, studies continued by establishing the influence of the amount of the catalyst Dowex-50 on esther yields.

b) Influence of the catalyst Dowex-50 amount on esther yields.

The study occurred at 78°C, using 0.25 g Dowex-50/gr m-nitrobenzoic acid, 0.5 g Dowex-50/ gr m-nitrobenzoic acid, 0.6 g Dowex-50/gr m-nitrobenzoic acid, m-nitrobenzoic acid 0.072 mol/l and ethanol 3.46 mol/l and the results are shown in table 2 and figure 3.

Table2. Influence of the amount of Dowex-50 catalyst on esther yields

Reaction time, h	**Yield in esther %**		
	0.25 g Dowex-50/ gr. m-nitrobenzoic acid	**0.5 g Dowex-50/ gr. m-nitrobenzoic acid**	**0.6 g Dowex-50/ gr. m-nitrobenzoic acid**
1	16	48	54
2	36	75	77
3	52	84	86
4	60	87	90
5	68	89	92
6	73	91	94
7	78	91	94
8	81	91	94
9	84	91	94

The results from table 2 and figure 3 showed that process performances for estherification of m-nitrobenzoic acid with ethanol depend on the amount of catalyst.

c) Influence of the reaction time and temperature on esther yield.

The studies on yield variations depending on the reaction time and temperature were made in heterogeneous catalysis, using: 0.5 g catalyst Dowex-50/gr. m-nitrobenzoic acid, m-nitrobenzoic acid 0.072 mol/l and ethanol 3.46 mol/l. The recorded results are showed in table 3 and figure 4.

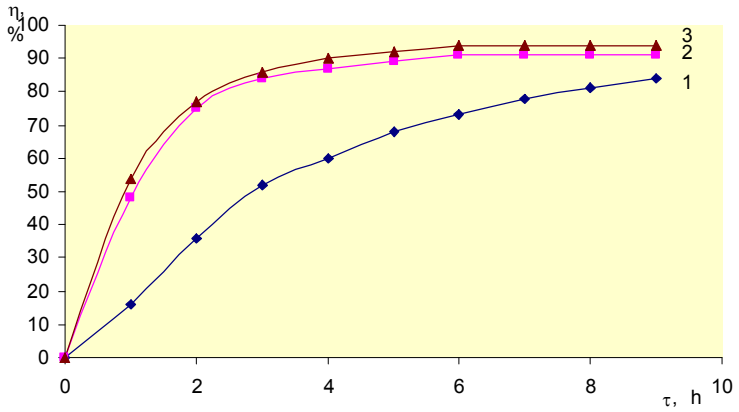


Figure 3. Influence of the amount of catalyst Dowex-50 on esther yields: 1-0.25 gr. Dowex-50/gr. m-nitrobenzoic acid; 2-0.5 gr. Dowex-50/gr. m-nitrobenzoic acid; 3-0.6 gr. Dowex-50/gr. m-nitrobenzoic acid.

Table 3. *Influence of the reaction time and temperature on esther yield*

Time h	Yield in esther %		
	60°C	70°C	78°C
1	15	32	57
2	31	53	74
3	42	65	83
4	53	76	88
5	58	81	90
6	64	84	91
7	68	85	92
8	70	85	92

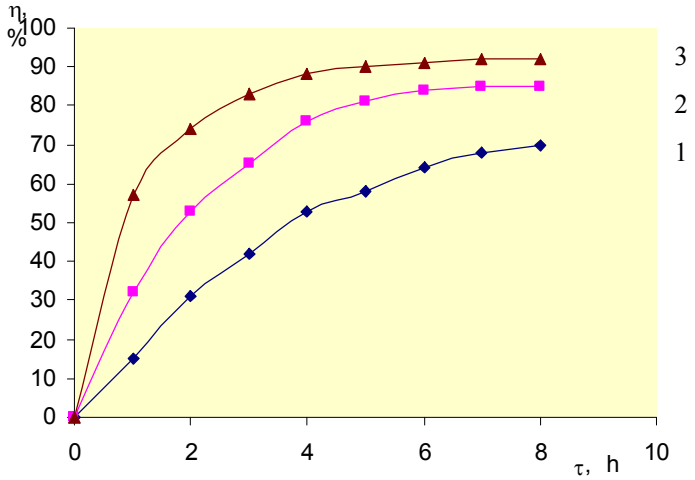


Figure 4. Influence of reaction time and temperature on esther yield: 1-t=60°C; 2-t=70°C, 3-t=78°C

The results of this study showed that both time and temperature have a major influence on the yield value for the estherification reaction of m-nitrobenzoic acid with ethanol.

All of the data above show that the esther yield depends on: reaction temperature and time and also on the used amount of Dowex-50 catalyst.

In order to establish optimum values for the estherification process of m-nitrobenzoic acid with ethanol in heterogeneous catalysis using Dowex-50, modeling and optimization studies have to be performed.

The modeling of this process would be made by an experimental planning method, using regression equations.
The regression equation empirical modeling was made by using the following data:

- concentration of m-nitrobenzoic acid: C_{Ao}=0.072 mol/l;
- concentration of ethanol C_{Bo} = 3.456 mol/l;
- mass ratio gr.catalyst/gr. m-nitrobenzoic acid - C_C.

Modeling of estherification reaction of m-nitrobenzoic acid with ethanol

Experiment design

The main factors that influence the estherification of m-nitrobenzoic acid with ethanol were considered to be: temperature (X_1), duration of estherification process (X_2) and mass ratio gr.catalyst/gr. m-nitrobenzoic acid (X_3).
As optimization criteria or response function was chosen the reaction yield (Y %).
In order to settle the correlation between the estherification yield Y, and the above mentioned parameters (independent variables) the following model of polynomial equation type (1) has been proposed:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \quad (1)$$

where $b_0, b_1 ... b_{123}$ are the regression coefficients.
The model coefficients are estimated using the experimental results obtained from the design points by a full factorial design. The coefficients were calculated using the equations [3, 7]:

$$b_0 = \overline{Y}_{1-8}, \quad b_j = \frac{\sum_{i=1}^{8} x_{ji} \cdot Y_i}{\sum_{i=1}^{8} x_{ji}^2}, \quad b_{jk} = \frac{\sum_{i=1}^{8} x_{ji} \cdot x_{ki} \cdot Y_i}{\sum_{i=1}^{8} x_{ji}^2 \cdot x_{ki}^2}, \quad b_{jkl} = \frac{\sum_{i=1}^{8} x_{ji} \cdot x_{ki} \cdot x_{li} \cdot Y_i}{\sum_{i=1}^{8} x_{ji}^2 \cdot x_{ki}^2 \cdot x_{li}^2} \quad (2)$$

where *i=1-8* number of experiments and j, k, l = 1-3 number of variables.
The full factorial design has the advantage of no excessive experiments in comparison with the number of coefficients to be determined. 12 experiments are used to estimate the model coefficients [6, 7]. 2^3 factorial experiments, at the corner of cube, that represents the experimental data area, are performed. The last four additional experiments were performed in the center of the experimental program, for an independent estimation of „pure" experimental error variance [6].
In order to define the experimental domain explored, the range of variable values are chosen in such a way that limits are set as wide as possible, while all the experiments are feasible.
To set the range of independent variables, for each variable (temperature, duration of estherification process and mass ratio gr.catalyst/gr. m-nitrobenzoic acid) a basic value z_{i0} and a variation step Δz_{i0} of each variable were established. Adding the variation step at the basic

value gave the upper level value, while by subtraction of the step value the lower level of variable was obtained.

The coded value of z_i denoted of X_i is determined with the Eq.(3) [3, 8]:

$$X_i = \frac{z_i - z_{i0}}{\Delta z_{i0}} \tag{3}$$

So, the upper level is coded with 1, the lower level with —1 and the basic level with 0 [8].

The real values of the process variables with their limits and coding being given in Table 4.

Table 4. The codification of the independent variables

Nr. crt.	Variable	Cod	Real basic value (0)	Variation step	Maximum real value (+1)	Minimum real value (-1)
1	Temperature (^{0}C)	X_1	70	8	78	62
2	Time (hours)	X_2	6	2	8	4
3	Mass ratio gr.catalyst/gr. m-nitrobenzoic acid	X_3	0.417	0.167	0.584	0.250

The plan of the factorial experiment, of 2^3 type, along with experimental yields Y(%), as the real answer of the system are given in Table 5.

Table 5. Experimental matrix

Exp.no.	X_1	X_2	X_3	Y(%)
1	1	1	1	92.5
2	1	-1	1	83.6
3	1	-1	-1	60.8
4	1	1	-1	81.12
5	-1	1	1	67.8
6	-1	1	-1	49.05
7	-1	-1	1	54.72
8	-1	-1	-1	42.15
9	0	0	0	83.7
10	0	0	0	82.9
11	0	0	0	83.8
12	0	0	0	85.1

Validation of the model

The validation of the model was carried out by an appropriate analysis of variance. The *Fisher test* was applied to determine the F value, with Eq. (4) [9]:

$$F = \frac{(n-1)\sum_{i=1}^{n}(Y_{ei} - \overline{Y}_e)^2}{(k-1)\sum_{i=1}^{k}(Y_{eki} - \overline{Y}_{ek})^2} \tag{4}$$

where:

Y_{ei} = the experimental values of the dependent variable (yield %);

$\overline{Y}_e$ = the average value of the dependent variable;

Y_{eki} = the experimental values of dependent variable into the center of the programme;

$\overline{Y}_{ek}$ = the average value of the experimental values into the center of the programme;

n = the total number of experiments from the experimental matrix;

k = the number of experiments into the centre of the programme.

The fitted model is considered adequate if the variance due to the lack of fit is not significantly different from the pure error variance.

F value calculated with Eq. (4) is compared with F_{tab} the value of quantile for the F distribution for certain significance level and degree of freedom [3, 8, 9].

If $F>Ftab$ it can be said that the deviation of the experimental data from the average value is not the result of experimental errors, but it is determined by the influence of independent variables (temperature, duration of estherification process and mass ratio gr.catalyst/gr. m-nitrobenzoic acid) on the yield.

The multiple correlation coefficients are also calculated in order to establish the correlation between the dependent variable and the three independent variables as a whole Eq. (5) [8]:

$$R_{YX_1X_2X_3} = \sqrt{1 - \frac{\sum_{i=1}^{8}(Y_{ei} - \overline{Y}_i)^2}{\sum_{i=1}^{8}(Y_{ei} - \overline{Y}_e)^2}} \quad (5)$$

If the $R_{YX_1X_2X_3}$ value is close to the unity, the independent variables have a significant importance on the dependent variable.

The significance of coefficients was evaluated using the *Student test*, for certain significance level and degrees of freedom [7, 8, 10]. The deviation of the calculated values with the proposed model and experimental data must be between +10 and -10 for a good accordance. The optimal values of independent variables are calculated using the *Solver* instrument of *MS Excel*.

Coefficients computation

The coefficients of the model were calculated using the relations (2).

The values from statistical table of the *Fisher test* is $F_{tab}(\alpha=0,05,\ v1=N-(k+1)=8$ *şi* $v2=m0-1=3) =8.84$ and the calculated value is $F=183.77$.

Because $F>F_{tab}$, it results that the deviation of experimental values from the average value is not the result of experimental errors, but is determined by the influence of independent variables.

The equation of the model is expressed by Eq. (6):

$$Y = 66.4675 + 13.0375X_1 + 6.15X_2 + 8.1875X_3 + 1.155X_1X_2 - 2.2X_1X_2X_3 \quad (6)$$

The correlation coefficients have the following values: $R_{YX_1X_2X_3}$ = 0.99802 close to unity. This fact demonstrates the important influence of the independent variables on the dependent variable. (Table 6).

Table 6. Significance of the mathematical model

Exp. no.	X_1	X_2	X_3	Y(%)	Y_{calc}(%)	Deviation(%)
1	1	1	1	92.5	92.80	0.321
2	1	-1	1	83.6	82.59	-1.226
3	1	-1	-1	60.8	61.81	1.638
4	1	1	-1	81.12	80.82	-0.368
5	-1	1	1	67.8	68.81	1.471
6	-1	1	-1	49.05	48.04	-2.108
7	-1	-1	1	54.72	54.42	-0.547
8	-1	-1	-1	42.15	42.45	0.701

Testing the model coefficients by using the *Student test* leads to the conclusion that b_{13} and b_{23} coefficients are insignificant for *Y*.
The calculated deviations are between +10 and –10 and a good accordance between experimental values and calculated values exists.

Analysis of the mathematical model

The optimization method leads to the conclusion that this function has a maximum distinct, point. For this function, is calculated the yield into *maximum point*. The maximum point is X_1 = 1.21, X_2 = 0.58 and X_3 = 1.12 corresponding to a yield of 94 %. Transposed to real variables, these values correspond to a temperature of 80^0C, reaction time of 7.2 hours and a mass ratio gr.catalyst/gr. m-nitrobenzoic acid of 0.6.

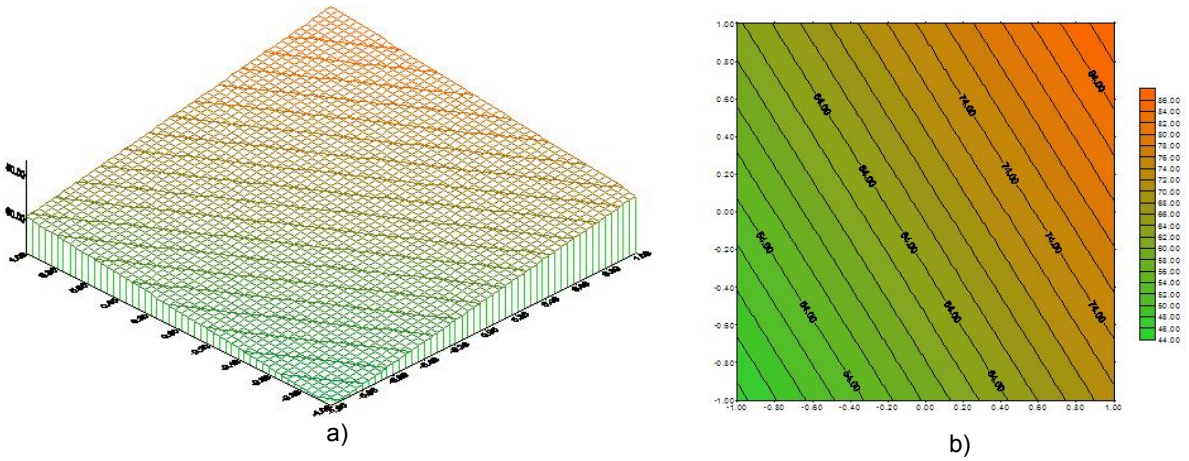
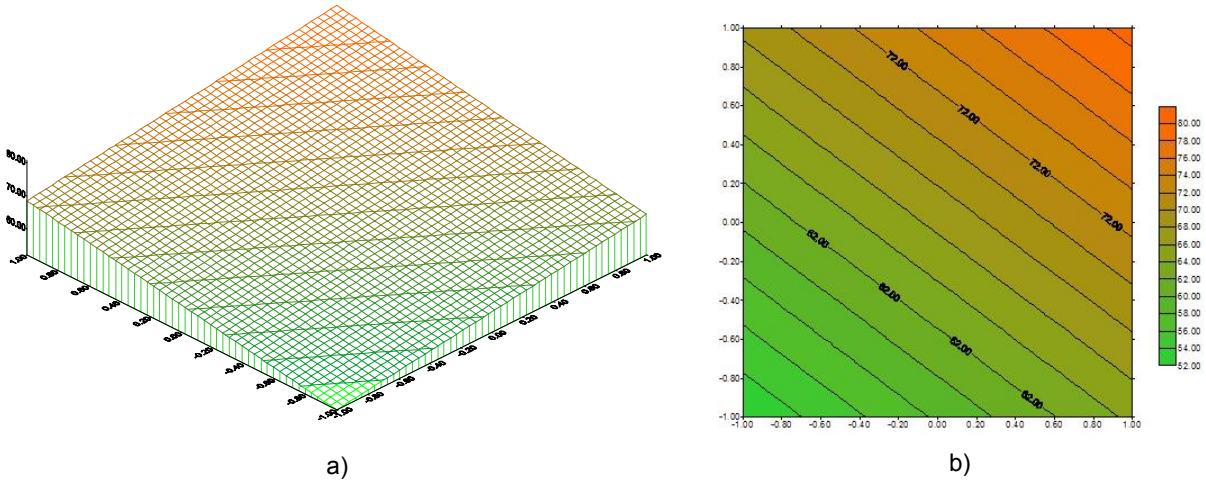
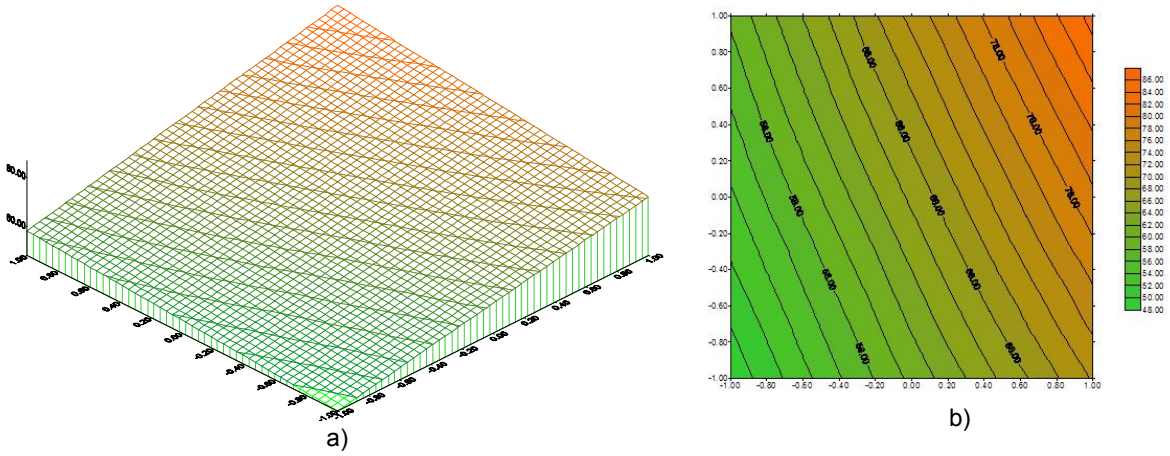


Figure 5. Variation of *Y* function vs X_1 and X_3 variables, $Y=Y(X_1,0,X_3)$: a) three-dimensional; b) isolines.



a) b)

Figure 6. Variation of *Y* function vs X_2 and X_3 variables, $Y=Y(0,X_2,X_3)$: a) three-dimensional; b) isolines.



a) b)

Figure 7. Variation of *Y* function vs X_1 and X_2 variables, $Y=Y(X_1,X_2,0)$: a) three-dimensional; b) isolines.

The analysis of the expression for Y function (Eq. 6) leads to the conclusion that the X_1 variable (temperature, ^{0}C) exhibits the most important influence on the yield of the estherification of m-nitrobenzoic acid with ethanol. The influence of X_1 variable is almost 6.68875 times higher than of X_2 and almost of 4.85 times higher than X_3.

Figs. 5, 6 and 7 show the dependence of the yield *Y* on X_1 and X_3 variables, or X_2 and X_3 variables, or X_1 and X_2 variables.

Conclusions

Even if the estherification process is known for quite some time, the case of heterogeneous catalysis was very poorly studied.

Thus, this paper is focused on catalysis nature influence on the global yield. So we compared the reaction performances in the case of homogeneous reaction (using H_2SO_4 as catalyst) versus heterogeneous catalyzed reaction (using Dowex-50).

By laboratory scale experiments we determined that by using the heterogeneous catalysis higher yields are obtained.

It was also studied the influences of three parameters, such as: reaction temperature and time and also of the amount of catalyst Dowex-50 on the global yield.
The gathered data were used for mathematic modeling and optimization of the studied estherification process. An empirical model was elaborated by a 2^3 factorial experiment design type, considering temperature, duration of estherification process and mass ratio gr.catalyst/gr. m-nitrobenzoic acid as independent variables, while the yield was chosen as optimization criteria. The mathematical model was verified and found adequate, the average deviation having value of -0.015 %, being within admissible limits of deviation (±10 %).
The optimal values of independent variables were determined that corresponds to a temperature of 80^0C, a time of 7.2 hours and mass ratio gr.catalyst/gr.m-nitrobenzoic acid of 0.6.
An analysis of the model was performed in order to apply this process for efficient synthesis of pesticides with antifungal activity and to discuss the influence of variables on estherification process of m-nitrobenzoic acid with ethanol. The model was found adequate.

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