Neural Network Based Modelling of Ethyl-2-Chloro-Phenoxy Acetate Chlorosulphonation Process

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The most difficult and costly step in the industrial manufacturing of the Romener® drug is the chlorosulphonation of ethyl 2-chloro-phenoxyacetate, which is influenced by three main parameters: molar ratio between the reagents, temperature and time. In order to establish the optimum reaction conditions, a planned factorial experiment of first-degree order was accomplished, in which the real values of the parameters and their limits of variation were chosen arbitrarily. Feedforward neural networks with a single hidden layer were used in direct and inverse modeling of the process, to predict the yield of the reaction for different reaction conditions and the reaction conditions for a pre-established yield. The neural modeling of the cholorosulphonation process enabled to settle the optimum values of the parameters for a maximum yield in ethyl 2-chloro-4-chlorosulphonyl-phenoxyacetate. A real and complete characterization of the chlorosulphonation process was accomplished by neural network based modeling.

Keywords: chlorosulphonation, ethyl 2-chloro-4-chlorosulphonyl-phenoxyacetate, Romener®, neural networks, mathematical modeling

The key intermediate in the industrial manufacturing of the Romener® drug is the ethyl 2-chloro-4-chlorosulphonyl-phenoxyacetate, obtained by the chlorosulphonation of ethyl 2-chloro-phenoxyacetate [1-5]. The Romener® acts on the central nervous system being clinically used as antidepressant, anticonvulsant, and cerebral stimulant medication [6]. In order to obtain a maximum yield in ethyl 2-chloro-4-chlorosulphonyl-phenoxyacetate,the chlorosulphonation process was carried out under different conditions by varying the main parameters influencing the process under study.

Nowadays the high complexity of most processes increases the demand for performant models. Most of these processes are highly non-linear and dynamic, requiring complex modeling techniques. Neural networks are eligible modeling candidates for such processes, since they have the ability to map a variety of input-output patterns quite easily. Neural networks can learn what happens in the process without actually modeling the physical and chemical laws that govern the system, so they are useful for modeling complex non-linear processes where understanding is limited.

Many approaches are known in literature about efficient modeling of chemical processes using neural networks. Some examples of modeling methodologies can be enumerated: *direct modeling* [7-9], neural networks based on *soft sensors* [10], *inferential modeling* [11], *inverse neural network modeling* [12-14]. Different types of neural networks are used in the chemical reaction engineering, the type of the network being correlated with the nature of the application and of the chemical system: *feedforward neural networks* for stationary conditions [13, 14], *recurrent neural networks*, useful for long term predictions [15], *stacked neural networks* [16], *hybrid models*, which combine phenomenological models with neural ones [17], *neural networks trained with static and dynamic operating data* [18]. These problems are reviewed in our previous work [19].

The present paper emphasizes the utility of using neural networks for chlorosulphonation process modeling. Simple topologies of neural networks provide accurate and complete information about the reaction. On one hand, the reaction yield is predicted for different working conditions and, on the other hand, the reaction conditions are determined to lead to an imposed yield. In this way, experiments are avoided, saving time and materials. The novelty of the paper consists in a new methodology for chlorosulphonation process modeling that provides useful information for the chemical synthesis.

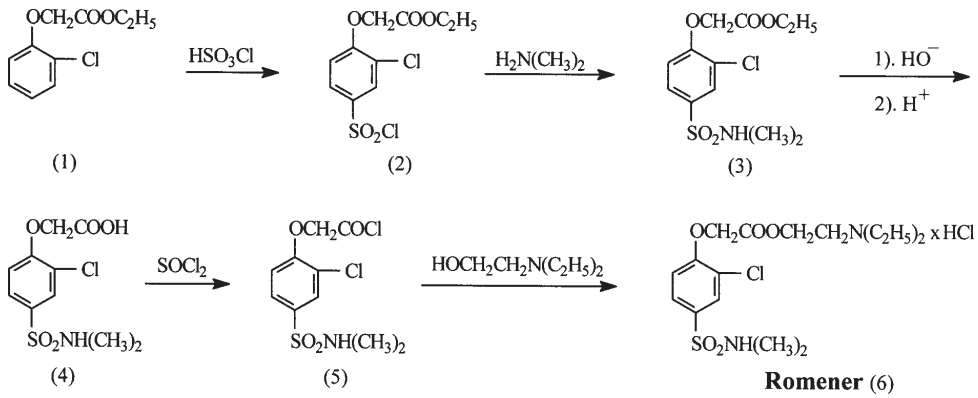

Fig. 1. Synthetic route for Romener® obtaining

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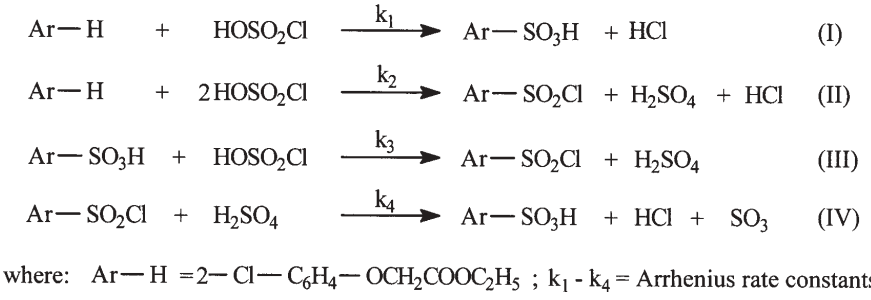

Fig. 2. The main reactions describing the ethyl 2-chloro- phenoxyacetate chlorosulphonation process

Experimental part

The Romener® is industrially manufactured starting from ethyl 2-chloro-phenoxyacetate (1) which, by cholorosulphonation, gives the 2-chloro-4-chlorosulphonyl-phenoxyacetate (2). By amidating (2) with dimethylamine, ethyl 2-chloro-4-dimethylamidosulphonyl-phenoxyacetate (3) is obtained and submitted subsequently to hydrolyze to the acid (4). The reaction of the last with $SOCl_2$ provides 2-chloro-4-dimethylamidosulphonyl-phenoxyacethyl chloride (5) that finally reacts with dimethylaminoethanole to afford Romener (6) (fig. 1).

The key step in the Romener technological process is the chlorosulphonation of ethyl 2-chloro-phenoxyacetate, described by the pseudo-equilibrium main reaction I-III, and the side reaction IV (fig. 2).

From a kinetic study of the chlorosulphonation process, equation (1) that describes the qualitative distribution of the reaction products at pseudo-equilibrium moment was derived [6].

$$C_{CISE}/C_{SE} = k_3[C_{Eo}(M-1) - C_{CISE}]/k_4(C_{H2So4} + C_{CISE}) \quad (1)$$

where:

C_{Eo} is initial concentration of ethyl 2-chloro-phenoxyacetate [mol/L];

C_{CISE}- momentary concentration of chlorosulphonated ester [mol/L];

C_{SE} - momentary concentration of sulphonated ester [mol/L];

C_{H2SO4} - initial concentration of H_2SO_4 in the employed HSO_3Cl [mol/L];

M - chlorosulphonic acid/ester molar ratio.

According to equation (1), the parameters that influence the chlorosulphonation are the following: chlorosulphonic acid/ester molar ratio, *M*, temperature, *t*, through the Arrhenius rate constants k_3 and k_4, concentration of H_2SO_4 in HSO_3Cl, C_{H2SO4}, and time, τ, taking into account the fact that the chlorosulphonation is a pseudo-equilibrium process. The influence of C_{H2SO4} can be avoided by adding SO_3 or pyrosulphuryl chloride in the reaction system.

In order to settle down the optimum reaction conditions which afford a maximum yield in 2-chloro-4-chloro-sulphonyl-phenoxyacetate, a planned factorial experiment of first-degree order was followed, the limits of variation for the three considered parameters (*M*, *t* and τ) being given in table 1.

The general experimental procedure applied for the synthesis of 2-chloro-4-chlorosulphonyl-phenoxyacetate is the following: 10 g ethyl 2-chloro-phenoxyacetate (0.05 mole) were added dropwise in about 15 min over various amounts of chlorosulphonic acid (as noticed in the factorial experiment, *i.e.* molar ratio toward the ester: 2.5 (13.57 g; 7.75 mL), 4.5 (24.16 g; 13.75 mL) and 6.5 (34.83 g; 19.87 mL)) cooled at 5°C, so that the temperature was maintained bellow 10°C over the period of reagents

Table 1
EXPERIMENTAL DATA

No.	M	t (°C)	τ (h)	η
1	2.5	25	0.8	16.43
2	2.5	35	0.8	17.12
3	2.5	35	1.6	41.09
4	2.5	25	1.6	17.22
5	6.5	35	1.6	95.89
6	6.5	25	0.8	95.20
7	6.5	25	1.6	98
8	6.5	35	0.8	89.04
9	4.5	30	1.2	84.52
10	4.5	30	1.2	84.24
11	4.5	30	1.2	82.83
12	4.5	30	1.2	85.69

contacting. The reaction mixture was then stirred at the temperature (25°C, 30°C, and 35°C, respectively) and the time (0.8, 1.2 and 1.6 h) prescribed in the factorial experiment. The chlorosulphonated ester was isolated by precipitation on a water-ice mixture followed by filtration, washed with water to a neutral *p*H and finally dried under vacuum. The product resulted as a white powder melting at 70°C.

Neural network modeling

When a neural network approach to a problem is used, what is usually sought is some kind of a model, which represents the transformation from a set of inputs to a set of outputs. Such a model is obtained by *training* the network. In the training phase, the network is repeatedly presented with input/output pairs, which have to be related by the transformation, which is being modeled. The advantage of a neural network is that it can then *generalize* (within limits) from these examples to other inputs that were not seen yet. As a rule, the model is sought from an available set of data that clearly contain a number of very interesting relationships, feature correlations and other information, which cannot be deduced in a straightforward manner from the first principles, by theoretical calculations or even with numerical methods [20].

The *architecture* of a neural network is determined by the manner in which the outputs of the neurons are connected to other neurons. In the standard architecture, the neurons of a network are divided into several groups called layers. Basically, single and multiple layer architecture are possible. A *multi-layer neural network* has *input, hidden* and *output layers* consisting of input, hidden and output neurons, respectively. The most common neural network architecture is the *multi-layer*

feed-forward neural network (often called *multi-layer perceptron, MLP*).

In this work, the number of hidden layers and units was established by training a different range of networks and selecting the one that best balanced generalization performance against network size.

Firstly, the data are split into training and validation data sets because it is more important to evaluate the performance of the neural network on unseen data than training data. In this way, we can appreciate the most important feature of a neural model - the generalization capability.

The best network topology was determined based upon the mean of squared errors (MSE) on the training data. Hidden neurons as well as output layer neuron use hyperbolic tangent as non-linear activation functions. The network was trained using the back propagation algorithm. We consider that the training is terminated at the point where the network error (MSE) becomes sufficiently small.

The mean squared error was computed using the following formula:

$$MSE = \frac{\sum_{j=1}^{P}\sum_{i=1}^{N}(d_{ij} - y_{ij})^2}{N \cdot P} \quad (2)$$

where:

P is the number of output processing elements (in this case, $P = 1$),

N - the number of exemplars in the data set, y_{ij} is the network output for exemplar *i* at processing element *j*, and d_{ij} is the desired output for exemplar *i* at processing element *j*.

The inputs of the neural networks projected were molar ratio, *M*, temperature, *t*, and time, τ, and the output is the yield of the reaction, η (table 1). A topology with a single hidden layer with 5 neurons was obtained, having a good performance in the training phase: MSE = 0.000145 and r = 0.999 (the correlation between the experimental data and the output of the neural network). This feedforward neural network can be noted as MLP (3:5:1), referring to the number of neurons in the input, hidden and output layers, respectively (fig. 3).

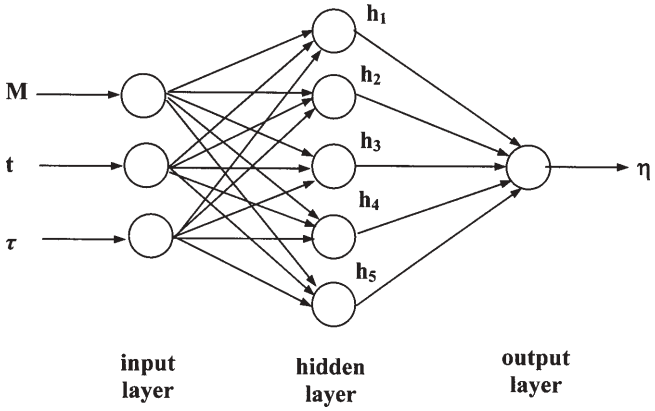

Fig. 3. MLP (3:5:1) for reaction yield modelling

The direct neural modeling allows the estimation of the reaction yield for different reaction conditions (molar ration between reactants, temperature, time), even for the situations where experimental data are not available.

Neural networks can also solve an inverse problem: imposing the final yield and the working conditions – temperature and time – what is the optimal value for the molar ratio? A neural network which answers to such a problem has *t*, τ and η as inputs and *M* as output. Several tests in inverse neural network modeling led to an optimal topology MLP (3:5:1) with MSE = 0.000123 and r = 0.999 for the training phase.

In this paper, a special software application - *NeuroSolutions* - was used in order to project and obtain predictions of neural networks.

Results and discussions

The predictions of the neural networks on the training data from table 1 were compared to the experimental ones in order to verify how the networks projected for direct and inverse neural modeling have learned the behaviour of the process. The correlation between the two sets of data, over 0.99 and MSE less than 0.00015, shows a good concordance between the model and the experimental results. This fact is also emphasized in figures 4 and 5, which present the neural network predictions and the experimental yield at different temperatures and molar ratios.

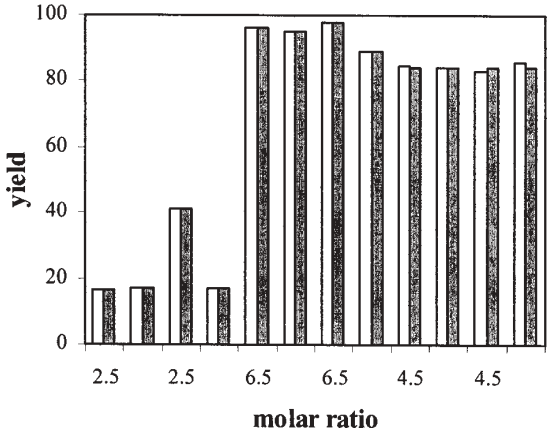

Fig. 4. Reaction yield variation with molar ratio obtained as neural network prediction (gray bars) on training data and by experiments (white bars)

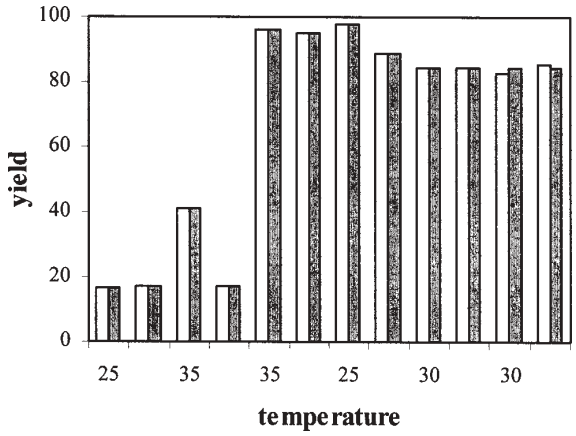

Fig. 5. Reaction yield variation with temperature obtained as neural network prediction (gray bars) on training data and by experiments (white bars)

A key issue in neural network based process modeling is the robustness or generalization capability of the developed models, *i.e.* how well the model performs on unseen data. Thus, a serious examination of the accuracy of the neural network results requires the comparison with experimental data, which were not used in the training phase (previously unseen data). That is why the validation data sets (supplementary experimental data) were considered and the training process was carried out without them. The predictions of the networks on validation data are given in table 2.

Table 2
PREDICTIONS OF MLP (3:5:1) IN VALIDATION PHASE OF DIRECT MODELING

M	t (°C)	τ (h)	η experimental	η network
4	30	1.8	62	71
4.5	35	1.5	76	79
5	38	2.1	84	89
6	36	1.6	92	95
6.5	32	2.1	93	97
7	34	1.9	95	97

One can notice a satisfactory agreement between the two categories of data: experimental and neural network predictions. For this reason the projected neural model MLP (3:5:1) can be used to make predictions under different reaction conditions, substituting the experiments that are time and material consuming. Table 3 is an example of obtaining and interpreting the simulation results. The predictions follow the general trend of parameter variation, even that an extrapolation is performed for M = 8.

A multitude and diversity of information can be extracted from the data in table 3. For instance, for a molar ratio bellow 4, the maximum yield in chlorosulphonated ester, η_{max}, does not exceed 75. 36 % even at the highest limits of the temperature and duration considered in the experiment. Moreover, for *M* values above 5.5, the increasing of η_{max} is insignificant (*e.g.* for M = 5.5, t = 30°C and τ = 2h, η = 98.03 %, whereas for M = 8, t = 25°C and τ = 2h, η = 98.53 %). The general trend can be noticed that for the same reaction duration the temperature required for the maximum yields decreases with increasing molar ratio.

Graphical representations (figs. 6 a-f) of the yield versus time for the three considered values of the temperature (*i.e.* 25°C, 30°C, and 35°C, respectively) in the range of M = 4-7, afford the following observations: for *M* varying from 4 to 5, the increase of temperature from 25°C to 35°C results in a significant rise of η_{max} (*e.g.* for M = 4, t = 25°C and τ = 2 h, η = 51.75 %, while for M = 4, t = 35°C and τ = 2 h, η = 95.85 %), whereas for the same period, the increase of the temperature from 30°C to 35°C does not bring noticeable improvements of η_{max}. For instance, with M = 5.5 and τ = 2 h, the yield curves at 30° and 35°C are almost overlapped. Following up the yield curves for molar ratios higher than 5.5 one can observe that η_{max} in chlorosulphonated ester is obtained for lower temperatures. Thus, for τ = 2 h and M = 5.5, η_{max} values are to be found on the curves plotted for t = 30°C, and for M = 7.5, η_{max} values are obtained at 25°C, an inversion of the yield curves related to the temperature being noticed.

The decrease in the chlorosulphonated ester yield with increasing temperature for M > 5 could be explained by the increase of the k_4 constant in equation (1), on one hand, and by the C_{H2SO4} increase as a consequence of the increased amount of used HSO_3Cl, on the other hand. The both above-mentioned factors cause the pseudo-

Table 3
NEURAL NETWORK PREDICTIONS IN DIRECT MODELING

M	t (°C)	τ (h)	η
3	25	1	18.14
3	25	1.5	20.78
3	25	2	40.76
3	30	1	19.39
3	30	1.5	32.93
3	30	2	63.49
3	35	1	32.47
3	35	1.5	55.26
3	35	2	67.93
3.5	25	1	21.94
3.5	25	1.5	34.84
3.5	25	2	69.10
3.5	30	1	30.40
3.5	30	1.5	60.31
3.5	30	2	77.86
3.5	35	1	57.39
3.5	35	1.5	69.39
3.5	35	2	75.36
4	25	1	23.39
4	25	1.5	32.92
4	25	2	51.75
4	30	1	51.15
4	30	1.5	76.57
4	30	2	89.00
4	35	1	77.47
4	35	1.5	91.14
4	35	2	95.85
4.5	25	1	37.64
4.5	25	1.5	59.25
4.5	25	2	79.52
4.5	30	1	77.04
4.5	30	1.5	90.57
4.5	30	2	95.10

M	t (°C)	τ (h)	η
4.5	35	1	85.49
4.5	35	1.5	93.82
4.5	35	2	97.06
5	25	1	65.40
5	25	1.5	83.87
5	25	2	92.31
5	30	1	89.12
5	30	1.5	95.22
5	30	2	97.19
5	35	1	88.50
5	35	1.5	94.80
5	35	2	97.58
5.5	25	1	86.15
5.5	25	1.5	93.56
5.5	25	2	96.41
5.5	30	1	93.24
5.5	30	1.5	96.85
5.5	30	2	98.03
5.5	35	1	89.72
5.5	35	1.5	95.15
5.5	35	2	97.82
6	25	1	93.83
6	25	1.5	96.69
6	25	2	97.85
6	30	1	94.68
6	30	1.5	97.52
6	30	2	98.42
6	35	1	90.28
6	35	1.5	95.21
6	35	2	97.91
6.5	25	1	96.40
6.5	25	1.5	97.84
6.5	25	2	98.44

M	t (°C)	τ (h)	η
6.5	30	1	95.20
6.5	30	1.5	97.82
6.5	30	2	98.63
6.5	35	1	90.58
6.5	35	1.5	95.12
6.5	35	2	97.90
7	25	1	97.37
7	25	1.5	98.34
7	25	2	98.73
7	30	1	95.34
7	30	1.5	97.94
7	30	2	98.74
7	35	1	90.73
7	35	1.5	94.92
7	35	2	97.83
7.5	25	1	97.37
7.5	25	1.5	98.17
7.5	25	2	98.50
7.5	30	1	96.22
7.5	30	1.5	97.63
7.5	30	2	98.24
7.5	35	1	94.18
7.5	35	1.5	96.66
7.5	35	2	97.76
8	25	1	97.54
8	25	1.5	98.21
8	25	2	98.53
8	30	1	96.61
8	30	1.5	97.74
8	30	2	98.29
8	35	1	95.07
8	35	1.5	96.95
8	35	2	97.87

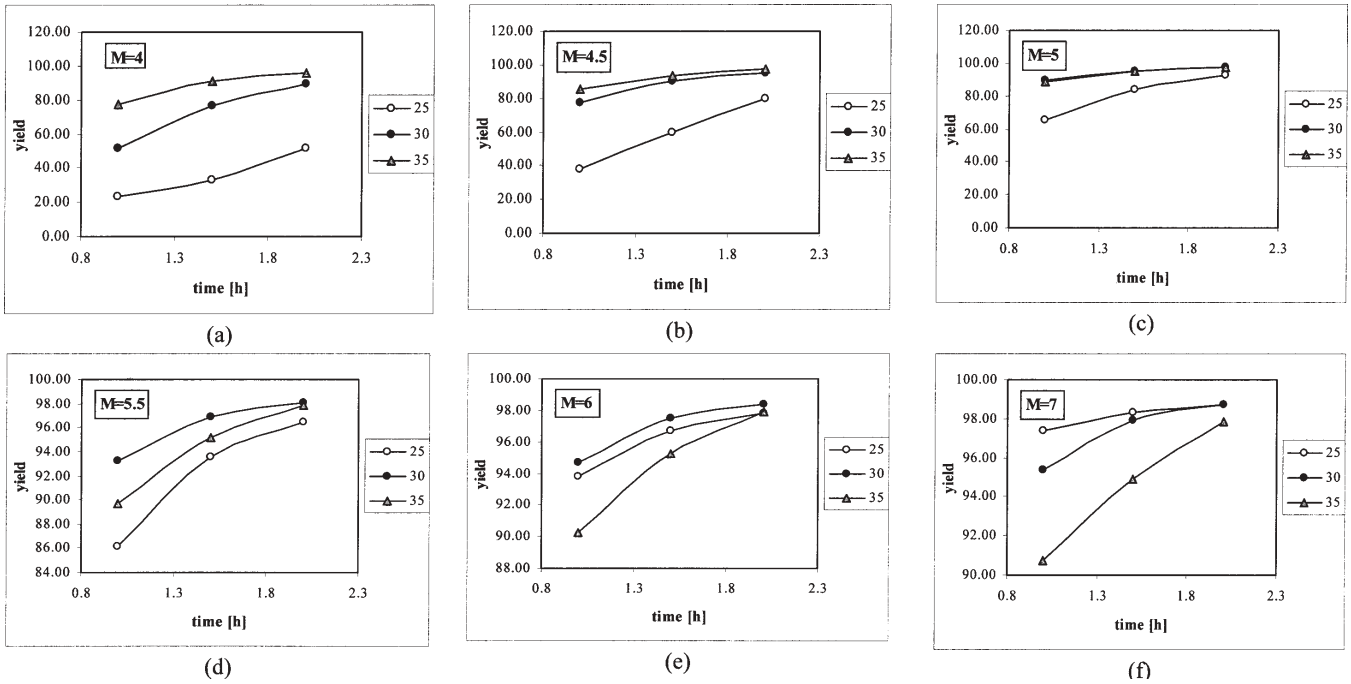

Fig. 6. Variation in time of the predicted yield for different molar ratios

Table 4
NEURAL NETWORK PREDICTION IN INVERSE MODELLING

No.	t (°C)	τ (h)	η	M
1	25	2	96	6.37
2	25	2	97	6.42
3	25	2	98	6.45
4	**30**	**2**	**96**	**4.47**
5	**30**	**2**	**97**	**4.47**
6	**30**	**2**	**98**	**4.48**
7	35	2	96	6.36
8	35	2	97	6.37
9	35	2	98	6.39

equilibrium shifting toward the side reaction of chlorosulphonated ester hydrolysis to sulphonic acid, according to reaction (IV). Taking into account all these observations, in order to obtain maximum values for the chlorosulphonation yield for the duration of 2 h, the reaction can take place either at M = 4 -5.5 and t = 30 - 35°C or at M > 5.5 and t = 25 - 30°C.

Due to the fact that the differences between η_{max} obtained for smaller molar ratios and higher temperatures versus higher molar ratios and smaller temperatures are insignificant (*e.g.* for M = 5 at 35°C, η_{max} = 97.5 whereas for M = 7 at 25°C η_{max} = 98.73) and, moreover, the temperatures values required for the process are low and not energy-consuming results that at the industrial level is preferable to work at M = 4.5 - 5 and 35°C. This conclusion is also supported by the fact that after chlorosulphonation, the excess of the HSO_3Cl is destroyed with a water-ice mixture, which for higher *M* gives greater amount of acidic water wastes.

Neural modeling of the ethyl 2-chloro-phenoxyacetate chlorosulphonation offers more accurate results as compared with the empirical modeling using statistic methods and regression equations from which the optimum values deduced for the parameters were: M = 7, t = 32°C and τ = 2 h [21].

Supplementary information is obtained by inverse neural modeling, with MLP (3:5:1), an optimization problem that represents the identification of reaction conditions (molar ratio), which leads to an imposed reaction yield, with pre-established temperature and time. Table 4 contains a series of predictions produced by neural model. It is very interesting and important to find out that a high yield (within the domain 96 ÷ 98) results for t = 30°C, *t* = 2 h and relatively small molar ration M = 4.5, instead of other reaction conditions that imply high values for molar ratio. The optimal solutions are numbered 4, 5 and 6 and are bold marked in table 4.

Conclusions

The chlorosulphonation of ethyl 2-chloro-phenoxyacetate to obtain ethyl 2-chloro-4-chlorosulphonyl phenoxyacetate is the key step in the industrial manufacturing of the Romener®, which is a drug acting on central nervous system. The main parameters influencing the chlorosulphonation process (*i.e.* molar ratio between the reagents, temperature and time) were established by a kinetic study. In order to find out the optimum conditions affording the maximum yield in ethyl 2-chloro-4-chlorosulphonyl-phenoxyacetate, a planned factorial experiment of first-degree order was accomplished, in which the real values of the process variables and their limits of variation were chosen arbitrarily.

Simple feedforward neural networks were used for direct and inverse modelling of the process. MLP (3:5:1), with molar ratio, temperature and time as input variables and 5 hidden neurons into an intermediate layer accurately predicted the yield of the reaction in a direct modeling. An inverse neural modeling is performed with MLP (3:5:1) and represents the identification of reaction conditions (temperature, time and molar ratio), which leads to an imposed reaction yield. The main conclusion of this procedure is that the optimum values of the parameters which afford a maximum yield in 2-chloro-4-chlorosulphonyl phenoxyacetate are the following: chlorosulphonic acid/ethyl 2-chloro-phenoxyacetate molar ratio = 4.5 - 5, temperature = 35°C and time = 2 h.

We can conclude that direct and inverse neural network modelling technique describes well the behaviour of the real chlorosulphonation process. Consequently, the

accurate predictions obtained by simulations on neural model are useful information for the chemical synthesis.

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