Optimization and Modeling of Glyphosate Removal by Nanofiltration at a Pilot Scale, Using Response Surface Methodology

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Abstract The removal of glyphosate by nanofiltration of contaminated water with a glyphosate commercial formulation at a pilot scale was studied. The combined effect of glyphosate concentration in feed [Gly], pH and the transmembrane pressure (TMP) at 20 °C was investigated and optimized for the first time using Response Surface Methodology. The optimum values of these factors were 160 mg/L, 10 and 4 bar respectively. A rejection of glyphosate of 99.6% was estimated and verified under these optimal conditions. Glyphosate remaining in permeate was below the limit established by the U.S. EPA (0.7 mg/L). The acute toxicity tests with fish in permeate showed that the rest of the toxic components of the glyphosate formulation were also removed. The high rejections of glyphosate despite its molecular weight below the molecular weight cut-off of the membrane were related to the combined effect of Donnan Exclusion and Dielectric Exclusion. The adjusted model was adequate with an $R^2 = 0.96$. The linear and quadratic effects of pH and [Gly] factors were statistically significant (p_{value} <0.05), as well as the antagonistic interaction between the two factors. The pH was the factor with major effect on rejection, followed by [Gly], the TMP effects were not relevant from the practical point of view.

Keywords: glyphosate, nanofiltration, modeling, optimization, design of experiments, response surface methodology

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1. Introduction

Glyphosate (n-phosphonomethyl glycine) which is an active ingredient in several commercial products, is an organophosphate herbicide of wide spectrum, post-emergent and non-selective. In recent years, its use has grown significantly. For example, in the US, the use of glyphosate increased by 10,000 tons per year from 1992 to 80,000 tons in 2007 [1]. In Argentina, the use of glyphosate increased from 1 million to 180 million liters from 1997 to 2007 [2].

While the amount of herbicides present in water varies considerably among regions, all ecosystems are polluted [3]. Even though many studies have reported low concentrations, some others have reported glyphosate concentrations as high as 1700 µg/L [4]. According to a research performed by the United States Geological Service, glyphosate can be listed as the most common pesticide detected in the monitoring of water contamination in that country [5].

Initially, glyphosate is a free acid which is then converted into a salt to increase its solubility in water. Commercial formulations are obtained from the salt; a large number of them are based in glyphosate isopropylamine (IPA) salt [6]. The most common

commercial formulations of glyphosate are the following: Roundup Original, Roundup Ultra Max, Honcho, Glyphomax, Glyphomax Plus, Cornerstone, Glyfos, Credit. These formulations generally include a surfactant that improves the capacity of glyphosate to penetrate the cuticle of plants. For the least common formulations, the information about the surfactants present in them is not reported by the manufacturers. This must be understood as a matter of serious concern considering the several studies that have proved that the presence of surfactant makes the commercial product even more toxic that glyphosate in technical degree, as well as a salt or as free acid [7,8]. Intoxication in human beings depends on all the components of the formulation [9].

Recently, in March 2015 a research team of 17 experts from 11 countries met at the International Agency for Research on Cancer IARC which is an agency specialized in cancer of the World Health Organization. In this meeting the carcinogenicity of herbicide glyphosate was classified as probably carcinogenic to humans (Group 2A) [10].

The eventual supply of waters contaminated with herbicides based in glyphosate to water purification plants requires certain procedures, different from the conventional ones. These procedures have to eliminate not only the active agent but also the rest of the components of the formulation. Nanofiltration (NF) eliminated

efficiently glyphosate from aqueous solutions. There are four previous studies, in three of them glyphosate was recovered from saline wastewater of its manufacturing process [11,12,13] in the other study, Saitua et al., 2012, obtained drinking water from water contaminated with a commercial formulation of glyphosate [14]. Beyond the different operating conditions in none of the previous cases the operating factors for the removal of glyphosate were optimized. The present work involves optimization of different factors affecting the removal of glyphosate. General practice for optimizing the process responses consists of varying one factor and keeping the other ones at a constant level (one factor at a time). The major disadvantage of this single variable optimization is the disregard of interactive effects between the studied variables. Consequently, the net effect of various parameters on removal of glyphosate was not exhibited. In order to overcome this problem, optimization studies were carried out using Response Surface Methodology (RSM) [15,16,17]. This technique is an integration of experimental strategies, mathematical methods and statistical inference, used to develop, improve and optimize processes, and it can also be employed to evaluate the relative importance of each one of the factors, even in presence of complex interactions. RSM reduces the number of experimental trials needed to evaluate multiple factors and their interactions. Therefore, it is less laborious and time consuming than other approaches. The main objective of the present paper was to establish for the first time the optimal conditions and the combined effects of the glyphosate concentration in feed [Gly], pH and the transmembrane pressure, TMP, in the removal of glyphosate for NF using RSM. Other objective was to check the overall effectiveness of the process in the elimination of all unknown toxic components of the formulation of glyphosate using acute toxicity test in fish [18].

2. Materials and Methods

2.1. Materials

The spiral-wound membrane used in this research was a NF-300 membrane (GE-Osmonics), a thin-film composite polyamide membrane. According to the manufacturer, this membrane has a nominal molecular weight cut-off of 180 Da. The membrane was characterized as negatively charged in aqueous solution at pH above 4.7 [19].

Studies were performed using a glyphosate commercial formulation, its commercial name is Estrella. This product is delivered by Milkaut Plant, Santa Fe, Argentina. Its active component is glyphosate IPA salt with a 48% w/v concentration. Glyphosate IPA general characteristics have been presented in Table 1. Glyphosate IPA behaves as a strong electrolyte when found in a solution totally dissociated in glyphosate anion and isopropilamine cation. Glyphosate anion is very polar, an amphoteric specie, and soluble in water with high hydrofilicity and high sensitivity to pH.

Table 1. General information of the glyphosate Isopropylamine (IPA) salt

Compound	Glyphosate Isopropylamine (IPA) salt
CAS Number	38641-94-0
Chemical Formula	$C_6 H_{17} N_2 O_5 P$
Molecular Weight	228.18 g/mol
Structural Formula	
Solubility at 25ºC	900000 ppm
Density	1.74 g/ml
Half-life (Avg days)	35
log K_{ow}	-5.4
pH in solution at 1%	4.7

2.2. Acute Toxicity Tests in Fish

Glyphosate commercial formulation toxic effects were evaluated by an Acute Toxicity Test which uses fish as experimental model. It is a common technique recommended by U.S. Fish and Wildlife Service Columbia National Fisheries Research Laboratory. The tests were conducted with fish of the poecilia reticulate species reproduced in our laboratory to a size of 0.7-1 cm. For the test, 10 specimens were exposed for a 96 h period in 2 L containers with 1 L of solution. The test evaluated dead fish number in each container after the 96 h period. Dead fish were removed every 24 h. The minimum commercial formulation dose which caused total mortality (100%) contained 38.4 mg/L of glyphosate IPA salt (see Table 2). Fish mortality did not occur when used pure glyphosate acid in concentrations over 100 mg/L. Toxicity tests in NF permeate were performed following the same protocol.

Table 2. Acute toxicity test of the commercial formulation of glyphosate

Test	Volume commercial formulation (μL)	Glyphosate IPA salt, concentration (mg/L)	Fish mortality %
1	100	48	100
2	90	43.2	100
3	80	38.4	100
4	70	33.6	0
5	50	24	0

2.3. Experimental Design

The selected factors and their corresponding experimental levels were determined based on previous experiences [14]. The experimental design used for this investigation was Box-Behnken type for three levels and three factors (13 runs) with two replications in the centre of the plan, considering glyphosate rejection as a response (R_g %) [20]. Table 3 shows the levels of the actual and coded factors

Table 3. Factors levels and coded values used in the experimental design

Factors	Code	-1	0	+1
[Gly] mg/L	X_1	41	132	221
pH	X_2	5	7.5	10
TMP bar	X_3	4	6.5	9

2.4. Nanofiltration Experiment

The experiences were carried out in a nanofiltration pilot plant described in a previous work [19]. The operating temperature was 293 K. The feed flow was fixed at 417 L/h high enough to prevent concentration polarization. The membrane module was operated in the cross-flow mode; both permeate and retentate were recycled. The flow rates were determined using flow meters (Cole-Parmer). Synthetic samples were prepared by adding the required amounts of commercial formulation to distilled water (pH 5.7 ± 0.2 and conductivity 1.0 μS/cm). Several solutions were prepared with different concentrations (41, 132 and 221 mg/L) of glyphosate IPA salt, and then, pH was adjusted with HCI or NaOH (Sigma-Aldrich). Initially 20 L of the feed solution was charged into the feed tank and pumped for 2 h until a steady permeate flux was reached. In all runs the reduction of permeate flow was insignificant regard the permeate flow with distilled water (less than 5%). Samples of permeate and feed were collected and analyzed per triplicate and subsequently, average value was calculated. Fifteen experimental runs were performed at random order (see Table 4). At the end of the each run, an easy washing with distilled water for 1 h was enough to restore the initial permeate flux. The rejection of glyphosate (R_g %) was calculated from the following equation:

$$R_g \% = \left[1 - \left(C_p / C_f\right)\right].100 \qquad (1)$$

where C_p and C_f are the mean concentration of glyphosate in permeate and in the feed solution, respectively.

Glyphosate quantity present in samples was measured as phosphorus (P). The pattern was prepared with a 99% purity glyphosate acid provided by Monsanto. Phosphorus concentrations were measured by USN-ICP-OES using a Sequential Inductively Coupled Plasma Spectrometer (Baird ICP 2070) with ultrasonic nebulization.

2.5. Model Fitting

Using DOE module (STATISTICA 8.0 Stat Soft Inc.), a complete second degree model like the one shown below was adjusted:

$$R_g \% = b_0 + b_1 x_1 + b_2 x_2 + b_3 x_3 + b_{11} x_1^2 + b_{22} x_2^2$$
$$+ b_{33} x_3^2 + b_{12} x_1 x_2 + b_{13} x_1 x_3 + b_{23} x_2 x_3 + \varepsilon \qquad (2)$$

where "b" represents regression coefficients of the model, found by the least squares method, x_i are the factors or codified variables; and ε is the statistic error or residual.

The statistical significance test of the model was developed through Analysis of Variance (ANOVA); to perform the same test for individual coefficients Student's t-test was used. In order to find the most suitable model for the experimental results, insignificant coefficients (p value > 0.05) were eliminated step by step, adjusting

once again the model according to other parameters, until the model of minimal bias was found, where the C statistic (which is a measure of the total mean square error for the regression model) is minimum or approximately matches with the number of the *p* model parameters [21].

In order to determine the adequacy of the model, the lack-of-fit test, the graphic analysis of the residuals and the adjusted coefficient of multiple determination (R^2_{adj}) criteria were used. The lack-of-fit test was performed by means of ANOVA, where the sum of squares due to residuals SS_R was divided in two components, sum of square due to pure error SS_{PE}, and sum of square due to lack-of-fit SS_{LOF}. A test statistic was calculated $F_0 = MS_{LOF}/ MS_{PE}$, which was compared to Fisher F statistic tabulated $F_{\alpha,m-p, m-n}$; if $F_0 < F_{\alpha,m-p, m-n}$ there was no evidence of lack-of-fit of the model, thus, it was possible to combine the mean square lack-of-fit MS_{LOF} and the mean square pure error MS_{PE} to estimate the residual variance σ^2.

Since the hypothesis testing procedures used to determine the statistical significance of the model parameters assumed that the ε_i were normal and independently distributed with media zero and a constant variance σ^2, it was necessary to verify that no residuals or error assumptions were disrupted. This was made by analysing the following plots: the normal probability plot of the residuals, the estimated values versus the residuals and residuals versus the order followed by the experimental runs. Finally, the tridimensional response surface and its contours (constant response curves) were drawn from the adjusted model. From this plot, the optimum point was directly located and the effect of the factors [Gly], pH and TMP on R_g % response was analysed.

3. Results and Discussion

Table 4 shows the R_g % values for each run of the Box-Behnken experimental design. The high rejections of glyphosate (≥98%) despite its molecular weight below the molecular weight cut-off (MWCO) of the membrane were related to the combined effect of Donnan Exclusion and Dielectric Exclusion [22,23,24]. The high hydrophilicity of glyphosate (hydration of the molecule) also contributed to retention [25].

Table 4. Experimental design for Rejection Glyphosate (Rg %)

Run N°	Coded variables			Actual variables			Response
	X_1	X_2	X_3	[Gly] (mg/L)	pH	TMP (bar)	R_g (%)
1	-1	-1	0	41	5	6.5	98.0
2	1	-1	0	221	5	6.5	98.9
3	-1	1	0	41	10	6.5	99.1
4	1	1	0	221	10	6.5	99.6
5	-1	0	-1	41	7.5	4	99.2
6	1	0	-1	221	7.5	4	99.3
7	-1	0	1	41	7.5	9	98.9
8	1	0	1	221	7.5	9	99.2
9	0	-1	-1	132	5	4	98.9
10	0	1	-1	132	10	4	99.6
11	0	-1	1	132	5	9	98.5
12	0	1	1	132	10	9	99.5
13	0	0	0	132	7.5	6.5	99.3
14	0	0	0	132	7.5	6.5	99.2
15	0	0	0	132	7.5	6.5	99.2

Table 5. Effects estimated for Rg % (complete second degree model)

	Effect	Std. Error	t (2)	p value	-95% Conf. Limit	+95% Conf. Limit
Mean	99.05	0.014	7099.4	0.0000	98.96	99.08
X_1	0.48	0.034	13.9	0.0051	0.33	0.62
X_1^2	0.21	0.025	8.4	0.0138	0.10	0.32
X_2	0.87	0.034	25.4	0.0015	0.72	1.02
X_2^2	0.16	0.025	6.3	0.0241	0.05	0.27
X_3	-0.21	0.034	-6.1	0.0254	-0.36	-0.06
X_3^2	-0.04	0.025	-1.5	0.2677	-0.15	0.07
X_1X_2	-0.21	0.048	-4.4	0.0474	-0.42	-0.01
X_1X_3	-0.04	0.048	-0.8	0.4816	-0.25	0.17
X_2X_3	0.20	0.048	4.1	0.0547	-0.01	0.40

Table 5 shows the estimated effects for the three studied factors. The pH (X_2) had the major impact on rejection, followed by [Gly] (X_1), showing statistically significant linear and quadratic effects, as well as interactive effect ($X_1.X_2$). Even though, TMP (X_3) linear effect was statistically significant ($p_{value} < 0.05$), however it was very small, therefore being non-relevant from the practical point of view. On the other hand $X_1.X_3$; $X_2.X_3$

and X_3^2 interactive and quadratic effects were not statistically significant.

Several authors have reported that the pH has significant effects on the membrane charge and solute speciation [26,27,28]. The pH increase not only rose the negative charge density of the membrane by a major ionization of it, but also it produced a change in the ionic specie of glyphosate that also increased its negative charge. Figure 1 shows the fraction of the different glyphosate ionic species as a function of pH. For example, at a pH below 6, there were two ionic species present H_2G^{-2} and HG^{-3} with two and three negative charges respectively and in a 50% (F = 0.5) each one. At a pH = 7.5 the present specie in a 100% had three negative charges. The increased charge density of the membrane and the negative charge of glyphosate incremented the electrostatic repulsion. All the above mentioned explained the remarkable effect of pH on rejection shown by the model. Song et al., 2013 have observed the same behavior in the recovery of glyphosate from saline wastewater using hollow fiber nanofiltration membranes [13].
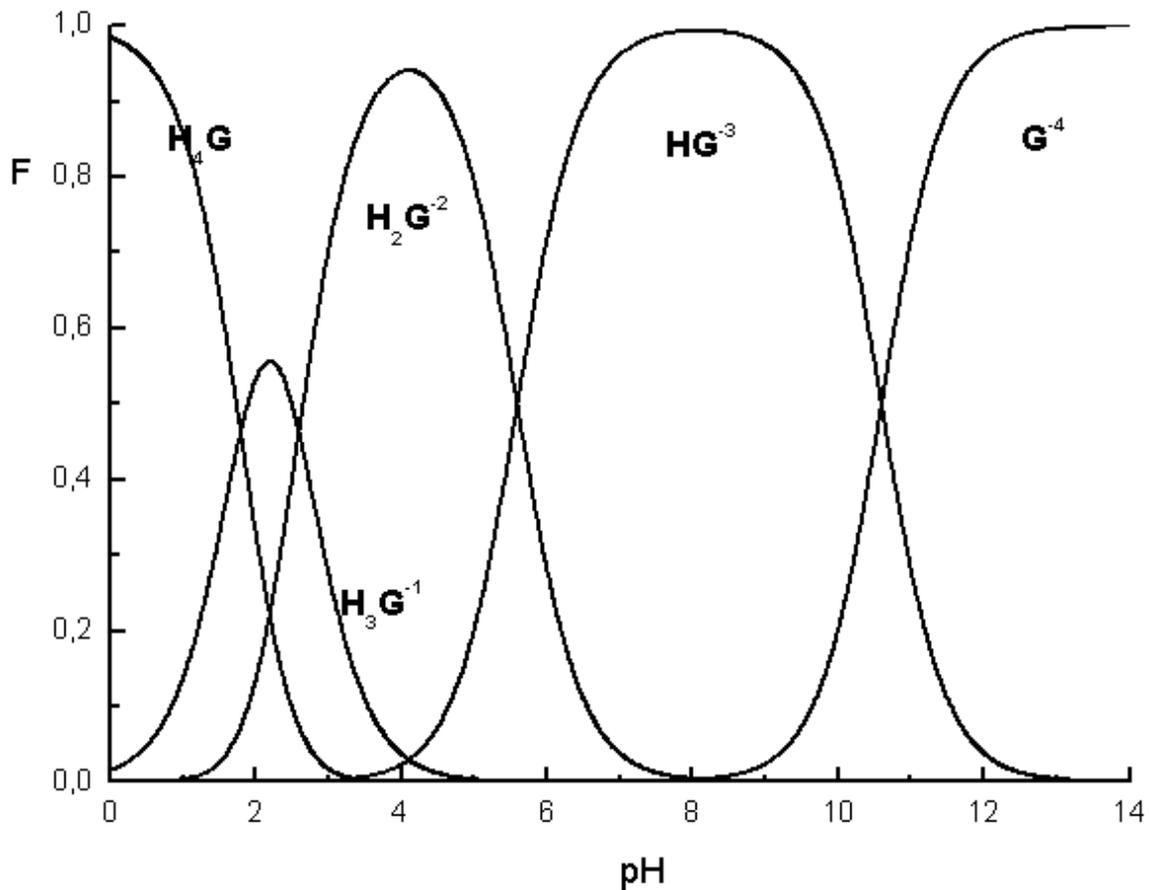
Figure 1. Speciation of Glyphosate in aqueous solution as a function of pH

Figure 2 shows the pH effect over Rg % for the three concentration levels that were studied. It could be seen that the rejection was greater at higher concentrations which could be attributed to prevailing dielectric exclusion mechanism on the Donnan exclusion. In a recent study, it was concluded that in the process of ion permeation through membrane, the dielectric exclusion increased when increasing electrolyte concentration [29].

It could also be observed two different behaviours: the first one was when the pH varied between 5 and 7.5, and the second one was when it varied between 7.5 and 10. In the first range, an antagonistic interaction between the concentration and the pH was observed (evidenced by the decline in the slope), which means that the effect of increasing the pH decreases as the concentration increases, probably due to the shielding of the fixed charge of the membrane.

Above pH 7.5 the slopes were almost similar indicating the absence of interaction which could be interpreted as the increase in the charge of the membrane and the speciation of glyphosate at such a high pH neutralized to some extent the screening effect.

The effect of TMP on the rejection of glyphosate was very small. With the increase of the TMP the retention remained nearly constant [13]. It is believed that the solvent flow increase was compensated with a solute flow increase, something reasonable if it is considered that the solute molecular weight is inferior to MWCO membrane.
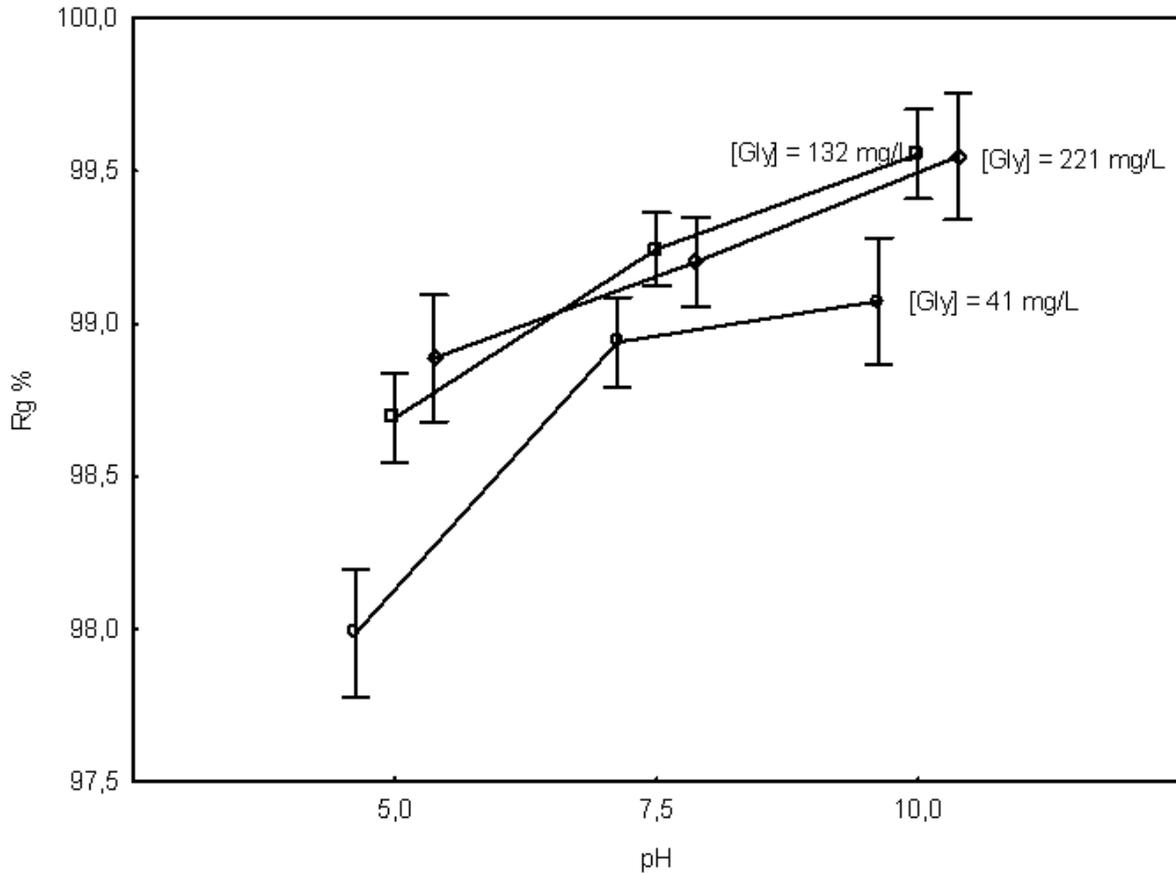
Figure 2. Rejection % (R_g%) as a function of pH and [Gly]. Marginal means and confidence intervals (95%).

As a result of the procedure explained above (2.5. Model fitting), the following model in codified variables was ajusted:

$$R_g \% = 99.27 + 0.24X_1 + 0.43X_2 - 0.10X_3 - 0.21X_1^2 \quad (3)$$
$$- 0.16X_2^2 - 0.11X_1.X_2 + 0.10X_2X_3$$

ANOVA values shown in Table 6 indicate that the lack-of-fit of the model was not statistically significant ($F_0 = 9 < F_{0.05, 5, 2} = 19$). The value of $R^2 = 0.96$ indicated that the 96 % of the observed variation on the response (Rg%) is explained by the model. The graphic analysis of the residuals showed that they followed approximately a normal distribution and were independent, with no pattern or rare tendency. Thus the fitted model was adequate to describe glyphosate rejection behaviour based on the factors studied.

In order to simplify the exploration of the response surface, TMP was fixed in its lowest level, 4 bar, which allows to obtain the best result and the response surface contours of the process were drawn considering pH and [Gly] (Figure 3).

Figure 3 shows the nature of the response surface, which shows a maximum at [Gly] = 160 mg/L; pH = 10 when TMP = 4 bar, with an optimum rejection of 99.6%. Due to the large flat zone that exists around the stationary point, it is possible to operate in a region delimitated by a pH between 9 and 10 and a concentration of glyphosate between 120 and 200 mg/L. Under such conditions, the process is robust and it is possible to obtain rejection values ≥ 99.5% which correspond to glyphosate concentrations in the permeate below 0.7 mg/L. This was the limit established by the U.S. EPA [30].

Saitua et al. working with the same membrane but with a different commercial formulation of glyphosate, achieved lower rejections (from 72.5 to 92.5%) [14]. These results show that the type of formulation affects rejection, which could be related to its ionic strength, as well as the molecular size and/or the ionic charge of the other chemical compounds present.

In order to experimentally check the optimal point, three confirmation runs were performed under the conditions above mentioned, these showed to be in agreement with the previously established optimal point.

Table 6. Analysis of Variance (ANOVA)

	SS	df	MS	F_0	p value
$X_1 + X_1^2$	0.6225	2	0.3112	133	0.0074
$X_2 + X_2^2$	1.6098	2	0.8049	346	0.0029
X_3	0.0883	1	0.0883	38	0.0254
$X_1.X_2$	0.0458	1	0.0458	20	0.0474
$X_2.X_3$	0.0392	1	0.0392	17	0.0547
Lack of Fit	0.1018	5	0.0204	9	0.1060
Pure Error	0.0047	2	0.0023		
Total SS	2.4950	14			
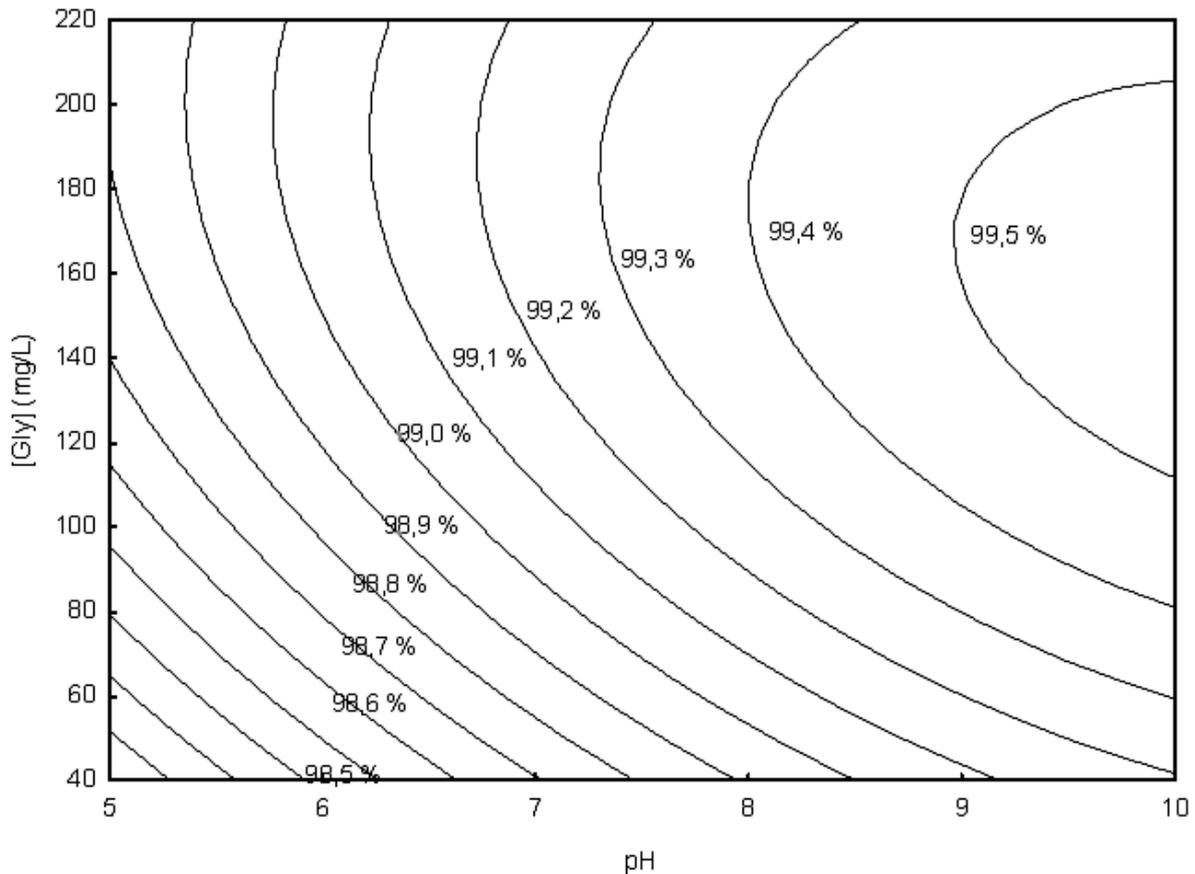
Figure 3. Contours of Rejection % (R_g%) as a function of pH and [Gly] at TMP = 4 bar

4. Conclusions

The RSM and DOE were used for the first time to the study and optimization of a NF process of waters contaminated with a glyphosate commercial formulation at a pilot scale. The results showed that the RSM is the suitable method to optimize glyphosate removal by NF. The optimization was successful, achieving almost complete elimination of glyphosate. At the studied ranges, optimum levels of the factors were the following: [Gly] = 160 mg/L; pH =10 and TMP = 4 bar. A rejection of glyphosate of 99.6% was verified under these optimal conditions. The highs rejections of glyphosate despite its molecular weight below the molecular weight cut-off of the membrane are related to the combined effect of Donnan Exclusion and Dielectric Exclusion. The residual concentration of glyphosate remaining in the permeate was below the limit established by the U.S. EPA (0.7 mg/L). For all runs, the acute toxicity tests with fish in the permeate showed that the rest of the toxic components of the formulation of glyphosate were also removed.

The adjusted model was adequate with an $R^2 = 0.96$. The linear and quadratic effects of pH and [Gly] factors were statistically significant ($p_{value} < 0.05$), as well as the antagonistic interaction between the two factors. This interaction was explained on the basis of the transport mechanism in NF membranes. The pH was the factor of greater effect on rejection, followed by [Gly], the effects of TMP was not important from the practical point of view, therefore, it was possible to work at low pressures, with a consequent energetic saving.

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Statement of Competing Interests

The authors have no competing interests

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