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Treball Final de Grau

Macrocyclic Lactone degradation process optimization in alkaline conditions.

Optimització del procés de degradació d'una lactona macrocíclica en condicions bàsiques.

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UNIVERSITAT DE BARCELONA

"La vida no és allò que tenim i fem, sinó allò que som en essència."

Anònim.

En primer lloc, m'agradaria donar les gràcies als meus tutors del treball. Al Dr. Roger Bringué pel suport aportat durant tot el projecte i l'imprescindible toc d'humor que ha mostrat sempre davant de les adversitats que han pogut sorgir. També, i molt especialment, a en Jordi Homs, per la seva dedicació i interès en tots els aspectes del treball i, sobretot, per l'oportunitat de realitzar un projecte d'aquest calibre dins l'empresa Zoetis Manufacturing &Research Spain, S.L.

De la mateixa manera, agrair al Dr. Josep Grau tot el coneixement transmès sobre el funcionament del sistema Biowaste, així com els somriures regalats en els moments més difícils. Pel que fa a la part experimental, donar les gràcies a en Jordi Rich per la seva paciència i col·laboració, que han sigut claus en el desenvolupament del treball.

M'agradaria nombrar a tot l'equip d'enginyeria i manteniment per l'excel·lent feina feta, especialment a l'Emili Espigulé per la seva predisposició i ajuda contínues. Molt sincerament, agrair a la Natàlia Matas el suport i els coneixements aportats en l'àmbit de seguretat i medi ambient i, indiscutiblement, a en David Font, pels seus consells dins i fora del projecte.

Finalment, donar les gràcies a la meva família i amics pels ànims i el recolzament transmesos durant tot el grau i el projecte. Sense ells tot això no hagués estat possible.

CONTENTS

SUMMARY

The aim of this project is to evaluate, define and optimize the degradation process of a Macrocyclic Lactone in alkaline conditions inside a batch reactor at high temperature. Therefore, ML properties and behavior under different conditions will be studied. In addition, two experimental studies will be performed to evaluate the effect of alkali and temperature in the molecule degradation pathways. For instance, kinetic parameters such as degradation rate constants and activation energy will be extracted from the experimental results in order to determine the sensitivity of the reaction towards temperature.

Otherwise, the Biowaste system installation, where the chemical treatment is carried out, will be deeply analyzed to better understand how the equipment works and which are the stages involved in one cycle. Moreover, mains water and electric energy consumptions will be quantified to see if any improvements can be applied to the system.

The benefits obtained from the optimization of the reaction will be quantified, such as the reduction in sodium hydroxide concentration or the increase in the installation yield, among others.

Keywords: Macrocyclic Lactone, degradation, alkali, temperature, optimization, kinetic parameters, Biowaste system.

RESUM

L'objectiu d'aquest estudi és avaluar, definir i optimitzar el procés de degradació d'una lactona macrocíclica en condicions bàsiques, en un reactor tanc agitat que treballa en règim discontinu a temperatura elevada. Per aquest motiu, s'estudiaran les propietats específiques i el comportament d'aquest tipus de molècules sota condicions diferents. A més, es realitzaran dos estudis experimentals a fi d'avaluar l'efecte d'una base alcalina i de la temperatura en la degradació de la molècula. Els paràmetres cinètics com les constants de velocitat i l'energia d'activació s'extrauran dels resultats experimentals per tal de determinar la sensibilitat de la reacció amb la temperatura.

Per altra banda, la instal·lació del sistema Biowaste, on es duu a terme el tractament químic, s'analitzarà detingudament per tal de comprendre millor el funcionament d'un cicle i les etapes que hi intervenen. Tanmateix, el consum d'aigua de xarxa i d'energia elèctrica seran quantificats amb l'objectiu d'estudiar una possible implementació de millores en el sistema.

Finalment, els beneficis obtinguts de l'optimització de la reacció seran quantificats, com ara la reducció en la concentració d'hidròxid de sodi o l'increment en el rendiment de la instal·lació, entre d'altres.

Paraules clau: Lactona macrocíclica, degradació, base, temperatura, optimització, paràmetres cinètics, sistema Biowaste.

1. INTRODUCTION

The project has been developed in the leading animal health company Zoetis Manufacturing & Research Spain, SL, located in la Vall de Bianya. The main activity of the plant is the manufacturing of different specialties for veterinary use, such as:

- Gels for veterinary use
- Injectable and Oral pharmacological products
- Biological vaccines

In the same way, the plant has a Research and Development Department which performs experimentation studies with animals and investigates for a better veterinary prevention.

1.1. MACROCYCLIC LACTONES

Macrocyclic Lactones (MLs) are widely known as anthelmintic compounds to treat internal and external parasitic infections caused by nematodes, insects, ticks and mites in animals such as cattle, sheep, pigs, horses, dogs and cats. They are hugely important as animal health medicines with registrations over 60 countries.

MLs are divided into the subclasses Avermectin (AVM) and Milbemycin (MLB), which slightly differ in chemical structure but have similar properties. For instance, the ML involved in this project (compound A) is a Milbemycin type and its structural formula is shown in Figure 1.

On the other hand, this molecule is registered in the European Pharmacopeia, where individual and general quality standards, dosage forms and methods of analysis are described in a collection of monographs.

Most relevant physical properties of the molecule are summarized in *Table 1*.

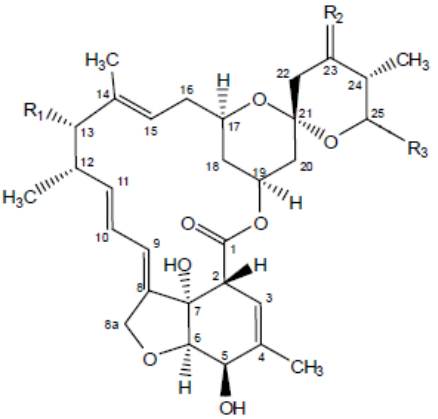


Figure 1. Chemical structure of the compound A

Table 1. Physical properties

Physical Properties	
Physical appearance	White to pale yellow powder
Density	1,23 g/cm^3
Melting point	145 to 154 ºC
Solubility in water	0,51 mg/L
Solubility in acetonitrile	0,62 mL/g

1.2. **PRESENT SITUATION**

Most of the products manufactured at the site contain this compound A, considered an Active Pharmaceutical Ingredient (API) due to its ecotoxicity and so potential environmental impact. Although there is still no framework in Europe regulating API releases to water, good operating practices are being implemented to control its handling.

The table below contains some Ecotoxic information extracted from the MSDS of the molecule, where EC50 and LC50 are standard measures of drug's potency.

Product		Species	Test Results
Compound A	EC50	Daphnia Magna (Water Flea)	30 ppt, 48 Hours
		Selenastrum capricornutum (Green Alga)	> 87 ppb, 72 Hours
	LC50	Lepomis macrochirus (Bluegill Sunfish)	0.62 ppb, 96 Hours
		Oncorhynchus mykiss (Rainbow Trout)	0.16 ppb, 96 Hours

Figure 2. Ecotoxic information for compound A

Due to its criticality, historically, the plant has implemented an additional chemical pretreatment for all the waste streams containing this API, before being discharged to the waste water treatment plant of the site.

Otherwise, analytical controls are performed annually to determine molecule's concentration at different stages of the treatment process, basically before and after the chemical treatment and the waste water treatment plant of the site.

1.3. **BIOWASTE SYSTEM**

The Biowaste System is an automated process which consists in degrading the Active Pharmaceutical Ingredient (compound A) contained in the waste streams produced in the manufacturing areas and laboratories of the plant. This waste streams are mainly aqueous as they are generated in the cleaning in place (CIP) of the formulation tanks. The current treatment is carried out inside a batch reactor in alkaline conditions with sodium hydroxide, at high temperature (80ºC), during at least 3 hours. Presently, an average of 5 cycles per day is carried out at the site. The parameters of the system are summarized in *Table 2*.

Finally, the waste streams are pumped to the wastewater treatment area before being discharged to the public sewer.

Table 2. Biowaste conditions

1	**Volume treated**	178 L
2	**Temperature**	80ºC
3	**Pressure**	<1,2 bars
4	**NaOH concentration**	0,8M
5	**Time**	3h
6	**Agitation**	ON

1.3.1. System Compounds

1. Plastic reservoir of 2000 L
2. Stainless Steel AISI 316L reservoir of 780 L
3. Stainless Steel AISI 316L reactor of 270 L
4. Heat transfer system through coil
5. PVC deposit for concentrated sodium hydroxide of 300 L
6. Dosing and drain pumps
7. Valves and accessories

The whole installation is shown in the picture below, from left to right: Reactor of 270 L, reservoir of 780 L and plastic reservoir of 2000 L.

Figure 3. Biowaste system installation

1.3.2. The process

A representative flow chart of the process is presented in Figure 4, with a brief description of the stages. Every cycle can be divided in three different parts: preparation for the reaction conditions, chemical treatment and process completion. Once the treated product has been sent to the WWTP of the site, a new cycle starts (discontinuous arrow). As mentioned before, the most lasting stage is the chemical treatment, so attention will be mainly focused on optimizing this part.

However, any other optimization will be considered in order to improve the installation yield and reduce costs.

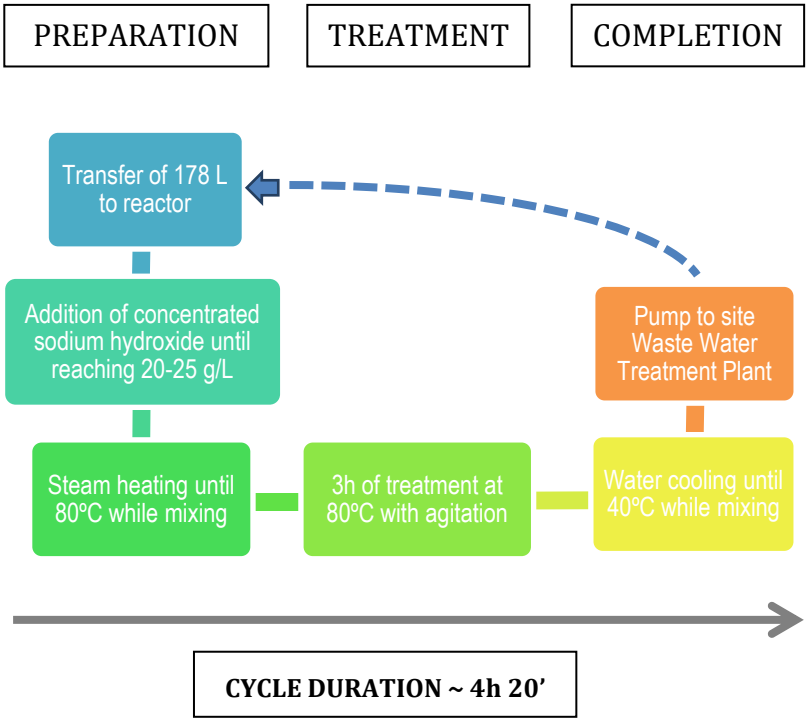
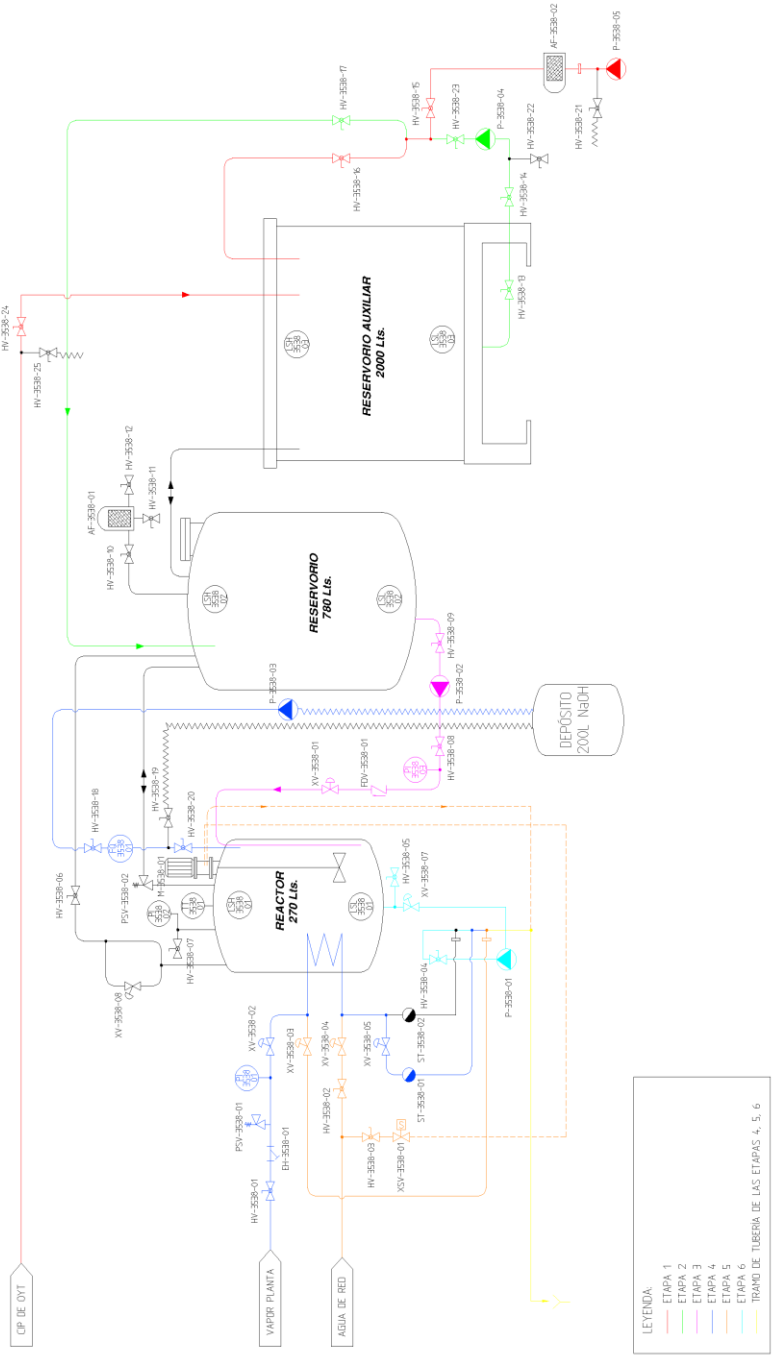


Figure 4. Biowaste system flow chart

Indeed, for a better understanding of the Biowaste system, the P&ID of the process is shown next page, with all the detailed stages classified by colors and numbers. In the flow chart above, stages 1 and 2 appearing in the P&ID of the system are not included, as they are not representative for the process. Stage 1 corresponds to the manual transfer of the waste streams to the plastic reservoir of 2000 L, and stage 2 represents the automatically transfer of the waste streams from the plastic reservoir to the reservoir of 780 L.


RESERVORIO AUXILIAR
2000 Lts.
RESERVORIO
780 Lts.
REACTOR
270 Lts.
DEPÓSITO
200L NaOH
AF-3538-02
P-3538-05
HV-3538-17
HV-3538-15
HV-3538-23
P-3538-04
HV-3538-22
HV-3538-21
HV-3538-16
HV-3538-14
HV-3538-13
HV-3538-24
HV-3538-25
AF-3538-01
HV-3538-12
HV-3538-11
HV-3538-10
HV-3538-09
P-3538-03
P-3538-02
HV-3538-08
XV-3538-01
FDV-3538-01
HV-3538-18
HV-3538-19
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XV-3538-08
HV-3538-05
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HV-3538-04
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XSV-3538-01
PSV-3538-01
DH-3538-01
HV-3538-01
CIP DE OYT
VAPOR PLANTA
AGUA DE RED
LEYENDA:
ETAPA 1
ETAPA 2
ETAPA 3
ETAPA 4
ETAPA 5
ETAPA 6
TRAMO DE TUBERÍA DE LAS ETAPAS 4, 5, 6

2. OBJECTIVES

The aim of this project is to study the degradation process of a macrocyclic lactone in alkaline conditions inside a batch reactor at high temperature, in order to optimize the reaction and to increase the installation yield. The study will be mainly focused on reducing any of the following parameters:

1. Sodium hydroxide concentration
2. Temperature
3. Reaction time

To achieve these objectives, an experimental study will be developed to analyze the influence of the previous parameters in the molecule degradation pathways. Furthermore, kinetic parameters will be extracted from the experimental studies to better understand the behavior of the reaction under heat and alkali conditions. Otherwise, water, sodium hydroxide and electric energy consumption will also be considered as to minimize costs and improve system resources.

3. CHEMICAL REACTION

3.1. CHEMICAL STABILITY OF ML_S

An extended bibliographic research has been done to better understand MLs behavior under different conditions. It is known that these molecules tend to be unstable under normal conditions so it is recommended to be refrigerated and to avoid exposure to light and to extreme pH conditions.

Although there is evidence of degradation in acidic conditions too, attention will be focused on the molecule degradation pathways in alkaline conditions and in presence of heat as the current process is carried out.

3.1.1. Effect of alkaline conditions

Different experimental studies performed with AVMs *(Pivnichny and co-workers, 1988)* have shown that the biological activity of these compounds is quite sensitive to minor molecular modifications, in particular, structural changes at C2 in presence of alkali due to the potentially reactive hexahydrobenzofuran ring system.

The following scheme shows the stereochemical changes at C2 of an Avermectin type in alkaline conditions. Even though compound A is a Milbemycin, the following reaction patterns can also be considered as the chemical structure of the 16-membered macrocyclic lactone ring is the same in both molecules.

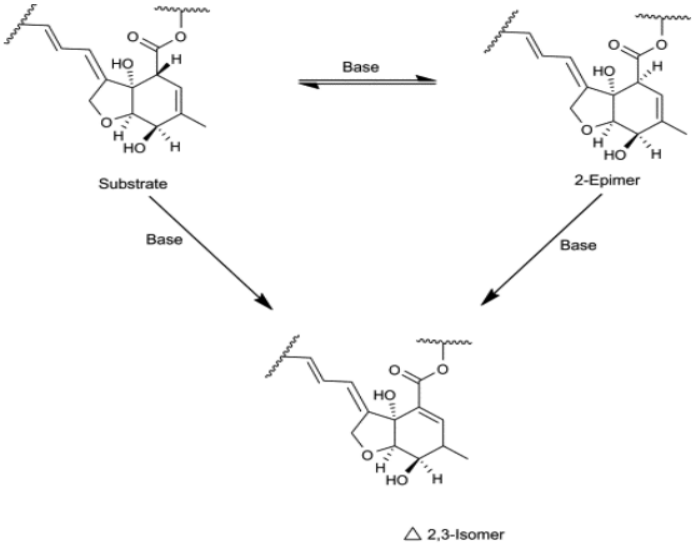

Figure 2. Avermectin reactivity in alkaline conditions

4. EXPERIMENTAL SECTION

Previous to study any possible optimization, is important to know better how the molecule reacts with sodium hydroxide under Biowaste conditions inside the reactor. Therefore, a preliminary experimental study was developed to simulate the process in the same conditions and verify if the current treatment is effective and indeed can be optimized. Otherwise, an experimental kinetic study was also developed in order to analyze the kinetics of the reaction, as it was not considered in the preliminary study. The experiments were performed by evaluating the effect of different temperatures and sodium hydroxide concentrations in the molecule degradation pathways.

These studies were carried out by means of an analytical and instrumental method[1], High-Performance Liquid Chromatography (HPLC). This technique is used to separate components of a mixture based on the different chemical interactions between the analytes and the stationary phase of the chromatographic column.

4.1. TEST MATERIALS, ANALYTICAL STANDARDS AND REAGENTS

The test materials and the analytical standard below in *Table 3* and *Table 4* were used in the site qualification experiments.

Table 3. Summary of test materials

Material	Source
Compound A	Hisun
Sodium hydroxide	Merck

[1] The analytical method used in the experiments can be consulted in the appendices

Table 4. Analytical standard

Material	Purity (%)
Compound A	94.0

The different reagents listed below were also necessary to carry out the experiments:

- Acetonitrile: for HPLC grade and solvent
- Milli-Q water: Solvent
- Ammonium acetate: Used for mobile phase preparation
- Glacial acetic acid: Used for adjusting pH
- Methanol: for HPLC grade

4.2. **EQUIPMENT AND CHROMATOGRAPHIC CONDITIONS**

Equipment and other devices characteristics used during the experiments are described below, as well as chromatographic conditions listed in *Table 5.*

Liquid Chromatographs:	Waters 2695 Separations Module (HPLC 13)
UV Detectors:	Waters 2489 Dual λ Absorbance Detector
	Waters 2996 PDA Detector
Integrator – Recorder:	Empower 3
Automatic Injector:	Waters Auto sampler
pH meter:	±0,05 precision units of pH
Analytical balance:	±0,1 mg resolution

Table 5. Summary of chromatographic conditions

1	**Column**	Pico Tag C18, 150x3.9 mm
2	**Detector**	A variable wavelength detector that can operate at 242 nm
3	**Flowrate**	2.5 ml/min
4	**Injector**	Capable of reproducibly delivering 10 µl sample solution
5	**Column temperature**	50ºC

4.3. **EXPERIMENTAL PROCEDURE**

The first steps of the experimental procedure were focused on studying the solubility of compound A in different solvent proportions acetonitrile – Milli Q water. Initially, two different solutions of 100 mL were proposed:

- 60:40 (60 mL acetonitrile, 40 mL water)
- 20:80 (20 mL acetonitrile, 80 mL water)

The concentration of the active compound in each solution should have been **1% w/v**, considering a possible worst case of concentration in the Biowaste system. However, as compound A is practically insoluble in water, it was dissolved with acetonitrile but precipitated once water was added to the solution. After a few more experimental tests, the final solution was prepared at a concentration of **0,1% w/v** with a proportion of 50:50 acetonitrile – Milli Q water. Indeed, the total volume used was 200 mL in order to prevent acetonitrile's evaporation, as its boiling point is 82ºC.

The following tables show the different experimental conditions in which the experiments were carried out.

Table 6. Experimental conditions for the preliminary study

T (ºC)	NaOH concentration	Reaction time (h)	Extractions (1 mL)
80	0,6M	3	9 (1h x 15', 2h x 30')
	0,3M	1,5	7 (x 15')
	0,1M	1,5	7 (x 15')
50	0,6M	3	9 (1h x 15', 2h x 30')
	0,3M	1,5	7 (x 15')
	0,1M	1,5	7 (x 15')

Table 7. Experimental conditions for the kinetic study

T (ºC)	NaOH concentration	Reaction time (h)	Extractions (1 mL)
80	0,6M	0,33	4 (x 5')
50	0,3M	1	6 (x 10')
	0,1M	1,5	9 (x 10')
22	0,3M	3	2 (at 2h and 3h)

The experimental procedure was the same in both studies, except for the experiment at room temperature from the kinetic study, which did not present heating. The steps followed are described below:

1. Weight 0,2g of compound A (test material)
2. Add into 100mL Acetonitrile
3. Gently heat and mix the solution
4. Carefully add 100mL Milli-Q water
5. Let the solution heat until desired temperature
6. Extract 1 mL from the solution at the beginning of each experiment
7. Before reaching final temperature, carefully add corresponding sodium hydroxide
8. Extract 1mL from the solution when required and dilute 1/10 with mobile phase (60:40 Acetonitrile – Milli-Q water)
9. Finally adjust the pH of the samples until 7.0 with glacial acetic acid
10. Once the HPLC is conditioned and the chromatograph stabilized inject the samples and standard solutions

Notes on the procedure

Step 6: The first extraction is done before adding sodium hydroxide to quantify initial compound A concentration.

Step 7: Initial reaction time (t=0) is considered to be when sodium hydroxide is added to the solution.

Step 9: The adjusting of the pH should be quick in order to stop the reaction. Take into account that once the sample has reached pH 7.0, this time should be considered final reaction time, and not when the sample is extracted.

4.4. **RESULTS AND DISCUSSION**

Meanwhile the experimental part was carried out, many representative changes were observed. The following pictures show the color change of the solutions when sodium hydroxide was added. Notice that initially all the samples were colorless.

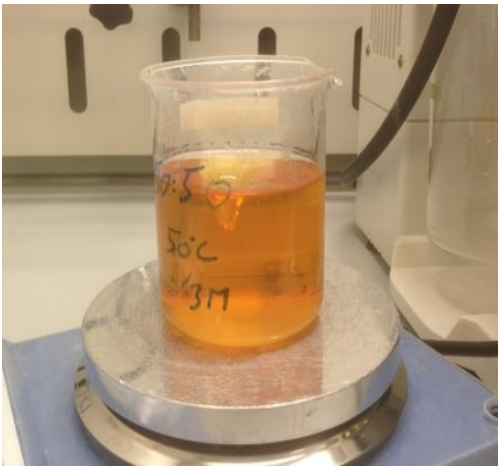

Figure 3. Sample 5 (50ºC, 0.3 M NaOH)

Figure 4. Sample 1 (80ºC, 0.6M NaOH)

Comparing the pictures above it can be easily seen that the color and intensity of the samples is significantly different, depending on temperature and sodium hydroxide concentration. However, samples at the same temperature showed the same tonality with slightly different intensity, almost imperceptible at 80ºC, whatever sodium hydroxide concentration was. Regarding this, the color of the samples could be considered a mainly effect of temperature[2]. In order to demonstrate that color is an indicator of the molecule's degradation, a blank sample was prepared with sodium hydroxide and heated until 50ºC, observing no color change.

Otherwise, it was observed that as reaction time passed, the color started to fade, indicating the progress of the reaction.

4.4.1. Analytical results

4.4.1.1. Preliminary study results

This part contains the experimental results of the six experiments performed in the first study. Compound A concentration has been quantified through the chromatograms, by implementing sample and standard areas and concentrations in the calculations.[3]

The following tables present compound A concentration in % (w/w) at different reaction times for each experiment, until it becomes 0%, which is within 30 minutes in most of them. Therefore, no kinetic information could be extracted from this preliminary study, as there is insufficient data.

[2] Further information will be extracted from the kinetic study results
[3] See part *4.1.1 Calculations* from the analytical method

Table 8. Experimental results for sample 1

	Experimental conditions	Time (min)	% A
Sample 1	T=80ºC	0	0,10097
	[NaOH] = 0,6M	15	0
	$\%A_o$ = 0,1	30	0

Table 9. Experimental results for sample 2

	Experimental conditions	Time (min)	% A
Sample 2	T=80ºC	0	0,11000
	[NaOH] = 0,3M	15	0,00524
	$\%A_o$ = 0,1	30	0

Table 10. Experimental results for sample 3

	Experimental conditions	Time (min)	% A
Sample 3	T=80ºC	0	0,10775
	[NaOH] = 0,1M	15	0
	$\%A_o$ = 0,1	30	0

Table 11. Experimental results for sample 4

	Experimental conditions	Time (min)	% A
Sample 4	T=50ºC	0	0,10235
	[NaOH] = 0,6M	15	0,00031
	$\%A_o$ = 0,1	30	0

Table 12. Experimental results for sample 5

	Experimental conditions	Time (min)	% A
Sample 5	T=50ºC	0	0,09538
	[NaOH] = 0,3M	15	0,00013
	$\%A_o$ = 0,1	30	0,00027

Table 13. Experimental results for sample 6

	Experimental conditions	Time (min)	% A
Sample 6	T=50ºC [NaOH]= 0,1M $\%A_0$ = 0,1	0	0,09772
		30	0,00258
		60	0,00022
		90	0

Reviewing sample 1 experimental results, which intended to simulate the Biowaste system, it is clear that the current process is effective, as it degrades the molecule within **15 minutes** in synthetic conditions, while the real treatment is carried out during **3h** with the waste streams.

Comparing experiments at the same temperature, for example at 80ºC, the expected result was an increase in the reaction time as sodium hydroxide concentration decreased. However, samples 2 and 3 did not accomplish these expectations, as the experimental results show that a concentration of 0,1M is more effective than the 0,3M in the degradation time. This experimental error may be due to a late adjusting of the pH, as it was not adjusted immediately after the extractions but once all the experiments finished. For instance, sample 2 was neutralized before sample 3, so real reaction time and concentration values do not correspond to 15 minutes.

Otherwise, at 50ºC the experimental results do show concordance between degradation time and sodium hydroxide concentration. Notice that in sample 5, there is an increase of concentration from 15 minutes to 30 minutes, which is not possible. It can be considered noise interference in the HPLC, as the real concentration should be almost 0%.

Overall, results show how a reduction of temperature until 50ºC is still effective for the treatment, as well as a decrease in sodium hydroxide concentration. As there are two possible concentrations at 50ºC and the influence of temperature in the molecule's degradation is not strictly clear, final conclusions and optimization parameters will be extracted from the kinetic study.

4.4.1.2. Kinetic study results

This study was carried out more carefully in terms of extractions and adjusting of the ph. The attention was focused on comparing the effect of sodium hydroxide concentrations (0,3M and 0,1M) at the same temperature (50ºC), as well as the influence of temperature on the molecule degradation pathways. Therefore, samples were collected more frequently and neutralized immediately after with glacial acetic acid until ph 7.

The following tables show compound A concentration in % (w/w) in front of time for each of the 4 experiments performed.

Table 14. Experimental results for sample 1*

	Experimental conditions	Time (min)	% A
Sample 1*	T=80ºC	0	0,10431
	[NaOH] = 0,6M	5	0
	$\%A_o$ = 0,1	10	0

Table 15. Experimental results for sample 2*

	Experimental conditions	Time (h)	% A
Sample 2*	T=22ºC	0	0,09438
	[NaOH] = 0,3M	2	0,05116
	$\%A_o$ = 0,1	3	0,04547

Table 16. Experimental results for sample 3*

	Experimental conditions	Time (min)	% A
Sample 3*	T=50ºC [NaOH] = 0,3M $\%A_o$ = 0,1	0	0,09505
		10	0,00396
		20	0,00062
		30	0,00014
		40	0

Table 17. Experimental results for sample 4*

	Experimental conditions	Time (min)	% A
Sample 4*	T=50ºC [NaOH] = 0,1M $\%A_o$ = 0,1	0	0,09481
		10	0,02477
		20	0,01217
		30	0,00545
		40	0,00229
		50	0,00087
		60	0,00030
		70	0,00013
		80	0,00018
		90	0

Notice that in sample 4* at minute 80, there is an increase of concentration, which is not possible, as it occurred with sample 5 from the preliminary study. Again, it will be considered noise interference in the HPLC.

Figure 5 shows the chromatogram of Sample 4* with a compare of all the extractions in different colors (black arrow). Notice that compound A retention time is between 12 and 13 minutes.

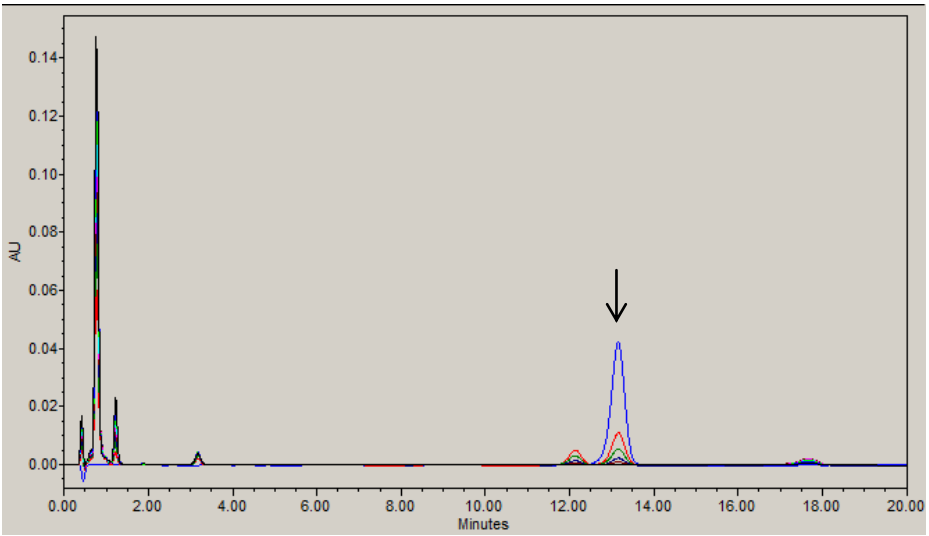

Figure 5. Sample 4* chromatogram

Comparing the different peaks, there is a significant difference between the absorbance of the initial sample (blue peak) and the sample extracted after 10 minutes (red peak). This shows how fast the degradation at the beginning of the reaction is, as for the other samples extracted later on time the difference in absorbance is not so exaggerated.

On the other hand, analyzing experimental results, Figure 6 show the evolution of compound A concentration versus time for each experiment. Otherwise, Figure 7 and Figure 8 show, respectively, the effect of different sodium hydroxide concentrations at the same temperature (50ºC) and the influence of different temperatures in the molecule's degradation pathways.

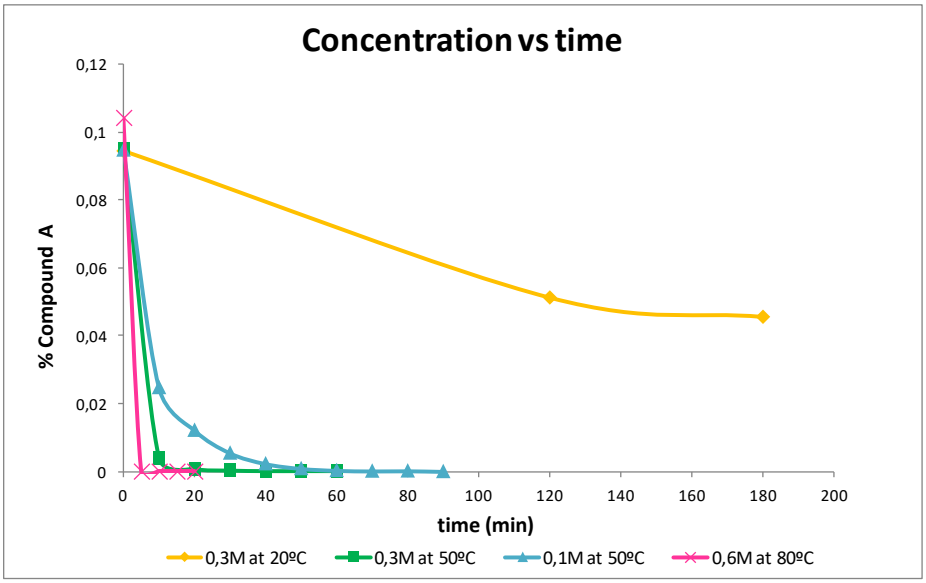

Figure 6. Evolution of compound A concentration vs time

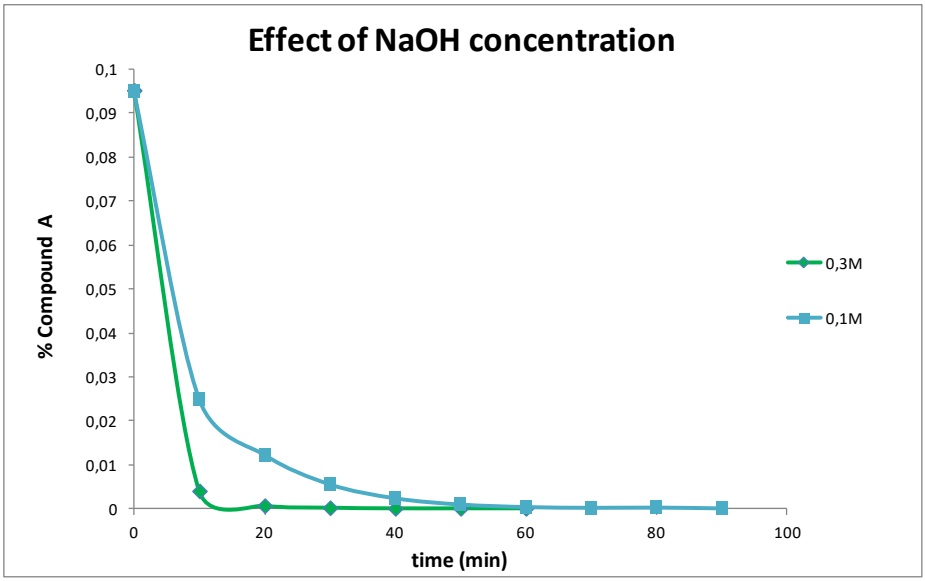

Figure 7. Effect of NaOH concentration in the molecule's degradation

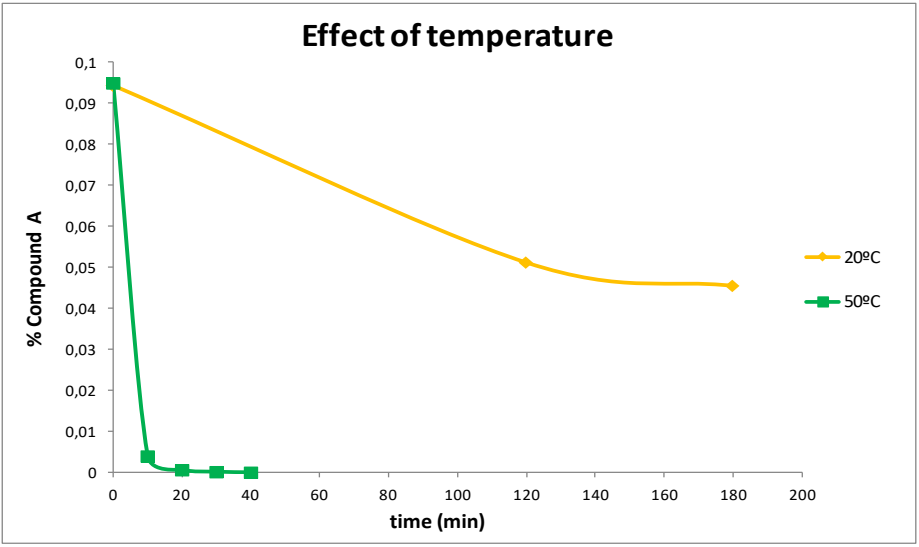

Figure 8. Influence of temperature in the molecule's degradation

Comparing the experiments in Figure 6, it can be seen how surprisingly fast is the degradation of the molecule at the beginning of the reaction (within first 10 minutes) for those samples exposed to heat, especially in sample 1*. However, once concentration has reached values close to 0%, the curve becomes more stable. For the experiment at room temperature (sample 2*), the decrease in concentration is not as exaggerated as for the others, although sodium hydroxide concentration is the same in samples 2* and 3*. This seems to indicate the relevant influence of temperature in the molecule's degradation, rather than sodium hydroxide concentration.

Otherwise, analyzing samples at the same temperature (Figure 7), it can be observed that degradation is quite faster with higher sodium hydroxide concentration, as it was expected in the preliminary study. However, slopes are not so different, especially at the beginning of the reaction (first minutes). The difference between degradation times within experiments is around 40 minutes.

Finally, the influence of temperature can be analyzed from Figure 8. In the experiment without heat, the degradation is so slow that after 3h of reaction the remaining concentration is half the initial. Indeed, after 2h, the decrease in concentration is lower than at the beginning, as in the last 30 minutes of reaction the curve is almost stable.

In order to see the difference between the two experiments, the last quantified compound A concentration for sample 2* (after 3h), was **10 times** higher than the first one (after 10 minutes) in sample 3*, although sodium hydroxide concentration was the same. Therefore, temperature may be considered a critical parameter of the degradation reaction.

Another relevant result of both studies was observed during the pH measure of the samples, before being neutralized, as it was almost the same in all the extractions. An example is shown in Table 18 below.

Table 18. Sample 3* extractions and pH measures

	Reaction time (min)	pH
Sample 3*	10	13,55
	20	13,58
	30	13,55
	40	13,56
	50	13,56
	60	13,55

As it occurred in all the experiments[4], it seems that sodium hydroxide is not consumed along the reaction, although its concentration affects the degradation of the molecule in different ways. Therefore, due to its role in the degradation reaction, sodium hydroxide could be considered to act as a catalyst.

[4] Other samples and its corresponding pH measures can be consulted in the appendices

4.4.2. Determination of kinetic parameters

In the adjusting of the experimental results to kinetic parameters, it was observed that the best fit was to a first order reaction. Therefore, the experimental first-order degradation rate constants (k_{exp}) were calculated from the slopes of logarithm plots of compound A concentration vs. time, in accordance with the following equation:

$$ln\ (A_t / A_0) = - k_{exp} \cdot t \cdot c_{NaOH} \quad (1)$$

Where A_0 is the initial compound A concentration and A_t is the remaining concentration of the molecule at time *t*. Although sodium hydroxide is considered a catalyst and its concentration (c_{NaOH}) through time remains constant, it has to appear in the equation in order to be able to compare the degradation constants (k_{exp}), as it is different in each experiment and could affect further calculations.

Therefore, equation (1) can also be written as:

$$ln\ (A_t / A_0) = - k' \cdot t \quad (2)$$

Where k' is:

$$k' = k_{exp} \cdot c_{NaOH} \quad (3)$$

The effect of heat on the stability of the molecule was studied by using the Arrhenius equation. The activation energy was calculated from the slope of the following equation plot:

$$ln\ k_{exp} = ln\ A - E_a / (R*T) \quad (4)$$

Where k_{exp} is the first-order degradation rate constant, A is the Arrhenius factor, E_a is the activation energy of the reaction, R is the gas constant of 8,314 $J \cdot K^{-1} \cdot mol^{-1}$ and T is the absolute temperature in Kelvin.

Notice that for samples 3* and 4*, an average of the degradation constants has been used as the experiments were carried out at the same temperature. The other kinetic parameters used in the plotting of equation (2) were those from sample 2*.

Kinetic parameters and activation energy calculations are shown in Table 19 and Table 20 below.

Table 19. Kinetic parameters

Sample	**C_{NaOH} (M)**	**T(ºC)**	**K_{exp} ($L \cdot mol^{-1} \cdot s^{-1}$)**
2*	0,3	20	0,00023
3*	0,3	50	0,01190
4*	0,1	50	0,01528

Table 20. Activation energy calculations

20 ºC		**50ºC**	
k_{exp} ($L \cdot mol^{-1} \cdot s^{-1}$)	0,00023	$\overline{k_{exp}}$ ($L \cdot mol^{-1} \cdot s^{-1}$)	0,01359
ln k_{exp}	- 8,36149	ln k_{exp}	- 4,29863
1/R*T ($mol \cdot J^{-1}$)	0,00041	1/R*T ($mol \cdot J^{-1}$)	0,00037

From the table above, representing the parameters inside the box, the apparent activation energy of the reaction calculated was:

Ea = 107 kJ/mol

Comparing the experimental degradation rate constants from Table 19, it can be easily seen how an increase in temperature from 20ºC to 50ºC caused a significant increase in the degradation rate. However, experiments at the same temperature (50ºC) showed similar rate constants, as the kinetic constant depends only on the temperature.

Otherwise, the apparent activation energy calculated indicates an important sensibility of the reaction with temperature, which confirms the statements mentioned along the experimental results and discussion.

4.4.3. Optimized parameters and recommendations

Reviewing experimental and kinetic results, the recommended optimized parameters to implement in the Biowaste system are summarized in the table below, in comparison with the current ones.

Table 21. Comparison of Biowaste system parameters

Actual process	Optimized process
T = 80ºC	T = 50ºC
C_{NaOH} = 0,8M	C_{NaOH} = 0,3M
Treatment time = 3h	Treatment time = 1h

Although temperature is a critical parameter of the reaction, the experimental results show how a reduction of temperature until 50ºC is still effective for degrading the molecule. Sodium hydroxide concentration has been set in 0,3M, although a concentration of 0,1M could be also feasible. However, as the composition of the waste streams is unknown, a higher concentration is recommended in order to prevent any interaction that could reduce or affect sodium hydroxide activity. Treatment time has been reduced until 1h, as in synthetic conditions (Sample 3*) the molecule is degraded within 40 minutes. Again, as experimental conditions are not strictly applicable to the real system, reaction time has been set over 40 minutes.

5. INSTALLATION OPTIMIZATION

Apart from optimizing the reaction, the whole installation was analyzed in order to study any possible improvement and reduce additional costs. Therefore, refrigeration water, sodium hydroxide and electric energy consumptions were evaluated and quantified.

5.1. REFRIGERATION WATER CONSUMPTION

Taking a look at the P&ID on page 7, the refrigeration system of the installation is an open system, as all the refrigeration water used is directly sent to the waste water treatment plant of the site instead of recirculating and reusing it. Therefore, attention was focused on quantifying the water consumption per cycle in the Biowaste system.

5.1.1. Calculations

In order to estimate water consumption, flow rate and refrigeration time were quantified. The representative flow rate was calculated in an experimental way, by filling a recipient of known volume and quantifying the filling time. Three trials were performed and the results are summarized in the table below.

Table 22. Flow rate trial results

Volume (L)	Time (s)
20	24,41
20	23,27
20	23,89
Average	23,86

Therefore, the flow rate of the system in L/h is:

$$\frac{20\ L}{23{,}86\ s} \cdot \frac{3600\ s}{1h} = 3018\ L/h$$

If we take into account that the refrigeration time is approximately 70 minutes, the water consumption per cycle is:

$$3018\ \frac{L}{h} \cdot \frac{1h}{60\ min} \cdot 70\ min = 3521\ L$$

The number of cycles performed per day is 5, and the system works 6 days per week. Therefore, if 30 cycles are carried out per week and considering that one year has 47 operating weeks, the annual consumption in m^3 is approximately:

$$Cycles\ /\ year = 30 \cdot 47 = 1410$$

$$1410\ \frac{cycles}{year} \cdot 3521\ \frac{L}{cycle} \cdot \frac{1\ m^3}{1000\ L} = \mathbf{4965\ m^3/\ year}$$

5.1.2. Alternative refrigeration systems

Taking into account the high amount of refrigeration water wasted, three alternative refrigeration systems were proposed and evaluated.

1. Natural refrigeration of the product: The first alternative proposed was to let the product refrigerate in an auxiliary tank until desired temperature (40ºC) before pumping it to the WWTP of the site, instead of using water to cool it. To do it, refrigeration time was estimated by implementing energy balance and heat transfer equations.

2. Install a heat exchanger (closed system): The second one consisted in making use of a cold source at 7ºC by the Biowaste system to install a heat exchanger and create a closed refrigeration system.

3. Reuse the refrigeration water to feed DM Water Treatment plants: In this case, the refrigeration water from the Biowaste system would be lead to an accumulation tank in order to feed the Demineralization Water Treatment plants of the site, as the consumption of mains water to feed these plants is significantly high (about 3000 L/h).

Acquisition, sustaining and disposal costs of each alternative were evaluated by implementing a Life Cycle Cost analysis (LCC), which considers all the costs associated with the acquisition and ownership of a system (or equipment) over its full life. It is measured in Net Present Value (NPV), a financial tool for evaluating economic value added. It is the present value of an investment's future net cash flows, minus the initial investment for a given threshold discount rate.

The best option was to implement the 3rd alternative, reusing refrigeration water to feed DMW plants, as acquisition and sustaining costs were significantly lower than in the other alternatives, and so was the NPV.[5]

Above all, considering the optimized treatment process parameters, if temperature is set at 50ºC no refrigeration stage will be needed, as the product can be send to the WWTP of the site at this temperature. This would reduce completely the refrigeration water consumption of the system.

[5] The LCC analysis of the three alternatives can be consulted in the appendices.

5.2. **SODIUM HYDROXIDE CONSUMPTION**

Sodium hydroxide consumption per cycle in the Biowaste system was quantified through the dosing pump parameters from the table below.

Table 23. Dosing pump parameters

Flow rate (g /min)	1758
Dosing time (min)	7

Therefore, sodium hydroxide consumption per cycle is:

$$7\,min \cdot 1758\,\frac{g\,NaOH}{min} = 12306\,g\,NaOH/cycle$$

Implementing 48% concentrated sodium hydroxide density at 20ºC[6] and considering that 1410 cycles are performed in one year:

$$12306\,\frac{g\,NaOH}{cycle} / 1520\,\frac{g\,NaOH}{L} = \mathbf{8\,L\,NaOH/cycle}$$

$$8\,\frac{\mathrm{L\,NaOH}}{\mathrm{cycle}} \cdot 1410\,\frac{cycles}{year} = \mathbf{11280\,L\,NaOH/year}$$

Take into account that these consumptions correspond to the actual process, once the optimized parameters are applied to the Biowaste system, the consumption will be significantly reduced.

[6] Extracted from the SDS of sodium hydroxide in the appendices.

5.3. **ELECTRIC ENERGY CONSUMPTION**

In order to quantify the electric energy consumption of the Biowaste system, a portable network analyzer was connected to the equipment during two days. After the analysis, corresponding daily consumption peaks were compared to verify that the plots were similar, as the number of cycles performed per day was the same. Therefore, as there was no difference, potency and intensity plots from the first day were analyzed, which are shown, respectively, in Figure 9 and Figure 10 below.

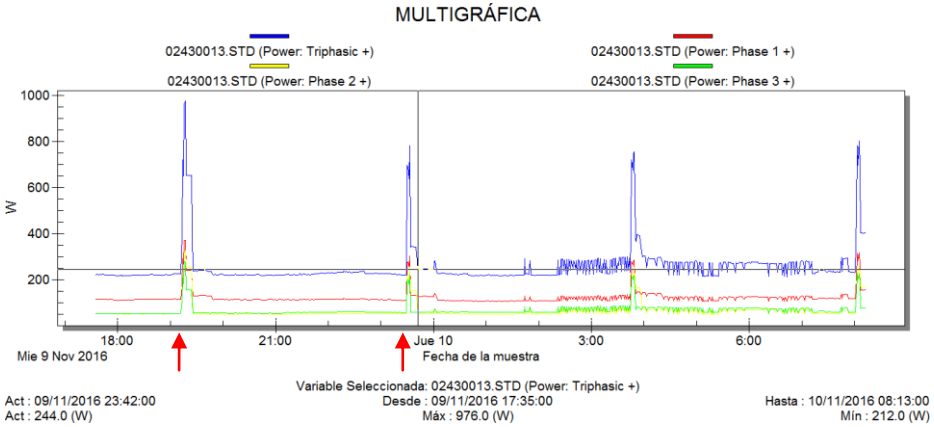

Figure 9. Potency plot of the Biowaste system

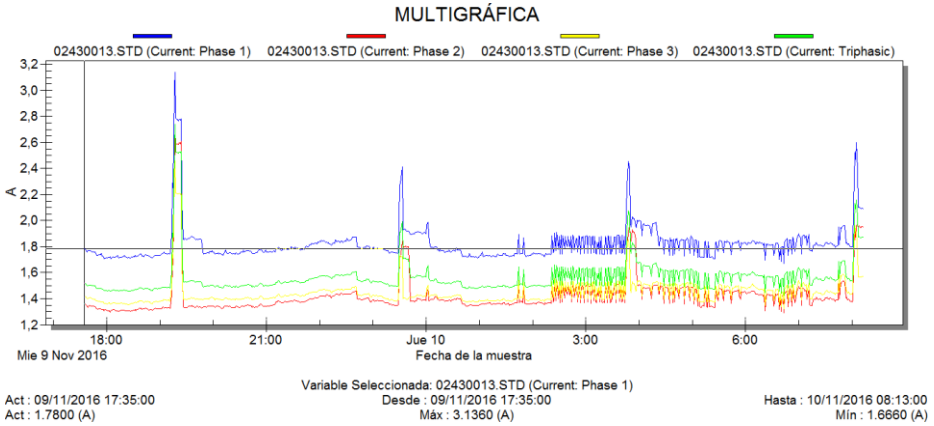

Figure 10. Intensity plot of the Biowaste system

Each figure respresents the same 3 entire cycles carried out in the system during this part of the analysis, as the axis time of the two plots coincide. An example of a cycle duration is shown in Figure 9, within red arrows. Observing the two graphics, colors red, green and yellow correspond to the different triphasic phases, while the blue line represents the total.

Otherwise, the 4 peaks appearing in Figure 9 and Figure 10 correspond to the maximum values of potency and intensity at the beginning of each cycle, due to the electric consumption of the drain and transfer pumps.

The absolute electric energy consumption in kW/h was automatically registered every minute during the analysis. The table below shows an example of the data registered during the first cycle. [7]

Table 24. Absolute electric energy consumption

Date	Time	kW/h
9/11/2016	19:10:00	0,358
9/11/2016	19:11:00	0,362
9/11/2016	19:12:00	0,366
9/11/2016	19:13:00	0,372
…	...	…
9/11/2016	23:26:00	1,421
9/11/2016	23:27:00	1,425
9/11/2016	23:28:00	1,428
9/11/2016	23:29:00	1,432

The total electric energy consumption of the cycle was obtained using the values from the boxes above, as they correspond to the initial and final absolute consumptions. Therefore, the electric energy consumption per cycle in the Biowaste system is:

Electric energy consumption = 1,432 – 0,358 = 1,074 kW/h ≈ **1 kW/h**

[7] Intermediate values are not included in the example table as they are not representative for the calculations.

5.4. **BENEFITS**

Many benefits are derived from the optimization of the reaction and the improvements in the Biowaste system installation, such as:

1. Reduction of sodium hydroxide concentration: Two new sodium hydroxide concentrations have been proposed and are equally feasible for the chemical treatment.
2. Reduction of mains refrigeration water: Three alternatives have been proposed to reduce the refrigeration water consumption of the installation. Moreover, as a result of the optimization study, no refrigeration stage will be needed in the optimized process.
3. Temperature reduction: A decrease in temperature from 80ºC to 50ºC has been proved effective in degrading the molecule, reducing the heating steam consumption of the system.
4. Optimization of the reaction time: Treatment time for the optimized process has been set in 1h, reducing 2h the initial reaction time.
5. Increase of the installation yield: Nowadays the installation is operating at the 100% of its capacity, whereas with the optimized process it would be duplicated.
6. Decrease in the electric energy consumption: In the optimized process, the electric energy consumption per cycle would be under 1kW/h, as agitation and sodium hydroxide dosing time will be reduced.

Table 25 next page shows the comparison of the most relevant parameters in the Biowaste system between the current process and the optimized one.

Table 25. Comparison of most relevant parameters between processes

PARAMETRES	ACTUAL PROCESS	OPTIMIZED PROCESS
Volume treated (L /cycle)	178	178
NaOH concentration (M)	0,8	0,3
NaOH volume (L /cycle)	8,10	3,47
Temperature (ºC)	80	50
Treatment time (h)	3	1
Cycles /day	5	~10
Refrigeration water consumption (L /cycle)	3521,03	0
Electric energy consumption (kWh /cycle)	1	<1

The reduction of the parameters inside the boxes has been quantified in % as they are the most significant results of the optimization process.

Table 26. Parameters reduction in %

Reducing consumption	%
Sodium hydroxide	57
Mains refrigeration water	100

6. NEXT STEPS

After the optimization study, next steps are mainly focused in two different ways:

1. Performing the simulation in plant with the optimized parameters and developing a subsequent analysis at the entrance and output of the Biowaste system to quantify compound A concentration.

2. Implementing alternative sodium hydroxide manipulations for safety improvements, including:

    2.1. Use of 30% concentrated sodium hydroxide to unify its purchase and decrease the risk while manipulation.
    2.2. Install a 1000 L refillable tank of PVC with secondary containment instead of using 25L jugs with manual transfer to the accumulation tank (actual process).
    2.3. Estimating the total budget and savings of the new installation.

7. CONCLUSIONS

The present study has proved that the degradation reaction involved in the Biowaste system can be optimized, reducing parameters such as temperature, sodium hydroxide concentration and treatment time. In addition, as a result of a careful analysis of the installation, many improvements have been proposed to reduce mains refrigeration water consumption.

Otherwise, to our surprise, the electric energy consumption of the system was found to be irrelevant compared to the mains water and sodium hydroxide.

As expected, much information was extracted from the experimental kinetic study, understanding better the influence of sodium hydroxide and temperature in the degradation of the molecule. For instance, temperature was determined a critical parameter of the reaction, as degradation rate constants and apparent activation energy showed a significant sensibility of the reaction towards temperature. Moreover, sodium hydroxide was found to act as a catalyst and not as a reagent, with a notable concentration influence in the degradation rate.

Nevertheless, a deeper kinetic study would be helpful to completely define the behavior of the molecule under heat and alkali conditions. Therefore, as a recommendation, an experimental kinetic study with only influence of temperature is suggested.

Above all, final verification of the present study is pending on the simulation in plant with the suggested optimized parameters.

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ACRONYMS

ML Macrocyclic Lactone

MLs Macrocyclic Lactones

AVM Avermectin

MLB Milbemycin

API Active Pharmaceutical Ingredient

MSDS Material Safety Data Sheet

CIP Cleaning In Place

WWTP Waste Water Treatment Plant

HPLC High Performance Liquid Chromatography

NaOH sodium hydroxide

$\mathbf{A_o}$ Initial compound A concentration, % (w/w)

$\mathbf{A_t}$ Compound A concentration at time t, % (w/w)

t time (h, min, s)

T Temperature, ºC, K

$\mathbf{k_{exp}}$ Experimental firs order degradation rate constant, $L \cdot mol^{-1} \cdot s^{-1}$

$\mathbf{c_{NaOH}}$ Sodium hydroxide concentration, M

Ea Activation energy, kJ/mol

R gas constant, $J \cdot K^{-1} \cdot mol^{-1}$

LCC Life Cycle Cost

DMW Demineralization Water

NPV Net Present Value

SDS Safety Data Sheet

APPENDICES

APPENDIX 1: ANALYTICAL METHOD

4. Analytical method

4.1. Devices

- Liquid chromatograph equipped with an oven for controllable columns at 50 ± 1ºC
- UV Detector working at 242 nm
- Integrator-Recorder
- Manual/Automatic injector
- Chromatographic Column Waters Pico Tag C18
- pH-meter with ±0,05 precision units of pH
- Analytical balance with ±0,1 mg resolution

4.2. Reagents

- Moxidectin standard: Standard solution of Moxidectin with known purity
- Acetonitrile (HPLC grade)
- Milli-Q water
- Ammonium acetate (reagent)
- Glacial acetic acid (reagent)
- Methanol (HPLC grade)

4.3. Mobile Phase preparation

Sufficient mobile phase must be prepared to carry out all the essays. To prepare 2 L of mobile phase proceed as follows:

1. Add 15,4 g of ammonium acetate to 800 ml of water and shake until dissolved
2. Add 1200 ml of Acetonitrile and mix well
3. Adjust the pH until 6,0 with glacial acetic acid

4.4. Solvent preparation (60/40 Acetonitrile-Water)

To prepare 1L of solvent proceed as follows:

1. In a 1000 ml flask, add:
   - 600 ml acetonitrile
   - 400 ml Milli-Q water
2. Shake manually until dissolved
3. Filter and degas

4.5. System Equilibration

1. Wash the column with Acetonitrile (HPLC grade) at a flowrate of 2,5 ml/minute during 30 minutes.
2. Change to compound A solvent (Mobile Phase) at the same flowrate
3. Wait until obtaining a stabilized base line

4.6. Preparation of the Standard Solution

Prepare an equivalent Compound A Standard Solution of 0,1% concentration (x2). Label the flasks with Standard A and Standard B. If solid compound A (100% K/A) is used dissolve with acetonitrile. Otherwise dissolve with the solvent (Compound A Technical Concentrate).

Dilute to 1/10 with the same solvent to obtain a final concentration of 0,01%. The solid compound A remains at concentration of 0,1%.

4.7. Sample preparation

Prepare a 0,1% solution with solvent. To adjust the pH until 7.0, immediately add glacial acetic acid after the extractions in order to stop the reaction. Take into account that once the sample has reached pH 7.0, this time should be considered final reaction time, and not when the sample is extracted.

4.8. Chromatographic conditions

a) Column: Waters Pico Tag C18
b) Column temperature: 50ºC
c) Flowrate: 2,5 ml/minute
d) Injection volume: 10µL
e) Wavelength: 242 nm

4.9. Method

Once the chromatograph is stabilized in the conditions listed above, inject the sample and standard solutions.

4.10. System Suitability

The concordance between standards must be between 98.0-102.0% and de %RSD between replicate injections should be within 2.0%.

4.11. Calculations

$$\frac{\text{Sample Area}}{\text{Standard Area}} \times \frac{\%\,\text{Standard}}{\%\,\text{Sample}} \times \%\,\text{STD Purity} = \%\,\text{Compound A (w/w)}$$

APPENDIX 2: pH MEASURES AND EXTRACTIONS

In the tables below are shown the extractions and its corresponding pH measures of each sample from the kinetic study.

Table 27. pH measures for Sample 1*

	Reaction time (min)	pH
Sample 1*	5	13,52
	10	13,67
	15	13,69
	20	13,70

Table 28. pH measures for Sample 2*

	Reaction time (h)	pH
Sample 2*	2	13,63
	3	13,56

Table 29. pH measures for Sample 4*

	Reaction time (min)	pH
Sample 4*	10	13,17
	20	13,33
	30	13,32
	40	13,29
	50	13,26
	60	13,27
	70	13,26
	80	13,29
	90	13,29

As it happened with Sample 3*, pH also remains constant in the rest of the samples, as sodium hydroxide is not consumed along the reaction.

APPENDIX 3: LIFE CYCLE COST ANALYSIS

Assumptions and summary tables of the three alternatives analyzed with the LCC are shown below.

Table 30. Assumptions

Assumptions				
Discount Rate	**8,50%**	Updated 28/10/2016		
Project Life	**15**	**Years**		
Tax Provision	**28,00%**	Updated 28/10/2016		

Discount rate and Tax provision factors depend on the cost of money at the site where the LCC analysis is carried out, in this case *Zoetis Manufacturing &Research Spain, S.L.*

Table 31. Cost analysis for the heat exchanger

Tab	Description	Comments	Payment Method	Year	Amount
Heat exchanger	Acquisition cost		Capital	0	$ 10.129
	Sustaining cost (annual)		Expense	1 - 20	$ -
	Periodic overhaul (every 5 years)		Expense	5, 10, 15	$ -
	Disposal costs		Expense	20	$ 1.200
	Reliability (mission time is 1 year)	90,00%			
	Failures per year	0,1			
	MTTR (hours)	15			
	Maintenance Rate (hourly)	$30			
	Annual Maintenance Labor	$47	Expense	1 - 20	$ 47
	Repair Parts (per failure)	$1.500	Expense	1 - 20	$ 458
	PM (hours)	16			
	Annual PM Labor	$480	Expense	1 - 20	$ 480
	PM Parts	$500	Expense	1 - 20	$ 600
	Availability	470			
	Cost of downtime (hourly)	$0			
	Cost of downtime (annual)	$0	Expense	1 - 20	$ -
	Energy Cost ($/kwh)	$0,085			
	HP	6			
	kw	4,5			
	Annual Energy Consumption		Expense	1 - 20	$ 179

Table 32. Cost analysis for the natural refrigeration alternative

Natural refrigeration	Acquisition cost		Capital	0	$ 24.383
	Sustaining cost (annual)		Expense	1 - 20	$ -
	eriodic overhaul (every 10 years)		Expense	10	$ -
	Disposal costs		Expense	20	$ 3.000
	Reliability (mission time is 1 year)	50,00%			
	Failures per year	0,7			
	MTTR (hours)	16			
	Maintenance Rate (hourly)	$30			
	Annual Maintenance Labor	$333	Expense	1 - 20	$ 333
	Repair Parts (per failure)	$2.300	Expense	1 - 20	$ 2.054
	PM (hours)	20			
	Annual PM Labor	$30	Expense	1 - 20	$ 30
	PM Parts	$1.000	Expense	1 - 20	$ 1.200
	Availability	1974			
	Cost of downtime (hourly)	$0			
	Cost of downtime (annual)	$0	Expense	1 - 20	$ -
	Energy Cost ($/kwh)	$0,085			
	HP	3			
	kw	1,9			
	Annual Energy Consumption		Expense	1 - 20	$ 313

In this case, the acquisition cost is higher as two stainless steel AISI 316L tanks of 250L are needed to refrigerate the product. In addition, the automation system is also included in the acquisition cost.

Table 33. Cost analysis of the third refrigeration alternative

Water for ADM plant	Acquisition cost		Capital	0	$ 2.700
	Sustaining cost (annual)		Expense	1 - 20	$ -
	Periodic overhaul (every 10 years)		Expense	10	$ -
	Disposal costs		Expense	20	$ 1.000
	Reliability (mission time is 1 year)	95,00%			
	Failures per year	0,1			
	MTTR (hours)	10			
	Maintenance Rate (hourly)	$30			
	Annual Maintenance Labor	$15	Expense	1 - 20	$ 15
	Repair Parts (per failure)	$300	Expense	1 - 20	$ 75
	PM (hours)	0			
	Annual PM Labor	$0	Expense	1 - 20	$ -
	PM Parts	$0	Expense	1 - 20	$ -
	Availability	8759			
	Cost of downtime (hourly)	$0			
	Cost of downtime (annual)	$0	Expense	1 - 20	$ -
	Energy Cost ($/kwh)	$0,085			
	HP	0			
	kw	0,0			
	Annual Energy Consumption		Expense	1 - 20	$ -

This last option is the less expensive in acquisition costs as the only equipment needed is a plastic accumulation tank of 10000L.

Finally, the NPV is automatically calculated for each alternative, resulting in the table below:

Table 34. Summary of NPV for the three alternatives

Summary		
Option	**NPV**	**IRR**
Best Equipment	$2.700	N/A
Better Equipment	$10.129	N/A
Good Equipment	$24.383	N/A

In this case the NPV and the acquisition cost of each alternative coincide, as there are no cash flows during the project life, only the initial inversion. Therefore, as the alternative of reusing the refrigeration water to feed the DM Water plants is the less expensive, is considered the best option.

APPENDIX 4: SAFETY DATA SHEETS

simar s/a
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SOSA CAÚSTICA, Líq. 48/50%

Ficha de datos de seguridad (de acuerdo con 93/112/CEE)

1. IDENTIFICACIÓN DEL PRODUCTO Y DE LA EMPRESA.

1.1. Identificación del producto.

Nombre químico: Hidróxido sódico.
Fórmula química: NaOH
Nº CAS: (1310-73-2)
Nº EINECS: (215-185-5)
Sinónimos: Sosa cáustica; Sosa; Hidrato de sodio; Cáustico blanco; Lejía de sosa.

1.2. Identificación de la empresa.

SIMAR, S.A
C/ Països Baixos, 3
08700 Igualada
Barcelona.
Tfno: 803.61.00 Fax: 804.52.08

Tfno. Instituto Nacional de Toxicología: 91.562.04.20

2. COMPOSICIÓN / INFORMACIÓN SOBRE LOS COMPONENTES.

Componente	Concentración	Símbolo de riesgo	CAS
Hidróxido sódico	48-50%	Corrosivo, C	1310-73-2

3. IDENTIFICACIÓN DE LOS PELIGROS.

Corrosivo. Corroe el tejido en presencia de humedad. Fuerte irritante para los ojos, la piel, las membranas mucosas y por ingestión.

3.1. Datos sobre el riesgo para la salud.

Inhalación: Corrosivo. Produce sensación de quemazón, tos y dificultad respiratoria.

Contacto con la piel: Corrosivo. El contacto del producto con la piel produce enrojecimiento, graves quemaduras cutáneas y dolor.

Contacto con los ojos: Corrosivo en contacto con los ojos. produce enrojecimiento, dolor, visión borrosa y quemaduras profundas graves.

Ingestión: Corrosivo. Su ingestión produce dolor abdominal, sensación de quemazón, diarrea, vómitos y colapso.
La ingestión de sosa cáustica puede incluso causar perforación intestinal.

4. PRIMEROS AUXILIOS.

Inhalación: Mantener al paciente en posición semiincorporada en reposo y en un lugar donde pueda respirar aire limpio.
Administrar respiración artificial si estuviera indicada y proporcionar asistencia médica.

Contacto con la piel: Quitar las ropas contaminadas, aclarar la piel con agua abundante durante 15 minutos como mínimo. Acudir a los servicios médicos para tratar las zonas quemadas.

Contacto con los ojos: Lavar inmediatamente en agua durante un mínimo de 15 minutos. Acudir siempre al oftalmólogo.

Ingestión: Tras la ingestión del producto, enjuagar la boca y dar a beber agua fría, leche, jugo de fruta o vinagre diluido.
No provocar el vómito. En caso de vómito, repetir el tratamiento. No dar nada de comer a un paciente inconsciente. Acudir a un médico urgentemente.

5. MEDIDAS DE LUCHA CONTRA INCENDIOS.

El producto no es inflamable ni combustible, pero en contacto con el agua puede producir calor suficiente para la ignición de productos combustibles.

A temperatura elevada: por corrosión de los metales, formación de hidrógeno inflamable y explosivo.

En caso de producirse un incendio en el entorno, estarán permitidos todos los agentes extintores.

6. MEDIDAS A TOMAR EN CASO DE VERTIDO ACCIDENTAL.

En caso de derrame, evitar que el producto llegue a ríos y canales.

Absorber con arena o tierra. Neutralizar finalmente con ácido muy diluido.

Una vez neutralizado el producto derramado llevarlo, a ser posible, a un vertedero controlado. No actuar sin la protección adecuada.

7. MANIPULACIÓN Y ALMACENAMIENTO.

7.1. Manipulación.

El equipo de protección personal deberá prevenir cualquier posibilidad de contacto de la piel y los ojos con el producto. Se usará máscara facial, gafas, guantes de goma, trajes tipo antiácido o impermeable, botas y delantal de plástico.

Se ha de disponer de duchas y lavaojos, e instruir al personal de los riesgos. No fumar ni beber ni comer cuando se maneje o en almacenamiento.

7.2. Almacenamiento.

Separado de ácidos fuertes, metales, alimentos, piensos y materiales combustibles.

Producto no corrosivo para goma, ebonita y plásticos tipo PVC a temperatura ordinaria (40ºC máximo).

Ligeramente corrosivo para el hierro y cobre, hasta el 50% y 50ºC, que provoca un aumento de concentración de estos y otros metales que puede ser perjudicial en ciertos usos.

Para temperatura superior a 50ºC deberán usarse aceros inoxidables y níquel.

Evitar siempre aluminio, estaño, cinc y sus aleaciones (bronce, latón, cromo, plomo, etc.) ya que puedan generar productos explosivos.

Corrosivo para los tejidos y el cuero.

Los tanques han de ser de acero al carbono revestido interiormente de

pintura tipo epoxi para evitar aumento de concentración de hierro. Prever la posibilidad de recirculación a través de cambiadores de calor, para calentar en tiempo frío por encima de 15ºC, siendo conveniente su calorifugado en lugares con bajas temperaturas. Las cambiadoras de calor deberán ser de inoxidable o níquel. Tuberías, bombas y válvulas: inoxidable o níquel.

Juntas: goma, plásticos tipo PVC blando.

Mangueras: goma o plásticos reforzados para temperaturas menores de 40ºC. Restringir su uso a tramos cortos.

Mantener en lugar seco y bien cerrado.

El contacto con la humedad o con el agua puede generar el suficiente calor para producir la ignición de sustancias combustibles.

8. CONTROLES DE EXPOSICIÓN/ PROTECCIÓN INDIVIDUAL.

8.1. Límites de exposición.

Hidróxido sódico: TLV 0.02 mg/m³.

8.2. Protección personal.

Es necesario el uso de traje de protección, guantes protectores, botas y delantal de plástico. Para la protección de la vista debe usarse pantalla facial o protección ocular.

9. PROPIEDADES FÍSICAS Y QUÍMICAS.

Aspecto: Líquido viscoso.
Color: Incoloro.
Olor: Inodoro.
Punto de ebullición: 143ºC
Densidad: (20ºC) 1520 kg/m³
pH (100 g/l agua, 20ºC): 14
Presión de vapor (20ºC): 2 hPa (mbar)
Solubilidad en agua (20ºC): 52%
Viscosidad a 20ºC: 78 mPa·s

10. ESTABILIDAD Y REACTIVIDAD.

Estable. No se conocen causas de inestabilidad.

La sustancia es una base fuerte, reacciona violentamente con ácidos y es corrosiva en ambientes húmedos para metales tales como el cinc, aluminio, estaño y plomo, originando hidrógeno (combustible y explosivo).

Ataca a algunas formas de plástico, caucho y recubrimiento.

Absorbe rápidamente dióxido de carbono y agua del aire.
Genera calor en contacto con la humedad o el agua.

11. INFORMACIÓN TOXICOLÓGICA.

Límite I.P.V.E. 200 mg/m³
LD_{50}: 500 mg/Kg
La ingestión de 5-8 gramos suele provocar la muerte.

12. INFORMACIONES ECOLÓGICAS.

12.1. Impacto medioambiental y ecológico.

El producto produce alcalinización del terreno y los efluentes.
Arrastrar en abundante agua. Evitar que el producto entre en alcantarillas o llegue a cauces de agua.

12.2. Toxicidad.

Peligroso para la fauna y la flora a altas concentraciones. Corrosivo y alcalino, tiene un efecto tóxico sobre peces y plancton. 20 mg/l son mortales para los peces. No provoca la consumición biológica del oxígeno.
A partir de un valor pH provoca efectos corrosivos sobre los peces que pueden ser mortales. Es posible una neutralización en estaciones de depuración.
Toxicidad aguda:
Nocivo para peces: CL_{50}, 96 h (Oncorhynchus mykiss) = 45,4 mg/l (pH=8)
Dafnias: mortal a 156 mg/l (9.1 > pH > 9.5)
Algas: mortal a pH > 8.5

13. CONSIDERACIONES SOBRE LA ELIMINACIÓN.

Para la eliminación del producto, éste se deberá neutralizar con ácido clorhídrico muy diluido. Evacuar el efluente con abundante agua y bajo control del pH. Prestar atención al calor de disolución y a proyecciones producidas por reacción con agua.

14. INFORMACIÓN RELATIVA AL TRANSPORTE.

Nº CEE: 011-002-01-3
Nº ONU: 1824

14.1. Por carretera/ferrocarril.

Clase ADR/RID: 8
Código: C 5
Grupo de embalaje: II
Paneles: 80/1824

14.2. Por vía marítima.

Clase IMDG: 8
Grupo de embalaje: II

15. INFORMACIÓN REGLAMENTARIA.

15.1. Aviso de riesgos específicos.

Clasificación CEE: Corrosivo.
Símbolo de peligro: C
Pictograma:

15.2. Frases R.

R35- Provoca quemaduras graves.

15.3. Consejos de prudencia. Frases S.

S2- Manténgase fuera del alcance de los niños.

S26- En caso de contacto con los ojos, lávenlos inmediata y abundantemente con agua y acúdase a un médico.

S37/39- Usen guantes adecuados y protección para los ojos y la cara.

S45- En caso de accidente o malestar, acuda inmediatamente al médico.

16. OTRAS INFORMACIONES.

Se considera que los datos aquí expuestos son correctos de acuerdo con los conocimientos actualizados, que nuestra fuente de aprovisionamiento posee sobre sus productos. No obstante, no se asegura ni garantiza que sea exhaustiva ni absolutamente exacta. Corresponde, y es responsabilidad

exclusiva del usuario, decidir si dicha información es apropiada para un empleo en particular.