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Design of an industrial process for the topiramate production.

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Hi ha una força motriu més poderosa que el vapor,
l'electricitat i l'energia atòmica: la voluntat.

Albert Einstein

En primer lugar, quería agradecer a mis tutores, el Dr. Manel Vicente y la Dra. Esther Chamarro por su ayuda y dedicación, desde el primer hasta el último día. Han sido un gran apoyo a lo largo de estos meses.

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SUMMARY

Topiramate is a sulfamate substituted monosaccharide derivative which is useful in the treatment of epilepsy (in children and adults), obesity, bipolar disorder, neuropathic pain, migraine and smoking cessation. The production of topiramate consists in two stages, the synthesis of technical topiramate from DAF's, and the purification of technical topiramate to achieve commercial topiramate with 98.9% of purity.

The aim of the project is to plan a batch process in an industrial scale for the synthesis and purification of topiramate. The size of the batch should be enough to allow the annual production of 20,000 kg/year of Topiramate. The batch size is fixed in 1000 kg/batch by "la Agencia Española del Medicamento". (1)

One of the aims of this project is to realize the production with the minimum number of required equipments. This equipments have been dimensioned as well as the mass balance has been made. The heat exchanger system has been dimensioned in the worst operating conditions, to oversize the system and guarantee that if there are any disturbance the system will be able to heat or cool the solution.

The required pipes, valves and pumps have been chosen, taking into account the control parameters in the P&iD.

To carry out the production program, it has been considered that production takes place 24 hours/day, in three shifts, 7 days/week and 48 weeks/year. It has been considered that the plant works approximately 220 days/years and the rest of the days will be for repairing breakdowns in some equipment's, or delays in the receipt of raw materials.

Besides, it has been estimated the occupation time of each equipment and determined the bottleneck of the process. The production is schedule in overlapping campaigns, assuming that the plant works in multipurpose production.

Keywords:.Topiramate, basic enginyering, batch process, scheduling.

RESUM

El topiramato es un fármaco antiepiléptico y estabilizador del estado de ánimo usado principalmente para tratar la epilepsia (tanto en niños como en adultos), problemas de obesidad, trastornos de bipolaridad, dolores neuropáticos, migrañas… La producción del fármaco se realiza en dos etapas, la primera consiste en la síntesis del topiramato técnico a partir de DAF, i la segunda etapa consiste en la purificación del topiramato técnico hasta el comercial cuya pureza será del 98,9% .

El objetivo principal del proyecto es planificar la producción en discontinuo por lotes a nivel industrial para las etapas de síntesis y purificación del producto. El tamaño de lotes debe ser el suficiente para permitir una producción anual de 20.000 kg/año de topiramato el tamaño del cual está limitado en 1000kg/lote por La Agencia Española del medicamento.

Uno de los propósitos del proyecto, es realizar la producción del fármaco con la menor cantidad de equipos. Estos equipos han sido dimensionados a partir de los cálculos realizados en el balance de materia. El intercambiador de carcasa y tubos ha sido diseñado en las condiciones de operación más desfavorables, para de esta manera, al sobredimensionar el sistema se garantiza que, en caso de haber una perturbación en el sistema, el área de intercambio sería suficiente para calentar o enfriar la solución.

Las válvulas, bombas y tuberías han sido escogidas según las necesidades del sistema y teniendo en cuenta los parámetros de control en el Pi&D.

Para llevar a cabo el programa de producción, se ha considerado que la producción se realiza en 3 turnos, trabajando 24h/día, 7 días/semana y 48 semanas/año. Por tanto, se considera que la planta funcionará aproximadamente 220 días/año y el resto de días se realizará el mantenimiento de los equipos, mejoras en el sistema…

Además, se ha estimado el tiempo de ocupación de cada equipo para determinar cuál es la etapa limitante y determinar el tipo de producción más adecuada. La producción se realizará en campañas con solapamiento, debido a que el tiempo de lote es menor y se optimizan mejor los tiempos de ocupación de los equipos trabajando a su vez como una planta multipropósito.

Paraules clau: topiramato , ingeniería bàsica, procesos en discontinuo, scheduling.

1. INTRODUCTION

Topiramate is a sulfamate substituted monosaccharide derivative which is useful in the treatment of epilepsy (in children and adults), obesity, bipolar disorder, neuropathic pain, migraine and smoking cessation. It acts as a carbonate dehydratase inhibitor, sodium channel blocker, AMPA antagonist, GABA agonist and glutamate antagonist.

This product is indicated as initial monotherapy for patients who are 2 years of age and older with partial onset or primary generalized tonic-clonic seizures.

Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36 kg. It is chemically designated as 2,3:4,5Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:

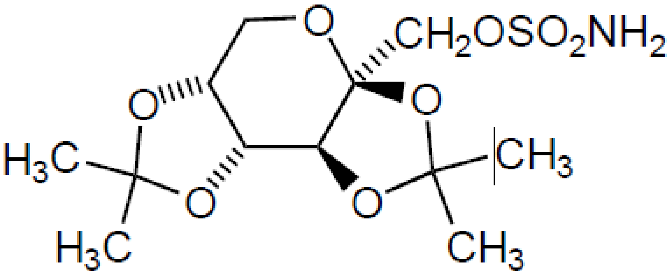


Figure 1:Topiramate structure

Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of between 9 to and 10. It is soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL.

In 2010 Topiramate became a generic active ingredient that had a potential market in Europe, United Estates and South America. As a result, many industries have been recently created to assess the possibility of its synthesis and marketing.

MECHANISM OF ACTION

Topiramate belongs to a class of drugs called sulfamate-substituted, monosaccharide anticonvulsants or antiepileptic drugs. It is still unknown how the drug works. It is thought that it works on certain chemicals, receptors, channels and enzymes .

Preclinical studies have revealed four properties that may contribute to Topiramate's efficacy for epilepsy and migraine prophylaxis:

- Topiramate at pharmacologically relevant concentrations blocks voltage-dependent sodium channels
- Augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor.
- Antagonizes the AMPA/kainite subtype of the glutamate receptor.
- Inhibits the carbonic anhydrase.

The most common side effects of topiramate are:

- Loss of appetite, nausea, diarrhea, weight loss, nervousness, speech problems, tiredness, increased bruising and tingling in arms and legs.
- It effects negatively on the fetus of pregnant women provoking birth defects in some cases.
- High ammonia levels.
- Kidney stones.
- Effects on thinking an alertness (confusion, concentration problems, loss of memory, deficit of attention).
- Loss muscle coordination.
- Eye problems.
- Metabolic acidosis.
- Suicidal thoughts or actions.

1.1. SYNTHESIS OF TOPIRAMATE

Since 1996, when topiramate was marketed, there have been many patents in the synthesis of topiramate. All of them need DAF as an intermediate product but there are different methods of synthesis depending on the reactive that will be used.

The different reactive that can be used are sulfonamide, sulfonyl chloride and sulfuryl chloride. All of them gave good results but the second and the third one has some drawbacks due some unstable and high operation temperatures. Because of these facts the best option is the sulfonyl chloride which has two stages:

- The first one is the production process in the synthesis of DAF's:

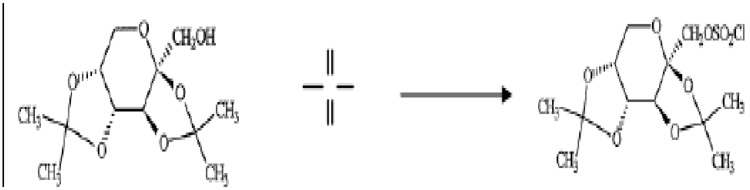


Figure 2. DAF's reaction

- The second one is the Synthesis of Topiramate:

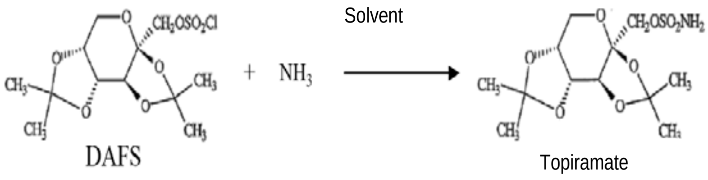


Figure 3. Topiramate reaction

In this case all of the patents use the same conditions, and it is used pyrimidine as detainer of HCl. The differences in the patents can be found in the selection of the solvent that will be used. In these cases, it will be used methylene chloride. All the draft will be based in the patent: US5387700. (3)

1.2. BATCH PROCESSES

In the last decades, batch processes have been used in manufacturing of sport shoes, active pharmaceutical ingredients (APIs), purifying water, inks, adhesives…

These types of processes are very useful specially in fine chemical and pharmaceutical sectors, for their high profitability and their low production volume.

Batch processes have some benefit factors front continuous one:

- It can reduce initial capital investment.
- It is useful for low annual production volume, less than 1kt/year.
- Seasonal production or uncertain demand and short product lifetime.
- It gives flexibility when has operational problems and feedstock variation.

Batch processes are very useful when the reaction time is very long, handling slurries at low flow rate, and rapidly fouling materials. (2)

Of point of view of the design of the basic engineering in the batch plan several plants are designed to be started and dropped frequently for:

- Charging (fill with material).
- Task performing for a specified period of time.
- Shutting down and draining (discharging).
- Cleaning.

2. OBJETIVES

The aim of this project is to study the production process of topiramate allowing to answer the production demands of 20,000 kg/year of topiramate from the DAF's concentrate solution.

The production will be performed in 20 lots/year of 1000 kg each one. To achieve the goals, the following tasks have been proposed:

- Selecting the necessary equipment to reach the annual production, taking as premise the minimum number of equipment.
- Carry out the mass balance and the block and process diagrams, assuming that the final production in the purification process is 1000 kg of topiramate with a 98.9% of purity.
- Size all the necessary equipment's involved in the production process.
- Piping and instrumentation diagram (P&ID).
- Determinate the necessary time to produce one batch and plan the annual production demand assuming the different types of campaigns .
- Production Scheduling.

3. PRODUCTION PROCESS

The Topiramate production process has two differentiated processes: the First process involves the synthesis of topiramate and the second one involves the purification of the previous one .

All the process is going to be studied by batches. Another important aspect is the excess of ammonia. This excess increases the reaction conversion.

The chemical reaction of the production process of topiramate is:

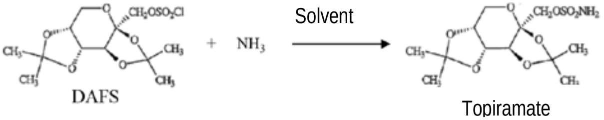


Figure 4. Topiramate reaction

Once the topiramate has been produced a purification of the process is needed to remove the impurities and dry the final product in the desired specification.

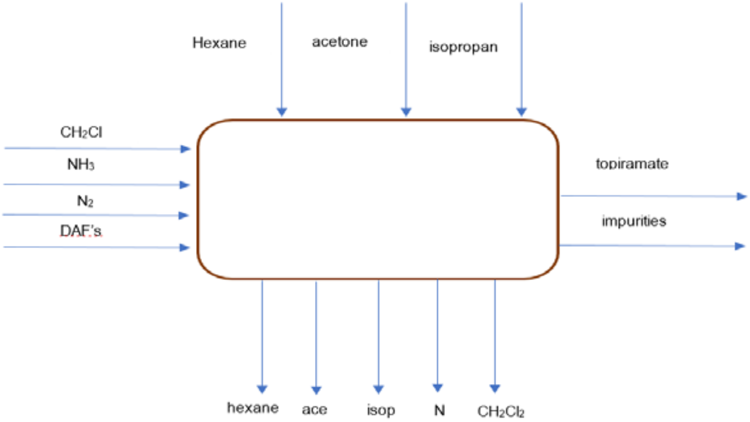


Figure 5. Global diagram of the inputs and oupots of Topiramate production.

3.1. RECIPIE

All the data has been obtained from the patent : US 2012/0232258 A1 and the TGF of Anna Mosser to compare the patent with the pilot plant, and to know which was the amount of topiramate allowed by "La Agencia Oficial del Medicamento" (4)

The block diagram shows the synthesis process of technical topiramate and the purificaction process of this product to obtain the comercial topiramate .

First of all, all the vessels must be inerted with N_2 for 30 minutes approximately.

When V-01 has been inerted, introduce automatically the concentrated solution of DAF's (40%) and turn on the agitation system. Subsequently add the dichloromethane to dilute the solution at 20% which takes 30 minutes.

Once elapsed dilution time, which is assumed approximately 30 min, the ammonia solution is charged slowly during 1 hour into the vessel to provide the required acid medium. Once this procedure is completed agitate the solution during 5 hours until the reaction is completed.

Once the reaction has finished , the solution has to be filtred , in 25 kg lots, and stirred to the second vessel , this procees lasts 1 hour and 30 minutes.

The mixture that has been charged in the second vessel has to be heated up to 65ºC while being agitated to homogenized all the solution and to make sure that the heat exchange will be the same in the whole the vessel. When the mixture has reached the 65ºC, it will be distilled under vacum to remove about 2940 kg of diclrohomethane, which lasts 2 hours.

Subsequently add the hexane solution in V-02 in 10 minutes, the resultant mixture has to be cooled down to 0ºC while being agitated during 30 minutes until the solution is homogenized.

Once this procedure is completed agitate the solution during 4 hours until the crystalization is completed. After that transfer the mixture to the load centrifuge RINA SERIE 300 which has lots of 500 kg and three charges will be needed, each charge takes about an hour and 30 minutes.

While the centrifugation is taking place, fill in the isopropanol and ethyl acetate in the third vessel during 40 minuts. Immediately when the centrigufation has finished add the topiramate from the centrifugate in the V-03 while beeing agitated during 30 minutes until the topiramaten has been disolved.

Once this procedures has been done, filtered the mixture and stirred the solution to the V-04 (about 1.30 hours) and add slowly the hexane solution during 10 minuts.

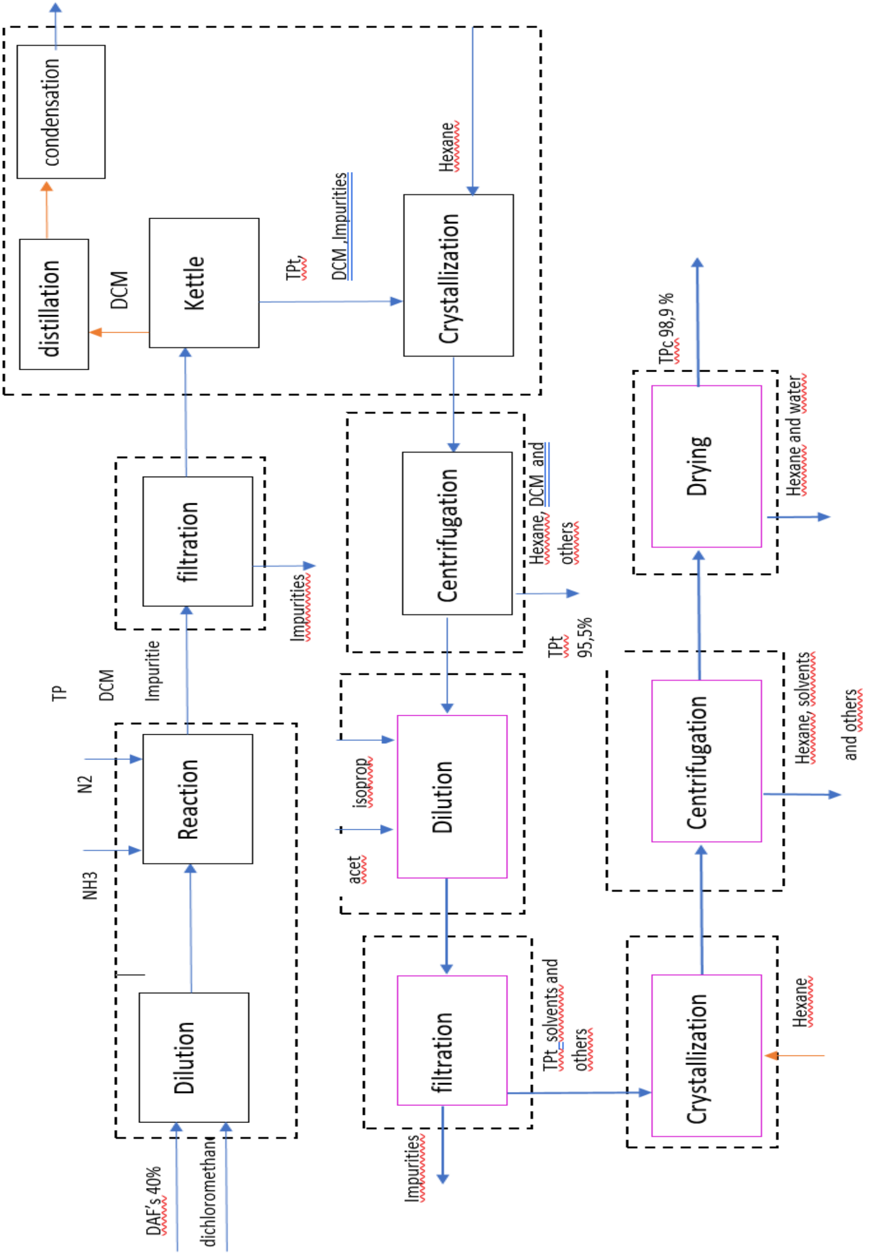
Subsequently when this procedure is done, the resultant mixture has to be cooled down to 0ºC while is being agitated during 30 minuts until the solution is homogenized.

After 4 hours of crystalization the slurry has to been transferred to the load centrifuge, this procedure takes aproximatelly 3 hours, 1.30 hours for each charge.

Finally as soon as the centrifugation is done, stirred the topiramate to a plate dryer to eliminate all the humidity.

3.2. BLOCK DIAGRAM

Block flow diagram gives general information of the process that is being studied. The discontinuous lines in the diagram show the processes carried out in each vessel. The synthesis and the purification process are differentiated as black lines and pink lines in each stage.


DAF's 40%
dichloromethan
Dilution
NH3
N2
Reaction
TP
DCM
Impuritie
filtration
Impurities
Kettle
DCM
distillation
condensation
TPt
DCM ,Impurities
Hexane
Crystallization
Centrifugation
Hexane, DCM and
others
TPt
95,5%
isoprop
acet
Dilution
filtration
Impurities
TPt solvents and
others
Hexane
Crystallization
Centrifugation
Hexane, solvents
and others
Drying
Hexane and water
TPc 98,9 %

3.3. EQUIPMENT SELECTION:

The aim of the project is to carry out the production process with the minimum equipment, multitasking each part of the processes to maximize the efficiency of each machine.

Therefore, with the occupation time of each equipment it has been decided that it will be needed:

- 4 vessels (V-01, V-02, V-03, V-04), vessel one and two will be used in the synthesis process and the others in the purification process.
- 1 filter.
- 1 microwave dryers.
- 1 centrifuge
- 4 centrifuge pumps.

In the first vessel is carried out the dilution of DAF's adding dichloromethane, and the reaction of DAF's with ammonia to produce topiramate. After that it is used a filter before feeding the solution to the second vessel. In this vessel it will take place the concentration and crystallization stages.

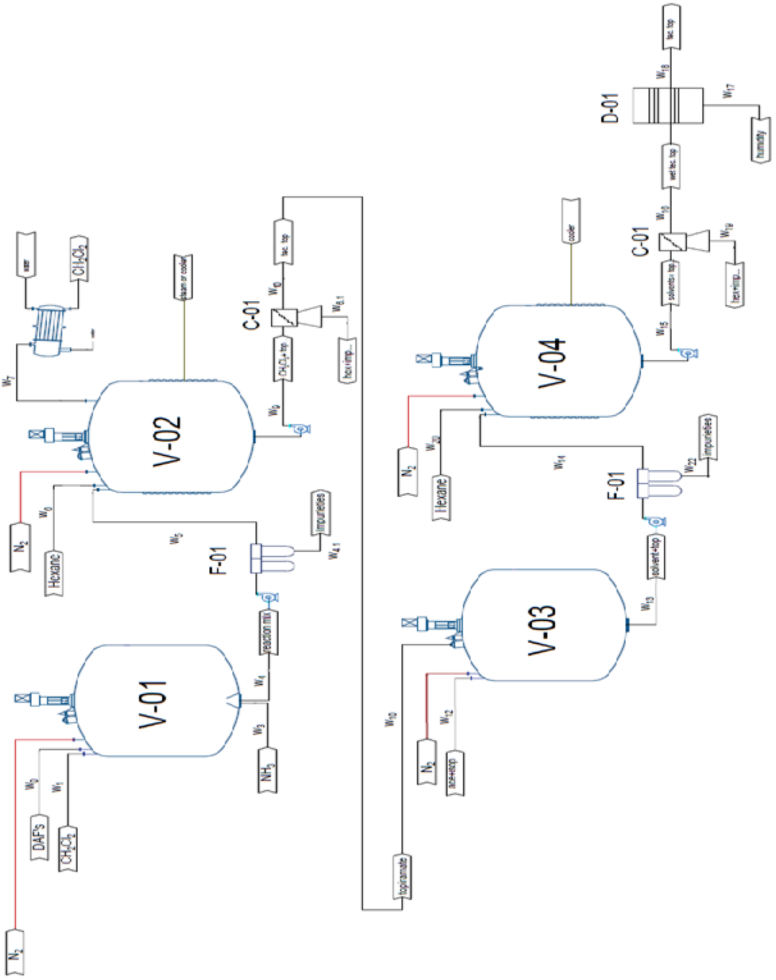
Once it has finished the crystallization, the fluid is taken to a centrifuge.

When the synthetization process of technical topiramate has been finished, it takes place the dissolution of topiramate with ethyl acetate and isopropanol. Once this process has been done it is used a filter before feed the solution to the fourth vessel, where it takes place the crystallization process.

After the crystallization, the fluid is taken to a centrifuge to separate the solid (topiramate) from the liquid (hexane, ethyl acetate, isopropanol…). Finally, it takes place the drying process to eliminate all the moisture that topiramate could have.

4. BASIC ENGINEERING

In the figure it is shown the block diagram of the process.



4.1. MASS BALANCE

Table 1. Mass global balance of synthesis of topiramate

	w0	w1	w2	w3	w4	w4.1	w5	w6	w7	w9	w10	w6.1
top					1112.45		1112.45			1056.83	1051.54	60.91
CH2CL2	2205.26	3675.44	5880.71		5880.71		5880.71		2940.35	2940.35		2829.66
hexano								651.30		651.30	110.69	529.38
impurezas					441.47	46.11	395.36			417.29	55.34	361.94
isopropanol												
acetato												
DAF's	1470.18		1470.18									
NH3				83.74								
total	3675.44	3675.44	7350.88	83.74	7434.62	46.11	7388.51	651,304663	2940.35	5065.77	1217.57	3881.89

	w10	w12	w13	w14	w15	w16	w17	w18	w19	w20	w22
top	1051.54		1051.54		998.96	993.97		989.00	9.00		
CH2CL2											
hexano	110.69		110.69		745.64	160.69	158.69	2.00	584.96	634.96	
impurezas	55.34		55.34	43.02	43.03	9.00		9.00	34.02		12.33
isopropanol		253.56	253.56	253.56	253.56				253.56		
acetato		145.68	145.68	145.68	145.68				145.68		
DAF's											
NH3											
total	1217.57	399.24	1616.82	1604.49	2186.86	1163.66	158.69	1000.00	1027,21438	634.96	12.33

4.2. EQUIPMENT DESIGN.

In this section, all the process required equipment will be itemized, sized, the material will also be chosen and the auxiliary equipment will me mentioned.

As it has been mentioned previously, the process has four vessels, a one strainer, a one centrifuge, and a one dryer. Both vessels, one and two, have the same dimensions due to that the quantity they contain is similar, it happens the same with vessels three and four. Consequently, the auxiliary equipment (agitation system, jacket, condenser…) it will be designed

The material used in all the equipment will be stainless steel because of its high corrosion strength. The most used materials are AISI 304L and AISI 316L. Both are austenitic stainless steel easily deformable. The difference between AISI304L and AISI 316L is that AISI 316L has better corrosion resistance due to the addition of molybdenum. However, AISI 304L has a better welding capacity. Due to it is not corrosive fluid it will be chosen AISI 304L.

4.3. VESSELS.

4.3.1. V-01

In V-1 takes place the dilution of DAF’s adding dichloromethane to the concentrate DAF’s solution. Subsequently the reaction is carried out. The V-01 is pressurized up to 2 atm and previously has been inerted with nitrogen. Due to the pressure condition this vessel must have a greater thickness than V-02. Once the reaction is finished the fluid is taken to the strainer.

In this vessel a jacket is not needed because it works at 20ºC.

The next table contains a summary of the vessels characteristics. However, all the calculations can be consulted in the appendix 2.

Table 2. Characteristics of V-01

Magnitudes	Vessel 1/2
High(m)	2.85
Diameter(m)	1.90
Section (m2)	2.81
Capacity (m3)	8
Exchange area(m2)	16.9

Auxiliary equipment's.

As mentioned before in the V-01 is required:

- An Agitation system to homogenize the solution.
- A pressurized system with nitrogen to ensure that the system is working at 2 atmospheres.
- Scatter to introduce slowly the ammonia and facilitate the homogenization due to the fact that the bubble size is smaller and therefore there is more contact between the reactants.

Agitation system

The impeller has been chosen depending on:

- The flow model (axial, radial or tangential)
- The viscosity of the fluid

In this process is needed an agitation system to ensure an axial flow model, specifically two turbines with blades inclined 45 ª separated 0.75m of high in V-01. This impeller will have six blades and it is especially effective for heat exchanges with vessel walls or internal coils. (5)

Expected at very high Reynolds number, four baffles are needed to prevent vortexing and rotation of the liquid mass as a whole.

The impellers should be of steel AISI 304L due to the resistant corrosion effects.

The next table contains a summary of the agitation system. However, the calculations can be consulted in the appendix 2.

Table 3. Agitation system characteristics

Stirrer diameter (m)	0.64
High of stirrer (m)	2.21
High of the stirrer (m)	0.95
Width and number of baffles (4) (mm)	200
Distance between baffle and vessel(mm)	3.787
Rotational speed (rpm)	60-120
theoretical agitation power (KW)	6
Motor efficiency	0.7
Real agitation power (kW)	8.6

- <u>Operation conditions</u>:

Through the entire period of occupation of the first vessel, that works at 2 atmospheres, some variations are produced in the occupancy level. These variations are shown in the following diagrams:

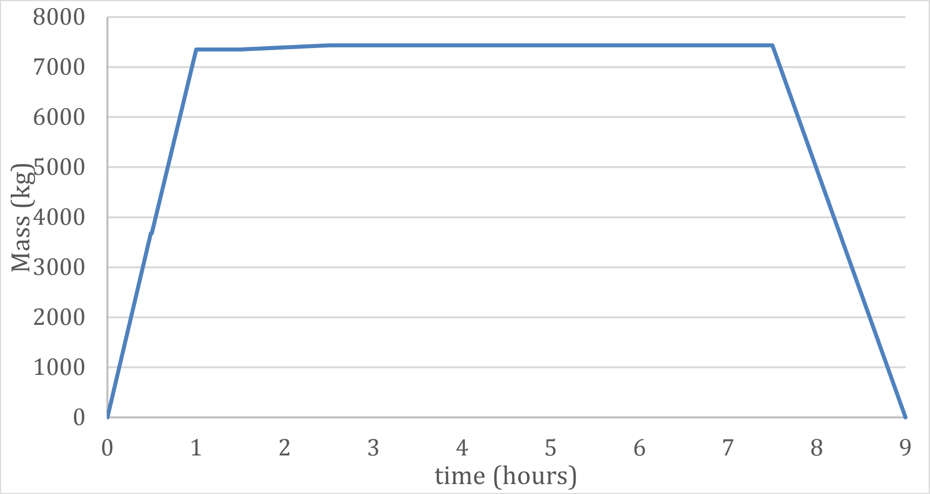


Figure 6. Mass variations in V-01

The temperature of vessel 1 remains constant over time at 20ºC because it works over pressurised and it is not needed a heat exchanger

4.3.2. V-02:

In V-02 takes place the distillation, heating the fluid to 65ºC, and the crystallization cooling the fluid to 0ºC. In this vessel is necessary a jacket because of the heat exchanger system. This vessel has the same dimensions of vessel 1 as it has been commented before

- Agitation system

In V-02 is needed an agitation system to ensure an axial flow model, but in this case it will be necessary two types of impellers because firstly it is carry out the distillation and it is needed a turbine with blades inclined 45 ª and after that it occurs the crystallization and the solution will contain some solids (topiramate) and it will be necessary a U-shaped anchor agitator.

The turbine impeller will have six blades and it is especially effective for heat exchanges with vessel walls or internal coils.

Expected at very high Reynolds number, four baffles are needed to prevent vortexing and rotation of the liquid mass as a whole.

The impellers should be of steel AISI 304L due to the resistant corrosion effects. This stirrer will have the same dimension than the previous one due to the vessel and the density are the same.

The next table contains a summary of the agitation system. However, the calculations can be consulted in the appendix 2.

Table 4. Agitation system characteristics

Stirrer diameter (m)	0.64
High of stirrer (m)	2.21
High of the stirrer (m)	0.95
Width and number of baffles (4) (mm)	200
Distance between baffle and vessel(mm)	3.80
Rotational speed (rpm)	60-120
theoretical agitation power (KW)	6
Motor efficiency	0.7
Real agitation power (kW)	8.6

Anchor agitation is designed for a wide range of viscosities. It can be used in mixing, dissolving and homogenization processes. It has a variable operation speed from 30 o 120 rpm, and in V-02 will be 30 rpm.

Table 5. Agitation system characteristics

Stirrer diameter (m)	1.86
High of stirrer (m)	2.85
High of the stirrer (m)	0.02
Width and number of baffles (4) (mm)	200
Distance between baffle and vessel(mm)	3.79
Rotational speed (rpm)	30
Width of stirrer	0.19

theoretical agitation power (kW)	5.18
Motor efficiency	0.7
Real agitation power (W)	7.4

- <u>Jacket</u>

The V-02 needs a heating system to heat the solution to carry out the distillation and subsequently cool the solution to continue with the crystallization in this vessel.

The fluid that comes from the filter will be 20 ºC hot, for the first vessel, while steam will be at 120 ºC through the jacket. To maintain the vessel at 65ºC, steam will circulate at 120ºC. After that the solution has to be cooled down to 0ºC, to do so, a mixture of glycol and water will circulathe through the jacket at -30ºC.

According to the legislation, the surface of the equipments in which circulates a fluid below 5ºC or over 50ºC has to be isolated. Therefore, the outside of the jacketed will be covered with with glass wool of 70 mm thick, which is considered the minimum required to cover industrial equipment.(6)

The next table contains a summary of the jacket specifications; however all the calculations are explicitly explained in the appendix 2. (7)

To heat and cool the system:

Table 6. Jacketed vessels characteristics to heat and cool the system

Heat exchange [kJ]	$2.13\cdot10^5$
Area of contact [m^2]	2.4
Wsteam [kg/h]	194.2
Area of lateral exchange [m^2]	16.79

Heat exchange [kW]	-78.32
Area of contact [m^2]	10.75
Wsteam [kg/h]	5855
Area of lateral exchange [m^2]	16.79

The necessary area to be able to heat the solution to 65 º is 3.92 m^2 and the area of the jacket vessel is 16.79 m^2 . However, the required area to be able to cool the solution to 0ºC is 10.75 m^2 and the area of the jacket vessel is 16.79 m^2. Therefore, there is enough exchange area to heat and cool the solution.

- Coil and steam

As said before, to heat the solution up to 65ºC it is used water steam circulating through jacketed at 120ºC and two atm.

Also later is requires to cool the solution to 0 ºC as it has been said, to do so , it will circulate through the jacket coolant flow rate (mixture of glycol and water) at -30ºC. This coolant fluid will be offered by plant services.

- Condenser (heat exchanger):

The distillate obtained must be condensed with a heat exchanger that will be designed imposing the length of the heat exchanger, 4 metres, the thickness of the internal tubes, 20 millimetres, and the speed at which the fluid circulates inside the tubes.

The coolant inlet temperature will be 25 ºC and the outlet temperature will be 40 ºC, working at atmospheric temperature. The distillate will remain at 65ºC and slowly will changed the state of steam to fluid.

Furthermore, the following heuristic may be used to estimate the tube passes. The estimated values include the removal of tubes to provide and entrance area for shell nozzle sizes of one-fifth the shell diameter. The formula indicates that square tube layouts must be separated 1.25 time the tube outside the diameter.

The arrangements of the fluid in the shell and tube exchangers are: the steam that has to be condensate circulates through the shell, however the cooler water circulates through the tubes. This is because it is considered that the water is dirtier than the steam.

In the condenser it is needed some baffles are needed to direct some fluid across the tube bundle. They run perpendicularly to the shell and hold the bundle, preventing the tubes from sagging over a long length.

The characteristics of the tubes are fixed. The triangular tube layouts and square tube layouts must be separated 1.25 time the tube outside diameter.

Besides one passes will be chosen where the heuristic.

The characteristics of the tube-and-shell exchanger are shown below, although the calculations can be found in the appendix 2.

Table 7. Characteristics of shell and tube exchanger

Initial conditions	
Heat exchange (KW)	129
Exchange area (m2)	5.39
Global transfer coefficient (J/m2·s·k)	750
Fluid temperature	
T1 of distillate	65
T2 of distillate	65
t1 of cooling water	30
t2 of cooling water	40
Sizes of heat exchanger	
Length (m)	4
Internal diameter (mm)	20
Number of tubes	24
Diameter of tube bundles (mm)	166
Tube distance (mm)	25
Shell diameter(mm)	199

- <u>Operating conditions:</u>

Through the entire period of occupation of the second vessel, that works at atmospheric pressure, some variations are produced with the occupancy level and the temperature of this. These variations are shown in the following diagrams

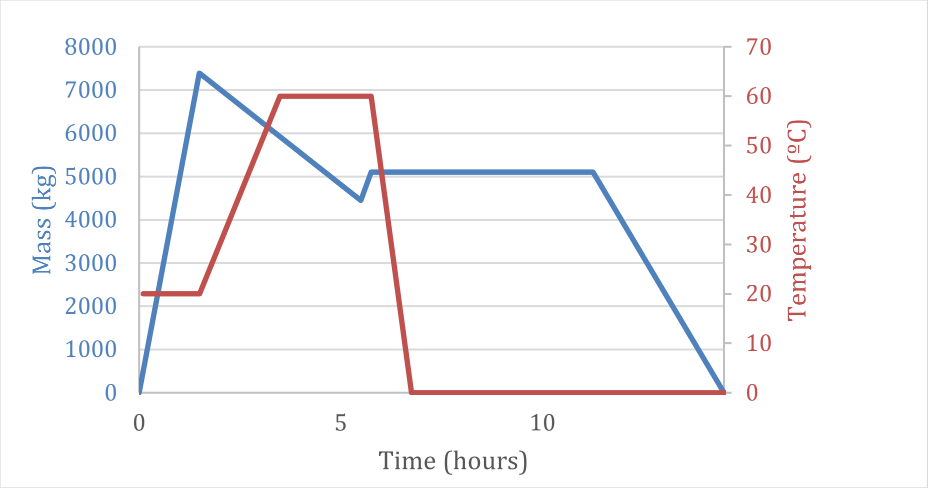


Figure 7. Mass and temperature variations in V-02

The graphic shows that there are some variations in the level due to the variation of the mass. Also the temperature of the vessel it oscillates between 0ºC and 60ºC, this fact is because first of all it is needed to heat the solution to carry out the distillation, once the distillation has been done the solution is cooled to 0ºC to carry out the crystallization.

4.3.3. V-03:

In this part of the process takes place the purification of the topiramate, the removal of the impurities to obtain topiramate with a 98.9% of purity. This process consists in adding some solvents to drag the impurities with them and cool the solution to crystalize the desired product.

In V-03 takes place the dilution of topiramate, adding “isopropanol” and ethylene acetate. Subsequently the agitation is turned on to carry out the dilution. Once the dilution is finished the fluid is taken to the strainer.

In this a jacketed is not needed because it works at 20ºC.

The next table contains a summary of the vessels characteristics, both of them have the same dimensions. However, all the design calculations can be checked out in the appendix 2.

Table 8. Characteristics of V-03 and V-04

Magnitudes	Vessel 3/4
High(m)	1.79
Diameter(m)	1.19
Section (m2)	1.11
Capacity (m3)	2
Exchange area(m2)	6.71

- <u>Auxiliary equipments.</u>

As mentioned before the V-03 and V-04 require an agitation system to homogenize the solution.

- <u>Agitation system</u>

The impeller has been chosen depending on:

- The flow model (axial, radial or tangential).
- The viscosity of the fluid.

In this process is needed an agitation system that assures an axial flow model, but in this case the solution initially contains some solids, topiramate, and it is necessary a U-shaped anchor agitator.

The anchor agitation is designed for a broad range of viscosities. It can be used in mixing, dissolving and homogenization processes. It has a variable speed operation ranging from 30 to 120 rpm, and in V-03 it will be 60 rpm

Expected at very high Reynolds number, four baffles are needed to prevent vortexing and rotation of the liquid mass as a whole.

The impellers should be of steel AISI 304L due to the resistant corrosion effects.

The next table contains a summary of the agitation system, all the design calculations can be checked out in the appendix 2.

Table 9. Agitation system characteristics

Stirrer diameter (m)	1.17
High of stirrer (m)	1.17
High of the stirrer (m)	0.01
Width and number of baffles (4) (mm)	200
Distance between baffle and vessel(mm)	3.79
Rotational speed (rpm)	30
Width of stirrer	0.12
theoretical agitation power (W)	614
Motor efficiency	0.7
Real agitation power (W)	876

- <u>Operation conditions:</u>

Through the entire period of occupation of vessel one, that works at atmospheric pressure. However, some variations are produced with the occupancy level. These variations are shown in the following diagrams:

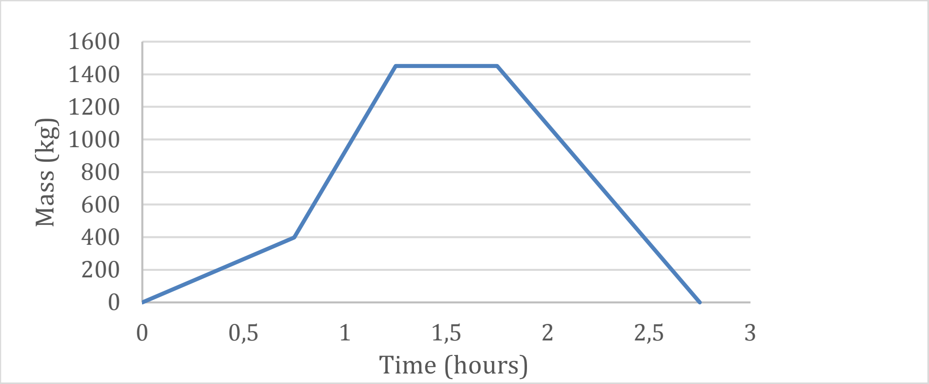


Figure 8. Mass variations in V-03

The temperature of this vessel it remains constant due to the fact that there is only a dilution and it is considered that over time the temperature is 20ºC .

4.3.4. V-04

In V-04 takes place the crystallization, cooling of the fluid to 0ºC. In this vessel it is necessary a jacket because of the heat exchanger required in the system.

This vessel has the same dimensions as V-03 as it has already been commented before

- Agitation system:

In V-04 is needed an agitation system to ensure an axial flow model, but in this case the solution initially contains some solids (topiramate) and it is necessary a U-shaped anchor agitator.

The anchor agitation is designed for a wide range of viscosities. It can be used in mixing, dissolving and homogenization processes. It has a variable operation speed from 30 to 120 rpm, and in V-02 will be 30 rpm .

Table 10. Agitation system characteristics of V-04

Stirrer diameter (m)	1.17
High of stirrer (m)	1.8
High of the stirrer (m)	0.02
Width and number of baffles (4) (mm)	200
Distance between baffle and vessel(mm)	3.79
Rotational speed (rpm)	30
Width of stirrer	0.12
theoretical agitation power (W)	614
Motor efficiency	0.7
Real agitation power (kW)	2

The real power was 876.2 W but in the industry the minimum real agitation is 2 kW, that's why it has been considered this agitation power.

- Jacket

The V-04 needs a heating system to cool the solution to carry through the crystallization in V-04.

The fluid that comes from the filter will be at 20ºC, for the third vessel, while glycol will be at -30ºC through the jacket. To maintain the vessel at 0ºC, will circulate through the jacket coolant flow rate (mixture of glycol and water) at -30ºC.

The next table contains a summary of the jacket specifications, however all the design calculations can be checked out in the appendix 2.

Table 11. Jacketed vessels characteristics

Heat exchange [kW]	-52.5
Area of contact [m^2]	6
Wsteam [kg/h]	1570
Area of lateral exchange [m^2]	6.7

The necessary area to be able to cool the solution to 0 º C is 6.05 m^2 and the area of the jacket vessel it's 6.72 m^2 therefore, there is enough exchange area to cool the solution to perform the crystallization

- <u>Cooler</u>

As it has already been said before, to cool the solution up to 0ºC to perform the crystallization it is used a coolant circulating through the jacketed at -30ºC . The coolant is a mixture of glycol and water and will be offered by plant services.

- <u>Operating conditions:</u>

Through the entire period of occupation of vessel four, that works at atmospheric pressure. Some variations are produced with the occupancy level and the temperature. These variations are shown in the following diagrams:

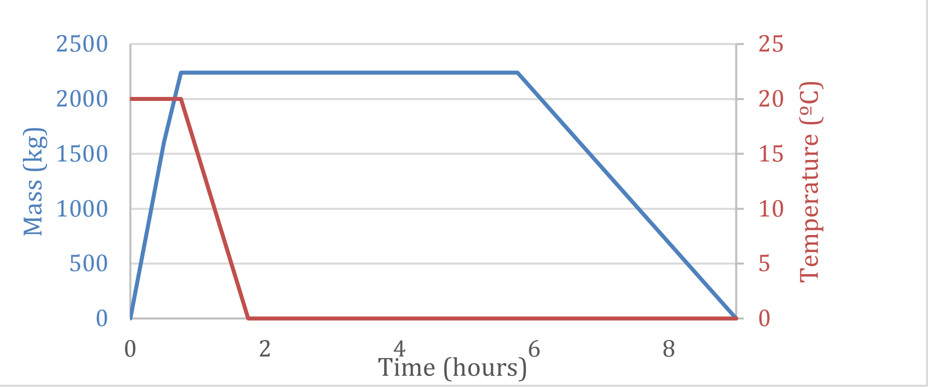


Figure 9. Mass and temperature variations in V-04

The graphic shows that there are some variations in the level due to the mass variation. Besides the temperature of the vessel oscillates between 0ºC and 20ºC, this fact is because in the beginning the solution it is at 20ºC but then it needs to be cooled down to 0ºC to carry out the crystallization.

4.4. CENTRIFUGE

A batch centrifuge is used to separate the solids from the liquids in the feed stream. In this process is needed to separate the solid (topiramate) from the liquid (hexane, dichloromethane…)

The needed centrifuge will be RINA Serie 300, that works automatically and it has a vertical axis. (8)

The most common uses of this type of centrifuge are in the chemical industry, pharmaceutical.

As discussed above, Rina works automatically, and there are two types: filterer (F) and decanter (D). In topiramate production process it will be necessary a filterer centrifuge to eliminate all the impurities and the liquid in the topiramate slurry.

The Rina batch operation is:

1. First of all, it is needed to intertie the centrifuge.
2. The feed slurry is feed.
3. Previously wring.
4. Washer
5. Final wring.
6. Solid discharging or download.

The centrifuge dimensions will be shown in the Table 13.

Table 12. Characteristics of the centrifuge

Model	Capac. dm3	Charge kg	Veloc. rpm	Weight kg	dimensions width/long/height mm
300F1250x710	440	550	1200	6600	2000x2565x2600

The mass charge will be 550 kg because it is better to perform two charges, and works with an small volume of slurry because it is more easy, it needs lees time to charge and it will be cheaper to buy a smaller centrifuge and it also occupies less space in the plant.

4.5. TRAY DRYER

At the end of the process is necessary to eliminate all the moisture that can have the topiramate. That's why it will be used a tray dryer.

Tray dryer is an enclosed insulated chamber in which trays are placed on top of each other. Heat transferation is done by circulation of hot air using an electric heater or steam in radiator coils. Blower fans are installed inside to ensure proper circulation and transfer of heat. Outside the dryer a control parameter of temperature is fixed.

The advantages of this type of dryer:

- In the tray dryers the loading, unloading, etc. can be done without losses.
- The tray dryer operates batch wise. Batch drying is used extensively in the manufactures of the pharmaceuticals.
- Each batch of the material can be handled as a separated.
- The batch sizes in this type of industry process are smaller the ones used in the chemical industry
- The same equipment can be used in drying a wide variety of the materials.
- Valuable products can be handled efficiently.

But there are some disadvantages that must be taken into account in the operation time: tray dryers require more labour to load and unload the product, so the operating time is higher. Hence increases in the cost.

The dimensions of the dryer in the topiramate production will be:

- 10 trays
- Each tray will have 4 cm of thickness.
- The total charge for each batch will be 500 kg.
- The porousness of the tray will be about 30 or 40%

The dryer can operate at atmospheric or vacuum pressure. If it works at vacuum pressure the air does not circulate through the solid, a temperature gradient is generated where only the tray is heated. Because of this the dryer will be operated at atmospheric pressure knowing that if the temperature it increases a lot, the topiramate can be discomposed.

It will be necessary to perform two drying processes because it has been chosen a small dryer to make the investment cheaper, and it also takes up less space in the plant.

4.6. PIPING

Piping:

Industrial process piping can be manufactured from wood, fiberglass, glass, steel, aluminum, plastic, cooper and concrete. In this case the piping system will be made out of stainless steel, specifically of AISI 304L, as mentioned before AISI has a high corrosion resistance, it is easily deformable, and it has good welding capacity.

To calculate the pipes dimensions, the speed of the fluid has been imposed knowing that it should be between 1 and 2 m/s. In this case it has been chosen the lowest speed to oversize the system and avoid possible failures. Reducing the speed, the diameter increases and consequently the dropping pressure reduces.

Once the speed has been imposed, it will be calculated the pipe dimensions and subsequently it will be chosen by commercial catalogues:

One important thing to consider is the importance of the pipe color-coding to be able to keep track of what is in each pipe and where it is going. The color of a label is one of the most important labeling features because people will be able to see it from a distance.

The fluids that circulate through the system and the color of each pipe will be:

- Water steam to heat the V-02, the color of the pipe will be red because it is steam and it will be necessary auxiliary white lines to indicate that it is water steam.
- Ammonia to do the reaction in V-01, the color of the pipe will be orange to indicated that an acid circulates through the pipe.
- N_2 to inert all the vessels, the color of the pipe will be yellow to indicate that is a vapor and it will be necessary auxiliary double lines to indicate that it is nitrogen gas.
- Cooler to cool the V-02 and V-01, the color of the pipe will be white that indicates that a refrigerant fluid circulates through the pipe.

Table 13. Piping sizes

	V-01	V-02	V-03	V-04
d_{ext} (mm)	65	36	23	23
d_{int} (mm)	53	30	19	19
e (mm)	3	2	1	1
d_{nom} (")	2 1/2	1 1/2 --> 2	1	1 --> 2

All the pipes have been designed around the vessels. It will be considered that the best option, once it has been normalized the pipe's size of V-02 will be 2", is excepting the feeding pipes in each vessel that will be 1". This size is due to the fact that it circulates slurry through the pipe and if the size is too small it can be plugged. The same thing happens with the pipes of vessel 4

Valves:

A valve is a device that regulates, directs or controls the flow of a fluid by opening, closing, or partially obstructing various passageways. Valves can be classified according to how they are actuated: hydraulic, pneumatic, manual, solenoid valve or motor.

In this project four types of valve are clearly differentiated, ball valves, butterfly valves, security valves and check valve.

Ball valves are a form of quarter-turn valve which uses a hollow, perforated and pivoting ball to control flow through it. It is open when the ball's hole is in line with the flow and closed when is pivoted 90 degrees. This valve it will be used in controlling the level of the vessel. If there are any disturbances in the level, the valve manipulates the flowing fluid preventing its passage. In this way a spill is prevented.

Butterfly valve is a valve that isolates or regulates the flow of a fluid. The closing mechanism is a disk that rotates. The operation is like that of a ball valve. Butterfly valves are generally favored because they cost less than another valve designs. The disc is positioned in the center of the pipe. A rod passes though the disc to an actuator on the outside of the valve. The rotation of the actuator turns the disc either parallel or perpendicular to the flow. This type of valve that will be used in controlling the temperature of the vessel. The control valve will manipulate a flowing fluid to compensate for the load disturbance and keep the regulated process variable chosen as possible to the desired set point.

Check valve or non-return valve is a valve that normally allows fluid to flow through it in only one direction. This valve are two-port valves, they have two openings in the body, one for the fluid to enter and the other for fluid to leave. It will be used in the N_2 system and with pumps.

Safety valve is a valve that acts as a fail-safe. It will be useful in the autoclave vessel which automatically releases a substance from the pressurized vessel when the pressure or temperature exceeds the preset limits.

Pumps

Pumps can be classified by their method of displacement into impulse pumps, speed pumps, gravity pumps, positive displacement pumps, steam pumps and valveless pumps. But there are two basic types of pumps: positive displacement and centrifugal. Although centrifugal pumps are the most common.

Centrifugal pumps develop pressure by increasing the velocity of the liquid and this is literally flung out of the cutwater. However positive displacement pumps allow liquid into an open cavity, trap the liquid in the pumps, transport liquid from the suction to discharge port and mechanically force liquid out of the pump.

The usually parameters needed to be able to choose the pump type are:

- Required flow impulse of the system.
- Total dynamic head (TDH): it must be known the difference between the total load and the total suction pressure, considering the friction losses.
- Position of the pump: it is necessary to know the arrangement of each pump because these effects the pump lock.
- Operating conditions: the pressure of suction and the temperature and the corrosivity of the fluid will determinate the material of the pump.
- Physical properties of the fluid: density of the circulant fluid, which will allow to calculate the viscosity of the fluid.
- Corrosivity and the presence of suspension solid.

In addition, the cavitation is a hydrodynamic effect that occurs when the liquid in a pump turns into vapor steam at low pressure. It occurs because there is not enough pressure at the suction end of the pump, or insufficient Net Positive Suction Head available (NPSHa). Cavitation happens when the temperature and pressure of the liquid at the suction of the impeller equals the vapor pressure. It can happen at low pressures and normal operating conditions. Therefore, the pressure in the stream must be greater than the vapor pressure of the fluid inside the pump.

In this project, it has have been selected centrifugal pumps for this operating conditions and characteristics also being the most common pumps used in the industry. Furthermore, the viscosity, density, corrosivity and toxicity of the fluid are too low.

The material of the pump will be AISI 304L due to the corrosion resistance and the low corrosivity of the fluid it is not necessary AISI 316L.

It will be necessary one pump after each vessel to guarantee the circulation of the fluid.

4.7. MICRONIZATION

In pharmacology, it is very important the bioavailability which it refers to the degree and rate at which the drugs administrated are absorbed by the body’s circulatory system. When a drug is administrated intravenously, it has a bioavailability of 100% but if it is taken orally, it quickly reaches the stomach, dissolves and the bioavailability is lower. To increase this parameter, it is needed to reduce the particle size.

In this process once obtained the commercial topiramate the particles sizes have to be reduced to guarantee the bioavailability.

Due to this it is needed a micronization which reduces particles down to the micrometre or, in some cases, nanometer size. It is usually used to improve the bioavailability of poorly soluble APIs by increasing particle surface area and accelerating dissolution rates. In this process the particle size of topiramate will be reduced to 10 µm.

The desired particle size is achieved by means of three variables: the flow rate, the venturi pressure and the pressure of the micronization chamber. Therefore, an increase in the micronization pressure or decrease in the flow rate speed involves a decrease in particle size.

First of all, topiramate will be injected under high pressure in a gridding chamber using gas flow, it can be used compressed air or nitrogen. The particles of the product dragged by the flow at very high speed, due to the geometry of the chamber, which are subjected to speed and direction variations with auto collision and consequent dimension reduction to values settled by the “la Agencia Española del Medicamento”.

It will be used a traditional technique of micronization due to the easiness of the process but the sizing and specification of this is outside the scope of the project.

All the equipments have been sized and specified with the exception of pumps and micronizer which are designed by vendor and are out of the reach of this project.

4.8. PLANT SERVICIES AND STORAGE

In the production process of topiramate it is needed some services that will be offered by the plant:

- Nitrogen steam that will be used to inert all the vessels when needed. First of all the hydraulic closure is done adding some of the solution to guarantee the process. Also, it is used to discharge faster providing more pressure in the vessel.
- Water steam that it is needed to heat the solution in V-02 to carry out the distillation at 60ºC. Also, it is used to keep the vessel temperature constant in 60ºC.
- Cooling fluid it is used to cool the V-02 and V-04 at 0ºC, the coolant is a mixture of glycol and water that circulates through the jacketed at -30ºC.
- Ammonia that it is necessary to carry out the reaction in the V-01, the ammonia will be provided in liquid phase and in containers. The container required dimensions are 850 L, with a 450 kg of capacity and 2.15 m of length.

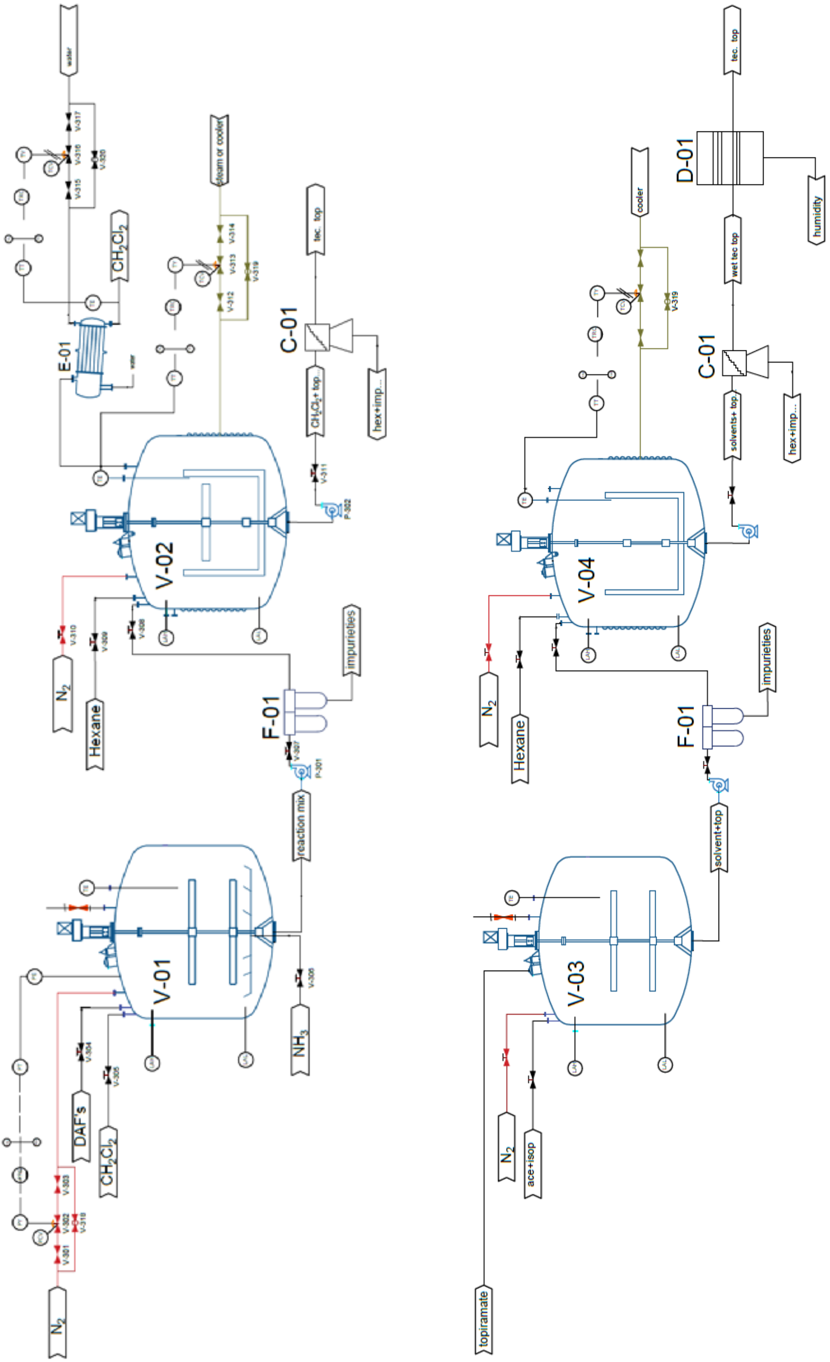
5. PI&D

In this section it will be shown the Pi&D (Piping & Instruments Diagram) of the process. The Pi&D is a detailed diagram in the process industry which shows the piping and vessels in the process flow, together with the instrumentation and control devices.

First of all, it will be show the Pi&D of the topiramate production process. It will be shown in two sections, synthesis of topiramate and purification process.

After that, it will be shown the control parameters of each vessel.

The Pi&D has been made with AutoCAD.


water
V-317
V-316
V-315
V-320
TIC
TRC
TT
CH_2Cl_2
TE
E-01
water
steam or cooler
V-314
V-313
V-312
V-319
tec. top
C-01
CH_2Cl_2+ top...
hex+imp...
V-311
P-302
V-02
V-310
V-309
V-308
N_2
Hexane
LAH
LAL
impurieties
F-01
V-307
P-301
reaction mix
V-01
TE
V-306
NH_3
V-304
V-305
DAF's
CH_2Cl_2
V-301
V-302
V-318
V-303
N_2
topiramate
N_2
ace+isop
V-03
solvent+top
F-01
impurieties
N_2
Hexane
V-04
cooler
V-319
C-01
solvents+ top
hex+imp...
wet tec top
D-01
humidity
tec. top

5.1. CONTROL PARAMETERS

5.1.1. Vessel 1

It will be needed the control of the different parameters of the vessel:

- Level of liquid inside de V-01, with an alarm that indicates if the filling level it's too high or too low. The aim of this type of control is to make sure that there will not be a spill over. In case that the level of the liquid will be too high, the control system will close all the feeding valves.
- An anticipated control of the DAF's concentration it is needed to know the amount of solvent needed to dilute the solution to make sure that the reaction with ammonia will work on the optimal parameters. This preventive control is necessary to ensure the concentration of one of the reactants.
- Control of pressure in V-01 because it is an autoclave vessel that works at 2 atmospheres. If the pressure increases, the reaction it will not work on the optimum parameters and it can end up with a leakage due to the fact that it is working with organic volatile compounds, which can produce an accumulation of gases inside the V-01 and overpressure inside the vessel. Because of this, it is needed a vent valve for avoid overpressure inside the vessel.
- Control of the temperature inside the vessel with a temperature meter to prevent an increment of this in the vessel. If the temperature of the reaction increases uncontrollably the vent valve will be opened to decrease the pressure and consequently the temperature. In this vessel it is not needed a jacketed due to it works at 20ºC and the reaction it is not exothermic.

5.1.2. Vessel 2

- Control of temperature inside the vessel 2 to prevent an increase or decrease of the fluid inside the vessel. This temperature meter acts modifying the coolant or steam flow inside the jacketed to work on the optimum parameters. In this vessel the importance of having the desired temperature it is very important to work in the optimum conditions, assuring that the distillation will be produce at 60ºC and the crystallization would be done at 0ºC.

- The liquid level inside de V-02, with an alarm that indicates if the filling level it's too high or too low .The aim of this type of control is to make sure that there will not be a spill over. In case that the level of the liquid will be too high, the control system will close all the feeding valves.

5.1.3. Vessel 3

- Level of liquid inside de V-03, with an alarm that indicates if the filling level it's too high or too low. The objective of this type of control is assure that there will not be a spill over. In case that the level of the liquid will be too high, the control system will close all the feeding valves.
- Control of temperature inside the vessel with a temperature meter to prevent an increment of the temperature in the vessel and to prevent an overpressure inside the vessel because an increment on the temperature. In this vessel the temperature will be constant due the fact that only a dissolution occurs. Because of this it is not necessary a jacketed.

5.1.4. Vessel 4

- Control of temperature inside the vessel 4 to prevent an increase or decrease of the fluid inside the vessel . This temperature meter acts modifying the coolant flow inside the jacketed to work on the optimum parameters. In this vessel the importance of having the desired temperature it is very important to work in the optimum conditions, assuring that crystallization can be done at 0ºC.
- Level of liquid inside de V-04, with an alarm that indicates if the filling level it's too high or too low . The objective of this type of control is to assure that there will not be a spill over. In case that the level of the liquid is too high, the control system will close all the feeding valves.

5.1.5. Condenser

- Control of cooler flow to assure that there will be enough flow to condensate the dichloromethane. This flow meter acts modifying the coolant flow inside the condenser.

6. SCHEDULING

Once the process is fully understood, the equipment sizing and the tasks have been decided it is time to set the pace of production to achieve the annual of product production.

General considerations.

Scheduling of batch operations is an important area of batch process systems engineering which attention has been increasing in the last decade.

Scheduling is the process of arranging, controlling and optimizing work and workloads in a production process of manufacturing process. It is used to allocate the plant and machinery resources, plan production processes and purchase materials.

The scheduling problem is to:

- Determine the order in which tasks use equipment and resources are used.
- The detailed timing of the execution of all tasks so as well as optimizing the plant performance.

Scheduling is a critical issue in batch processes and is crucial for improving production operation.

6.1. BATCH TIME

The annual minimum production of topiramate to be achieved is one that is able to meet the needs of the annual demand of 20,000 kg. As already mentioned above, the nominal batch size that has been chosen is 1000 kg topiramate in each lot, so the production scheduling has to ensure the production of 20 lots.

To carry out the production program, it is considered that production takes place 24 hours/day, with three shifts, 7 days/week and 48 weeks/year. It is considered that the plant works approximately 220 days/years and the rest of the days will be for repairing breakdowns in some equipment's, or delays in the receipt of raw materials.

Assuming this type of delays the real-time production of the plant is 4500 h/year

In this process the limiting factor is not the labour time operation but the time occupation of the equipment, that determinates the time of each batch.

Table 14. Time study for a batch

	Operation	TO [h]	Labor time operation [h]
V-01	charge solution	0.50	0.25
	charge Ch2CL	0.50	0.25
	agitation	0.50	0.00
	NH3	1.00	0.25
	time of reaction	5.00	0.50
	empty vessel	1.50	1.00
	cleaning	1.50	1.50
	total	10.50	3.75
F-01	first charge	0.50	0.25
	cleaning	0.50	0.50
	second charge	0.50	0.25
	cleaning	0.50	0.50
	total	2.00	1.50
V-02	charge	1.50	0.00
	heat	2.00	0.25
	distillation	2.00	0.25
	charge hexane	0.25	0.25
	cool	1.00	0.25
	crystallization	4.00	0.50
	quality control	0.50	1.00
	empty vessel	3.25	0.00
	cleaning	1.50	1.50
	total	16.00	4.00
C-01	charge	0.17	1.00
	centrifuge	0.33	0.00
	empty	0.67	0.50
	cleaning	0.33	0.50
	total time	1.50	2.00

	Operation	TO [h]	Labor time operation [h]
	charges *3	4.50	6.00
V-03	charge isop+acet	0.75	0.75
	introduce topiramate	0.50	1.00
	agitation	0.50	0.00
	empty vessel	1.00	0.75
	cleaning	1.50	1.50
	total	4.25	4.00
F-01	first charge	0.50	0.25
	cleaning	0.50	0.50
	total	1.00	0.75
r4	charge	0.50	0.00
	charge hexane	0.25	0.25
	cool	1.00	0.25
	crystallization	4.00	0.50
	empty vessel	3.25	0.00
	cleaning	1.50	1.50
	total	10.50	2.50
C-01	charge	0.17	1.00
	centrifuge	0.33	0.00
	empty	0.67	0.50
	cleaning	0.33	0.50
	total time	1.50	2.00
	charges ·2	3.00	4.00
D-01	charge	0.50	1.00
	dry	5.63	0.00
	empty	0.25	1.00
	cleaning	1,00	1.50
	Total time	6.38	3.50
	Charge·2	12.75	7.00

The following table shows the estimated time duration of each stage in the production process of topiramate:

Table 15. Ocupation time of equipments

	ti	tf	OT_j
V-1	0	10.50	10.50
F-1	7.50	9.50	2
V-2	7.50	23.50	16
C-1	18.75	23.25	4.50
V-3	18.75	23.00	4.25
F-1	20.50	21.50	1
V-4	20.50	31.00	10.5
C-1	26.25	29.25	3
D	29.25	42.00	12.75

Also in this process, it is used the same filter and centrifuge in both of processes , production and purification, therefore the occupation time of each team is :

Table 16. Ocupation time of each equipment

	Tmin	Tmax	OT_j
V-1	0	10.5	10.5
F-1	7.50	21.50	14
V-2	7.50	23.50	16
C-1	18.75	29.25	10.5
V-3	18.75	23	4.25
V-4	20.5	31	10.5
D-1	29.5	42	12.5

As it can be seen, vessel 2 regulates the limitation time of the whole process, which it takes sixteen hours and the required time of production process is 42 hours

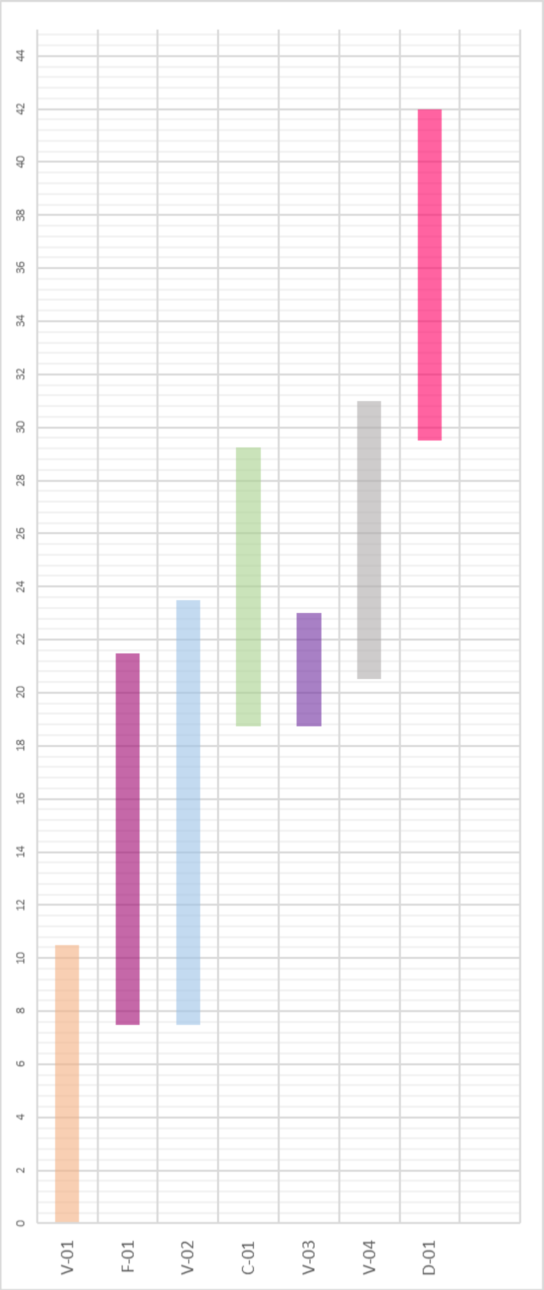


Figure 10. Ocupation time in 1 lot

Production in non-overlapping campaign.

Production in non-overlapping campaign consist in producing one lot after another, successively without starting the next batch without completing the previous one.

$$Msn = BT \cdot N$$

$$\mathrm{N} = \frac{\mathrm{MSn}}{\mathrm{BT}} = \frac{4500 h/year}{42\ h/batch} = 107.14\ batches/year$$

$$107.14\frac{batches}{year} \cdot \frac{1000kg}{batch} = 107140\ kg/year$$

It will be able to work with non-overlapping campaign because of the aim of this project is to produce 20,000 kg/year. It should be checked which of the production methods is the best option to guarantee the annual production

Production in overlapping campaign

Production in overlapping campaign consists in optimizing the production time starting the next lot without letting the previous one finish.

In this type of production, the cycle time is been given by the occupation time of the limiting equipment, in the production of topiramate the limiting equipment is the Vessel 2, where is it carried out the distillation and the crystallization. The cycle time is 16 hours (CT).

$$Msn = BT + (N-1) \cdot CT$$

$$N = \frac{MSn - BT}{CT} + 1 = \frac{4500\frac{h}{year} - 42\frac{h}{batch}}{16\frac{h}{batch}} + 1 \quad = 279.62\ \frac{batch}{year}$$

The table of the production in an overlapping campaign it can be found in appendix

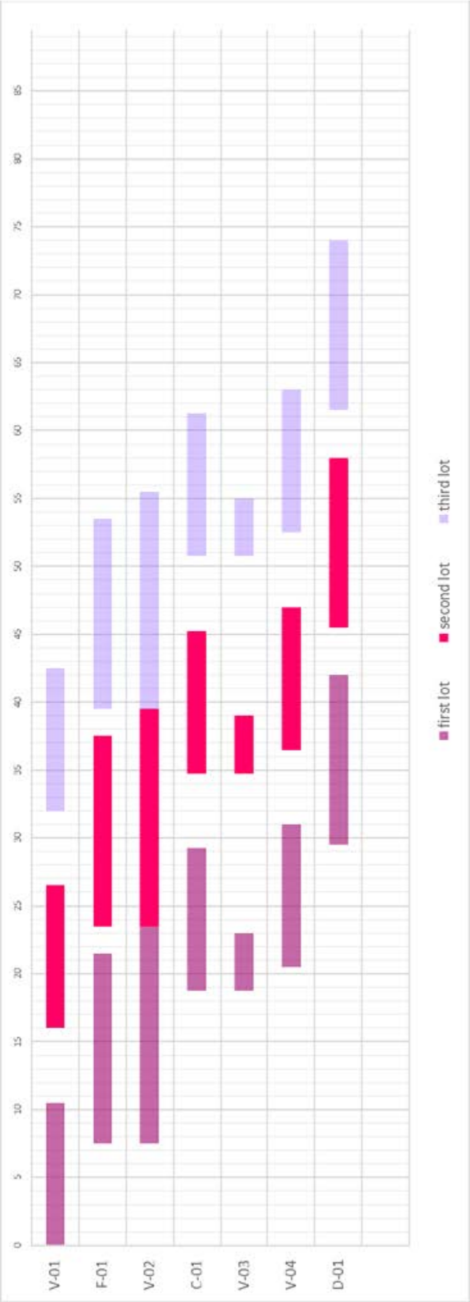


Figure 11. Ocupation time in overlapping campaign

The production in overlapping campaign allows producing more lots than the necessary, therefore allows that once the production process is finished it can be used for another process.

Both types of production will be able to produce the necessary annual demand of topiramate, but there are some benefits in the production in an overlapping campaign:

- The time of a cycle is lower than in non-overlapping campaign, making it easier to produce other products while the production of topiramate has been done. Therefore, in a year, more than one product can be produced.
- Besides the equipment's has more occupation time avoiding that some equipment will not be paused for much time.

Hence it will be produced topiramate in overlapping campaign to enable to produce the product in less time and the plant will be work in 0 wait.

6.2. HIGHEST CAPACITY

The highest production process it will be when it works with an overlapping campaign because it allows to produce more lots in less time due to the fact that the occupation time it is more profitable.

$$Msn = BT + (N-1)\cdot CT$$

$$N = \frac{MSn - BT}{CT} + 1 = \frac{4500\,\frac{h}{year} - 42\,\frac{h}{batch}}{16\,\frac{h}{batch}} + 1 \quad = 279.62\ \frac{batch}{year}$$

As it has seen before the highest production will be produce in 279,62 batches:

$$279.62\ \frac{batch}{year}\cdot\frac{1000kg}{batch}\cdot\frac{1t}{1000kg} = 279.62\,\frac{t}{year}$$

6.3. MULTIPURPOSE PRODUCTION

As it has been mentioned before it will be produced topiramate in an overlapping campaign to enable to produce the product in less time and the plant will be work in 0 wait.

In normal conditions to produce 200000 kg of topiramate, 20 lots are needed, so there are different production campaigns. By “La Agencia Española del Medicamento “, the batch size is specified in 1000 kg. As mentioned above, 20 lots are necessary, but it could be produce in one, two ore more campaigns

6.3.1. Working in one campaign.

Working in one campaign involves that 20 lots are produced:

$$Msn = BT + (N-1) \cdot CT$$

$$Msn = 42 + (20-1) \cdot 16 \rightarrow 346\ h$$

If it works in one campaign the occupation time is 346 h, this entails 8% of the total occupation time. This type of production has some disadvantages. For example, there is too much stock, and a high volume of storage is necessary. Due to this fact it is considered working in two or four campaigns.

6.3.2. Working in two and four campaigns.

Working in two campaign involves that 10 lots are produced in each campaign:

$$Msn = BT + (N-1) \cdot CT$$

$$Msn = 42 + (9-1) \cdot 16 \cdot 2 \rightarrow 372\ h$$

Working in four campaign involves that 5 lots are produced in each campaign:

$$Msn = BT + (N-1) \cdot CT$$

$$Msn = 42 + (5-1) \cdot 16 \cdot 4 \rightarrow 424\ h$$

N. CONCLUSIONS

Once having concluded this project, here are exposed the conclusions obtained:

- It is wanted to carry out the production process with the minimal number of equipments, concluding that there must be four vessels, one filter, one centrifuge and one dryer, each one with its respective auxiliary equipments.
    - Initially it was considered that only two vessels were needed, but the fact that the synthesis and production process volumes are too different, and there will be oversizing in purification process it has been decided that it is needed 4 vessels.
- The design of the outer jacketed in V-02 and V-04 is enough for the heat exchange because it has been oversized so there is no need to design the bottom part of the vessel. The jacketed has been dimensioned in the worst operating conditions, to oversize the system and guarantee that if there are any disturbance the system will be able to heat or cool the solution.
- In the anchor impellers the flow is turbulent although it should be laminar, probably this because the agitation power which it is too fast and it should be less than 30 rpm to guarantee the laminar flux.
- The pipping size of the system is about 1 “, in some cases when a liquid circulates through the pipes, but when the reaction has been done and there is a slurry, the pipping has to be higher to guarantee the circulation and prevent that the solid clogging the pipe.
- Working in two campaigns or four campaigns is better than working in only one, due to the fact that working in only one it is better for the producing view but there is too much stock. However, working in two or more campaigns it is better for the operational, logistic and sales, point of view. Therefore, the plant will work in four campaigns because the occupancy of the equipments is not 100%. This allows the plant to work in multipurpose as it has been mention before.

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ACRONYMS

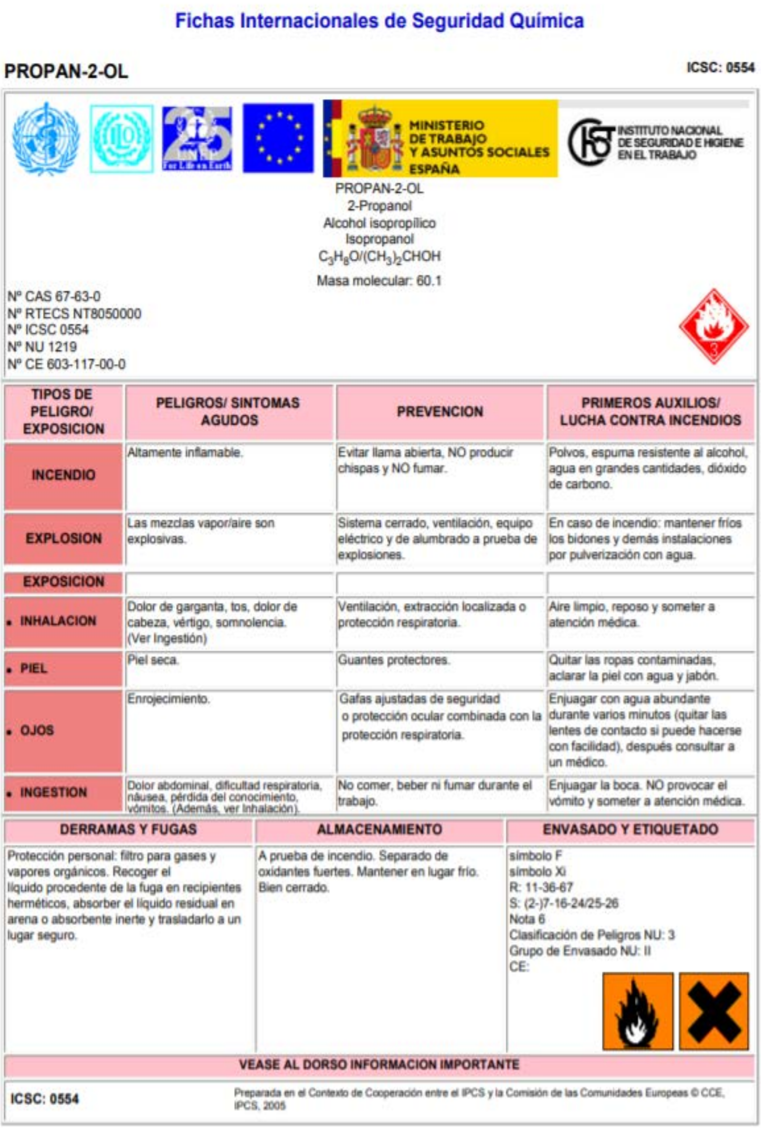
A	Area [m^2]
acet	Ethylene acetate
atm	Atmospheres
BT	Batch time [h]
C-01	Centrifuge
CH_2Cl_2	Dichloromethane
Cp	Calorific capacity [J/(kg·K)]
CT	Cycle time [h]
D	Diameter [m]
DCM	Dicloromethane.
Dint	Internal diameter [m]
Dext	External diameter [m]
D	Dryer
Da	Impeller diameter [m]
DAF’s	Diacetonefructose chlorosulfate
e	Thickness [m]
F-01	Filter
h	Height [m]
h	Hour
isop	Isopropanol
K	Kelvin
kg	Kilograms

L	Length [m]
LT	Level transmitter
m	Meter
min	Minutes
Msn	Make span [h]
N	Number of batches/lots
N	Turn speed [rpm]
N_2	Nitrogen
Np	Power’s number
NPSHa	Net positive suction heat available
ºC	Celsius
OTi	Equipment operating time [h]
P	Power [W]
P-01	Pump
Pi&D	Piping and Instrumentation Diagram
Pr	Real power [W]
PT	Pressure transmitter
Pt	Theoretical Power [W]
Q	Heat exchange [W]
Re	Reynold’s number
rpm	Revolutions per minute
s	Section [m^2]
T	Temperature
t	Time [s]
T1	Inlet temperature of distillate [ºC]
T2	Outlet temperature of distillate [ºC]
t1	Inlet temperature of coolant [ºC]
t2	Outlet temperature of coolant [ºC]

TDH	Total dynamic heat
TP	Topiramate
Tpc	Commercial Topiramate.
TPt	Technical topiramate
U	Heat transfer coefficient [$W/m^2 \cdot kJ$]
V	Volume [m^3]
V-01	Vessel 1
V-02	Vessel 2
V-03	Vessel 3
V-04	Vessel 4
w	Mass flowing [kg/s]
W	Watts [J/s]
ΔP	Pressure drop [Pa]
ΔT	temperature difference [K]
ΔT_{ml}	Average temperature logarithmic [K]
λ	latent heat [J/kg]
ρ	weight density of fluid [kg/m^3]
μ	Absolute (Dynamic) viscosity [$kg \cdot m^{-1} \cdot s^{-1}$]

APPENDICES

APPENDIX 1: SAFETY DATA SHEETS (9)



Fichas Internacionales de Seguridad Química

PROPAN-2-OL **ICSC: 0554**

MINISTERIO DE TRABAJO Y ASUNTOS SOCIALES ESPAÑA

INSTITUTO NACIONAL DE SEGURIDAD E HIGIENE EN EL TRABAJO

PROPAN-2-OL
2-Propanol
Alcohol isopropílico
Isopropanol
$C_3H_8O/(CH_3)_2CHOH$
Masa molecular: 60.1

Nº CAS 67-63-0
Nº RTECS NT8050000
Nº ICSC 0554
Nº NU 1219
Nº CE 603-117-00-0

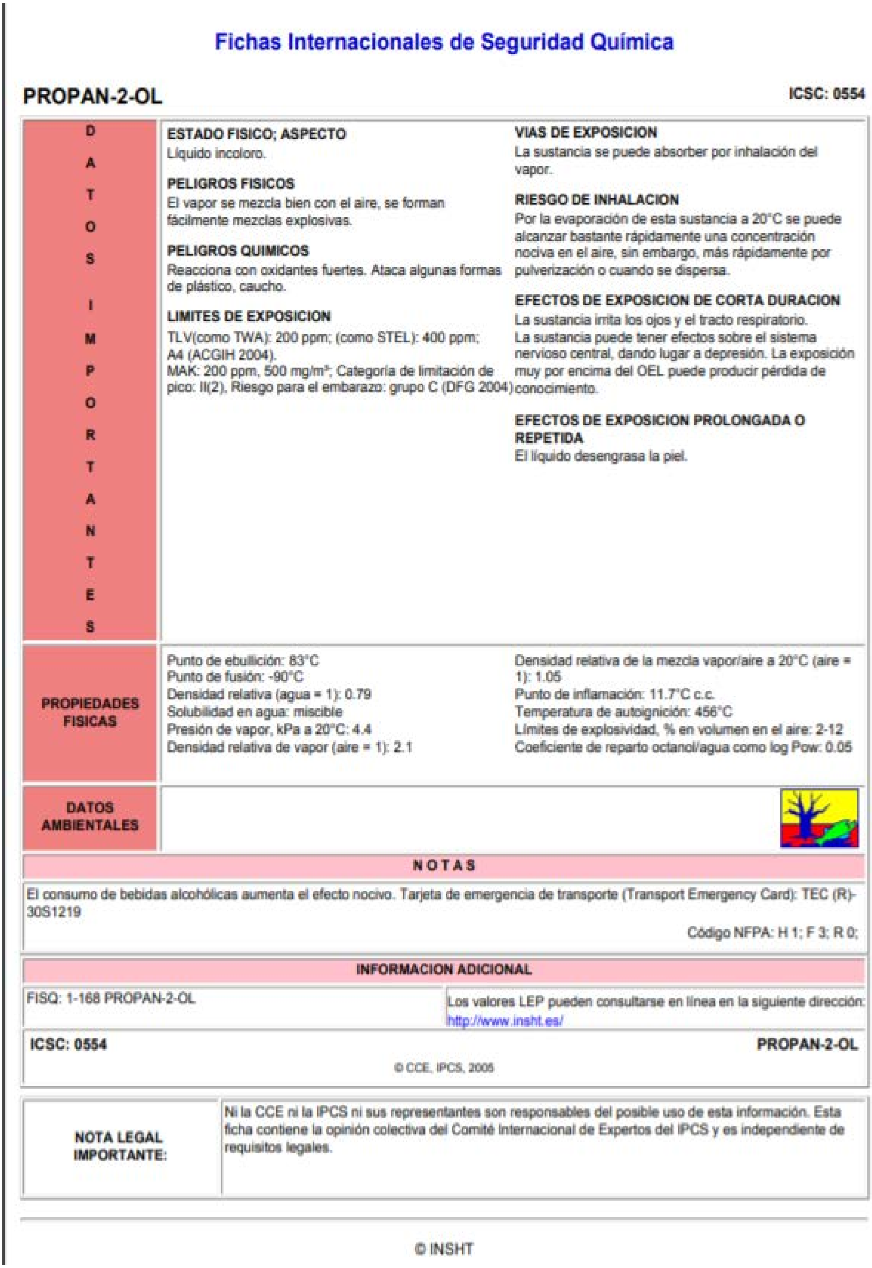
TIPOS DE PELIGRO/ EXPOSICION	PELIGROS/ SINTOMAS AGUDOS	PREVENCION	PRIMEROS AUXILIOS/ LUCHA CONTRA INCENDIOS
INCENDIO	Altamente inflamable.	Evitar llama abierta, NO producir chispas y NO fumar.	Polvos, espuma resistente al alcohol, agua en grandes cantidades, dióxido de carbono.
EXPLOSION	Las mezclas vapor/aire son explosivas.	Sistema cerrado, ventilación, equipo eléctrico y de alumbrado a prueba de explosiones.	En caso de incendio: mantener fríos los bidones y demás instalaciones por pulverización con agua.
EXPOSICION			
• **INHALACION**	Dolor de garganta, tos, dolor de cabeza, vértigo, somnolencia. (Ver Ingestión)	Ventilación, extracción localizada o protección respiratoria.	Aire limpio, reposo y someter a atención médica.
• **PIEL**	Piel seca.	Guantes protectores.	Quitar las ropas contaminadas, aclarar la piel con agua y jabón.
• **OJOS**	Enrojecimiento.	Gafas ajustadas de seguridad o protección ocular combinada con la protección respiratoria.	Enjuagar con agua abundante durante varios minutos (quitar las lentes de contacto si puede hacerse con facilidad), después consultar a un médico.
• **INGESTION**	Dolor abdominal, dificultad respiratoria, náusea, pérdida del conocimiento, vómitos. (Además, ver Inhalación).	No comer, beber ni fumar durante el trabajo.	Enjuagar la boca. NO provocar el vómito y someter a atención médica.

DERRAMAS Y FUGAS	ALMACENAMIENTO	ENVASADO Y ETIQUETADO
Protección personal: filtro para gases y vapores orgánicos. Recoger el líquido procedente de la fuga en recipientes herméticos, absorber el líquido residual en arena o absorbente inerte y trasladarlo a un lugar seguro.	A prueba de incendio. Separado de oxidantes fuertes. Mantener en lugar frío. Bien cerrado.	símbolo F símbolo Xi R: 11-36-67 S: (2-)7-16-24/25-26 Nota 6 Clasificación de Peligros NU: 3 Grupo de Envasado NU: II CE:

VEASE AL DORSO INFORMACION IMPORTANTE

ICSC: 0554

Preparada en el Contexto de Cooperación entre el IPCS y la Comisión de las Comunidades Europeas © CCE, IPCS, 2005



Fichas Internacionales de Seguridad Química

PROPAN-2-OL **ICSC: 0554**

DATOS IMPORTANTES

ESTADO FISICO; ASPECTO
Líquido incoloro.

PELIGROS FISICOS
El vapor se mezcla bien con el aire, se forman fácilmente mezclas explosivas.

PELIGROS QUIMICOS
Reacciona con oxidantes fuertes. Ataca algunas formas de plástico, caucho.

LIMITES DE EXPOSICION
TLV(como TWA): 200 ppm; (como STEL): 400 ppm; A4 (ACGIH 2004).
MAK: 200 ppm, 500 mg/m³; Categoría de limitación de pico: II(2), Riesgo para el embarazo: grupo C (DFG 2004)

VIAS DE EXPOSICION
La sustancia se puede absorber por inhalación del vapor.

RIESGO DE INHALACION
Por la evaporación de esta sustancia a 20°C se puede alcanzar bastante rápidamente una concentración nociva en el aire, sin embargo, más rápidamente por pulverización o cuando se dispersa.

EFECTOS DE EXPOSICION DE CORTA DURACION
La sustancia irrita los ojos y el tracto respiratorio. La sustancia puede tener efectos sobre el sistema nervioso central, dando lugar a depresión. La exposición muy por encima del OEL puede producir pérdida de conocimiento.

EFECTOS DE EXPOSICION PROLONGADA O REPETIDA
El líquido desengrasa la piel.

PROPIEDADES FISICAS

Punto de ebullición: 83°C
Punto de fusión: -90°C
Densidad relativa (agua = 1): 0.79
Solubilidad en agua: miscible
Presión de vapor, kPa a 20°C: 4.4
Densidad relativa de vapor (aire = 1): 2.1
Densidad relativa de la mezcla vapor/aire a 20°C (aire = 1): 1.05
Punto de inflamación: 11.7°C c.c.
Temperatura de autoignición: 456°C
Límites de explosividad, % en volumen en el aire: 2-12
Coeficiente de reparto octanol/agua como log Pow: 0.05

DATOS AMBIENTALES

NOTAS

El consumo de bebidas alcohólicas aumenta el efecto nocivo. Tarjeta de emergencia de transporte (Transport Emergency Card): TEC (R)-30S1219

Código NFPA: H 1; F 3; R 0;

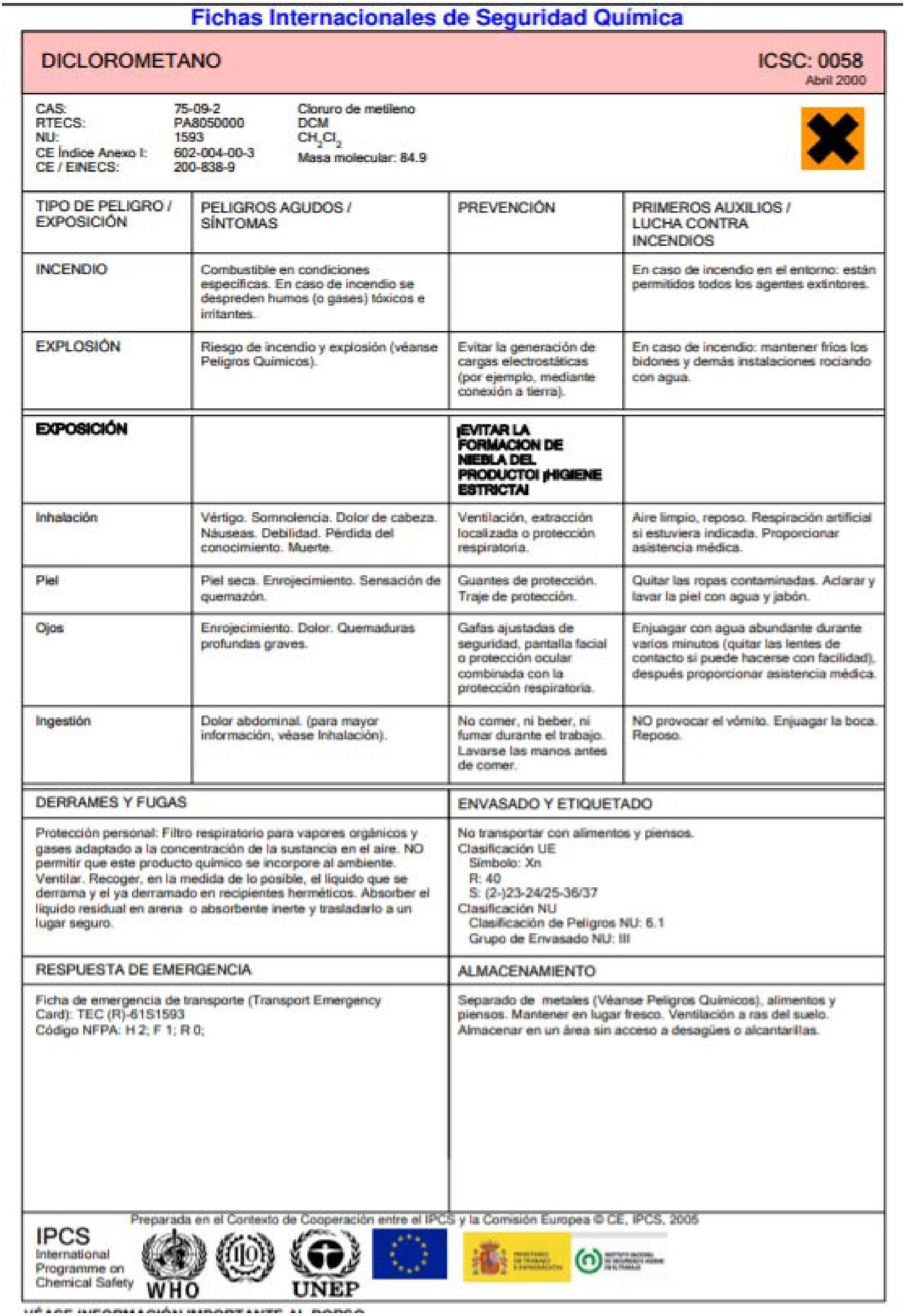
INFORMACION ADICIONAL

FISQ: 1-168 PROPAN-2-OL

Los valores LEP pueden consultarse en línea en la siguiente dirección: http://www.insht.es/

ICSC: 0554 **PROPAN-2-OL**

NOTA LEGAL IMPORTANTE: Ni la CCE ni la IPCS ni sus representantes son responsables del posible uso de esta información. Esta ficha contiene la opinión colectiva del Comité Internacional de Expertos del IPCS y es independiente de requisitos legales.



Fichas Internacionales de Seguridad Química

DICLOROMETANO **ICSC: 0058**

Abril 2000

CAS:	75-09-2	Cloruro de metileno
RTECS:	PA8050000	DCM
NU:	1593	CH_2Cl_2
CE Índice Anexo I:	602-004-00-3	Masa molecular: 84.9
CE / EINECS:	200-838-9	

TIPO DE PELIGRO / EXPOSICIÓN	PELIGROS AGUDOS / SÍNTOMAS	PREVENCIÓN	PRIMEROS AUXILIOS / LUCHA CONTRA INCENDIOS
INCENDIO	Combustible en condiciones específicas. En caso de incendio se desprenden humos (o gases) tóxicos e irritantes.		En caso de incendio en el entorno: están permitidos todos los agentes extintores.
EXPLOSIÓN	Riesgo de incendio y explosión (véanse Peligros Químicos).	Evitar la generación de cargas electrostáticas (por ejemplo, mediante conexión a tierra).	En caso de incendio: mantener fríos los bidones y demás instalaciones rociando con agua.
EXPOSICIÓN		**¡EVITAR LA FORMACION DE NIEBLA DEL PRODUCTO! ¡HIGIENE ESTRICTA!**	
Inhalación	Vértigo. Somnolencia. Dolor de cabeza. Náuseas. Debilidad. Pérdida del conocimiento. Muerte.	Ventilación, extracción localizada o protección respiratoria.	Aire limpio, reposo. Respiración artificial si estuviera indicada. Proporcionar asistencia médica.
Piel	Piel seca. Enrojecimiento. Sensación de quemazón.	Guantes de protección. Traje de protección.	Quitar las ropas contaminadas. Aclarar y lavar la piel con agua y jabón.
Ojos	Enrojecimiento. Dolor. Quemaduras profundas graves.	Gafas ajustadas de seguridad, pantalla facial o protección ocular combinada con la protección respiratoria.	Enjuagar con agua abundante durante varios minutos (quitar las lentes de contacto si puede hacerse con facilidad), después proporcionar asistencia médica.
Ingestión	Dolor abdominal. (para mayor información, véase Inhalación).	No comer, ni beber, ni fumar durante el trabajo. Lavarse las manos antes de comer.	NO provocar el vómito. Enjuagar la boca. Reposo.

DERRAMES Y FUGAS

Protección personal: Filtro respiratorio para vapores orgánicos y gases adaptado a la concentración de la sustancia en el aire. NO permitir que este producto químico se incorpore al ambiente. Ventilar. Recoger, en la medida de lo posible, el líquido que se derrama y el ya derramado en recipientes herméticos. Absorber el líquido residual en arena o absorbente inerte y trasladarlo a un lugar seguro.

ENVASADO Y ETIQUETADO

No transportar con alimentos y piensos.
Clasificación UE
  Símbolo: Xn
  R: 40
  S: (2-)23-24/25-36/37
Clasificación NU
  Clasificación de Peligros NU: 6.1
  Grupo de Envasado NU: III

RESPUESTA DE EMERGENCIA

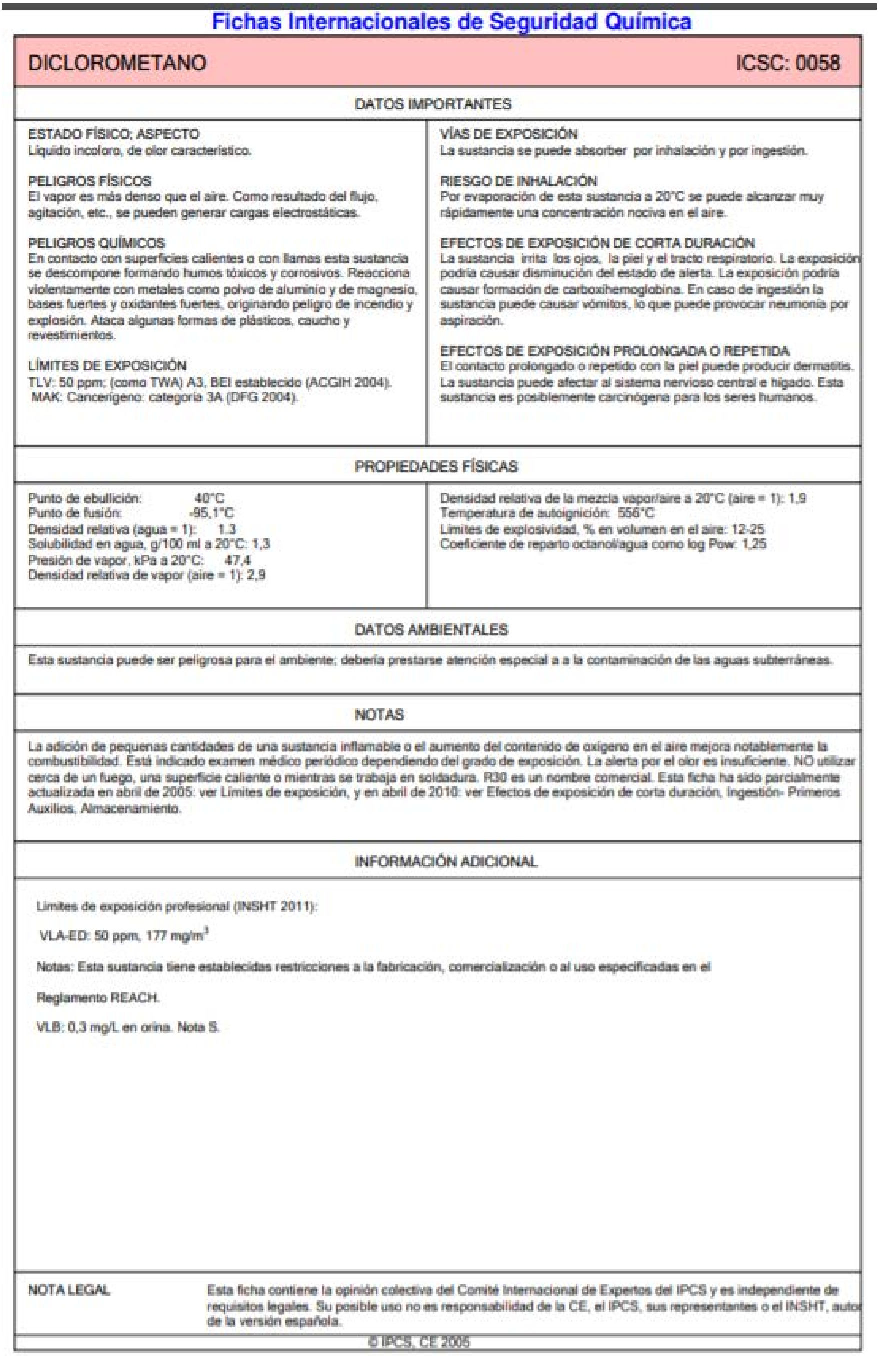
Ficha de emergencia de transporte (Transport Emergency Card): TEC (R)-61S1593
Código NFPA: H 2; F 1; R 0;

ALMACENAMIENTO

Separado de metales (Véanse Peligros Químicos), alimentos y piensos. Mantener en lugar fresco. Ventilación a ras del suelo. Almacenar en un área sin acceso a desagües o alcantarillas.

Preparada en el Contexto de Cooperación entre el IPCS y la Comisión Europea © CE, IPCS, 2005

IPCS
International
Programme on
Chemical Safety



Fichas Internacionales de Seguridad Química

DICLOROMETANO **ICSC: 0058**

DATOS IMPORTANTES

ESTADO FÍSICO; ASPECTO
Líquido incoloro, de olor característico.

PELIGROS FÍSICOS
El vapor es más denso que el aire. Como resultado del flujo, agitación, etc., se pueden generar cargas electrostáticas.

PELIGROS QUÍMICOS
En contacto con superficies calientes o con llamas esta sustancia se descompone formando humos tóxicos y corrosivos. Reacciona violentamente con metales como polvo de aluminio y de magnesio, bases fuertes y oxidantes fuertes, originando peligro de incendio y explosión. Ataca algunas formas de plásticos, caucho y revestimientos.

LÍMITES DE EXPOSICIÓN
TLV: 50 ppm; (como TWA) A3, BEI establecido (ACGIH 2004).
MAK: Cancerígeno: categoría 3A (DFG 2004).

VÍAS DE EXPOSICIÓN
La sustancia se puede absorber por inhalación y por ingestión.

RIESGO DE INHALACIÓN
Por evaporación de esta sustancia a 20°C se puede alcanzar muy rápidamente una concentración nociva en el aire.

EFECTOS DE EXPOSICIÓN DE CORTA DURACIÓN
La sustancia irrita los ojos, la piel y el tracto respiratorio. La exposición podría causar disminución del estado de alerta. La exposición podría causar formación de carboxihemoglobina. En caso de ingestión la sustancia puede causar vómitos, lo que puede provocar neumonía por aspiración.

EFECTOS DE EXPOSICIÓN PROLONGADA O REPETIDA
El contacto prolongado o repetido con la piel puede producir dermatitis. La sustancia puede afectar al sistema nervioso central e hígado. Esta sustancia es posiblemente carcinógena para los seres humanos.

PROPIEDADES FÍSICAS

Punto de ebullición: 40°C
Punto de fusión: -95,1°C
Densidad relativa (agua = 1): 1.3
Solubilidad en agua, g/100 ml a 20°C: 1,3
Presión de vapor, kPa a 20°C: 47,4
Densidad relativa de vapor (aire = 1): 2,9
Densidad relativa de la mezcla vapor/aire a 20°C (aire = 1): 1,9
Temperatura de autoignición: 556°C
Límites de explosividad, % en volumen en el aire: 12-25
Coeficiente de reparto octanol/agua como log Pow: 1,25

DATOS AMBIENTALES

Esta sustancia puede ser peligrosa para el ambiente; debería prestarse atención especial a a la contaminación de las aguas subterráneas.

NOTAS

La adición de pequeñas cantidades de una sustancia inflamable o el aumento del contenido de oxígeno en el aire mejora notablemente la combustibilidad. Está indicado examen médico periódico dependiendo del grado de exposición. La alerta por el olor es insuficiente. NO utilizar cerca de un fuego, una superficie caliente o mientras se trabaja en soldadura. R30 es un nombre comercial. Esta ficha ha sido parcialmente actualizada en abril de 2005: ver Límites de exposición, y en abril de 2010: ver Efectos de exposición de corta duración, Ingestión- Primeros Auxilios, Almacenamiento.

INFORMACIÓN ADICIONAL

Límites de exposición profesional (INSHT 2011):

VLA-ED: 50 ppm, 177 mg/m^3

Notas: Esta sustancia tiene establecidas restricciones a la fabricación, comercialización o al uso especificadas en el

Reglamento REACH.

VLB: 0,3 mg/L en orina. Nota S.

NOTA LEGAL Esta ficha contiene la opinión colectiva del Comité Internacional de Expertos del IPCS y es independiente de requisitos legales. Su posible uso no es responsabilidad de la CE, el IPCS, sus representantes o el INSHT, auto de la versión española.

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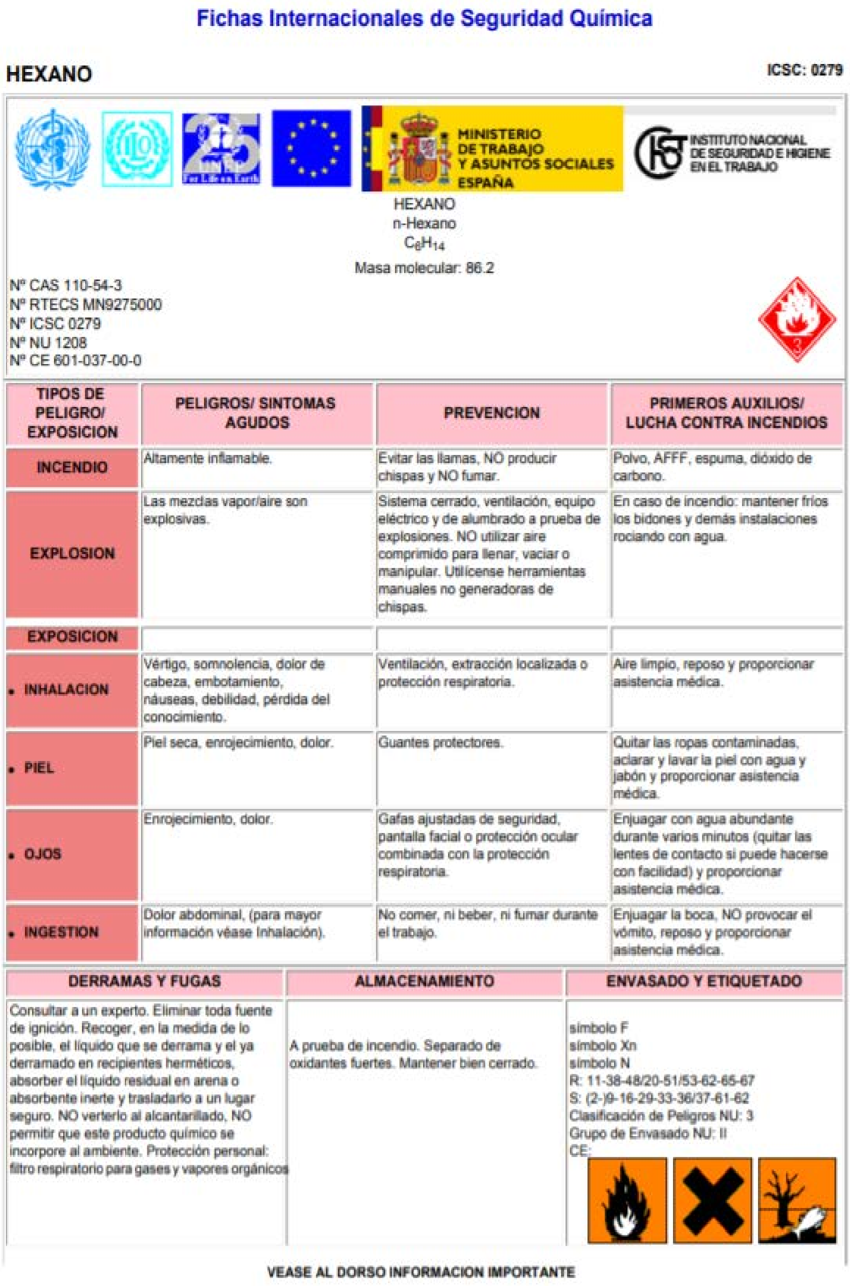


Fichas Internacionales de Seguridad Química

HEXANO **ICSC: 0279**

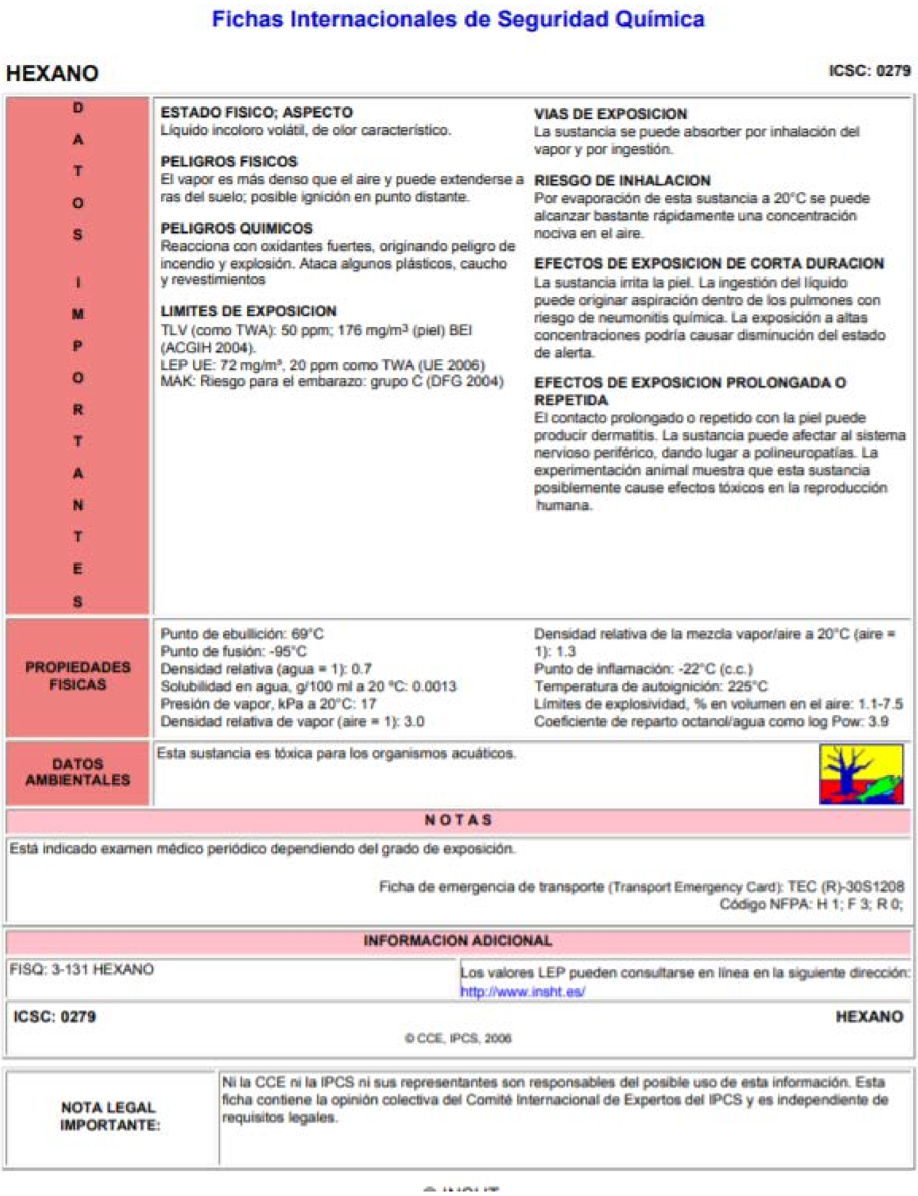
HEXANO
n-Hexano
C_6H_{14}
Masa molecular: 86.2

Nº CAS 110-54-3
Nº RTECS MN9275000
Nº ICSC 0279
Nº NU 1208
Nº CE 601-037-00-0

TIPOS DE PELIGRO/ EXPOSICION	PELIGROS/ SINTOMAS AGUDOS	PREVENCION	PRIMEROS AUXILIOS/ LUCHA CONTRA INCENDIOS
INCENDIO	Altamente inflamable.	Evitar las llamas, NO producir chispas y NO fumar.	Polvo, AFFF, espuma, dióxido de carbono.
EXPLOSION	Las mezclas vapor/aire son explosivas.	Sistema cerrado, ventilación, equipo eléctrico y de alumbrado a prueba de explosiones. NO utilizar aire comprimido para llenar, vaciar o manipular. Utilícense herramientas manuales no generadoras de chispas.	En caso de incendio: mantener fríos los bidones y demás instalaciones rociando con agua.
EXPOSICION			
• **INHALACION**	Vértigo, somnolencia, dolor de cabeza, embotamiento, náuseas, debilidad, pérdida del conocimiento.	Ventilación, extracción localizada o protección respiratoria.	Aire limpio, reposo y proporcionar asistencia médica.
• **PIEL**	Piel seca, enrojecimiento, dolor.	Guantes protectores.	Quitar las ropas contaminadas, aclarar y lavar la piel con agua y jabón y proporcionar asistencia médica.
• **OJOS**	Enrojecimiento, dolor.	Gafas ajustadas de seguridad, pantalla facial o protección ocular combinada con la protección respiratoria.	Enjuagar con agua abundante durante varios minutos (quitar las lentes de contacto si puede hacerse con facilidad) y proporcionar asistencia médica.
• **INGESTION**	Dolor abdominal, (para mayor información véase Inhalación).	No comer, ni beber, ni fumar durante el trabajo.	Enjuagar la boca, NO provocar el vómito, reposo y proporcionar asistencia médica.

DERRAMAS Y FUGAS	ALMACENAMIENTO	ENVASADO Y ETIQUETADO
Consultar a un experto. Eliminar toda fuente de ignición. Recoger, en la medida de lo posible, el líquido que se derrama y el ya derramado en recipientes herméticos, absorber el líquido residual en arena o absorbente inerte y trasladarlo a un lugar seguro. NO verterlo al alcantarillado, NO permitir que este producto químico se incorpore al ambiente. Protección personal: filtro respiratorio para gases y vapores orgánicos	A prueba de incendio. Separado de oxidantes fuertes. Mantener bien cerrado.	símbolo F símbolo Xn símbolo N R: 11-38-48/20-51/53-62-65-67 S: (2-)9-16-29-33-36/37-61-62 Clasificación de Peligros NU: 3 Grupo de Envasado NU: II CE:

VEASE AL DORSO INFORMACION IMPORTANTE



Fichas Internacionales de Seguridad Química

HEXANO **ICSC: 0279**

DATOS IMPORTANTES

ESTADO FISICO; ASPECTO
Líquido incoloro volátil, de olor característico.

PELIGROS FISICOS
El vapor es más denso que el aire y puede extenderse a ras del suelo; posible ignición en punto distante.

PELIGROS QUIMICOS
Reacciona con oxidantes fuertes, originando peligro de incendio y explosión. Ataca algunos plásticos, caucho y revestimientos

LIMITES DE EXPOSICION
TLV (como TWA): 50 ppm; 176 mg/m³ (piel) BEI (ACGIH 2004).
LEP UE: 72 mg/m³, 20 ppm como TWA (UE 2006)
MAK: Riesgo para el embarazo: grupo C (DFG 2004)

VIAS DE EXPOSICION
La sustancia se puede absorber por inhalación del vapor y por ingestión.

RIESGO DE INHALACION
Por evaporación de esta sustancia a 20°C se puede alcanzar bastante rápidamente una concentración nociva en el aire.

EFECTOS DE EXPOSICION DE CORTA DURACION
La sustancia irrita la piel. La ingestión del líquido puede originar aspiración dentro de los pulmones con riesgo de neumonitis química. La exposición a altas concentraciones podría causar disminución del estado de alerta.

EFECTOS DE EXPOSICION PROLONGADA O REPETIDA
El contacto prolongado o repetido con la piel puede producir dermatitis. La sustancia puede afectar al sistema nervioso periférico, dando lugar a polineuropatías. La experimentación animal muestra que esta sustancia posiblemente cause efectos tóxicos en la reproducción humana.

PROPIEDADES FISICAS

Punto de ebullición: 69°C
Punto de fusión: -95°C
Densidad relativa (agua = 1): 0.7
Solubilidad en agua, g/100 ml a 20 °C: 0.0013
Presión de vapor, kPa a 20°C: 17
Densidad relativa de vapor (aire = 1): 3.0
Densidad relativa de la mezcla vapor/aire a 20°C (aire = 1): 1.3
Punto de inflamación: -22°C (c.c.)
Temperatura de autoignición: 225°C
Límites de explosividad, % en volumen en el aire: 1.1-7.5
Coeficiente de reparto octanol/agua como log Pow: 3.9

DATOS AMBIENTALES

Esta sustancia es tóxica para los organismos acuáticos.

NOTAS

Está indicado examen médico periódico dependiendo del grado de exposición.

Ficha de emergencia de transporte (Transport Emergency Card): TEC (R)-30S1208
Código NFPA: H 1; F 3; R 0;

INFORMACION ADICIONAL

FISQ: 3-131 HEXANO

Los valores LEP pueden consultarse en línea en la siguiente dirección: http://www.insht.es/

ICSC: 0279 **HEXANO**

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Fichas Internacionales de Seguridad Química

AMONIACO (ANHIDRO)

ICSC: 0414

MINISTERIO DE TRABAJO Y ASUNTOS SOCIALES ESPAÑA

INSTITUTO NACIONAL DE SEGURIDAD E HIGIENE EN EL TRABAJO

AMONIACO (ANHIDRO)
Trihidruro de nitrógeno
NH_3
Masa molecular: 17.03

Nº CAS 7664-41-7
Nº RTECS BO0875000
Nº ICSC 0414
Nº NU 1005
Nº CE 007-001-00-5

TIPOS DE PELIGRO/ EXPOSICION	PELIGROS/ SINTOMAS AGUDOS	PREVENCION	PRIMEROS AUXILIOS/ LUCHA CONTRA INCENDIOS
INCENDIO	Inflamable.	Evitar las llamas, NO producir chispas y NO fumar.	En caso de incendio en el entorno: usar medio de extinción adecuado.
EXPLOSION	Las mezclas gas/aire son explosivas.	Sistema cerrado, ventilación, equipo eléctrico y de alumbrado a prueba de explosiones.	En caso de incendio: mantener fría la botella por pulverización con agua.
EXPOSICION		¡EVITAR TODO CONTACTO!	
• **INHALACION**	Sensación de quemazón, tos, dificultad respiratoria, jadeo, dolor de garganta. (Síntomas de efectos no inmediatos: véanse Notas).	Ventilación, extracción localizada o protección respiratoria.	Aire limpio, reposo, posición de semiincorporado y atención médica. Respiración artificial si estuviera indicado.
• **PIEL**	Enrojecimiento, quemaduras, dolor, ampollas. EN CONTACTO CON LIQUIDO: CONGELACION.	Guantes aislantes del frío, traje de protección.	EN CASO DE CONGELACION: Aclarar con agua abundante. NO quitar la ropa y solicitar atención médica.
• **OJOS**	Enrojecimiento, dolor, quemaduras profundas graves.	Pantalla facial o protección ocular combinada con la protección respiratoria.	Enjuagar con agua abundante durante varios minutos (quitar las lentes de contacto si puede hacerse con facilidad), después consultar a un médico.
• **INGESTION**			

DERRAMAS Y FUGAS	ALMACENAMIENTO	ENVASADO Y ETIQUETADO
Evacuar la zona de peligro; consultar a un experto; ventilación. NO verter NUNCA chorros de agua sobre el líquido. Eliminar el gas con agua pulverizada. Protección personal: traje de protección completa incluyendo equipo autónomo de repiración.	A prueba de incendio. Separado de oxidantes, ácidos, halógenos. Mantener en lugar frío y bien ventilado.	Botellas con accesorios especiales. símbolo T símbolo N R: 10-23-34-50 S: (1/2-)9-16-26-36/37/39-45-61 Clasificación de Peligros NU: 2.3 Riesgos subsidiarios de las NU: 8

VEASE AL DORSO INFORMACION IMPORTANTE

ICSC: 0414

Preparada en el Contexto de Cooperación entre el IPCS y la Comisión de las Comunidades Europeas © CCE, IPCS, 2005

Fichas Internacionales de Seguridad Química

AMONIACO (ANHIDRO) **ICSC: 0414**

DATOS IMPORTANTES	**ESTADO FISICO; ASPECTO** Gas licuado comprimido incoloro, de olor acre. **PELIGROS FISICOS** El gas es más ligero que el aire. **PELIGROS QUIMICOS** Se forman compuestos inestables frente al choque con óxidos de mercurio, plata y oro. La sustancia es una base fuerte, reacciona violentamente con ácidos y es corrosiva (p.ej: Aluminio y zinc). Reacciona violentamente con oxidantes fuertes y halógenos. Ataca el cobre, aluminio, cinc y sus aleaciones. Al disolverse en agua desprende calor. **LIMITES DE EXPOSICION** TLV (como TWA): 25 ppm; (como STEL): 35 ppm (ACGIH 2004). MAK: 20 ppm, 14 mg/m³; Categoría de limitación de pico: I(2). Riesgo para el embarazo: grupo C (DFG 2004)	**VIAS DE EXPOSICION** La sustancia se puede absorber por inhalación. **RIESGO DE INHALACION** Al producirse una pérdida de gas se alcanza muy rápidamente una concentración nociva en el aire. **EFECTOS DE EXPOSICION DE CORTA DURACION** La sustancia es corrosiva para los ojos, la piel y el tracto respiratorio. La inhalación de altas concentraciones puede originar edema pulmonar (véanse Notas). La evaporación rápida del líquido puede producir congelación. **EFECTOS DE EXPOSICION PROLONGADA O REPETIDA**
PROPIEDADES FISICAS	Punto de ebullición: -33°C Punto de fusión: -78°C Densidad relativa (agua = 1): 0.7 a -33°C Solubilidad en agua: Buena (54 g/100 ml a 20°C) Presión de vapor, kPa a 26°C: 1013	Densidad relativa de vapor (aire = 1): 0.59 Temperatura de autoignición: 651°C Límites de explosividad, % en volumen en el aire: 15-28
DATOS AMBIENTALES	La sustancia es muy tóxica para los organismos acuáticos.	

NOTAS

Los síntomas del edema pulmonar no se ponen de manifiesto a menudo hasta pasadas algunas horas y se agravan por el esfuerzo físico. Reposo y vigilancia médica son por ello imprescindibles. Debe considerarse la inmediata administración de un spray adecuado por un médico o persona por él autorizada. Con el fin de evitar la fuga de gas en estado líquido, girar la botella que tenga un escape manteniendo arriba el punto de escape.

Tarjeta de emergencia de transporte (Transport Emergency Card): TEC (R)-20S1005 o 20G2TC

Código NFPA: H 3; F 1; R 0;

INFORMACION ADICIONAL

FISQ: 1-030 AMONIACO (ANHIDRO)	Los valores LEP pueden consultarse en línea en la siguiente dirección: http://www.insht.es/

ICSC: 0414 **AMONIACO (ANHIDRO)**

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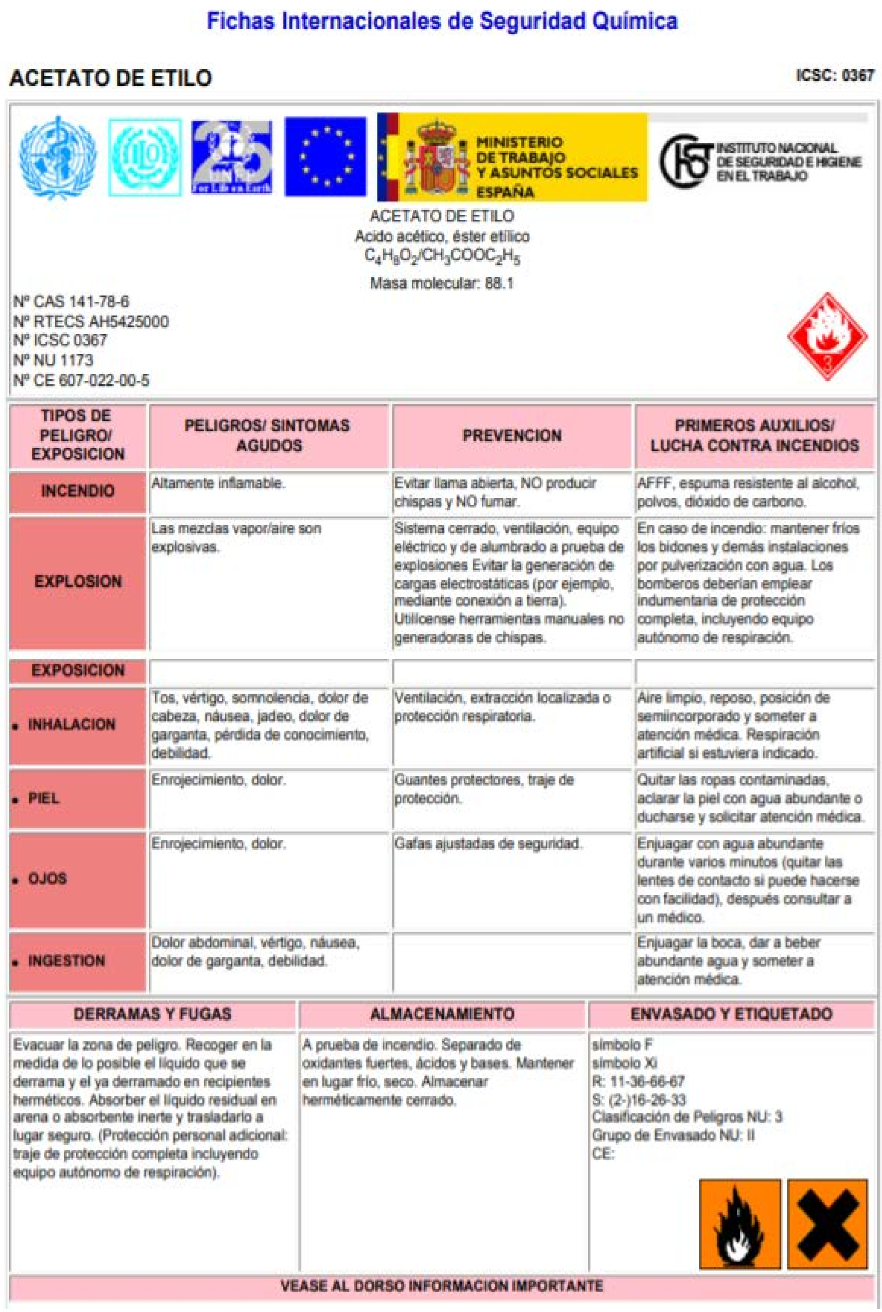


Fichas Internacionales de Seguridad Química

ACETATO DE ETILO

ICSC: 0367

MINISTERIO DE TRABAJO Y ASUNTOS SOCIALES ESPAÑA
INSTITUTO NACIONAL DE SEGURIDAD E HIGIENE EN EL TRABAJO

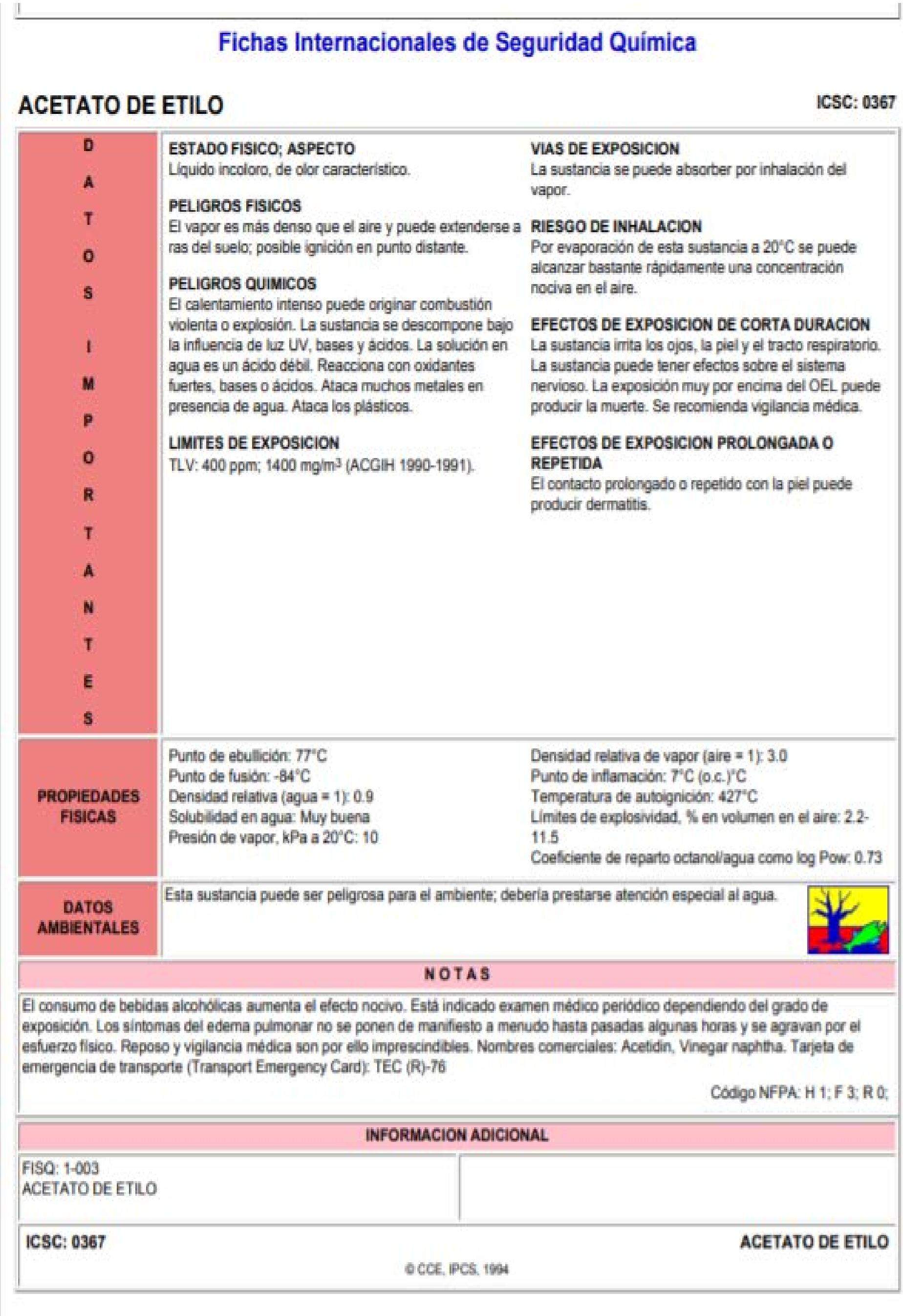
ACETATO DE ETILO
Acido acético, éster etílico
$C_4H_8O_2/CH_3COOC_2H_5$
Masa molecular: 88.1

Nº CAS 141-78-6
Nº RTECS AH5425000
Nº ICSC 0367
Nº NU 1173
Nº CE 607-022-00-5

TIPOS DE PELIGRO/ EXPOSICION	PELIGROS/ SINTOMAS AGUDOS	PREVENCION	PRIMEROS AUXILIOS/ LUCHA CONTRA INCENDIOS
INCENDIO	Altamente inflamable.	Evitar llama abierta, NO producir chispas y NO fumar.	AFFF, espuma resistente al alcohol, polvos, dióxido de carbono.
EXPLOSION	Las mezclas vapor/aire son explosivas.	Sistema cerrado, ventilación, equipo eléctrico y de alumbrado a prueba de explosiones Evitar la generación de cargas electrostáticas (por ejemplo, mediante conexión a tierra). Utilícense herramientas manuales no generadoras de chispas.	En caso de incendio: mantener fríos los bidones y demás instalaciones por pulverización con agua. Los bomberos deberían emplear indumentaria de protección completa, incluyendo equipo autónomo de respiración.
EXPOSICION			
• **INHALACION**	Tos, vértigo, somnolencia, dolor de cabeza, náusea, jadeo, dolor de garganta, pérdida de conocimiento, debilidad.	Ventilación, extracción localizada o protección respiratoria.	Aire limpio, reposo, posición de semiincorporado y someter a atención médica. Respiración artificial si estuviera indicado.
• **PIEL**	Enrojecimiento, dolor.	Guantes protectores, traje de protección.	Quitar las ropas contaminadas, aclarar la piel con agua abundante o ducharse y solicitar atención médica.
• **OJOS**	Enrojecimiento, dolor.	Gafas ajustadas de seguridad.	Enjuagar con agua abundante durante varios minutos (quitar las lentes de contacto si puede hacerse con facilidad), después consultar a un médico.
• **INGESTION**	Dolor abdominal, vértigo, náusea, dolor de garganta, debilidad.		Enjuagar la boca, dar a beber abundante agua y someter a atención médica.

DERRAMAS Y FUGAS	ALMACENAMIENTO	ENVASADO Y ETIQUETADO
Evacuar la zona de peligro. Recoger en la medida de lo posible el líquido que se derrama y el ya derramado en recipientes herméticos. Absorber el líquido residual en arena o absorbente inerte y trasladarlo a lugar seguro. (Protección personal adicional: traje de protección completa incluyendo equipo autónomo de respiración).	A prueba de incendio. Separado de oxidantes fuertes, ácidos y bases. Mantener en lugar frío, seco. Almacenar herméticamente cerrado.	símbolo F símbolo Xi R: 11-36-66-67 S: (2-)16-26-33 Clasificación de Peligros NU: 3 Grupo de Envasado NU: II CE:

VEASE AL DORSO INFORMACION IMPORTANTE



Fichas Internacionales de Seguridad Química

ACETATO DE ETILO **ICSC: 0367**

DATOS IMPORTANTES	**ESTADO FISICO; ASPECTO** Líquido incoloro, de olor característico. **PELIGROS FISICOS** El vapor es más denso que el aire y puede extenderse a ras del suelo; posible ignición en punto distante. **PELIGROS QUIMICOS** El calentamiento intenso puede originar combustión violenta o explosión. La sustancia se descompone bajo la influencia de luz UV, bases y ácidos. La solución en agua es un ácido débil. Reacciona con oxidantes fuertes, bases o ácidos. Ataca muchos metales en presencia de agua. Ataca los plásticos. **LIMITES DE EXPOSICION** TLV: 400 ppm; 1400 mg/m^3 (ACGIH 1990-1991).	**VIAS DE EXPOSICION** La sustancia se puede absorber por inhalación del vapor. **RIESGO DE INHALACION** Por evaporación de esta sustancia a 20°C se puede alcanzar bastante rápidamente una concentración nociva en el aire. **EFECTOS DE EXPOSICION DE CORTA DURACION** La sustancia irrita los ojos, la piel y el tracto respiratorio. La sustancia puede tener efectos sobre el sistema nervioso. La exposición muy por encima del OEL puede producir la muerte. Se recomienda vigilancia médica. **EFECTOS DE EXPOSICION PROLONGADA O REPETIDA** El contacto prolongado o repetido con la piel puede producir dermatitis.
PROPIEDADES FISICAS	Punto de ebullición: 77°C Punto de fusión: -84°C Densidad relativa (agua = 1): 0.9 Solubilidad en agua: Muy buena Presión de vapor, kPa a 20°C: 10	Densidad relativa de vapor (aire = 1): 3.0 Punto de inflamación: 7°C (o.c.)°C Temperatura de autoignición: 427°C Límites de explosividad, % en volumen en el aire: 2.2-11.5 Coeficiente de reparto octanol/agua como log Pow: 0.73
DATOS AMBIENTALES	Esta sustancia puede ser peligrosa para el ambiente; debería prestarse atención especial al agua.	

NOTAS

El consumo de bebidas alcohólicas aumenta el efecto nocivo. Está indicado examen médico periódico dependiendo del grado de exposición. Los síntomas del edema pulmonar no se ponen de manifiesto a menudo hasta pasadas algunas horas y se agravan por el esfuerzo físico. Reposo y vigilancia médica son por ello imprescindibles. Nombres comerciales: Acetidin, Vinegar naphtha. Tarjeta de emergencia de transporte (Transport Emergency Card): TEC (R)-76

Código NFPA: H 1; F 3; R 0;

INFORMACION ADICIONAL

FISQ: 1-003
ACETATO DE ETILO

ICSC: 0367 **ACETATO DE ETILO**

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APPENDIX 2: CALCULATION MANUAL

V-01 and V-02 :

If the total mass is known, the volume will be known because both magnitudes are related by density. Supposing that the volumes are additive:

$$V = \pi r^2 h$$

$$V = 3 \cdot \pi r^3$$

$$r = \sqrt[3]{\frac{V}{3 \cdot \pi}}$$

$$Lateral\ area\ of\ heat\ exchange = \pi \cdot d \cdot h$$

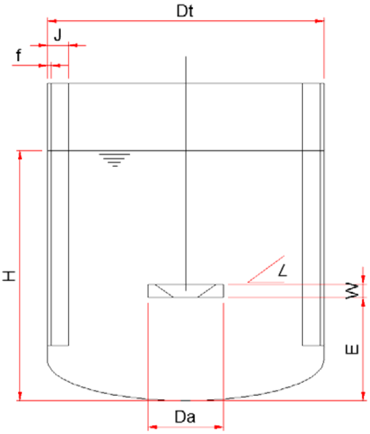
Magnitudes	Vessel 1	Vessel 2	Vessel 4	Vessel 4
High(m)	2,85	2.78	1,79	1,71
Diameter(m)	1,90	1.85	1,19	1,14
Section (m2)	2,81	2.68	1,11	1,0225
Capacity (m3)	8	7.5	2	2
Exchange area(m2)	16,9	16.15	6,71	6,135

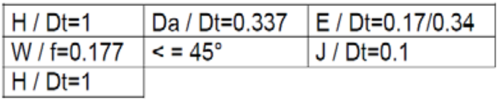
By heuristics its known that the height should be 1.5 of the diameter this is because if the vessel is too high, it will only have radial mixture, whereas if it is too high it will not have radial or axial mixture

The dimensions of the second vessel are very similar to V-01, so it has been decided to size both of them with the same dimensions. Nonetheless vessels have at the top and the bottom a concavity

Agitation system :

The geometric similarities with the inclined blades impeller are :





H / Dt=1	Da / Dt=0.337	E / Dt=0.17/0.34
W / f=0.177	< = 45°	J / Dt=0.1
H / Dt=1		

1. First of all it is calculated the blade diameter knowing that the diameter of the vessel 1 is 1.90m

$$Da = 0.337 \cdot Dt \rightarrow 0.64\ m$$

2. Subsequently it has been calculated the high of the stirrer :

$$\frac{E}{Dt} = \frac{0.17}{0.34} \rightarrow E = 0.50 \cdot Dt \rightarrow 0.95\ m$$

3.

4. Knowing that it is needed four baffles inclined 45 º, it has to been calculated the width of them:

$$J = 0.1 \cdot Dt \rightarrow 0.19\ m \approx 200mm$$

5. The distance between baffle and vessel it has been chosen , and it is 0.4 mm , knowing that it could be calculated the W:

$$\frac{W}{f} = 0.177 \rightarrow W = 0.177 \cdot f = 0.0708\, m$$

6. Once all the specifications of the impeller are known , it is necessary to calculate the motor efficiency .

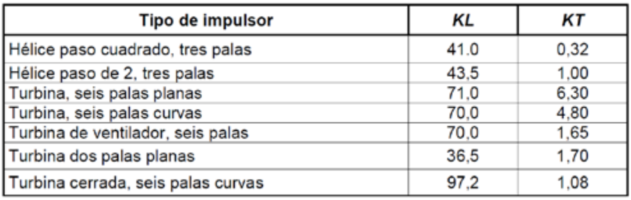
a. First of all it is needed calculate the Reynolds:

The rotational speed of this type of impeller it could be between 60-120 rpm , in our case it has been chosen 60 rpm

$$Re = \frac{N \cdot d^2 \cdot \rho}{\mu} \rightarrow 1.8 \cdot 10^6\, m$$

The flux of the fluid is turbulent due to the rotational speed of the impeller and the lower viscosity of the fluid.

b. Once it has been calculated the Reynolds it will be calculated the theoretical agitation power , using the next table:



Tipo de impulsor	*KL*	*KT*
Hélice paso cuadrado, tres palas	41.0	0,32
Hélice paso de 2, tres palas	43,5	1,00
Turbina, seis palas planas	71,0	6,30
Turbina, seis palas curvas	70,0	4,80
Turbina de ventilador, seis palas	70,0	1,65
Turbina dos palas planas	36,5	1,70
Turbina cerrada, seis palas curvas	97,2	1,08

$$Pt = KT \cdot N^3 \cdot Da^5 \cdot \rho \rightarrow 5.75\, kW$$

But it is know that the motor efficiency it is always less than the theoretical , and there are losses of efficiency by friction. Assuming this it has been assumed that the total efficiency is 0.7

$$Pt = \frac{Pt}{0.7} = 8.6\, kW$$

To calculate the agitation system of the impeller in the V-03 it have been made the same calculations but assuming that the dimensions of the vessel are different.

AGITATION ANCORA IMPELLER

The geometric similarities with the inclined blades impeller are :

1. First of all it is calculated the blade diameter knowing that the diameter of the vessel 2 is 1.90m

$$Di = \frac{1.90}{1.02} \rightarrow 1.863\ m$$

2. Subsequently it has been calculated the width of the stirrer :

$$Wi = 0.1 \cdot Di = 0.186\ m$$

3. The distance between baffle and vessel it has been chosen , and it is 0.4 mm , knowing that it could be calculated the W:

Dt/Di=1.02	c/Di =0.01	Hi/Di=1
W/Di=0.1	W/f=0.177	

$$\frac{W}{f} = 0.177 \rightarrow W = 0.177 \cdot f = 0.0708\ m$$

4. Once all the specifications of the impeller are known , it is necessary to calculate the motor efficiency .
    1. First of all it is needed calculate the Reynolds:

    The rotational speed of this type of impeller it could be between 60-120 rpm , in our case it has been chosen 60 rpm

$$Re = \frac{N \cdot d^2 \cdot \rho}{\mu} \rightarrow 1.8 \cdot 10^6\ m$$

The flux of the fluid is turbulent due to the rotational speed of the impeller and the lower viscosity of the fluid.

    2. Once it has been calculated the Reynolds it will be calculated the theoretical agitation power , using the next table:

$$Pt = KT \cdot N^3 \cdot Da^5 \cdot \rho \rightarrow 5.75\ kW$$

But it is know that the motor efficiency it is always less than the theoretical , and there are losses of efficiency by friction. Assuming this it has been assumed that the total efficiency is 0.7

$$Pr =\cdot \frac{Pt}{0.7} \rightarrow 8.6\ kW$$

To calculate the agitation system of the impeller in the V-03 it has been made the same calculations but assuming that the dimensions of the vessel are different.

Heat exchanger of vessel 2 in the crystallization and distillation :

1. The necessary heat exchange to heat the solution to 65º :

$$Q = m \cdot Cp \cdot \Delta T$$

$$Q = 7388.51 \cdot (54.53 \frac{J}{mol \cdot K} \cdot \frac{1 mol}{0.0849\ kg} \cdot (65º - 20º\ )$$

$$Q = 213{,}465.85\ kJ$$

2. The necessary area of exchange is calculated regarding the worst condition during the operation process :

$$\Delta \mathrm{Tml} = \frac{120 - 65}{\ln(\frac{120}{65})} = 89.71\ ºC$$

$$Q = \mathrm{U} \cdot \mathrm{A} \cdot \Delta\mathrm{Tml}$$

$$A = \frac{\mathrm{Q}}{\Delta\mathrm{Tml} \cdot \mathrm{U}} = \frac{\frac{213{,}465.85}{0.5\ h}\ \frac{kJ}{mol \cdot K}}{0.55\ \frac{kJ}{mol \cdot K} \cdot (89.71ºC)} = 2.4\ m^2$$

3. The necessary steam flow to heat the solution is calculated :

$$Q = wv \cdot \lambda v$$

$$wv = \frac{Q}{\lambda v} = \frac{426931.7\ \frac{kJ}{h} \cdot \frac{1h}{3600s}}{2.199 \cdot 10^3 \frac{kJ}{kg}} = 0.05393 \frac{kg}{s} = 194.15 \frac{kg}{h}$$

4. It is needed to know if the vessel has the necessary area of heat exchange, and it is calculated :

$$V = 8\, m^3$$

$$V = \pi \cdot r^2 \cdot h$$

$$r = 0.9468\, m$$

Area of exchange :

$$A = \pi \cdot d \cdot h = \pi \cdot 1.8936 \cdot 2{,}84 = 16.79\, m^2$$

The necessary area to be able to heat the solution to 65 º is 3.92 m2 and the area of the jacket vessel it's 16.79 m2 therefore there is enough exchange area to heat the solution.

Jacket vessel to crystallization

The vessel need a jacketed to keep the temperature around 0 º to carried out de crystallization

1. First of all is calculated the necessary heat exchange :

$$Q = \frac{m}{t} \cdot Cp \cdot (\Delta T)_{masa}$$

$$Q = \frac{5099.46\, kg}{1\, h} \cdot \left(\frac{651.3}{3591.95} \cdot 1.8 + \frac{2940.3}{3591.95} \cdot 0.64\right) \cdot (-65ºC)$$

$$Q = -78.325\, kW$$

2. The necessary area of exchange is calculated regarding the worst condition during the operation process :

$$\Delta\mathrm{Tml} = \frac{-30 - (-10)}{\ln(\frac{30}{10})} = -18.2\ ºC$$

$$Q = \mathrm{U} \cdot \mathrm{A} \cdot \Delta\mathrm{Tml}$$

$$A = \frac{Q}{U \cdot \Delta\mathrm{Tml}} = -\frac{78.325 kW}{0.4 \frac{kJ}{m^2 s \cdot K} \cdot (-18.2ºC)} = 10.75\ \ m^2$$

It is needed more exchange area that the available area due to de oversized considering the worst condition in the estimate values.

3. The necessary refrigeration flow it is calculated :

$$Q = w_{\,ref} \cdot Cp_{ref} \cdot (\Delta T)_{ref}$$

$$w_{\,ref} = \frac{Q}{w_{\,ref} \cdot Cp_{ref}} = -\frac{78.325kW}{\left(-30-(-10)\right) \cdot 2.408\frac{kJ}{kg \cdot K}} = \frac{1.63kg}{s}$$
$$= 5854.85\ kg/h$$

Distillation heat exchange:

1. First of all is calculated the necessary heat exchange knowing the value of the mass flow distilled :

$$Q = wv \cdot \lambda v$$

1.1 Previously it is needed to calculate the thermal conductivity

$$\lambda v = 4.186 \cdot 10^{7} \cdot (1-0.66274)^{0.4092} = 2.638 \cdot 10^{7}\frac{J}{kmol}$$

$$Q = 2.638 \cdot 10^{7}\frac{J}{kmol} \cdot \frac{1kmol}{84.933kg} \cdot 1470\frac{kg}{h} = 4.64 \cdot 10^{8}\frac{J}{h}$$

$$Q = 4.64 \cdot 10^{5}\frac{kJ}{h} \cdot \frac{1h}{3600s} = 129\ kW$$

2. The necessary area of exchange is calculated:

$$\Delta\mathrm{Tml} = \frac{(65-25)-(65-40)}{\ln(\frac{65-25}{65-40})} = 31.91\ ºC$$

$$Q = \mathrm{U} \cdot \mathrm{A} \cdot \Delta\mathrm{Tml}$$

$$\mathrm{A} = \frac{\mathrm{Q}}{\Delta\mathrm{Tml} \cdot \mathrm{U}} = \frac{129\mathrm{kW}}{0.750\frac{\mathrm{kJ}}{\mathrm{m2} \cdot \mathrm{s} \cdot \mathrm{K}} \cdot (39.91ºC)} = 5.39\ m^{2}$$

Estimate values of the condenser:

1. First of all it is know that heat flow of condensation it is the same of the evaporation

$$Qev = \mathrm{Q\ con}$$

$$\Delta\mathrm{Tml} = \frac{\Delta\mathrm{T1} - \Delta\mathrm{T2}}{\ln\left(\frac{\Delta\mathrm{T1}}{\Delta\mathrm{T2}}\right)} = 31.91ºC$$

$$Q = \mathrm{U} \cdot \mathrm{A} \cdot \Delta\mathrm{Tml}$$

$$\mathrm{A} = \frac{\mathrm{Q}}{\Delta\mathrm{Tml} \cdot \mathrm{U}} = \frac{129\mathrm{kW}}{0.750\frac{\mathrm{kJ}}{\mathrm{m2} \cdot \mathrm{s} \cdot \mathrm{K}} \cdot (31.91ºC)} = 5.389\ m^2$$

2. Fixed the length of the heat exchanger and the diameter of the tubes :

$$\mathrm{L} = 4\mathrm{m}\ \ \mathrm{d} = 0.02\mathrm{m}$$

$$\text{transbersal tube area} = \pi \cdot r^2 = 0.251m^2$$

$$\text{latereal tube area} = \pi \cdot d \cdot l = 0.251m^2$$

$$\text{Number of tubes} = \frac{\text{heat exchange area}}{lateral\ area} = \frac{17.19964}{0.251} = 68.435\ \text{tubos}$$

3. If it is supposed square layout with one single step :

$$\mathrm{k1} = 0.215\ \text{and}\ \mathrm{n1} = 2.207$$

$$\mathrm{Db} = \mathrm{do} \cdot \left(\frac{\mathrm{Nt}}{\mathrm{k1}}\right)^{\frac{1}{n1}} = 0.272\ \mathrm{m}$$

$$\text{Distance between tubes} = 1.25 \cdot 0.2 = 0.025\ \mathrm{m}$$

Piping :

To know the pipes dimension it is necessary to impose a flow speed, knowing by heuristics that the velocity should be between 1 and 2 m/s . It has been chosen 1 m/s to ensure that the flux circulates.

1. First of all it is needed to calculated the section of the pipe, knowing the mass flowing of each pipe, the speed of the fluid and the density :

$$S = \frac{w}{\rho \cdot v}$$

2. Subsequently it is calculated the internal diameter of the pipe:

$$dint = \sqrt{\frac{4 \cdot sección}{\pi}}$$

3. Once the internal diameter has been selected, it could be determinate the thickness, but it is important to know the yield strength of the pipe . This parameter depends on the temperature of each pipe and the material . Assuming that all the pipes have the same material and the variations of the temperature are not high :

$$e = \frac{17 \cdot r}{142}$$

$$dext = dint + 2 \cdot e$$

Once all the pipes has been selected, piping’s have been selected according to the normalized pipes catalog: