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Design of a batch plant for azithromycin manufacture

Diseño de una planta para la fabricación de azitromicina

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Aos meus pais, Rodrigo e Teresa.

A Eugenia, Pedro e Andrea.

Ó meu incansable titor José María Gutiérrez.

E a toda persoa que comprenda, espere ou apacigüe.

REPORT

CONTENT

SUMMARY

Azithromycin is a drug that is used in the presence of a large number of bacterial infections or as a reducer of viral symptoms. Due to the exceptional situation of COVID-19, its potential to treat the symptoms of a wide range of respiratory diseases has been further investigated. This led to it being classified as a key drug in stopping the first waves of future infectious threats. Therefore, the production of azithromycin may be of interest to new manufacturers who want to take advantage of this market opportunity.

The objective of this project is the development of a novel process for the large-scale industrial production of azithromycin, by studying the different industrial solutions available, based on market needs.

The selection of the synthesis recipe is the starting point from which the process design is elaborated. Including the appropriate adaptations, scaling is carried out to obtain a process design according to the industrial production capacity. This project addresses the specification of the stages, operations and equipment that constitute the process is made, as well as detailing the conditions and work needs.

Based on the original distribution of the tasks in the different equipment of the process, planning and optimization strategies are applied to obtain a reorganization that allows a planning of the process that achieves the established production objectives. Bearing in mind that it is a widely studied process, this stage is fundamental, if a certain economic return is to be obtained, since increases of up to four times the production capacity of the original distribution are achieved.

Finally, to complete the objective of the project with the design of an industrially viable process, a selection is made of the main equipment in the commercial catalogue available, looking for the most appropriate technology according to the needs of the process, but also taking into account the economic viability of the project.

Key words: *azithromycin, process synthesis, basic design, production planning*.

1. INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), has become a threat to humanity in a few months, triggering an unexpected health crisis. Billions of people have already been infected by the virus and millions of deaths worldwide have been worldwide.

This virus is mainly transmitted via small respiratory droplets, through sneezing coughing or when people interact with each other for some time nearby, although aerosol transmission has recently been suggested too. An infected person can also transmit the virus an average of two and a half days before starting to show symptoms. In addition to this, there is an important percentage of people who have an asymptomatic infection by the SARS-CoV-2, which means that they are not aware of the infection but they can still spread the disease.

Since it is a new virus, nobody has prior immunity to it, which means that the entire human population is potentially susceptible to SARS-CoV-2 infection. Consequently, there is a high risk to the general population, in special for vulnerable individuals whose epidemiological situation represents an important hazard to their health (European Centre for Disease Prevention and Control 2020).

Although there is a lot of hope put into the new vaccines, the limited production rate and the strict shipping requirements make them only accessible for a very small amount of people at the moment. Moreover, there is not a specific treatment for this disease and the treatment options are currently available for the diseas1e are limited. There is a permanent need for short-term treatment for the current pandemic, in order to minimize the damage caused in people's health while waiting for the generalization of the vaccine. Broad-spectrum, historically safe, low cost and globally distributed drugs are commonly used as a pragmatic strategy during a global health crisis and consequent economic recession. Repositioning and studying these types of drugs can also create the best of tools against the next infectious threats.

Azithromycin is an antibiotic used to treat a wide range of infections including respiratory tract infections such as pneumonia, enteric infections such as typhoid fever, and genitourinary infections such as *Chlamydia*. It has also been used in patients with

malaria. The surprising complementation with the immune system, due to its massive localization in phagocytic cells and the subsequent delivery to infection sites as part of the innate immune system, has allowed this macrolide to successfully mitigate a large number of infections during the last 50 years and it is a hallmark of this broad-spectrum treatment. These amazing properties have prompted ongoing research around the world not only on its antibacterial efficacy but also on the antiviral properties of azithromycin.

Azithromycin is a derivative of erythromycin, and both belong to the subclass of macrolide antibiotics known mainly for their bactericidal properties, which is achieved by reversible binding to the P site in the 50S subunit of the bacterial ribosome. The chemical structure of macrolides consists of a macrocyclic lactone ring to which various deoxy sugars bind. And azithromycin differs structurally from the rest by substituting a methyl group for a nitrogen atom at carbon 9 of the lactone ring. This gives the molecule, in addition to its activity against a greater number of bacteria, particularly against gram-negative bacteria, greater ease of absorption with fewer side effects. Its classification, along with the other antibiotics in its family, as an effective strategy against inflammatory diseases, draws a broad-spectrum pharmacological profile for this drug (Firth and Prathapan 2020).

Drugs classified as broad-spectrum, due to their study, use and replacement for a multitude of diseases and their low cytotoxicity with few side effects, constitute a set of potentially effective and relatively safe emergency treatments against pandemics. Moreover, azithromycin is classified by the World Health Organization (WHO) as one of the safest drugs for any national health system, in addition to having a long history of repositioning security and regular administration around the world.

In addition to its widely known efficacy to treat certain types of atypical pneumonia caused by, among others, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Coxiella burnetii*, in the last months it has also been used to treat the covid19 due to its anti-inflammatory and potential antiviral effect.

The reported anti-inflammatory activity of azithromycin could help with the inflammatory phase of the COVID19 disease that develops during the second week of infection. Moreover, there is evidence that suggests that azithromycin has in vitro anti-

viral properties, against different viruses, including SARS-CoV-2. This is possible explained due to the increase in the endosomal and lysosomal pH when it is present inside the cells, attenuating the viral replication which requires a specific acidic environment.

Azithromycin arises as an accessible, cheap and safe that could have an important role in COVID19 history. Not only shows a good spectrum for the treatment of concurrent bacterial infections such as atypical pneumonia, but also could play an important role both in the viral replication phase, due to its antiviral effect, and the inflammatory phase of the COVID19. Which, along with its logistical advantage of the accessibility of this patent-free drug, is an advantage over the candidate treatments that are currently in trials and that are hardly able to combat the economic affordability of azithromycin (Damle et al. 2020).

2. OBJECTIVES

Azithromycin is a pharmaceutical active ingredient that is used to treat numerous affections, which offers great potential when facing infectious threats as COVID-19. For this reason, the development of a novel process for large-scale industrial production of azithromycin is particularly interesting.

Based on this, the objective of this work is the development of a batch plant for the production of azithromycin, through the study of different industrial solutions for the synthesis of azithromycin, following the steps below:

- Selection of the azithromycin production through a market study, taking into account the impact of the pandemic on it.
- Selection of the production recipe through the research of the available patents and technology.
- Process synthesis by scaling from process recipe to suitable industrial batch production. Specify the stages, operations and equipment.
- Basic design and selection of equipment based on the conditions and needs of the process.
- Planning and optimization of plant production through a scheduling strategy to increase production.

3. PRODUCTION REQUIREMENTS

The determination of the production requirements for the new manufacturing facility, as well as the viability of the business itself, have been determined by studying the market and the exceptional situation caused by the COVID-19 pandemic. The commercial formats, the dosage of the drug and the current consumption required by the market were considered, and some assumptions were made about these considerations. A conservative conjecture was made in order to have an initial estimate of the plant's production capacity. Therefore, we must bear in mind that the real production needs would be adjusted according to the real demand at the time of construction of the manufacturing plant.

It is commercially distributed in 250, 500 and 600 mg immediate-release tablets, 2 g microsphere prolonged-release powder, oral suspension (100-200 mg / 5 ml), and intravenous preparation (500 mg / 10 ml lyophilized bottle). According to the data provided by the CIMA (Spanish Agency for Medicines and Health Products) the most marketed formats of this product are in 3 tablets of 500 mg or 6 of 250 mg azithromycin, 3 sachets of powder for oral suspension of 500 mg or 6 of 250 mg azithromycin, bottles of 15 ml of powder for oral suspension of 200 mg azithromycin/ 5 ml or bottles of 30 ml of powder for oral suspension of 200 mg azithromycin /5 mL. Furthermore, we could also see that on a massive scale the active ingredient format used is azithromycin as dihydrate, compared to the limited use in its monohydrated form.

The general dosage of this medicine consists of single doses of 500 mg tablets every 24 hours for at least 3 or 5 days and can be extended up to 10 days. The defined daily dose (DDD) covering from 300 and 500 mg depending on the type of oral or parental dosage. For a conservative estimation, the lower value will be considered. Knowing these values and the evolution of the Dose/Inhabitant/Day (DHD) indicator, which has an average value of 1.17 DHD, we could estimate the consumption of azithromycin.

$$DHD = \frac{nº\ env \cdot FF/env \cdot C/FF \cdot 1000}{DDD \cdot nºhab \cdot 365\ días} \quad (1)$$

DHD = Dose / Inhabitant / Day indicator.
N.° env. = Number of boxes dispensed in a year.
FF/env. = Number of pharmaceutical forms per box.
C/FF = Active ingredient content by pharmaceutical form.

DDD = Defined Daily Dose indicator.
N.° hab. = Number of inhabitants of the study population.

The sale price of azithromycin treatments is around 5.62€. At this price we must deduct the VAT of 4% on the sale of drugs and the Equivalence Surcharge of an additional 0.5% subtracted from the supplier, to obtain the sale price of the product. The value that we obtain after applying these deductions corresponds to the sale price of the pharmaceutical specialty, of which between 3-10% corresponds to the price of the API sold by the manufacturer. The lowest value will be considered to obtain a conservative estimate.

$$API\ sales\ price = \frac{Price/env \cdot (1 - TAX) \cdot APIsold\ \%}{FF/env \cdot C/FF} \quad (2)$$

Price/env = Price per box.
TAX = Sales tax.
APIsold = Percentage of the API price sold by the manufacturer.
FF/env. = Number of pharmaceutical forms per container.
C/FF = Active ingredient content by pharmaceutical form.

The main pharmaceutical companies authorized to market azithromycin are Laboratorios CINFA S.A, Laboratorios NORMON S.A, SANDOZ Farmacéutica S.A, Laboratorio STADA S.L, TARBIS Farma S.L, PFIZER S.L, ALMUS Farmacéutica S.A, KERN Pharma S.L, MYLAN PharmaceuticasS.L, RATIOPHARM España S.A, TEVA Pharma S.L.U, ARAFARMA Group S.A, Laboratorio Rubió S.A. The latter, which is the main manufacturer in Spain, is planning to triple its production in response to the needs derived from the use of azithromycin in coronavirus infections.

From the point of view of the pharmaceutical companies that commercialize azithromycin and that the COVID-19 pandemic represents a strong peak in the consumption of this drug. Because of the accessibility and the significative market potential, it is proposed to capture 15% of the European and American markets. Based on this, the production capacity of the plant will be estimated.

$$Production\ Capacity = nº\ env \cdot FF/env \cdot C/FF \cdot MS\ \% \quad (3)$$

N.° env. = Number of boxes dispensed in a year.
FF/env. = Number of pharmaceutical forms per box.
C/FF = Active ingredient content by pharmaceutical form.

Production Capacity = Tons of product manufactured per year at the plant.
MS = Market share.

The calculation of possible consumption leads to the decision to design a process that allows a production capacity of 34 t/year of production, covering part of the growing demand of 226 t/year. Taking into account that the selling price of azithromycin is 107.34 €/g, it is expected to obtain an annual revenue of the order of 3.6 M€.

Table 1. Production values

Production Capacity [t/year]	34
API sales price [€/g]	107.34
Annual revenue [€/year]	3 649 628

This profit can be seen as a reasonably satisfactory result, bearing in mind that, due to the existing competition because of being a widely established process, the profit margin on the selling price of the product is adjusted; in addition to the low risk that represents betting on a product that almost necessarily undergoes a growth in its consumption, and with a long history of stability because it is habitual in the clinical setting.

The design of the process and planning decisions made are based on the production capacity assumed.

4. SELECTION OF THE MANUFACTURING PROCESS

The selection process, for the most suitable manufacturing process of azithromycin, has taken into account the advantages and disadvantages provided by each of the patents studied, as well as the effectiveness of carrying out each of the processes in the construction of a real plant.

4.1. STATE OF THE ART

Azithromycin was first presented in U.S. Patent 4,886,792 (Djokic et al. 1989), where the existence of the dihydrate form of azithromycin is shown. However, there were already indications of having isolated "erythromycin derivatives", but not in their crystalline form. Such as obtaining amorphous azithromycin powder shown in U.S. Patent 4,517,359 (Kobrehel et al. 1985), which isolates multiple erythromycin derivatives by evaporating their chloroform solution under vacuum. Or the amorphous foam of azithromycin obtained by evaporation of a solution of methyl chloride in ethanol-water, the mechanism of which is previously reported in U.S. Patent 4,474,768 (Bright et al. 1984).

As indicated in U.S. Patent 6,013,778 (Heggie et al. 1988), the most generalized process for obtaining azithromycin consists of the transformation of erythromycin A into azithromycin through the following mechanisms: First, conversion of erythromycin A into its oxime; Beckmann rearrangement of oxime to obtain the 6,9-imino ether of erythromycin A; reduction of the 6,9-imino ether to 9-deoxo 9a-aza-9a-homoerythromycin and, finally, reductive N-methylation to obtain azithromycin as the final product.

To carry out the reduction of the 6,9-imino ether, reducing agents are used in stoichiometric amounts or hydrogenation under high pressure with platinum. The cyclic amine is then isolated, which is then subjected to reductive methylation, using Eschweiler-Clarke conditions (formaldehyde and formic acid in chloroform) as described in U.S. Patent 7,235,646 B2 (Mistry et al. 2007). Or by hydrogenation of formaldehyde and hydrogen in the presence of a noble metal catalyst as described in U.S. Patent 4,517,359 (Kobrehel et al. 1985).

All processes share the methylation of 9-Deoxo-9a-aza-9a-homoerythromycin-A to

obtain 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A from which we can obtain different salts of azithromycin, among which the monohydrate, the dihydrate and the anhydride stand out. The dihydrate form constitutes practically all the azithromycin products marketed in Spain because it presents one of the obtaining and purification processes with fewer steps, in addition to being one of the most stable forms.

In the European Patent 0,298,650 (Allen et al. 1992) a crystallization of azithromycin in ethanol-water is shown giving rise to a monohydrate hygroscopic form. From the monohydrate hygroscopic form, they describe a method for the obtaining the dihydrate form. This involves recrystallization from a mixture of solvents containing tetrahydrofuran and an aliphatic hydrocarbon (C5-C7) in the presence of water. There are some downsides to this process, such as the higher recovery costs implied by the use of organic solvent mixtures, or the risk associated with working with hydrocarbons.

Another process for obtaining azithromycin dihydrate is described in the U.S. Patent 5,869,629 (Bayod Jasanda et al. 1999). Here, recrystallization of the hygroscopic form of azithromycin is carried out in acetone-water and the suspension is stirred for 24 hours. It is the long stirring time, which requires the conversion of monohydrate to dihydrate, the disadvantage of this process.

Moreover, the dihydrate form can be produced with the crystallization of azithromycin monohydrate, dissolving it in acetone-water and then through a pH adjustment obtaining the dihydrate as a precipitate, European Patent 0,941,999 (Heggie et al. 1999).

There is a tendency to design the processes to obtain the dihydrate form as the final product, being the monohydrate a previous step. The reason is that, as indicated by U.S. Patent 2002/0,111,318 A1 (Rengaraju 2002) "*The monohydrate form of azithromycin is difficult to handle during its formulation into capsules […] due to its hygroscopicity. Hence the stable dihydrate form is used [...] Due to this […] methods of conversion of unstable monohydrate form to stable dihydrate form is required.*" Furthermore, due to its hygroscopic nature, the monohydrate form is notoriously difficult to prepare and maintain in a form that has constant and reproducible water content, since minimal variations in time exposure or relative humidity alter the product, due to its ease of use

collecting varying amounts of water. This implies that during its formulation its handling is particularly difficult since higher relative humidity levels are required to avoid electrostatic problems (for example, flow rates, dust with potential for explosion). These problems have been overcome by obtaining the dihydrate form more stable and less hygroscopic under the conditions of drug formulation (Allen et al. 2001).

Despite the mentioned above, labors of research and investigation continued on obtaining a stable monohydrate form. Patents such as U.S. Patent 2004/0,053,862 A1 (Centellas et al. 2004) describe how to obtain a form of azithromycin monohydrate that is stable and not hygroscopic, by adding an alkaline solution to a hydrochloric acid solution of azithromycin. However, the result is not entirely satisfactory since it has been reported that azithromycin is unstable in acidic conditions.

Notwithstanding the above, U.S. Patent 7,683,162 B2 (Gutman et al. 2010) seeks to obtain an azithromycin monohydrate that is substantially free of organic solvents and that does not degrade. The process is based on the dissolution of the precursor in ethanol, adding water in order to precipitate the azithromycin monohydrate, which will be subsequently filtered and dried. However, even though some pharmaceutical companies have already decided to launch products with the content of this active principle, this technology is under development and pending optimization.

U.S. Patent 2003/0,139,583 A1 (Singh et al. 2003) describes a detailed process for obtaining the anhydrous form. In this study, the best alternatives are selected to obtain the dihydrate form (using U.S. Patents 4,328,334, 4,474,768 and 4,517,359) and finally through a process that comprises the elimination of an organic solvent from a solution of the dihydrate in the organic solution or from a solution of the dihydrate in a mixture of the organic solvent and water to provide the anhydrous compound.

W.O. Patent 2007/015,265 A2 (Madhaorao et al. 2007) reports a broader procedure as it also tries to cover the production of erythromycin. Novelty, it indicates how to jump from erythromycin without purifying to 6,9-Imio ether, sending us the purification to erythromycin base. And then it uses a Pt/C catalyst to obtain 9-Deoxo-9a-aza-9a-homoerythromycin A. It would be an interesting proposal for a pharmaceutical company that produces erythromycin that wishes to expand its catalogue by also producing

azithromycin. Returning to the patent, it is worth highlighting the novel dihydrate purification process, diluting it in a solvent such as acetone or lower chain alcohol to extract impurities by adding old carbon.

Other purification alternatives are also listed in patent U.S. Patent 2002/011,138 A1 (Rengaraju 2002) using different combinations of solvents. Despite this, the recrystallization process prior to filtering and washing is relatively greater compared to the previous alternative, which could be a disadvantage for production planning.

After studying the pros and cons of the different processes, and once the possible alternatives shown in the different patents have been considered, it was decided to use the process of patent U.S. Patent 2003/0,139,583A1 (Singh et al. 2003) as a basis, as it brings together interesting strategies from other patents and part of the erythromycin base as raw material, which is widely distributed for the production of derivatives. Since this process goes one step further and seeks to study the anhydrous alternative, the innovative step of purification of azithromycin dihydrate from W.O. Patent 2007/015,265 A2 (Madhaorao et al. 2007) is included before obtaining the anhydrous form. Since as mentioned above, the dihydrate form is widely accepted by the market.

4.2. PRODUCTION RECIPE SELECTED

The process selected for the industrial production of azithromycin consists of six stages. The first five stages follow the recipe described in patent U.S. Patent 2003/0,139,583 A1 (Singh et al. 2003) and the final stage follows the purification process described in W.O. Patent 2007/015,265 A2 (Madhaorao et al. 2007). The stages of the resulting process will be detailed below.

4.2.1. Stage 1: Preparation of Erythromycin-A Oxime

The first step consists of the synthesis of Erythromycin-A Oxime. The synthesis is based on the reaction between four compounds: Erythromycin-A or Erythromycin base, hydroxylamine hydrochloride, sodium hydroxide and acetic acid.

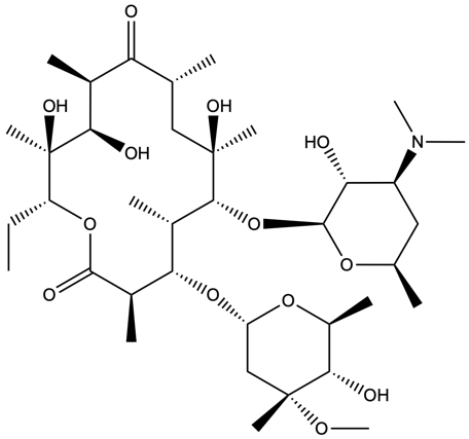

Figure 1. Erythromycin-A

A solution of 1.40 kg of hydroxylamine hydrochloride in isopropyl alcohol and water is prepared. Sodium hydroxide, 0.81 kg, is added in portions, at a temperature of about 20 °C. After the drop, the pH was adjusted to 7.0 with acetic acid. Erythromycin base, 1.5 kg, is added and the resultant solution is kept at 45-55 ° C for 28 hours. The reaction mixture is cooled to room temperature and the reaction is terminated by adding the mixture of water and ammonia. The crude product is treated with water to remove inorganic salts and get 1.40 kg of erythromycin-A oxime as a white crystalline product.

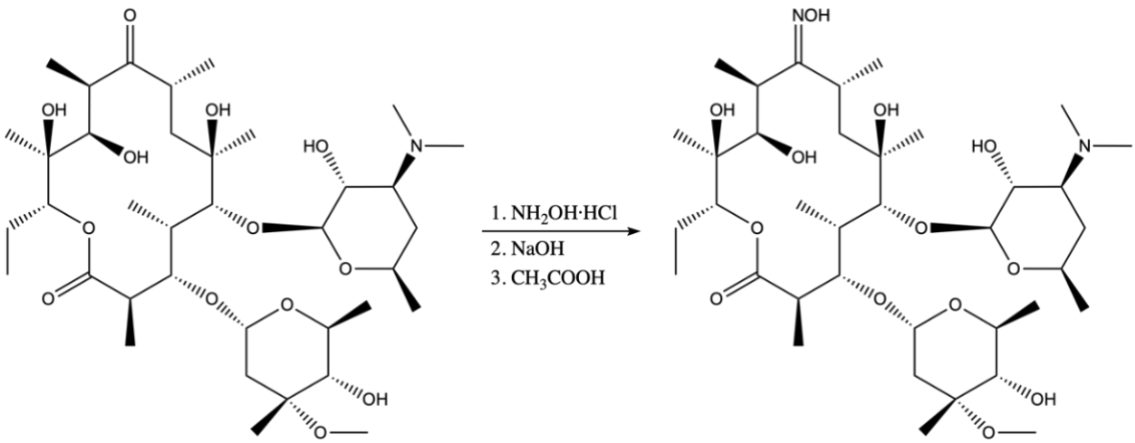

Figure 2. Synthesis of Erythromycin-A Oxime

4.2.2. Stage 2: Preparation of 9a-Aza-9a-homoerythromycin-A

An among of 1.15 kg of Erythromycin Oxime, are dissolved in acetone and water and maintained at a temperature of 0-5 °C. The pH of the reaction mixture was adjusted to roughly between 2.5 and 2.8 with hydrochloric acid. Sodium bicarbonate, 0.48 kg, is added portions to the cooled reaction mixture. After the addition of the sodium bicarbonate, methane sulfonyl chloride, 0.5 kg, are added. The reaction mixture is stirred for 1 hour at 0-5 °C. The pH of the reaction mixture is adjusted with aqueous sodium

hydroxide and the title product is filtered from a white crystalline material in high purity. Yield 1.00 kg.

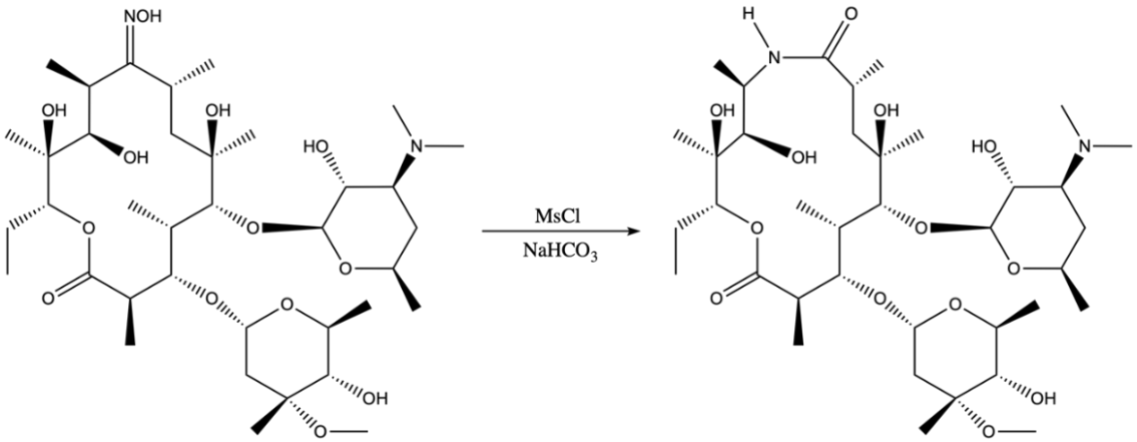

Figure 3. Synthesis of 9a-Aza-9a-homoerythromycin-A

4.2.3. Stage 3: Preparation of 9-Deoxo-9a-aza-9a-homoerythromycin-A

An among of 1.00 kg of 9a-Aza-9a-homoerythromycin-A, is stirred in methanol and water. Sodium borohydride, 1 kg, is added over four hours. The temperature is maintained below 5 °C. After completion of the sodium borohydride addition, the reaction mixture is stirred for an additional six hours at <5 °C, and for an additional twenty-four hours, at room temperature. The reaction is finished after the addition of water and chloroform. The chloroform layer is separated and cold water is added. The product is then extracted with chloroform by a pH adjustment using dilute hydrochloric acid and sodium hydroxide.

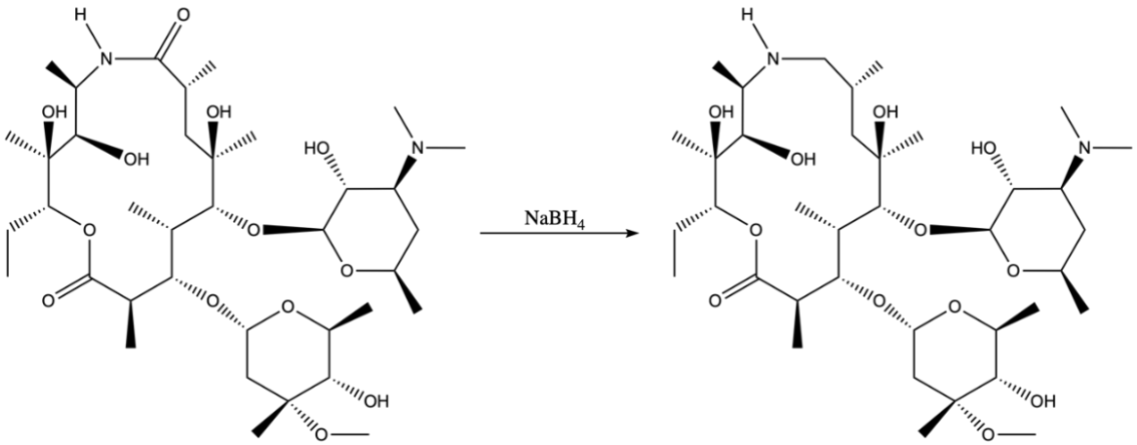

Figure 4. Synthesis of 9-Deoxo-9a-aza-9a-homoerythromycin-A

Initially, the mixture (water and chloroform) is stirred at pH 2.5 to 2.8 for 1 hour. The pH of the water layer is adjusted to 9.5 to 9.8, and the mixture is stirred for one-half

hour. This sequence is repeated with additional chloroform three times. Consecutively, the water layer is separated and an additional portion of chloroform is added and the extraction repeated one additional time. After the extraction, the chloroform extracts are combined, dried over potassium carbonate, filtered and used in the next step without additional treatment.

4.2.4. Stage 4: Preparation of 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A

The 9-Deoxo-9a-aza-9a-homoerythromycin-A is treated with formaldehyde, 0.17 L, and formic acid, 0.105 L, the reaction mixture is stirred for four hours, under nitrogen and heated at reflux for twelve hours. The reaction is cooled, treated with water and the pH is adjusted to values covering 4.0 to 4.5. Chloroform is added and the mixture stirred, and the chloroform layer separated. The aqueous layer is adjusted to pH 6.0 to 6.5 and extracted twice with chloroform. Additional chloroform is added to the aqueous layer and the pH is adjusted with stirring to about pH 2.0 to 3.0 with dilute hydrochloric acid. The mixture is stirred vigorously, and the chloroform layer is separated. The pH is adjusted to about pH 6.0-6.5 with dilute sodium hydroxide and extracted twice with chloroform.

The sequence above is repeated five times on the aqueous layer. The chloroform layers are combined, dried over KCO and concentrated under vacuum. The solid residue is dissolved in isopropyl alcohol and the title product crystallized by adding water. The product is 0.55 kg of azithromycin.

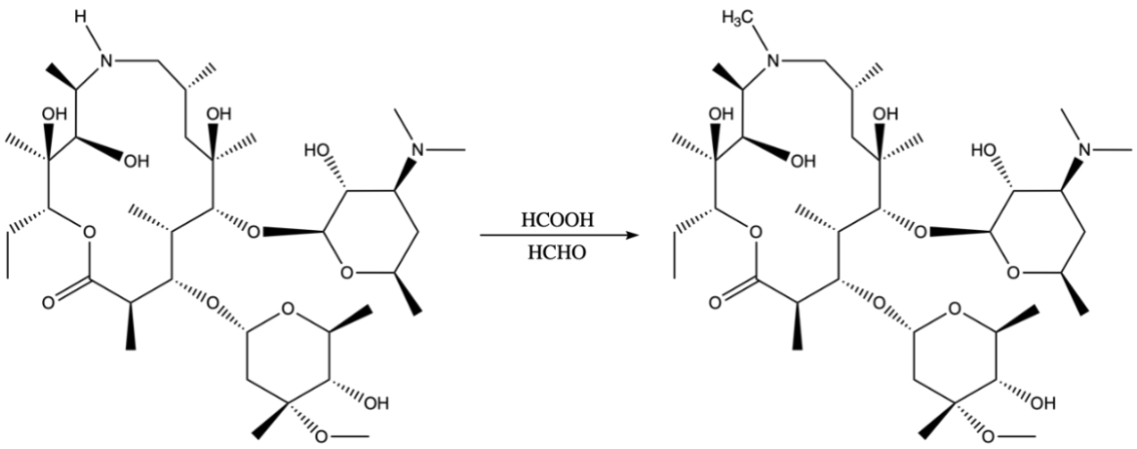

Figure 5. Synthesis of 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A

4.2.5. Stage 5: Preparation of Azithromycin Dihydrate

An among of 0.5 Kg of 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A, is dissolved in water, making the solution acidic (pH of 2.5 to 5.0) with dilute hydrochloric acid. After 20 minutes stirring, the pH is raised with dilute sodium hydroxide and the solution is stirred for twelve hours. The product is crystallized as a white crystalline material in high purity, 0.48 kg.

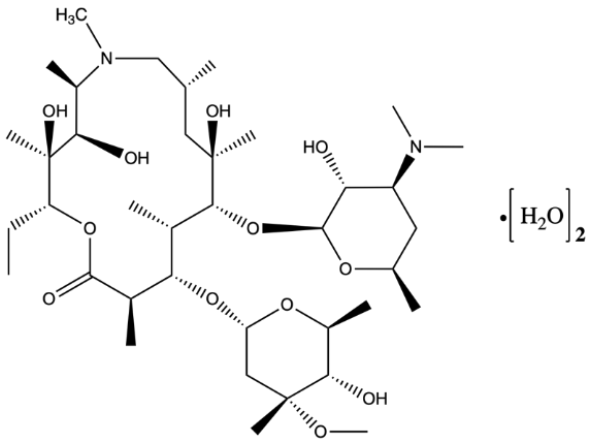

Figure 6. Azithromycin Dihydrate

4.2.6. Stage 6: Purification of Azithromycin Dihydrate

An among of 10 gm of azithromycin dihydrate is dissolved in 30 mL of acetone for 30 minutes with stirring till a clear solution is obtained. Consecutively, 0.3 mg of charcoal are added to this solution, the mixture is stirred for 30 minutes and subsequently filtered. To the filtrate, 180 mL of water are added to 50 to 55 °C within 12 hours. The aqueous filtrate is cooled to room temperature and then chilled to 0 to 5 °C. Azithromycin dihydrate is filtered from the aqueous filtrate and washed with refrigerated water (0 to 5 °C) and finally dried at 65 °C. The final product of azithromycin dihydrate has a purity between 95% to 100%.

5. PROCESS SYNTHESIS

Process synthesis studies the search for a feasible industrial production process, based on a laboratory recipe. In order to scale the quantities produced in the laboratory to the large quantity that is industrially pursued, each of the stages of the selected patent must be studied extensively to select the most suitable industrial solution.

When selecting the industrial solution, the quantity of product to be processed has a significant influence on the assessment of the different technologies. Consequently, the selection of a batch size has an impact on obtaining more beneficial results.

It is possible to estimate the number and size of the batches based on the annual production and production times. The selected annual production is 34 t/year, estimated in the 3th section of this project, and the synthesis process is around a production time of about 8 days, as detailed in the 7th section. Due to the numerous steps involved in the process and the fact that operating the process continuously avoids the need to invest in intermediate storage equipment, the plant must operate 24 hours a day. Taking into account also the number of working days and the necessary stops for maintenance, the annual production of the plant is 80 batches of 425 kg of azithromycin dihydrate.

The synthesis stages are reflected in the creation of state-task networks (STN), which organize not only each of the operations that make up each stage, but also the inputs and outputs, as well as the process conditions that condition the selection of procedures and equipment that are more suitable.

The following section details the considerations are taken for both the scaling of the laboratory recipe, and the industrial production size. For decision-making, bibliographic material, heuristic rules resulting from industrial experimentation and commercial catalogues are also used.

5.1. STAGE 1: Erythromycin-A Oxime

In the first stage, erythromycin-A oxime is synthesized from erythromycin base, hydroxylamine hydrochloride, sodium hydroxide and acetic acid, as stated previously. Despite the small number of tasks in this stage, each one requires a large amount of time for the reaction and crystallization. Therefore, the main objective is to reduce operating times.

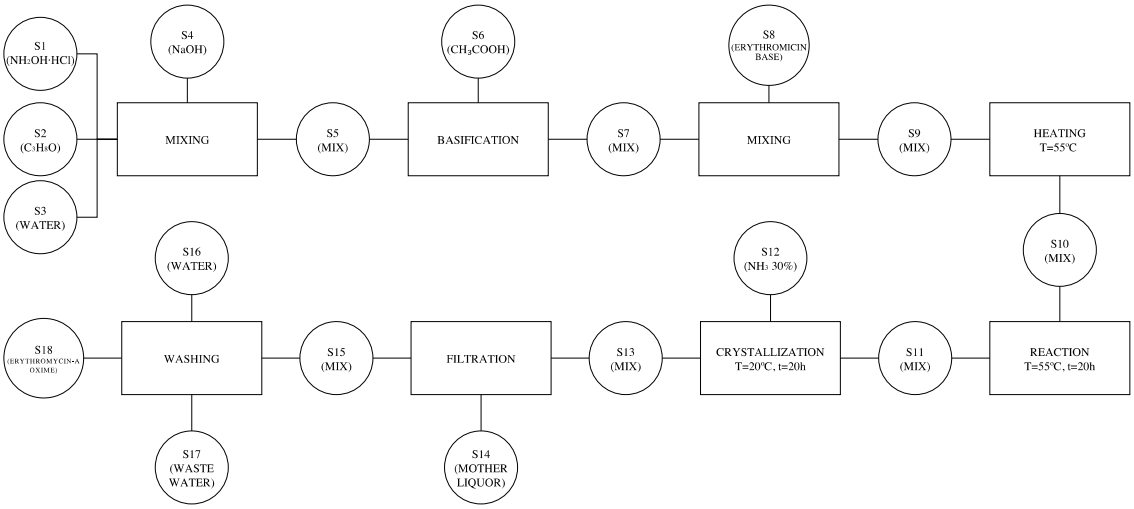

Figure 7. STN for Stage 1

In order to execute the different duties in this stage, a reactor is necessary. Moreover, because this stage encompasses two of the longest-lasting tasks in the process, it has been decided that they are carried out in separate containers. As a direct consequence of the aim to reduce time expenditure by overlapping tasks, a crystallization reactor also is necessary. The components and sub-components of that equipment are discussed concerning the needs of the process.

Firstly, a dilution of part of the reagents in the solvent is carried out in the reactor (R-01). On the one hand, isopropyl alcohol and water, as liquids at room temperature, are charged to the reactor through pipes. On the other hand, the solids, hydroxylamine hydrochloride and then the sodium hydroxide, are charged from the top of the reactor in portions. The mixture is then acidified with acetic acid to adjust the pH to 7.0. Despite being a liquid, because it is a small quantity, it can also be supplied through the upper part of the reactor as a solid. Apart from that, in a second mixing, erythromycin base is also added through the upper part of the reactor because it is a solid. Conventional mixing equipment adapted to the dimensions of the tank can be used to carry out the tasks, since none of the compounds that intercede in the process requires special characteristics.

Regarding the heating process and the reaction, it is necessary to have a half-pipe jacketed. In order to raise the temperature inside the tank, the heating fluid used is low-pressure steam. The heat transfer area and mixing conditions allow a uniform temperature distribution within the tank. The optimal reaction temperature is established in the patent between 45-55 °C. Industrially, temperature control can be carried out with

more precision than in the tests carried out in the laboratory, which allow us to maintain the value that best favors the progress of the reaction thermodynamically. In the absence of thermodynamic and kinetic data for the reaction, the highest value, 55 °C, is considered the most favorable. This helps with the shortening of the reaction time, due to the greater precision in maintaining the temperature inside the tank at a favorable set-point, with an estimated reduction in time of around 15%, considering 20 hours as necessary to carry out the reaction.

After the reaction stage, the solution is sent to the crystallization reactor (CR-01). The characteristics that, a priori, indicate the type of crystallization process to be used are described in the selected patent. Firstly, pH adjustment is necessary to induce precipitation. This increase in pH is achieved with the addition of ammonia in a 30% (w/w) aqueous solution to the crystallization reactor, by pipe. Secondly, it is indicated to cool the reaction mixture to room temperature to favor the crystallization process. To boost the process in order to reduce the operating time, it is sought to keep the operating temperature stable, at 20 ºC.

Based on the presented above, the crystallization vessel is equipped, like the previous reaction equipment, with a half-pipe jacket to feed the fluid in charge of carrying out the thermal exchange, cold water. The crystallization reactor is also equipped with an impeller capable of scratching the walls of the reactor to dislodge any crystals that may form on it. The most recommended impeller for this type of batch process is the anchor type as it is the one that favours a better distribution of the mixture and therefore of temperatures inside the container.

The most generalized methods of crystallization are by cooling, concentration by evaporation, reaction, or the possible combinations of them. The most common combination has as the first step the concentration of the solute by evaporation, which is followed by precipitation by cooling. Notwithstanding this alternative, a priori more efficient, on certain occasions it could induce an increase in operating times, due to the need to heat and evaporate, continuing with the precipitation of the mixture, that must be cooled again. It is also to take into account that the implementation on an industrial scale of crystallization by cooling is more favourable, due to the high precision achieved in the control of temperatures, compared to the difficulties that the implementation of

crystallization by evaporation may present. (Korovessi et al. 2006). That is why the cooling crystallization method is assumed to be the most suitable for this process thanks to its easy industrial application and simple operation to obtain the desired results. As is rightly mentioned in the patent, it is combines with the precipitation of the product because of pH adjustment needed deriving from the insolubility of the oxime after the addition of ammonia.

Despite the considerations taken, the minimum temperature set and the mixing conditions seek to decrease the crystallization time, generally, an operation of this type is estimated to take about 20 hours of crystallization to obtain the desired crystalline product.

Finally, for conditioning of the product based on its use in the next stage, the mixture is washed and filtered. Given that experimentation is essential at this stage, in order to obtain the desired results, the selection of the filtration equipment is made based on those that will provide greater flexibility and adaptability during operation, thus allowing to achieve the desired results. Therefore, it is decided to choose a suitable type of filter for batch operation and a slow filtration speed as it is a small crystal pharmaceutical product. Consequently, the filtration is carried out in a filter press (FN-01), one of the most versatile and common filters in batch operations, in addition to being the best technology in terms of washing the cake. The drag of inorganic salts, avoiding the appearance of impurities in the product, is achieved by washing the cake with water. Both the mixture from the tank and the washing water are loaded into the filter through pipes. A centrifugal pump is used to drive the mixture, as it is suitable for driving fluids with solid particles.

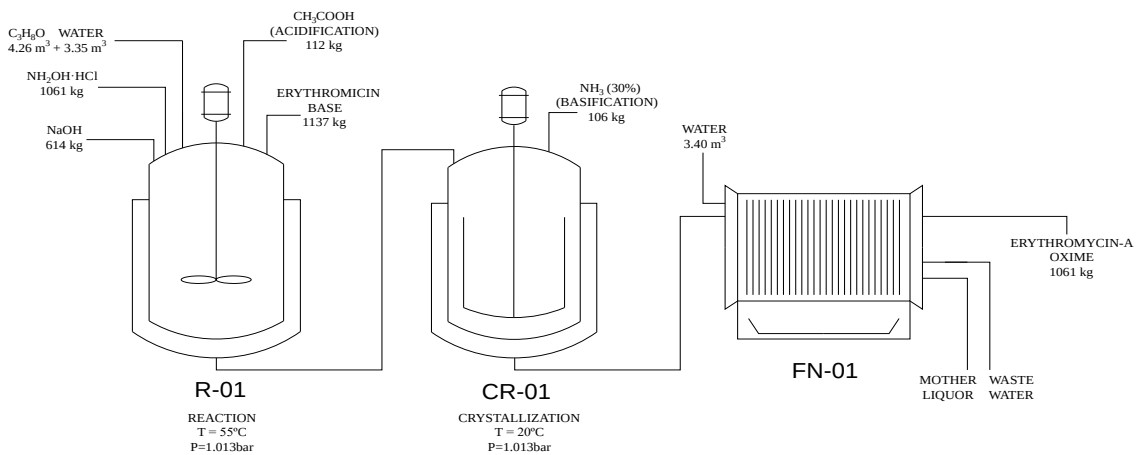

Figure 8. Equipment diagram for Stage 1

The alternative of drying the product could be evaluated to facilitate its storage, however, since in the following stages the product is diluted in water, in order to avoid the excessive energy and time consumption that a drying stage entails, the stages are carried out successively, dispensing with the storage of intermediate products. Ergo drying is carried out only in the stage of obtaining the final product.

Material balance for the stage 1 is summarize in Table 2.

Table 2. Material balance for Stage 1

Compound	Quantity [kg]	Quantity [kmol]	Volume [m^3]
$NH_2OH \cdot HCl$	1061.21	15.27	-
C_3H_8O	3350.38	-	4.26
Water	3350.38	-	3.35
NaOH	613.98	15.35	-
CH_3COOH	111.59	1.86	-
Erythromicin Base	1137.01	1.55	-
NH_3 (30%)	105.82	1.86 (pure)	-
Water	3395.86	-	3.40
Erythromycin-A oxime	1061.21	1.42	-

5.2. STAGE 2: 9a-Aza-9a-homoerythomycin-A

In this stage, 9a-Aza-9a-homoerythromycin-A is synthesized from erythromycin-A oxime. This synthesis has a smaller number of tasks to be carried out compared to the first one, but in the same way, the industrial implementation of its crystallization stage must be carefully studied. Even though the reaction of this stage is of a much shorter time, tasks such as crystallization require a considerable increase in the operating time, therefore the reduction of those times are also pursued.

As in the previous stage, a priori, a reactor and a crystallizer are necessary. The components and sub-components of that equipment are discussed concerning the needs of the process.

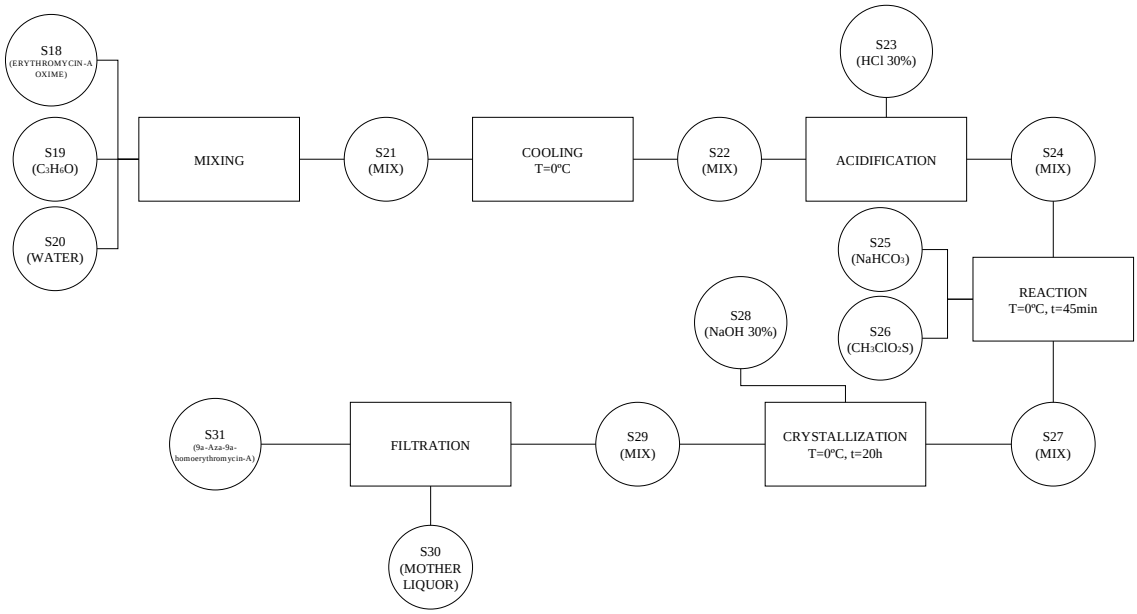

Figure 9. STN for Stage 2

First, the reaction mixture is prepared by charging water and acetone to the reactor through pipes and the solid crystal of erythromycin-A oxime, obtained in the previous step, is charged from the top of the reactor (R-01), reusing this container already emptied from the previous stage, since, as shown below, the technical characteristics required for this task are similar. These compounds do not present difficulties to be mixed, reason why a standard mixer in coherence with the dimensions of the container allows to obtain the desired results. Before adding the rest of the compound in the reaction mixture, the temperature of the mixture is lowered to 0 °C. Consequently, the selected reactor has a half-pipe jacket through which refrigerated water circulates as a cooling fluid. Also, for this case, the most recommended impeller for this type of batch process is the anchor type, since it is the one that favours a better distribution of the mixture and, therefore, of temperatures within the container.

After that, the pH of the mixture is adjusted to 2.5 by adding hydrochloric acid 30% (w/w) by pipe. Sodium bicarbonate is then added to the acidified reaction mixture in portions. Finally, methane sulfonyl chloride is added, from the top of the reactor.

The operating temperature for carrying out the reaction is 0 ºC. Due to the greater industrial precision to keep the temperature inside the tank in a favourable set-point, a time reduction of about 15% can be estimated, resulting approximately 45 min of agitation the time needed to carry out the reaction.

After the reaction step, the solution is charged to the crystallization reactor (CR-01), reusing this container already emptied from the previous stage, since, as shown below, a crystallization by cooling is also carried out, therefore the technical characteristics required for this task are similar. The discharge of the reactor is carried out by pipe, prioritizing the possibility of their evacuation by gravity. A pH adjustment is necessary to induce precipitation. This increase in pH 7 is achieved with the addition of sodium hydroxide 30% (w/w) to the crystallization reactor, by pipe. The mixture is kept at a temperature of 0 ºC to favor the crystallization process and, as a result, a reduction of the operating time is obtained.

The crystallization vessel is also equipped with a medium jacket to feed the refrigerated water in charge of carrying out the heat exchange. Like the crystallizer needed in the previous stage, the vessel is equipped with an impeller capable of scratching the walls of the reactor to dislodge any crystals that may form in it. And anchor type impeller, to favor a better distribution of mixture and temperature inside the container.

Again, as it has already been described, the cooling crystallization method is used combined with the precipitation of the product due to the pH adjustment, and an operating time of approximately 20 hours is estimated to obtain the desired crystalline product.

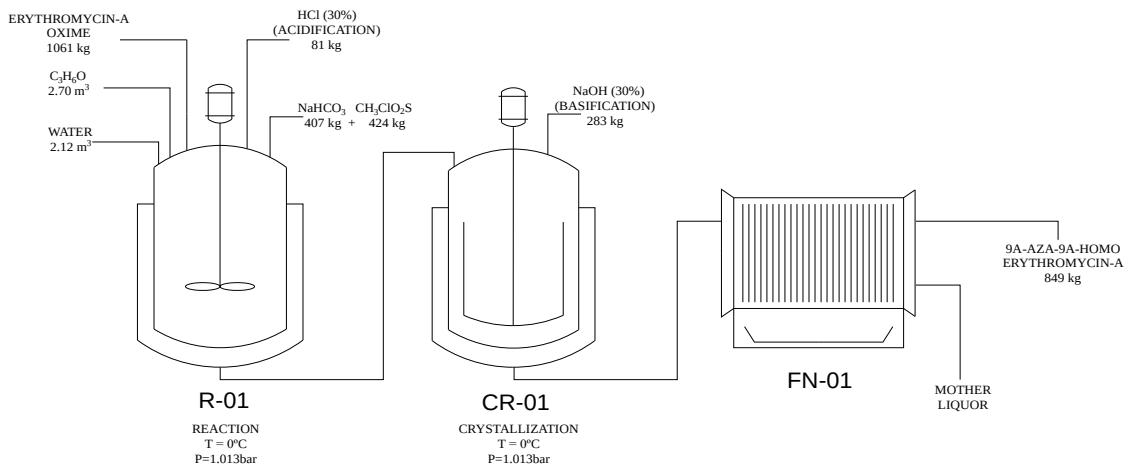

Figure 10. Equipment diagram for Stage 2

Finally, for the conditioning of the product based on its use in the next stage, the mixture is filtered. Once again, filtration is carried out in a filter press (FN-01), allowing the reuse of the filter from the previous stage, demonstrating the versatility of the selected

system. The tank mix is loaded into the filter through pipes and a centrifugal pump is used to drive the mixture. The solid product is used in the next stage, and the mother liquor is discarded.

Material balance for the stage 2 is summarize in Table 3.

Table 3. Material balance for Stage 2

Compound	Quantity [kg]	Quantity [kmol]	Volume [m^3]
Erythromycin-A oxime	1061.21	1.42	-
C_3H_6O	2122.41	-	2.70
Water	2122.41	-	2.12
HCl (30%)	81.55	0.67 (pure)	-
$NaHCO_3$	407.50	4.85	-
CH_3ClO_2S	424.48	3.71	-
NaOH (30%)	282.96	2.12 (pure)	-
9a-Aza-9a-homoerythromycin-A	848.96	1.13	-

5.3. STAGE 3: 9-Deoxo-9a-aza-9a-homoerythromycin-A

In this stage, 9-Deoxo-9a-aza-9a-homoerythromycin-A is synthesized from 9a-Aza-9a-homoerythromycin-A. This synthesis is one of the most complex of the process and therefore several tasks are required. Despite this, it seeks to reduce operating times, since many of these tasks allow better precision and control on an industrial scale.

To perform this step a reactor is required, as well as the components and subcomponents of which are discussed during this description of the synthesis process.

First, a dilution of the reactants is carried out in the solvent inside the reactor. On the one hand, the liquids, methanol and water, are loaded into the reactor (R-01) through pipes and, on the other hand, the solids are loaded from the top of the reactor one by one. First the crystal of 9a-Aza-9a-homoerythromycin-A, synthesized in the previous step and then the sodium borohydride in portions. Simultaneously, the mixture is cooled at a temperature of 5 °C for 8 hours and, after that, the reaction takes place at room temperature for 20 hours. In both cases, the operating time is around 15% less than in

laboratory operation, due to the improvement in the control of operations offered by the industrial operation. To carry out the tasks, conventional mixing equipment adapted to the dimensions of the tank is used, since none of the compounds with which it works requires special characteristics. A half-pipe jacket reactor is used to lower the temperature inside the tank and promotes the start of the reaction, using refrigerated water as the cooling fluid. The heat transfer area and mixing conditions allow for a uniform temperature distribution within the tank.

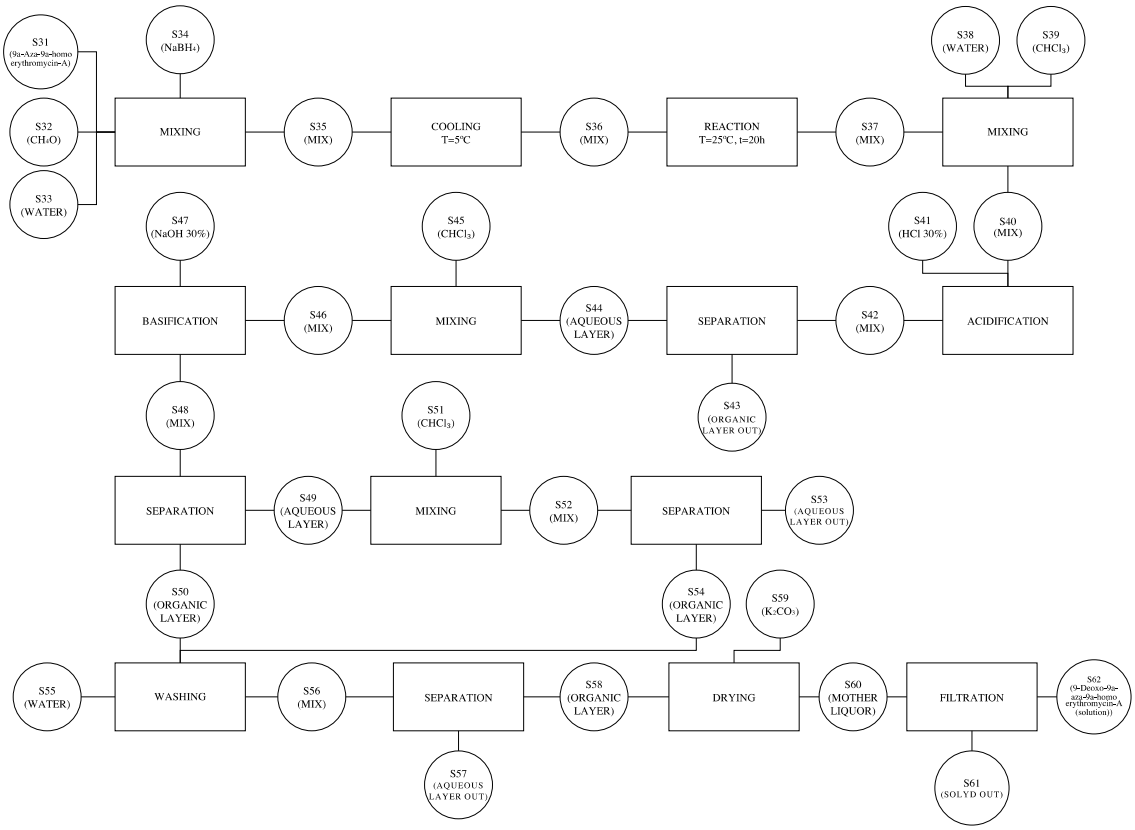

Figure 11. STN for Stage 3

After completion of the reaction, the resulting product is mixed with chloroform and water that are piped into the reactor and hydrochloric acid 30% is added to the reactor by pipe to acidify the mixture to pH 2.5. This allows the fatty acids to be displaced towards the organic chloroform phase, while the product remains in the aqueous phase. After 1 hour of stirring, thanks to the difference in densities between chloroform layer (1483 kg/m^3) and water layer (998 kg/m^3), the organic phase can be removed from the container by sedimentation from the bottom of the reactor. This phase is used to carry away most of the fatty acid products and is therefore discarded.

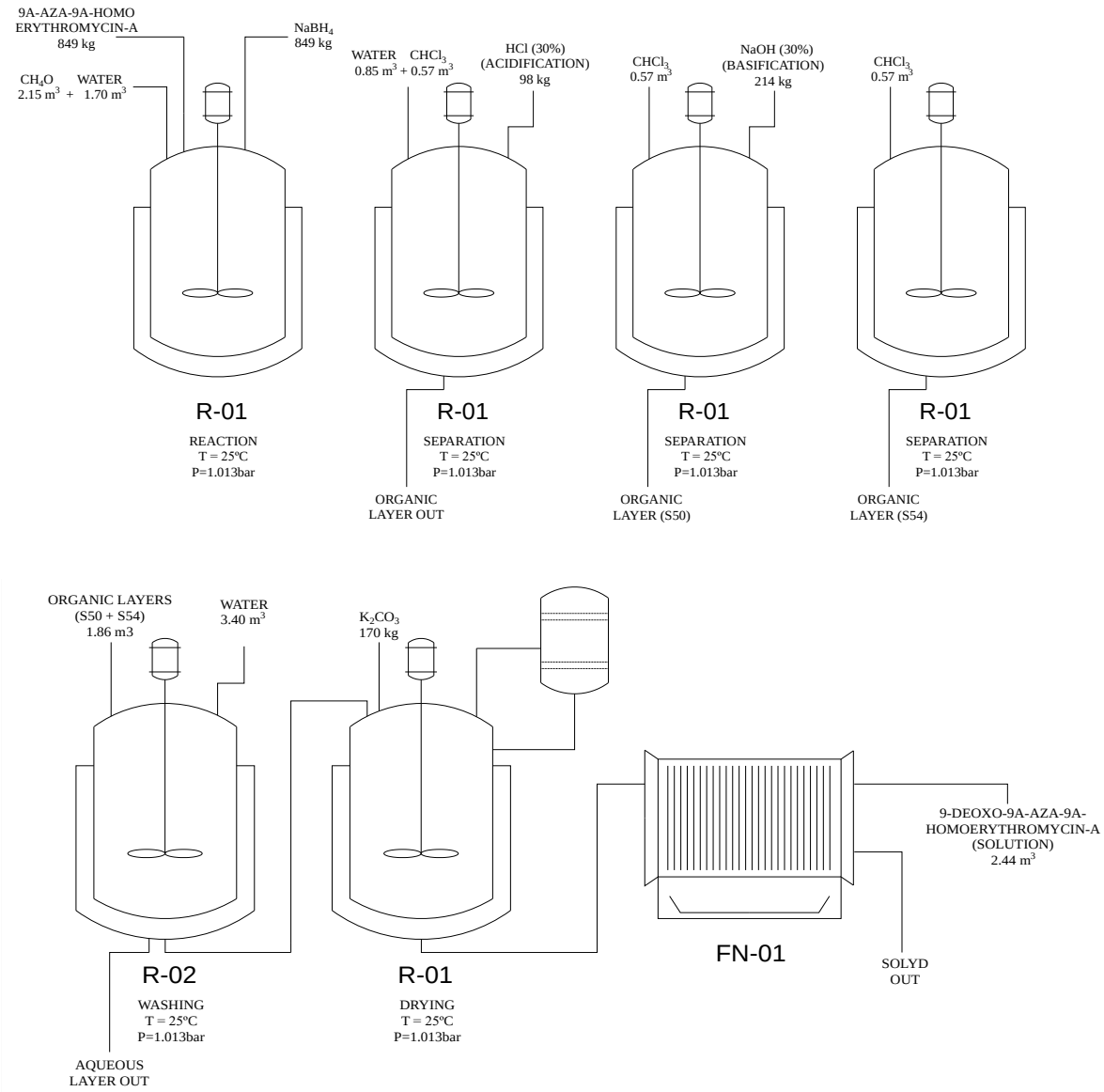

Figure 12. Equipment diagram for Stage 3

Sodium hydroxide is then added to the top of the tank, to raise the pH to 9.8, followed by the addition of a new part of chloroform to the mixture, which is then stirred for 1 hour. The basification of the aqueous medium displaces the product of interest towards the organic phase, that allows the extraction of the product with chloroform. Due to the difference in densities, the organic phase can be removed from the container by sedimentation from the bottom of the reactor and transferred by pipe to another container with stirring, a new reactor vessel (R-02). Once the organic phase has been transferred, a new part of chloroform is added to the aqueous phase and it is stirred again. Thanks to this, it is possible to extract part of the product that is still trapped in the aqueous phase.

The organic phase is transferred by pipe to the same container as the previous organic phase, to combine the two chloroform extracts that carry the product. After transferring the second organic phase, the remaining aqueous phase is removed from the interior of the reactor and discarded. Even though several stages are established in the patent, two stages are sufficient to obtain the required results, due to the rigorous control over the operating conditions.

Table 4. Material balance for Stage 3

Compound	**Quantity [kg]**	**Quantity [kmol]**	**Volume [m^3]**
9a-Aza-9a-homoerythromycin-A	848.96	1.13	-
CH_4O	1697.93	-	2.15
Water	1697.93	-	1.70
$NaBH_4$	848.96	22.44	-
Water	848.96	-	0.85
$CHCl_3$	848.96	-	0.57
HCl (30%)	97.86	0.81 (pure)	-
$CHCl_3$	848.96	-	0.57
NaOH (30%)	214.23	1.61 (pure)	-
$CHCl_3$	848.96	-	0.57
Water	3395.86	-	3.40
K_2CO_3	169.79	0.84 (pure)	-
9-Deoxo-9a-aza-9a-homoerythromycin-A (solution)	3395.86	12.27	2.44

The chloroform extracts are washed by addition and mixed with cold water. Again, the organic phase can be removed from the container by sedimentation from the bottom of the reactor and, again, transferred through the pipe to another container with stirring (R-01). The washing water is also discarded.

The recovered organic phase is treated with a drying agent to remove all traces of water that the organic solvent carries. The drying agent used is potassium carbonate and

its addition is carried out through the upper part of the container. Finally, the mixture is filtered to eliminate the hydrated potassium carbonate residues and purify the solution of 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A that is used in the next stage.

Once again, filtration is carried out in a filter press (FN-01) by loading the tank mix into the filter through pipes, and a centrifugal pump is used to drive the mixture as it is suitable for driving fluids with solid content.

Material balance for the stage 3 is summarize in Table 4.

5.4. STAGE 4: 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A

In this stage, 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A is synthesized from 9-Deoxo-9a-aza-9a-homoerythromycin-A. This synthesis is one of the most complex and therefore several tasks are required. Despite this, it seeks to reduce operating times, since many of these tasks allow better precision and control on an industrial scale than on a laboratory scale.

To carry out this stage, reaction and crystallization equipment is necessary. The tasks that require more operating time are sought to isolate them in separate containers. This allows a better overlap of tasks in order to reduce the total operating time. The components of those equipment are discussed in relation to the needs of the process.

First, a dilution of the reactants is carried out inside the reactor by stirring for 3 h. As they are all liquid, formaldehyde, formic acid and the 9-Deoxo-9a-aza-9a-homoerythromycin-A solution from stage 3, they are charged by pipeline. Due to the flammability of the mixture, the inside of the reactor must have an inert atmosphere, therefore, nitrogen is previously introduced. To carry out the tasks, a conventional mixing equipment adapted to the dimensions of the tank is used, since none of the compounds with which it is worked requires special features (R-02). After that, the mixture is heated to a temperature of 50ºC, below its boiling temperature and stirring is continued for 10 h. In both cases, the operating time is reduced due to the improvement in the control of operations offered by the industrial operation. A half-pipe jacket is used to raise the temperature inside the tank, powered energetically with low-pressure steam. The heat transfer area and mixing conditions allow for a uniform temperature distribution within the vessel.

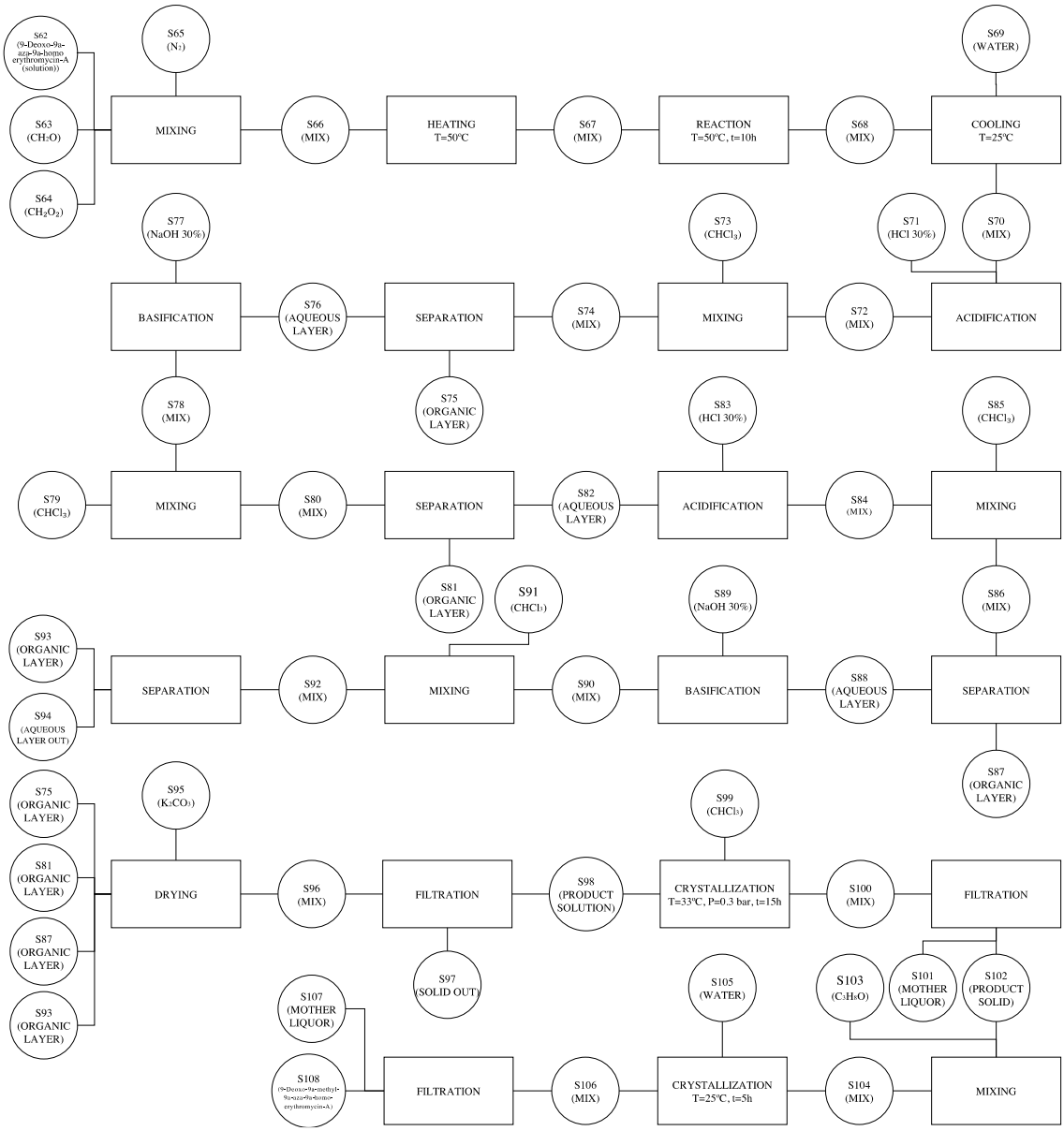

Figure 13. STN for Stage 4

Once the reaction is completed, the heating is stopped and, taking advantage of the need to treat the mixture with water, cold water is used to lower the temperature inside the reactor by quenching, solving simultaneously the task of cooling.

Due to the addition of water, the mixture is approximately pH 7. Hydrochloric acid 30% (w/w) is added by pipe to acidify the mixture to pH 4.5 inside the reactor, and the first extraction with chloroform is performed. Chloroform is added through the pipe, it is stirred for 1 hour to drag part of the product of interest to the organic phase and it is settled by sedimentation at the bottom of the reactor. This phase is stored in another

vessel with agitation (R-01).

The remaining aqueous phase still in the reactor is basified to pH 6.5 adding sodium hydroxide 30% (w/w) by pipe to the reactor, and the second extraction of part of the product is carried out with chloroform. Once the extraction is carried out in the same way as the previous one, the phase is stored in the same vessel as the first extraction (R-01). Now the remaining aqueous phase still in the reactor is acidified to pH 2.0 adding hydrochloric acid 30% (w/w) to the reactor by pipe, and the third extraction of part of the product with chloroform is carried out. Once the extraction is carried out in the same way as the previous ones, the phase is stored in the same vessel as the other extractions (R-01). Finally, the remaining aqueous phase still in the reactor is basified to pH 6.0 adding hydrochloric acid 30% (w/w) by pipe to the reactor, and the fourth extraction of the remaining product with chloroform is carried out. Once the extraction is carried out in the same way as the previous ones, the phase is stored in the same tank as the other extractions (R-01). With this combination of extractions at different pH, extraction of most of the product trapped in the aqueous phase is ensured.

The recovered organic phase is treated with a drying agent to remove all traces of water that the organic solvent carries. The drying agent used is potassium carbonate and its addition will be carried out through the upper part of the container. Finally, the mixture is filtered to eliminate the hydrated potassium carbonate residues and purify the solution. Once again, filtration is carried out in a filter press (FN-01) by loading the vessel mix into the filter through pipes, and a centrifugal pump is used to drive the mixture.

The filtered solution is crystallized by evaporation under vacuum, to avoid product spoilage. The objective is to evaporate part of the solvents, mainly chloroform, and achieve the precipitation of the solid product by concentration. In order to avoid downtime by being able to carry out other tasks in this equipment, evaporation is carried out in an agitated vessel with a half-pipe jacket supplying the heating through the walls and a vacuum system. Based on this, the necessary evaporation equipment is incorporated into the R-02 reaction vessel, and therefore the unit can be used both for this special task, as well as for the rest of conventional tasks. To achieve evaporation of part of the solvent, the operating conditions are 0.3 bar and 28 ºC. Since the working

temperature is not high when working under vacuum, the heating fluid necessary for supplying heat during operation is low-pressure steam. A conventional stirring system is used because, in the evaporative crystallization, supersaturation occurs at the evaporation surface, so there are no problems of deposition on walls. On the other hand, it is necessary to incorporate equipment for the condensation of the vapours in order to facilitate their handling. Therefore, a reactor with a built-in condenser is necessary, using cold water as refrigerant fluid. An operation time of 15 h is estimated for this task.

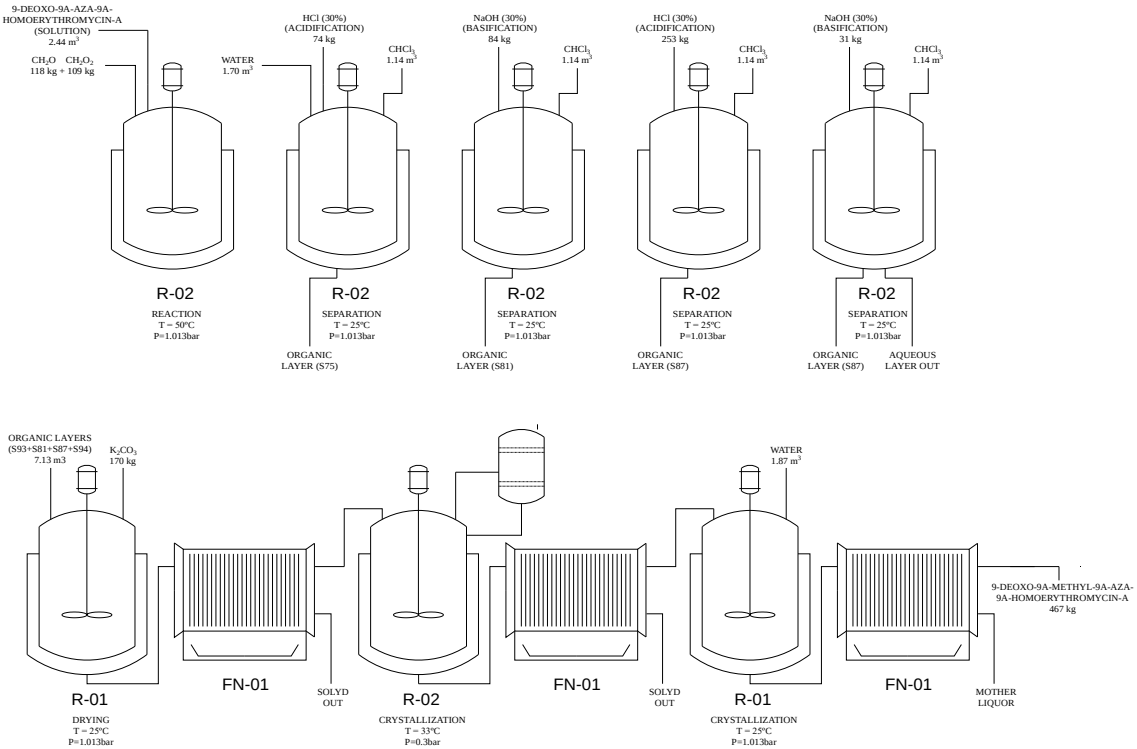

Figure 14. Equipment diagram for Stage 4

Once again, filtration is carried out in a filter press (FN-01) by loading the tank mix into the filter through pipes, and a centrifugal pump is used to drive the mixture.

To finish, the recrystallization of the product is carried out to eliminate the impurities that the crystals may trap. The operation consists of dissolving the filtered solid product in isopropyl alcohol, releasing the impurities. Adding water to the mixture again induces the precipitation of the product as solid crystals, leaving the impurities dissolved in the solvent.

This task is carried out in an agitated tank that guarantees a new mixture of the antisolvent (R-01). Again, a conventional stirring system adapted to the dimensions of

the container is used, since there is no risk of crystal deposition on the walls in the crystallization reactor. In this type of crystallization, the time required is not always long, and it may be advisable to carry out the operation on the same equipment as the other because it does not have to result in excessively long equipment occupation times. An operation time of 5 h is estimated for this task.

Table 5. Material balance for Stage 4

Compound	**Quantity [kg]**	**Quantity [kmol]**	**Volume [m^3]**
9-Deoxo-9a-aza-9a-homoerythromycin-A (solution)	3395.86	0.84 (pure)	2.44
CH_2O	117.67	3.92	-
CH_2O_2	108.75	2.36	-
Water	1697.93	-	1.70
HCl (30%)	73.98	0.61	-
$CHCl_3$	1697.93	-	1.14
NaOH (30%)	84.23	0.63	-
$CHCl_3$	1697.93	-	1.14
HCl (30%)	253.07	2.08	-
$CHCl_3$	1697.93	-	1.14
NaOH (30%)	31.20	0.23	-
$CHCl_3$	1697.93	-	1.14
K_2CO_3	169.79	1.23	-
C_3H_8O	1867.72	-	2.38
Water	1867.72	-	1.87
9-Deoxo-9a-methyl-9a-aza-9a-homo-erythromycin-A	466.93	0.64	-

Once again, filtration is carried out in a filter press (FN-01) by loading the tank mix into the filter through pipes, and a centrifugal pump is used to drive the mixture. The solid product is used in the next stage, and the mother liquor is discarded.

Material balance for the stage 4 is summarize in Table 5.

5.5. STAGE 5: Azithromycin Dihydrate

In this stage, dihydrate form of azithromycin is obtained from 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A. Although the fact that the number of tasks in this stage is not very high, it seeks to reduce operating times since tasks such as crystallization have very high operating times.

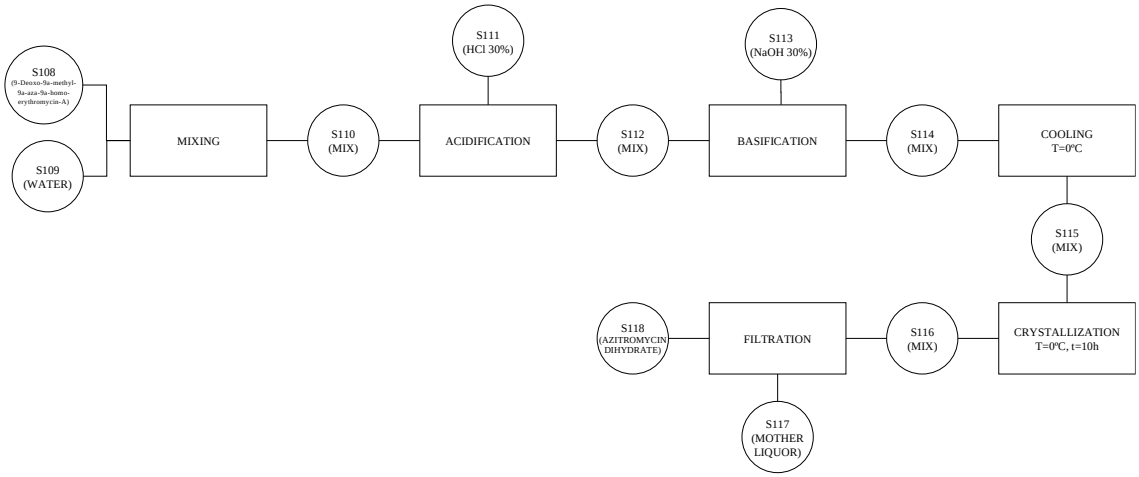

Figure 15. STN for Stage 5

To carry out this stage, crystallization equipment is necessary. The tasks that require more operating time are sought to isolate them in separate vessels. This allows a better overlap of tasks in order to reduce the total operating time. The components and sub-components of those equipment are discussed in relation to the needs of the process.

First, a dilution and basification are carried out inside the vessel (CR-01) by stirring. Water is loaded into the reactor through pipes. Compound solid, 9-Deoxo-9a-methyl-9a-aza-9a-homoerythromycin-A synthesized in the previous step, and hydrochloric acid 30% (w/w), to lower to pH 2 are loaded by pipe to the reactor. After stirring for 20 min, the mixture is raised to pH 7 with the addition of dilute sodium hydroxide 30% (w/w) by pipe to the reactor, the temperature is lowered to 0 ºC and the mixture is stirred for 10 hours. The azithromycin dihydrate crystallizes as a white crystalline material in high purity.

Based on this, the crystallization vessel is equipped, with a half-pipe jacket to feed the fluid in charge of carrying out the thermal exchange, in this case cold water. The crystallization reactor is also equipped with an impeller capable of scratching the walls of the reactor to dislodge any crystals that may form on it. The most recommended

impeller for this type of batch process is the anchor type as it is the one that favours a better distribution of the mixture and temperatures inside the container.

Once again, filtration is carried out in a filter press (FN-01) by loading the crystallization slurry into the filter through pipes, and a centrifugal pump is used to drive the mixture. The mother liquor is discarded and the solid product from the filtration is used in the next stage.

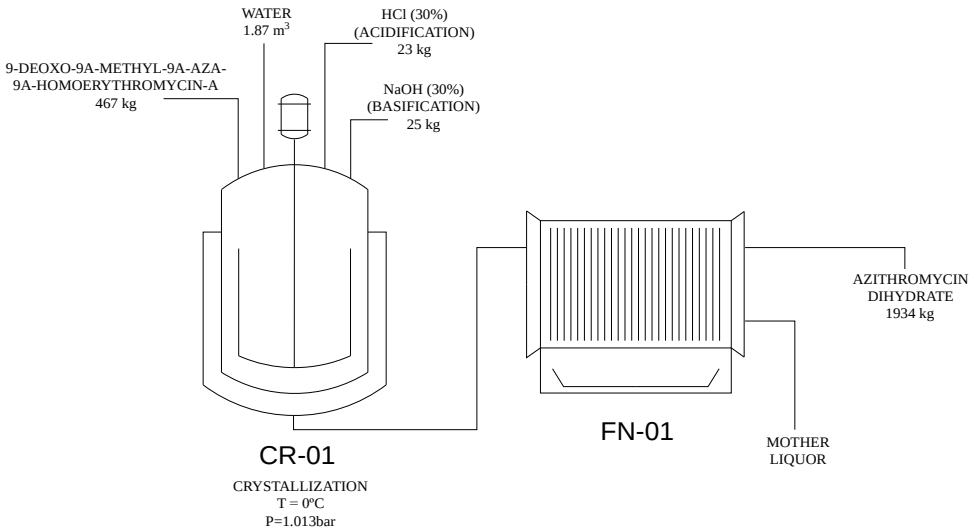

Figure 16. Equipment diagram for Stage 5

Material balance for the stage 5 is summarize in Table 6.

Table 6. Material balance for Stage 5

Compound	Quantity [kg]	Quantity [kmol]	Volume [m^3]
9-Deoxo-9a-methyl-9a-aza-9a-homo-erythromycin-A	466.93	0.64	-
Water	1867.72	-	1.87
HCl 30% (w/w)	22.70	0.62 (pure)	-
NaOH 30% (w/w)	24.88	0.62 (pure)	-
Azithromycin dihydrate	1933.97	0.57	-

5.6. STAGE 6: Purification

In this stage, azithromycin dihydrate is purified to obtain a product that can be used as an API. Notwithstanding that the number of tasks in this stage is not very high, it seeks to reduce operating times since several tasks have very high operating times.

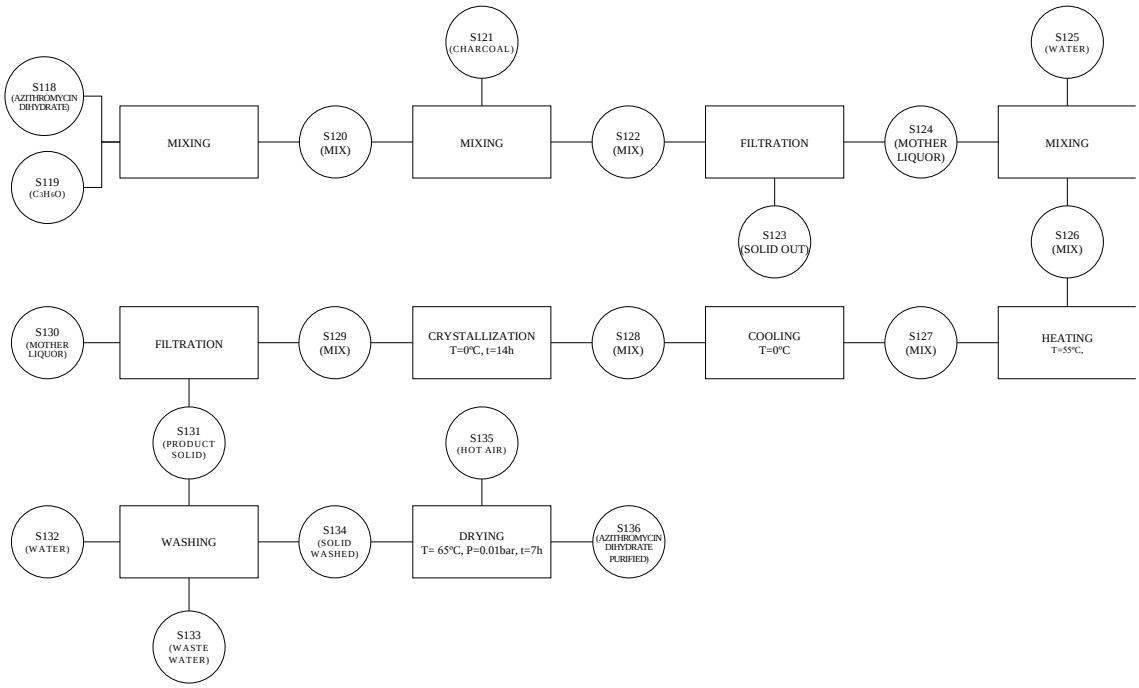

Figure 17. STN for Stage 6

To carry out this stage, mixing equipment and crystallization equipment is necessary. The components and sub-components of those equipment are discussed in relation to the needs of the process.

First, a dilution of the impure product is carried out with an absorbent agent that traps the impurities released in the crystal solution. Acetone is loaded into the vessel (R-01) through the pipe and the solid crystals of azithromycin dihydrate through the upper part of the container. Once the crystals have dissolved, after 20 min of stirring, the charcoal is charged from the top of the reactor and stirred for another 20 min. After that, the mixture is subjected to filtering to drag out the solid carbon particles, which carry the impurities that the azithromycin crystals trapped.

Once again, filtration is performed in a filter press (FN-01) loading the crystallization mixture into the filter through pipes, and a centrifugal pump is used to drive the mixture.

The mother liquor of the filtrate, in which the product is found, is charged by pipe to

the crystallization equipment (CR-01) and mixed with water at 55 ºC. In this case, as the quenching effect would not be enough to maintain the temperature during the time of the task, it was decided to directly heat the mixture with low-pressure steam through a half-pipe jacket.

The mixture is then cooled to 0 °C to induce the crystallization of azithromycin dihydrate by cooling. The temperature reduction is carried out with the circulation of cold water through the half-tube jacket. Azithromycin dihydrate crystallizes as a white crystalline material with a purity of 95% to 100%. The estimated time to carry out this task is 14 hours.

Based on this, the crystallization vessel is equipped with a half-pipe jacket to feed the fluids responsible for carrying out the heat exchange. The crystallization reactor is also be equipped with an impeller capable of scratching the reactor walls to dislodge any crystals that may form in it. The most recommended impeller for this type of batch process is the anchor type since it is the one that favours a better distribution of the mixture and, therefore, of temperatures within the container.

Once again, a filtration is carried out in a filter press (FN-01) loading the crystallization mixture into the filter through pipes. The drag of inorganic salts, avoiding the appearance of impurities in the product, is achieved by washing the cake with water. Both the mixture from the tank and the washing water is loaded into the filter through pipes, through a centrifugal pump that drive the mixture. The mother liquor and the wash water are discarded and treated as waste.

The last stage prior to the storage of the pure product consists of vacuum its drying vacuum, intending to obtain the crude compound in the form of crystals and with a purity of 95% to 100% (w/w). The filter cake has low residual humidity, thus reducing the high energy cost of evaporation from drying.

According to the patent, the drying temperature is 65 °C, which would imply a long operating time. An increment of the operating temperature could be a good strategy to reduce the operating time, unless, as indicated in the patent US7,235,646 B2, the drying stage can result in the transformation of the dihydrate form into the monohydrate form, producing the decomposition of the product. This is why a reduction in pressure is

chosen, and as the patent previously mention indicates, the use of a pressure of 0.01 bar implies an operating time of 7 hours, approximately.

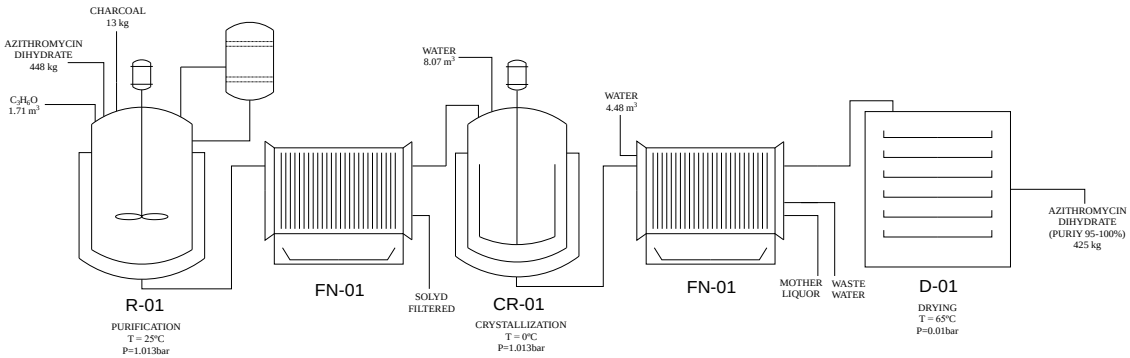

Figure 18. Equipment diagram for Stage 6

The most appropriate methodology depends fundamentally on the characteristics of the solid, as well as the characteristics of the liquid such as quantity and vapour pressure. In this case, it is a system with small particle size and with a low humidity of water and residual acetone.

Table 7. Material balance for Stage 6

Compound	**Quantity [kg]**	**Quantity [kmol]**	**Volume [m^3]**
Azithromycin dihydrate	448.25	0.57	-
C_3H_6O	1344.76	-	1.71
Charcoal	13.45	1.12	-
Water	8068.56	-	8.07
Water	4482.53	-	4.48
Azithromycin dihydrate (Purity 95-100 %)	425.00	0.54	-

Taking into account that the system must be dried, it is decided to choose a tray dryer (D-01) that operates under vacuum, which is also widely used to dry pharmaceutical products susceptible to decomposition (Perry et al. 1997). It is a tray dryer with the right dimensions to provide uniform drying. Once the drying is finished, crystals of

azithromycin dihydrate are obtained with a purity of almost 100%.

Material balance for the stage 6 is summarize in Table 7.

5.7. Summary of the synthesis process equipment

Taking into account all the characteristics of the different tasks that constitute the process, all the necessary equipment is detailed throughout the synthesis process. In the vast majority of cases, the choice of generic, more versatile equipment allows several tasks of a similar nature to be carried out in the same unit.

Equipment such as the FN-01 filter, the R-01 reactor or the crystallizer, demonstrate their versatility by performing tasks in almost all stages of the process, which works in favour of the use of equipment volume. Other equipment, such as the R-02, are complemented with sub-components to cover other, more specific, tasks in addition to conventional tasks.

Table 8. Equipment and tasks, original organization

UNIT	STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5	STAGE 6
R-01	MIXING BASIFICATION HEATING REACTION	MIXING COOLING ACIDIFICATION REACTION	MIXING COOLING REACTION WASHING SEPARATION DRYING	MIXING CRYSTALLIZATION		MIXING
R-02			MIXING ACIDIFICATION SEPARATION BASIFICATION	MIXING HEATING REACTION COOLING ACIDIFICATION SEPARATION BASIFICATION CRYSTALLIZATION		
CR-01	CRYSTALLIZATION	CRISTALLYZATION			MIXING ACIDIFICATION BASIFICATION COOLING CRYSTALLIZATION	MIXING HEATING COOLING CRYSTALLIZATION
FN-01	FILTRATON WASHING	FILTRATION	FILTRATION	FILTRATION	FILTRATION	FILTRATION WASHING
D-01						DRYING

In Table 8, the equipment needs are summarized, together with the grouping of tasks attached to each of them. Either way, this constitutes an initial, provisional organization,

that can be altered at the planning stage, through the reorganization and decoupling of tasks or the duplication of equipment, to obtain a more favourable reorganization in terms of production capacity and economic profitability.

6. BASIC DESIGN

The design of a process for the industrial-scale manufacture of a chemical compound involves the design or selection of the process equipment. The characteristics of the equipment will be conditioned by parameters defined in the synthesis of the process such as the type and quantities of material with which it works and the tasks to be performed. Based on these characteristics, the dimensions of the equipment and the operating modes are defined. However, specifically designed equipment will not be the valued option, since most industrial equipment tends to be standardized, due to the over-cost of manufacturing specific equipment.

This is why the process equipment is selected from the commercial catalog based on the parameters established by the basic design, and as a feedback form, the process synthesis is adapted to the commercially available equipment proposal.

This section describes the most appropriate commercial solutions for all the process equipment, based on the technical descriptions of each equipment (*Appendix 1*) and the characteristics of the unit operations performed in the process.

6.1. REACTORS

Reactors are the main element in chemical processes with chemical reaction, so a suitable commercial solution is key for guaranteeing to obtain the desired product conversions.

The process for the manufacture of azithromycin dihydrate uses 3 reactors: one stirred tank reactor R-01, a stirred tank reactor R-02 with a vacuum operation system and a crystallization reactor CR-01. The R-01 and R-02 reactors are polyvalent and are used for different tasks of reaction, mixing and decantation throughout the process. CR-01 crystallizer is a more specific reactor used in crystallization tasks, although it has a certain versatility when carrying out different crystallization tasks.

Multipurpose reactors R-01 and R-02

R-01 and R-02 reactors perform multiple tasks during the process, among which we could highlight the conditioning of the reactions carried out in the mixing operations, the thermal exchange or the acidity regulation of the mixture. Furthermore, they can also

perform other complementary operations such as the separation of the product by decantation, or, in the specific case of the R-02, by crystallization by evaporation in vacuum, when is needed.

As a result of the existence of 4 reaction operations with long operation times (more than 15 hours), several pieces of equipment are destined for the reaction tasks with the main purpose of avoiding limitations in the planning process. Consequently, it is possible to reduce procedure times by the association and dissociation of tasks. Moreover, similar procedures can also be carried out if they have the same necessities regarding equipment volume in the same reactors, which allows a better adjustment of the characteristics of each reactor to the tasks group assigned.

Based on the material quantities calculated in the material balance, the equipment size requirements for the two reactors are 10 m^3 for the R-01 reactor and 7.5 m^3 for the R-02 reactor. Another parameter to consider is the nature of the operation and the materials that houses the reactor, as this determines the thickness and type of materials used on the walls of the equipment.

The operating, pressure and temperature conditions move between a normal operating range, 0-55 ºC and 1-0.3 bar, so they would not imply any kind of limitation. Despite the corrosivity hazard of working with bases such as NaOH or acids such as HCl, the most dangerous situation occurs in stage 1 when NaOH concentrations reach 7% and working at these concentrations does not pose a risk when working with most standard marketing materials. Based on this, the equipment is stainless steel AISI304, which allows working with this type of products without over-increasing the costs of the initial investment.

After a comparative study of the commercial solutions offered by different equipment manufacturers, the most suitable solution for the R-01 and R-02 reactors is the range Agitated Reactor of Bachiller (Bachiller 2021), with nominal capacity of 10 and 7.5 m^3, respectively.

The reactors are capable of operating between absolute vacuum pressures up to 50 bar and withstand temperatures from -50 to 400 ºC, meeting beyond expectation the technical requirements of the process. In the case of the R-02 reactor, steam jet ejectors

are used to carry out vacuum distillation because they are versatile and economical and produce low pressures of up to 0.13 mbar. (Sinnot 2008). Apart from that, the reaction equipment allows to carry out the tasks of thermal transfer with a half-pipe jacket, as well as the incorporation of any conventional agitation or automatic charging systems, and also incorporate elements of temperature control, pressure and level, to control the correct progress of the process at all times.

Crystallization reactor CR-01.

Crystallizers, as in most processes of the pharmaceutical industry, are one of the key equipment to effectively purify the final product and in its crystalline form. In this process, they will be responsible for carrying out the tasks of cooling crystallization because it is necessary to use special agitation equipment that scratches the walls to avoid the deposition of solid crystals.

Due to the existence of 4 crystallization operations with long operating times, one interesting possibility is to duplicate the equipment that performs crystallization tasks in favour of the overlapping of workloads in the planning process. In addition, the same crystallizers could be used to perform similar tasks with similar equipment volume needs, and thus achieve a better adjustment of the characteristics of each crystallizer to the assigned task group.

Based on the material quantities calculated in the material balance, the equipment size requirement for CR-01 crystallizer is 10 m^3. Another parameter to consider is the nature of the operation and the materials that houses the crystallizer, as this determines the thickness and type of materials used on the walls of the equipment.

Operating conditions pressure and temperature move between a normal operating range, 0-55 ºC and 1 bar, so they would not imply any kind of limitation. Since the materials used are the same, the material chosen for the crystallizers is also AISI304 stainless steel.

After a comparative study of the commercial solutions offered by different equipment manufacturers, the most suitable solution for CR-01 crystallizer is the range Agitated Reactor of Bachiller (Bachiller 2021), with nominal capacity of 10 m^3.

Crystallizer are capable of operating between absolute vacuum pressures up to 50 bar and withstand temperatures from -50 to 400 ºC, meeting beyond expectation the technical requirements of the process. On another note, the crystallization equipment allows to carry out the tasks of thermal transfer with a half-pipe jacket, as well as the incorporation of a stirring system with scraper type anchor, or automatic loading systems, and incorporating temperature, pressure and level control elements to control the correct progress of the process at all times.

6.2. FILTER

Filters are a commonly used tool in synthesis processes that include crystallization or absorption stages since it is necessary to recover the solid product that is kept in its crystalline form within the mother liquor and the separation of the solid remains of absorbent agents that carry the impurities of solutions of interest. In the first case, the separation of solid crystals from the mother liquor mainly seeks to obtain a significantly drier product, which advantageously affects the factors of saving heat energy, storage or transport. In the second case, the filter is part of a mechanism for purifying the solutions containing the product of interest.

In the proposed process, 6 different crystallization operations and 3 solutions purification operations are performed, however, only one filter, FN-01, will be required. On top of that, it should be taken into account that the 9 filtering operations have different quantities to be treated and volumes of both solid and liquid product. And that in any of the stages is required to perform a solid cake wash. This is why the selection of a widely versatile filtering unit is required.

Filter FN-01

The FN-01 filter in this process plays a very critical role, since, being used at all stages of the process, failures in its operation would induce delays in the whole process. That is why the selection of a versatile, efficient and robust equipment is key.

Depending on the quantities of material calculated in the material balance, the filter needs to be able to separate solid cakes up to a weight of 1061 kg and 823 L of volume from solutions up to 10 m^3. First, a solid cake of 1061 kg and 823 L volume must be recovered and washed with 3.4 m^3 of water from a solution of almost 10 m^3, to obtain as

a glass product solid of erythromycin-A oxime. In the second stage 5.3 m^3 of solution are filtered to extract a solid cake of 9a-Aza-9a-homoerythromycin-A with a weight of 849 kg. In the third stage 424 kg of the drying agent K2CO3 is removed, which labour was dragging the remains of water that could be trapped in the almost 3 m^3 of organic solution of interest. In the fourth stage, another 424 kg of K2CO3 from a 7.3 m^3 solution are removed. And later this solution is treated to extract 467 kg of the crystalline form of 9-Deoxo-9a-methyl-9a-aza-9a-homo-erythromycin-A. In stage 5 by processing a solution of 2.3 m^3, 448.25 kg of azithromycin dihydrate are obtained as a solid cake. And finally, the filter is also used in stage 6 to remove impurities through the filtering of 25 kg of activated carbon cake, and to recover and wash, with 4.5 m^3 of water, 425 kg of azithromycin dihydrate 95-100% of a solution of 8.5 m^3.

After a comparative study of the commercial solutions offered by different equipment manufacturers, the most suitable solution for the FN-01 filter is the PKF 100 press filter model from Putch (Putch 2021), with a holding capacity of up to 1508 L and a weight of 2800 kg of dry product, using 42 plates with dimensions of 1200 mm x 1200 mm resulting in a filter area of 95.3 m2. Because the cakes on this process have a thickness of 33 mm it is, therefore, perfectly adapted to the specific technical requirements. This equipment also has a programmable control system that allows the correct adaptation to the different tasks of filtering and washing of the cake, providing the necessary flexibility in this process. On another note, it has an automatic cleaning system for the filtering fabrics, which also prolongs the useful life of the same, allowing savings in labor and the cost of maintenance.

6.3. DRYER

The main function of dryers is to achieve a dry and pure product, increasing its useful life, favouring the storage mode and guaranteeing its quality.

Dryers are a tool that is usually only used at the end of the process. This is due to its high energy consumption and long operating times. This also prevents the drying of intermediate products that have to be dissolved again. Moreover, to ensure the minimum requirement of energy, time and volume required, a previous filtering or separation step is incorporated, which removes as much solvent as possible. In this way, only a dry cake of the solid product of interest is introduced to the drying equipment.

In the proposed process a single drying operation is performed at the end of the process which is carried out in the dryer D-01. Therefore, the most suitable drying equipment is selected to carry out this task.

Dryer D-01

The last stage of the process consists of drying the cake of Azithromycin dihydrate to obtain as product 425 kg of solid crystals of purity 95-100%. As detailed in the synthesis of the process, a tray dryer that operates under vacuum pressure is the technology that best adapts to the requirements of this task.

The resulting vacuum operation is usually a requirement of this operation in this branch of industry, as boiling temperatures are required to be reached, but handling high temperatures can result in the decomposition of the material. The operation at 0.01 bar allows therefore to work at a temperature not exceeding 65 ºC, obtaining results even, in terms of operating times, more effectively.

After a comparative study of the commercial solutions offered by different equipment manufacturers, the most suitable solution for the D-01 tray dryer is the E1,75 S model of the Italvacuum Multispary static vacuum dryer (Italvacuum 2021), which counts with consolidated experience applied to the processes of the pharmaceutical industry.

Proof of its long trajectory in the implementation of its technology in the pharmaceutical sector is its developed rapid washing system, which guarantees a total cleaning and sanitizing of the equipment complying with FDA (Food and Drug Administration) standards and CGMP (Current Good Manufacturing Practice).

To generate the vacuum inside the chamber, the selected drying equipment uses a high vacuum unit model Saurus 939, developed specifically, and a vacuum condensation unit that reduces drying times and recovery the extracted solvents.

The heat supply needed for the drying operation is made through the surfaces of the chamber and a series of radiant plates that raise the temperature inside the chamber. The heating of the fluid through the dryer circuit will be done through an exchanger located at the top that uses low-pressure steam as heating fluid.

The capacity of the dryer is measured according to the number and dimensions of the trays, with 52 trays of 600x480x40 (W x D x H). A maximum capacity of 634 L is achieved, which fits perfectly the technical requirements of the process. It should be noticed that, even though the final size of the lot is 425 kg, which is equivalent to 360 L, the cake that is inserted in the dryer occupies a larger volume.

7. PRODUCTION PLANNING

The production capacity of a plant is conditioned by the design of the process based on the optimal operating conditions, and the selection of the equipment and management of its use. In addition, the production capacity is especially conditioned by the planning of the production process. This factor is so relevant that it can significantly affect the size of production, with hardly any need for new economic investment. However, both parts of the synthesis, design and planning process must be complemented in order to get more satisfactory results.

The available labor time is necessary data for planning. In the operation of a plant of this type, there are estimated to be 300 working days available, taking into account maintenance shutdowns, which is equivalent to 7,200 working hours available. A planned stoppage of one or two days is carried out between campaigns of 5-10 batches in which a deep cleaning and preventive maintenance of the process equipment is carried out to ensure the correct traceability of the product, a very important parameter. in this type of industry.

In this section, the different alternatives for planning production campaigns over the course of a year are studied. The analysis is focused not only on the study of the times of the synthesis operations for a single batch of product, but also on the organization of the annual production of batches. This makes possible the selection of the planning that entails a higher economic reward, sometimes accompanied by the maximum production capacity of the process designed for the manufacture of azithromycin dihydrate.

The following tools are used for planning. Equipment occupation time (OT_{ij}) is the time required by equipment *j* to complete stage *i* of the process. Cycle time (CT) is the time that a cycle lasts, calculated as the difference between the cycle ends (t_e) and the time it begins (t_s). Batch time (BT) is the time required for producing a single batch.

Production planning can be carried out following strategies of both non-overlapping and overlapping of loads, with duplication of equipment or with parallel production lines.

The strategy of non-overlapping loads implies that a new batch cannot be started until the previous one is finished, allowing greater slack when it comes to solving incidents between batches. The time of the fabrication of the batch is the determinant in the production.

The load overlap strategy allows a batch to start before the previous one ends. The occupation time of the equipment that determines the cycle time would be the determining factor in production.

The equipment duplication strategy allows improving load overlap combinations by decoupling tasks to teams in order to reduce occupation times. The occupation time of the equipment that determines the cycle time would be the determining factor in production.

The strategy with parallel production lines allows dividing the production time at the cost of implementing a duplicate equipment line. The number of lines implemented would be the determining factor in production.

The comparison of the different alternatives is carried out with the calculation of productivity by time (P_t), with the batch size (M_B) and the cycle time (CT).

$$P_t = \frac{M_B}{CT} \tag{4}$$

However, the cycle time and the volume of equipment cannot be treated independently, therefore, to carry out the comparison between the case studies, the productivity by the total volume of equipment used (Vt) and time (P_{tv}), is taken into account.

$$P_{tv} = \frac{M_B}{CT \cdot V_t} \tag{5}$$

In this way, it is understood that productivity can be increased by increasing the batch size, or by reducing the cycle time or the volume of equipment. Given that most of the equipment size has been set, the variables to be modified in the cases presented below will refer to the cycle time and the occupation volume, variables generally limited by the bottleneck concerning the time and the bottleneck concerning the volume.

STUDY OF PLANNING STRATEGIES

Equipment occupation times are defined based on the operating times of the different tasks performed. Despite the fact that the steps can take a long time, the occupation of each team is only carried out at certain moments of the process, leaving it empty without

performing any operation the rest of the time.

Table 9. Task times of original strategy

STAGE	Unit	t [h]		t_i [h]		OT_i [h]
		Start	End	Load + Operation	Unload + Cleaning	
1	**R-01**	**0.00**	22.50	20.50	2.00	22.50
	CR-01	20.50	43.50	20.00	3.00	23.00
	FN-01	40.50	43.75	2.50	0.75	3.25
2	**R-01**	43.75	46.75	1.00	2.00	3.00
	CR-01	44.75	67.75	20.00	3.00	23.00
	FN-01	64.75	67.50	2.00	0.75	2.75
3	**R-01**	67.50	100.50	31.00	2.00	33.00
	R-02	98.50	102.00	1.50	2.00	3.50
	R-01	100.50	103.50	1.00	2.00	3.00
	FN-01	101.50	103.50	1.50	0.50	2.00
4	**R-02**	102.00	121.00	17.00	2.00	19.00
	R-01	119.00	123.00	2.00	2.00	4.00
	FN-01	121.00	123.00	1.50	0.50	2.00
	R-02	121.00	138.00	15.00	2.00	17.00
	FN-01	136.00	138.50	2.00	0.50	2.50
	R-01	138.50	145.50	5.00	2.00	7.00
	FN-01	143.50	146.25	2.00	0.75	2.75
5	**CR-01**	146.25	159.75	10.50	3.00	13.50
	FN-01	156.75	159.50	2.00	0.75	2.75
6	**R-01**	159.50	162.25	0.75	2.00	2.75
	FN-01	160.25	162.25	1.50	0.50	2.00
	CR-01	162.25	179.25	14.00	3.00	17.00
	FN-01	176.25	179.50	2.50	0.75	3.25
	D-01	179.50	**188.50**	7.00	2.00	9.00

Table 10. Ocupation times original strategy

Unit	ts [h]	te [h]	OTj [h]
R-01	0.00	162.25	**162.25**
R-02	98.50	138.00	39.50
CR-01	20.50	159.75	139.25
FN-01	40.50	179.50	139.00
D-01	179.50	188.50	9.00

Good productivity of the process is achieved with the correct management of the programming of operating times simultaneously with the selection of the equipment.

And for this reason, the operation times of each of the tasks that make up the process are detailed as well as the occupation times of each of the equipment. For this, the parameters specified in the recipe and the appropriate scaling considerations according

to the technologies used are taken as a basis. In addition, the loading and unloading times should be specified depending on the nature of the fluid, and the unloading and cleaning times of the equipment depending on the characteristics of the equipment and the processed mixture.

The times of use of the equipment depending on the sequence of stages of the studied process is described in Table 9. And the occupation times for each of the equipment is described in Table 10.

From these values, the batch time, 188.50 h, and the cycle time, 188.50 h, are determined for the non-overlapping strategy. This means a production of 38 batches per year, resulting in a production of 16 t of azithromycin dihydrate, not complying with the initial prediction of 34 t per year. The productivity by time is 2.62 and the productivity by volume of equipment and time is 0.07. To calculate this last parameter, the volume of equipment is used, which is described in Table 11 calculated from the needs of the process.

Table 11. Required volumes original strategy

Unit	V (m^3)
R-01	10
R-02	10
CR-01	10
FN-01	10
D-01	0.5

The two-lot schedule following the no-overlap strategy is shown in Figure 19.

The limitation of the batch size determined by the conventional processing capacities of the equipment requires a more in-depth study of the planning to be carried out in order to increase the annual production and productivity of the plant.

Due to the long existence of this synthesis process, the production of azithromycin dihydrate is highly optimized taking into account the different planning strategies, leading to a reduction in the cost of this drug. Due to these low costs, the search to obtain a certain economic return with the synthesis of this drug includes as necessary the optimization of the process to allow the maximum possible production, that is, the shortest operating time of the process.

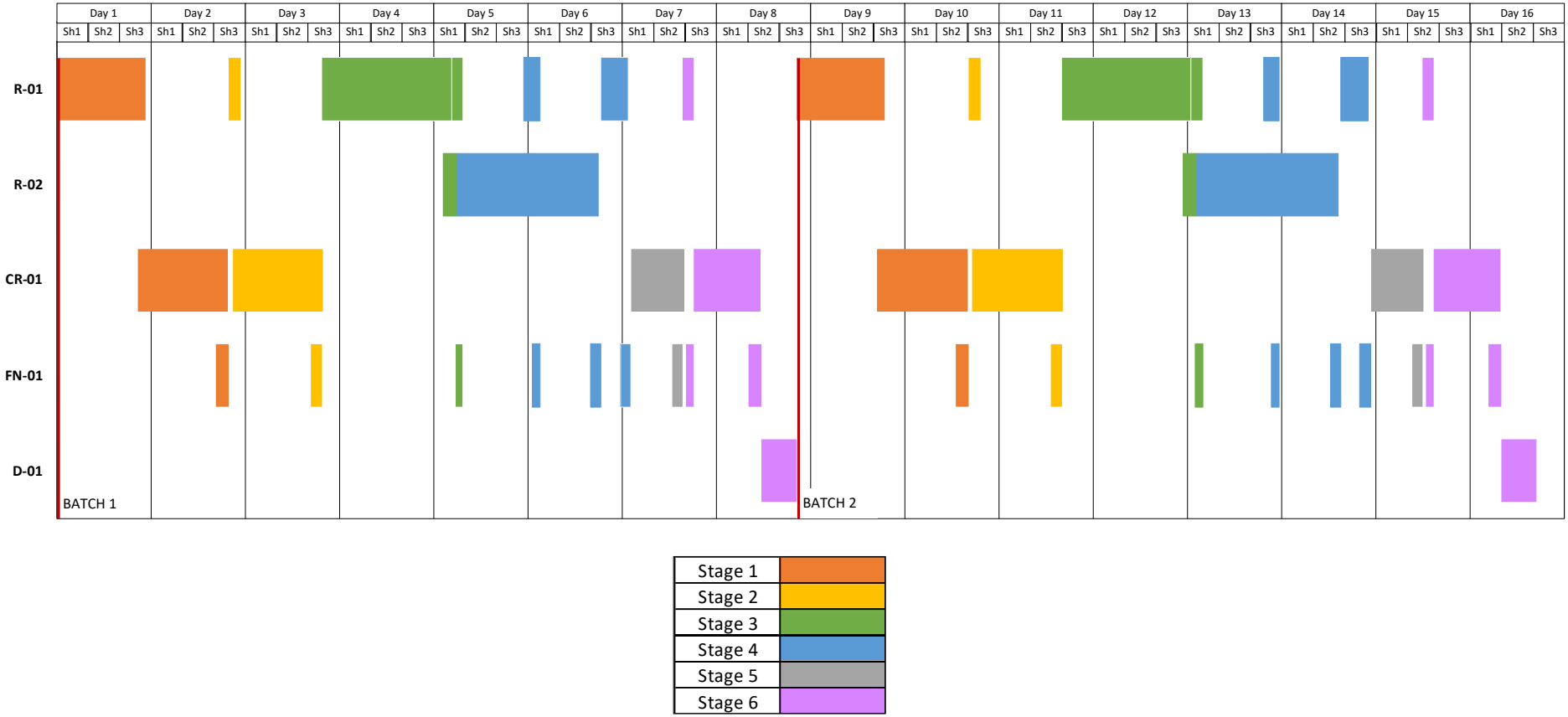

Figure 19. Schedule of two batches in non-overlapping strategy

The productivity of the process can be enlarged by increasing the batch size, or by reducing the cycle time or the volume of equipment. If a batch size of 425 kg of azithromycin dihydrate has been set, the variables to be modified will be referred to the cycle time and the occupation volume, variables generally limited by the bottleneck concerning the time and the bottleneck with regarding the volume.

When carrying out debottlenecking concerning the time, the following aspects should be taken into account, such as the assignment of teams, the detailed study of the time-limiting task or team, the performance of multiple tasks on the same team and the addition of transfers (serial design) or propose an out-of-phase parallel design strategy. Analyzing the base case considering each of these aspects, the most advantageous solution shall be concluded.

The base case already proposes the operation of multiple tasks in the same equipment, producing that R-01 (OT = 162.25 h) and CR-01 (OT = 139.25 h) are the limiting units. What a priori means savings in equipment investment can lead to a reduction in productivity by limiting planning. In order to avoid this limitation, a transfer of tasks was proposed in the limiting units, duplicating these teams.

A new R-03 reactor allows the reorganization of the reaction and mixing tasks, having found that the reactors present similar characteristics. Therefore, there are three reactors: on one side, R-01 and R-02 are equal; and on the other side, R-03, with less volume as a consequence of the reorganization of tasks, can operate under vacuum. For the dissociation of one of the crystallization tasks, the unit is duplicated by incorporating a new CR-2 crystallizer. In addition, in view of the limitation in optimizing planning that a non-overlapping strategy supposes, an overlap of the batches is carried out, to reduce the waiting time of the equipment, since, in this way, a new batch can be started almost 50 hours before the end of the previous one.

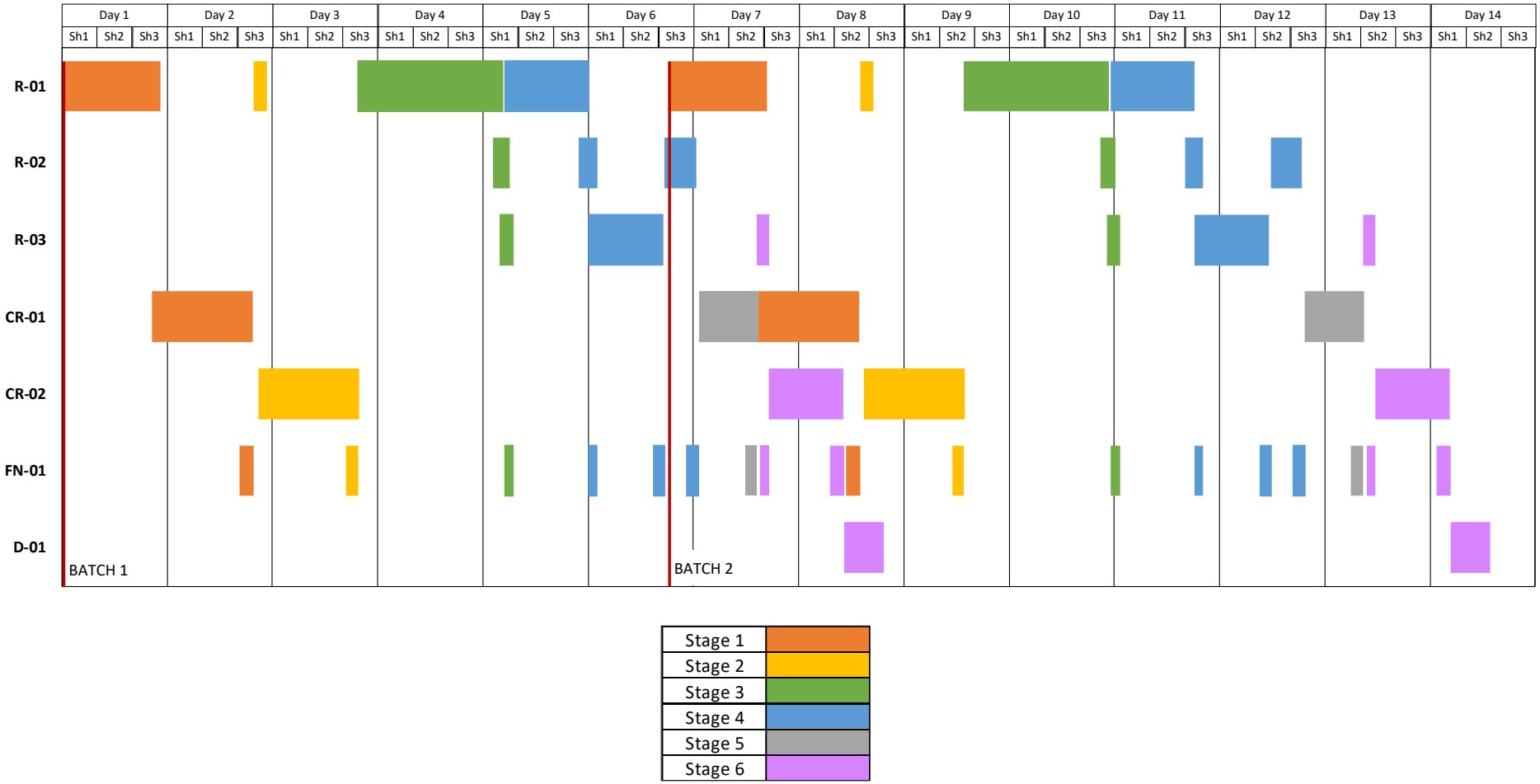

Figure 20. Schedule of two batches in overlapping strategy

From these values, the batch time, 187.50 h, and the cycle time, 138.50 h, are determined for the overlapping strategy. This means a production of 52 batches per year, resulting in a production of 22 t of azithromycin dihydrate, 40% more than the basic case. The productivity by time increases to 3.07, but the productivity by volume of equipment decreases to 0.06 because more volume of equipment is used, Table 12.

Table 12. Required volumes final strategy

Unit	V (m^3)
R-01	10
R-02	10
R-03	7.5
CR-01	10
CR-02	9
FN-01	10
D-01	0.5

As seen in Figure 20, there are a lot of downtimes that decrease the productivity of the process. In view of this, a new provision for overlapping loads that implies a better use of equipment is studied below.

Table 13. Batch(A) 1

STAGE	Unit	t [h]		t_i [h]		OT_i [h]
		Start	End	Load + Operation	Unload + Cleaning	
1	**R-01**	**0.00**	22.50	20.50	2.00	22.50
	CR-01	20.50	43.50	20.00	3.00	23.00
	FN-01	40.50	43.75	2.50	0.75	3.25
2	**R-03**	43.75	46.75	1.00	2.00	3.00
	CR-01	44.75	67.75	20.00	3.00	23.00
	FN-01	64.75	67.50	2.00	0.75	2.75
3	**R-01**	67.50	100.50	31.00	2.00	33.00
	R-02	98.50	102.00	1.50	2.00	3.50
	R-03	100.00	103.00	1.00	2.00	3.00
	FN-01	101.00	103.00	1.50	0.50	2.00
4	**R-01**	101.00	120.00	17.00	2.00	19.00
	R-02	118.00	122.00	2.00	2.00	4.00
	FN-01	120.00	122.00	1.50	0.50	2.00
	R-03	120.00	137.00	15.00	2.00	17.00
	FN-01	135.00	137.50	2.00	0.50	2.50
	R-02	137.50	144.50	5.00	2.00	7.00
	FN-01	142.50	145.25	2.00	0.75	2.75
5	**CR-02**	145.25	158.75	10.50	3.00	13.50
	FN-01	155.75	158.50	2.00	0.75	2.75
6	**R-03**	158.50	161.25	0.75	2.00	2.75
	FN-01	159.25	161.25	1.50	0.50	2.00
	CR-02	161.25	178.25	14.00	3.00	17.00
	FN-01	175.25	178.50	2.50	0.75	3.25
	D-01	178.50	187.50	7.00	2.00	9.00

Table 14. Batch(B) 2

STAGE	Unit	t [h]		t_i [h]		OT_i [h]
		Start	End	Load + Operation	Unload + Cleaning	
1	**R-02**	52.50	75.00	20.50	2.00	22.50
	CR-01	73.00	96.00	20.00	3.00	23.00
	FN-01	93.00	96.25	2.50	0.75	3.25
2	**R-03**	96.25	99.25	1.00	2.00	3.00
	CR-01	97.25	120.25	20.00	3.00	23.00
	FN-01	117.25	120.00	2.00	0.75	2.75
3	**R-01**	120.00	153.00	31.00	2.00	33.00
	R-02	151.00	154.50	1.50	2.00	3.50
	R-03	152.50	155.50	1.00	2.00	3.00
	FN-01	153.50	155.50	1.50	0.50	2.00
4	**R-01**	153.50	172.50	17.00	2.00	19.00
	R-02	170.50	174.50	2.00	2.00	4.00
	FN-01	172.50	174.50	1.50	0.50	2.00
	R-03	172.50	189.50	15.00	2.00	17.00
	FN-01	187.50	190.00	2.00	0.50	2.50
	R-02	190.00	197.00	5.00	2.00	7.00
	FN-01	195.00	197.75	2.00	0.75	2.75
5	**CR-02**	197.75	211.25	10.50	3.00	13.50
	FN-01	208.25	211.00	2.00	0.75	2.75
6	**R-03**	211.00	213.75	0.75	2.00	2.75
	FN-01	211.75	213.75	1.50	0.50	2.00
	CR-02	213.75	230.75	14.00	3.00	17.00
	FN-01	227.75	231.00	2.50	0.75	3.25
	D-01	231.00	**240.00**	7.00	2.00	9.00

Due to the similarity between the different units of the same nature, the same task can be carried out in several equipment, so that a reorganization of the occupation of the groups leads to a reduction of unproductive hours due to overlapping loads. As seen in Figure 21.

Therefore, the suggestion is that two nested batch schedules are proposed that start practically consecutively, giving rise to the production of two batches almost simultaneously. In addition, it considers the reorganization of similar tasks in the same units, which allows opting for groups more related to the processes covered, and the reduction of the appearance of cross-contamination.

Thus, although not all teams are involved in all stages of the process as shown in Table 15, the utilization time of the volume of equipment is longer because the duplication of machinery allows a better overlap of tasks.

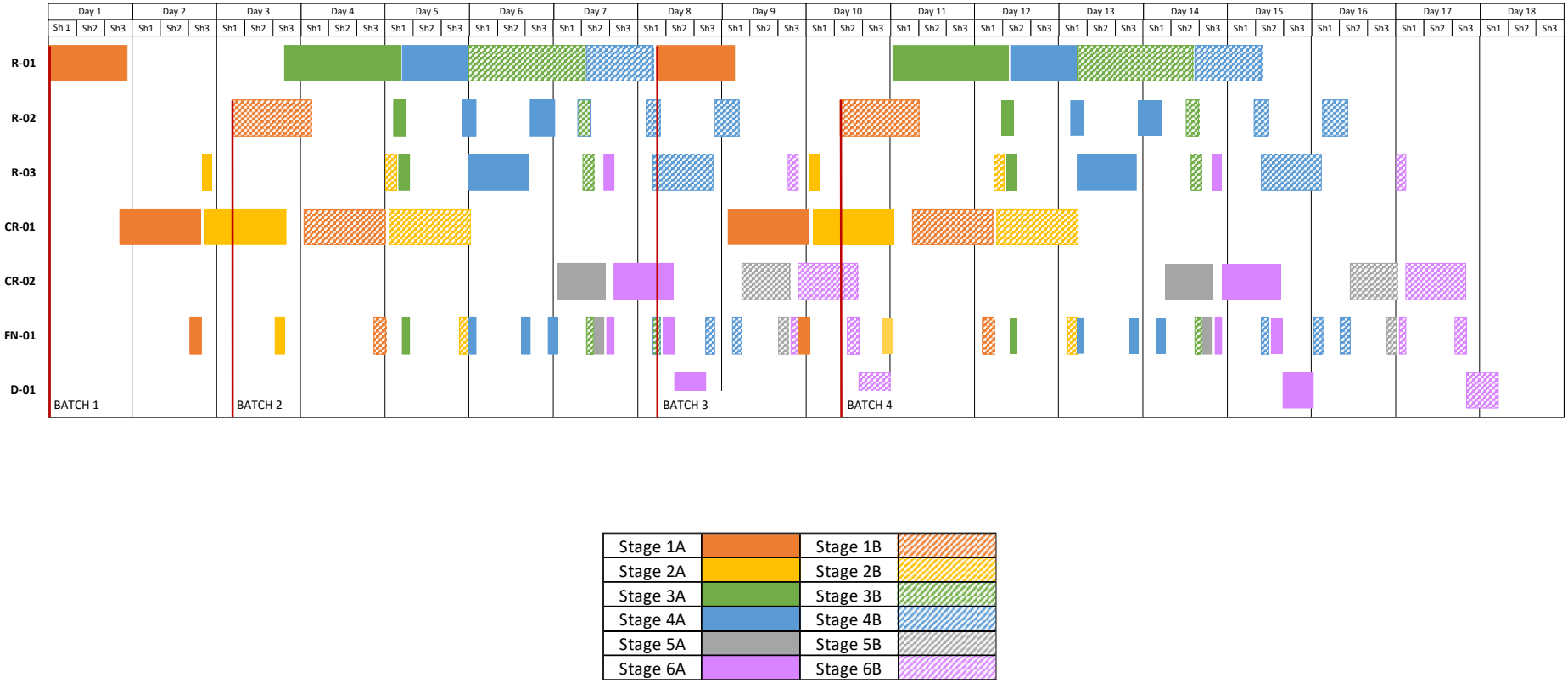

Figure 21. Schedule of two campaigns in overlapping strategy

Table 15. Equipment and tasks, original organization

UNIT	STAGE 1	STAGE 2	STAGE 3	STAGE 4	STAGE 5	STAGE 6
R-01	**X**		**X**	**X**		
R-02			**X**	**X**		
R-03		**X**	**X**	**X**		**X**
CR-01	**X**	**X**				
CR-02					**X**	**X**
FN-01	**X**	**X**	**X**	**X**	**X**	**X**
D-01						**X**

In this way, it is possible to achieve a production value close to the market segment considered, achieving a certain economic return with the start-up of the process.

The values for the final planification are a batch time for the two batches of 240 h, and a cycle time of 170 h, using a two type of batches overlapping strategy. This means a production of 84 batches per year, resulting in a production of 35.7 t of azithromycin dihydrate, coming true the initial prediction of 34 t per year. The productivity by time is duplicated to 5.00, almost the double of the original organization, and the productivity by volume of equipment and time to 0.09.This margin between the theoretical production and the target production, of a certain margin of manoeuvre before small contingencies of operation or quality, and allows a certain slack or flexibility to adapt the production to the requirements of the contemporary market.

In order to analyze the different alternatives considered, a comparative table is made between the number of equipment used and the calculated productivity, Table 16.

Table 16. Equipment and tasks, original organization

Layout	Nº Units	Cycle time	Pt (kg/h)	Ptv (kg/h·m³)
No-overlap	5	165.25h/425kg	2.62	0.07
Overlap	7	138.25h/425kg	3.07	0.06
Two campaings	7	170h/850kg	5.00	0.09

From these results, both productivities are represented to visualize which are the best alternatives, Figure 22.

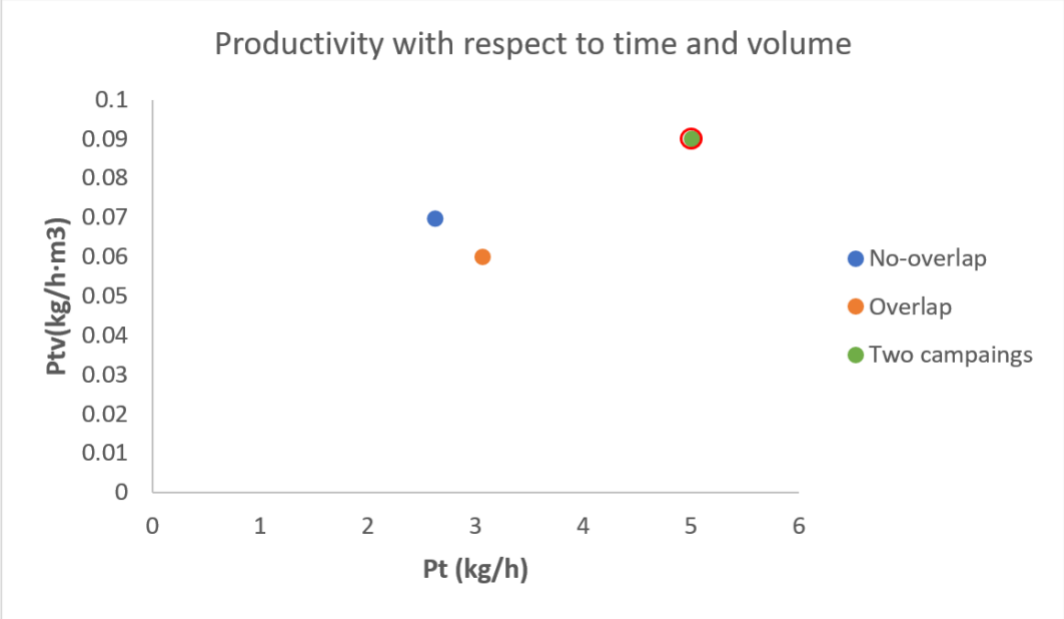

Figure 22. Graphic of productivity.

An overlapping load organization with the introduction of two new vessels achieves an increase in productivity over time, at the cost of sacrificing the use of the volume of equipment, however it is not enough to justify the investment in equipment. However, in the case of the organization in two campaigns, this investment is justified, since it is possible to double the production in a similar cycle time and with a better use of the volume of equipment.

Therefore, the organization in two campaigns implies a productivity boost at the expense of an increase in the number of teams and, consequently, an increase in the initial investment cost. Nonetheless, this increase in productivity would also mean an increase in the income of the production process, enough to conclude that this would be the planning in which the process begins to be competitive.

8. CONCLUSIONS

The COVID-19 crisis exposes a clear opportunity, or need, to increase the production of the so-called key drugs in the first responses to unknown pathologies. However, pharmaceuticals are a widely studied and exploited industry. This is why, although the production of pharmaceuticals usually requires a wide range of complexity, and consequently would also be expected to have a high added value, the remuneration obtained is not so high. In addition, the production of these generic drugs is shifted to countries where labour costs are grossly cheaper.

Consequently, in order to be competitive against a widely globalized market such as the pharmaceutical industry market, it is essential to reduce production costs, with the search for more efficient processes on a larger scale. Another way to achieve a higher economic return is to increase production capacity, and this can be achieved by implementing a good production planning strategy.

Azithromycin synthesis for pharmaceutical use can be carried out through different processes described in different patents resulting in different forms of the product. Consequently, it is concluded that the most complete and convenient formula is azithromycin dihydrate. Even if the synthesis process is based on one of the patents, the step-by-step or technology supplementation of other patents, even of different forms of the product at some intermediate stage, allows the adoption of less complex industrial processes, working under less demanding conditions and working with less hazardous compounds.

After the synthesis of the process, an industrial solution is created, based on the information provided by the literature, the industrial experience condensed into the heuristic rules and the general rules for the dimensioning of the scaling. The application of the industrial solution is accomplished with the selection of the equipment considered suitable according to the operation, the volumes to manage and even the needs of planning.

The result of a good planning of the process operation and the selection of the units suitable to favour the overlapping of loads is the scope of the target annual production selected during the market survey.

Both the strategies for the organization of the campaigns and the lot size of them are conditioned by the selected teams. This is why feedback is needed between all phases of the design, to improve productivity in order for the process to be competitive. Simple strategies such as duplication of equipment, redistribution of tasks or overlapping loads achieve extraordinary results, among them, the doubling productivity is highlighted. In this way, not only is it possible to achieve the productive objective, but also it is possible to be flexible to the demands of the market.

As future work of continuation of the project, it could be interesting a study of the profitability of expanding the process upstream, implementing the production of erythromycin. Since, by integrating the production of erythromycin into the process, the stage of obtaining erythromycin base would be saved, obtaining erythromycin-A oxime directly from crude erythromycin, which could be economically favorable.

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APPENDIXS

APPENDIX A: TECHNICAL DATA OF SELECTED EQUIPMENT

The technical data of the selected commercial equipment is compiled from the manufacturer's information in this section.

Appendix A.1: Reactors R-01, R-02 and R-03 and crystallizers CR-01 and CR-02.

The reactors and crystallizers selected for the process are the Agitated Reactor model of the manufacturer Bachiller. In the absence of the datasheet of the selected equipment, a basic design is made that approximates the characteristics of the same.

The dimensioning of reaction and crystallization equipment shall be determined based on heuristic design relationships.

$$V_{reactor} = \pi \cdot \frac{D_{reactor}^2}{3} \cdot H_{reactor} + \frac{4 \cdot \pi}{3} \cdot \frac{D_{reactor}^2}{3} \quad \text{(A.1)}$$

$$H_{reactor} = \frac{3}{2} \cdot D_{reactor} \quad \text{(A.2)}$$

The heads for the containers are assumed of torispherical geometry because they are the most commonly used in pressure vessels due to their lower manufacturing cost. The geometry of a torispherical head is shown in Figure 23 and its dimensions shall be calculated by means of the equations specified by DIN 28011, assuming a minimum thickness of 7 mm as indicated in the heuristics for vessels between 1 and 2 m in diameter (Sinott 2012).

Table 17. Head torispherical dimensions.

External head diameter	$d_a = D_{reactor} + 2s$	(A.3)
Crown radius	$r_1 = d_a$	(A.4)
Knuckle radius	$r_2 = 0{,}1 d_a$	(A.5)
Straight flange height	$h_1 = 3{,}5s$	(A.6)
Depth of dishing	$h_2 = 0{,}1935 d_a - 0{,}455s$	(A.7)
Total internal head height	$h_3 = h_1 + h_2$	(A.8)

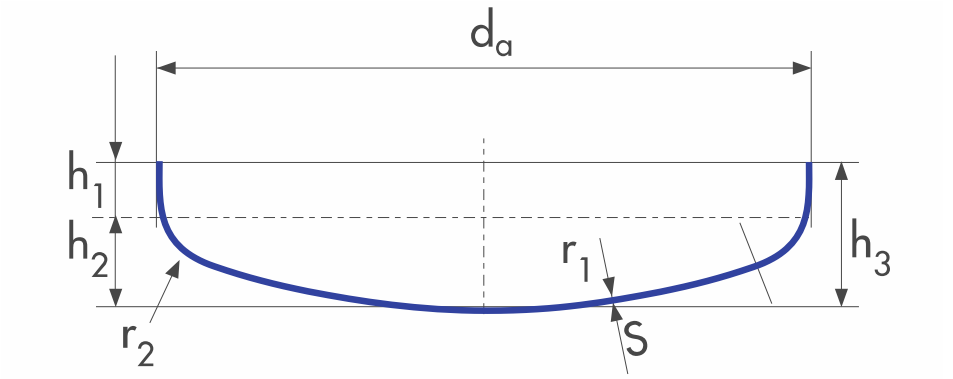

Figure 23. Head torispherical, image from (Slawinski 2021).

The selection of a half-pipe jacket as a heat exchange system limits the heat exchange area to the part of the outer surface of the tank.

$$S_{contact} = \pi \cdot H_{reactor} \cdot D_{reactor} + A_{head} \tag{A.9}$$

$$A_{head} = \sqrt{(D_{reactor} - 0{,}1 \cdot D_{reactor})^2 - \left(\frac{D_{head}}{2} - 0{,}1 \cdot D_{reactor}\right)^2} \tag{A.10}$$

Table 18. Technical data for Reactors by manufacturer Bachiller.

		R-01/R-02	**R-03**	**CR-01**	**CR-02**
Capacity[m³]		10	7.5	10	9
Diameter [m]		1.60	1.40	1.60	1.50
Height [m]		2.40	2.20	2.40	2.30
Heating area [m²]		13.05	10.62	13.05	12.10
Impeller		Turbine	Turbine	Anchor	Anchor
Vacuum system		No	Yes	No	No
Head data [m]	da	1.61	1.41	1.61	1.51
	r1	1.61	1.41	1.61	1.51
	r2	0.16	0.14	0.16	0.15
	h1	0.02	0.02	0.02	0.02
	h2	0.31	0.27	0.31	0.29
	h3	0.33	0.29	0.33	0.31

Appendix A.2: Filter FN-01.

The filter selected for the process is the PKF 100 press filter model from the manufacturer Putsch.

Table 19. Technical data for model PKF 100 filter by manufacturer Putsch.

Design of filter plates		Membrane filter plates
Filter plate size [mm]		1200x1200
Cake thickness [mm]		33
Filter area [m^2]		95,3
Chamber volume [L]		1508
Number of chambers [L]		42
Operating pressure		116 psi
Head data [m]	a	7160
	b	2700
	c	3190
	d	1660
	e	2150

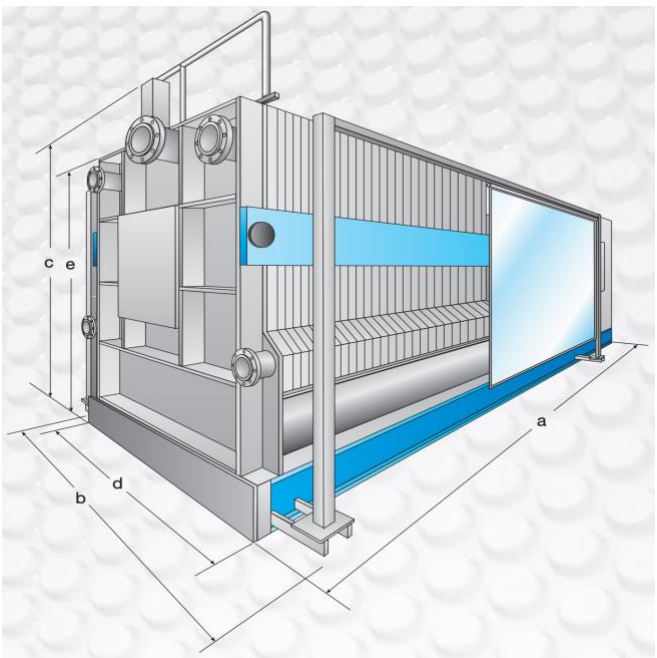

Figure 24. Scheme of the filter provided by manufacturer Putsch, image from (Putsch 2021).

Appendix A.3: Drier D-01

The selected dryer for the process is the E1,15 S model of Multispray static vacuum tray dryer from the manufacturer Italvacuum.

Table 20. Technical data for model E1,15S Multispray drier by manufacturer Italvacuum.

Inner volume [L]	1960
Inner dimensions (W x D x H) [mm]	1270x1060x1455
Number of heating shelves	13
Heating shelves dimension (W x D) [mm]	1200x1000
Number of trays	52
Trays dimensions (W x D x H) [mm]	600x480x40
Useful surface area [m^2]	15

*W = width D = depth H = height

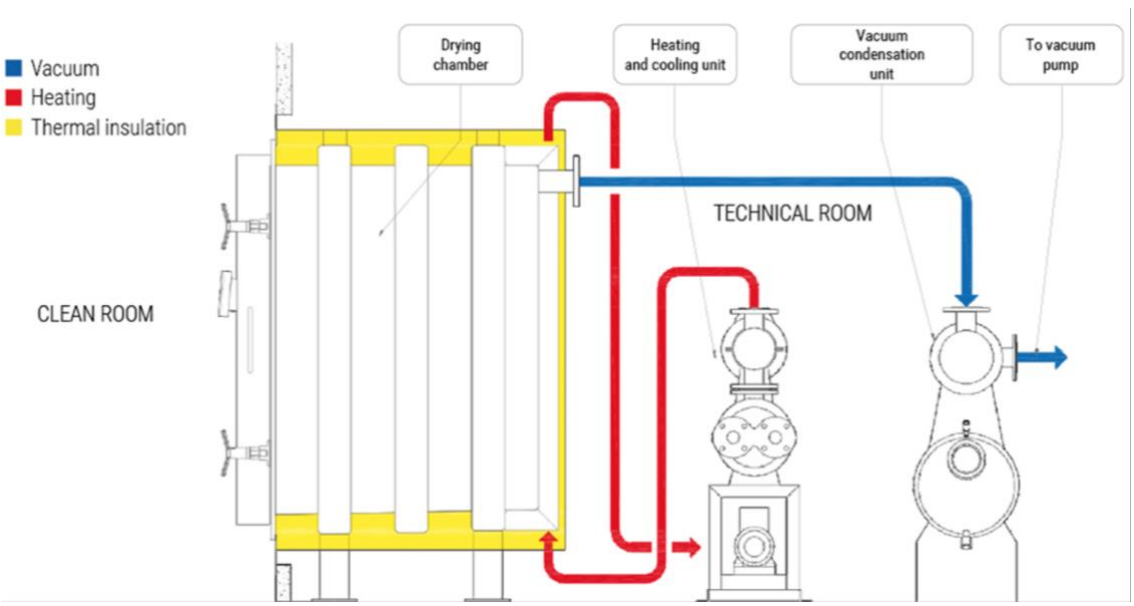

Figure 25. Scheme of the tryal drier provided by manufacturer Italvacuum, image from (Italvacuum 2021)