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Design of a batch plant for ivabradine manufacture

Disseny d'una planta per a la fabricació d'ivabradina

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Als meus pares, pel seu suport incondicional. Per tots els esforços que han fet al llarg de la meva vida. Per tot el que han deixat de fer, per poder donar-m'ho. Per l'educació rebuda tan dins com fora de casa. Per les experiències que sense la seva ajuda no haurien estat possibles. Per haver buscat sempre el millor per mi. Per ser responsables de qui sóc a dia d'avui. Gràcies Gemma i Pere.

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REPORT

CONTENTS

SUMMARY

Heart failure is a disease that affects over 37.7 million people worldwide. Due to its major concern, several investigations are taking place nowadays, resulting in a variety of drugs with significant impact in the treatment of different heart pathologies. This is the case of ivabradine, a compound that has represented an alternative to classic heart treatments during recent years and which generic medicine is just available. Thus, representing a huge market opportunity for new manufacturers willing to produce this active ingredient. The aim of this project is to provide a feasible manufacturing process for this compound on an industrial scale, in addition to basic equipment selection and emphasis on the production programming.

A broad study of the state of the art of patents for ivabradine synthesis is performed with the purpose of selecting the most suitable patent to take to the industrial scale for the manufacture of ivabradine, as well as acknowledging alternatives for the operations and compounds selected on each stage of the production process. Moreover, production requirements and batch size are determined. The work is complemented with the selection of the main equipment required, according to the actual commercial offer, for the industrial execution of the synthesis designed. Finally, effort is dedicated to the study of the production schedule in order to optimize the available resources and increase the annual production of the active principle.

Key words: Ivabradine, process synthesis, production planification, equipment selection.

1. INTRODUCTION

With over 37.7 million people affected worldwide, heart failure (HF) has become a major concern in medicine. Acute heart failure (AHF) is referred as a life-threating situation requiring immediate treatment as a consequence of worsening HF. This pathology is mainly caused by defects, either structural or functional, in myocardium causing ventricular dysfunction but also by extrinsic factors (Othman et al. 2019). This syndrome is just one part of a major group known as Cardiovascular diseases (CVD) which also comprehends coronary artery disease (CAD) and stroke; growing health concern lately as one of the leading causes of disability and death (Sathyamurthy and Newale 2018).

3-[3-({[(7S)-3,4-dimetoxibiciclo[4.2.0]octa-1,3,5-trien-7-il]metil}(metil)amino) propil]-7,8-dimetoxi-1,3,4,5-tetrahidro-2H-3-benzazepin-2-ona (Figure 1), from now on Ivabradine (commercially known as Procoralan© or Corlanor©, among others) (PubChem 2005) is an Active Pharmaceutical Ingredient (API) used in pharmacology as an effective heart rate (HR) reducer. The main consequences of an elevated HR include an increase of the consumption/demand of oxygen in the heart or ventricular dysfunction, resulting in heart deterioration thus, increasing the possibility of HF (Othman et al. 2019). Therefore, Ivabradine is capable of treating HF in a wide range of patients leading to an encouraging therapy for heart-related diseases in comparison to other common drugs, which present side effects in several sick individuals. In addition to that, it is thought that Ivabradine can present positive results in the cure of other heart-related illnesses such as, CAD and Inappropriate Sinus Tachycardia (IST) (Koruth et al. 2017).

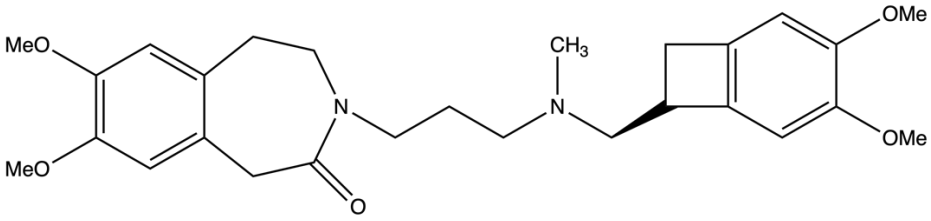

Figure 1. Ivabradine molecule

Ivabradine's mechanism of action consists in the inhibition of the pacemaker current or, more commonly known as the "funny" or f current (I_f). As stated in (Koruth et al. 2017) *"The sinoatrial node […] cells have an ability to generate a cyclical change in*

their resting membrane potential, which drives it […] for spontaneous depolarization" and *"Depolarization is initiated by the opening of specific ion channels that conduct a slow, inward-depolarizing mixed sodium-potassium current, […] the "funny" current"*. Moreover, ivabradine acts as a cation movement blocker which at its turn decreases pacemaker action, reducing heart rate (Koruth et al. 2017). As a result of its particular mechanism of action, it does not interact with other heart functions whereas other medicines do. Some of this features could be intracardiac conduction or cardiac inotropy (contractility), among others (Sathyamurthy and Newale 2018; Koruth et al. 2017).

Before the discovery of the clinical use of this API, the main drugs in use for the reduction of HR in the treatment of HF were those known as beta-blockers (BB). Their positive outcome in treatment has made them of widely use in clinical treatment but the appearance of ivabradine has supposed a change in the procedures. Although its proven positive result, in clinical practice, several patients are not able to take the required doses not only due to contraindications but also incapability to tolerate beta-blockers (Sathyamurthy and Newale 2018). Finally, as beta-blockers and Ivabradine mechanisms of action differ from each other, Ivabradine provides an alternative becoming a drug for the treatment of a wider range of patients including both users and non-users of beta-blockers.

Furthermore, beta-blockers alone are, in some cases, unable to reduce HR as much as necessary (to around 60-70 bpm) but simultaneous treatment with ivabradine and beta-blockers lead to the accomplishment of the necessary HR decrease (Sathyamurthy and Newale 2018; Borer and Tavazzi 2016; Koruth et al. 2017; Othman et al. 2019). In addition, some studies have shown HR decrease was not clearly related to the beta-blocker dose, limiting their possible use (Borer and Tavazzi 2016). As a consequence, combination of ivabradine and beta-blockers is common in the therapy of different heart problems, leading to noticeable benefits for patients (Sathyamurthy and Newale 2018).

The main benefits of ivabradine in the treatment of HF were assessed in many studies but one of the biggest and most important ones was the *Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial* (SHIFT). SHIFT study aimed to prove the results of treatment of patients with symptomatic heart failure with a HR greater than 70 bpm through the use of ivabradine. The clinical study was carried out on a

population of over 6,500 patients (Böhm et al. 2010; Swedberg et al. 2010). Considerable 26% reduction in hospitalization due to worsening HF was proven (Borer and Tavazzi 2016). As a matter of fact, comparable results were obtained in other studies like the one presented in (Othman et al. 2019). On the other hand, the study proved ivabradine showed better results, meaning bigger reduction, only in patients with a higher HR baseline value (Böhm et al. 2010).

In conclusion, this study results gave support to the importance of heart rate reduction in patients suffering heart failure (Swedberg et al. 2010), aligning the reduction in the HR with the positive outcome of the treatment. These results led to the approval of ivabradine as a drug for HF treatment in Europe and US both by the European Medicines Agency (EMA) and the Food and Drugs Agency (FDA), in 2012 and 2015 respectively (Koruth et al. 2017). Note that ivabradine was already approved by the EMA in 2005 for the treatment of angina.

To sum up, Ivabradine has been shown as a clear heart rate reducer and useful for the treatment of heart failure, but it has been proposed as treatment for other pathologies. This is the case of CAD and IST, which were shown as positive diseases to treat with the use of ivabradine. Despite the positive outcome in other treatments, some studies like the *MorBidity-mortality EvAlUation of The I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction* (BEAUTIFUL) claimed its benefits were not as clear as considered before. The effect of heart rate reduction did not result in a beneficial outcome, either, for the over 11,000 patient population studied (Borer and Tavazzi 2016; Fox, Ford, Steg, Tendera, Ferrari, et al. 2008; Fox, Ford, Steg, Tendera, Robertson, et al. 2008; Fox et al. 2009). In this case, no effect was proven for the treatment of CAD and IST leading to the non-approval of ivabradine as a suitable drug for these treatments by the FDA (Koruth et al. 2017).

Despite the encouraging data depicted, some studies suggest ivabradine can present counterindications regarding atrial fibrillation (AF), a pathology causing irregular heart rhythm. Studies proposing either positive or negative effect have been mentioned in several papers. The aftereffect of ivabradine administered alone regarding AF, has not been fully determined yet. Whereas some papers affirm it has a positive outcome in AF patients (Fontenla et al. 2019; Frommeyer et al. 2017) others imply a worsening diagnostic or even ivabradine to be the cause of it (Martin et al. 2014). The conclusion

at this point is that further studies and clinical tests need to be performed in order to determine which is the true effect of the drug regarding this pathology (Lu et al. 2016).

On the other hand, when prescribed together with beta-blocker substances the outcome is shown to be positive in the studies performed until this moment (Fontenla et al. 2019; Lu et al. 2016; Abdel-Salam and Nammas 2016). Nevertheless, as mentioned before, the application of beta-blockers could be contraindicated or not possible on certain patients making ivabradine not suitable either, so the combination of both should be dispensed wisely.

Finally, ivabradine can be responsible of other side effects related to its prescription, which include: bradycardia and hypertension (FDA 2015a).

All in all, medicine is facing important challenges and concerns nowadays and, particularly in heart-related diseases, ivabradine emerges as an important drug for the industry.

In addition to that, European first approval patent by EMA for *Procoralan,* first commercialized form of ivabradine, dates from 2005 with the approval of the generic medicine in 2017. On the other hand, FDA approval for ivabradine dates from 2015 (Koruth et al. 2017; FDA 2015b). For this reason, these approval dates, specially the generic medicine approval in 2017, represent a market niche around the production of this API.

The development of this production line requires a further study of the different patents, not only to choose the best process for the production of ivabradine but also which is the best ivabradine salt to produce.

The criteria followed to for this choice considers different variables: including current market ways of commercialization, difficulties of the production process and reactions, safety, yield, purity, steps, raw materials, stability, etc.

2. OBJECTIVES

According to the heart problems affecting nowadays society presented in the previous point, ivabradine emerges as an encouraging drug to fight these diseases. Furthermore, the approval of the generic medicine represents an opportunity for the development of novel industrial solutions for production of ivabradine on a large scale.

The objective of this work is to provide further study on the manufacture of ivabradine and develop an industrial solution for the synthesis of ivabradine in a batch plant. To do so, the following tasks require to be accomplished:

- Selection of the API annual production result of the market requirements of the product.
- Selection of the manufacturing process as a result of the investigation and research of the different patents available that best fit the annual production.
- Development of the synthesis process to apply the selected patent to a suitable industrial batch procedure, scaling from the laboratory scale patents to the industrial batch plant. Including the different stages and operations as well as the general equipment required
- Basic design according to the process synthesis in order to select the suitable equipment and its characteristics to accomplish the manufacture of ivabradine and meet the annual production set.
- Development of the production planning of the plant over a year, optimizing the available resources through scheduling strategy to increase production.

3. PRODUCTION REQUIREMENTS

In order to determine the production requirements of the brand-new manufacturing installation as well as the feasibility of the business itself, the market has been studied. The commercial formats, market requirements and the share were considered, and some assumptions were made regarding these considerations. It is important to mention that a conservative guess was done in order to have an initial estimation for the production capacity of the plant. Real production requirements would be adjusted according to the real demand of the hypothetical final manufacture plant.

Ivabradine, in the different commercial brands, is commercialized in two formats featuring different salts of ivabradine (hydrochloride, hydrobromide, oxalate among others depending on the manufacturer):

i. 50 pills composed of 5 mg of ivabradine
ii. 50 pills composed of 7.5 mg of ivabradine

According to the information previously mentioned, around 37.7 million people worldwide are affected by heart failure (Othman et al. 2019) and are potential patients to be treated with ivabradine pills.

Regular administration of ivabradine goes between 2.5 mg to 7.5 mg twice a day (FDA 2015a).

Ivabradine specialty's sales price in Spain goes between 28.85€ to 43.27€ for formats (i) and (ii) respectively. It is important to note that, previously to patent expiry, thus generic drug appearance, the price of format (i) was around 70€.

According to the Spanish market, a 4% VAT as well as an additional 0.5% in concept of other taxes is applied to the retail price of the pharmaceutical specialty. In addition to that, the price of the API sold by the manufacturer represents between a 3-5% of the obtained sales price of the pharmaceutical speciality. In this case, as a means to have a conservative calculation, the lower value will be considered.

With this consideration, the retail price per kilogram of ivabradine produced can be calculated using

$$API\ sales\ price = nº\ of \frac{pills}{box} \cdot ivabradine \frac{mass}{pill} \cdot \left(\frac{1kg}{10^6 mg}\right) \cdot \frac{price\ (€)}{box} \cdot (100 - tax\%) \cdot 3\% \qquad (1)$$

It is important to give consideration to the fact that ivabradine is consumed daily. Heart rate reduction is of vital importance for people with high heart pace and/or other

heart problems. On account of drug consumption for market requirements, an average daily consumption per person and day was considered to be 10mg of ivabradine.

There are currently many ivabradine manufacturers: *Les Laboratories Servier*, *Laboratorios CINFA S.A, Laboratorios NORMON, SANDOZ Farmaceutica, Laboratorio STADA S.L, TECNIMEDE, Laboratorios ALTER, AUROVITAS, Laboratorios BLUEPHARMA, COMBIX, KERN PHARMA*. Consequently, it is not ridiculous to consider the company's production to assume a 15% of the market share.

With this considerations, annual production of ivabradine in the batch plant can be calculated using equation (2).

$$Market\ volume = Average\ daily\ dose \cdot n^{a}\ patients \cdot \left(\frac{1\ tone}{10^{9} mg}\right) \cdot market\ share\ \% \qquad (2)$$

Finally, company's billing can be directly calculated using equation (3).

$$Anual\ revenue = sales\ price \cdot annual\ production \qquad (3)$$

According to all the considerations and steps previously followed the sales price per kilogram of the API is 2,952 €/kg. The total consumption per year of ivabradine according to the patients is of 123 t/year, so the production required will be of around 18.5 t/year. All the following design and planification is performed following this consideration.

Table 1. Plant production figures

CHARACTERISTIC	**VALUE**
API sales price [€/kg]	2,952
Market volume [t/year]	123
Plant annual production [t/year]	18.5
Annual revenue [€/year]	54,612,000

4. SELECTION OF THE MANUFACTURING PROCESS

In order to determine the most suitable manufacturing process for the production of ivabradine, several patents have been studied, taking in consideration their main advantages and drawbacks. The process selected is widely explained.

4.1. STATE OF THE ART

Several patents show different paths for the synthesis of ivabradine that can be exported to a large-scale production in a batch plant. The API can also be combined to form acid addition salts for its use as drug.

Ivabradine is a viscous substance which makes its handling difficult in industrial procedures, not only for its flow problems throughout piping but also for the different stages of the manufacturing procedure, compared to the use of a salt. Thus, production of ivabradine in a salt form makes it more attractive for its industrial application and further commercialization (Ujvari et al. 2011; Westheim and BV 2013). In this sense, the use of a salt usually gives higher melting point and further stability leading to better handling.

Different salts are considered in the bibliography which provide different advantages and disadvantages regarding stability, compatibility, solubility and other aspects to think about during industrial production. All in all, the salts more widely studied and considered are hydrochloride, hydrobromide, oxalate and lactic acid salts, among others.

It is of important mention that most ivabradine products commercialized in Spain are mainly constituted of hydrochloride salts or, in some cases, oxalate salts. Ivabradine not in a salt form is also used.

The usual composition of ivabradine drugs for pharmaceutical use is as follows (Lynch et al. 2018):

- Diluent: 40-80 %wt
- Lubricant 0.2-10 %wt
- Ligand 5-50 %wt
- Ivabradine complex: 5-50 %wt

Manufacture and use of ivabradine as drug and acid addition salts thereof for pharma use were firstly described in the European Patent EP 0 534 859 by laboratories *Servier*, first company to commercialize the drug (Peglion et al. 1993). In this case, the

process disclosed an ivabradine hydrochloride salt. Despite the encouraging benefits of the use of ivabradine for the treatment of heart diseases, the first synthesis processes showed poor yield making its industrial implementation not feasible.

Some patents have pointed ivabradine is a polymorph substance and presents different crystalline states as well as the amorph form. The use of these different formulations of ivabradine can lead to different outcome in its application, being crystalline forms more stable and in some cases, having better properties. In this case, amorph hydrochloride form is instable, very hygroscope and, in conclusion, might need further treatment for industrial production. (Westheim and BV 2013; Ujvari et al. 2011)

Ivabradine and pharmaceutically accepted salts thereof can be combined with other substances to form a complex salt in order to enhance ivabradine's stability for its commercialization. This combination enables the use of amorph ivabradine and not a crystalline form thereof, which might be more difficult to obtain in plant production. This complex provides the stability required with the use of around 80-90% of amorph ivabradine (Eupen Van et al. 2015).

In patent WO 2008/146308 (Singh et al. 2008) a path to synthesize ivabradine is shown through a condensation synthesis of two reactants in acetone and the presence of potassium carbonate. The resulting compound needs to be purified by column chromatography and reduced with palladium hydroxide in glacial acetic acid under hydrogen atmosphere. When ivabradine is obtained, the hydrochloride salt is manufactured by addition of hydrochloric acid. The process presents drawbacks as one of the reactants is synthesised through a borane tetrahydrofuran complex which is not stable at room temperature. In addition to that, hydrochloric acid needs to be removed through the use of distillation which, at its time, might lead to decomposition of product, even under vacuum, and further purification would need to be performed. This purification is usually done by chromatography which, at its time, is an operation of difficult application in an industrial scale.

The process is similar to the one provided in (Sada et al. 2014) for the synthesis of the hydrochloride salt. The range of temperatures used, the solvents to perform the different steps and the catalyst featured for the final hydrogenation can be comparable, being the same in some cases. In this case, an ivabradine intermediate is synthesised before the hydrochloride salt whereas on the other patent the salt is first generated and

then the final synthesis step is performed. As previously mentioned, the handling of a salt might be more suitable for the application of the industrial process. Finally, despite the fact of providing interesting data and alternatives to other patents for the chemicals used in the production of ivabradine hydrochloride, the lack of yield and purity data makes it difficult to trust the process without knowing the outcome.

Polymorphic ivabradine forms are presented in WO 2011/138625 (Ujvari et al. 2011). The advantage of the use of polymorphic forms represents an alternative to other processes as these forms can have different physicochemical properties more suitable for the industrial application. These advantages can be unpredictable before synthesising a new form but include different solubilities, better flowing and filtration properties or superior pharmacokinetics and release profile. Including greater stability and melting point.

Different ivabradine salts and polymorphisms are presented in the patent for example hydrobromide and oxalate salts which only some polymorphic forms are suitable for pharmacological use due to stability reasons.

The synthesis process starts from a propionitrile compound and follows 6 synthesis steps prior to the final synthesis step of a preliminary compound to the ivabradine salt. The preliminary compound can be transformed to the suitable salt by salt formation including hydrogen chloride, bromide or iodide; oxalic acid, nitric acid or perchloric acid. Further recrystallization and purification processes are followed in order to obtain the suitable form and purity for pharmaceutical application of the salt.

In this case the process followed consists of the synthesis of several compounds which might be of difficult application in an industrial scale. Also, the lack of yield data makes the choice of this patent as the recipe too risky. Nevertheless, the patent provides interesting information both giving support and presenting alternatives to other processes studied.

Included in this consideration, the most suitable substances for the crystallisation of different ivabradine salts can be found. In the case of ivabradine hydrochloride, crystallisation is also performed by cooling in an organic solvent, preferably a polar one like acetonitrile. It can also be carried out by the addition of a solvent which dissolves less the compound such as ethyl acetate to a single or double alcoholic solution (methanol or ethanol, preferably). (Ujvari et al. 2011)

For the synthesis of ivabradine hydrobromide is preferable the use of methanol or ethanol as organic solvent. In the case of oxalate, the most suitable way for crystallization is the mixture of an organic solvent and water plus the addition of a polar organic solvent.

The patent gives support in the use of K_2CO_3 as a reactant and the use of a Pd/C catalyst for the hydrogenation reaction. In addition to that, temperature ranges mentioned in the patent might be of interest in other patents studied.

In patent WO 2014/188248 (Sada et al. 2014) synthesis of three different ivabradine salts is proposed. These salts are hydrochloride, oxalate and L-tartate ivabradine salt. The synthesis process is similar in all three alternatives. The process follows similar steps in the three salts. A compound called dehydro-ivabradine is synthesised and is used as the reactant for all three processes with a yield of 93%. This compound follows an addition reaction where a dehydro-ivabradine salt is produced and a catalysed hydrogenation is followed to obtain the ivabradine salt. Further recrystallisation processes are followed to achieve the pharmaceutical industry required purities.

For the synthesis of ivabradine oxalate, oxalic acid dihydrate is dissolved in methanol and reacts with a solution of dehydro-ivabradine in methanol while heated. Once cooled is crystallized and filtered at 0-5 ºC to be washed and recrystallized by using methanol. The resulting solid is a dehydro-ivabradine oxalate salt which will be furtherly treated through the mentioned catalysed hydrogenation reaction in methanol media at 55-60 ºC and 5 bars. The resulting product is washed and treated with isopropanol and left to recover obtaining ivabradine oxalate of a 98.5% purity. The yields of the two steps explained are 63 and 77% respectively. In this case, the yields appear to be low considering the different solvents and reactants used and the final purity might not be encouraging enough to select a process with such low yields.

For the synthesis of ivabradine L-tartrate, the initial reactant is, as mentioned the dehydro-ivabradine. The reactant is dissolved in MIBK and L-tartaric acid dissolved in acetone is added dropwise. Dehydro-ivabradine L-tartrate precipitates and is filtered and washed in methanol and MIBK. The solid follows a pressurized catalysed hydrogenation in methanol medium and in inert atmosphere. After a 22-hour reaction the product is filtered evaporated and treated with ethyl acetate for the final obtention of ivabradine L-tartaric salt with a purity of 98.9%. The yields of the two steps are 84 and

72% respectively. Despite the increase in purity and yields in comparison with the compared process, the purity values do not meet common pharmaceutical standards and recrystallizations and purification processes might be followed for its industrial application increasing, considerably, operational costs and residue generation.

A similar process is followed for the production of ivabradine hydrochloride. Dehydro-ivabradine is mixed in acetonitrile and HCl is added dropwise. The mixture is cooled down and let crystallise for 24 hours. The resulting product is dissolved in alcohol and let react under pressure with hydrogen in presence of a catalyst for over 18 hours. The solvent is evaporated under pressure and purification steps are followed and crystallisation step is performed in acetonitrile solution. Another recrystallisation step in the same solvent with the result of 99.9% purity ivabradine hydrochloride. The yields of the two steps are 74% and 80% respectively.

The patent presents some drawbacks as it is the use of acetonitrile. Acetonitrile is a classified solvent to be used in pharmaceutical industry, which means, its presence is forbidden in the final product. For this reason, its removal from the final product is a key step for the further commercialization of the API. It must be noted that heating leads to the anhydrous form of the ivabradine salts (hydrochloride) and low enough temperature removal must be followed to avoid this results. (Westheim and BV 2013)

Alternative solvent systems are presented in patent WO 2013/064427 as crystallisation can be achieved out of a mixture of an 1-4 carbon aliphatic alcohol such as ethanol or a mixture of two alcohols and the presence of aliphatic/alicyclic hydrocarbon of 5-8 carbons like n-pentane/hexane/heptane or cyclohexane including a mixture of at least two of them. The use of the hydrocarbon works as a diminisher of ivabradine hydrochloride solubility, commonly known as antisolvent action, enhancing the yield of the crystallisation specially at reduce temperature.

Despite its drawbacks, the reason to use acetonitrile is for its capacity and good performance in the removal of impurities in the crystallisation (Singh et al. 2008).

The yield results are not as good as the ones in the L-tartrate process. Nevertheless, they are still encouraging, and the resulting purity meets the pharmaceutical industry requirements. It has to be noted that even before the final recrystallisation the purity is already of 99.5%.

After studying the pros and cons of different processes, and once considered the possible alternatives shown in some other patens, the process selected for the industrial application is the one shown for the production of ivabradine hydrochloride in patent WO 2014/188248. The different steps of this process will be widely explained in the following points of this work, alternatives and in favour statements from other patents are included.

4.2. PRODUCTION PROCESS SELECTED

The process selected for the industrial production of ivabradine is the one corresponding to patent WO 2014/188248 A1 (Sada et al. 2014). For this recipe, four main stages or processes are succeeded and will be explained as follows.

4.2.1 Stage 1: Preparation of dehydro-ivabradine

The first step consists in the synthesis of the intermediate *3-[3-[[[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-l,3,5-trien-7-yl]methyl]methylamino]propyl]-l,3-dihydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride* or dehydro-ivabradine. The synthesis of dehydro-ivabradine is based on the reaction between two compounds: *3-(3-chloropropyl)-7, 8-dimethoxy- 1,3-dihydro-2H-3-benzazepin-2-one,* from now on referred as Compound A, shown in Figure 2; and (*lS)-4,5-Dimethoxy-l.-[(methylamino)methyl] benzocyclobutane*, from now on referred as Compound B, shown in Figure 3.

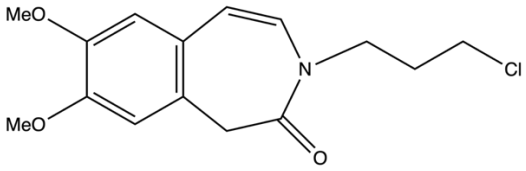

Figure 2. Compound A or 3-(3-chloropropyl)-7, 8-dimethoxy- 1,3-dihydro-2H-3-benzazepin-2-one

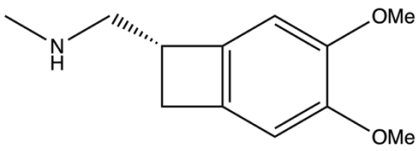

Figure 3. Compound B or (lS)-4,5-Dimethoxy-l.-[(methylamino)methyl] benzocyclobutane

In a 6 1 multiple neck flask under nitrogen atmosphere 364 g of compound A, 170 g of potassium carbonate, 31.4 g of potassium iodide and 2600 ml of methyl-isobutyl ketone (MIBK) are sequentially loaded. The unblocked amine (compound B) dissolved

in the remaining MIBK (1000 ml) is added and the reaction is heated to 85-90°C. The reaction is left under stirring while heating for 48 hours, controlling it by HPLC. Reaction is shown in Figure 4. Next, the mixture is cooled down to 60-70°C and the organic phase is washed 2 times with 1000 ml and 500 ml of water. The organic phase is acidified with 33% w/w HCl keeping the temperature around 40°C. Organic phase is dismissed. Product is contained in the aqueous phase which is washed five times with 1.5 L of MIBK still at 40ºC. Extra 800 mL of MIBK are added and the dissolution is basified with 143 g of NaOH 30%. Organic phase is kept and washed with water, the result dried and concentrated until dryness obtaining 537 g of oil. The yield of this stage is 93%.

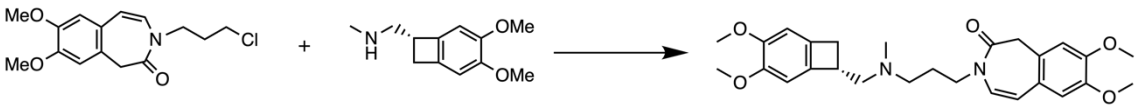

Figure 4. Obtention of dehydro-ivabradine

As stated in the patent WO 2016/193386 (Del Río Pericacho, Arredondo Martínez, and URQUIMA 2016) the required compound A for this step is likely to be a compound with either a single or double bond in the aliphatic ring. The reaction is taken in either polar aprotic or protic environment in presence of a base which can be from triethylamine and alkalimetal carbonates, bicarbonates and hydroxides. According to the patent it is suitable to be potassium carbonate and is the one followed in the selected patent as well as in other studied documents (Ujvari et al. 2011). The solvent can be of different natures including tetrahydrofuran, toluene, acetone acetonitrile dimethyl formamide or a C1-C4 linear aliphatic alcohol like methanol. In the studied case MIBK is used even though according to patent WO 2016/193386, the most suitable solvent is dimethyl formamide for its effect on fastening reaction rate. Despite the fact of the use of another solvent, alternatives should be considered for the industrial implementation of the process. The patent also provides an alternative to the reaction temperature to be set at 55-75ºC.

4.2.2 Stage 2: Preparation of dehydro-ivabradine hydrochloride

The obtained oil from the previous stage is mixed and evaporated with 1 L of acetonitrile. The result is mixed again with acetonitrile and dried with Na_2SO_4. A HCl solution in acetonitrile 4.5w% is added dropwise keeping the temperature 20-25 ºC while the seed crystal is added. The reaction is shown in Figure 5. The solution is then

crystalized keeping temperature between 0 and 5 ºC for 24 hours. Finally, crystals are cleaned with cold acetonitrile, obtaining 430 g, with a yield of the 74%.

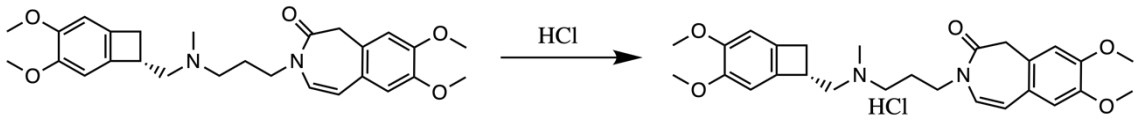

Figure 5. Obtention of dehydro-ivabradine hydrochloride

According to patent WO 2016/193386 (Del Río Pericacho, Arredondo Martínez, and URQUIMA 2016) the conversion of any of the ivabradine bases to its salt is suitable using the corresponding acid in the suitable solvent which include: ketones, alcohols, nitriles, ethers, halogenated hydrocarbons or esters. In the selected process, the solvent used is acetonitrile, as listed in the alternatives. The previously mentioned drawbacks must be considered, though (Westheim and BV 2013).

4.2.3 Stage 3: Preparation of ivabradine hydrochloride

Ivabradine hydrochloride is obtained through a hydrogenation reaction with the presence of a catalyst as shown in Figure 6. According to the patent, 50 g of the previously obtained dehydro-ivabradine hydrochloride are dissolved in 500mL of methanol and the solution is inserted in a pressurized reactor (autoclave) in nitrogen atmosphere. 5 g of Pd/C of catalyst at 5% are added, the reactor is pressurized at 4-5 bars and reaction is kept at these conditions for 18 hours at 30-35 ºC. Once finished, checking with the use of HPLC, the solvent is evaporated at reduced pressure. Then the result is dissolved with 150 mL of acetonitrile and evaporated again. The dissolution is repeated with 1250 mL of acetonitrile for crystallization with a purity over 99.5%. The yield of this stage is 80%.

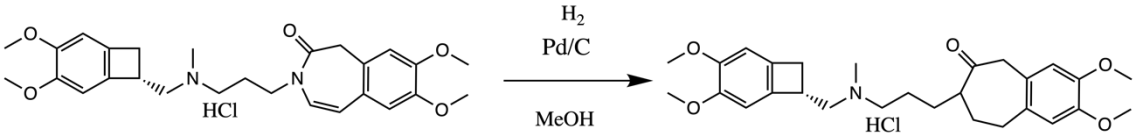

Figure 6. Obtention of ivabradine hydrochloride

Other suitable catalysts as alternative to the palladium/carbon one can be find in the patent WO 2016/193386 (Del Río Pericacho, Arredondo Martínez, and URQUIMA 2016) including platinum, nickel among others in an oxide form like the palladium-on-carbon used. The use of Pd/C as a catalyst is also supported by other authors mentioned in this research (Ujvari et al. 2011).

According to literature, crystallization is performed in cold conditions similar to the crystallization of stage 2. The temperature set proposed is 0ºC (Westheim and BV 2013).

4.2.4 Stage 4: Crystallization of ivabradine hydrochloride

A purification step is followed. 40 g of ivabradine hydrochloride is taken up to 1000 mL of acetonitrile and is washed with 200 mL of acetone. The product is filtered, washed with 400 mL of acetone and dried at 60 ºC for 24 hours. It can be noted that the final drying process must guarantee the total elimination of acetonitrile for the final pharmaceutical application.

As stated in literature, the second crystallization is performed in the same conditions as the one in stage 3.

An alternative for drying proposed in the literature for the elimination of acetonitrile is to set temperature to 85ºC during 4 hours.(Westheim and BV 2013).

The main reason for the selection of this patent is the good results relating to the yield of the different stages. Among the patents studied, even though some of them presented encouraging processes and purities, the yields were really low. For this reason, the equilibrium between yields and final purity of this last process described in patent WO 2014/188248 A1, appears to be the most suitable for the industrial application.

On the other hand, the issues related to the handling of the products as well as their dangers for the health and environment must be considered and reduced to the minimum during the process synthesis.

5. PROCESS SYNTHESIS

Process synthesis is the result of the deep study of a laboratory recipe in order to transform the procedure into a feasible industrial process. Once the patent is selected, each step of it must be widely understood in order to select the suitable industrial solution to scale up the production from some grams of products to tones.

In this case, process synthesis can be divided in the same steps defined in the recipe considering the main 4 stages of production for the ivabradine salt. It must be considered that the process synthesis is developed in accordance to the production demand. The different operations to perform in order to accomplish the desiered product can differ depending on the volumes and the quantities managed. For this reason, this process synthesis must be developed according to a batch size.

Batch size is calculated regarding different considerations: annual production, opeation times, labour, etc. As stated in point 3 of the present work, the annual production has been defined to be 18.5 t/year. Moreover, after the study of the patent, it can be determined that the process is long and complex, taking around 5-6 days to complete all the steps of the synthesis. Thus, a 24/7 operation is required for its production. Furthermore, it is assumed a 6-to-9-week period of maintanance in addition to other planned stops.

All in all, regarding these considerations and annual labour days an initial yearly production of around 50 batches is assumed, with a batch size of 400 kg of ivabradine hydrochloride of 99.9% purity. This round amount results in a slightly bigger annual production of 20 t/year which works as a buffer for any inconvenience that might appear during production through out the year, guaranteeing a minimum production of 18.5 t/year. Fruther study about this topic is shown in section 7 of the present work.

Following the different stages of the laboratory procedure, a useful tool for process representation and understanding to accomplish an industrial solution is the state-task networks (STN). In STN only two different nodes are possible: state nodes, representing all the material input and outputs in every step of the process and their condition, and task nodes, representing all the operations needed to transform materials in each step of the process (Kondili, Pantelides, and Sargent 1993).

STNs have been applied in every step of the recipe for better understanding of all the tasks and subtasks needed to obtain the proper synthesis of ivabradine

hydrochloride. Once all the stages are properly analysed assumptions on the most suitable operation to chose can be made.

5.1. GENERAL CONSIDERATION

Despite the disctinctive features of the diferent steps, there are some considerations that can be assumed as standard throughout all processes.

Reactors will be used for the mixing steps and the different reactants will be loaded sequently, adding first the liquid compounds through piping and afterwards the solid compounds from top of the reactors with the subsequent mixing time. Premixing can be also considered in some steps. Liquids will be pumped straight from the correspondant tank. If possible, reactants will be loaded in as close to the temperature of operation as possible in order to reduce the heating/occupation time in the equipment. Reaction vessels are assumed to be filled between 40-100% of the total volume of the reactor in order to achieve desired operation conditions. This assumption is based on rules of thumb.

The downloading of the output streams will be performed by means of gravity for liquids where possible.

For heat exchange operations, cooling will be performed with cooling tower water for high temperatures and glycol-water solution (-15ºC) for low/sub-zero temperatures, on the other hand, low quality steam will be use for heating (4-6 bars). Thermic oils are not required as heating temperatures are not high enough for them to be used. Half pipe jacketed reactors will be the equipment selected to perform the heat exchange in the industrial operations. In the case of regular reactors, the half-pipe set-up can be connected to different heating fluid feeds for the different heating and cooling operations required, vapor and cooling tower water, thus all being performed using the same equipment. For crystallization reactors, as cooling is performed directly with glycol-water solution, fluids cannot be mixed in the jacket, so the unique heating fluid permitted in the half pipe is the glycol water solution.

Drying operations as general consideration are performed at the end of the process and not done repetively in the same stage in order to reduce unnecesary energy consumption.

Further and more particular considerations are to be consdiered in the specific sections for each stage of the process.

All the considerations and assumptions made in this process synthesis are intended to keep reaching the same yields and purities as stated in the patent. All the assumptions are made based on literature, rules of thumb, industrial experience and current commercial solutions in order to adapt a laboratory experimental process to an industrial scale.

5.2. STAGE 1

The STN for the first stage of patent WO 2014/188248 A1 is showed in Figure 7. In the first stage, dehydro-ivabradine is sythesised from the reactants A and B, as stated previously. For this step the total number of states is 36 and the tasks performed are 19. This synthesis is by far the one with more tasks required which does not mean the most difficult one in performance. Due to this big number of tasks, assumptions are intended to reduce operation times.

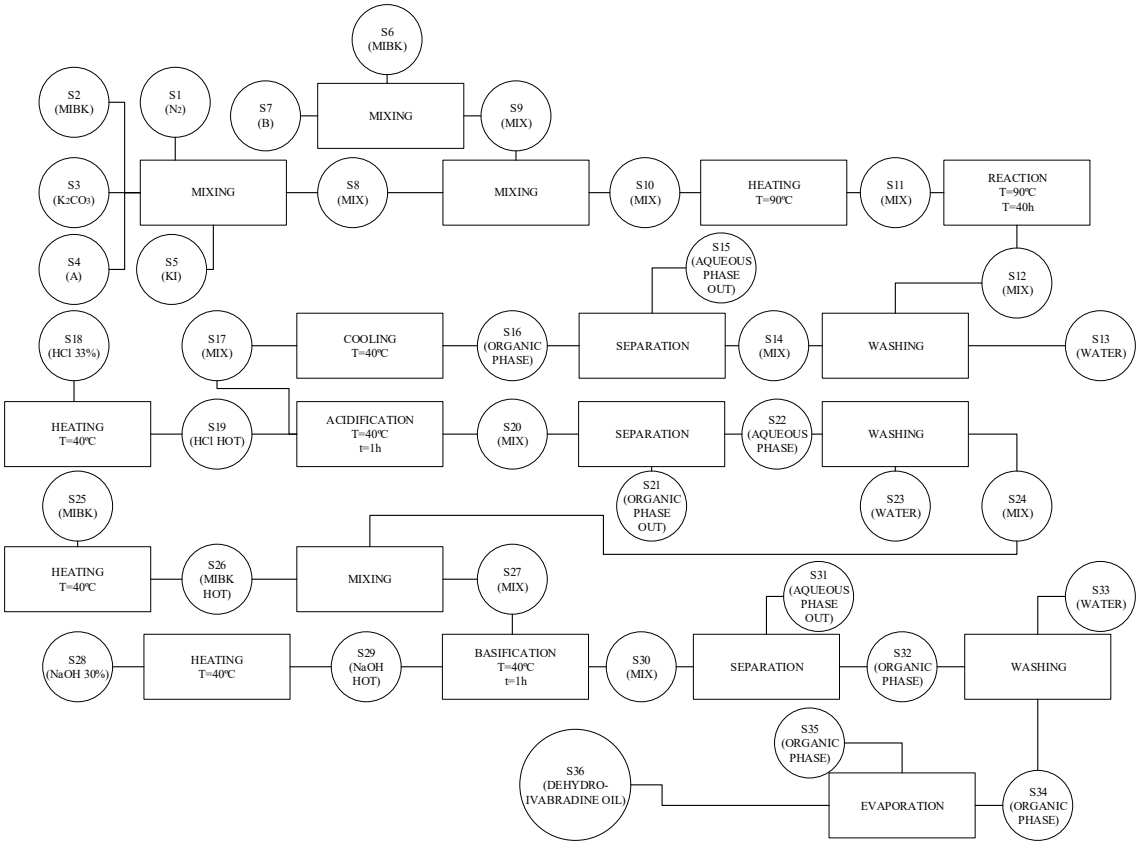

Figure 7. STN for stage 1 of patent WO 2014/188248 A1

In order to perform this step a reactor is required. The components and subcomponents of this piece of equipment will be discussed during this process synthesis discussion. A diagram of the equipment required, and significant data of the

process is shown in Figure 8. Notation and colours used during the explanation is referred to the one in the Figure 8.

First of all, two separate pre-mixing are required. One of this mixing is done in the final reactor whereas the other needs to be performed in another container. From one side, MIBK is loaded in the reactor through piping and the solids are loaded from the top of the reactor one by one: K_2CO_3, KI and reactant A; all in N_2 atmosphere (R-01, black). On the other hand, in a separate tank component B and MIBK are pre-mixed and added to the reactor once the first mixing task is finished (R-02, black). A third mixing step is required to obtain the reaction dissolution once all the components are added to the reactor. Given the nature of the components, no particular mixing equipment is required, and a standard mixer for the dimensions of the vessels is assumed to achieve the desired results (R-01, black).

The solution is brought to reaction temperature. To do so, the reactor selected is a half-pipe jacked reactor using between 4 to 6 bar steam as a heating fluid. For both heat transfer area and mixing conditions, uniform temperature distribution inside the reactor is assumed as long as the proper volume level is maintained (between 40-100%).

In the patent, temperature is set between 80 to 90 ºC. Even though the lack of thermodynamic and kinetics data for the reaction, it is well known that there are a wider variety of measures to control temperature in an industrial scale in comparison to laboratory experiments. For this reason, reaction temperature is selected to be the highest value presented in the patent, 90ºC. Thanks to that and the better temperature control it is assumed that reaction kinetics are enhanced, and reaction time might be decreased reaching the same conversion values as in the patent. All in all, time is considered to decrease by 15%, reaching the 40h reaction time.

Once the reaction is over, the resulting product is washed with water. Water is fed by pipe to the reactor and after mixing with the solution two phases are formed. Thanks to the difference in densities between MIBK (802 kg/m^3) and water (1000 kg/m^3) the aqueous phase can be removed from the vessel through sedimentation from the bottom of the reactor (R-01).

Note that an initial cooling step is avoided in comparison to the patent. Once the reaction is finished, heating is stopped and the addition of cool water for washing is enough for this first reduction of temperature by quenching. Note that, despite in the patent various washing steps are stated it is assumed that a singular stage with the

maximum proportional volume presented (1.75 m^3) is enough to obtain the required results.

The reaction medium is then cooled down to the temperature of 40ºC by means of the same half-pipe jacket used for the heating. In this case, cooling is performed by cooling tower water. Same assumptions for mixing and uniform temperature distribution for previous steps are assumed for this one.

A HCl 33% w/w solution is added to the reaction vessel keeping temperature at 40ºC. In order to achieve this, HCl feed pipe is electrically heated to reach the reaction temperature. As the amount of HCl is not as big as the other dissolution volumes and the target temperature is not considerably high, this kind of heating can be assumed for this step. The acidification process presented in the patent comprehends the addition of the acid dropwise, so in the industrial application, HCl is added intermittently in the reactor while mixing in order to achieve a dropwise-like operation (R-01, black).

Once the HCl addition is finished a two-phase system is obtained. By means of the same principle as stated in previous steps, the two phases are separated through sedimentation. In this case though, the organic phase is discarded (top phase) thus, aqueous phase (bottom phase) is needed to be transferred to a new container. In this second reactor (R-02, blue), the aqueous phase is washed with MIBK. For this step, two washing cycles are considered enough to achieve the necessary results instead of the 3 equal-volume cycles stated in the patent.

While the washing step is done, the reactor keeping the organic phase is emptied and cleaned to be used again, discarding this phase and leaving it for residue treatment (R-01, black). On the second reactor (R-02, blue), the aqueous phase is transferred again to the clean reactor (R-01, blue) and the MIBK for washing is discarded and sent to residue treatment. This is the first washing step.

The second washing step is performed the same way but switching reactors. Now the aqueous phase is loaded in reactor R-01 where MIBK is added again. Once washing is finished, the aqueous phase is transferred to the clean reactor R-02 (green) and the remaining organic phase is discarded proceeding the same way as stated previously for residue treatment. The washed aqueous phase is kept in reactor R-02 for the following process steps.

The temperature through the process is kept at 40ºC and MIBK is added again for the basification step (R-02, green). NaOH 30%wt is added the same way as for the HCl, meaning same kind of pipe heating and intermittent addition. Once the solution is

basified, two phases are formed, and aqueous phase is discarded by the same means as it has been done in the previous two-phase separation steps.

After a final washing step with water by the same means of the previous washing steps, the resulting solution is distilled to obtain dehydro-ivabradine in an oil form. Regarding the volumes managed throughout the process and considering the MIBK must be evaporated, resulting in the obtention of dehydro-ivabradine in the residue of the column, the first solution to think about is the batch-stripper-like configuration. In a batch stripper, feed stream is charged to the top of the column (distillate) and the products are obtained through the bottom (residue). Even though this configuration is considered suitable for processes where the amount of product in the residue is low compared to the amount of component evaporated, it has not had the popularity and wide application of classic batch distillation. Due to lack of thermodynamic data for the patent studied and the poor industrial development and application of stripper batch distillation, a less optimal distillation solution as is classic batch evaporation is selected in this case (Korovessi and Linninger 2006).

In addition to that, the differences in properties to the organic solvent MIBK in comparison to dehydro-ivabradine makes it assumable that this separation is not complex. Furthermore, there are no composition requirements for the distillate so the column can be operated with a single stage to perform evaporation.

The distillation solution consists in a column attached to the reactor used in the previous steps (R-02 and CL-02, green). During evaporation operation the reactor acts as the reboiler, by means of the same heating set-up used previously, the residue is obtained from the reactor and the distillate from the top of the column.

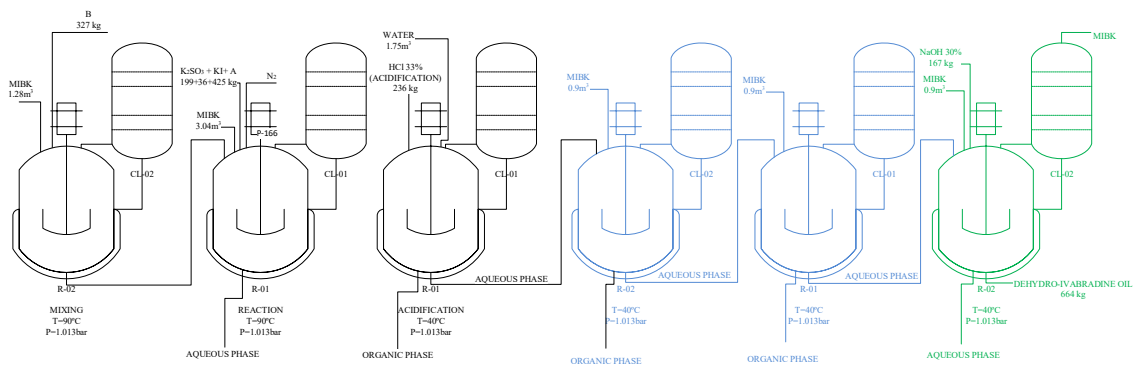

Figure 8. Equipment selection for stage 1

Balances for stage one are summarized in Table 2

Table 2. Balances for Stage 1

Compound	Quantity [kg]	Quantity [kmol]	Volume [m^3]
A	425	1.44	-
B	327	1.58	-
K2CO3	199	1.44	-
KI	36	0.22	-
MIBK	3466	-	4.32
Water	1752	-	1.75
HCl (33%)	142	1.28 (pure HCl)	-
MIBK	749	-	0.93
NaOH (30%)	167	4.18	-
Dehydro-ivabradine	624	1.34	-

5.3. STAGE 2

The STN for the second stage of patent WO 2014/188248 A1 is showed in Figure 9. In this stage, dehydro-ivabradine hydrochloride salt is synthesized from the dehydro-ivabradine oil. For this step the total number of states is 13 and the tasks performed are 6. This synthesis has a reduced number of tasks to be performed in comparison to the first one but presents new problems to be resolved for the industrial application of the patent as it a crystallisation step. Despite the reduced number of tasks, assumptions are intended to reduce operational times too, as some tasks require a considerable amount of time to be performed

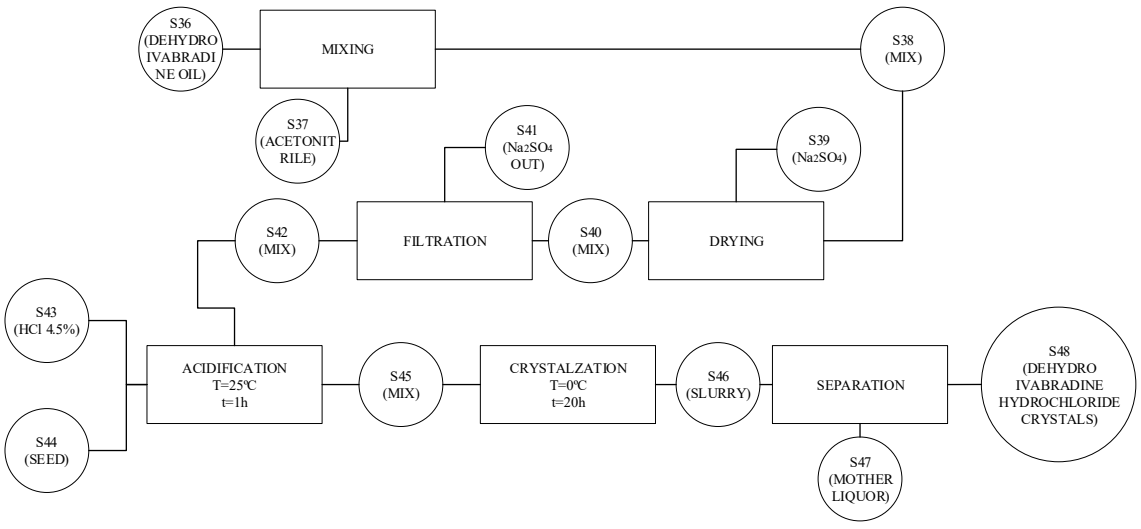

Figure 9. STN for stage 2 of patent WO 2014/188248 A1

A diagram of the equipment required, and significant data of the process is shown in Figure 10. Notation and colours used during the explanation is referred to the one in the Figure 10.

According to the patent, the resulting oil is diluted and evaporated in acetonitrile before being diluted again in acetonitrile. Considering the performance of the previous stage and the results obtained in the oil of dehydro-ivabradine, the first diluting and evaporation steps have a significant impact in the laboratory scale but is considered minor for the industrial application if solvent is properly evaporated. Considering that the evaporation of MIBK is enough to eliminate the solvent completely, this first dissolution in acetonitrile can be avoided in this stage. For this reason, dehydro-ivabradine oil is added mixed directly with the acetonitrile and dried with Na_2SO_4. This step is performed in the reactor R-01 (green) and the Na_2SO_4 is added in the solid form. Once the product is dried after mixing with the drying agent, the solution and the Na_2SO_4 must be filtered.

Filtration is performed by means of a commercial filter (F-01). The solution is passed through the filter before being loaded to the crystallization reactor (CR-01). This way, the crystallizer is loaded with the solution free of Na_2SO_4.

Several considerations must be taken into account in the crystallization step. According to the selected patent, crystallization is started at certain pH by the addition of HCl dissolved in acetonitrile. The feeding strategy selected for this material is the same as for the HCl or NaOH previously loaded in other reactors. The addition must be intermittent, so a dropwise-like operation is achieved.

The crystallization vessel is equipped with an anchor-like impeller capable of scrubbing the inner walls of the reactor for removing the crystals that might form on it. The agitation mode is assumed to reach a considerably uniform temperature distribution and perfect mixing. Moreover, as for the other reaction equipment used, the crystallizer has a half-pipe jacket capable of being fed with different heating fluids. As the crystallization is performed at 0-5ºC the cooling fluid will be a water-glycol mixture. Final operation temperature is set to 0ºC. Once crystallization is finished, the addition of water for cleaning inside the reactor will dilute the crystal leftovers that might be stuck on the walls of the reactor helping the cleaning tasks.

According to literature, crystallization can be performed through different methods: cooling (as stated in the patent), concentration of the solute by evaporation or addition of a reagent. Furthermore, a combination of different factors can be used. For example, evaporation and cooling in order to obtain a more concentration solution that will start crystallizing easier once is cooled down. Whereas cooling has an easier implementation in the industrial scale, as mentioned when talking about temperature control, the evaporation process presents further difficulties once brought in the industrial scale (Korovessi and Linninger 2006).

For these reasons, due to the lack of solubility data, the most feasible solution considered for this industrial application is crystallization by cooling. Evaporation is discarded for its difficulties in the industrial application plus the increase in operational times. The need of evaporating and cooling the solution not only once but several times might increase the operational time dramatically for this stage and this means a considerable withdraw in the studied process. All in all, the cooling method is assumed to be the best method for this process thanks to its easy industrial application and simple operation to obtain the desired results as well as it is the proposed method in the patent.

It has to be noted that the mechanism for the process proposed in the patent is a combination between precipitation of the product due to pH, due to the addition of HCl making the amine insoluble and crystallization by cooling, helped with the addition of a seed of the crystals.

Finally, a seed is added for the crystallization to trigger. Even though in the patent the seed is added halfway with the HCl solution, it is considered more suitable to add the seed once the reactor is cooled down to the crystallization temperature. In this case, the seed is mixed with acetonitrile to obtain a slurry like feed to be added to the reactor, enhancing the mixing and the start of crystallization in the reactor. This stream must be fed as near to the stirrer as possible in order to perform a good distribution of the seed all over the reaction vessel. This is presented in the literature as one of the best ways to add a seed in the industrial scale without a major perturbation in the system (Korovessi and Linninger 2006).

Although this operation is stated to last for over 24h, the different considerations taken, the lower temperature set, the mixing conditions and the seed addition gives the change to consider a decrease in crystallization time by around a 15%, reaching 20h of crystallization obtaining the same results as stated in the patent.

The resulting slurry is filtered by a suitable commercial centrifuge (CN-01) assuming a 10% of the product is lost in the mother liquor. Mother liquor is discarded and sent to residue treatment. Filtration is performed in similar conditions to the previously used centrifuge.

Dehydro-ivabradine hydrochloride crystals are obtained.

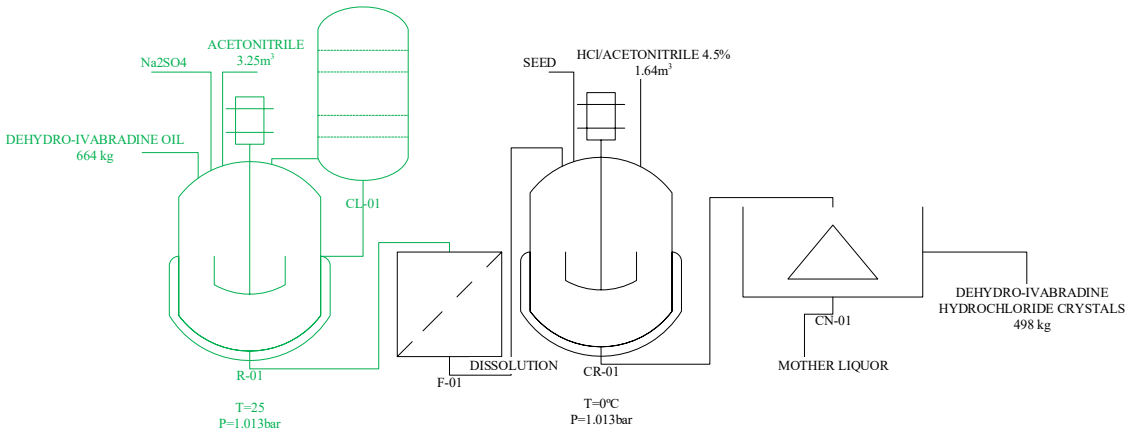

Figure 10. Equipment selection for stage 2

Balances for stage one are summarized in Table 2

Table 3. Balances for stage 2

Compound	**Quantity [kg]**	**Quantity [kmol]**	**Volume [m^3]**
Dehydro-ivabradine	624	1.34	-
Acetonitrile	2556	-	3.25
HCl (4,5%) acnitrile	1347	1.66 (pure)	-
Dehydro-ivabradine HCl	498	0.99	-

5.4. STAGE 3

The STN for the third stage of patent WO 2014/188248 A1 is showed in Figure 11. In this stage, ivabradine hydrochloride salt is synthesized from the dehydro-ivabradine hydrochloride crystals through a hydrogenation reaction. For this step the total number of states is 14 and the tasks performed are 5. This synthesis includes a crystallization with many similarities to the one performed in the previous stage but adds a hydrogenation step with interesting outcomes in its industrial application. As for previous steps, operational time is still trying to be reduced.

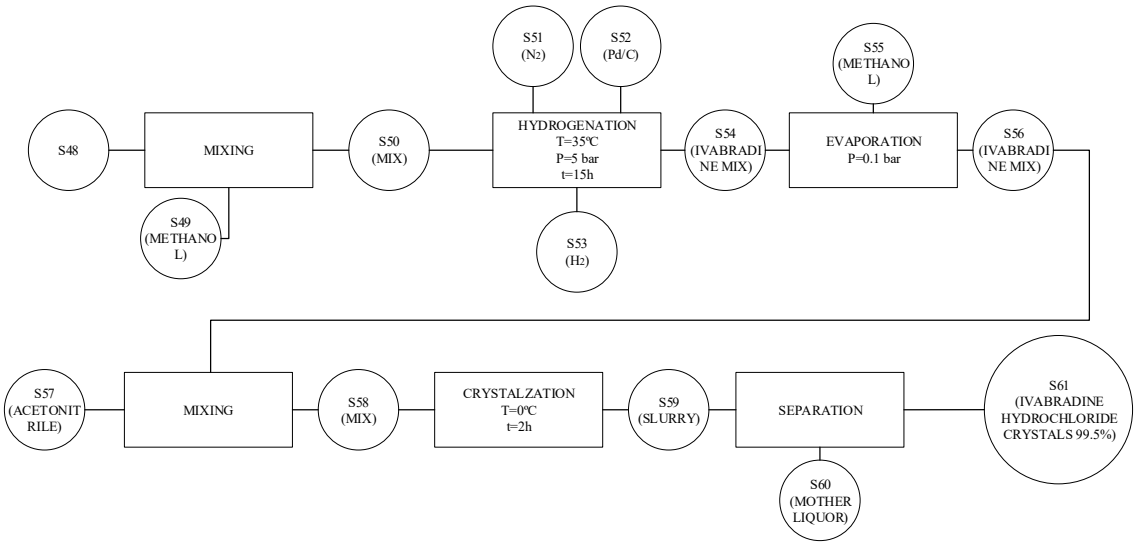

Figure 11. STN for stage 3 of patent WO 2014/188248 A1

A diagram of the equipment required, and significant data of the process is shown in Figure 12. Notation and colours used during the explanation is referred to the one in the Figure 12.

Stage 3 of the synthesis of ivabradine hydrochloride consists of a hydrogenation reaction, for this reason, a commercial hydrogenation reactor is required (R-03). According to the complexity and differences of hydrogenation reactions in comparison to other industrial processes, it has been considered the need of a hydrogenation reactor exclusively for this step. The vessel is not used in any other task of the process except for this reaction.

The hydrogenation reactor is inertized in nitrogen atmosphere and loaded with methanol by piping. Base reactant obtained in the end of stage 2, dehydro-ivabradine hydrochloride crystals are loaded into the hydrogenation reactor and mixing is activated until dissolution is achieved. The Pd/C catalyst is now loaded to the reactor.

Hydrogen is now loaded into the reactor until 5 bars of pressure are reached and the temperature is set to 35ºC. Highest temperature and pressure values presented in the patent are selected.

Hydrogen is fed into the reaction vessel from the bottom using a disperser. The mixer of the reactor is so that enables recirculation of the unreacted gas enhancing reaction conditions and conversion. The inlet of hydrogen is controlled by pressure and added continuously as the gas is consumed and pressure drops.

Heat exchange is performed with an internal heat exchanger as presented in the more common commercial solutions for hydrogenation reactors. Two tube bundle internal heat exchangers are the more feasible solution for the reactor needed in this step.

For the temperature and pressure set, mixing equipment and heat exchange method set, a good distribution of mass and temperature is assumed. In addition to that, control of the reaction conditions in a commercial reactor could be better in comparison to the laboratory set-up presented in the patent. As a result, conversion is enhanced, and reaction times can be reduced obtaining the same results in terms of yield and purity of the product. Thus, reaction time is reduced from 18h to 15h.

The solvent, methanol, requires to be evaporated, so resulting product is transferred to the reactor with the distillation column attached, R-01 and CL-01 (red). Despite the properties between the components to separate are different enough to perform an easy separation, raw ivabradine hydrochloride might be sensible to high temperatures. For this reason, evaporation cannot be performed in the same conditions as stage 1 even though same equipment is used. As a consequence, the solvent is distillated at reduced pressure as proposed in the patent. As a pressure value for operation is not mentioned, a safety value of 100mbar is set. At this value, it can be guaranteed that methanol boiling point in the dissolution is low enough to be evaporated at 35ºC (reaction temperature on the previous step), avoiding product decomposition. Moreover, it can be assured that, at this temperature and pressure, methanol in dissolution can be evaporated completely leaving the product free of methanol presence.

The patent proposes a new dissolution step with acetonitrile. This step is performed in order to eliminate the residual methanol from previous step and perform the crystallization free from methanol. This step has significant impact on laboratory scale, but it is considered that it can be avoided in an industrial scale due to the reduce pressure distillation performed previously. It is considered that, thanks to the conditions in which the evaporation is performed (100mbar) the totality of methanol is eliminated and no further stages for its elimination are required.

Once distillation of methanol is performed, product is fed to the crystallization vessel (CR-01, blue) and diluted with acetonitrile in order to perform crystallization. Crystallization conditions are kept the same as in the other crystallization steps.

Due to the lack of solubility data, the most feasible solution considered for industrial application is crystallizing by cooling setting final operation temperature at 0ºC and 2 hour operation. In addition, lack of data in the patent notes a further study need to be performed in order to obtain optimal values for temperature and time, even though temperature set is supported by other patents already (Westheim and BV 2013). As a particular crystal size is not required, a low temperature is set in order to enhance nucleation and a quick formation of crystals to shorten operation times. These assumptions are supported by the different literature presented previously in addition to the selected patent.

Once crystallization is over, the slurry is centrifugated to discard excess solvent.

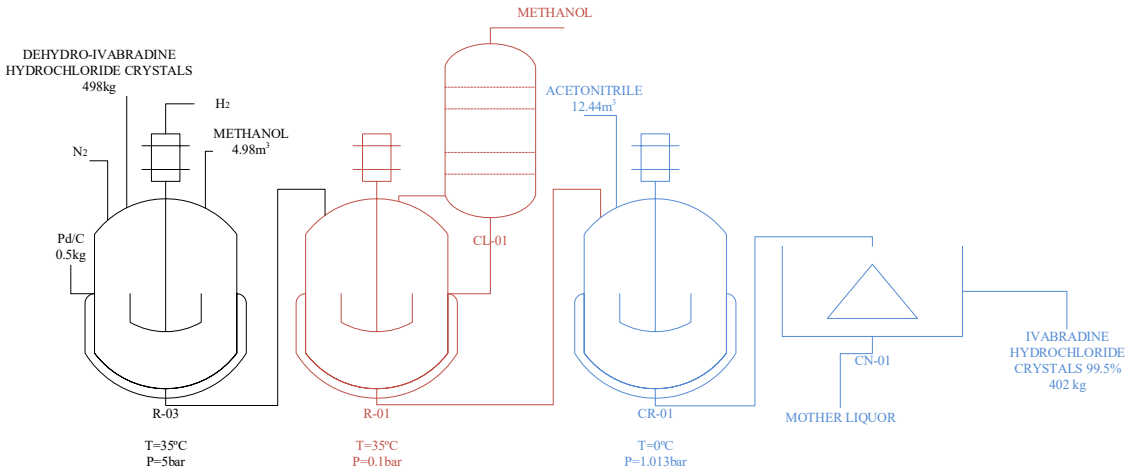

Figure 12. Equipment selection for stage 3

Balances for stage one are summarized in Table 4

Table 4. Balances for stage 3

Compound	**Quantity [kg]**	**Quantity [kmol]**	**Volume [m^3]**
Dehydro-ivabradine HCl	498	0.99	-
Methanol	3940	-	4.98
Catalyst	$492 \cdot 10^{-3}$	-	-
Hydrogen	2	0.99	-
Acetonitrile	9777	-	12.44
Ivabradine HCl (99.5)	402	0.79	-

5.5. STAGE 4

The STN for the fourth stage of patent WO 2014/188248 A1 is showed in Figure 13. In this stage, ivabradine hydrochloride salt from previous stage is dissolved, washed and crystallized again to obtain higher purity crystals. For this step the total number of states is 16 and the tasks performed 8. The steps are significantly less than in other stages, but its importance is still high in order to obtain a pharmaceutical quality product. As stated previously, the most efficient path is studied in terms of operational time.

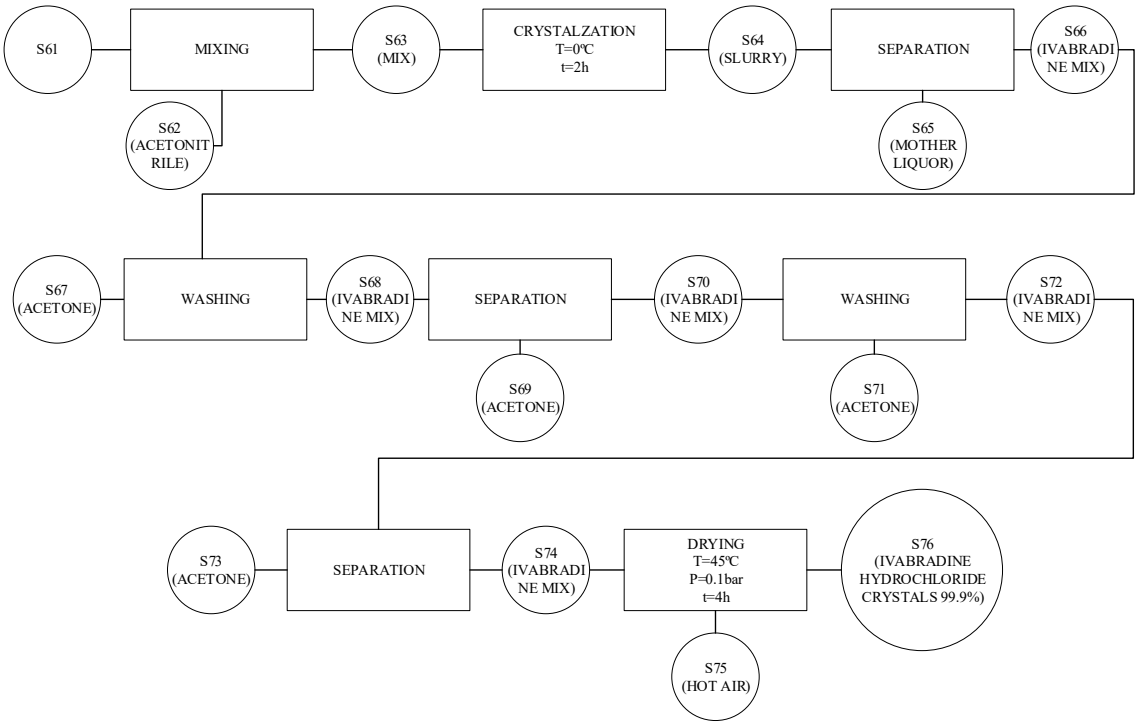

Figure 13. STN for stage 4 of patent WO 2014/188248 A1

A diagram of the equipment required, and significant data of the process is shown in Figure 12. Notation and colours used during the explanation is referred to the one in the Figure 14.

The centrifugated ivabradine hydrochloride is loaded to the reactor filled with acetonitrile to perform a new dissolution (CR-01, green). Ivabradine hydrochloride is crystallized in the same conditions as in stage 3.

Once crystallization is over, the slurry is centrifugated (CN-01, blue) to perform a first drying step for the obtention of the purified ivabradine crystals by the same means as previously performed centrifugation. Mother liquor is discarded and treat as a

residue. Furthermore, during centrifugation the crystals are showered with acetone for the elimination of impurities in two washing steps. Note that acetone is used due to its insolubility with ivabradine crystals. Once the first acetone washing is over, the product is centrifugated to eliminate acetone and showered again with acetone before being finally centrifugated.

A final drying step requires to be performed in order to obtain the pure crystals with complete removal of acetone, acetonitrile and any other solvent leftover to assure pharmaceutical quality product. According to the patent, a 24h drying step at 60ºC needs to be performed but, due to the long operational time, alternatives are considered. According to literature, drying can be performed at 85ºC for 4 hours reducing dramatically the time of this operation and the one for the production of the batch (Westheim and BV 2013). Nevertheless, as presented in the literature review, drawbacks are shown for drying at high temperature for the risk of product decomposition. Finally, considering the different alternatives, reduced pressure conditions are the more suitable ones in order to reduce operation times and avoiding high temperatures that might be problematic to achieve during operation in the dryer. In conclusion, temperature is set to 45ºC, 100mbar and 4 hours considering the complete elimination of acetonitrile.

Drying can be performed in different equipment according to literature. In this case the most suitable equipment are the drum dryer and the tray dryer. For the dimensions of the batch and drying time, the process selected is drum drying, as it is more suitable for big batches and shorter operation times. This way, the whole batch can be loaded simultaneously and can achieve operation conditions more effectively. Furthermore, this equipment presents a better performance for big volume batches and easier handling of the product in a rather shorter drying time. On the other hand, tray drying is also considered but it presents greater limitations in the handling of the product, loading and downloading times as well as dimensions and batch size. In addition to that, tray drying is more suitable for longer drying stages from 12-24 hours (Perry and Green 1997).

The centrifugated crystals are loaded in a drum dryer where they will stay for 4 hours with hot air setting an operation temperature of 45ºC. Once drying is finished, ivabradine hydrochloride crystals 99.9% purity free from acetonitrile are obtained.

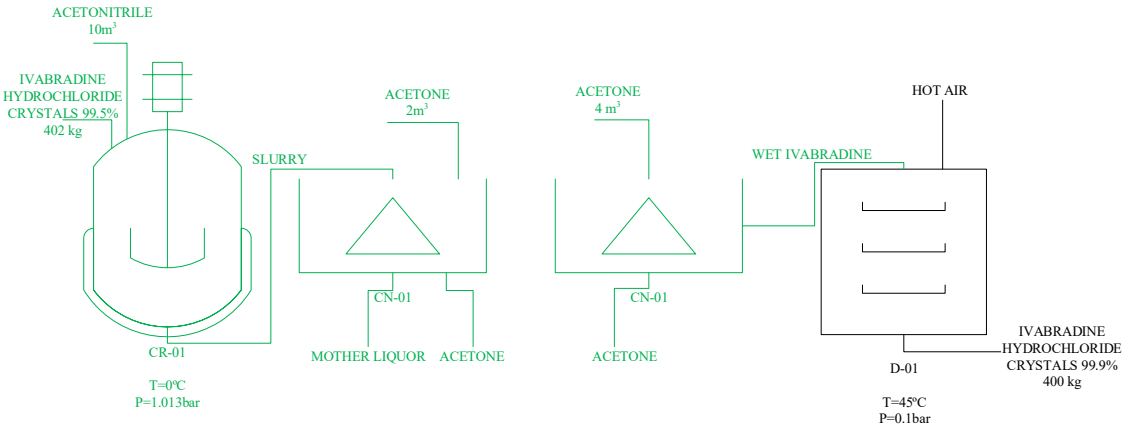

Figure 14. Equipment selection for stage 4

Balances for stage one are summarized in Table 5

Table 5. Balances for stage 4

Compound	**Quantity [kg]**	**Volume [m^3]**
Ivabradine HCl (99.5%)	402	-
Acetonitrile	7892	10.00
Acetone	4723	6.00
Ivabradine HCl (99.9%)	400	-

6. BASIC DESIGN

Designing a process for the manufacturing of a chemical industrially goes beyond the capacities and control of the engineer in charge of the design. The quantities of material, dimensions of equipment, and operation modes might be defined during the process synthesis and the calculations perfomed. Nevertheless, most of the times the equipment resulting from the engineering calculations and considerations is not the one that can be finally installed in the facility. Industrial equipment can be really expensive and neither manufacturers are keen to produce nor clients to buy specific designed equipment. Thus, industrial equipment is usually standarized, making it another consideration to take into account during the design to adapt the process synthesis to the commercial equipment available.

Once the process syntehsis is completed and all the unit operations for the manufacturing process are determined, as well as the main characteristics of the equipment, it is the moment to select the most suitable commercial solution.

The aim of this point is to provide the right reactors, columns, centrifuges, etc that can execute the process designed better.

The relevant technical data and other additional data for all the equipment selected below are presented in Apendix 1.

6.1. REACTORS

Reactors are usually the main element of a chemical process and need wide understanding in order to provide a feasible solution for the process studied.

In the process proposed for the manufacture of ivabradine, 4 different reactors are considered, withs its particularities: two differents size reactors with evaporation equipment attached (R-01 and R-02), a hydrogenation reactor (R-03) and a crystallizer (CR-01). Reactors R-01 and R-02, are multi-purpose and are used for different tasks, not only reaction but also evaporation, and filled with different reactants at differents stages of the process. CR-01 is not as all-purpose as the others as it is a more specific reactor used only for crystallization tasks, even though it can perfom three different crystallization steps. Finally, R-03 is a single-purpose reactor, used exclusively to perform the hydrogenation, as it is a sensible reaction that requires specific design.

6.1.1 Multi-purpose reactors: R-01 and R-02

Reactors R-01 and R-02, as stated before, are the most versatile pieces of equipment in the process. Its funcionts go from premixing to reboiler in a evaporation as well as the classic reactor operation for different steps like basification and acidification. In this case, two separate reactors are considered for various reasons inlcuding ocupation time and reactor size.

On the one hand, the longest operation of the process is the reaction step in stage one which takes over 40h. Thus, it is important to provide a second reactor in order to have some room in the planning and the operation of the reactors.

On the other hand, the operation of the process manage a wide range of volumes depending on the reaction or the task. As stated before, rules of thum provide on optimal occupation of the reactor going from 40-100% of the total volume. As a consequence, different reactor sizes are required for the different volumes managed.

All in all, according to the balances and quantites of product used, the sizes of the reactors might be of around 4 and 7 m^3. It must be noted that the sizes are tied to the market offer of reactors as the equipment will not be designed specifically for this application.

Furthermore, not only the sizes are important but the materials used for the equipment. The general consideration is to select an AISI304 or AISI316 material for the equipment, as the most general and standard steel for chemical applications with not singular considerations. Although this general concern, the solutions used in the different reactors vary in properties and they must be taken into account for the selection of the material.

In the studied case, acidification and basification reactions, which might be critical for some materials, are performed. These reactions are performed with dissolution of HCl 33% and NaOH 30% which represent a serious harm for the equipment even at low concentrations in the reaction vessel, once mixed with all the other components. For this reason, common stainless steels used as AISI304 or AISI316 are discarded in favour to enamel reactors.

Enamel reactors present an encouraging alternative to stainless steel for the use of corrosive reactants at wider range of concentrations and temperatures. Even though it might be harder to handle during operation for the risk of its fragility, it is the material selected for these reactors.

According to the commercial solutions studied by different equipment manufacturers, the most suitable solution for reactors R-01 and R-02, considering the balances of product are the *BE6300* and the *BE4000* by the *De Dietrich* (De Dietrich 2020a), with a nominal capacity of 6300 and 4000L, respectively.

The reactors are able to operate between pressure of -1/6 bar and at temperatures from -25 to 200 ºC both inside the reactor and the jacket, according to *De Dietrich*. This values fulfill all the requirements for the process for the different temperatures of operation as well as the vacuum conditions of some tasks. Furthermore, pressure for the vapor in the jaket can be assumed by the equipment. In addition to that, coating's chemical and thermal properties are suitable for the studied process, offering a great thermal shock resistance for the regular operation of the process.

6.1.2 Hydrogenation reactor: R-03

Hydrogenation reaction is of critical importance for the synthesis process as well as a complex reaction. For this reason, it has been decided that the hydrogenation reaction is completed in a reactor dedicated exclusively to this purpose. This way, it can be guaranteed that the rector selected is suitable for this process without taking into account other tasks, as well as, minoring the risk of possible breakdowns for excessive usage or not suitable components.

The most suitable solution selected is the one provided by manufacturer *EKATO*. In this case, a high-performance hydrogenation reactor is proposed. Hydrogen is fed from the bottom of the reactor equipped with a primary disperser. In addition to that, the reactor is equipped with a self-aspirating turbine that recirculates the unreacted hydrogen from the head space in order to provide enough reactant and ideal conditions for the reaction at every moment (Ekato 2020).

Further and specific study of the reactor is required by the manufacturer to obtain the optimal design and operation, but the volume for the reactor is 6 m^3.

6.1.3 Crystallizer: CR-01

Crystallizer is an important piece of equipment for the process as three crystallizing tasks are performed and the final product is manufactured in crystal form.

As in other reactors for the process, in this case the selected equipment is a coated reactor for crystallization. In addition, an anchor-like impeller is used for the mixing of the slurry. The total volume of the equipment is 16 m^3. The volume gives great

versatility among the different tasks to be performed as there is great variability in the volumes managed. It is assumed that the different tasks can be performed. The equipment is provided by the manufacturer *Pfaudler*, a reactor of the series *BE16000* (Pfaudler 2020b).

The *BE16000* by *Pfaudler* provides a suitable reactor for this process with a range of pressures between -1/6 bar and temperatures -25/200 ºC, right for the operating values on the three crystallizations performed. Furthermore, this series of reactors allow the change of the agitator according to the process and the features required at a certain step of it that, together with the wide number of different agitators to choose, is assumed to provide the desirable results. The selected agitator is the *ANC Anchor*, which provides the suitable mixing and thermal exchange for the process studied. Even though, different alternatives can be studied depending on the crystallization for the optimal operation (Pfaudler 2020b, 2020a)

6.2. EVAPORATION COLUMNS

Evaporation is required at certain points of the process in order to evaporate a solvent. As it is stated in the process synthesis, the evaporation steps are performed in reactors R-01 and R-02 at the defined conditions.

6.2.1 Evaporators CL-01 and CL-02

Columns for evaporation are required for the two selected reactors R-01 and R-02 and are coded as CL-01 and CL-02. The operation of these columns is the direct attachment to the defined reactor, where each of these reactors acts as the reboiler.

The operation of the column is simple given the characteristics of the solvents to evaporate and the differences with the other compound to be separated. In this case, the solvents are methanol and acetonitrile which have a low boiling point that simplifies the conditions of the evaporation. For this purpose, equipment selected will be structured packing columns performing a single-stage evaporation in a 2 m high column.

Manufacturer *De Dietrich* provides a solution for this separation with the patented structured packaging *DURAPACK*® The structured packing provides an increase in the area of the column in order to maximize the mass transfer. Built in borosilicate glass 3.3 it is assembled with 200mm height layers of corrugated plates with notches positioned alternatively with channels at an angle of 45º. In addition to that, the packing of the

column provides a better performance avoiding splashing of the liquid phase along the column.

According to *De Dietrich* portfolio and the technology presented, columns for batch operation and vacuum conditions are provided (De Dietrich 2020b). The most suitable model is the *DIN600*, a 5m high column with 600mm diameter built in *QVP® glass* (De Dietrich 2020c).

A column is set for each of the mentioned reactors building the tandem R-01-CL-01 and R-02-CL-02, as represented in the presented diagrams. The same provider has been selected for both the reactor and the column in order to assure perfect fitting between the equipment.

6.3. CENTRIFUGE

Centrifuges become of pivotal importance in crystallization related synthesis processes as the valuable solid product is kept inside the liquid mother liquor. The separation of the solid crystals from the slurry and the importance of obtaining a product significantly drier for the following steps of the process.

In the proposed process, 3 different crystallization operations are performed and, as a consequence, the use of a centrifuge, CN-01, is required. It has to be noted that the 3 crystallization operations comprehend two different products crystallized, as well as, different quantities of crystals and volumes of slurry to be processed. Thus, the centrifuge selected must have certain versatility and be able to process different products in a single piece of equipment.

Moreover, the final crystallization stage includes two washing operations by means of showering the obtained crystals with acetone, so the centrifuge must include these features in its design.

6.3.1 Centrifuge: CN-01

According to the synthesized process, the centrifuge must be able to process two different products, dehydro-ivabradine hydrochloride and ivabradine hydrochloride crystals. On the one hand, for dehydro-ivabradine hydrochloride the dry quantity to be treated is 498kg and a volume of over 5m^3 of dissolution. On the other hand, for the case of ivabradine hydrochloride crystals, the dry quantity treated is 400kg and a volume of over 12.5 m^3 and 10m^3 for 99.5 and 99.9% purity respectively. Furthermore,

for the ivabradine hydrochloride 99.9% purity, a total amount of 6 m^3 of acetone divided in two cleaning steps of 2 and 4 m^3 respectively has to be considered, too.

Once studied different commercial alternatives, the most feasible option is the equipment provided by the manufacturer *Riera Nadeu*. The different models offered are oriented to operate in different processes of the chemical industry and a specific model dedicated for pharma plants. The model selected is the *700F* from the series *RINA Serie 700 Pharmaceutical*. In particular, the model selected is 1400mm, which is able to proceed a cake weight maximum capacity of 690 kg which is enough for the quantities required to proceed (Riera Nadeu 2020).

In addition to this, these centrifuges offer the possibility of washing the crystals in the centrifuge by showering the desired component, in this case, acetone.

6.4. DRYER

Due to its big energy demand, the drying stages are performed to the end of the process to avoid, to the extent of possible, drying big quantities of product that will be wet again. For this reason, drying is avoided until the final step of the process so that a quality product is achieved at the end of it reducing the amount of energy used for drying.

6.4.1 Drum dryer: D-01

According to the process studied, the dryer D-01 is required to perform the drying of ivabradine hydrochloride crystals at the end of the process, resulting in 400kg of dried crystals. Industrially, the most common solutions comprehend tray and drum driers. Thus, both solutions are studied. On the one hand, tray driers offer a better performance in long period drying stages but present drawbacks in the quantities managed as well as the handling, loading and unloading of the product. On the other hand, drum driers offer an easier handling and bigger volumes to process but are less suitable for long drying operations (Perry and Green 1997).

Based on the alternatives, the quantities and operation time, the most suitable equipment selected is the use of a drum drier. In accordance with the commercial alternatives available nowadays, the equipment selected is the vacuum drum driers provided by *OLSA*. Selected equipment offers a solution for pharmaceutical industry able to operate in vacuum conditions in order to dry at lower temperature minoring the risk of decomposition of the product treated. Moreover, always according to the

manufacturer, good homogeneity in the final product and easy operation and fast operation can be achieved.

The commercial model selected is *DMX-3*, offering a maximum loading weight of 550kg, which is considered sufficient for the obtention of the final 400kg of dry ivabradine hydrochloride. The operation is 4 hours long at the conditions of 100mbar pressure and 45ºC drying temperature. It is considered that at the set conditions the totality of the acetonitrile present in the crystals is eliminated, obtaining a product of the required purity for the pharmaceutical application (OLSA 2020c, 2020a, 2020b).

7. PRODUCTION PLANNIG

The obtaining of a well-designed process, the performance of operations and the management of the equipment usage are of pivotal importance in order to obtain the desired results without conditioning the operation of the plant. On an industrial scale, in addition to a developed process synthesis and the optimal operation conditions, planification is a key component for increasing productivity. Once the manufacturing process is well performed and the set objectives of production are achievable, it is time to optimize any aspect of the process susceptible in order to obtain the mentioned increase in production.

As mentioned, despite being usually forgotten in the designing stages of a chemical process, one aspect that provides a great margin of benefits if optimized with little investment is production planification and programming. The study of the timings of the chemical synthesis, not only in one batch but in all the production over a certain period of time, can give great outcome with little effort. For this reason, good planification of the batches or campaigns produced over a year can provide great benefits both in annual production and resource exploitation.

The aim of this point is to study the alternatives of campaign planification during a year to obtain an increase in the annual production of the designed process for ivabradine manufacture.

For the study provided below, some concepts and equations need to be defined.

The occupancy time (OT_j) is the time at which an equipment *j* finishes the process *i* that performs and is ready to be used again. Batch time (Bt) is the required time to produce a single batch. Cycle time (Ct) is the time required to finish a cycle, understood as the difference between the end (t_e) and the start (t_s) of two subsequent batches, as shown in equation (4). Cycle time can also be calculated as the maximum value of occupancy time of an equipment in a batch as shown in equation (5)

$$Ct = t_e - t_s \tag{4}$$

$$Ct = max\ (OT_j) \tag{5}$$

Finally, the makespan (Mt_N) is the time required to produce an amount of *N* batches, as shown in equation (6). Where N is the number of batches of a certain campaign, Bt is the batch time and Ct is the cycle time.

$$Mt_N = Bt + (N-1)\,Ct \quad (6)$$

There can exist different strategies in production planification, in this case, overlapping and non-overlapping planification are presented. On the one hand, non-overlapping strategy consists in a restriction in which a new batch cannot be started until the previous one is finished, being the batch time the hindrance for increasing production. On the contrary, on an overlapping planification this restriction disappears, and a batch can start before the previous one is finished. In this last case, the batch time decreases in importance and is the occupancy time of the equipment and the cycle time the ones that take relevancy.

7.1. ORIGINAL PLANNING

In the process developed for the manufacture of ivabradine, the occupancy times for the equipment and the batch time are defined based on the operation times of each stage and the different tasks performed.

Despite the great amounts of time managed for the different reactions and other operations performed, the process has to be divided considering the equipment used. Although the steps might take a lot of time, every piece of equipment only intervenes in certain moments of the process, with the possibility of being kept empty and without performing any operation for a long period of time. The right management of these different times, the equipment alternatives and the scheduling of the tasks is where a major gain of time and productivity can be achieved.

For this reason, a detailed study of the timings of the tasks as well as the occupancy times for each equipment in each step is performed. For this purpose, some assumptions are made:

- Loading and unloading tasks are considered to last 0.25 hours for each component loaded or unloaded. For the case of slurries, a higher value of 0.5 hours is assumed.
- During unloading and cleaning of an equipment, the operation in the following unit can start even though this step is not finished. Unloading time is considered in the loading task of the next unit.
- Premixing and mixing tasks are assumed to be 0.25 hours for each mixing operation performed.

- Heating and cooling tasks go from 0.5-1 hour depending on the temperature and the quantity of material affected
- Cleaning operations last for 1 hour for general equipment and 1.5 hours for the crystallizers
- The second and third crystallization task are assumed to last for 2 hours
- All other operations times: reaction, crystallization, drying, etc. are defined in the process synthesis.

All the occupancy times for each unit and stage, as well as the time for loading-operation and unload-cleaning times, is summarized in Table 6. The times are divided according to the order in which the different units are used in the studied process.

Table 6. Value of operation times for each stage and unit

STAGE	Unit	t [h]		t_i [h]		OT_j [h]
		Start	End	Load + Operation	Unload + Cleaning	
1	**R-02**	**0.00**	1.50	0.75	0.75	1.50
	R-01	0.75	47.00	45.25	1.00	46.25
	R-02	46.00	48.00	1.00	1.00	2.00
	R-01	47.00	49.00	1.00	1.00	2.00
	R-02	48.00	52.75	3.50	1.25	4.75
2	**R-01**	51.50	54.50	2.00	1.00	3.00
	CR-01	53.50	77.00	21.50	2.00	23.50
	CN-01	75.00	79.00	3.00	1.00	4.00
3	**R-03**	78.00	96.00	16.75	1.25	18.00
	R-01	94.75	97.75	1.75	1.25	3.00
	CR-01	96.50	102.00	3.50	2.00	5.50
	CN-01	100.00	104.00	3.00	1.00	4.00
4	**CR-01**	103.00	108.50	3.50	2.00	5.50
	CN-01	106.50	112.25	4.25	1.50	5.75
	D-01	110.75	**117.75**	6.00	1.00	7.00

Once these timings are studied, the occupancy times for each equipment are summarized in Table 7. From these two analyses, the values for batch and cycle times can be easily determined.

Batch time is 117.75 hours and cycle time, according to equation (5), is the highest occupancy time, 97 hours.

Table 7. Occupancy time per unit

Unit	t_s [h]	t_e [h]	OT_j [h]
R-02	0.00	52.75	52.75
R-01	0.75	97.75	**97.00**
CR-01	53.50	108.50	55.00
CN-01	75.00	112.25	37.25
R-03	78.00	96.00	18.00
D-01	110.75	117.75	7.00

In the case studied, the original guess to perform the preliminary annual production and batch size is considered with a non-overlapping method, as well as the following considerations. The annual labor is set at 301 days (43 weeks) working at 3 shifts with operation 24/7. The designated 9 weeks of stop of production respond to the need of preventive maintenance done on a yearly basis and additional production breaks. For the non-overlapping method, it is considered that, every two batches, a break of 48 hours between the two-batch campaigns is done for deep cleaning and minor preventive and corrective maintenance purposes. All in all, these considerations suppose a production of 50 batches per year, resulting in a production of 20.000 kg of ivabradine hydrochloride, fulfilling the initial prediction of 18.5 tonnes per year with a buffer of 1.5 tonnes for any inconvenience, problems in operation and quality issues.

An example of the schedule of two batches in non-overlapping strategy is shown in Figure 15. The occupancy of each unit is shown with different colors according to the stage that is performed.

At this point, a further study in the planification is performed in order to obtain a better use of the equipment and planification to increase annual production and the productivity of the plant.

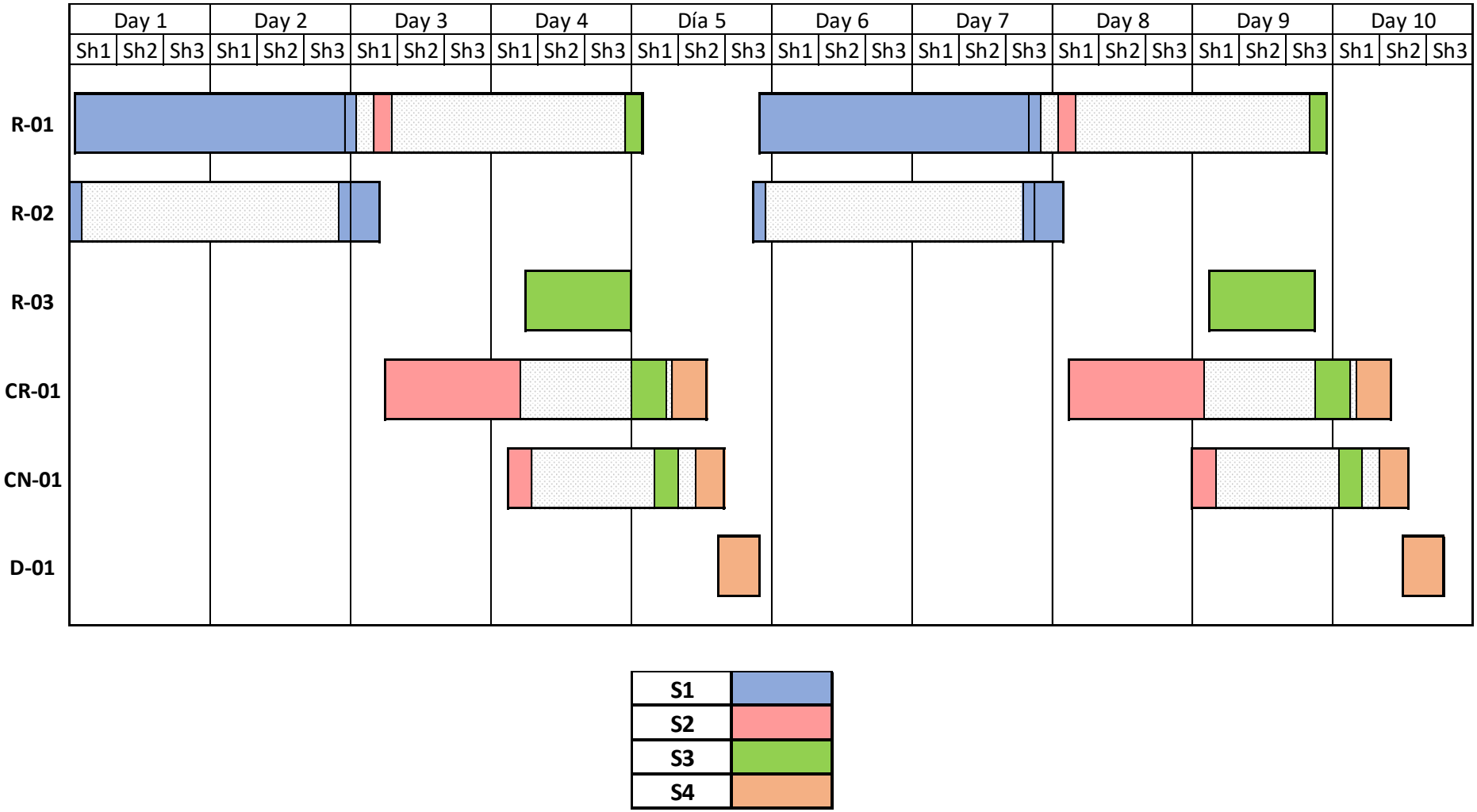

Figure 15. Schedule of two batches in non-overlapping strategy

7.2. OVERLAPPING PLANNING

In order to increase the productivity and the annual production the constraint of non-overlapping production is avoided. This way, new batches can be started before the previous one is finished, setting the start of the batch up to 20 hours before the start in the non-overlapping strategy.

In this case, the length of the production times corresponds to the length of each campaign. For example, according to equation (6), the makespan of a 50 batches campaign results in 203 days of production, in comparison with the 301 required with the non-overlapping method.

The time reduction is significant in this case but not reasonable. It must be considered that planned production breaks between batches are required for cleaning and maintenance purposes as defined previously. For this reason, different number of batches per campaign are considered. It must be noted that, for this kind of organization the three-shift schedule and the 24-hour operation takes importance, as it is the way of being able to overlap the different batches.

In addition, other advantages can be obtained with the overlapping mode, as the annual production will be achieved. For example, the use of campaigns of different length gives the flexibility to adapt the production to the day-to-day market requirements.

Taking all the considerations pointed, the most suitable solution for this case is to operate in campaigns of 5 batches, resulting in 10 campaigns for the obtention of the same production as with the non-overlapping planification. In this case, according to equation (6), the makespan is 21 days, with batch time=117.75 hours, cycle time=97 and N=5. Added with the 48-hour stop between campaigns, the annual production is of 65 batches (26 tones). In this case, the initial production set is achieved in 230 days of production.

The 5-batches campaigns are selected as a feasible schedule which allows the adaption of the production to market requirements, letting an increase or decrease in the number of batches per campaign if a rise in production is required. In addition to that, the significant growth in production, makes feasible the assumption of a bigger market share than the presented 15%.

An example of the schedule of two batches in overlapping strategy is shown in Figure 16. The occupancy of each unit is shown with different colors according to the stage that is performed.

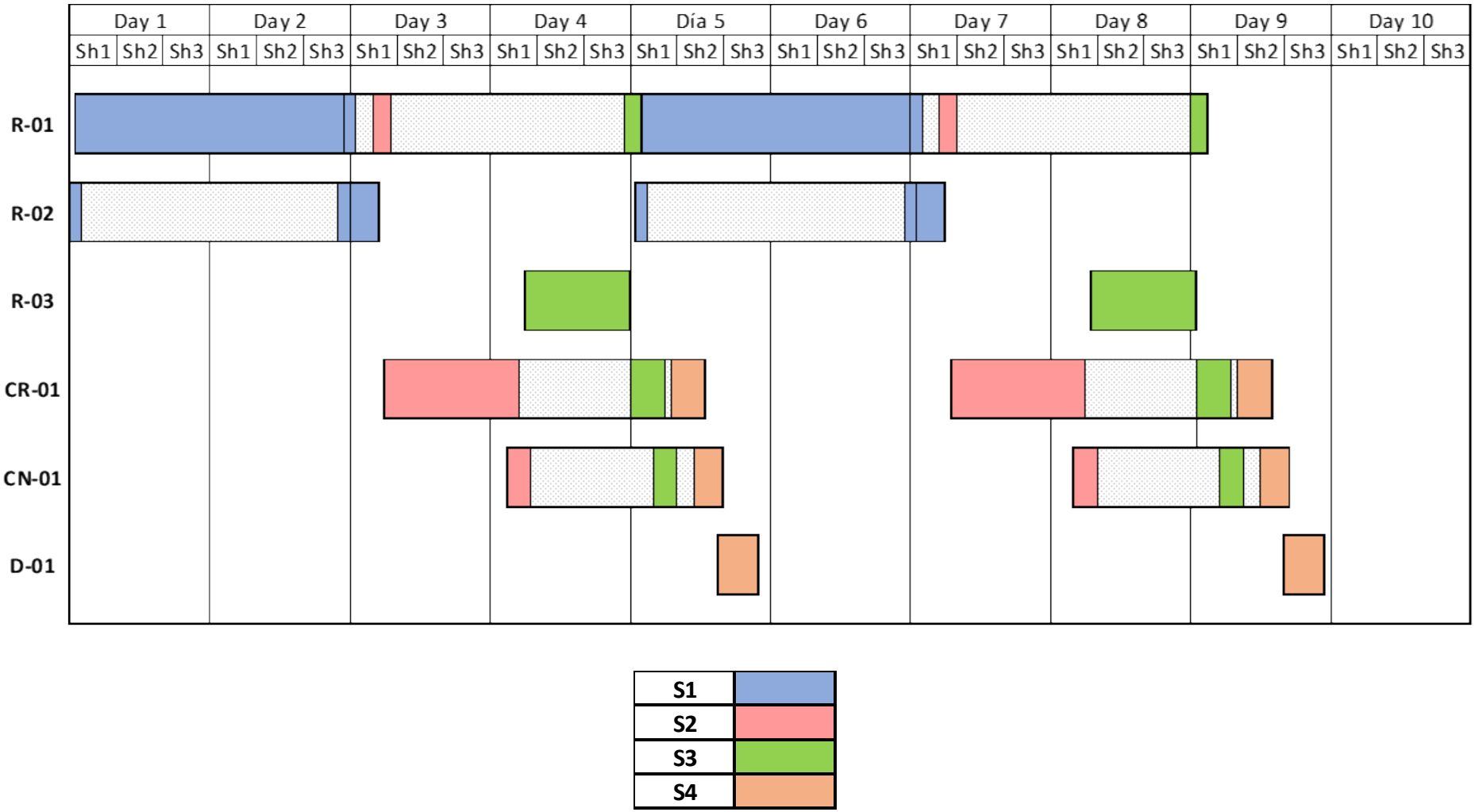

Figure 16. Schedule of two batches in overlapping strategy

8. CONCLUSIONS

- The literature review has determined the existence of several patents and processes for the manufacture of different ivabradine salts for pharmaceutical purposes. Despite the fact that a single patent was selected for the design of the industrial process, the existence of other paths has complemented the synthesis processes giving alternatives to find easier processes, less extreme conditions and safer compounds in order to meet both the synthesis and the production requirements.
- The process synthesis has resulted in a feasible process for the set production objectives according to literature, industrial experience and rules of thumb.
- The scale up from the patent and process synthesis to the industrial application has resulted in the selection of the suitable equipment considering size, industrial application and simple operation.
- The annual production objectives set have been met according to the equipment selection and the operation as well as the batch size determined.
- A planification study for one-year-long production has been performed resulting in alternatives for increasing the production with an overlapping scheduling strategy.
- Campaign-strategy alternatives have been shown for production increase resulting in 30% higher productivity and allowing the adaption of production to day-to-day market requirements.

9. FUTURE WORK

After the completion of the present project, further work can be performed on this topic which could not be included here:

- Development of experimental and simulation work for bigger accuracy in the selection of the suitable process, design of the selected equipment as well as more precise operation conditions and occupancy times determined.
- Further study of the production planification, identifying critical equipment for the synthesis process and proposing improvement beyond the overlapping strategy, such as duplicating limitation units. Thus, increasing production and optimizing resources.

10. NOTATION

%wt	Mass percentage
A	Figure 2. Compound A or 3-(3-chloropropyl)-7, 8-dimethoxy- 1,3-dihydro-2H-3-benzazepin-2-one
AF	Atrial Fibrillation
AHF	Acute Heart Failure
AISI	American Iron and Steel Institute
API	Active Pharmaceutical Ingredient
B	Figure 3. Compound B or (lS)-4,5-Dimethoxy-l.-[(methylamino)methyl] benzocyclobutane
BB	Beta-Blockers
BEAUTIFUL	MorBidity-moratlity EvAlUation of The I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction
Bt	Batch time [h]
CAD	Coronary Artery Disease
CL-01	Evaporation Column 1
CL-02	Evaporation Column 2
CN-01	Centrifuge 1
CR-01	Crystallizer 1
Ct	Cycle time
CVD	Cardiovascular Disease
D-01	Dryer 1
EMA	European Medicines Agency
F-01	Filter 1
FDA	Food and Drugs Agency
HF	Heart Failure
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
I_f	f Current
IST	Inappropriate Sinus Tachycardia
MeOH	Methanol
MIBK	Methyl Isobutyl Ketone

Mt_N	Makespan time for N batches campaign [h]
N	Number of batches of a campaign [-]
OT_j	Occupancy time [h]
P	Pressure [bar]
Pd/C	Palladium on Carbon catalyst 5%wt, (50% wet)
R-01	Reactor 1
R-02	Reactor 2
R-03	Hydrogenation reactor
SHIFT	Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial
STN	State-Task Network
T	Temperature [ºC]
t	Time [h]
t_e	Ending time [h]
t_i	Operation time [h]
t_s	Starting time [h]
US	United States of America
VAT	Value-Added Tax

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INDEX OF FIGURES AND TABLES

INDEX OF FIGURES

INDEX OF TABLES

APPENDIXS

APPENDIX A: COMMERCIAL EQUIPMENT TECHNICAL DATA

The technical data of the selected equipment provided by the different manufacturers, as well as addition information is presented below.

Appendix A.1: Reactor R-01 / R-02 and Columns CL-01/CL-02

The design for the reactors R-01 and R-02, provided by *De Dietrich*, in the series *BE4000* and *BE6300*, is shown in Figure A 1. Data is shown in Table A 1.

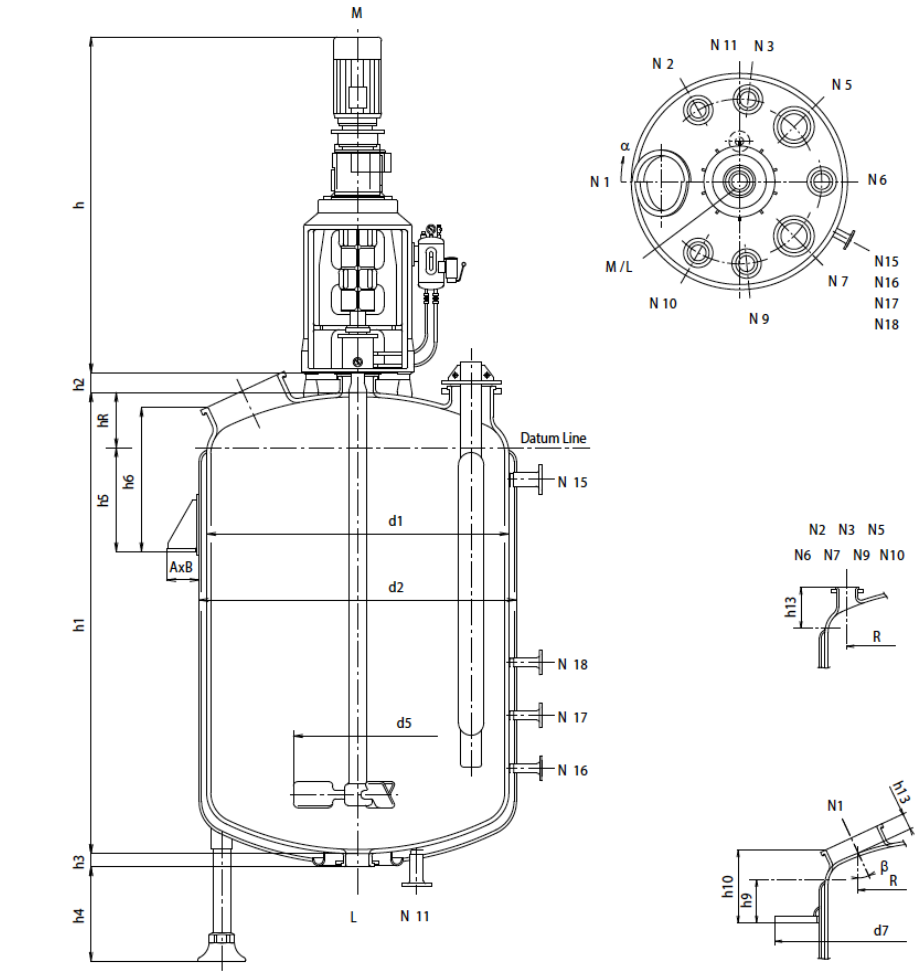

Figure A 1. BE series reactors parameters by De Dietrich

(image from (De Dietrich 2020a)*)*

Table A 1. Technical data reactor R-01 and R-02

			BE4000	BE6300
NOMINAL CAPACITY [L]			4000	6300
TOTAL CAPACITY [L]			5381	8204
JACKET CAPACITY [L]			560	712
HEATING AREA (WITH JACKET) [M^2]			13.4	18.1
MAIN DIMENSIONS [MM]		d1	1800	2000
		d2	1900	2100
		d5	750	850
		h1	2500	3050
		h2	130	130
		h3	70	85
		hR	330	365
NOZZLES ON VESSEL	M	DN	200	200
	L		100	150
	N1	DN/h13	500/150	500/150
		R/Beta	630/25º	700/25º
	N2		150/330	150/365
			725/65º	800/60º
	N3		150/330	150/365
			725/95º	800/95º
	N5		250/335	250/390
			675/135º	750/135º
	N6	DN/h13	150/330	150/365
		R/Alpha	725/180º	800/180º
	N7		250/355	250/390
			675/225º	750/225º
	N9		150/330	150/365
			725/265º	800/265º
	N10		150/330	150/365
			725/295º	800/300º
JACKET NOZZLE	N11	DN/alpha	50/90º	80/90º
	N15		50/208º	80/208º
	N16		50/208º	50/208º
	N17		50/208º	50/208º
	N18		-	50/208º
DRIVE		MDL Type	100	100
		h*	2155	2155

Selected equipment to perform the evaporation is two structured packing columns of height 2 m and diameter 0.6m also provided by manufacturer *De Dietrich*. The packing technology is *DURAPACK®,* technical data available by manufacturer can be found in Table A 2 and the structured pack in Figure A 2.

Figure A 2. Example of DURAPACK® element for the column structured packing (image from (De Dietrich 2020c)*)*

Table A 2. Technical data for structured packing DURAPACK® by De Dietrich

Diameter [mm]	600
Height [mm]	2000
Material	Borosilicate glass 3.3
Specific surface [m^2/m^3]	300
Density [kg/m^3]	400
Free area [-]	80%
Slope	45º
Max. shock temperature [ºC]	120
Thermal coefficient of linear expansion [K^{-1}]	3.25 x 10^{-6}

Appendix A.2: Reactor R-03

An example of the proposed design of the hydrogenation reactor provided by manufacturer *EKATO* with relevant components can be found in Figure A 3. Selected reactor volume is 6 m^3. No additional data was available by manufacturer.

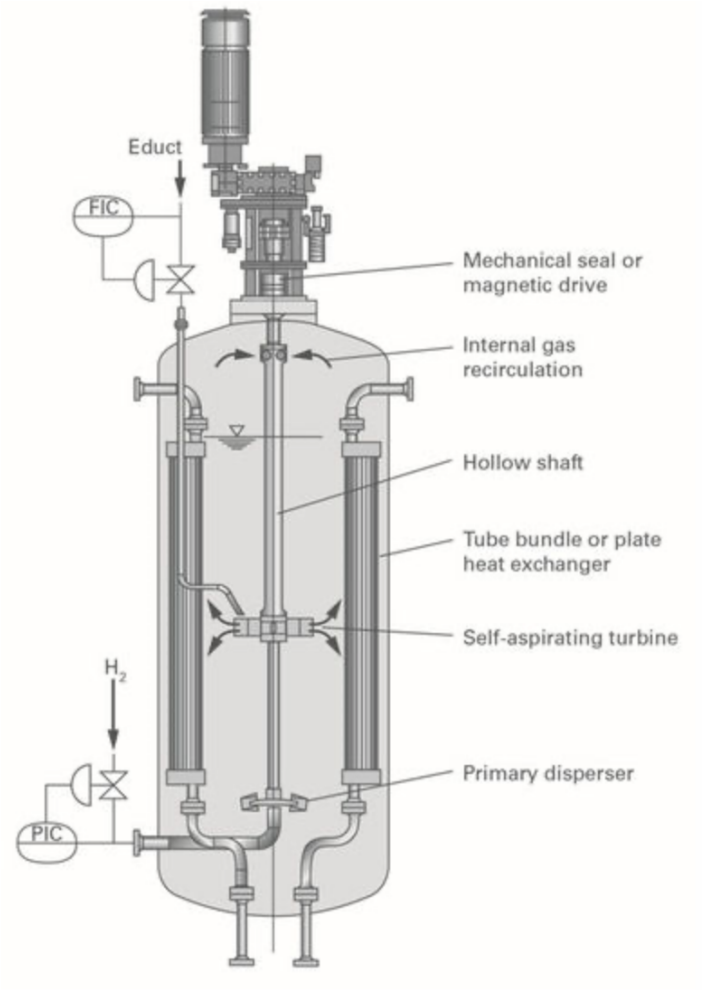

Figure A 3. Proposed design for hydrogenation reactor by manufacturer EKATO (imatge from (Ekato 2020)*)*

Appendix A.3: Crystallizer CR-01

The vessel selected for the crystallization steps is the *BE16000* designed by manufacturer *Pfaudler*. Additional data for the equipment can be found in Table A 3. A picture of the equipment as well as the agitator alternatives, including the selected *Anchor ANC*, is shown in Figure A 4.

Table A 3. Technical data for equipment BE16000 by Pfaudler

Nominal volume [L]	16000
Overall capacity [L]	18200
Overall jacket volume [L]	1451
Heat exchange surface [m^2]	29.56
Total weight [kg]	15010

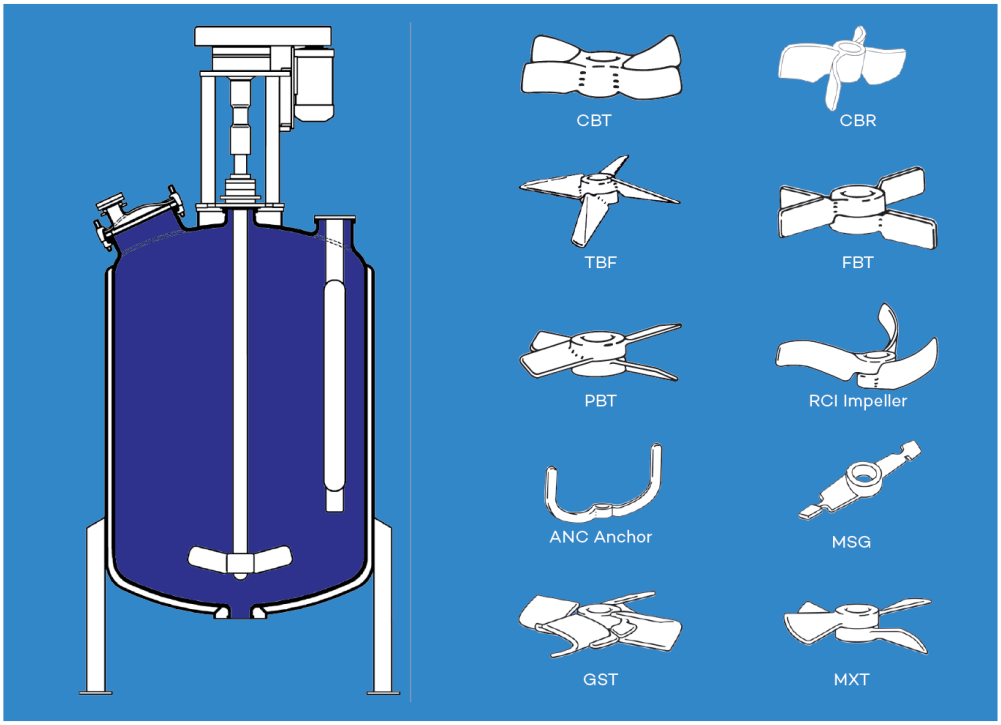

Figure A 4. Example of BE series reactor and agitator alternatives by Pfaudler

(imatge from (Pfaudler 2020b)*)*

Appendix A.4: Centrifuge CN-01

The selected centrifuge is provided by manufacturer *Riera Nadeu*, from the *RINA Serie 700 Pharmaceutical*, model *700F*. The technical data for the selected model is presented in Table A 4

Table A 4. Technical data for selected 700F model centrifuge by manufacturer Riera Nadeu

Basket diameter [mm]	1400
Basket height [mm]	700
Cake thickness max. [mm]	210
Cake volume capacity max. [L]	550
Cake weight capacity max. [kg]	690
Filtering area [m^2]	3.08
Speed [rpm]	1135
G Factor max.	1000
Centrifuge weight [kg]	17655
Dimensions WxLxH [mm]	2450x3640x2980

Appendix A.5: Drier D-01

The selected drum drier to operate in the final drying step of the process is the model *DMX-3* from manufacturer *OLSA*. Technical data for the selected equipment can be found in Table A 5. The design of the drum drier is shown in Figure A 5.

Table A 5. Technical data for model DMX-3 drier by manufacturer OLSA

Total volume [L]	1140
Loading volume [L]	820
Max loading weight [kg]	550
Vessel inner diameter [mm]	1100
Vessel length [mm]	1200
Dust filter [m^2]	0.75
Solvent recovery tank [l]	250
Heating system [kcal/h]	45000
Dimensions WxLxH [mm]	1330x2900x2420

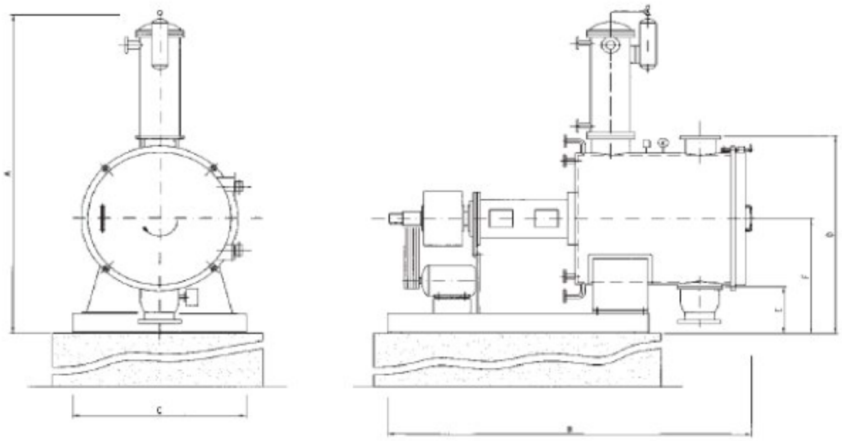

Figure A 5. Design of the drum drier provided by manufacturer OLSA

(imatge from (OLSA 2020b)*)*

APPENDIX INDEX OF FIGURES AND TABLES

APENDIX INDEX OF FIGURES

APENDIX INDEX OF TABLES