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Treball Final de Grau

Tramadol Hydrochloride: Study of the Production Process and Equipment Selection.

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M’agradaria expressar el meu sincer agraïment al Dr. Manel Vicente i a la Dra. Esther Chamarro per la seva amable ajuda i dedicació en aquest projecte. La seva experiència i suport han tingut un gran impacte en el desenvolupament del treball i en la meva motivació. A més, el seu sentit de l'humor ha fet que el temps que hem compartit treballant junts sigui molt agradable. He après molt durant aquest procés i han aconseguit despertar el meu interès en aquest tema.

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SUMMARY

Tramadol is an Active Pharmaceutical Ingredient (API) found in various pharmaceutical formulations, designed to treat moderate to severe pain.

The objective of this project is to study and determine the production process of tramadol through literature research on existing patents and ensuring adherence with Good Manufacturing Practices (GMP) regulations. The production process has been determined by studying equipment occupation times, and batch and cycle times.

Initially, this study involves conducting a market analysis to determine the desired production quantity based on the product's characteristics and properties. It has been established that the annual production of tramadol will be 20 tons, meeting 10 % of the European demand. Assuming the plant operates for approximately 40 weeks per year, a batch size of 500 kg has been defined.

The focus of the process is on the purification stage of tramadol, considering it is cheaper to purchase the isomeric mixture of the product as a raw material. For the discontinuous operation process, four vessels and two filters are required, including a bag filter and a Nutsche filter. The selected vessels have different characteristics depending on their task, capable of performing chemical reactions, crystallizations and/or mixtures. The filters, on the other hand, have been chosen accordingly. The Nutsche filter is used in two stages of the process, although only one has been found necessary for reasons of process optimization.

An analysis of the operation times for each equipment has been conducted, allowing the determination of Key Performance Indicators (KPIs). By studying the operation times, the batch time of 51 hours and 30 minutes and the cycle time of 34 hours and 45 minutes have been determined. An analysis has been performed for production in campaigns, considering overlapping, and diverse campaign production options have been proposed for a year. In terms of KPIs, the maximum production capacity of tramadol per year and the minimum production time for the estimated quantity of 20,000 kg/year have been calculated. The maximum production

capacity for the plant is 129 batches/year, equivalent to 64,500 kg of tramadol/year. The minimum production time is 1,406 hours and 45 minutes, which correspond to 58.61 days.

Keywords: Tramadol, API, batch process, patent, occupation time, batch time, cycle time, batch size, isomeric mixture, KPI, campaigns.

RESUM

El tramadol és un API (*Active Pharmaceutical Ingredient*) present en diverses especialitats farmacèutiques, l'objectiu del qual és tractar el dolor moderat o intens.

El present projecte té com a objectiu l'estudi i determinació del procés productiu de tramadol a partir de la recerca bibliogràfica de patents existents i complint amb la normativa GMP (*Good Manufacturing Practices*). S'ha pogut determinar de quina manera es duu a terme aquesta producció mitjançant un anàlisi dels temps d'ocupació dels equips i dels temps de *batch* i de cicle.

Aquest estudi, en un inici, passa per la realització d'un estudi de mercat on, entenent les característiques i propietats del producte, s'ha procedit a determinar la quantitat de producció desitjada. S'ha establert que la producció anual de tramadol serà de 20 tones, complint amb el 10 % de la demanda a nivell europeu. Sota la premissa que disposem d'una planta que treballa unes 40 setmanes a l'any, s'ha definit una mida de lot de 500 kg.

El procés s'ha limitat a l'etapa de purificació del tramadol, considerant que surt més rentable comprar com a matèria primera la mescla isomèrica del producte.

Per a la realització del procés, que opera en discontinu, es necessita disposar de 4 tancs agitats i de dos filtres; un de bosses i un *Nutsche*. Els tancs, que s'han definit per al procés, tenen característiques diferents en funció de la tasca que realitzen ja que poden dur a terme reaccions químiques, cristal·litzacions i/o agitacions. Els filtres, en canvi, tan sols s'han seleccionat. El filtre Nutsche està present en dues etapes del procés, tot i que s'ha decidit disposar-ne només d'un per motius d'optimització del procés.

S'ha realitzat un anàlisi dels temps d'operació per a cada un dels equips presents i en base a això, s'han pogut determinar els KPIs (*Key Performance Indicators*). Amb l'estudi dels temps d'operació s'ha programat la producció d'un lot, la qual cosa ha permès saber el temps de *batch*, que és de 51 hores i 30 minuts i el temps de cicle, que és de 34 hores i 45 minuts. S'ha fet aleshores, un estudi per a la producció en campanyes, és a dir, una producció amb solapament i s'han proposat diverses opcions de producció al llarg d'un any. Respecte als KPIs, s'ha calculat

quina és la màxima capacitat de producció de tramadol en un any i el temps mínim de producció per a la quantitat estimada de 20,000 kg/any. La capacitat màxima de producció de tramadol per a la planta en qüestió pren el valor de 129 lots/any o, dit d'una altra manera, de 64,500 kg tramadol/any. El temps mínim de producció és de 1,406 hores i 45 minuts, que equivalen a 58.61 dies.

Paraules clau: Tramadol, API, procés *batch*, patent, temps d'ocupació, temps de *batch*, temps de cicle, mida de lot, mescla isomèrica, KPI, campanyes.

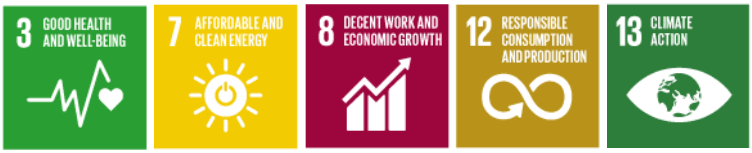
SUSTAINABLE DEVELOPMENT GOALS

The Sustainable Development Goals (SDGs) are a set of global goals for sustainable health at all levels: from the planetary biosphere to the local community. The SDGs are dictating the official agenda at the international level for governments and institutions. The goals aim to continue the progress made by the Millennium Development Goals (MDGs) set in Agenda 21 after the Rio de Janeiro summit in 1992. In 2015, the UN critically evaluated the progress of established objectives and developed the 2030 Agenda for Humanity and the 17 Sustainable Development Goals. These goals address social, economic, and environmental challenges to promote sustainable development.

Regarding the process of purification of trans tramadol, it is important to highlight that the sustainable development goals are directly related to the health and well-being of people, including access to safe and effective medicines (SDG 3).

Furthermore, the process of purification of trans tramadol also relates to the goal of ensuring sustainable production and consumption (SDG 12), as efforts are made to minimize the amount of toxic waste (SDG 7) generated during the manufacturing process. Proper disposal of these wastes is important to protect the health of workers in the pharmaceutical industry and the environment (SDG 13).

The 17 Sustainable Development Goals can be classified into the 5 Ps: People, Planet, Prosperity, Peace and Partnership.



1. INTRODUCTION

An Active Pharmaceutical Ingredient (API) refers to an active chemical substance that can be transformed into a medicine after being properly processed. The API is what provides therapeutical effects to the patient. [1]

The term has been widely used in the pharmaceutical industry for decades. However, the World Health Organization (WHO) has been one of the key entities in promoting its use. Plus, it is the entity that regulates medicines internationally.

In *Table 1* below, there are exposed the different kinds of analgesics existing.

Table 1. Types of Analgesics and Description of their differences [2]

TYPES		**CHARACTERISTICS**	**EXAMPLES**
Primaries (its main effect is to relieve pain)	Opioids	- Moderate or severe pain. - Mechanism of action: acting on opioid receptors in the brain and spinal cord to block pain transmission.	Morphine, codeine, oxycodone, fentanyl.
	Not opioids	- Minor or moderate pain. - Mechanism of action: inhibit the production of prostaglandins (chemicals that cause inflammation and pain).	Paracetamol, ibuprofen, naproxen.
	Topics	- Directly applied to the skin to relieve localized pain. - Creams, ointments, patches.	Contains ingredients such as: lidocaine, capsaicin.
Secondaries (other indications)	Adjuvants	- For neuropathic pain. - They help relieve pain in certain conditions.	Antidepressants and anticonvulsants.

Tramadol is the API of various opioid analgesic drugs such as Adolonta, Diliban or Enanplus. In each of them, it can be found in very different concentrations.

Tramadol was first synthesized in 1962 at Grünenthal Research Laboratories by Drs Flick and Frankus (Aachen, Germany). It was introduced in the German market in 1977, and it is the most widely sold opioid analgesic in the world. [3]

Initially, it was controversial, as some reports were generating concerns about its use because it was causing adverse effects, such as convulsions, and it possibly interacted with other compounds having negative effects on patients. Further studies determine the causes of these side effects, which in fact are generated from the different enantiomers possible for the molecule.

1.1. STRUCTURE AND PROPERTIES OF TRAMADOL

Tramadol is an organic chemical compound with formula $C_{16}H_{25}NO_2$ and IUPAC name 2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexanol. As seen in *Figure 1*, its molecule consists of a cyclohexane ring with two stereogenic centers: the first one carrying a benzene radical with a methoxy group (-O-CH3) on it, or in other words, methoxyphenyl; and the second one carrying a dimethylaminomethyl radical plus a hydroxyl group. [4]

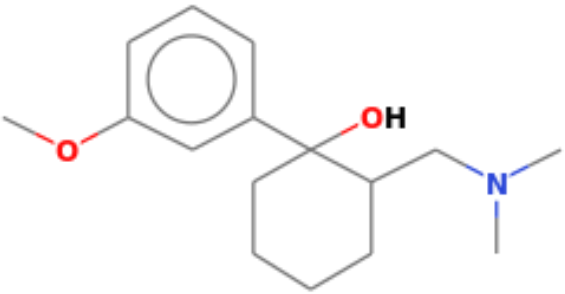


Figure 1. Chemical Structure of Tramadol (NIST) [5]

It is commonly seen as tramadol hydrochloride, which is a salt form for tramadol, with formula $C_{16}H_{25}NO_2 \cdot HCl$. Tramadol hydrochloride is more soluble in water than pure tramadol. For this reason, it is marketed in the form of tramadol hydrochloride for oral or parenteral administration.

Tramadol is a synthetic opioid[1] analgesic used to treat pain in adults and can possibly produce side effects such as drowsiness or dizziness.

It can exist in four different configurational forms. (1R,2S)-isomer and (1S,2R)-isomer, both being cis isomers; and (1R,2R)-isomer and (1S,2S)-isomer, being the trans isomer form for tramadol. All of them, represented in *Figure* 2.

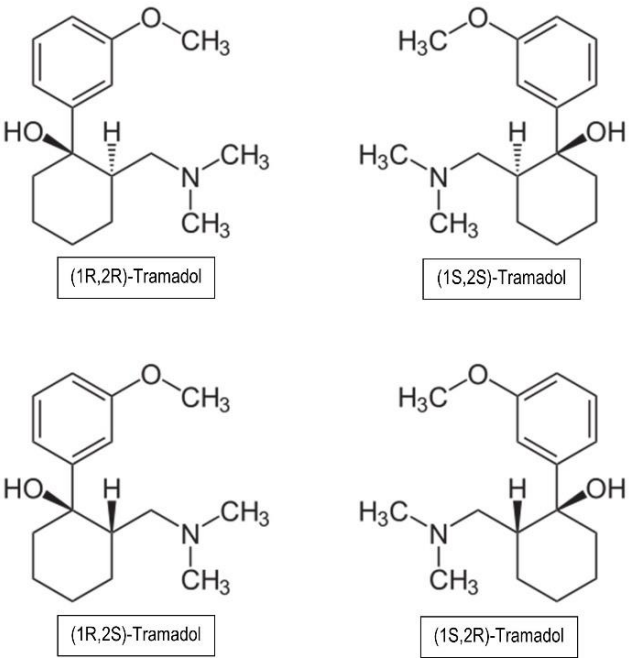


Figure 2. Isomers of Tramadol

Tramadol is different from other opioid medicines as it not only acts as an opioid, but also affects monoamines such as norepinephrine and serotonin.

As an opioid, it is analogue to codeine, and it helps relieve pain.

Tramadol's mechanism of action involves the opioid receptors humans have in the brain, in the spinal cord or in the peripheral nervous system. There are three types of receptors, which

[1] Opioid refers to those drugs that have analgesic properties, i.e., that act against pain and on the opioid receptors in the brain and spinal cord to block the sensation of pain.

include the μ-receptors, the δ-receptors, and the κ-receptors. The interaction between the opioid and each kind of receptor can provoke different effects on the body, being the μ-receptors more efficient in evading ache, in contrast to κ-receptors being responsible for effects such as analgesia, sedation or dysphoria.

Tramadol possesses a weak affinity for the μ-receptors, but even less for the δ-receptors, and the κ-receptors. The (+) enantiomer, meaning the trans isomers of tramadol, binds more strongly to the opioid receptors than the respective (-) enantiomer. This happens because the (+) enantiomer is four times more potent than the (-) enantiomer.

On the other hand, as mentioned before, tramadol also affects monoamines in the brain. It makes our nerve cells release norepinephrine and serotonin. Tramadol inhibits its uptake, leaving these substances among nerve cells and, consequently improving communication between nerve cells, enhancing mood and mitigating pain.

Tramadol's oral absorption in the upper small intestine and bloodstream varies depending on the dose taken. Generally, by oral administration, from 95 % to a 100 % of it is absorbed in the upper small intestine; being 70 % of the tramadol bioavailable, due to a 30 % first pass metabolism in single doses.

In multiple doses, the amount that is bioavailable is 90 %. Also, the steady state is reached in 36 hours. After oral administration, tramadol is rapidly absorbed, with peak serum concentrations (in the blood) reached, for capsules within two hours, and for sustained release tablets within five hours.

It is recommended that the oral daily dose is between 50 and 100 mg every four or six hours and the analgesia last about six hours after a single dose of 100 mg.

In the scale of potency of medicines of the World Health Organization it is considered a Step 2 option and is about 1/10th less potent than morphine.

1.2. MARKET STUDY

When it comes to marketing, tramadol can be found alone but also, combined with other APIs. In Spain it is marketed on its own and combined with paracetamol or dexketoprofen. There are 37 supplying laboratories in Spain for drugs containing tramadol. [6]

The organization that controls legalization and marketing of drugs in Europe is the European Medicines Agency (EMA). In Spain, the entity responsible for this is CIMA AEMPS.

Tramadol can be found in different forms such as tablets, solutions or granulates. The administration can be by oral or parenteral means, being only in amount of a 3 % of the second option. Pharmaceutically, it can be presented as a prolonged release tablet, an effervescent tablet, an oral solution, an injectable solution, or a granulate for oral solution. In *Figure 3* below, are shown the percentages for pharmaceutical forms in Spain.

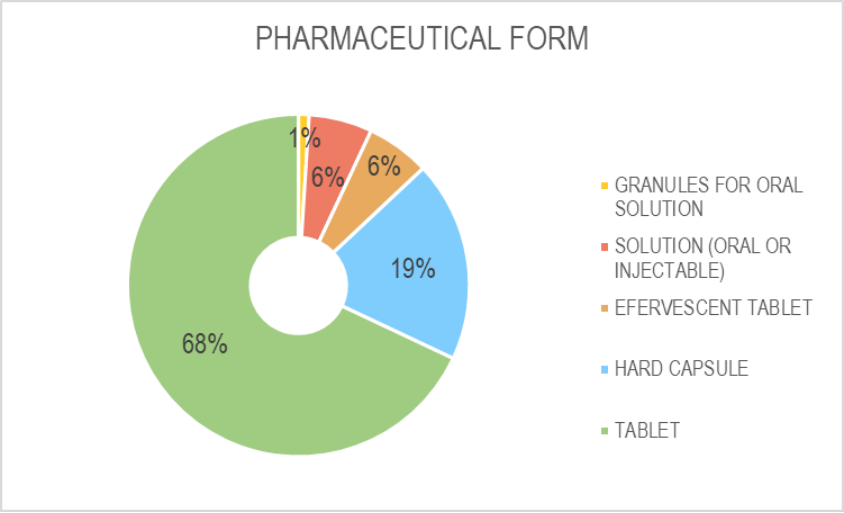


Figure 3. Percentages for Pharmaceutical Forms in Spain [6]

Also, it is possible to find tramadol in different concentrations as shown in *Figure 4*.

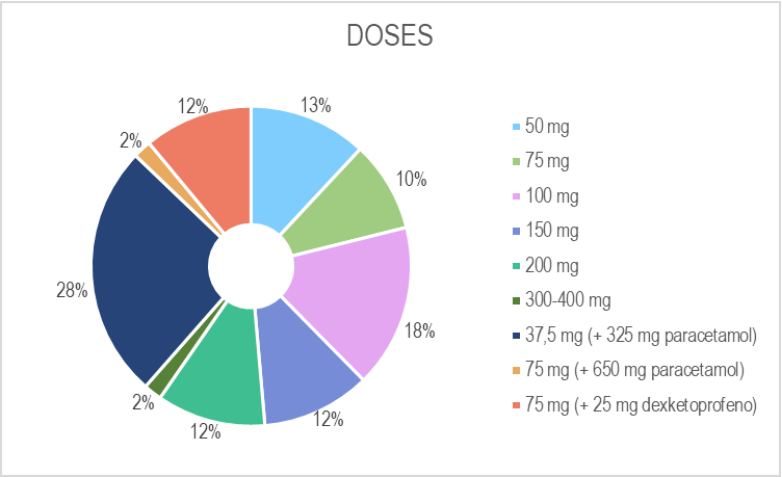


Figure 4. Percentages for Doses Marketed in Spain for Tramadol

As seen in *Figure 4*, tramadol is also commonly commercialized in the company of paracetamol or dexketoprofen.

There are lots of pharmaceutical specialties. Some examples of them in Spain are: Adolonta, Diliban, Enanplus, Gelotradol, Paxiflas, Pazital or Pontalsic. Manufactured by Cinfa, Normon, Stada or Sandoz.

To proceed to the design and study of the obtaining process of tramadol it is necessary to know its market price and consume to be able to estimate the amount of product that is willing to be elaborated.

To calculate the price of the drug it has been picked the commercialized boxes of 60 capsules of 50 mg tramadol each. The public sale price (PVP) for the specialty is 6.21 €/box. This price includes a 4 % VAT and a 0.5 % health surcharge. Therefore, the net price is 5.94 €/box.

Each box contains 3 g of tramadol and, as the API cost represents 5 % of the net price, the cost of tramadol per box is 0.30 €. This results in a price for tramadol API of 0.10 €/g or, in other words, 100 €/kg. [7]

On the other hand, it is needed some information about user consumption.

The intake of opioids in Spain, and particularly tramadol, has been determined by consulting the Spanish Agency for Medicines and Medical Devices (AEMPS).[8] The data obtained is expressed in terms of DHD (Doses per day).

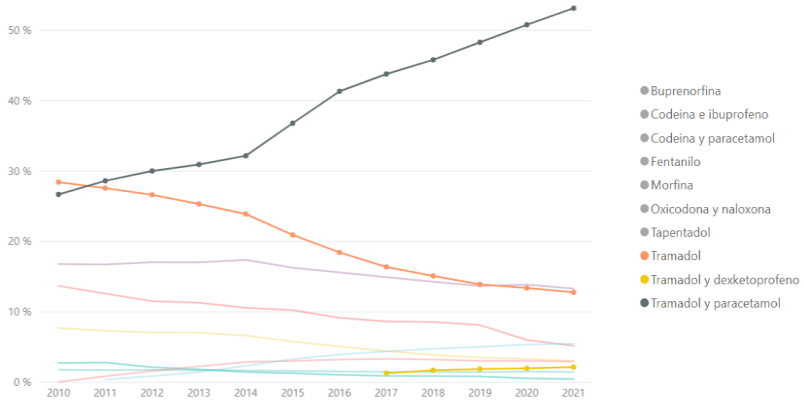


Figure 5. Evolution for Consume of opioids in Spain (in percentages) [8]

In previous *Figure 5*, it can be observed the consumption trend in Spain of the most used analgesics. The consumption of tramadol alone has significantly decreased in recent years. However, despite this reduction, its consumption in the company of paracetamol has considerably increased. In *Figure 6*, it is shown the consumption of tramadol in all forms in Spain over these recent years.

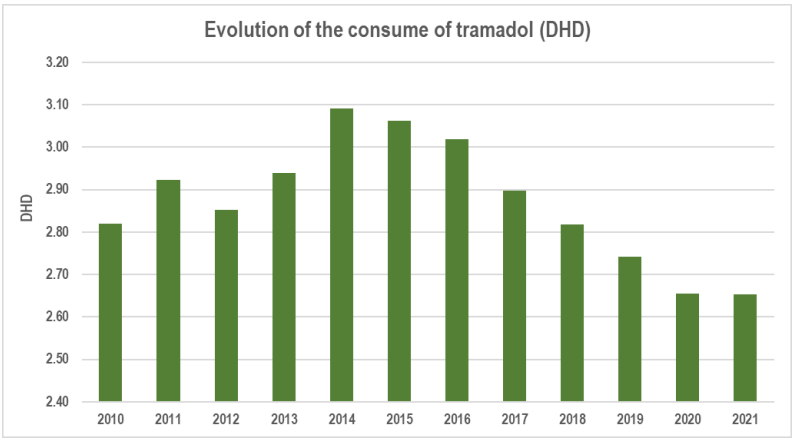


Figure 6. Evolution of the Consume of Tramadol over the years (DHD)

As found, the consume of tramadol in Spain in 2021 was 2.65 DHD (for 1,000 habitants and per day). Also, it was found thanks to the World Health Organization that the DDD[2] of tramadol is 0.300 g/day. [9]

Using this information, the daily consumption of tramadol per each 1,000 habitants is calculated to be 0.795 g/day. In Spain, the total daily consumption it is found to be 38 kg/day using the total population which is 47,420,000 habitants. Or in other words, 14,000 kg/year. To find the amount of tramadol consumed in Europe, it has been estimated using the value of the amount of tramadol consumed in Spain.

In Europe it is consumed an amount of tramadol of approximately 200 tons/year.

As a company policy, it has been decided to meet 10 % of the demand. Twenty tons per year will be produced.

In Spain, the production of drugs is regulated by strict legislation that aims to ensure their safety, efficacy, and quality. Once the amount of a drug to be produced for a certain period of time has been established and approved by the relevant authorities, it cannot be changed without undergoing a new process of testing and revision by the administration. This is because any modification to the production amount could potentially affect the quality, safety, or efficacy of the drug, and therefore must be thoroughly evaluated before being authorized.

1.3. SYNTHESIS OF TRAMADOL

In the synthesis of tramadol there are involved two important mechanisms used in reactions of synthesis and that are widely applied in organic chemistry. These mechanisms are the Mannich and Grignard reaction. [10]

In the following *Figure 7*, there is a diagram showing the different steps followed in the synthesis of tramadol.

[2] DDD: assumed average maintenance dose per day for a drug used for its main indication in adults.

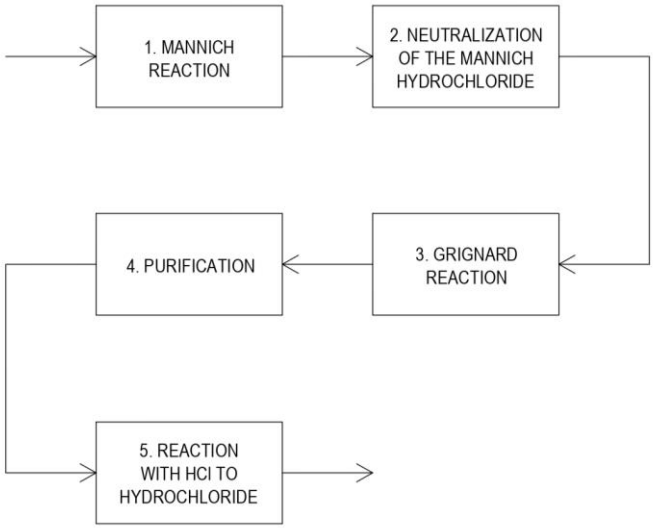


Figure 7. Process for the Synthesis of Tramadol

1. Mannich reaction

The Mannich reaction is an important tool in organic synthesis, and its versatility and ease of use have made it a popular choice for the preparation of a wide range of organic compounds. Its application in the synthesis of tramadol is just one example of the many ways in which this reaction can be used to create useful and important chemicals.

The Mannich reaction is an organic chemical reaction used to synthesize amino ketones. These compounds have many applications in organic synthesis, especially in the pharmaceutical industry. The reaction involves the condensation of an amine, an aldehyde, and a carbonyl compound, usually a ketone, to form an imine intermediate. The imine is then treated with an acid or base to form the amino ketone.

The Mannich reaction is used in the synthesis of tramadol. Tramadol is synthesized from the precursor compound cyclohexanone. The first step in the synthesis of tramadol is the Mannich reaction of cyclohexanone with formaldehyde and dimethylamine hydrochloride to form dimethylaminomethyl cyclohexanone hydrochloride, as shown in *Figure 8*.

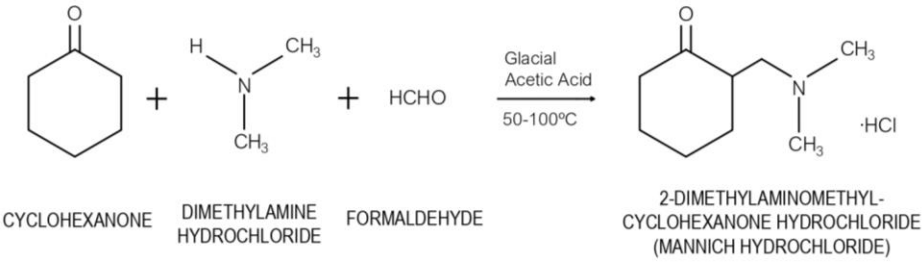


Figure 8. Mannich reaction mechanism for the Synthesis of Tramadol

2. Mannich base (neutralization) [3]

In *Figure 9*, there is a representation of the reaction carried in order to neutralize the mannich reaction product.

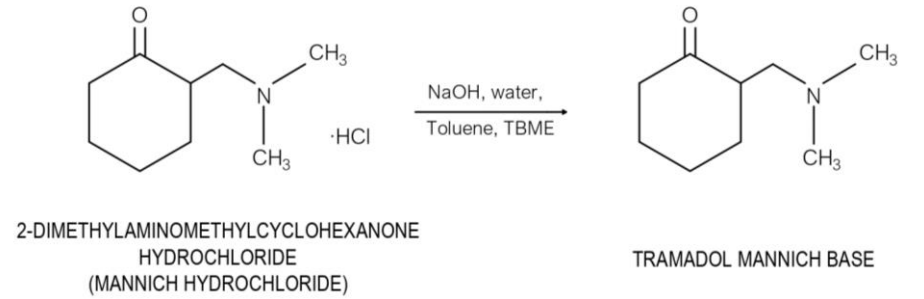


Figure 9. Reaction for the neutralization for the Mannich reaction product

3. Grignard reaction

The mechanism of the Grignard reaction is a versatile organic chemical tool that involves the addition of the Grignard reagent to a variety of electrophilic compounds, making this reaction an

[3] TBME: Methyl t-butyl ether.

important implement in organic synthesis. The reaction can be used to form carbon-carbon bonds, carbon-oxygen bonds, carbon-nitrogen bonds, and many other types of bonds.

The Grignard reagent is an organomagnesium halide compound, which is an organic compound that contains a magnesium atom and a halogen atom (bromine, chlorine, or iodine) bonded to carbon atoms. The carbon atom is typically an alkyl or aryl group.

In the synthesis of tramadol, the Grignard reaction is used to synthesize the key compound, 2-dimethylamonomethylcyclohexanone, which is then further reacted to form tramadol. The Grignard reaction is used to add 3-methoybromobenzene reagent to tramadol mannich base to form 2-[(dimethylamino)methyl]-1-(3-methoxyohenyl) cyclohexanol.

The organomagnesium halide compound, whose preparation involves the reaction of an alkyl or aryl halide with magnesium metal in the presence of anhydrous ether, acts as a powerful nucleophile that adds to a wide range of electrophilic compounds. In this case, to form carbon-oxygen bond in the place of the carbonyl group of the intermediate ketone.

The presence of tetrahydrofuran (THF) is crucial in the Grignard reaction. It is a solvent and helps to stabilize the Grignard reagent, which can be highly reactive and sensitive to decomposition. THF also helps to solubilize the reactants and products, making them easier to work with. In addition, THF helps to prevent the reaction from proceeding too quickly or violently.

Hydrogen chloride (HCl) is typically used in the Grignard reaction to neutralize the excess organomagnesium halide compound and any other reactive intermediates that may have formed during the reaction. HCl is added slowly to the reaction mixture, usually in the form of a solution in ether, to protonate the organomagnesium halide compound and any other reactive intermediates. This protonation reaction results in the formation of the desired product, as well as the precipitation of the magnesium halide salt that was formed during the reaction. The precipitated salt is then typically removed by filtration, leaving behind the desired product in solution.

The product of the Grignard reaction is a mixture of cis and trans isomers of tramadol which are obtained in variable ratios, depending on the reaction conditions.

In *Figure 10*, it can be observed the reaction mechanism which is carried out in the synthesis of tramadol process.

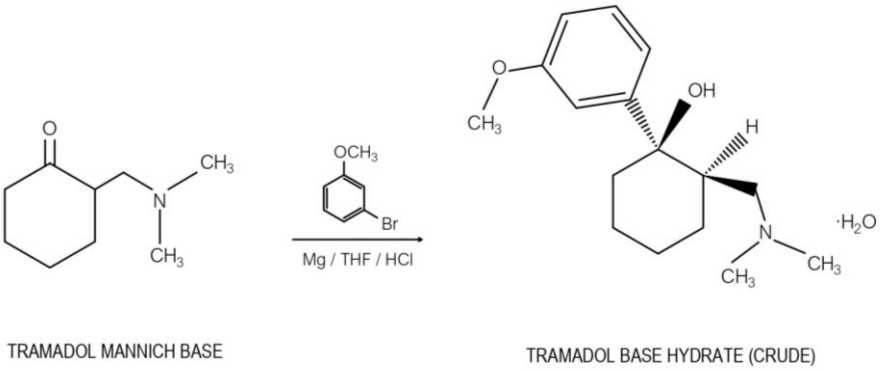


Figure 10. Reaction for the transformation of the Mannich base into Tramadol

4. Purification

In the final steps of synthesis of tramadol, we find a purification stage, meaning there is a need to leave behind unwanted compounds.

Ethyl acetate is often used as a purification solvent in organic chemistry because it has a low boiling point, it is non-toxic, and is easy to remove from the final product.

In the context of the synthesis of tramadol, ethyl acetate is used as a solvent to extract the tramadol product from the reaction mixture after the Grignard reaction and acidification steps have been completed, as it is shown in *Figure 11*. Ethyl acetate can dissolve many organic compounds, including tramadol, while leaving behind inorganic salts and other impurities that are not soluble in organic solvents.

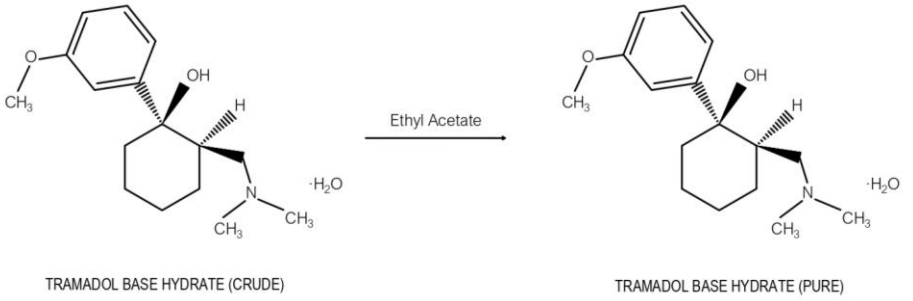


Figure 11. Purification of the Tramadol crude

After the ethyl acetate extraction, the tramadol product can be isolated by evaporating the ethyl acetate under reduced pressure, which leaves behind a purified solid product.

5. Formation of tramadol hydrochloride

Finally, the tramadol solid product is reacted with hydrochloric acid to obtain tramadol hydrochloride as in *Figure 12* shows.

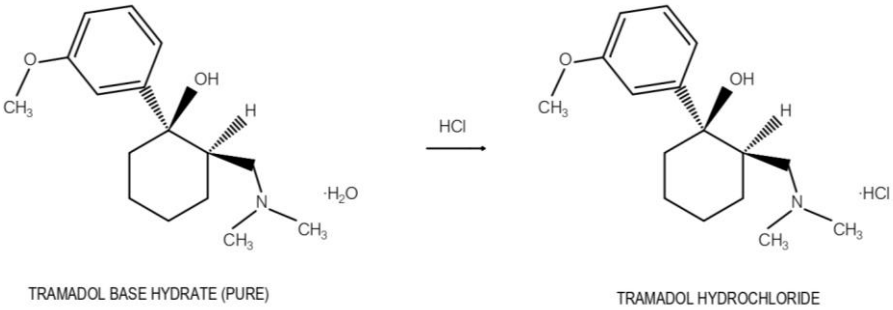


Figure 12. Acidification for the formation of Tramadol Hydrochloride

Subsequently, the purification of the trans isomer from the mixture of cis and trans tramadol hydrochloride (*Figure 13*) will be carried out.

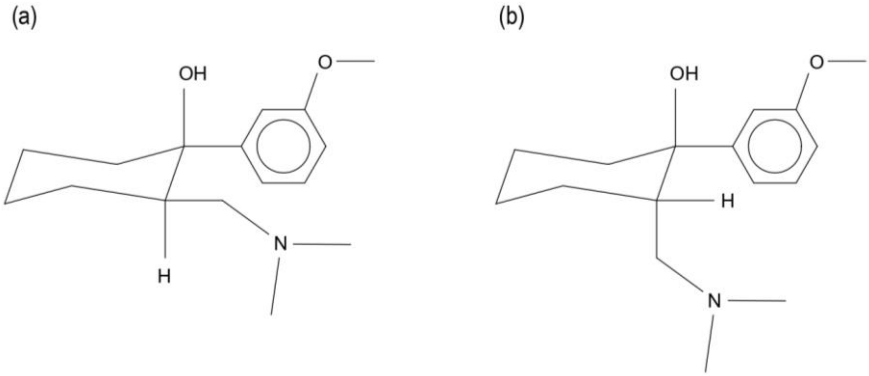


Figure 13. Configurational form for Trans (a) and Cis (b) isomers for Tramadol

2. OBJECTIVES

The present project aims to study and determine the production process of tramadol. This involves analyzing equipment occupation times and batch and cycle times to establish the production process.

This study involves a market analysis to determine the desired production quantity, assuming 10 % of the European demand will need to be covered and that the plant operates for approximately 40 weeks per year. The production process will be determined by analyzing equipment occupation, batch, and cycle times.

Specific objectives of this study include choosing a viable arrangement for the production process, by selecting or designing the required equipment. Also, analyzing the operation times for each equipment and determining the Key Performance Indicators.

An analysis of production in campaigns, considering overlapping will be made, as well as the calculations of the maximum production capacity per year and the minimum production time.

3. PATENT RESEARCH

The aim of this study is to investigate the process of separation and purification of a specific isomer of tramadol from a mixture, whether racemic or not. The focus of the research will be limited to this section and will exclude the synthesis of the compound, which is previously explained in detail. The main interest is to develop an efficient process for the separation of tramadol isomers based on previously patented methods. The resulting decision will be assessed by the efficacy and selectivity of these methods.

It has been observed that the trans isomer of tramadol is medically more active than the cis isomer and that the (+) form is more active than the (-) form.

From some bibliographic studies of different patents, it is concluded that both cis and trans isomers can be separated. In the next table (*Table 2*) there is a summary of the proposed processes by each patent.

Table 2. Summary of consulted patents

PATENT	LABORATORY	FINAL ISOMER	OPERATIONS	CONDITIONS
WO0228817A1 [11]	Gruenenthal Gmbh	Trans	1. Distillation	138 – 140 ºC
			2. Agitated vessel (reaction with ether)	1 atm
			3. Precipitation of isomers hydrochlorides	
			4. Crystallization while reaction with dioxane	
			5. Drying	
WO9936390A1 [12]	Macfarlan Smith Ltd	Trans	1. Agitation vessel (reaction with isopropanol and 48% hydrobromic acid)	pH 1; 1 atm
			2. Agitation vessel (1 hr)	15 – 25 ºC
			3 Agitation vessel (1 hr)	2 – 5 ºC

			4. Filter and wash with isopropanol and acetone	
			5. Agitation vessel (reaction with isopropanol and water)	1 atm
			6. Agitation vessel (1 hr)	15 – 25 ºC
			7. Agitation vessel (1 hr)	-10 – -15 ºC
			8. Filter and wash with isopropanol and acetone	
			9. Drying	
EP1785412A1 [13]	IPCA Laboratories Ltd	Cis	1. Agitation vessel. Reaction with achiral organic acid (salicylic or benzoic) and first solvent (organic solvent)	
			2. Distillation of first solvent	
			3. Crystallization while reaction with second solvent (alcohol)	
			4. Filtration/centrifugation	
			5. Washing with acetone	
			6. Drying	
EP0831082A1 [3]	Chemagis Ltd	Trans	1. Agitation vessel. Reaction with electrophilic reagent and hydrochloride	
			2. Crystallization while reaction with isopropanol	
WO9903820 [10]	Russinky Ltd	Cis	1. Crystallization while reaction with ethyl acetate	
			2. Agitation vessel (reaction with HCl)	
			3. Filtration	
			4. Drying	

After considering all options and observing high yields for most of them, it has been decided to implement a combination of patents EP0831082A1 and EP1785412A1. The trans isomer was selected as the most active and providing the best results for patients.

4. PRODUCTION PROCESS

The production of tramadol hydrochloride consists of a series of batch operations. This series includes reaction but also separation stages. In this study, we will focus on the production process of tramadol hydrochloride, specifically on the purification of one of its isomers: the trans isomer. We will assume that the mixture of cis and trans isomers of the compound hydrochloride has already been obtained and we will delve into the details of the purification process of the trans isomer as shown in *Figure 14*.

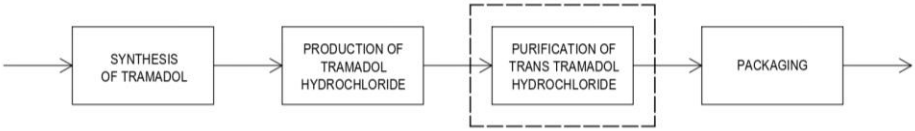


Figure 14. Obtention Process for Tramadol

The purification of the trans isomer can be a challenging task due to the similarity of its physical and chemical properties to the cis isomer. However, by employing specific separation techniques, the trans isomer can be isolated with high purity.

It is known that the hydroxyl group of the cis isomer undergoes some chemical reactions faster than the hydroxyl group of the trans isomer due to its configuration different forms.

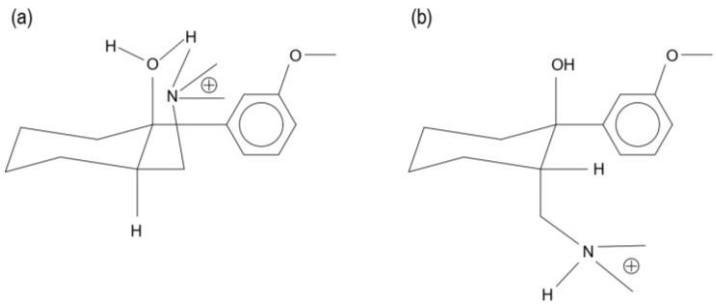


Figure 15. Reactivity for the trans (a) and cis (b) isomers of Tramadol

Looking closely at *Figures 15a and 15b*, it can be provided a possible explanation on the reason for the difference in reactivity of the hydroxyl group for both isomers. It can be attributed to the presence of a proton attached to the nitrogen atom of the protonated trans isomer (a). This proton can form a stable hydrogen bond with the oxygen atom of the hydroxyl group, which makes it less prone to react in any process involving protonation of the hydroxyl group (such as dehydration) or any reaction where the hydroxyl group acts as a nucleophile (such as a nucleophilic substitution or esterification). In contrast, the cis isomer (b) lacks the possibility of forming a stable intramolecular hydrogen bond, which means that any of the above-mentioned reactions can occur more easily. Moreover, the tertiary and benzylic nature of the hydroxyl group in the cis isomer further facilitates its reactivity.

4.1. RECIPE

Below, the recipe of the industrial process for the purification of tramadol will be presented as it would be carried out in the industry.

A total of 4,146 L of chlorobenzene are discharged into agitated vessel V-1 from its storage tank through its respective pipeline. The quantity to be discharged will be calculated using a weighing system. It is estimated that the entire process, including preparation for discharge, the actual discharge, and subsequent disconnection of the system, takes approximately 15 minutes. Then, 1,470 kg of TT+TC (initial reactant consisting of a mixture of tramadol hydrochloride isomers [60 % RR, SS and 40 % RS, SR]) are introduced through the lid, using a hopper. The TT+TC is discharged from a big bag of 1,500 kg, which takes approximately 45 minutes considering that it will not be done all at once, but gradually while agitating. After adding the first two components, it is determined that the mixture will be stirred for 30 minutes to ensure proper component mixing. Therefore, it takes 1 hour and a half to have the mixture ready to initiate the reaction with the electrophilic reagent, concretely thionyl chloride. This operation is carried out at atmospheric pressure and at an ambient temperature of 25 °C.

The thionyl chloride is added in company of a solvent, which is chlorobenzene. This mixture is going to be prepared in another stirred vessel V-2. Thionyl chloride and chlorobenzene are discharged in the stirred vessel (V-2), from its respective containers. For each carried out batch it is necessary to have a mixture of 301.5 L of $SOCl_2$ and 1,131 L of CBz available. To save time and resources, it will be produced three times this amount to have it available for the next two

loads. The amount to be discharged will be calculated through a weighing system and controlled through automatic valves. Then, 3,393 L of CBz and 904.5 L of $SOCl_2$ will be discharged. It is estimated that the entire process, including preparation for discharge, the actual discharge, and subsequent disconnection of the system, takes approximately 45 minutes in total. CBz is charged into V-2 through its respective pipeline coming from its storage tank; this procedure takes 15 minutes. $SOCl_2$ is charged from its container through a hose; and it takes 30 minutes. After charging the two components, it will be stirred for an additional 30 minutes to ensure a proper mixture. Therefore, it takes 1 hour and 15 minutes to have the mixture ready for discharging into vessel V-1. However, these times will not be considered in the overall process as the operation is carried out during operator availability and outside the progression of the production process.

V-2 will always be ready to use so, when needed 1,432.5 L of the mixture stored in it is going to be added to vessel V-1 over a period of 2 hours, dropwise, to ensure good contact between the reactants and achieve the expected reaction yield. The output volume of vessel V-2 is regulated by a control valve that measures the flow rate and adjusts it to achieve the desired outcome. Finally, it will be left to react and agitate for an additional 2 hours. The reaction is conducted at atmospheric pressure and ambient temperature of 25 °C. To maintain the temperature, a cooling system is installed, which consists of a half-pipe jacket, as the reaction is exothermic.

When the reaction and extra agitation time is finished, the outlet valve of vessel V-1 is opened, and the products flow out completely. The stream then passes through a bag filter (F-1). The filtration will have to be done in 2 cycles because the bag has a capacity of 25 kg. Within the filter, in total the 50 kg of solid impurities formed during the reaction are retained along with 0.1 % of solvent and what it carries dissolved ($SOCl_2$, liquid impurities, and consequently TT+TC, which is our final product). Liquid flows directly into the agitated vessel V-3. The process of emptying vessel V-1, filtering, and filling vessel V-3 has an approximate duration of 2 hours, meaning 45 minutes for each cycle and 30 minutes in between to clean the bag. After filtering the solid impurities, the filter will need to be cleaned again, action that will require 30 minutes.

Once vessel V-3 is filled, the solvent will be evaporated. To carry out this action, considering that the boiling points at atmospheric pressure of chlorobenzene and thionyl chloride are 132 and 76 °C, respectively; a vacuum service will be required to evaporate at 35 °C. Vapor pressures for chlorobenzene and thionyl chloride at 35 ºC are 0.027 atm and 0.239 atm, respectively. Also, a

heating jacket will be needed to heat the vessel to 35 °C and cool it down afterwards. It will take approximately 1 hour to create a vacuum, 45 minutes to heat the tank, 60 minutes to carry out the evaporation process and 60 more to release the vacuum and cool it down to 10 °C. The stream coming out of the evaporation process will be sent for recovery using a distillation or similar separation system followed by condensation. This aspect exceeds the scope of our current discussion. In vessel V-3 we will have a remaining quantity of 3,626 kg of substances. One of these substances will be TT+TC, which will have precipitated, although it will only represent approximately 17 % of the total stream.

The obtained product will be gravity-drained through a valve, allowing its transportation to a Nutsche filter (F-2). There, a first filtration will be carried out, resulting in an outlet waste stream of the remaining solvent, excluding the small amount that will remain with the solid, as it will come out wet. A small quantity of dissolved TT+TC will be lost during this initial filtration. Following this first filtration, toluene is introduced to clean the obtained solid, resulting in the first instance of a TT+TC product with a moisture content of 10 %. This process will be done twice as it has previously been decided that there is only going to be bought a unique Nutsche filter adaptable to first and second use (F-2) and its capacity will be about 2,000 L.

After, the TT+TC filtrate and clean product is transferred to a reactor (V-4), where subsequently 3,180 L of isopropanol will be introduced through the top. The isopropanol is sourced from a storage vessel (IBC) and flows into vessel V-4 in the same manner as the thionyl chloride reached vessel V-1. The discharge of isopropanol will last 45 minutes and will be carried out with the assistance of a weighing system that controls a valve in the pipeline entering the reactor. Reaction will be carried out and maintained for an hour and a half. Similar to solvent evaporation process in vessel V-3, in this case there are involved isopropanol and a small amount of toluene. It should be noted that the boiling points of isopropanol and toluene are 82.5 and 110.6 °C, respectively. Therefore, another vacuum service will be required to evaporate at 35 °C. The vapor pressures of isopropanol and toluene are 0.105 and 0.062 atm, respectively. Furthermore, the reactor vessel is equipped with a jacket to heat the vessel to 35 °C and cool it at the end of the operation. Thus, when the vessel is full, a vacuum of 0.062 atm is created, the vessel is heated to 35 °C, evaporation takes place, the vacuum is released, and finally, it is cooled down to 10 °C. This entire process will take 10 hours and 15 minutes. The same way as before,

the stream of solvent exiting this unit is challenging to recover. In the vessel, we will then have a total mass of 1,153 kg, of which 510 kg are TT+TC crystals.

The obtained product will be gravity-drained through a valve, allowing its transportation to the second Nutsche filter operation (F-2). In fact, this Nutsche filter is the same as the one used before. There, a first filtration will be carried out, resulting in an outlet waste stream of the remaining solvent, excluding the small amount that will remain with the solid, as it will come out wet. A small quantity of dissolved TT+TC will be lost during this initial filtration. Following this first filtration, toluene is introduced to clean the obtained solid, resulting in the first instance of a TT+TC product with a moisture content of 10 %. This filtration is going to be done just once, because the inlet stream is less voluminous than the 2,000 L capacity of the filter.

Finally, in the same Nustche filter (F-2) the drying of the product will be carried out. Since the vapor pressure of toluene is 0.062 atm, the filter will be subjected to this pressure, with the assistance of a vacuum service, to allow the solvent to evaporate at 35 °C.

To conclude the process, the containers, which are cardboard drums with an inner bag, weighing 20 kg, are filled, weighed, sealed, and properly labelled for either commercialization or storage. Each batch requires 25 drums and takes 6 hours and 15 minutes to package.

4.2. MASS BALANCE

It is important to study the mass balance to know the extent of primary materials required and the industrial product or by-products generated.

As observed previously, the process achieves a production of 500 kg per batch. The following table (*Table 3*) shows the mass balance. Mass balance can be easily observed with the aid of the process block diagram (*Figure 16*). The masses of the streams and the specific products to these streams are expressed in kilograms.

It is important to highlight that the input streams are coloured in green, the streams for recycling or disposal are in red, and the toluene streams for cleaning are in yellow. Stream 21 is depicted in blue as it represents the final product.

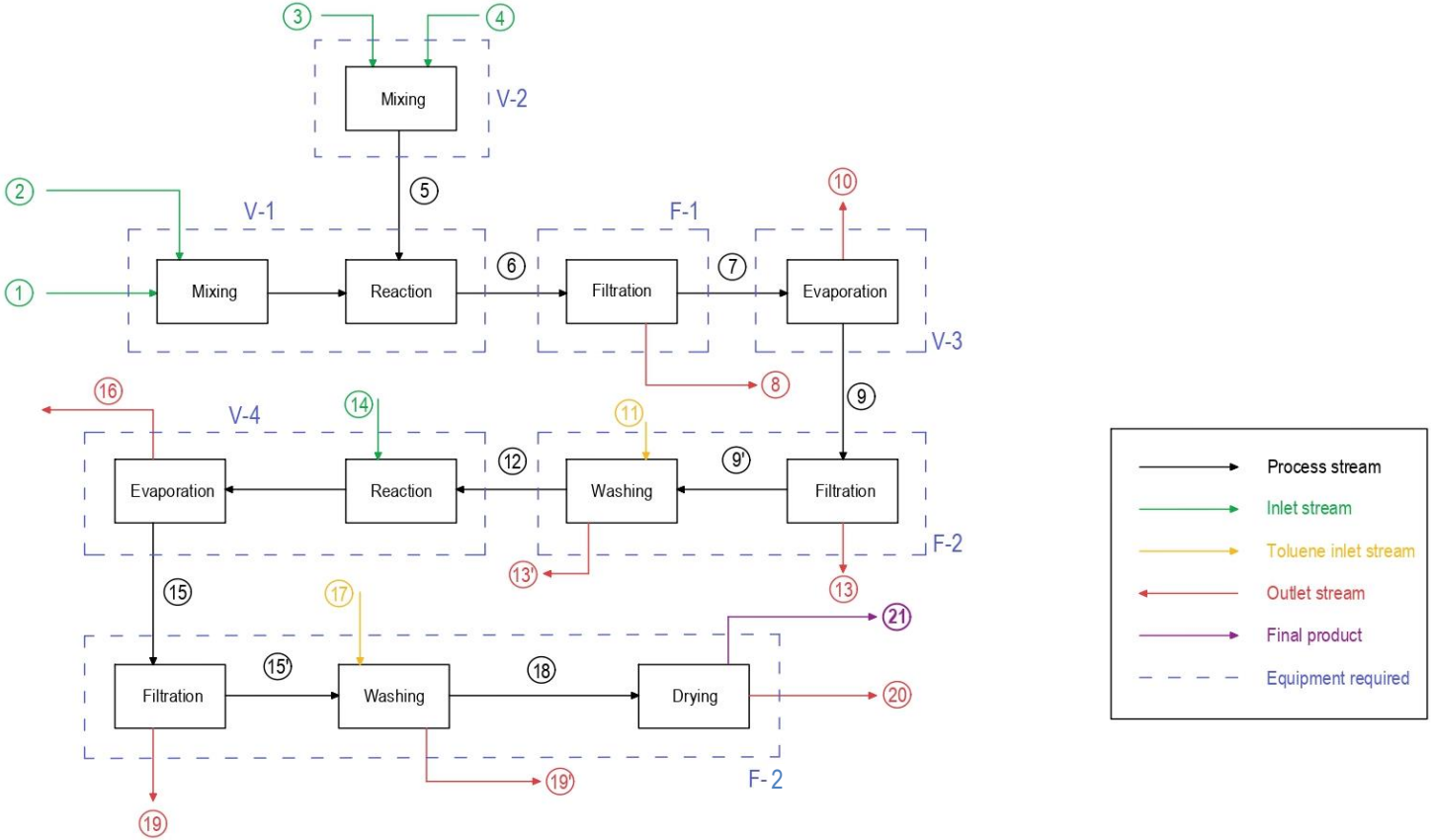


Figure 16. Block Diagram of the Process of purification of Tramadol

Table 3. Mass Balance for the Process of purification of Tramadol

	1	2	3	4	5	6	7	8	9	9'	10	11	12
TT	882.0					574.4	573.4	0.9	573.4	567.8			567.8
TC	588.0					43.2	43.2	0.1	43.2	42.7			42.7
TT+TC	1470.0					617.6	616.6	1.0	616.6	610.5			610.5
$SOCl_2$			494.5		494.5	49.5	49.46	0.042	7.4	0.2	42.0		
CBz		4602.0		1255.0	1255.0	5857.0	5852.0	5.0	1755.6	35.6	4096.4		
TOL												150.0	61.1
IPA													
Solid impurities						50.0		50.0					
Liquid impurities						1247.4	1246.3	1.1	1246.3	25.3			
TOTAL	**1470.0**	**4602.0**	**494.5**	**1255.0**	**1749.5**	**7821.5**	**7764.4**	**57.1**	**3626.0**	**671.6**	**4138.4**	**150.0**	**671.6**

	13	13'	14	15	15'	16	17	18	19	19'	20	21
TT	5.7			474.3	469.7	93.5		469.7	4.7		465.0	4.7
TC	0.4			35.7	35.4	7.0		35.4	0.4		35.0	0.4
TT+TC	6.1			510.0	505.0	100.5		505.0	5.0		**500.0**	5.0
$SOCl_2$	7.3	0.2										
CBz	1720.0	35.6										
TOL		89.0		18.3	1.5	42.7	100.0	60.0	16.9	41.4		60.0
IPA			2500.0	625.0	49.5	1875.0			575.5	49.5		
Solid impurities												
Liquid impurities	1221.1	25.3										
TOTAL	**2954.4**	**150.0**	**2500.0**	**1153.3**	**556.0**	**2018.2**	**100.0**	**565.0**	**597.3**	**90.9**	**500.0**	**65.0**

4.3. EQUIPMENT

In this section, the equipment available in a tramadol purification plant will be discussed. Also, it will provide information about their key characteristics and main functions.

AGITATED VESSEL (V-1)

This first vessel is where the reaction of cis tramadol and thionyl chloride takes place along with chlorobenzene as a solvent. The vessel has a capacity of 7,500 L and an agitation system to ensure an axial flow model. The operation is carried out at atmospheric pressure and at an ambient temperature of 25 °C. This is possible because the reactor is equipped with a half pipe jacket to ensure optimal conditions for the chemical process. It also incorporates a weighing system to monitor the quantities being fed into the vessel.

In Appendix 1 there is a table containing the basic information about this unit (*Table 10*). However, the following image (*Figure 17*) shows the vessel itself.

Figure 17. Illustration of Vessel V-1 [14]

AGITATED VESSEL (V-2)

Vessel V-2 serves a vital purpose in the production of tramadol even though it doesn't directly take part in the process. This vessel mixes and stores approximately 4,300 L of the pertinent mixture of thionyl chloride and chlorobenzene. The vessel has a capacity of 5,000 L.

Operating under ambient conditions at a temperature of 25 °C, V-2 ensures a stable environment for the mixture. The vessel operates at atmospheric pressure. It incorporates, just as vessel V-1 does, a weighing system to monitor the quantities being fed into the vessel.

Vessel V-2 is smaller than V-1 and does not need the half pipe jacket. There is a representative illustration of this vessel in *Figure 18* below and specification sheet in *Table 11* in Appendix 1.

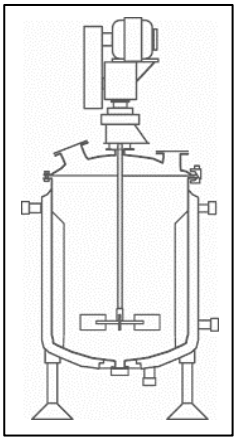


Figure 18. Illustration of Vessel V-2

IMPURITIES FILTER (F-1)

Filter F-1 is a bag filter consisting of a bag and a casing. Its purpose is to separate the impurities of the resulting product from the previous vessel. It operates while the vessel (V-1) is discharging.

The bag where the impurities are collected has a capacity of 25 kg. Consequently, the operation is carried out in two cycles. The following illustration (*Figure 19*) is a visual exemplification of this unit.

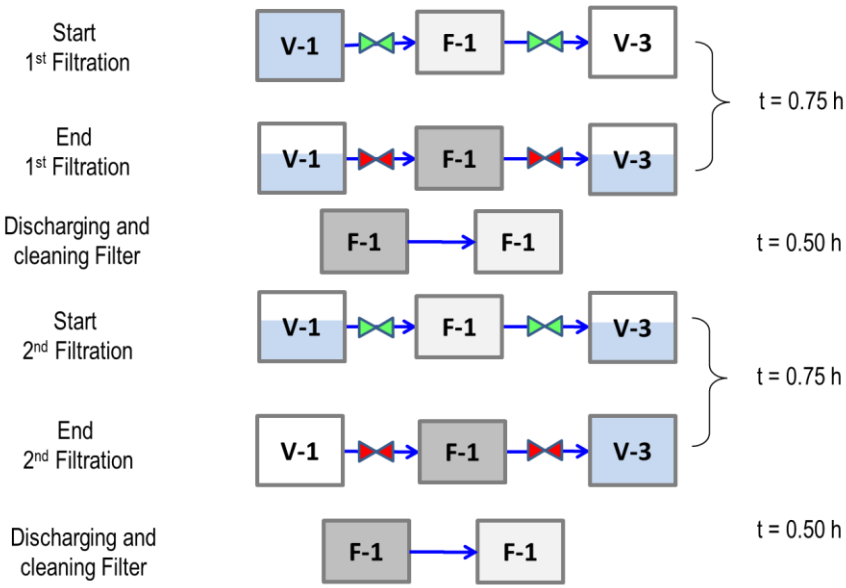


Figure 19. Filtration scheme in 2 Cycles [15] [16]

It offers a practical V-clamp closure and threaded couplings for easy installation. Each unit comes with stainless steel containment baskets that accommodate filter bags of different sizes. The filter has a single bag capacity, and its design emphasizes cost-effectiveness. It has a maximum operating pressure of 6.9 bar and can handle a maximum operating temperature of 93 °C. The concave lid with a V-clamp closure enhances its functionality. The filter is constructed with high-quality type 316 stainless steel (*Figure 20*).

Figure 20. Illustration of Filter F-1 [17]

AGITATED VESSEL (V-3)

Vessel V-3 plays a crucial role in the treatment of the mixture containing TT+TC. The vessel initially contains a mixture with a total remaining mass of 3,626 kg of substances. V-3 facilitates the evaporation of solvents present in the mixture. To achieve this, a vacuum service is employed to establish a vacuum, enabling the solvent to evaporate effectively at the designated temperature of 35 °C.

Figure 21. Illustration of vacuum vessel V-3 [18]

Vessel V-3, through its efficient evaporation process, contributes to the removal of solvents and aids in obtaining a product with the desired characteristics. The vessel's capacity, operating temperature, and use of a vacuum service ensure the successful execution of the solvent evaporation procedure. In *Table 12* from Appendix 1 there is the basic information about this unit.

AGITATED VESSEL (V-4)

In this reactor it is wanted to purify the product obtained by introducing isopropanol and evaporating it immediately after. With a specified capacity of 3,500 L, reactor V-4 is designed to accommodate the necessary volume of isopropanol required for the reaction.

During the reaction, the reactor is heated to an operating temperature of 35 °C, creating an optimal environment for the reaction to occur. The reactor operates at atmospheric pressure.

After receiving isopropanol V-4 it starts the procedure to evaporate at 35 °C, under vacuum conditions. By maintaining the specified operating conditions and employing proper agitation, reactor V-4 enables the successful reaction between the isopropanol and TC, contributing to the production of the desired product, TT.

This vessel is equal to vessel V-3 in terms of properties and conditions, but smaller. A representation of it can be observed in previous *Figure 21*. In *Table 13* from Appendix 1 there is the basic information about this vessel.

NUTSCHE FILTER (F-2)

The Nutsche filter play an essential role in tramadol's purification process. The difference between the two functioning cycles remains in the fact that the second one (F-2) performs an extra step of drying. The unit itself though, is the same.

F-2 is employed after vessel V-3. During the initial filtration process, F-2 separates the remaining solvent, excluding a small amount that remains with the solid as it exits the unit in a wet state. This step is shown in *Figure 22* below.

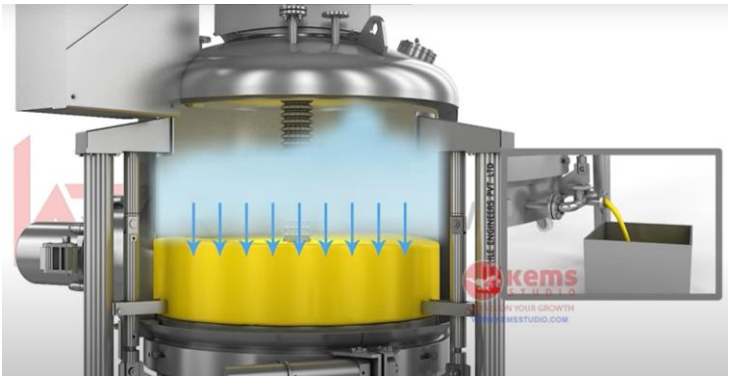


Figure 22. Illustration of Nutsche filter (first step of filtration) [19]

It should be noted that a minor quantity of dissolved TT+TC may be lost during this initial filtration. Following this step, toluene is introduced to cleanse the solid, resulting in the production of a TT+TC product with a moisture content of 10 %.

As in filter F-2, with the initial filtration process, it is separated the remaining solvent, excluding the small amount remaining with the wet solid. This step has been shown in *Figure 22* before. Following, toluene is introduced to cleanse the solid, resulting in a wet product of TT+TC.

Finally, the product is dried by bringing the filter to 0.062 atm, which is the value for the vapor pressure of toluene at the temperature of 35 °C. *Figure 23* below shows this step.

Figure 23. Illustration of Nutsche filter drying (last step of filtration) [19]

Nutsche filter operates at a pressure of 3 bars during filtration steps and has a capacity of 2,000 L, meaning that operation F-2 will require two cycles.

PLANT SERVICES

All vacuum, heating, and cooling services are intrinsic to the plant and serve not only for the specific process at hand.

4.4. TIME STUDY

To examine each unit involved in the process and their respective occupation times, it is necessary to delve into every operation that takes place. Indicative and conservative timings have been determined for each operation and are shown in the following *Table 4*.

Table 4. Time Study for a Batch

	Operation	OT [h]
V-1	Charge of CBz	0.25
	Charge of TT+TC	0.75
	Mixing	0.50
	Control	0.50
	Charge from V-2	2.00
	Reaction	2.00
	Discharge to F-1	2.00
	Cleaning	2.00
F-1	Charge from V-1	0.75
	Cleaning	0.50
	Charge from V-1	0.75
	Cleaning	0.50
V-3	Charge from F-1	2.00
	Vacuum	1.00
	Heating	0.75
	Evaporation	1.00
	Realeasing vacuum and cooling	1.00
	Crystallization	4.00
	Control	1.00
	Discharge to F-2	3.75
	Cleaning	2.00
F-2 (x2)	Charge from V-3	0.25
	Filtration	0.75
	Cleaning with TOL	0.25
	Second filtration	0.25
	Control	0.50
	Discharging to V-4	1.00
	Cleaning	0.50

	Operation	OT [h]
V-4	Charge from F-2	4.50
	Charge of IPA	0.75
	Reaction	3.00
	Vacuum	1.00
	Heating	0.50
	Evaporation	1.00
	Cooling to 10 ºC	0.75
	Crystallization	4.00
	Control	0.50
	Discharge to F-3	0.25
	Cleaning	2.00
F-2	Charge from V-4	0.25
	Filtration	0.75
	Cleaning with TOL	0.25
	Second filtration	0.25
	Drying	4.00
	Control	3.00
	Discharging FP	6.25
	Cleaning	0.50
	Final cleaning	1.50

There are some observations that should be made regarding the operation time study. Firstly, the loading of raw materials varies in duration due to their respective sources, whether they are transported via pipelines or containers or big bags.

Also, a mandatory control and cleaning process is conducted for all operations. The duration of these varies depending on the specific unit involved, with some units requiring longer periods than others.

Moreover, the bag filter (F-2) operates in two cycles, and it is important to note that the loading from V-1 corresponds to the unloading from F-1 into V-3, indicating that both processes occur simultaneously. Similarly, the Nutsche filter (F-2) also operates in two cycles, meaning it is utilized on two occasions within the operation.

The mandatory control in second operating time F-2 lasts 3 hours in order to do all the analysis for the approval of the batch and complement the respective documentation. Lastly, the unloading of the final product signifies the moment when the assigned operator carries out several tasks, including filling the containers, preparing them, weighing the contents, sealing them, applying labels, and palletizing them.

After establishing the operational times for each operation and unit, it is important to analyse the occupation time for each unit and which unit is the bottleneck. The information mentioned is put together in *Table 5*.

Table 5. Occupation Times

	t_i [h]	t_f [h]	$t_{Charging}$ [h]	$t_{Operation}$ [h]	$t_{Discharging}$ [h]	$t_{Cleaning}$ [h]	OT [h]
V-1	0	10.00	1.00	5.00	2.00	2.00	10.00
F-1	6.00	8.50	0.00	1.50	0.00	1.00	2.50
V-3	6.00	22.50	2.00	8.75	3.75	2.00	16.50
F-2	16.75	23.75	0.50	3.50	2.00	1.00	7.00
V-4	18.75	37.00	5.25	10.75	0.25	2.00	18.25
F-2	34.75	**51.50**	0.25	8.25	6.25	2.00	16.75

Since there are no units kept waiting between interactions with the process, the occupation time of each unit is equivalent to the sum of timings of charging, operation, discharging and cleaning. However, there is a unit used twice in the production process. This means, it must be studied whether it will be a factor to consider when programming operational times.

The marked box in *Table 5* represents the batch time. In the following section it will be discussed in greater depth.

4.5. SCHEDULING

The scheduling of batch operations is crucial for optimizing the performance of the plant in which they are involved. It is important to carefully plan the timing of execution for all the tasks involved.

In the plant being studied in this project, each batch operation produces 500 kg of tramadol. Considering an annual demand of 20,000 kg, the plant's minimum annual production is 40 batches per year. Considering that the plant operates 24 hours a day, 7 days a week, for a total of 287 days per year, the number of working hours is 6,888 hours per year. However, considering possible delays and emergency stops, the actual production time is 4,500 hours per year.

A zero-wait philosophy has been adopted to do all the calculations. This means filter F-2 will be used for the following batch immediately after being cleaned from the previous one.

4.5.1. Batch time and Cycle time establishment

The operation time refers to the duration in which the unit is actively performing tasks such as mixing, heating its contents, or applying vacuum to them. Otherwise, the occupation time is the entire duration of usage for a unit, starting from its initial charging to the final cleaning of the entire operation. This includes every instance when the unit is utilized. In the case of the units used twice during the process (F-2), their occupation time extends from the first charging of the first instance to the last cleaning after their final usage in the process.

Now, the batch time and the cycle time must be determined. The first one refers to the duration of finishing a complete batch, from the very beginning to the last control of the process. However, the second term, refers to the period that limits a batch process by overlapping of different cycles of production.

As seen previously in *Table 5*, the batch time for this process is of 51 hours and 30 minutes, being filter F-2 the last unit involved. This unit is going to be incorporated singularly in the upcoming data presentation because, despite its requirement in two different situations, it is the same element. See *Figure 24* for a representation of the batch disposal and occupation times.

The process of purification of tramadol will require the use of a unit twice, and consequently it must be studied its absolute occupation time for the equipment. In *Table 6*, there are shown the

occupation times for all the equipment, considering that F-2 can be used for the following batch when cleaned from the previous one. In other words, it is considered the production in batches with overlap.

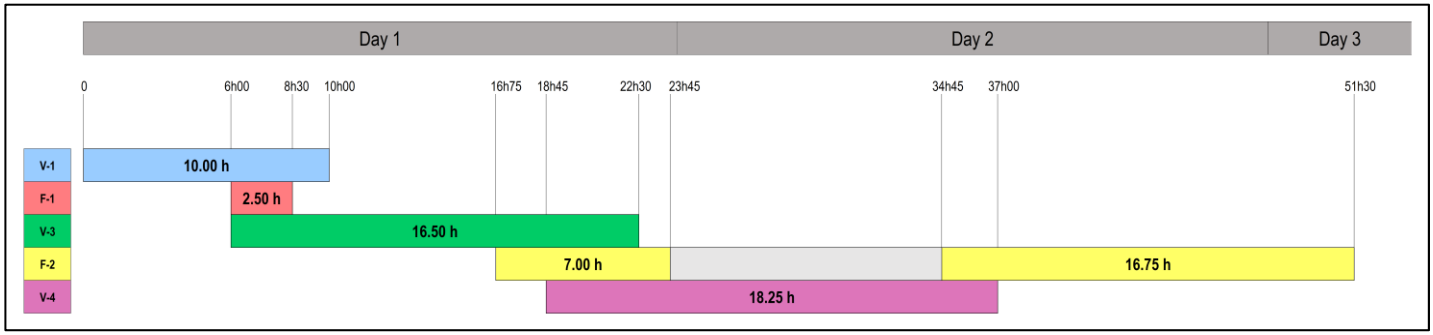


Figure 24. Batch time

Table 6. Occupation times for a batch and cycle time

	t_i [h]	t_f [h]	OT [h]
V-1	0	10.00	10.00
F-1	6.00	8.50	2.50
V-3	6.00	22.50	16.50
F-2	16.75	51.50	**34.75**
V-4	18.75	37.00	18.25

It is known that implementing a production in campaigns represents an optimization of time. So, to study the potential production process, two distinct approaches will be discussed. The first one involves non-overlapping campaigns, where a new batch commences only after the completion of the preceding one. However, this configuration is less efficient in terms of time utilization and cost savings.

In the case of non-overlapping campaigns, the cycle time aligns with the batch time. However, in overlapping campaign production, the concept of cycle time allows us to identify the unit with the longest occupation time. Consequently, this unit becomes the limiting factor for batch time. Considering the current situation of the plant, the cycle time corresponds to the Nutsche filter, which is of 34 hours and 45 minutes, as seen in *Table 6*. Thus, it determines the overall process time limitation. This means filter F-2 is the bottleneck.

On the other hand, there is the alternative approach through overlapping campaigns. In this case, each new batch begins before the previous one has been finished. This results in time savings. *Figure 25* provides a visual representation of this setup being F-2 the bottleneck.

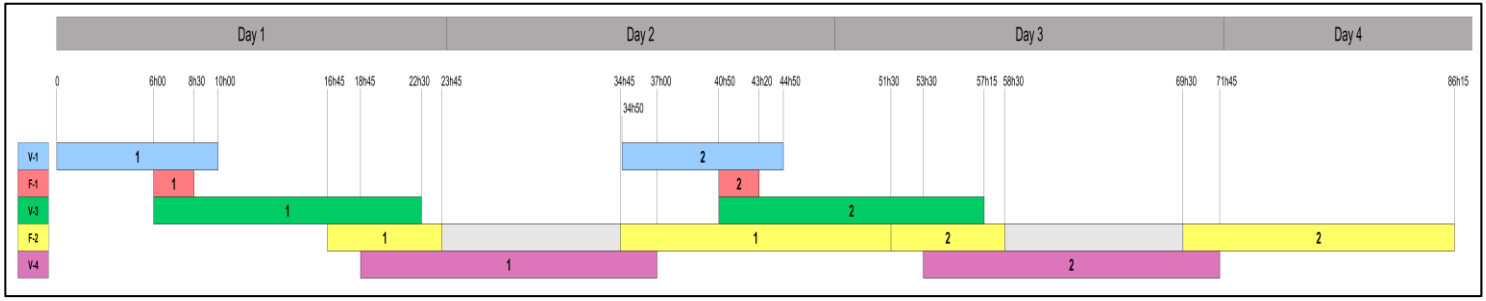


Figure 25. Diagram of overlapping campaign production

4.5.2. Campaigns

In addition to establishing the overlap of campaigns, it will also be analysed the required number of campaigns to meet the annual demand of tramadol. In this section, there are proposed different scenarios of possible distribution of campaigns to produce 40 batches within a year.

One approach involves working in a single campaign, dismissing the fact that we have a multipurpose batch plant available and that emergency stops can occur. The advantage of this production method lies in achieving the annual production within the shortest duration. However, there is an accumulation of excessive stock.

Another possibility is to work in two campaigns, with 20 lots each. This configuration enables the plant to produce multiple APIs since the equipment is also available for other processes. It facilitates efficient production, and the accumulation of stock is not excessively significant.

Working in 4 campaigns, each of 10 lots, it can be a feasible option. This way, there is done 1 campaign every 4 months. This approach extends the time required to produce tramadol, but it allows for a balanced stock.

Another approach is to produce in 10 campaigns, meaning each month 4 batches will be produced. This will result in a simplified stock but much easier to manage, while also leading to a more substantial increase in plant occupancy time compared to what has been observed so far.

The last viable option could be to produce in 20 campaigns, as in the previous case, with 4 batches per month, but not consecutively on this occasion. This means 2 batches in a row each 15 days.

Finally, an ultimate option will be presented just to compare to the other approaches. This will be doing 40 campaigns, or in other words, 40 individual non-consecutive batches.

To perform the necessary calculations, we use the equation:

$$\mathrm{MT_n} = \mathrm{BT} + (\mathrm{N} - 1) \cdot \mathrm{CT} \qquad (1)$$

$\mathrm{MT_n}$ represents the required time to produce the specified lots (N) and is expressed in hours/year. BT is the batch time in hours, and CT, the cycle time, also in hours.

In the following *Table 7,* the total times for the occupation of the plant in each case can be seen.

Table 7. Minimum Time of Production for Number of Campaigns

Campaigns	Lots/campaign	Total time [h]
40	1	2060.00
20	2	1725.00
10	4	1557.50
4	10	1457.00
2	20	1423.50
1	40	1406.75

Also, a visual representation can be seen in *Figure 26*.

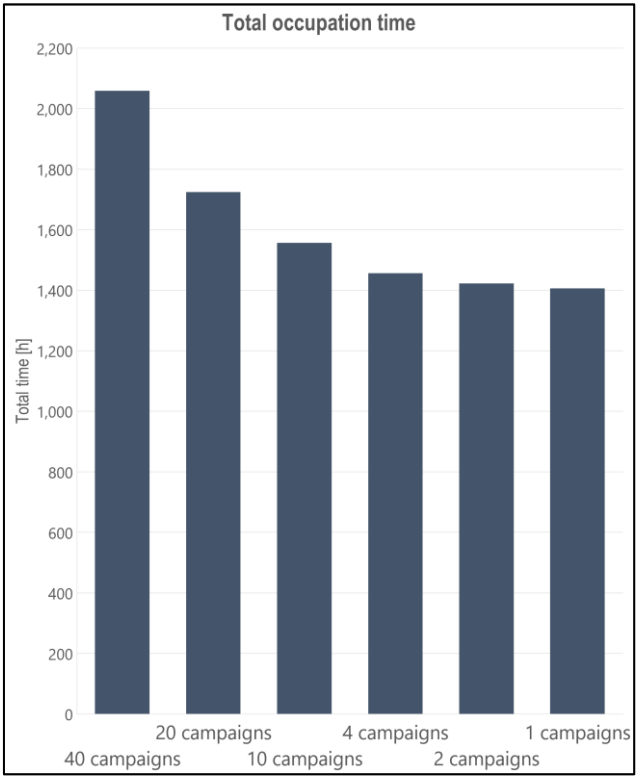


Figure 26. Visual representation for Minimum Time of Production

The determination of the optimal number of campaigns to produce 40 lots per year will be based on the specific needs of the plant. It should be noted that the plant is designed to produce other APIs as well, which further complicates the decision-making process. While the total time required for each case surpass that of a single campaign, they all still fall within the plant's estimated operating hours (4,500 h).

Some approaches not only mitigate stock-related challenges but also provide the opportunity to diversify production beyond tramadol alone, aligning with the multifunctionality of the plant.

4.5.3. KPIs calculation

Having thoroughly examined the various aspects concerning the timings of the entire purification process, it is essential to establish the Key Performance Indicator (KPI). Currently, the primary KPI employed within the company is the maximum production capacity of an API. This KPI allows to determine the maximum number of batches that can be produced per year, assuming the production line is dedicated exclusively to the manufacturing of tramadol, and that a single campaign is conducted without any line stoppages.

The calculation of this indicator is based on the batch time and the cycle time, as defined in *Equation (1)*. With this equation, we can accurately evaluate the quantity of tramadol manufactured in one year, considering the facilities and the process design determined in this project. This information is shown in *Table 8*.

Table 8. Process data and maximum production capacity

Batch size [kg/batch]	500
Running hours/year	4,500
Batch time [h]	51.50
Cycle time [h]	34.75
Maximum production capacity [lots/year]	129
Maximum production capacity [kg/year]	64,500

The minimum production time, which has been seen previously when analysed the production in one unique campaign of 40 batches, is another KPI that can be studied. In *Table 9*, there is the information needed to calculate the minimum production time.

Table 9. Process data and minimum production time

Batch size [kg/batch]	500
Annual production [kg/year]	20,000
Batch time [h]	51.50
Cycle time [h]	34.75
Minimum production time [h/year]	1406.75
Minimum production time [days/year]	58.61

5. CONCLUSIONS

The study successfully determined the production process for 20 tons of tramadol per year and the optimal lot size of 500 kg. The selection of necessary equipment, such as designed vessels and chosen filters, was carefully made considering the necessary amount of production.

Further elaboration on the filters and their selection criteria can be provided. Notably, the decision to utilize the same filter in two stages of the process was made, despite it not being utilized for drying in the first stage of usage. This highlights the versatility of the multiproduct plant and its multipurpose production line.

An analysis of timings resulted in the determination of the batch and cycle times, the maximum production capacity, and the minimum plant occupation time. These parameters play crucial roles in ensuring efficient operation and resource utilization. Furthermore, various campaign options were explored to identify the most effective production strategies.

It is important to note that the production of tramadol will be influenced by other campaigns for different products carried out in the plant. This means, a final solution has not been proposed, such a deeply study of the plant and its production processes should have to be made.

In conclusion, through this study, the production process of the 20 tons of tramadol was thoroughly analysed and KPIs were established. The results of this study give key information about how to manage the required production effectively.

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ACRONYMS

AEMPS: Spanish Agency for Medicines and Medical Devices

API: Active Pharmaceutical Ingredient

BT: Batch Time

CBz: Chlorobenzene

CIMA: Center for Information about Medicines

CT: Cycle Time

DHD: Doses per day

EMA - European Medicines Agency

F-1: Bag filter

F-2: Nutsche filter

GMP: Good Manufacturing Practices

HCl: Hydrogen chloride

IBC: Intermediate Bulk Container

IUPAC: International Union of Pure and Applied Chemistry

KPI: Key Performance Indicators

MDG: Millennium Development Goals

MTn: Minimum Time of Production

N: Number of Campaigns

NIST: National Institute of Standards and Technology

PVP: Public sale price

SDG: Sustainable Development Goals

$SOCl_2$: Thionyl chloride

TC: Tramadol Cis isomer

THF: Tetrahydrofuran

TT: Tramadol Trans isomer

UN: United Nations

VAT: Value Added Tax

V-1: Agitated vessel 1

V-2: Agitated vessel 2

V-3: Agitated vessel 3

V-4: Agitated vessel 4

WHO: World Health Organization

APPENDICES

APPENDIX 1: EQUIPMENT

Table 10. Vessel V-1 specification sheet

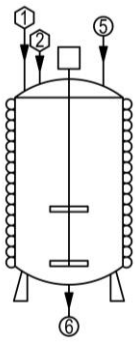
SPECIFICATION SHEET		Equipment	Reactor
		N Equipment	V-1
PROJECT		Purifcation of trans tramadol	
DESIGN			
Capacity [L]	7,500	Feeding inlets	3
Temperature [ºC]	25	Discharging outlets	1
Pressure [atm]	1	Material	316 stainless steel
Height [m]	3.7	Diameter [m]	1.6
HEAT TRANSFER			
Exchanger		Half pipe jacket with heat exchangers system	
Operation	Cooling	Fluid	Cold water
Exchange area [m^2]	18.75		
AGITATION			
Type	Paddle		
Impeller-bottom distance [m]	0.56		
Diameter [m]	1.40		
Agitation speed [rpm]	250		

Table 11. Vessel V-2 specification sheet

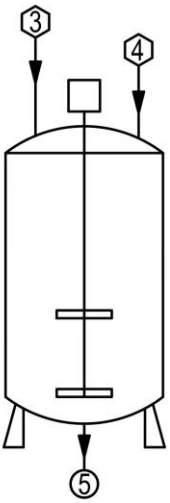
SPECIFICATION SHEET		Equipment	Reactor
		N Equipment	V-2
PROJECT		Purifcation of trans tramadol	
DESIGN			
Capacity [L]	5,000	Feeding inlets	2
Temperature [ºC]	25 - 30	Discharging outlets	1
Pressure [atm]	1		
Height [m]	2.5		
Diameter [m]	1.6		
Material	316 stainless steel		
AGITATION			
Type	Paddle		
Height [m]	0.375		
Diameter [m]	1.3		
Agitation speed [rpm]	300		

Table 12. Vessel V-3 specification sheet

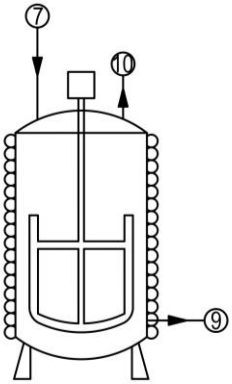
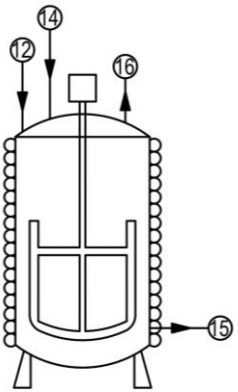
SPECIFICATION SHEET		**Equipment**	Reactor
		N Equipment	V-3
PROJECT		Purifcation of trans tramadol	
DESIGN			
Capacity [L]	7,500	**Feeding inlets**	1
Temperature [ºC]	35	**Discharging outlets**	2
Pressure [atm]	0.027	**Material**	316 stainless steel
Height [m]	3.50	**Diameter [m]**	1.70
HEAT TRANSFER			
Exchanger		Half pipe jacket with heat exchangers system	
Operation	Heating	**Fluid**	Water vapor
	Cooling		ETG
Exchange area [m^2]	18.70		
AGITATION			
Type	Anchor		
Height [m]	1.05		
Diameter [m]	1.3		
Number of baffles	2		
Agitation speed [rpm]	Speed controller		

Table 13. Vessel V-4 specification sheet

SPECIFICATION SHEET		Equipment	Reactor
		N Equipment	V-4
PROJECT		Purifcation of trans tramadol	
DESIGN			
Capacity [L]	3,500	Feeding inlets	2
Temperature [ºC]	35	Discharging outlets	2
Pressure [atm]	0.062	Material	316 stainless steel
Height [m]	2.50	Diameter [m]	1.40
HEAT TRANSFER			
Exchanger		Half pipe jacket with heat exchangers system	
Operation	Heating	Fluid	Water vapor
	Cooling		ETG
Exchange area [m^2]	11.00		
AGITATION			
Type	Anchor		
Height [m]	0.60		
Diameter [m]	1.2		
Number of baffles	2		
Agitation speed [rpm]	Speed controller		