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Basic design of a dexketoprofen trometamol production plant

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Our greatest glory is not in never falling,
but in rising every time we fall.

Confucius

Querría agradecer a mis tutores, el Dr. Manuel Vicente y la Dra. Esther Chamarro, por toda la ayuda y el apoyo que me han aportado durante la elaboración de este trabajo. Sus ánimos, paciencia y comprensión me han dado fuerzas para superar los miedos e inquietudes a lo largo de esta experiencia. Gracias por los conocimientos que me han transmitido, las conversaciones que hemos compartido y todas las llamadas y reuniones que hemos mantenido. De cada una de ellas he salido con más motivación para sacar adelante este proyecto y con más interés en aprender sobre lo que implica la Ingeniería Química.

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SUMMARY

Dexketoprofen trometamol is an active pharmaceutical ingredient belonging to the NSAID (Nonsteroidal Anti-Inflammatory Drugs) class, commonly used to treat mild to acute pain, such as postoperative pain. Its consumption has been increasing over the years, since, unlike the most widely used NSAID in Spain, ibuprofen, it has considerably fewer side effects at the gastric level, while maintaining its efficacy in pain inhibition.

The main objective of this work is to carry out a basic design for the production of this active ingredient. To this end, a market study has been performed, in which the annual European demand for dexketoprofen trometamol was estimated at approximately 100 tons. On the basis of this figure, it has been decided to cover 10 % of this demand, which equals about 10 t/year. This production is designed to be carried out in 20 batches, each containing 500 kg of DKT with 98 % purity, and packed in drums of 25 kg.

A patent search was then carried out to obtain information on how to produce the desired product, including operating conditions, reaction times and other relevant parameters, since this study does not delve into the kinetics of the synthesis. Among the different patents analyzed, patent CN101928214A was selected as the main reference for the process design. However, since the process described in this patent is too extensive for the purposes of this study, the battery limit was limited from the synthesis of dexketoprofen trometamol from dexketoprofen and tromethamine to the final packaging of dexketoprofen trometamol.

Based on the selected patent and the defined battery limit, a recipe adapted to industrial production has been developed, describing in detail each stage of the process and its respective operating conditions. Subsequently, a block diagram has been developed to visualize the process, together with a mass balance to determine the quantities of material required to produce 500 kg of product per batch.

Once the process and its unit operations have been defined, the required equipment has been specified. The reaction (V-1) and crystallization (V-2) tanks have been designed, both of 5.3 m^3.

A bag filter (F-1) has been selected for the separation of solid impurities, a Nutsche filter (F-2) for the purification and drying of the crystals, and a pin mill (M-1) for the size reduction of the final product. The corresponding technical specification sheets have been prepared for each of these units. From all this information and the adapted recipe, the P&ID (Piping and Instrumentation Diagram) of the designed process was drawn.

Next, a study of the occupancy time of each equipment has been carried out, obtaining a batch time of 32 h and a cycle time of 18.5 h, being the Nutsche filter (F-2) the limiting equipment for requiring the longest operation time. With this information, two types of batch production scheduling have been compared: overlapping and non-overlapping batches. The scheduling with overlapping batches has been chosen for being more efficient in terms of time.

Within this context, a constraint related to thermal services has been considered, since both the reaction tank (V-1) and the Nutsche filter (F-2) require steam water during a certain time in the overlapping schedule. Based on this constraint, two configurations have been evaluated: with and without heating services overlap.

For both configurations, a KPI analysis has been performed, determining the maximum production capacity and minimum production time: 17.48 t/year and 16.75 days/year for the configuration without services constraint, and 14.87 t/year and 19.46 days/year for the configuration with such constraint.

Finally, a campaign scheduling study has been carried out, in which it has been decided to distribute the production in 4 campaigns, one every 2.5 months of 5 batches each. This distribution avoids the accumulation of stock and leaves enough time between campaigns for the manufacture of other products in the plant.

Keywords: dexketoprofen trometamol, API, basic design, production plant

RESUMEN

El dexketoprofeno trometamol es un principio activo farmacéutico perteneciente a la clase de los AINE (Antiinflamatorios No Esteroideos), utilizado habitualmente para el tratamiento del dolor leve hasta agudo, como el dolor postoperatorio. Su consumo se ha ido incrementando a lo largo de los años, ya que, a diferencia del AINE más utilizado en España, el ibuprofeno, presenta bastantes menos efectos secundarios a nivel gástrico, manteniendo su eficacia en la inhibición del dolor.

El objetivo principal de este trabajo es realizar un diseño básico para la producción de este principio activo. Para ello, se ha realizado un estudio de mercado, en el que se ha estimado la demanda anual europea de dexketoprofeno trometamol en aproximadamente 100 toneladas. A partir de esta cifra, se ha decidido cubrir el 10 % de esta demanda, lo que equivale a unas 10 t/año. Esta producción está diseñada para lograr en 20 lotes, cada uno de los cuales contendrá 500 kg de DKT con una pureza del 98 %, y se envasará en bidones de 25 kg.

A continuación, se realizó una búsqueda de patentes para obtener información sobre cómo producir el producto deseado, incluidas las condiciones de funcionamiento, los tiempos de reacción y otros parámetros relevantes, ya que este estudio no profundiza en la cinética de la síntesis. Entre las diferentes patentes analizadas, se seleccionó la patente CN101928214A como referencia principal para el diseño del proceso. Sin embargo, dado que el proceso descrito en esta patente es demasiado extenso para los fines de este estudio, el límite de batería se limitó desde la síntesis de dexketoprofeno trometamol a partir de dexketoprofeno y trometamina hasta el envasado final de dexketoprofeno trometamol.

A partir de la patente seleccionada y del límite de batería definido, se ha elaborado una receta adaptada a la producción industrial, en la que se describe detalladamente cada etapa del proceso y sus respectivas condiciones de funcionamiento. Posteriormente, se ha desarrollado un diagrama de bloques para visualizar el proceso, junto con un balance de masa para determinar las cantidades de materia necesarias para producir 500 kg de producto por lote.

Una vez definido el proceso y sus operaciones unitarias, se ha especificado el equipo necesario. Se han diseñado los tanques de reacción (V-1) y cristalización (V-2), ambos de 5,3 m³. Se ha seleccionado un filtro de bolsas (F-1) para la separación de impurezas sólidas, un filtro Nutsche (F-2) para la purificación y secado de los cristales, y un molino de púas (M-1) para la reducción de tamaño del producto final. Para cada una de estas unidades se han elaborado las correspondientes fichas de especificaciones. A partir de toda esta información y de la receta adaptada, se dibujó el P&ID (Diagrama de Tuberías e Instrumentación) del proceso diseñado.

A continuación, se ha realizado un estudio del tiempo de ocupación de cada equipo, obteniéndose un tiempo de lote de 32 h y un tiempo de ciclo de 18,5 h, siendo el filtro Nutsche (F-2) el equipo limitante por requerir el mayor tiempo de operación. Con esta información se han comparado dos tipos de programación de producción de lotes: con solapamiento y sin solapamiento de lotes. Se ha elegido la programación con solapamiento por ser más eficiente en términos de tiempo.

Bajo este contexto, se ha considerado una restricción relacionada con los servicios térmicos, ya que tanto el tanque de reacción (V-1) como el filtro Nutsche (F-2) requieren vapor de agua durante cierto tiempo en la programación con solapamiento. Basándose en esta restricción, se han evaluado dos configuraciones: con y sin solapamiento de servicios térmicos.

Para ambas configuraciones se ha realizado un análisis de KPI, determinando la capacidad máxima de producción y el tiempo mínimo de producción: 17,48 t/año y 16,75 días/año para la configuración sin restricción de servicios, y 14,87 t/año y 19,46 días/año para la configuración con dicha restricción.

Por último, se ha realizado un estudio de programación de campañas, en el que se ha decidido distribuir la producción en 4 campañas, una cada 2,5 meses de 5 lotes cada una. Esta distribución evita la acumulación de stock y deja tiempo suficiente entre campañas para la fabricación de otros productos en la planta.

Paraules clau: dexketoprofeno trometamol, API, diseño básico, planta de producción

SUSTAINABLE DEVELOPMENT GOALS

Good health and well-being:

The designed process will provide another possibility and insight on the production of an Active Pharmaceutical Ingredient that will ease pain, ease post-operation experience and enhance well-being of the people.

Gender equality:

The facility will enforce a strict non-discrimination policy, ensuring equal hiring opportunities for all genders and actively promoting gender equality ideology.

Decent Work and Economic Growth:

This project will contribute to enhancing the growth of the pharmaceutical industry in Spain, which could lead to economic development and increase of job opportunities.

Industry, Innovation, and Infrastructure:

The implementation of the production plant will strengthen the national chemical industry and promote innovation and investment in research and development.

1. INTRODUCTION

Analgesic drugs are widely used across all ages of people around the world due to their painkilling effect. Compared to other medications, analgesic ones are used in much higher frequency in daily life to confront a considerable variety of situations such as muscle pain, tooth pain, stomachache, ... This is why this type of API (Active Pharmaceutical Ingredient) has experienced significant market growth over the past five years, with the market size estimated at USD 10.5 billion in 2024 and projected to reach USD 15.2 billion by 2033 [1].

Analgesic medications are mainly classified into the following categories: adjuvants, opioids and non-opioids.

Between those above, opioid analgesics once represented a high percentage of analgesic consumed for their high effectiveness in reducing severe pain, however, due to the risk of developing addiction, their use has been reduced. They have slowly been substituted by the non-opioids, mainly NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), nowadays often used in postoperative analgesia [2] [3].

Dexketoprofen trometamol is one of the main NSAIDs consumed in the world. It is remarkable for its better effect for pain inhibition in lower doses (twice the potency of the racemic form of ketoprofen), fast onset action within 30 min, and milder secondary symptoms compared to more commonly used medications such as paracetamol and ibuprofen.

Not only analgesic, but antipyretic and anti-inflammatory properties make DKT (Dexketoprofen trometamol) a very effective medicine for treating mild to acute pain in the short term and facing musculoskeletal pain, dental pain, and dysmenorrhea among others.

This drug was first developed in 1997 by the Menarini S.A. company in Barcelona. Its main goals were to decrease the time of onset action of the antipyretic agent, along with increasing its potency and diminishing its gastrointestinal side effects [4].

By the end of the 20th century, its appearance in the world provided more proof that in the case of arylpropionic acids, the S enantiomer form of the APIs presents fewer side effects compared to their racemic mixture (as ibuprofen, ketoprofen, fenoprofen, …).

Since those years, DKT has expanded its use from pain relieving to epilepsy and oncology related development and investigation, making it a compound constantly studied and developed.

1.1. STRUCTURE & PROPERTIES OF DEXKETOPROFEN TROMETAMOL

Dexketoprofen trometamol is the tromethamine salt form of dexketoprofen [5]. It is obtained through a stoichiometrically equimolar reaction between dexketoprofen and tromethamine in an organic solvent, with a 1:1:1 stoichiometry for dexketoprofen, tromethamine, and the resulting product (DKT).

With molecular formula $C_{20}H_{25}NO_6$, it is also named 2-(3-Benzoylphenyl)propanoic acid-2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) by the IUPAC (International Union of Pure and Applied Chemistry) system.

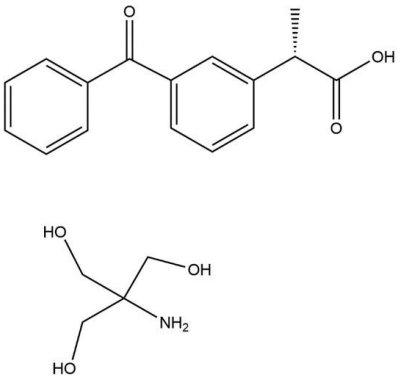


Figure 1. Chemical structure of DKT [5]

Ketoprofen is a derivative of propionic acid which presents 2 enantiomers: (R)-ketoprofen and (S)-ketoprofen. Dexketoprofen is the dextrorotatory S-enantiomer of ketoprofen, the main responsible one for its therapeutic effects [6] [7].

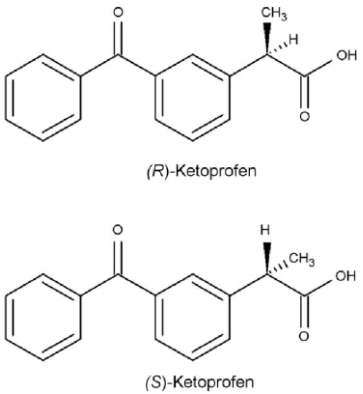


Figure 2. Chemical structure of ketoprofen's enantiomers [7]

It acts by inhibiting the effect of the COXs (cyclooxygenase) of the body, specifically cyclooxygenase-1 (constitutive COX-1) and cyclooxygenase-2 (inducible COX-2), which synthesize prostaglandins during inflammation of the body. Prostaglandins such as PGE_2 (Prostaglandin E2) are chemical messengers that make nociceptors (nerve endings that detect pain) sensitive to signals like bradykinin and histamine [8].

Depending on the selectiveness on inhibition of COX-2 activity, NSAIDs can be classified in non-selective or COX-2 selective. Even though dexketoprofen is classified as non-selective, it is considered to have a more selective mode of action on the COX-2 and therefore induces lighter gastric lesions compared to other non-selective NSAIDs that inhibit both the activity of COX-1 and COX-2. Inhibiting COX-1 blocks its protective activity in the stomach based on mucus secretion and reduction of acid secretion [9].

As commented before, another advantage of dexketoprofen is its rapid onset of action. It is usually administered to patients 15 minutes before a painful procedure. The analgesic effect begins approximately 30 minutes after administration and its effect remains for 4 – 6 h. It is absorbed by gastrointestinal conduct and excreted via the kidneys and thus, doesn't accumulate in the body [10].

The development of DKT proved the effectiveness and advantages of S enantiomer forms compared to racemic forms of arylpropionic acids. The R enantiomer, present in racemic compounds, is less effective in COX inhibition and associated with stronger gastrointestinal side

effects due to its ulcerogenic (formation of ulcers that derive stomach pain) properties and interference with metabolic processes.

Compared to other NSAIDs, dexketoprofen presents fewer side effects. Unlike ibuprofen, which is widely used in its racemic form (containing both R- and S-enantiomers), dexketoprofen contains only the active S-enantiomer. As a result, it achieves the same therapeutic effect at a lower dose, up to half that of most racemic NSAIDs. In summary, due to this and its rapid absorption and onset of action, dexketoprofen significantly reduces gastrointestinal side effects compared to other NSAIDs.

The tromethamine makes the drug more suitable for oral administration by enhancing the solubility in water of the drug, as it acts as the counter-ion.

1.2. MARKET STUDY

The market value of the API is a key factor in determining the economic feasibility of its industrial production. A market study is conducted to analyze demand and impact of the DKT on present society. The information gathered from it determines the quantity and form of DKT to be produced.

In Spain, DKT is marketed mainly by companies such as Menarini laboratories S.A., CINFA laboratories S.A., Normon laboratories S.A., among others.

DKT is commercialized in various concentrations and pharmaceutical forms: film coated tablets, granules for oral solutions, and injectable solutions, as Figures 3 and 4 show [11].

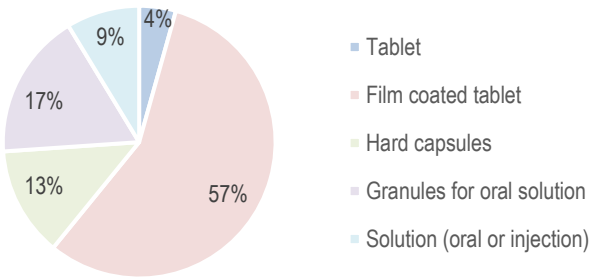


Figure 3. Distribution of Pharmaceutical Forms of DKT in Spain [%]

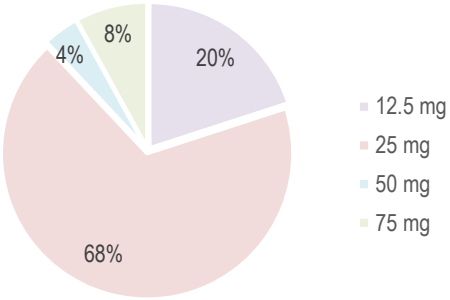


Figure 4. Distribution of Pharmaceutical Forms of DKT by Concentration [%]

From the above two figures, it can be observed that film coated tablets and doses of 25 mg are the most commercialized forms of DKT. Therefore, a standard box containing 20 film coated tablets, each with 25 mg of dexketoprofen trometamol, is selected as the reference for market price analysis.

The public retail price of the selected product is 4.00 € per box [12]. After removing VAT (Value Added Tax) of 4 % and the health surcharge of 0.5 %, the net price is 3.79 € per box.

Each box contains 0.5 g of DKT. Considering that the API accounts for 5 % of the net price, the estimated price of dexketoprofen is 0.19 € per box, which translates to 0.38 € per gram, or 382 € per kilogram.

Another important factor influencing the market value of DKT is its annual consumption, which will also be considered in this market study.

Evolution of the annual consumption of DKT over the last years in Spain is shown in Figure 5, based on data from the AEMPS (Spanish Agency of Medicines and Medical Devices) [13].

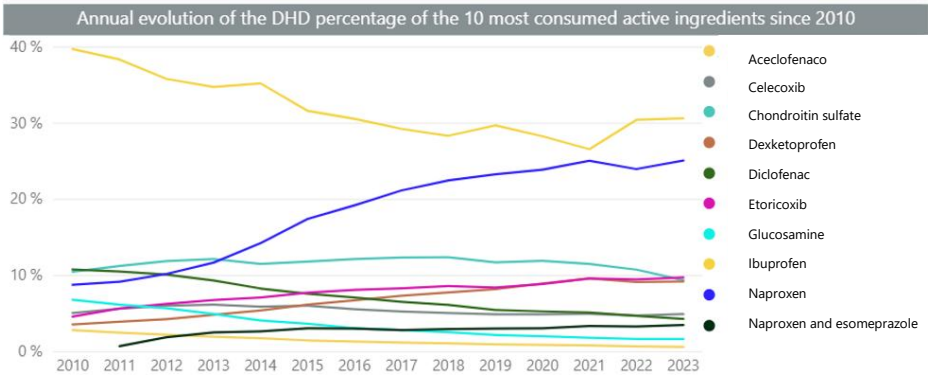


Figure 5. Annual Evolution of the DHD Percentage in Spain for the 10 Most Consumed Active Ingredients in the NSAID Class [13]

From Figure 5, it can be observed that although dexketoprofen is not the most consumed NSAID, it shows the second highest increase in consumption, only below naproxen.

This increase can also be perceived in Figure 6, which shows the DHD (Defined Daily Doses per 1000 inhabitants per day) [14] of dexketoprofen in Spain over the past 13 years [13]. A clear increase in consumption can be observed.

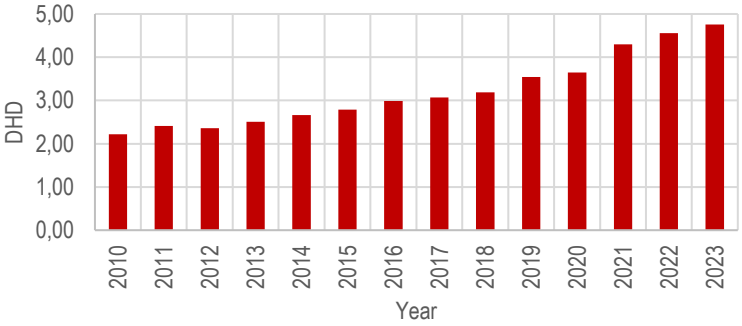


Figure 6. DHD evolution of dexketoprofen in Spain since 2010

In 2023, the daily consumption of dexketoprofen in Spain was 4.76 DHD. Considering the DDD (Defined Daily Dose [15]) of dexketoprofen is 75 mg/day [16] and Spain's population in 2023 was 48 446 594, the total national consumption in 2023 was approximately 6314 kg DKT.

By estimation, the total annual consumption of dexketoprofen in Europe is around 107 tons per year [17] [18].

From a company policy perspective, it has been decided to produce 10 % of the annual demand, which corresponds to a production target of 10 tons of dexketoprofen per year. This production volume will be achieved through 20 batches, each with a batch size of 500 kg of final product with a target purity of 98 % DKT.

2. OBJECTIVES

The main objective of this project is to develop a basic engineering design for a DKT production line capable of achieving 10 % of the annual European demand, equivalent to 10 tons per year.

This will be achieved by producing 20 batches of 500 kg each, with each batch stored in 20 drums of 25 kg. To thoroughly meet this goal with a complete and detailed approach, the following tasks must be carried out:

- A market study of DKT to determine the target production volume.
- A patent search and selection to gather information about the production process.
- Creation of a recipe adapted for industrial-scale production.
- Development of a block diagram to visualize the process and define the mass balance of the flows.
- Specification of the required equipment units.
- A time study to determine the time required to produce one batch.
- Batch production scheduling to organize batch sequencing.
- KPI determination to quantify the efficiency of the designed process.
- Campaign scheduling to compare how different production campaign configurations affect overall time use and assess which setup is more suitable, considering plant availability for manufacturing other compounds, among other factors.

3. PATENT SEARCH

The Patent search is conducted for gathering information on the production process and product synthesis of dexketoprofen trometamol. Table 1 presents the main patents reviewed and highlights the relevant information each contains in the form of a summary of contents.

Considering that the aim of this project is to design an industrial production process for dexketoprofen trometamol, the reaction mechanism will not be discussed in depth. Patents CN1418886A, EP1739072A1 and WO2011001213A1 are used solely as references to gather information about the drug.

Patent CN101928214A has been selected as the primary reference for the production process proposed in this work due to its comprehensive and detailed description of the operating conditions.

Table 1. Summary of Patent Search and Relevant Information on the Production of DKT

PATENT	SUMMARY OF CONTENT	OPERATIONS	CONDITIONS	TIME [h]
CN101928214A [19]	Synthesis of dexketoprofen glucosinamine salt from ketoprofen and octylamine. Separation of dexketoprofen from glucosinamine salt by acid-base reactions. Synthesis of DKT from DK (dexketoprofen) and T (tromethamine).	1. Synthesis of DK	80 ºC	0.5
		2. Crystallization	22 ºC → 5 ºC	12
		3. Washing	-	-
		4. Drying	50 – 55 ºC	10 – 12
		5. Reaction with base	40 ºC	-
		8. Crystallization	8 ºC	3
		9. Centrifugation	-	-
		10. Reaction with acid	< 25 ºC	
		11. Crystallization	7 ºC	12
		12. Centrifugation	-	-
		13. Drying	50 – 55 ºC	10 – 12
		14. Synthesis of DKT	-	0.5
		15. Crystallization	< 10	3
		16. Washing	-	-
		17. Drying	50 ºC	10
CN1418886A [20]	Method for synthesizing dexketoprofen N-Octylglucamine (N-O) salt.	1. Reaction	60 – 80 ºC	0.5
		2. Cooling	0 – 5 ºC	6 – 8
		3. Washing	-	-
		4. Drying	-	-
		5. Dissolving	60 – 80 ºC	-
		6. Cooling	35 – 45 ºC	8 – 12
		7. Washing	-	-
		8. Drying	-	-

PATENT	SUMMARY OF CONTENT	OPERATIONS	CONDITIONS	TIME [h]
EP1739072A1 [21]	Introduction to polymorphism of DKT, classifying in Form A and Form B. Presents a way of obtaining the more stable Form A.	1. Dissolving DK	45 – 55 ºC	0.5
		2. Cooling	30 – 40 ºC	-
		3. Reaction with T	50 – 55 ºC	-
		4. Cooling	to 0 – 5 ºC	10
		5. Crystallization	0 – 5 ºC	15
		6. Washing	-	-
		7. Drying	40 – 50 ºC under vacuum	> 1
WO2011001213_A1 [22]	Method for solving polymorphism of DKT and, from that, obtaining the more stable form of DKT. Solution by using a solvent in which DK is soluble, T less soluble, and DKT is insoluble.	1. Reaction of DK with T	-	30
		2. Washing	cold	-
		3. Drying	45 ºC in vacuum	16
		4. Dissolving DKT	50 - 60 ºC	0.25
		5. Cooling	Room temperature	1
		6. Filtering	-	-
		7. Drying	40 ºC	5

4. PRODUCTION PROCESS

Like many other API production processes, the DKT production will be based on batch operations. This approach is suitable given the annual production is below 500 000 kg, production rates may vary, and equipment reuse is desired [23] [24]. For the integrity and completion of this study, this project will focus mainly on the production from the synthesis of DKT from dexketoprofen and tromethamine, its subsequent purification and its final packaging as shown in Figure 7.

Figure 7. Limit battery of the project

4.1. RAW MATERIALS

To design a rational production process for the API, it is essential to study the characteristics and hazards of the raw materials involved.

The raw materials used in this process include two reactants, dexketoprofen and tromethamine, and a solvent mixture composed of ethanol and ethyl acetate.

Table 2 presents the main physical properties of these compounds, while Table 3 summarizes their associated hazards according to GHS (Globally Harmonized System of Classification and Labeling of Chemicals) [25].

Table 2. Physical parameters of raw materials at [1]Standard Temperature and Pressure conditions

Parameters	Dexketoprofen	Tromethamine	Ethanol	Ethyl acetate
State at STP[1]	Solid	Solid	Liquid	Liquid
Melting point [ºC]	94	175	-114	-84
Boiling point at 1 atm [ºC]	431	219	78	77
Density [kg/L]	1.2	1.5	0.789	0.902

Table 3. Hazards' information of the raw materials

Dexketoprofen	Tromethamine	Ethanol	Ethyl acetate
Acute toxicity	-	Flammable	Flammable
Hazardous to the aquatic environment	-	Irritant	Irritant

Ethanol and ethyl acetate present flammable hazards and flash points at 12 and -4 °C respectively, therefore, when designing the production process, inertization by N_2 before transferring them into any unit will have to be considered to avoid ignition in presence of oxygen.

4.2. RECIPE

The production process studied in this project is based mainly on patent CN101928214A, which describes production from a laboratory synthesis point of view. The following recipe is adapted to industrial production of a batch of 500 kg of DKT with purity of 98 %.

2843 kg of ethyl acetate and 812 kg of ethanol are loaded into an agitated vessel V-1, previously inertized by N_2, by pipelines from their respective storage tanks. A weighing load cell installed at the bottom of the tank controls the amount of solvent loaded. Mixing by paddle agitation is started, then 406 kg of dexketoprofen and 193 kg of tromethamine are added one after another into the vessel respectively by 2 industrial hoppers. Before loading into the tank, both are weighed in side-mounted load cells.

The mixture is heated to 50 °C by a coil heat exchanger and low pressure steam water while continuous mixing is maintained for half an hour. At the same time, reflux is started: the evaporated solvent is condensed in an external condenser by cooling water and goes back to the tank. During this half an hour, reaction happens and there is formation of dexketoprofen trometamol and other solid and liquid impurities.

The resulting solution is discharged from tank V-1 and, using a pump, passes through filter F-1 to remove solid impurities. The filtered solution is then transferred to another inertized agitated vessel V-2. In V-2 it is cooled below 10 °C by glycol solution through another coal heat exchanger while agitating gently, leading to the crystallization of DKT.

After 3 hours of agitation and crystallization, the contents are discharged and introduced into a previously inertized Nutsche filter F-2 located in a cleanroom by an Arquimedes' screw. Inside the vessel of the filter, under vacuumed conditions, the liquid phase is filtered. The crystals are washed twice using a mixture of ethanol (equal in weight to the filtered mass) and ethyl acetate (seven times the weight of the filtered mass). The filter increases its temperature by low pressure steam water, reduces its pressure and dries the washed crystals for 10 h removing the remaining liquids.

The crystals are discharged into a portable hopper, which transports them to a pin mill M-1 in which they are milled and sieved. The resulting particles exit the mill vertically, fall into a secondary hopper, and are then packed into 20 drums of 25 kg of capacity each as the final product.

4.3. BLOCK DIAGRAM AND MASS BALANCE

Figure 8 presents the block diagram outlining the key phases of the designed DKT production process.

Table 4 shows the mass balance performed to determine the quantities of material we will be working with in each operation, as well as the initial quantities of raw materials required to produce 500 kg of final product per batch: 406 kg of dexketoprofen, 193 kg of tromethamine, 812 kg of ethanol and 2843 kg of ethyl acetate.

High quantities of solvents are used to perform the reaction at low concentrations, thus enhancing selectivity.

Due to limited data on the DKT synthesis reaction and the solubility of its crystals, the following assumptions are made:

- The selectivity of DK toward DKT formation is 90 %.
- 10 % of DK reacts with Et (ethanol), forming liquid impurities.
- 10 % of T reacts with EtAc (ethyl acetate), forming solid impurities.
- The solid impurities retained in filter F-1 remain 10 % wet with other compounds.
- The solubility of DKT in the Et and EtAc mixture is 7 %.
- Hold-up losses are estimated as follows: 2 % in V-2, 1 % in M-1, and 0.5 % in PCK-1.

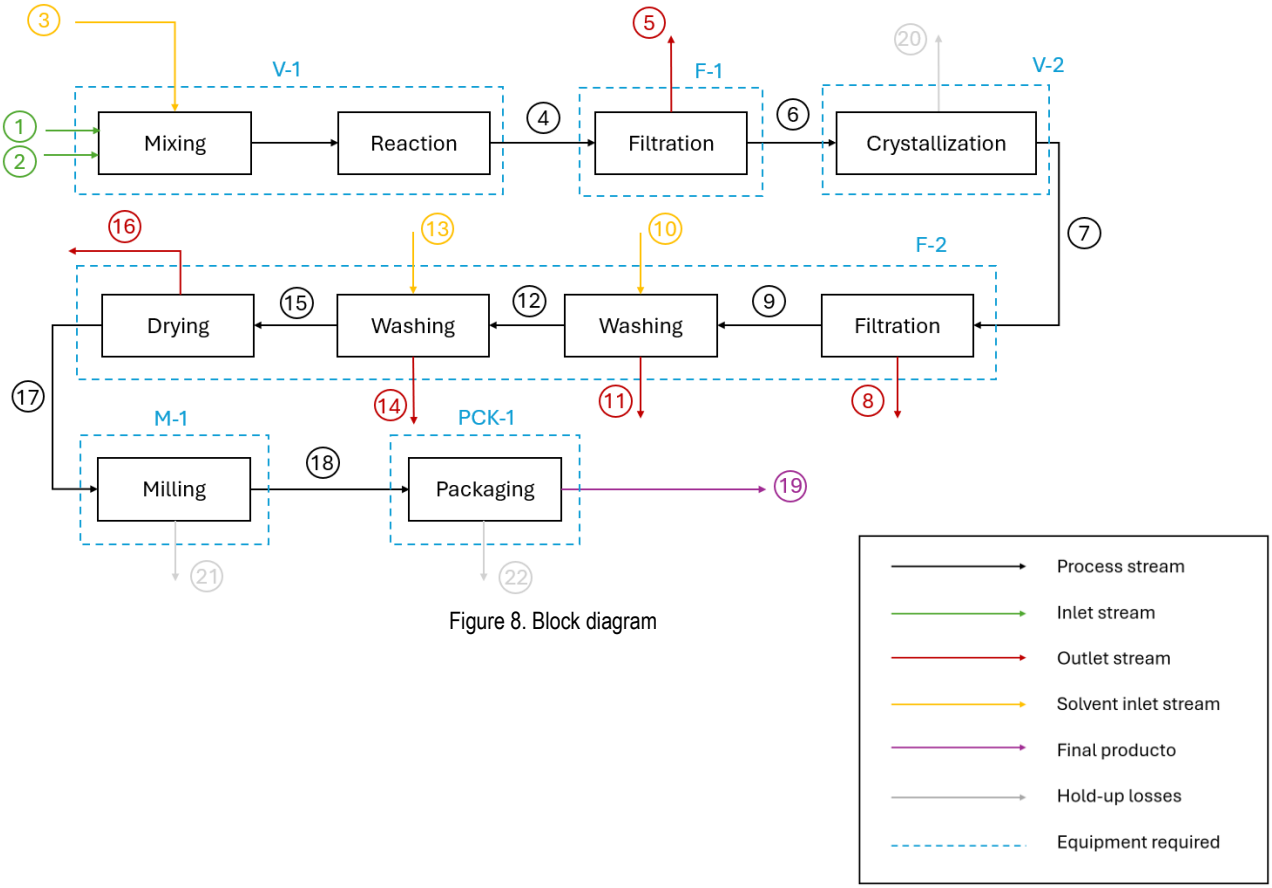


Figure 8. Block diagram

Table 4. Mass balance

kg	1	2	3	4	5	6	7	7	8	9	10	11
Final product	0	0	0	551	0	550	539	539	11	529	0	11
Tromethamine	0	193	0	0	0	0	0	0	0	0	0	0
Dexketoprofen	406	0	0	0	0	0	0	0	0	0	0	0
Ethanol	0	0	812	805	0	804	788	788	780	9	264	268
Ethyl acetate	0	0	2843	2828	1	2827	2770	2770	2740	31	1850	1846
Solid impurities	0	0	0	22	22	0	0	0	0	0	0	0
Liquid impurities	0	0	0	48	0	48	47	47	47	0	0	0
Product losses	0	0	0	0	0	0	0	0	0	0	0	0
Total	406	193	3655	4254	25	4230	4145	4145	3577	568	2114	2125

kg	12	13	14	15	16	17	18	19	20	21	22
Final product	518	0	10	508	0	508	503	500	0	0	0
Tromethamine	0	0	0	0	0	0	0	0	0	0	0
Dexketoprofen	0	0	0	0	0	0	0	0	0	0	0
Ethanol	5	264	264	5	5	0	0	0	16	0	0
Ethyl acetate	34	1850	1850	33	33	0	0	0	57	0	0
Solid impurities	0	0	0	0	0	0	0	0	0	0	0
Liquid impurities	0	0	0	0	0	0	0	0	1	0	0
Product losses	0	0	0	0	0	0	0	0	11	5	3
Total	557	2114	2125	546	38	508	503	500	85	5	3

5. EQUIPMENT SPECIFICATION

This section presents the equipment required to carry out the production process of DKT based on the previously described recipe. It explains the function of each unit and provides details of the selected equipment. The specification sheets for the main equipment units below can be found in Appendix 1.

Although there is a section on plant services and other equipment, this work does not go into detail regarding the selection study of these components. Therefore, a dedicated section on their specification is not provided.

5.1. AGITATED VESSEL V-1

In agitated vessel V-1, the mixing and the reaction of the reactants in the solvents are performed.

For this purpose, a vertical cylindrical tank made of stainless steel 316L has been designed with a total volume of 5.2 m³, a height of 3 m, and a diameter of 1.5 m. It is 20 % larger than the required process volume to ensure safety and uniform mixing. Both ends of the vessel present a torispherical head as Figure 9 shows [26]. This shape is chosen as its absence of corners avoids accumulation of product when charging and discharging.

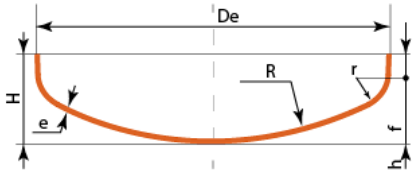


Figure 9. Graphic representation of a torispherical head [26]

This tank is also equipped with an external half pipe jacket by the side wall for heating the mixture and enhancing the dissolution. The jacket is covered by polyurethane foam insulation with a plastic cover for safety and avoiding heat loss reasons.

Agitation is achieved by a paddle type agitator, as ethanol and ethyl acetate are both low viscosity fluids. This agitator involves 2 impellers of axial agitation.

The top of this unit is connected to a condenser, a shell and tube heat exchanger that enables reflux operating and, by that, allows avoiding the loss of solvents or an increase in temperature and pressure in the tank.

For charging purposes, apart from the two connections connected to the condenser, the top torispherical head presents another 5 connections: two for solvent charging lines, one manhole for introducing solid reactants, one for the nitrogen inlet used for inertization, and one for a safety valve. For discharging operation, the vessel has a single outlet at the bottom.

This tank is also equipped with 3 load cells. One beneath the tank for weighing the solvents and two side-mounted load cells for weighing the solid reactants (DK and T) before loading them into the tank. These side-mounted cells are accessible to the operators' personnel by a two-level steel platform (lower level for supporting load cells beneath the tank and upper level for supporting the side cells besides being an operational surface for charging).

The specification sheet for this unit V-1 can be found in Table A1.1.

5.2. FILTER F-1

Filter F-1 is responsible for separating the solid impurities formed during the DKT formation reaction in vessel V-1.

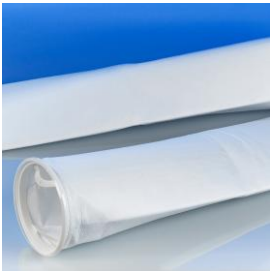
A polypropylene filter bag from Peiro S.A. [27] is selected for this purpose (see Figure 10 (b)), as this type of filter is commonly used in batch processes of the pharmaceutical field. The chosen filter bag has a capacity of 21 L, which allows the entire volume to be filtered in a single operation, requiring only one bag change per batch.

Polypropylene can withstand temperatures up to 90 °C, making it suitable for filtering the process stream, which exits V-1 at approximately 50 °C.

Figure 10 (a) shows the filter casing which is made of stainless steel. It features two welded joints, and uses a flanged connection. It is designed for top-feed configuration and can withstand pressures up to 2.5 bar [28].

The specification sheet for this filter F-1 can be found in Table A1.3.

(a)



(b)

Figure 10. Image of filter casing (a) [28] and filter bag (b) [27]

5.3. AGITATED VESSEL V-2

Following the previous filter bag F-1, an agitated vessel V-2 is set for cooling the mixture and enhancing crystallization of the product DKT formed in agitated vessel V-1.

Similar to V-1, V-2 is a stainless steel tank with a capacity of 5.2 m^3, equipped with a half pipe jacket covered with glass wool for heat insulation and a stainless-steel cladding. Like V-1, it is supported on a two-level platform.

Contrary to tank V-1, it only presents 3 connections on the upper head, one for charging the mixture, one for N_2 inertization and another for a safety valve.

Regarding the agitation, an anchor type agitator is chosen for a uniform suspension and gentle mixing, facilitating the formation of crystals.

The specification sheet for this agitated vessel V-2 can be found in Table A1.2.

5.4. NUTSCHE FILTER F-2

For the purification and drying process of the product, a Nutsche filter of model NFD-2000 from Made-in-China [29] (see Figure 11) is selected as F-2 due to its advantages of being able to be in charge of the filtering, washing and drying of the crystals formed in V-2, all in one unit. The main possible disadvantage it would present would be the limitation it would take in time.

Since all these operations occur in a single unit, the mixture from previous steps wouldn't be able to start filtering and washing until the Nutsche finishes drying the crystals it is processing, in case its vessel is not large enough to handle the entire batch at once. This would result in the Nutsche being really time-limiting and would increase the time needed for producing one batch. However, the selected model of Nutsche filter, with a vessel volume of 4.8 m^3, is capable of handling the entire contents discharged from V-2 in a single operation, so this does not pose a problem.

Figure 11. Nutsche filter image [29]

All mentioned operations, filtering, washing and drying, are performed in a closed system that avoids air pollution. Apart from the vessel, this Nutsche filter consists of a vacuuming system, filter floor, internal arms for cake washing and smoothing, and a cake discharge mechanism. Additionally, it is equipped with an automation and control system.

Figure 12 illustrates the step-by-step process performed by the Nutsche filter.

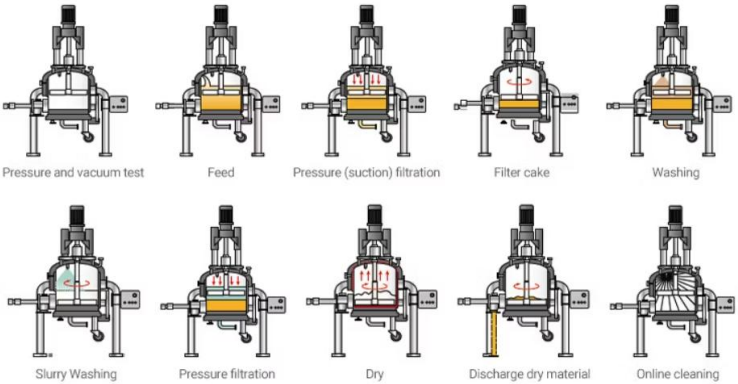


Figure 12. Operational stages of the Nutsche filter model [29]

The operation starts with a pressure and vacuum test to check that the vacuum system is working properly. Then, the mixture is fed into the filter, the pressure is reduced, and filtration takes place. Once the liquid has been removed, the internal arms stir the filter cake to make it more uniform and washing liquids (solvents) are added while the paddles mix the slurry. Filtration of the washing liquids is performed again under vacuumed conditions.

Based on the designed recipe, the washing is done twice. After that, the temperature is raised, and the crystals are dried. Once the drying time is completed, the crystals are discharged through a side outlet by the movement of the internal arms. Finally, online cleaning of the vessel is performed.

The specification sheet of this Nutsche filter F-2 is shown in Table A1.4.

5.5. MILLING AND SIEVING MILL M-1

After obtaining the dry crystals from the Nutsche filter, a pin mill of model PM-7 from Mill Powder Tech [30] was selected for the milling and sieving operation (see Figure 13 on the following page).

With a capacity ranging from 500 to 2000 kg/h, this mill achieves a particle fineness of 40 to 100 mesh. It is internally equipped with an interchangeable screen ring that ensures only particles of the target size pass through.

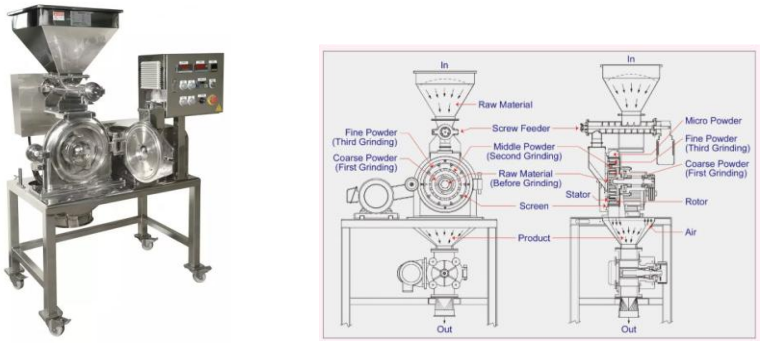
The mill includes a top feeding hopper through which solids enter the center of the chamber and undergo size reduction by the impact and shearing action of high-speed rotating pins. The processed particles then exit through the peripheral screen ring.

Any potential heat generated by the collisions can be controlled by a water-cooling system this unit includes.

Additionally, the mill presents interchangeable rotor and stator components, allowing it to switch between pin mill and knife-type mill configurations.

This mill was chosen not only for this flexibility, but also due to its relatively compact size compared to other common mills used in the pharmaceutical industry, such as the ball mill. Although the ball mill was initially considered as an option because of its lower energy consumption, it was discarded due to its large size and potential product loss.

Table A1.5 presents the specification sheet of pin mill M-1 model PM-7.



(a) (b)

Figure 13. Model PM-7 mill's photo (a) and unit diagram (b) [30]

5.6. PACKAGING SYSTEM PCK-1

The packaging system designed for handling the 500 kg of product includes the following components:

- A discharge hopper with a capacity of 450 L, designed to contain the milled product and to fill the drums efficiently.
- Twenty plastic bags of 25 kg of capacity, each placed inside a cardboard drum for protection and transport.
- A weighing system to ensure accurate filling of each drum.
- Five industrial pallets, each accommodating four boxes, for organizing and transporting the packaged product.

5.7. PLANT SERVICES

The heating and cooling operations described in the recipe are carried out using the following plant services:

- **Low pressure steam water (SW)** from a boiler for heating in reactor V-1 and for drying in the Nutsche filter F-2.
- **Glycol solution (GS)** for cooling the mixture in V-2.
- **Cooling water (CW)** from a refrigeration tower for condensing solvents during reflux in V-1 and cooling M-1 in case of overheating.
- **Nitrogen** for inertization.

5.8. OTHER EQUIPMENT

In addition to the main equipment units described in Sections 5.1 to 5.6, the following auxiliary components are required for material transfer:

- **One pump**: to transfer the stream from V-1 through F-1 to V-2.
- **One Archimedes' screw**: for transporting the slurry mixture from V-2 to F-2.
- **Three hoppers**: two for charging dexketoprofen and tromethamine into V-1 and one for collecting the crystals discharged from F-2 and transporting them to the mill M-1.

5.9. P&ID

The following Figure 14 presents the P&ID (Pipe & Instrumental Diagram) of the designed process.

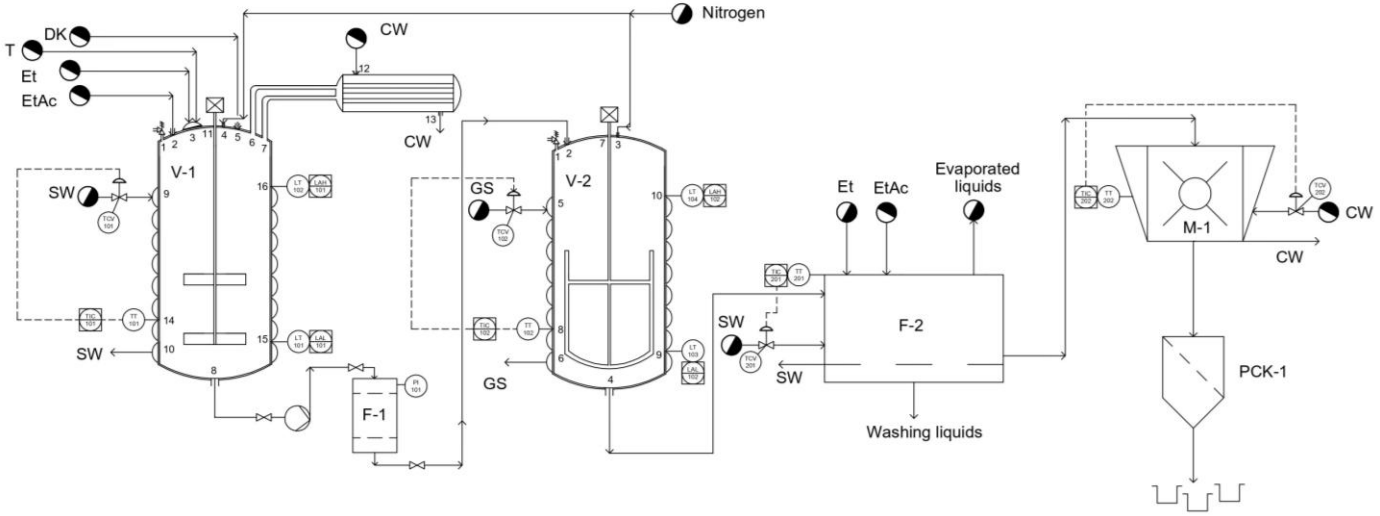


Figure 14. Pipe & Instrumental Diagram

6. PRODUCTION PLANNING

Time scheduling of the production plays a crucial role in achieving the desired production target of 10 tons per year. To successfully meet this goal, the production scheduling will involve: conducting a time study for producing one batch by estimating the occupation time of each unit, scheduling of the batch operations and planning of the campaigns.

6.1. TIME STUDY

The time that is spent producing one batch is obtained from an estimation of the time that each main equipment unit mentioned in Section 5 spends in performing their respective tasks, detailed to the time they spent in every corresponding operation. A supposition that there are enough personnel resources is made, so this factor won't be affecting the time of production. The operation times (OT) for each equipment unit are estimated in Table 5, using time values rounded to increments of 0.25 hours (equivalent to 15 minutes). The table also includes the start time (t_i) and end time (t_f) of each operation:

Table 5. Time Study of equipment units' occupation times

Equipment	Operation	OT [h]	t_i [h]	t_f [h]
V-1	Inertization	0.50	0.00	0.50
	Charge Ethanol + EtAc	0.25	0.50	0.75
	Charge DK	0.25	0.75	1.00
	Charge T	0.50	1.00	1.50
	Heating	0.50	1.50	2.00
	Reaction	0.50	2.00	2.50
	Control	0.50	2.50	3.00
	Discharge to F-1	0.50	3.00	3.50
	Cleaning	2.00	3.50	5.50

Equipment	Operation	OT [h]	ti [h]	tf [h]
F-1	Inertization	0.25	2.75	3.00
	Charge from V-1	0.50	3.00	3.50
	Cleaning	0.50	3.50	4.00
V-2	Inertization	0.50	2.50	3.00
	Charge from F-1	0.50	3.00	3.50
	Cooling	0.75	3.50	4.25
	Crystallization	3.00	4.25	7.25
	Control	0.50	7.25	7.75
	Discharge to F-2	0.75	7.75	8.50
	Cleaning	2.00	8.50	10.50
F-2	Inertization	0.50	7.25	7.75
	Charge from V-2	0.75	7.75	8.50
	Filtration	2.25	8.50	10.75
	Washing 1	1.25	10.75	12.00
	Washing 2	1.25	12.00	13.25
	Drying	10.00	13.25	23.25
	Control	1.50	23.25	24.75
	Discharge to M-1	0.50	24.75	25.25
	Cleaning	0.50	25.25	25.75
M-1	Charge from V-2	0.50	25.25	25.75
	Milling & sieving	1.50	25.75	27.25
	Cleaning	0.75	27.25	28.00
PCK-1	Charge from M-1	1.50	25.75	27.25
	Control	1.00	27.25	28.25
	Packaging	3.25	28.25	31.50
	Cleaning	0.50	31.50	32.00

For operations not described in the patents, durations were estimated through contextual analysis as detailed below:

The time required for inertization of units containing ethanol and ethyl acetate, as well as for cleaning operations, was estimated based on the size of the unit.

The heating and cooling times for units V-1 and V-2 correspond only to the time needed to reach the desired temperature, excluding the time the half-pipe jackets operate to maintain that temperature, so they are expected to last approximately 0.50 hours.

The quality control operation in unit V-1 involves analyzing the content composition before discharge to ensure the desired product specifications are met. This includes sample collection and laboratory analysis, estimated to take approximately 30 minutes (0.50 hours). Quality control operations in units F-2 and PCK-1 take longer due to more detailed product analysis and quality control measurements.

Packaging time for one industrial plastic drum of 25 kg is approximately 10 minutes. Thus, packaging 20 drums is estimated to take about 3.25 hours in total.

To estimate the start and end times of each operation, the following assumptions were made:

- The time for the stream to travel through the pipes from V-1 to F-1 and from F-1 to V-2 is negligible compared to the discharge and charge time spent in the reactor. Therefore, the discharge from V-1 and the charge to F-1 are assumed to begin simultaneously. Similarly, the discharge from V-2 and the charge to F-2 are also assumed to start at the same time.
- The drying phase of F-2, which lasts 10 hours, involves both vacuuming and heating processes; these operations are not discussed separately.
- Discharge to M-1 consists of transferring crystals into a portable hopper. Charging from F-2 involves not only feeding crystals to the mill but also transporting the hopper to the mill; hence, these two operations do not occur simultaneously.

All the above information is summarized in the following Table 6:

Table 6. Summary of OT, start time and end time of each equipment unit

	ti [h]	tf [h]	$t_{Inertization}$ [h]	$t_{Charging}$ [h]	$t_{Operation}$ [h]	$t_{Discharging}$ [h]	$t_{Cleaning}$ [h]	OT [h]
V-1	0.00	5.50	0.50	1.00	1.50	0.50	2.00	5.50
F-1	2.75	4.00	0.25	0.00	0.50	0.00	0.50	1.25
V-2	2.50	10.50	0.50	0.50	4.25	0.75	2.00	8.00
F-2	7.25	25.75	0.50	0.75	16.25	0.50	0.50	18.50
M-1	25.25	28.00	0.00	0.50	1.50	0.00	0.75	2.75
PCK-1	25.75	32.00	0.00	1.50	4.25	0.00	0.50	6.25

Batch time [h]	Cycle time [h]

Based on the data in Table 6, the Gantt diagram for the production of one batch is represented in Figure 15.

From this Table 6, Batch Time (BT) and Cycle Time (CT) are also determined. Batch Time (BT) is the total time needed to produce one batch, including operation and cleaning of all units. It is the end time of the last equipment unit: 32 hours. Cycle Time (CT) refers to the duration of the longest phase in the production process that limits the overall throughput, which in the case of one batch is the occupation time of the Nutsche filter F-2 at 18.5 hours.

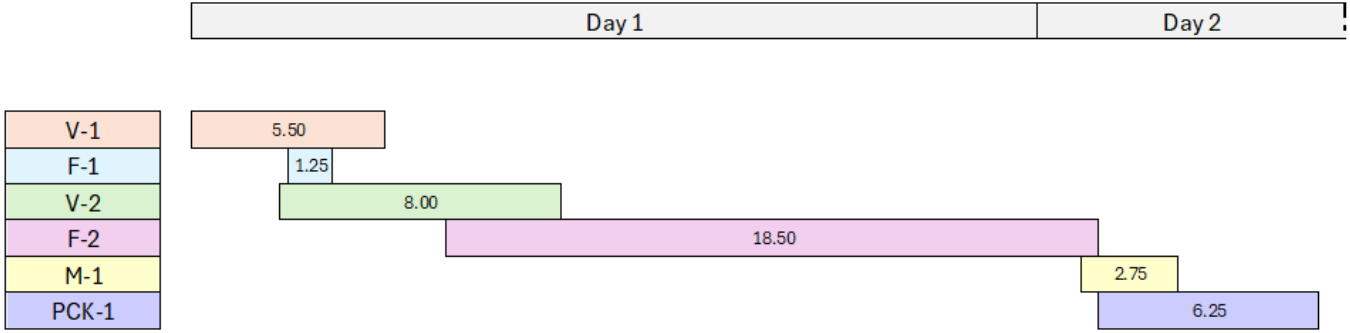


Figure 15. Gantt diagram for production of one batch of DKT

6.2. BATCH SCHEDULING

To produce the 20 batches, this section uses the time study data to schedule the production of consecutive batches and analyze different possible configurations in order to identify the most time-efficient solution.

From this perspective, there are two main types of configurations: overlapping and non-overlapping. The non-overlapping configuration involves starting a new batch only after the previous one has completely finished, ensuring that no equipment is operating simultaneously. Its main advantage is operational safety: if a unit experiences an issue, it can be identified and resolved without affecting the next batch.

The overlapping configuration, on the other hand, starts the next batch while the previous one is still in progress. Batches are initiated as closely as possible without using the same equipment at the same time. The time between the start of one batch and the start of the next one is the Cycle time. This is determined by the unit with the longest occupation time. In this case, it is the Nutsche filter F-2, which operates for 18.5 hours per batch. In the overlapping configuration, this unit begins its operations for the next batch immediately after completing those of the previous batch.

The time efficiency of these two types of configurations can be compared by calculating the time required to complete a campaign of the same number of batches. This makespan can be determined using the following equation [31]:

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

Where:

MS refers to the makespan for one campaign in hours

N is the number of lots per campaign

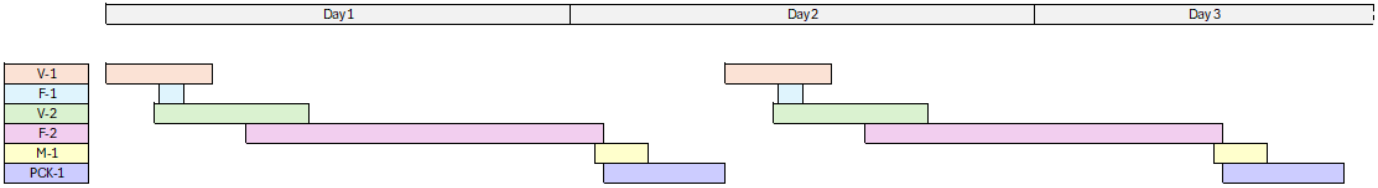
BT is the batch time in hours

CT is the cycle time in hours

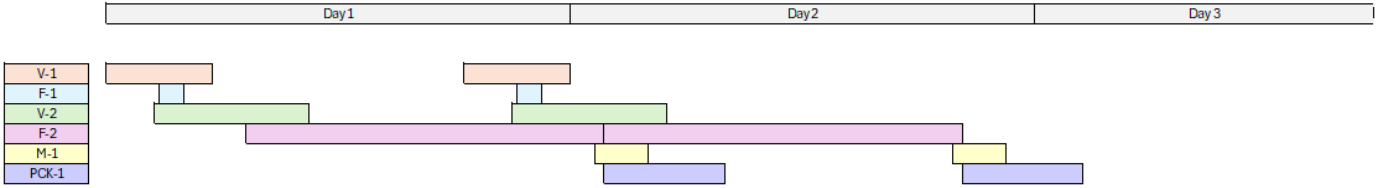
Using Equation 1, the makespan for a campaign of two lots for both the overlapping and non-overlapping configurations are presented in Table 7. The results indicate that the overlapping configuration reduces the total time by approximately 21 %. This time-saving advantage is further illustrated in the Gantt charts in Figure 16.

Table 7. Makespan comparation of non-overlapping and overlapping batch scheduling for production of two batches

Makespan [h]		**Saved time**
Non-overlapping configuration	Overlapping configuration	
64.00	50.50	21 %



(a)



(b)

Figure 16. Gantt diagram of non-overlapping (a) and overlapping (b) batch scheduling for production of two batches

6.2.1. Batch Scheduling Under Heat Exchange Service Limitations

From the primary objective of maximizing time efficiency, the non-overlapping configuration is discarded, making the overlapping configuration the preferred choice.

However, this production setup includes two units, V-1 and F-2, that both rely on the same heating service of steam water. If these units require heating simultaneously, there is a risk that the boiler may not have enough capacity to maintain efficient heat exchange. This introduces an additional constraint: the overlapping schedule must be adjusted to ensure that the heating service is not required simultaneously by multiple units.

This limitation does not apply to the cooling service. As the glycol solution is used exclusively by unit V-2, and the cooling of V-1's condenser and M-1 is handled by water from the cooling tower.

The operation time of these heat exchange services in the overlapping configuration is illustrated in Figure 17. It can be observed that the heating service would be needed at the same time for both maintaining the desired temperature in reactor V-1 and for drying in the Nutsche filter F-2.

To prevent this overlap, the second batch should be scheduled so that drying in the Nutsche filter begins only after the heating service has finished maintaining 50 ºC in reactor V-1. The Cycle time for this configuration is the sum of the Nutsche filter's occupation time and the adjusted time to avoid heating overlap: 21.75 hours.

The final time scheduling of consecutive batches under the overlapping configuration, with the added constraint of non-overlapping utility use, is shown in Figure 18.

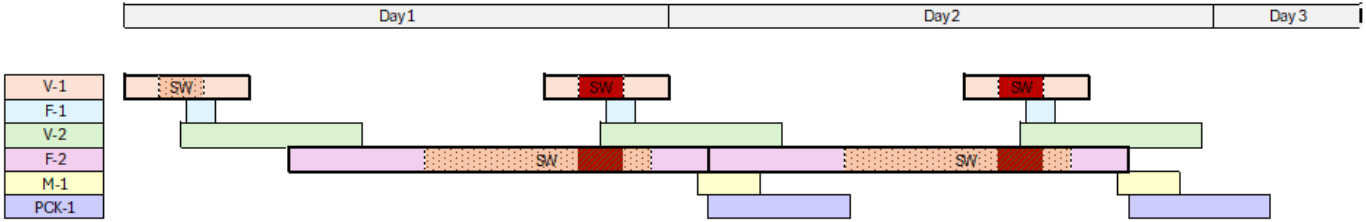


Figure 17. Gantt diagram illustrating heat service occupation in the overlapping batch configuration

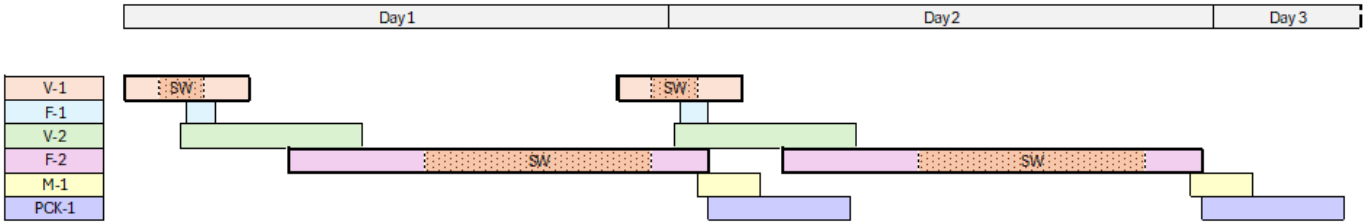


Figure 18. Gantt diagram of overlapping batch configuration under heat service restriction

6.3. DETERMINATION OF KPIS

KPIs (Key performance indicators) are parameters that measure in a quantifiable way the efficiency of a project [32].

The performance of this production process design project can be visualized by determining the KPIs of Maximum production capacity and Minimum production time.

Maximum production capacity refers to the highest amount of product the designed process can achieve by working unstoppably during the possible working hours. Supposing that in a year, taking out the vacations and maintenance periods, the industrial factory operates 6500 h nonstop, the Maximum production capacity can be calculated for the two types of batch scheduling (see Table 8) by Equation 1, finding the number of batches N while supposing makespan 6500 h.

Table 8. Maximum production capacity determination

Maximum production capacity		
	Without heat service limitations	**With heat service limitations**
Batch size [kg]	500	500
Running time [h/year]	6500	6500
Batch time [h]	32.00	32.00
Cycle time [h]	18.50	21.75
Maximum production capacity [lots/year]	349	297
Maximum production capacity [t/year]	17.48	14.87

Another relevant KPI for the developed production process is the Minimum production time required to achieve the production goal of 10 tons. Considering that the 20 batches are produced consecutively in one campaign, this KPI can be determined by isolating MS in Equation 1. The values obtained for the Minimum production time are presented in Table 9.

Table 9. Minimum production time determination

Minimum production time		
	Without heat service limitations	**With heat service limitations**
Batch size [kg]	500	500
Annual production [kg/year]	10 000	10 000
Batch time [h]	32.00	32.00
Cycle time [h]	18.50	21.75
Minimum production time [h/year]	402	467
Minimum production time [day/year]	16.75	19.46

6.4. PRODUCTION CAMPAIGNS PLANNING

This section analyzes multiple strategies for organizing production campaigns to meet the annual production of 20 batches, focusing on time efficiency and alignment with company policy.

One possibility is to produce all 20 batches in a single campaign. While this is the most time-efficient configuration, it carries a high risk of stock accumulation, which can lead to an increase in financial costs.

Therefore, dividing the 10 tons of production into multiple campaigns offers a more balanced and practical approach.

The total annual production time for different campaign configurations can be calculated using the following Equation 2:

$$MS_A = n_c \cdot (BT + (N - 1) \cdot CT) \qquad (2)$$

Where:

MS_A refers to the annual makespan, the total annual production time in hours

n_c is the number of campaigns

N is the number of lots per campaign

BT is the batch time in hours

CT is the cycle time in hours

The following tables (Table 10 and Table 11) and Figure 19 present the different production campaign configurations and their corresponding total production times, both for overlapping batch scheduling with heat service restriction and without heat service restriction.

Table 10. Time Analysis of Campaign Distributions in the No Heat Restriction Batch Configuration

Campaigns	Lots/campaign	Time/campaign [days]	Total time [h]	Changeover time [months]
1	20	19	383.5	10.0
2	10	9	397.0	5.0
4	5	5	424.0	2.5
5	4	4	437.5	2.0
10	2	2	505.0	1.0

Table 11. Time Analysis of Campaign Distributions in the Heat Restriction Batch Configuration

Campaigns	Lots/campaign	Time/campaign [days]	Total time [h]	Changeover time [months]
1	20	19	445.25	10.0
2	10	9	455.50	5.0
4	5	5	476.00	2.5
5	4	4	486.25	2.0
10	2	2	537.50	1.0

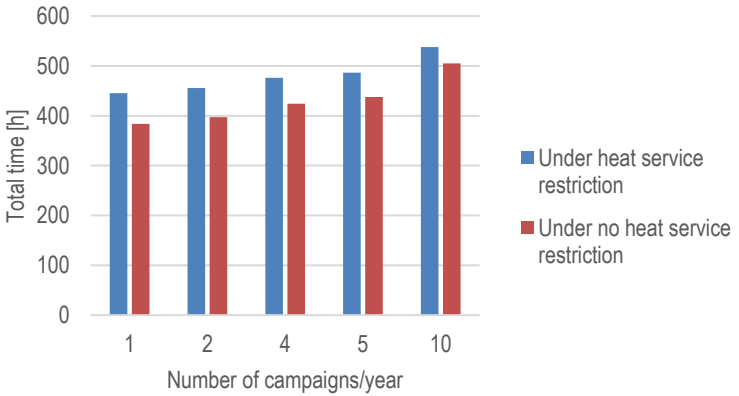


Figure 19. Total Production Time based on Number of Campaigns per Year for Batch Scheduling with and without Heat Service Restrictions

Considering that the factory operates approximately 6,500 hours per year, and even the configuration with the highest number of campaigns, 10 campaigns, uses less than 10% of that time, the total annual production time for a given campaign configuration is not a decisive factor in choosing the number of campaigns.

The optimal plan focuses then on avoiding stock accumulation, which can occur if too few campaigns produce many batches at once. Comparing the options of 4 and 5 campaigns for both overlapping and non-overlapping heating service schedules, 4 campaigns is the better choice because the longer changeover time allows greater flexibility to manufacture other products during that period.

Accordingly, the production load will be distributed across 4 campaigns, each consisting of 5 lots, spaced throughout the year. One campaign will be scheduled every three months approximately, starting in February and ending in November, while avoiding the holiday period in the middle of the year.

7. CONCLUSIONS

This project successfully designed a production line for achieving the target production of 10 tons per year of DKT with a purity of 98 %, based on the market study. This production goal is to be achieved through 20 batches of 500 kg of final product each.

Following a patent review, patent CN101928214A was selected as the primary reference for the process recipe. Using this recipe, the block diagram was developed and the required raw materials for one batch were determined through mass balance calculations.

The main equipment units for reaction, solid impurity filtration, crystallization, purification, drying, milling, and packaging were specified based on the operational conditions and material characteristics. Agitated vessels V-1 and V-2 were designed for the reaction and crystallization operations respectively. A filter bag was chosen to remove solid impurities, a Nutsche filter was selected to perform purification and drying, and a pin mill with an internal screen ring was selected for milling and sieving. For packaging, a drum filling system by a discharge hopper was determined.

A time study of equipment occupation allowed the determination of the batch time (32 hours) and cycle time (18.5 hours) of one batch. These values enabled a comparison between different batch scheduling configurations. The overlapping batch schedule was found to be more time-efficient. Within this context, the project assessed scenarios with and without heat service restrictions due to the simultaneous demand of heating service by units V-1 and F-2.

KPIs of Maximum production capacity and Minimum production time were calculated for both configurations: 17.48 t/year and 16.75 days/year for the overlapping heat service configuration and 14.87 t/year and 19.46 days/year for the non-overlapping heat service configuration. In both cases, the designed process is able to meet the annual production target within the 6500 available running hours in total.

Based on the above analysis, the production was finally scheduled in four campaigns of five batches each, distributed throughout the year.

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ACRONYMS

AEMPS:	Spanish Agency for Medicines and Medical Devices
API:	Active Pharmaceutical Ingredient
BT:	Batch Time [h]
COX:	Cyclooxygenase
CT:	Cycle Time [h]
CW:	Cooling water
DDD:	Defined Daily Dose
DHD:	Defined Daily Doses per 1000 inhabitants per day
DK:	Dexketoprofen
DKT:	Dexketoprofen trometamol
Et:	Ethanol
EtAc:	Ethyl acetate
F-1:	Filter bag
F-2:	Nutsche filter
GHS:	Globally Harmonized System of Classification and Labeling of Chemicals
GS:	Glycol solution
IUPAC:	International Union of Pure and Applied Chemistry
KPI:	Key Performance Indicator
M-1:	Pin mill
MS:	Makespan for 1 campaign [h]
MS_A:	Annual makespan [h]
N:	Number of batches
n_c:	Number of campaigns

N-O:	N-Octylglucamine
NSAID:	Non-Steroidal Anti-inflammatory Drug
OT:	Operation Time [h]
P&ID:	Pipe & Instrumental Diagram
PCK-1:	Packaging system
PGE_2:	Prostaglandin E2
STP:	Standard Temperature and Pressure
SW:	Steam water
T:	Tromethamine
$t_{Charging}$:	Charging time [h]
$t_{Cleaning}$:	Cleaning time [h]
$t_{Discharging}$:	Discharging time [h]
t_f:	End time [h]
t_i:	Start time [h]
$t_{Inertization}$:	Inertization time [h]
$t_{Operation}$:	Operation time [h]
V-1:	Reaction vessel
V-2:	Crystallization vessel
VAT:	Value added tax [€]

APPENDICES

APPENDIX 1: EQUIPMENT SPECIFICATION

Table A1.1. Specification sheet of agitated vessel V-1

SPECIFICATION SHEET		
UNIVERSITAT DE BARCELONA	**Project**	Basic design of a dexketoprofen trometamol production plant
	Equipment name	Reaction vessel
	Identification	V-1
	Type	Agitated tank
OPERATING CONDITIONS		
Temperature [ºC]		25
Max. pressure [atm]		< 2
DESIGN		
Capacity [m^3]		5.2
Diameter [m]		1.5
Height [m]		3.0
Bottom		Klopper
Material		Stainless steel 316L
AGITATION		
Type		Paddle
Impeller-bot. Distance [m]		0.50
Diameter [m]		0.42
Agitation speed [rpm]		Speed controller
Number of impellers		2
VESSEL HEAT TRANSFER		
Exchanger		Half pipe jacket
Operation		Heating
Exchange area [m^2]		12.4
Fluid		Low pressure steam water

CONNECTIONS	
1	Safety valve
2	Ethanol
3	Dexketoprofen and tromethamine
4	Nitrogen
5	Ethyl acetate
6	Outlet of reflux
7	Entry of reflux
8	Outlet stream
9	Steam water inlet
10	Steam water outlet
11	Agitator
12	Cooling water inlet
13	Cooling water outlet
14	TT/TC
15	LT/LAL
16	LT/LAH

EQUIPMENT DIAGRAM

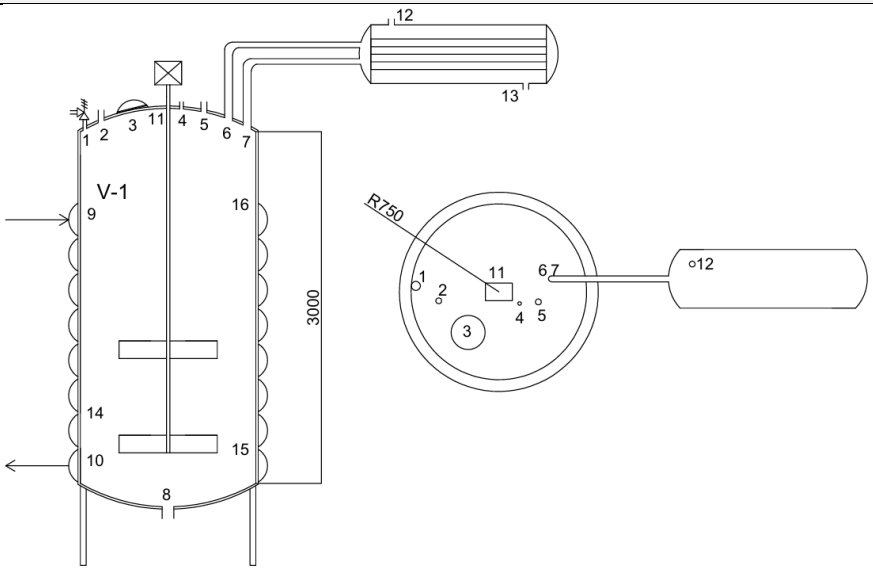

Table A1.2. Specification sheet of agitated vessel V-2

SPECIFICATION SHEET		
UNIVERSITAT DE BARCELONA	**Project**	Basic design of a dexketoprofen trometamol production plant
	Equipment name	Crystallization vessel
	Identification	V-2
	Type	Agitated tank
OPERATING CONDITIONS		
Temperature [ºC]		5 - 50
Max. pressure [atm]		< 2
DESIGN		
Capacity [m^3]		5.2
Diameter [m]		1.5
Height [m]		3.0
Bottom		Klopper
Material		Stainless steel 316L
AGITATION		
Type		Anchor
Impeller-bot. Distance [m]		1.12
Diameter [m]		1.34
Agitation speed [rpm]		Speed controller
Number of impellers		1
HEAT TRANSFER		
Exchanger		Half pipe jacket
Operation		Cooling
Exchange area [m^2]		12.4
Fluid		Glycol solution

CONNECTIONS	
1	Safety valve
2	Inlet stream
3	Nitrogen
4	Outlet stream
5	Glycol solution inlet
6	Glycol solution outlet
7	Agitator
8	TT/TC
9	LT/LAL
10	LT/LAH

EQUIPMENT DIAGRAM

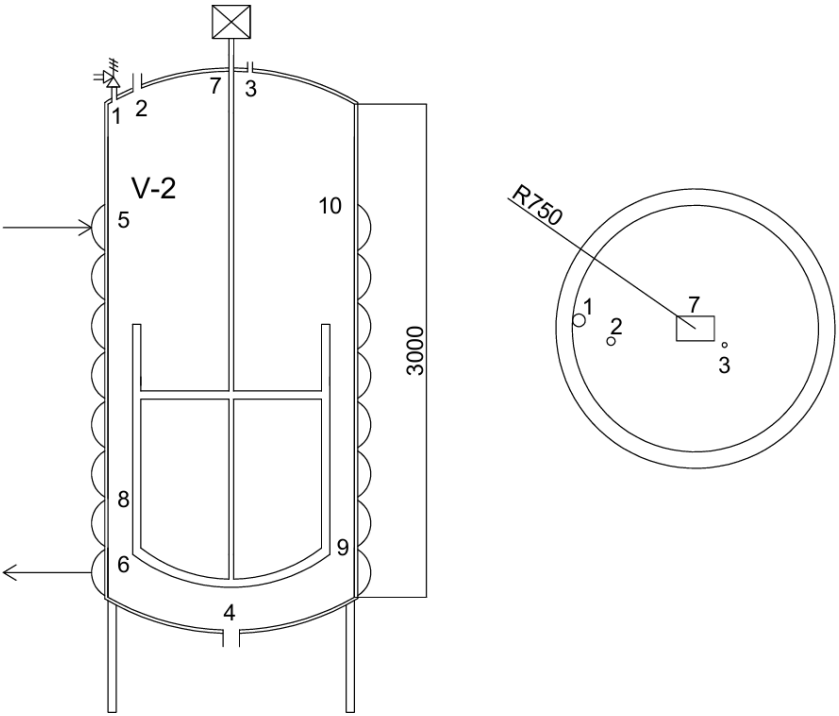

Table A1.3. Specification sheet of filter F-1

SPECIFICATION SHEET		
UNIVERSITAT DE BARCELONA	**Project**	Basic design of a dexketoprofen trometamol production plant
	Equipment name	Solid impurities filter
	Identification	F-1
	Type	Bag filter
OPERATING CONDITIONS		
Temperature [ºC]		< 90
Pressure [bar]		< 2.5
Max. flow [m^3/h]		40
FILTER BAG DESIGN		
Capacity [L]		21
Diameter [mm]		180
Height [mm]		810
Feeding inlets		1
Discharging outlets		1
Material		Polypropylene
CASING DESIGN		
Diameter [mm]		Adapted to filter bag
Height [mm]		Adapted to filter bag
Connection type		Eye bolts
Type of feed		Top feed
Material		Stainless steel 316L
EQUIPMENT IMAGE		

Table A1.4. Specification sheet of Nutsche filter F-2

SPECIFICATION SHEET		
UNIVERSITAT DE BARCELONA	**Project**	Basic design of a dexketoprofen trometamol production plant
	Equipment name	Purification-drying filter
	Identification	F-2
	Type	Nutsche filter
OPERATING CONDITIONS		
Temperature [ºC]		< 50
Pressure [bar]		0.3 – 2
DESIGN		
Filtering surface [m^2]		3
Nominal volume [m^3]		4.8
Inner diameter [mm]		2000
Shell height [mm]		1200
Filter cake height [mm]		400
Paddle lifting height [mm]		450
Stirrer Motor Power [kW]		18.5
Net weight [kg]		11 500
Total height [m]		5.1
Model		NFD-2000
Material		Stainless steel 316L
EQUIPMENT IMAGE		

Table A1.5. Specification sheet of mill M-1

IDENTIFICATION SHEET		
UNIVERSITAT DE BARCELONA	**Project**	Basic design of a dexketoprofen trometamol production plant
	Equipment name	Mill
	Identification	M-1
	Type	Pin mill
OPERATING CONDITIONS		
Temperature [ºC]		< 50 ºC
Pressure [bar]		2.5
DESIGN		
Capacity [kg/h]		500 – 2000
Length [mm]		2200
Width [mm]		1400
Height [mm]		3670
Output fineness [mesh]		20 – 120
Velocity [rpm]		Speed controller
Potency [kW]		50 – 60
Rotor type		Pin (changeable to knife)
Stator type		Pin (changeable to knife)
Screen position		Inside screen ring
Material		Stainless steel 316L
EQUIPMENT IMAGE