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Conceptual Process Design

Process Systems Engineering
DelftChemTech - Faculty of Applied Sciences
Delft University of Technology

Subject

A New Process Route to Prozac®

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SUMMARY

This design report is the final report of Conceptual Process Design of the plant for the production of an enantiomerically pure precursor of Prozac, (R)-3-chloro-1-phenylpropyl acetate.

Prozac is in a class of antidepressant medications and currently sold by Eli Lilly Co. As the patent protection on Prozac of Eli Lilly will be clear in February 2002, cheaper generic Prozac is expected in the market very soon which can make the market for this antidepressant very competitive. (R) enantiomer 3-chloro-1-phenylpropyl acetate, a precursor of Prozac is not yet available in the market, however, a big market for this precursor is expected due to its medical and economical potential.

It is aimed to design the plant with the annual production of 5 tons of (R)-3-chloro-1-phenylpropyl acetate with the proposed price of 10,000Dfl/kg. The product, enantiomerically pure precursor of Prozac, is formed during dynamic kinetic resolution in which the substrate (racemic mixture of 3-chloro-1-phenyl-1-propanol) is continuously racemized during enzymatic resolution. The dynamic kinetic resolution of this process employs the combination of lanthanum isopropoxide as a catalyst for racemization and an immobilized lipase B originated from *Candida Antartica.* The feedstock including propenyl acetate (acylating agent), the catalysts (lanthanum isopropoxide and lipase B) and the solvent (toluene) is commercially available, in which lanthanum isopropoxide counts for the major cost of raw materials. The racemic mixture of 3-chloro-1-phenyl-1-propanol is not commercially available therefore as the most important assumption of the design there will be a plant, which will supply this material for the plant of this project.

The total investment for this plant is determined to be 5.2 million Guilders (2.36 million Euro). The economical life of the plant will be 11 years in which 1 year for design and construction and 10 years of working period. The annual income is expected to be 51.2 million Guilders (23.2 million Euro) and the total production cost is determined to be 46.5 million Guilders per year (21.1 million Euro).

This report is divided into 12 chapters. The introduction chapter provides the conceptual design aspects. The process options and the option chosen are included in chapter 2. The kernel of the design so called Basis of Design forms chapter 3 in which background information such as feedstock, products, wastes, utilities, plant location, costs etc. are covered. The thermodynamic properties such as the equations and values for parameters, reaction equilibrium are written in chapter 4. The “back-bone” of the process such as the Process Flow Schemes (PFS), Batch Cycle Diagram, Process Stream Summary, Mass and Heat balances are covered in chapters 5 and 7. Chapter 6 provides the design of the control system of the plant. Process and equipment design and the resulting equipment data sheets are produced in chapter 8. Chapter 9 deals with the wastes produced by the plant while chapter 10 looks into the environmental and safety aspects. Economic evaluation based on income, investment and operating costs will result in chapter 11. The conclusions and recommendations are given in the last chapter of this report, chapter 12.

TABLE OF CONTENT

List of symbols

Symbol	***Description***	***SI Units***
A	area	m^2
c	ratio between H_s and D'	-
C_A	concentration of reactant	$kmol/m^3$
C_i	Liq. mole composition	-
C_G	capacity factor	-
C_P	heat capacity	kJ/kmol K
d	diameter	m
D	diameter	m
D'	diameter	m
F_C	flow rate of CW	kg/h
F_{LG}	flow parameter	-
F_t	temperature correction factor	-
g	gravitational acceleration	m^2/s
G	flow rate	kg/s
h	height	m
H	height	m
H	specific enthalpy	kJ/kmol
H	heat	kJ
$\Delta H_{f,}$	enthalpy of formation	kJ/kmol
ΔH_r	enthalpy of reaction	kJ/kmol
ΔH_v	enthalpy of evaporation	kJ/kmol
k	reaction constant	h^{-1}
L	liquid	-
L_s	flow path length	m
m	mass flow rate	kmol/h
M_L	the mass flow rate of liquid	kg/s
M_G	the mass flow rate of gas	kg/s
N_{mix}	mixing number	-
N_p	power number	-
P	pressure	Pa
P_d	discharge pressure	bar
P_s	suction pressure	bar
P_s	power input per stirrer	w
ΔP	pressure difference across the pump	N/m^2
Q	amount of heat	J
Q_P	flow rate	m^3/s
Q	heat transferred per unit time	kW
R	gas constant	J/mol K

Symbol	***Description***	***SI Units***
S	entropy	J/mol K
S	solid	-
t	temperature	^oC (K)
T	temperature	^oC (K)
ΔT_m	the main temperature difference, the temperature driving force	^oC (K)
t_m	mixing time	s
u	superficial velocity	ms
U	overall heat transfer coefficient	kw/m^2 K
v	velocity	m/s
V	volume	m^3
w	work	J(kJ)

Greek	***Description***	***SI Unit***
γ_j	activity coefficient of component I	-
ϕ_j^v	fugacity coefficient of component i	-
ε	total specific power input	w/kg
α	homogeneity factor	-
β	primary eddy size	-
γ	average viscosity index	-
μ	viscosity	$Nm^{-2}s$
ϕ_v	flow rate	m^3/s
σ	surface tension	-
ρ_L	density for the liquid	kg/m^3
ρ_g	density for the gas	kg/m^3
ε_L	liquid holdup	-
ς_0	orifice coefficient	-
η_p	pump efficiency	-
ξ	reaction degree	-

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CHAPTER 1 INTRODUCTION

Prozac is in a class of antidepressant medications that affects chemical messengers within the brain (neurotransmitters). The generic name for Prozac is Fluoxetine. Prozac has been introduced in 1988/89 by Eli Lilly Co. as a racemic mixture. Although fluoxetine is currently sold as the racemate (Prozac), related studies showed that the two enantiomers have different activities and rates of metabolism **[1]** **[2]**. Recently, interest has been shown for marketing the more active (R) – enantiomer as a so-called "Improved Chemical Entity" version of the drug **[3]**. Lilly submitted an approval application for (R)-fluoxetine in the US for the treatment of bulimia **[2]** **[4]**. Due to its medical potential (R)-fluoxetine attracts considerable interest.

The objective of the project is to design a plant for a production of an enantiomerically pure precursor of Prozac, (R)-3-chloro-1-phenylpropyl acetate. The production scale of the plant is to produce 5 tones of this precursor per year. The supplied form of the product is liquid in 50L containers and the product will be sold to Prozac manufacturers such as Eli Lily and its competitors. It is expected to have a market price of 10,000Dfl/kg of this product.

The patent protection on Prozac of Eli Lilly will be clear in February 2002. Eli Lilly hoped to keep the patent alive until December 2003, however the court's decision in August 2001 is against Eli Lilly and the patent should be clear the way for it to make a generic Prozac **[5]**. Barr Laboratories Inc., one of the potential competitors of Eli Lilly has promised to make a cheaper, generic Prozac **[5]**. Therefore, it is predicted that the market for this antidepressant will be very competitive

This precursor of Prozac is not currently available in the market. However, it is expected to have a big market for this precursor. As mentioned above that currently Prozac is sold as racemic product but it is expected in coming years pure enantiomer, (R)-fluoxetine, will have an attractive market due to its medical and economical potential. Pure enantiomers always have a remarkably higher economical value than that of their racemic mixture. There are only 3 steps from this precursor to Prozac **[6]**. As soon as the patent protection of Eli Lilly on Prozac expires in 2002, it is expected that many competitors will introduce generic Prozac to the market. These Prozac-manufacturers will be interested in the precursors of Prozac if they can be purchased at an acceptable price. Therefore, these competitors not only can still make a lot of profits but also reduce the production steps in making this antidepressant.

The chemical route of the process is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology. This is a new chemical route, which applies new catalyst and different starting raw materials and it is very promising in term of yield, reaction time compared to the existed route in literature **[7]** (refer to part 2.1 for the comparison of these routes).

(R)- 3-chloro-1-phenylpropyl acetate to be produced is in liquid form. The normal boiling point of this compound is estimated at 193^{o}C (please refer to chapter 4 of thermodynamics and table 3.2 for pure component properties). Overheating of the product should be avoided to prevent decomposition of this compound. This important properties has made the influences on the design of the purification section of the process, namely a distillation column operating under vacuum is designed for this purpose.

The feedstock for the plants includes racemic mixture of 3-chloro-1-phenyl-1-propanol, propenyl acetate, toluene (solvent), lipase B (originated from *Canida Antartica*) and lanthanum isopropoxide (catalysts). They are commercially available except for the racemic mixture. The racemic mixture is a starting material to produce the precursor therefore an important assumption has to be made that there will be a plant, which will produce this racemic mixture for the plant of this project.

Many difficulties such as lack of information in literature on thermodynamic data, pure component data of racemic mixture of 3-chloro –1-phenyl – 1 propanol (staring material of the process) and (R)-3-chloro-1-phenyl-propyl (the final product) are encountered during the design. Also, the information on the price of these materials is not available since they are currently not commercially available. Therefore, many assumptions, educated guessed are made during the design based on existing data and information, for example, thermodynamic data is assumed based on the results from the ASPEN plus simulation etc.

The wastes produced by the process include the biological catalyst (lipase B), toluene vapor and the air containing toluene. The treatment methods of the wastes in the design as mentioned in chapter 9 are chosen to ensure the process environmentally safe.

Hazard and Operability study (HAZOP) and Dow’s Fire and Explosion Index (FEI) are used to assess safety aspects from a process design point of view. The most dangerous unit, which is toluene storage tank and the most dangerous component (toluene) are taken for the determination of the degree of hazard in the plant.

The precursor of Prozac, (R)-3-chloro-1-phenyl-propyl acetate, will be few steps away to Prozac, which is a pharmaceutical product. Therefore, Good Manufacturing Practices are very important and a “must” for every pharmaceutical product and this plant is not an exception.

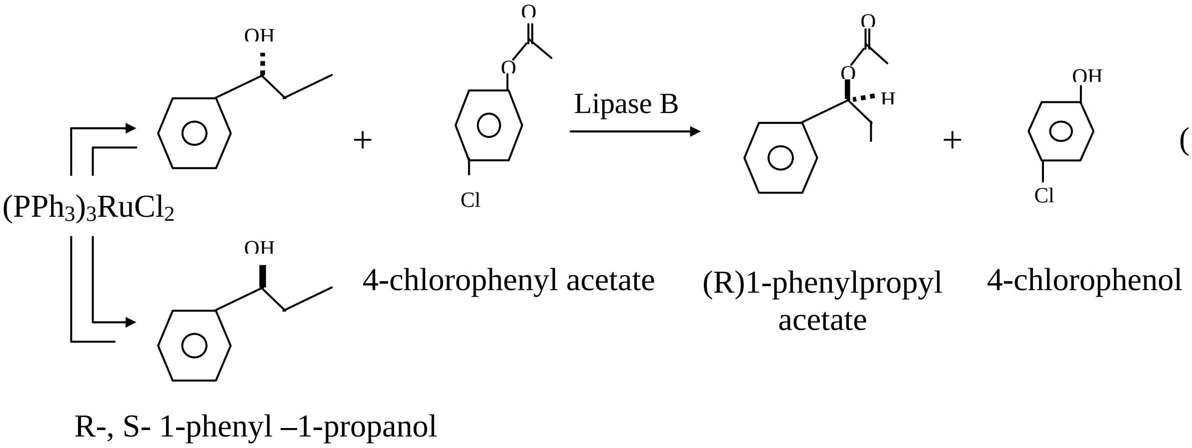
It is expected that this precursor of Prozac, 3-chloro-1-phenyl propyl acetate, will be able to compete in the market of Prozac and its intermediates. It is believed that the plant in the design is very safe for investment and very promising.

CHAPTER 2 PROCESS, OPTIONS AND SELECTION

2.1 Process options and option chosen

There are two options for producing *precursor of Prozac*, 3-chloro 1-phenylpropyl acetate.

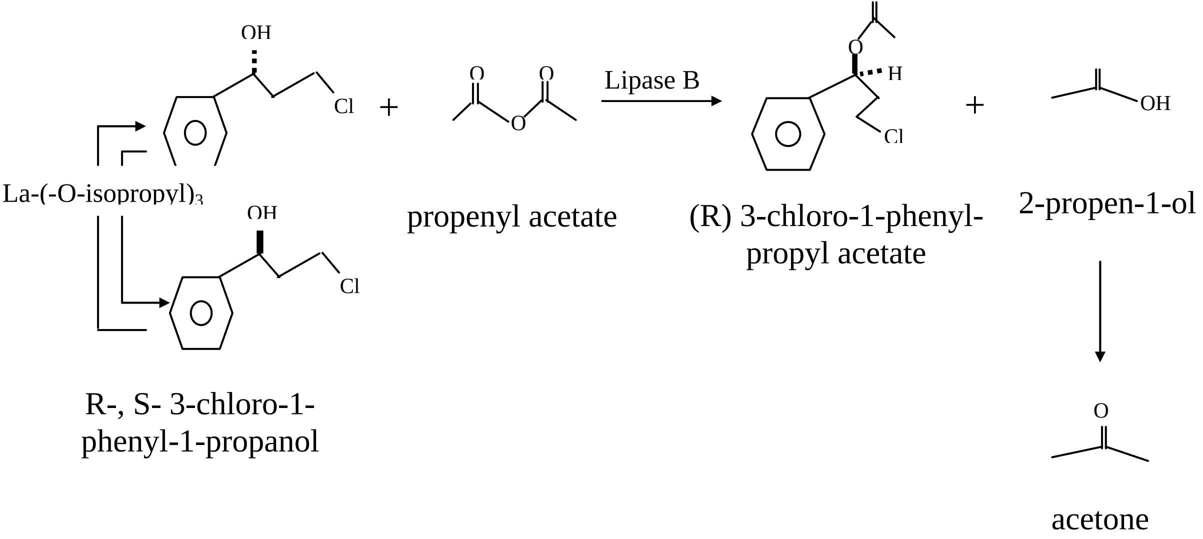
Chemical route 1



(1)

In this chemical route, the starting material is racemic mixture of 1-phenyl –1-propanol. Enzymatic resolution of this racemic substrate is completed by an immobilized lipase B from *Candida Antarctica* in the presence of a ruthenium catalyst. An acyl donor is 4-chlorophenyl acetate which is compatible with both the catalysts and results in an efficient dynamic kinetic resolution. The reaction is carried out at 70°C under argon atmosphere and the long reaction time of more than 40 hours is mainly a result of the rate-determining racemization. [7]

Chemical route 2



(2)

This chemical route is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology. The racemic mixture of 3-chloro-1-phenyl –1- propanol is a starting material in this route. Lanthanum isopropoxide is the catalyst for the racemization reaction instead of ruthenium catalyst. The same enzyme (lipase B from *Candida Antarctica*) as in the first chemical route is used for enzymatic resolution. Propenyl acetate is the acyl donor in this route. The product is (R) enantiomer of 3-chloro-1-phenylpropyl acetate. By-product is 2 propen-1-ol which is converted to acetone. The total time for the reactions in this chemical route is 4.5 hours. The reaction conditions are kept at 60^{o}C and 1 bar. At lower or higher temperatures the reaction still takes place however, at lower temperature the rate of reaction will be much lower and at higher temperature, the activity of enzyme might be lower. Therefore, the reaction should be at 60^{o}C and 1 bar as recommended by the people in Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology working in the project of developing this chemical route, namely Dr. Ulf Hanefeld.

Table 2.1: Decision criteria for choosing the chemical route

Chemical route	***Yield (%)***	***Availability of raw materials***	***Catalyst***	***By-product***	***Reaction time (hours)***
1	80 [7]	4-chlorophenyl acetate is not commercially available	ruthenium catalyst is not commercially available	4-chlorophenol is dangerous and smelly compound	40
2	nearly 100 (*)	propenyl acetate is commercially available (by Acros Organics)	lanthanum isopropoxide is commercially available (by Alfa chemicals)	acetone is harmless	4.5

Note: (*) the irreversible reaction () can easily happen, therefore there will be less and less of 2-propen-1-ol and the reaction goes only from left to right and the yield can be nearly 100%

According to table 2.1, chemical route 2 outcompetes chemical route 1. This also explains why TOCK (TU Delft) has put a lot of research efforts in studying and developing this chemical route.

⇒ ***Due to the above reasons the chemical route 2 is selected.***

The process options for chemical route 2

There are several process options for chemical route 2. (Please also refer to block schemes in appendix A1.1). The options are:

- Option 1: The catalyst (lanthanum isopropoxide) is first dissolved in toluene in dissolving tank. The enzyme (lipase B), catalyst (lanthanum isopropoxide) in solvent (toluene) and the reactants (3-chloro –1-phenyl-1-propanol and propenyl acetate) are added to the reactor. After 4.5 hours of reaction time the reaction mixture is fed to a filter where the solid (lipase B) is filtered out and re-used for the next batch. The liquid goes to precipitation tank. De-ionized water is added to the precipitation tank to precipitate out lanthanum isopropoxide. The hydrolysis reaction takes place in the precipitation tank where lanthanum hydroxide is formed from lanthanum isopropoxide. The solid (lanthanum hydroxide) will be filtered out and the liquid goes to the intermediate storage tank where the liquid of 20 batches is kept. The reason to store 20 batches is to obtain a reasonable flow rate to distillation column later in the process. The liquid in the intermediate storage tank containing large quantity of solvent (toluene), the product (3-chloro-1-phenyl propyl acetate) and the small quantity of water, isopropanol, acetone and unreacted reactants (propenyl acetate and racemic mixture of 3-chloro 1-phenyl –1-propanol) will then go to the vacuum evaporator where part of the solvent will be evaporated. Most of water, acetone and unreacted reactants will be evaporated from the evaporator due to their lower boiling points compared to that of toluene. The distillation column separates the product (3-chloro-1-phenyl propyl acetate) and the remaining solvent. The evaporator and the distillation column are operated under vacuum to avoid over heating the product. (Please refer to figure A1.1.1, appendix A1.1)

- Option 2: The process is similar to that of option 1 until the intermediate storage tank of the liquid of 20 batches. In this option, the evaporator will not be used, the liquid from intermediate storage tank will be fed directly to the distillation column which also operates under vacuum as in option 1 to obtain the desired purity of product of 99%. The product (3-chloro-1-phenyl propyl acetate) will be the bottom product and the mixture of solvent (toluene), water, isopropanol, acetone and unreacted reactants will be collected from the top of the distillation column. This mixture contains nearly 95% of toluene (please also refer to stream summary for the composition of this mixture from the top of distillation column) will be recycled. (Please refer to figure A1.1.2, appendix A1.1)

- Option 3: The process is similar to that of option 2 except that the mixture from the top of distillation column will be fed to the 2nd distillation column to obtain a higher purity of toluene. Toluene will be a heavy key component in this distillation column and will then be also recycled (Please refer to figure A1.1.3, appendix A1.1)

- Option 4: The process is similar to that of option 1 but instead of recycling, the mixture from the top of distillation column containing mainly toluene (nearly 95%) will be sold as technical grade toluene (Please refer to figure A1.1.4, appendix A1.1)

Table 2.2: Decision criteria for choosing the process option

Option	***Advantages***	***Disadvantages***	***Reasons for the decision***	***Decision***
1	- large part of the solvent is evaporated first before being fed to the distillation column → less duty for the distillation column	- more unit operation	- after running simulation in ASPEN, the use of the evaporator leads to the significant loss of the product. Nearly 50% of the product will be evaporated (refer to appendix A1.2 for details) → very low yield	*Rejected*

Table 2.2: Decision criteria for choosing the process option (con'td)

Option	*Advantages*	*Disadvantages*	*Reasons for the decision*	*Decision*
2	- mixture from the top of the distillation column is recycled → reduce the material cost for toluene	- toluene in the mixture is not pure (95% weight) - the recycled stream contains water and isopropanol which lead to undesirable reactions in the reactor .	-undesirable reactions: 1) reaction of lanthanum isopropoxide with water to form precipitate lanthanum hydroxide → loss of catalyst activity and it should be avoided because the catalyst is very expensive (55000 Dfl/kg as estimated from the price given by Alfa Chemicals) and it counts for the main cost of raw materials. 2) reaction of isopropanol with propenyl acetate → more propenyl acetate will be needed for the reaction	*Rejected*
3	- mixture from the top of the distillation column is fed to 2nd distillation column → recycled toluene has high purity → reduce the material cost for toluene	- more unit operation	- toluene is relatively cheap. - it is expensive to build another distillation column in term of equipment and utilities. Since the toluene is cheap so it is not worth to install another distillation column. - the margin for the process in very high , high profit can still be made without being needed to recycle a cheap raw material like toluene	*Rejected*
4	- extra unit operation (evaporator, another distillation column) is not needed - the mixture from the top of distillation column (toluene 95% wt) can be sold as technical grade	-	- extra unit operation (evaporator, another distillation column) is not needed - the mixture from the top of distillation column (toluene 95% wt) can be sold as technical grade → no waste of this stream → more profits can be made → do not need to take care of recycle stream	***Chosen***

⇒ ***Option 4 (of chemical route 2) is selected***

(Please refer to figure 3.1 in chapter 3 for a block scheme of the selected option. The description on how the process works in details and the batch cycle diagram are presented in part 3.2.2 of chapter 3)

2.2 Continuous, batch or combination

Douglas (1988) [8] listed the factors that favor batch operation while considering the option between batch and continuous. According to that, *batch process is chosen* because the production scale for this process is only 5000 kg/yr (which is nearly 11000 lb/yr less than 1×10^6 lb/yr).

An intermediate storage tank is used between the reaction part and separation part. Liquid in this tank will be fed to separation section. The components of the liquid in the intermediate tank are: water, isopropanol (from the hydrolysis reaction in the precipitation tank between lanthanum isopropoxide and water), unreacted reactants (propenyl acetate, racemic mixture of 3-chloro 1- phenyl-1-propanol), toluene and the product (the precursor of Prozac, 3-choloro-1-phenylpropyl acetate)

A batch separation section, which consists of a distillation column, is used to purify the product. The product is a heavy key component and toluene is the light key component

The plant will be designed is a product specific plant.

The assumptions are:

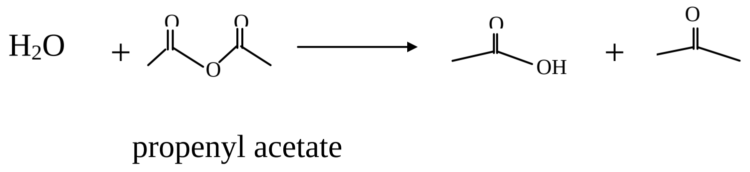
- The process will run 1 batch/ day and 100 batches/year to meet the requirements of the production scale. 100 batches/year is chosen for good design of batch reactor size (volume: 0.8 m^3, H = 1m, D = 1m).
- The intermediate storage tank is used to store 20 batches of reaction section and it is chosen to obtain a good flow rate to the distillation column. If less batches of reaction section are stored in the storage tank and then fed to distillation column, the flow rate to the distillation column will be very low which leads to very small diameter of the column and it is not practical. On the other hand if the flow rate to the distillation column is higher (more batches of reaction section are stored in the tank) the diameter of the distillation column will be much higher and it will lead to high cost of column design. The decision to store 20 batches of reaction section in the intermediate storage tank is made after running simulation in ASPEN and rough design of the dimensions of the distillation column.
- The distillation column operates for 16 hours/batch and there will be 5 separation batches per year.

2.3 Stochiometry and catalysts

Stochiometry

The ratio for 3-chloro-1-phenyl-1-propanol and propenyl acetate is 1:1.5.

There is always water in the reactants (for example 80 ppm) so it leads to hydrolysis of propenyl acetate:



(3)

If ratio 1:1 used, propenyl acetate will not be enough. The ratio 1:1.5 is chosen to make sure there will be enough propenyl acetate during the reaction. This ratio 1:1.5 is fixed after the discussion with the Principal of the project **[6]**

Catalysts
Name: Lanthanum isopropoxide
Amount: 3mol %
Form: powder

Name: Lipase-B enzyme originated from *Candida Antarttica* (CAL-B)
Amount: 8.8kg (for 100 batches)
Form: dry, spherically formed particles

As mentioned earlier the chemical route of the process is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology. In this chemical route the mentioned catalysts are used.

The amount of enzyme needed is calculated based on the reference in literature **[7]** (suggested by the Principal, Dr. Ulf Hanefeld, TOCK, TU Delft), which is 7.027kg of enzyme needed for each batch. After discussing with the Principal of the project, the loss in activity of enzyme is very low.

It can be assumed that every batch the enzyme will lose 0.1% of its activity and also 0.1% in the filter so in total 0.2% of enzyme lost in each batch. After 100 batches 20% of enzyme will be lost. Therefore, 20% more of the required amount of enzyme is added since the 1st batch. It means that 8.8kg of enzyme will be added since the first batch. After each batch the enzyme collected from the filter will be re-used for the following batches. After 100 batches, 20% of this amount of enzyme will be lost i.e. that there is still 80% of 8.8 kg remains active or 7.04kg of active enzyme. It can be summarized that if 8.8kg is added in the first batch, there will be sufficient enzyme till the last batch (100th batch) of the production year.

2.4 Reaction kinetics

(Please refer to reaction (2) of chemical route 2)

Due to lack of data, only the following kinetic data provided by the Principal **[6]** are available:

- 1st order reaction
- The racemization reaction takes 2.5 to 3hours for complete racemization at 60°C, 1 bar
- The acylation reaction takes 90 minutes
- In total the 2 reactions take 4.5 hours

CHAPTER 3 BASIS OF DESIGN

3.1 Description of the design

Prozac is in a class of antidepressant medications that affects chemical messenger within the brain (neurotransmitters). The generic name for Prozac is fluoxetine. Eli Lilly currently sells fluoxetine as the racemate (Prozac). Recently, interest has been shown for marketing the more active (R) – enantiomer due to its medical potential (please refer to chapter 1 for more details)

The goal of the design is to develop a Process Flow Diagram for a production facility for an enantiomerically pure precursor of Prozac (fluoxetine), which is (R)-3-chloro-1-phenyl propyl acetate. The production scale of the plant is to produce 5 tons of this precursor of Prozac a year. The supplied form of the product is liquid in 50L containers and the product will be sold to Prozac manufacturers such as Eli Lily and its competitors. It is expected to have a market price of 30,000Dfl/kg of this product.

The chemical route of the process is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology. This is a new chemical route developed using different catalyst and staring materials compared to the existed route in literature [7] (refer to part 2.1 for the comparison of these routes). It is very promising in term of yield and reaction time.

Many assumptions, educated guessed have to be made during the design due to lack of available data and information, for example, thermodynamic data and pure component data of racemic mixture of 3-chloro –1-phenyl – 1 propanol, staring material of the process, and (R)-3-chloro-1-phenyl-propyl acetate, the final product, or the price of these materials on the market etc. The assumptions and guessed are made based on limited available data and also on the accessible tools like ASPEN.

This chapter presents the options of the process and selected option. The block scheme, thermodynamic properties, pure component properties, and basic assumptions are also included. Margin as the total value of products less the total value of feedstock is calculated and presented in this chapter.

3.2 Process definition

3.2.1 Process concept chosen

(please also refer to chapter 2 for more information)

a) Process options and option chosen

There are two options for producing *precursor of Prozac,* 3-chloro 1-phenylpropyl acetate. The two chemical routes use the same enzyme lipase B for acylation reaction. Different starting materials and catalysts (for racemizaion reaction) are used in these chemical routes.

In the first chemical route, the starting materials are racemic mixture of 1-phenyl –1-propanol and 4-chlorophenyl acetate, ruthenium catalyst is used for racemization. The product is (R)1-phenylpropyl acetate.

The second chemical route is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology. The racemic mixture of 3-chloro-1-phenyl –1- propanol and propenyl acetate are starting materials in this route. Lanthanum isopropoxide is the catalyst for the racemization reaction instead of ruthenium catalyst. The product of this route is (R) enantiomer of 3-chloro-1-phenylpropyl acetate. The two products of these chemical routes are regarded similar in chemical structure except for chloro atom in the product of the second route. Both of the products are the precursor of Prozac.

Table 2.1 in chapter 2 presents the decision criteria for choosing the chemical route. Chemical route 2 is chosen due to its commercial availability of raw materials and catalysts compared to that of chemical route 1. The by product of chemical route 2 (acetone) is harmless while the by-product of chemical route 2 (4-chlorophenol) is dangerous and smelly. Chemical route 2 has a remarkably lower reaction time compared to the reaction time of first chemical route.

<u>The process options for chemical route 2</u>

There are several process options for chemical route 2 as mentioned in details in part 2.1 of chapter 2. It can be briefly summarized that there is an option (option 1) to use the evaporator followed by a distillation column (both operate under vacuum) for the separation section because the liquid in the intermediate storage tank contains large quantity of solvent (toluene), the product (3-chloro-1-phenyl propyl acetate) and the small quantity of water, isopropanol, acetone and unreacted reactants (propenyl acetate and racemic mixture of 3-chloro 1-phenyl –1-propanol). The evaporator will evaporate part of the solvent before the mixture is fed to distillation column for purification of the product.

In option 2, the liquid from intermediate storage tank will be fed directly to the distillation column, which also operates under vacuum as in option 1 to obtain the desired purity of product of 99%. The product (3-chloro-1-phenyl propyl acetate) with more than 99% weight will be the bottom product and the mixture of solvent (toluene, 95% weight), water, isopropanol, acetone and unreacted reactants will be collected from the top of the distillation column.

Option 3 is similar to that of option 2 except that the mixture from the top of distillation column will be fed to the 2nd distillation column to obtain a higher purity of toluene.

Option 4 is similar to that of option 1 but instead of recycling, the mixture from the top of distillation column containing mainly toluene (nearly 95%) will be sold as technical grade toluene

Option 4 is chosen based on the advantages discussed in table 2.2 (chapter 2). The main reasons for the decision are:
- Extra unit operation (evaporator, another distillation column) is not needed
- The mixture from the top of distillation column (toluene 95% wt) can be sold as technical grade, hence there will be no waste of this stream, more profits can be made and there is no need to take care of recycle stream

b) *Continuous, batch or combination*

Batch process is chosen because the production scale for this process is only 5000 kg/yr (which is nearly 11000 lb/yr less than 1×10^6 lb/yr). An intermediate storage tank is used between the reaction part and separation part. Liquid in this tank will be fed to separation section. A batch separation section, which consists of a distillation column, is used to purify the product. The product is a heavy key component and toluene is the light key component. (please refer to part 2.2, chapter 2 for more details)

c) *Stochiometry and catalysts*

Stochiometry

The ratio for 3-chloro-1-phenyl-1-propanol and propenyl acetate is 1:1.5.The ratio 1:1.5 is chosen to make sure there will be enough propenyl acetate during the reaction. This ratio 1:1.5 is fixed after the discussion with the Principal of the project **[6]** (please refer to part 2.3, chapter 2 for more details)

Catalysts

Name: Lanthanum isopropoxide	Name: Lipase-B enzyme originated from *Candida Antarttica* (CAL-B)
Amount: 3mol %	Amount: 8.8 kg for 100 batches
Form: powder	Form: dry, spherically formed particles

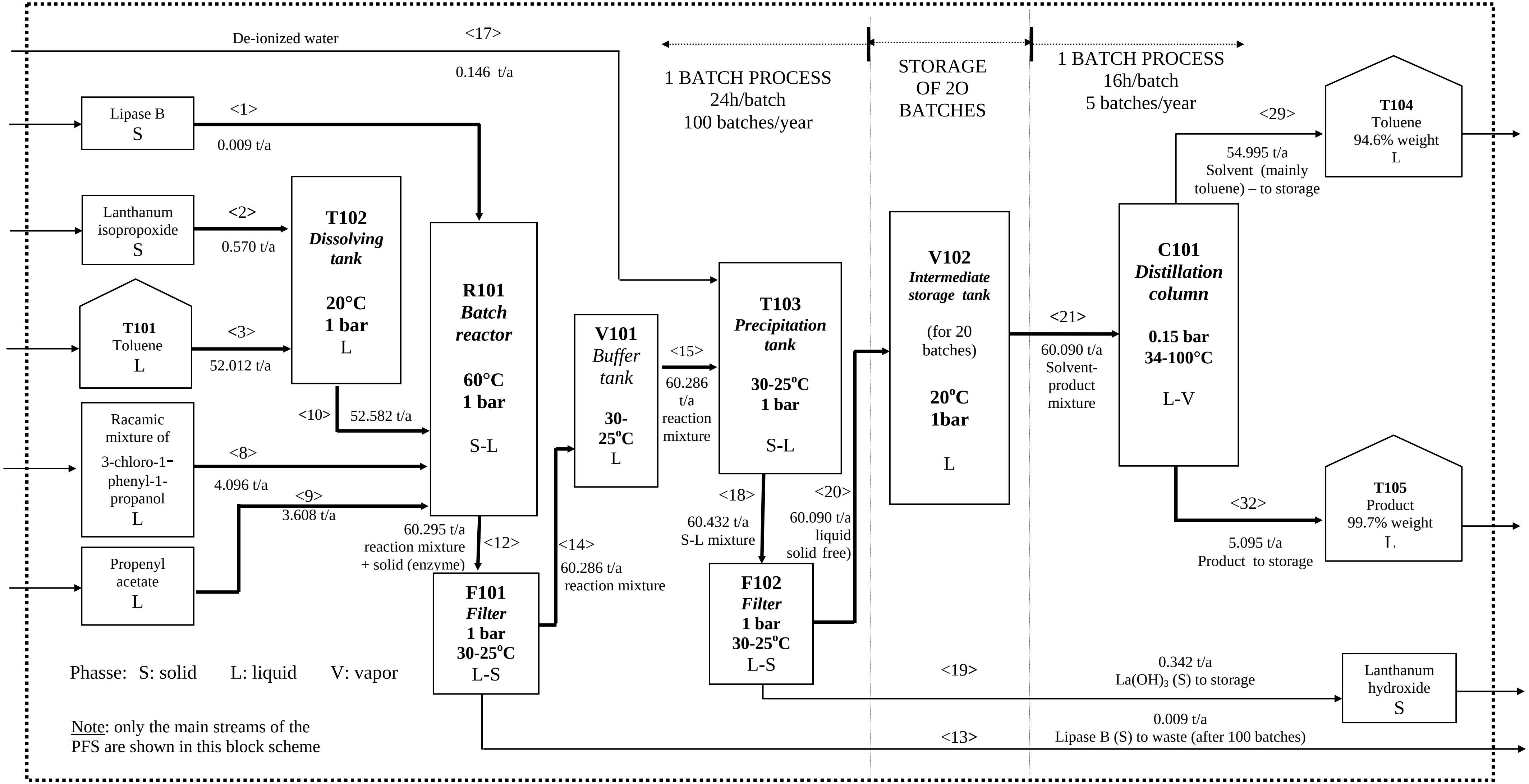
As mentioned earlier the chemical route of the process is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology. In this chemical route the mentioned catalysts are used.
(please refer to part 2.3, chapter 2 for more details)

d) *Reaction kinetics*

(Please refer to reaction (2) of chemical route 2)
Due to lack of data, only the following kinetic data provided by the Principal **[6]** are available:
- 1st order reaction
- The racemization reaction takes 2.5 to 3hours for complete racemization at 60°C, 1 bar
- The acylation reaction takes 90 minutes
- In total the 2 reactions take 4.5 hours

3.2.2 Block scheme

Figure 3.1: Block scheme of process to precursor of Prozac (3-chloro –1- phenyl propyl acetate)



Phasse: S: solid L: liquid V: vapor

Note: only the main streams of the PFS are shown in this block scheme

Description of the block scheme of process to precursor of Prozac (3-chloro-1- phenyl propyl acetate)
(please refer to figure 3.1 for the block scheme)

The process to precursor of Prozac (3-chloro-1- phenylpropyl acetate) works as described according to the following steps:

- All the raw materials are in the storage area. Toluene is in the storage tank. Other components are purchased in buckets or big cans since only relatively small amount is needed. Before each batch, the cans of catalysts, the buckets of propenyl acetate and racemic mixture of 3-chloro-1-phenyl-1-propanol are transported to the reaction area
- Before each batch the reactors, the buckets used for weighing raw material are cleaned according to Good Manufacturing Practices (please refer to chapter 9 of safety aspects).
- The reactor R101 and the dissolving tank T102 are injected with nitrogen to replace the air in these equipments in order to make sure that the internal of the dissolving tank and the reactor will be in dry conditions. The catalyst (lanthanum isopropoxide) is very sensitive to water so if there is water in the air lanthanum isopropoxide will react with water to form precipitate lanthanum hydroxide and it will lead to loss in activity of catalyst. Since this catalyst is extremely expensive (55000Dfl/kg as estimated from the price by Alfa Chemicals, please also refer to table 3.11 in chapter 3) and counts for most of the cost of raw materials of the process so the dry conditions in the reactor is very essential. Nitrogen will be injected and then released from the dissolving tank and from the reactor. The amount of nitrogen injected will be 1.5 times of the volume of these unit operations to ensure sufficient nitrogen for this drying step.
- Nitrogen is injected to dissolving tank T102 first.
- Then nitrogen is injected to the reactor R101, in the mean time toluene is pumped from the storage tank T101 to the dissolving tank T102
- The catalyst (lanthanum isopropoxide) is placed into the reactor manually via a hopper.
- Nitrogen is injected again to the top of dissolving tank T102 to replace a small amount of air coming into the tank when lanthanum isopropoxide is placed in the reactor. The amount of nitrogen injected is ½ of the volume of the tank because it is designed that the liquid occupies 80% of the tank so 20% of the volume is the empty headspace and the amount of nitrogen injected is equal to half of the volume (0.5V) of the tank or 2.5 times of the volume of this headspace.
- The catalyst is dissolved in toluene in dissolving tank T102. The tank T102 is at atmospheric pressure and normal temperature.
- The liquid from the dissolving tank T102 (lanthanum isopropoxide in toluene) is pumped to the reactor R101
- Racemic mixture of 3-chloro-1- phenyl-1-propanol and propenyl acetate are added manually to the reactor R101 through a hopper.
- The enzyme (lipase B originated from *Candida Antartica)* is placed manually into the reactor R101 through a hopper.
- Nitrogen is injected again to the top of the reactor R101 to replace a small amount of air coming into the tank when racemic mixture, propenyl acetate and enzyme

are added to the reactor. The amount of nitrogen injected is ½ of the volume of the reactor.

- The reactor is heated to 60^oC by means of steam.
- The reaction (reaction 2 in part 2.1) takes place for 4.5 hours (including heating time). The reactor is kept at 60^oC when the reaction takes place. The reaction is slightly exothermic (from the calculation of the heat of reaction, please refer to chapter 4 of thermodynamic properties) so cooling is needed during reaction using cooling water.
- After the reaction is completed, the reactor is cooled down using cooling water. The temperature of the liquid out of the reactor is 30^oC because the temperature of cooling water is between $20\text{-}25^oC$ so the liquid at the reactor exit will be cooled down to 30^oC after cooling time of 47 minutes.
- The solid-liquid reaction mixture passes through a filter F101 to filter out the enzyme lipase B, which will be used for the following batches. (Please also refer to part 2.3 of chapter 2 for more details about the reason for it).
- The liquid from the filter F101 goes to a buffer tank V101 and then pumped to from the buffer tank V101 to precipitation tank T103. The temperature of the liquid in the precipitation tank is $30\text{-}25^oC$ (It can be assumed that the temperature of the liquid is not changed through the pipes).
- De-ionized water is added to the precipitation tank T103 to precipitate out lanthanum isopropoxide. The hydrolysis reaction takes place in the precipitation tank where lanthanum hydroxide is formed from lanthanum isopropoxide. Isopropanol is also formed from this hydrolysis reaction:

  $$La[OCH(CH_3)_2]_3 + 3H_2O \rightarrow La(OH)_3 + 3(CH_3)_2CHOH$$

- The solid (lanthanum hydroxide) will be filtered out by using the filter F102 and the liquid goes to the intermediate storage tank V102 where the liquid of 20 batches is kept. The reason to store 20 batches is to obtain a reasonable flow rate to distillation column later in the process (please also refer to part 2.2 for reasoning of this decision). The liquid in the intermediate storage tankV102 containing large quantity of solvent (toluene), the product (3-chloro-1-phenyl propyl acetate) and the small quantity of water, isopropanol, acetone and unreacted reactants (propenyl acetate and racemic mixture of 3-chloro 1-phenyl – 1-propanol)
- The solid (lanthanum hydroxide) will be stored in the storage room and will be sold to other manufacturers who need this compound.
- The reaction part takes about 8 hours in total. 1 batch will be carried out per day, therefore after 20 days the liquid in the intermediate storage tank V102 will be fed to the distillation column C101.
- A distillation column C101 is used to separate the product (3-cholro-1-phenylpropyl acetate) from other components in the liquid mixture from intermediate storage tank: toluene (main component), water, isopropanol, acetone and unreacted reactants (propenyl acetate and racemic mixture of 3-chloro 1-phenyl –1-propanol). Toluene is a light key and the product is the heavy key of the distillation process. (Please refer to chapter 4 of thermodynamic properties and part 3.2.4 of list of pure component properties for the boiling point data of the components).
- The distillation column C101 operates under vacuum at 0.15-0.2bar to keep the temperature of the bottom will not exceed 120^oC because above this temperature the product might be decomposed **[6]**. At this pressure range, the temperature of

the column is in the range of 34-100°C. The temperature of the top is at 34°C so water can be used as coolant and it is practical for the process because water is a cheap cooling medium.

- The product is collected from the bottom of the column with the purity of 99.7% weight (obtained from the simulation in ASPEN), which meets the requirement for the purity of the product (should be above 99%). The product will be collected to the storage tank T105 and then filled into the 50L cans. The cans are stored in the storage and will be sold to the manufacturers who produce enantiomerically pure Prozac, for example Eli Lilly or its competitors.
- The mixture from the top of distillation column (nearly 95% weight for toluene) will be stored in the storage tank T104 and will be sold as technical grade toluene.
- After each batch of 16 hours, the distillation column is switched off until the next batch. The distillation column operates 5 batches/year.

3.2.3 Thermodynamic properties

(please also refer to chapter 4 for more information on thermodynamic properties)

a) Model for vapor/liquid equilibrium

There are three methods of calculating phase equilibrium: the equation-of-state method, the activity coefficient method and a special application method.

The equation-of-state method is used to describe both liquid and vapor phase behavior. This method is applicable for systems where the interaction of the components in the liquid phase is assumed to be minimal **[9]**. The activity coefficient method is a combination of two different methods: one to describe liquid phase behavior (γ_j in the unsymmetric form) and the other to calculate vapor phase properties (ϕ_j^v). This method should be used for highly non-ideal mixtures and for (chemical) systems with dissimilarity in size, shape and intermolecular forces **[9]**. The special application method is available for systems that for some reasons can't easily fall into one of the other two methods **[9]**. The models covered by this method are very dependent on the flowsheet simulator that is used. A typical model is for example the amines package for the removal of sour gases from hydrocarbon streams using MEA or DEA. This model falls for most simulators into the category of special applications **[9]**.

Since the system of the design is mostly organic compounds at low pressure, hence the equation-of-state method is not applicable. The chemicals involved in the system are acetone, toluene, propene acetate, 3-chloro-1-phenylpropyl acetate (precursor of Prozac) and 3-chloro-1-phenyl-1-propanol (raw material), which are coming from different groups and they are of course, dissimilar in size, shape and intermolecular forces, hence the activity coefficient method should be chosen to model vapor/liquid equilibrium for this system. Special application method is eliminated because the system can be already be described by activity coefficient.

In activity coefficient method, typical models to describe liquid phase behavior are Wilson, NRTL, Uniquac, Van Laar, UNIFAC. A special activity coefficient model is UNIFAC. This method can predict phase equilibrium for systems for which no experimental data are available. It doesn't depend on binary interaction parameters, but is based upon the so-called group contribution method **[10]**. Since the thermodynamic data for propene acetate, 3-chloro-1-phenylpropyl acetate (precursor of Prozac) and 3-chloro-1-phenyl-1-propanol (raw material) is hardly available (even in ASPEN SIMULATION engine), therefore UNIFAC is chosen to predict vapor/liquid equilibrium for this system.

It is aimed to separate the precursor (3-chloro-1-phenylpropyl acetate) from the others (mainly toluene). Because the most volatile component is toluene then toluene is chosen as the light key component while the heavy key is the precursor since it has the highest boiling point among the others.

T/x @p constant diagram is produced for the key components and can be viewed in chapter 4 (figure 4.1). The graph is obtained from ASPEN PLUS simulation engine. From this graph, it can be seen that the separation of product from solvent can be done easily by distillation.

b) Reaction enthalpy data

Since the reaction proceeds at 60°C, then the reaction enthalpy is calculated from the heat of formation of each component at 60°C. (*Note: Data of heat of formation at 60℃ for each component is taken from ASPEN SIMULATION engine*)

Table 4.1 (chapter 4) presents heat of formation of the components at 60°C. From this table, it is determined that the reaction is exothermic (please refer to chapter 4 for explaination)

c) Specific heat data

Typical constant pressure specific heat of each component can be obtained from ASPEN PLUS simulation engine. Specific heat of the components at 1atm (obtained from ASPEN) is given in table 4.2 (chapter 4)

d) Validation of method

For separations Carlson (1996) **[9]** suggests to check boiling points of the pure components against values from literature. Since for 3-chloro-1-phenylpropyl acetate and 3-chloro-1-phenyl-1-propanol, there is no data available in the literature hence they can’t be compared. Table 4.3 (chapter 4) gives the comparison of the boiling points of the components (toluene, acetone, isopropanol, water, propenyl acetate) obtained by using UNIFAC model and literature values.

It is found that the boiling point of each component from UNIFAC model is not different from that in the literature.

As for 3-chloro-1-phenylpropyl acetate, the boiling point is only available at 0.1 atm, the normal boiling point of 193°C is estimated from ASPEN.

3.2.4 List of pure component properties

Table 3.2: Pure component properties

Component name		***Technological Data***					***Medical Data***		***Notes***
Design	*Systematic*	*Formula*	*Mol. weight g/mol*	*Boiling point (1) °C*	*Melting point (1) °C*	*Density of liquid (2) g/cm^3*	*MAC value mg/m^3*	*LD50 Oral (3) g*	
Propenyl acetate	Propenyl acetate	$C_5H_8O_2$ $CH_3CO_2C(CH_3) = CH_2$	100.12	94-97	93	0.909	950	na	(4), L
(R)-, (S)-3-chloro-1-phenyl-1-propanol	(R)-, (S)- 3-chloro -1- phenyl-1-propanol	$C_9H_{11}OCl$	170.5	75		1.5412	na	na	(5), (6), L
Acetone	Acetone	$C_3H_6O_7$	58.08	56.5	-94.6	0.7908	1780	na	(5), L
Toluene	Toluene	C_7H_8	92.14	110.6	-95	0.8660	150	5	(5), L
(R)- 3-chloro-1-phenylpropyl acetate	(R)- 3-chloro-1-phenylpropyl acetate	$C_{11}H_{13}ClO_2$	212.5	84-85 (7) 193 (8)		1.5121	na	na	(5), (7), (8), L
Lanthanum isopropoxide	Lanthanum isopropoxide	$La[OCH(CH_3)_2]_3$	316.18	-	250-280	-	na	na	S
Lipase B catalyst from *Candida Antartica*		(CAL-B)	-	-	-	-	-	-	S
Deionized water		H_2O	18.01	100	0	1	-	-	L
Isopropanol	Isopopanol	C_3H_8O	60.1	81-83	-89.5	0.785	650	na	L
Lanthanum hydroxide	Lanthanum hydroxide	$La(OH)_3$	189.93	-	decomposes	-			S

<u>Notes</u>

L: liquid, S: solid (at normal tempature)

(1) At 1atm, unless specified
(2) Density at 25°C, unless specified
(3) Oral in g's for a male of 70kg's weight
(4) Medical data of isopropenyl acetate
(5) Density at 20°C relative to H_2O at 4°C
(6) Boiling point at 0.03atm
(7) Boiling point at 0.1atm
(8) Normal boiling point (estimated from ASPEN, also refer to chapter 4 of thermo. properties)

3.3 Basic assumptions

3.3.1 Plant capacity

The production scale of the plant is 5tons/year of 3-chloro-1-phenylpropyl acetate (precursor of Prozac).

The reaction part will be operated 100 batches for 100 working days (1batch/day). Every 20 batches will be operated for 20 consecutive working days followed by one day of a separation part. The separation part will be operated after 20 batches of reaction part, hence there will be 5 batches of separation part. The separation part takes 16 hours each batch and it is assumed that each batch of separation will take 24 hours in total (for heating the column at the beginning, cooling the column after 16 hours of operation, etc.). Therefore the plant will operate for 105 consecutive working days (100 days of reaction part + 5 days for separation part). After 105 of consecutive working days, the production line will be closed until following production year.

a) Feed stock

Feed conditions and composition

The conditions at which the feed enters the process are shown in the table below.

Table 3.3: Feed conditions

Pressure (bar)	1
Temperature (^oC)	20

Table 3.4: Feed composition

Components	*Stream number*	*Feed stream (t/a)*	*Weight percentage (%)*	*Notes*	*Additional information (ref. note number)*
Lipase B catalyst from *Candida Antartica*	<1>	0.009	0.02		
La-(-O-isopropyl)$_3$	<2>	0.570	0.95		
Toluene	<3>	52.012	86.26		
Racemic mixture of 3-chloro-1-phenyl-1-propanol	<8>	4.096	6.79		
Propenyl acetate	<9>	3.608	5.98		
Acetone		-	-	(1)	(1): only droplet of acetone needed at the beginning (consulted with the Principal)
Total		60.295	100.00		

Feed specifications

Table 3.5: Feed specifications

Components	*Stream number*	*Specifications*
Lipase B catalyst from *Candida Antartica*	<1>	Supplier: Boehringer Mannheim Enzyme and source: Lipase from *Candida Antartica*, fraction B Supply form: dry particles in glass containers (1kg each) (assumption because for small quantity Boehringer Mannheim supplies this catalyst in vials) Phase: solid Appearance: light-grey, spherically formed particles, 2mm in diameter Activity (hydrolysis)(100 mM tributyrin, pH 7.0, 25^{o}C): approx. 4.5 kU/g dry carrier Water content: <5% Storage conditions: dry conditions at –20 to 4^{o}C Handling: vials containing dry catalyst should be warmed to room temperature before opening. This prevents condensation of moisture onto the powder, which can cause loss of activity *(this information from Material Safety Data Sheet from the supplier)*
La-(-O-isopropyl)$_3$	<2>	Supplier: Alfa Aesar, A Johnson Matthey Company Johnson Matthey Catalog Company, Inc. Trade name: Lanthanum isopropoxide Supply form: in sealed plastic containers (1kg each) (assumption because for small quantity Alfa Chemicals supplies this catalyst in sealed small plastic containers) Phase: solid Appearance: white powder Hazard designation: highly flammable, corrosive Handling: *Information for safe handling*: Store in cool, dry place in tightly closed containers. Ensure good ventilation/exhaustion at the workplace. *Information about protection against explosions and fires*: Keep ignition sources away - Do not smoke. Protect against electrostatic charges. Fumes can combine with air to form an explosive mixture. Storage: (in the storage room) Store in cool, dry conditions in well sealed containers in a locked cabinet or with access restricted to technical experts or their assistants Store away from water, oxidizing agents Do not store together with acids *(this information from Material Safety Data Sheet from the supplier)*

Table 3.5: Feed specifications (cont'd)

Components	*Stream number*	*Specifications*
Toluene	<3>	Supplier: Acros Organics Supply form: toluene will be transferred from the tank behind the truck of the supplier to the storage tank of the plant (assumption since large amount of toluene is needed for the process. Acros Organics supplies this material in small quantities as 1L, 5L, 10L, 25L containers) Phase: liquid Appearance: clear colorless to very slightly yellow liquid Water content: <0.1% Hazard designation: highly flammable Storage conditions: the big storage tank of toluene is in the open air area of the plant. It should be made sure that it is in the area, which is not exposed to extremely high heat during summer. However, the plant is in Western Europe where the weather is not too hot in summer so it is not a big problem if the storage tank is not exposed to the heat above 30^{o}C. Handling: ignition source should be kept away since toluene is highly flammable *(the information from the specifications from the supplier and also some assumptions are made)*
Racemic mixture of 3 – chloro –1- phenyl – 1- propanol	<8>	Supplier: since this material is not commercially available so it is assumed that there will be a manufacturer will make this starting material for us. Supply form: liquid in 25L containers Phase: liquid Storage: cool, dry conditions in storage room *(all these specifications are the assumptions)*
Propenyl acetate	<9>	Supplier: Acros Organics Supply form: liquid in 25L containers Phase: liquid Appearance: clear colorless to very slightly yellow liquid Hazard designation: highly flammable Storage conditions: the containers are stored in the storage room Handling: ignition source should be kept away since propenyl acetate is flammable *(Only isopropenyl acetate is commercially available and provided by Acros Organics and other chemical companies. It is assumed that Acros Organics will provide this material. The information based on the specifications of isopropenyl acetate provided by Acros Organics*
De-ionized water	<17>	Supplier: Alfa Aesar, A Johnson Matthey Company Johnson Matthey Catalog Company, Inc. Supply form: 2L bottles Appearance: clear colorless liquid Storage conditions: the bottles are stored in storage room Handling: care must be taken with glass bottles *(the information from the specifications from the supplier and also some assumptions are made)*

b) Product

The product of this plant is (R)-3-chloro-1-phenylpropyl acetate, which is in stream 14 (bottom of the distillation column). The purity of the product is 99% (as a design parameter). The production scale of the plant is 5 tons/year.

The product will be sold to the manufacturers of Prozac such as Eli Lilly or its competitors. The product will be stored in 50L containers (cans) in product storage room and can be distributed 5 times a year (after each batch of separation) or it can be kept in the storage room for later distribution depending on the demands.

Table 3.6: The purity of the product ((R)-3-chloro-1-phenylpropyl acetate), precursor of Prozac

Components	*Stream number*	*t/a*	*Weight percentage (%)*	*Notes*	*Additional information (ref. note number)*
Precursor of Prozac (R)-3-chloro-1-phenylpropyl acetate	<32>	5.080	99.71		(1) The amounts of propenyl acetate, acetone, water, isopropanol are very small so they are neglected (2) Phase: liquid (3) Storage condition: The product from the bottom of the distillation column is collected to the storage tank and then 50L containers of the product will be filled and stored in cool storage room
Toluene	<32>	0.010	0.19		
Racemic mixture of 3-chloro-1-phenyl-1-propanol	<32>	0.005	0.10		
Total	<32>	5.095	100	(1) (2) (3)	

c) By-products

The by-products of the process are:

- technical grade toluene (the liquid in stream 13 from the top of distillation column). It contains mainly toluene (94.57% wt) can be sold as technical grade toluene to the manufacturers who do not need very pure toluene or to other manufacturers who can further purify and sell it as high purity toluene.
- lanthanum hydroxide (precipitate from precipitation tank and is collected from stream 10 after filtration process). It will be sold to the manufacturers who need this material.

Table 3.7: By-products

By-products	*Components*	*Stream number*	*t/a*	*Weight percentage (%)*	*Notes*	*Additional information (ref. note number)*
Technical grade toluene	Toluene	<29>	52.002	94.57		(1) The amounts of propenyl acetate, acetone, water, isopropanol are very small so they are neglected (2) Phase: liquid (3)Storage conditions: the big storage tank of toluene is in the open air area of the plant. It should be made sure that it is the area which is not exposed to extremely high heat during summer Handling: ignition source should be kept away since toluene is highly flammable (4) Technical grade toluene will be stored in a storage tank and will be pumped to clients' tanks when they come to purchase this material.
	Acetone	<29>	1.394	2.53		
	Propenyl acetate	<29>	1.205	2.19		
	Isopropanol	<29>	0.325	0.59		
	Water	<29>	0.049	0.09		
	Precursor of Prozac (R)-3-chloro-1-phenylpropyl acetate	<29>	0.016	0.03		
	Total	<29>	54.990	100	(1) (2) (3) (4)	
Lanthanum hydroxide	Lanthanum hydroxide	<19>	0.342	100	(1) (2) (3)	(1) Phase: solid (2) Storage conditions: in a cool, dry storage room, away from water and oxidizing agents (3) Lanthanum hydroxide will be packed in 25kg sealed bags

d) Wastes

After 100 batches of a production year, enzyme lipase B originated from *Candida Antartica* will be disposed as waste. The distillation column operates under vacuum therefore the vacuum pump is needed to pump the air out of the column (refer to part 8.2, chapter 8). The air pumped out from the column containing toluene and also some toluene vapor, are considered as waste gases (refer to chapter 9 for the information on how these wastes are handled in the design).

Table 3.8: Wastes produced in the process

Components	*Stream number*	*t/a*	*Additional information (ref. note number)*
Lipase B catalyst from *Candida Antartica*	<13>	0.009	(1) refer to table 9.1, chapter 8 for the quantity of the wastes
Toluene vapor	<33>	0.018	(2) refer to chapter 9 for the treatment of the wastes
Hazardous air	<33>	0.015	

3.3.2 Location

The plant is built in industrial area in Western Europe. The main feedstock is toluene, which is purchased from Acros Organics in large amount. Since Acros Organics is located in Belgium and Eli Lilly has the branch in Belgium, Germany and hopefully, there are competitors of Eli Lilly, which can be found in these countries. Therefore, the plant should be located close to the feedstock supply and convenient for product delivery, for example in the Netherlands.

3.3.3 Battery limit

a) Units inside battery limit

Table 3.9: Units inside battery limit

Unit	*Equipment number*	*Temp. (^oC)*	*Pressure (bar)*	*Remarks*
Toluene storage tank	T101	-10-30	1	This tank is outside the plant
Dissolving tank	T102	20	1	
Buffer tank	V101	30-25		The temperature of the liquid at the reactor exit is 30^{o}C so it is the assumed temperature range of liquid in buffer tank, and also precipitation tank (assumption that no temperature change through the pipes)
Precipitation tank	T103	30-25	1	

Table 3.9: Units inside battery limit (cont'd)

Unit	*Equipment number*	*Temp. (°C)*	*Pressure (bar)*	*Remarks*
Intermediate storage tank	V102	20	1	
Technical grade toluene (by-product) storage tank	T104	-10-30	1	This tank is outside the plant
Product storage tank	T105	20	1	
Reactor	R101	20-60	1	The liquid enters the reactor at 20°C (room temp.) but then heated up to 60°C and the reactor is kept at this temperature
Filters	F101 F102	30-25	1	Assumed temperature range for liquid in filtration process (liquid from the precipitation tank)
Distillation column	C101	34-100	0.15-0.2	
Other:				
- storage rooms for raw materials, product, by-product,		20	1	
- 8 pumps	P101-P108			

b) Utilities available outside battery limit

Nitrogen is needed for injection to the reactor to make sure the dry conditions in reactor, steam is needed for heating the reactor to 60°C and for the distillation column reboiler, cooling water for the cooling jacket and for the condenser of the distillation column. Power is needed for the pumps and electricity inside the plant.

Table 3.10: Utilities available outside battery limit

Utility	*Units*	*Price (Dfl/unit)*	*Quantity (unit/year)*	*Cost (Dfl/year)*
Nitrogen	m^3	7,500	319.0	2,400,000.0
Steam	t	30.00	18.0	547.2
Cooling water	t	0.10	921.0	92.1
Power	kWh	0.1016	1810.0	184.0

Remarks
(1): the price for nitrogen is estimated from the price by Sigma-Aldrich. It is sold at the price of 143.8 USD (360Dfl)/1 cylinder of 48 L. The conversion rate of USD to Dlf is 2.5
(2): the price of other utilities is taken from CPD Instruction manual **[11]** (the author of this manual took these data from "Cost data, WEBCI/DACE, 18th Edition November 1995
(3) refer to appendix A3.1 for the quantity of nitrogen
(4) refer to appendix A3.2 of utilities summary for quantity of the utilities

3.3.4 Definition of all in and out going streams/substances (passing the battery limit)

Table 3.11: In- and outgoing streams (passing battery limit)

Ingoing streams	*Stream number*	*kg/year*	*Price (Dfl/kg)*	*Dfl/year* (× 10^6)	*Euro /year* (× 10^6)	*Remarks*
Catalysts						
Lipase B catalyst from *Candida Antartica*	<1>	8.80	30,000.00	0.26	0.12	(1)
La-(-O-isopropyl)$_3$	<2>	569.70	48,500.00	27.60	12.6	(2)
Feed						
Toluene	<3>	52,012.00	15.00	0.77	0.35	(3)
Racemic mixture of 3-chloro-1-phenyl-1-propanol	<8>	4096.00	500.00	2.05	0.93	(4)
Propenyl acetate	<9>	3608.00	48.00	0.17	0.08	(5)
De-ionized water	<17>	145.94	40.00	0.01	0.005	(6)
Outgoing streams						
Product						
Precursor of Prozac (R)-3-chloro-1-phenylpropyl acetate	<14>	5095.00	10,000.00	50.95	23.16	(7)
By-products						
Technical grade toluene	<13>	54,990.00	3.00	0.17	0.08	(8)
Lanthanum hydroxide	<10>	342.00	500.00	0.17	0.08	(9)

Remarks:

(1) The price of enzyme is estimated based on the price of 4000Dfl/100g (given by the Principal [6]). The price of 3000Dfl/100g is estimated for purchasing of large quantity. (refer to part 2.3, chapter 2 for the amount of enzyme needed)

(2) The price of catalyst Lanthanum isopropoxide is estimated based on the price by Alfa Chemicals, which is 725Dfl/10g or 72,500Dfl/kg. Since this price is for purchasing small quantity. The price for purchasing large quantity is estimated to be 2/3 of the above price.

(3) The price of toluene is from Acros Organics

(4) The price of racemic mixture of 3-chloro-1-phenyl -1-propanol is estimated from the price of benzene and 3-chloro propionyl chloride.(please also refer to appendix A2.1 for estimation of the price of this racemic mixture)

(5) the price of propenyl acetate is estimated based on the price of isopropenyl acetate by Acros Organics

(6) The price of de-ionized water is estimated based on the price offered by Alfa Chemical. They sell at about 45Dlf /L for purchasing of small quantity.

(7) The price of the product (precursor of Prozac) is estimated based on the price of (R)-3-chloro-1-phenyl-1-propanol because this precursor is not commercially available. (R)-3-chloro-1-phenyl-1-propanol is chosen for the estimation of the price because it is also pure enantiomer and the chemical structure has a lot of similarities to the product. The price of (R)-3-chloro-1-phenyl-1-propanol is estimated from the price by Sigma-Aldrich. They sell this product at the price 217.5DM/5g i.e. about 45,000Dfl/kg. The price of the product (precursor of Prozac) is estimated to be approximately 20% of this price for large purchasing.

(8) The price of technical grade toluene (95% wt toluene) is estimated to be 3Dfl/kg after consult with some colleagues. The normal price in the world market for technical grade toluene (70% wt toluene) is in the range 0.25-0.5 USD/kg (i.e 0.6-1.25 Dfl/kg).

(9) The price to sell Lanthanum hydroxide is estimated based on the price of Alfa Chemicals. They sell this product at a price of almost 800Dfl/kg for purchasing small quantity

(10) The conversion rate from Dlf to Euro is 2.2

3.4 Estimation of margin and maximum allowed investment

3.4.1 Estimation of margin

Margin is estimated and presented in table 3.12 below.

Table 3.12: Estimation of margin

Ingoing streams	*Stream number*	*kg/year*	*Price (Dfl/kg)*	*Dfl/year* ($\times 10^6$)	*Euro /year* ($\times 10^6$)
Catalysts					
Lipase B catalyst from *Candida Antartica*	<1>	8.80	30,000.00	0.26	0.12
La-(-O-isopropyl)$_3$	<2>	569.70	48,500.00	27.60	12.60
Feed					
Toluene	<3>	52,012.00	15.00	0.77	0.35
Racemic mixture of 3-chloro-1-phenyl-1-propanol	<5>	4096.00	500.00	2.05	0.93
Propenyl acetate	<6>	3608.00	48.00	0.17	0.08
De-ionized water	<8>	145.94	40.00	0.01	0.005
Total raw materials cost				**30.86**	**14.09**
Outgoing streams					
Product					
Precursor of Prozac (R)-3-chloro-1-phenylpropyl acetate	<14>	5095.00	10,000.00	50.95	23.16
Total product value				**50.95**	**23.16**
By-products					
Technical grade toluene	<13>	54,990.00	3.00	0.17	0.08
Lanthanum hydroxide	<10>	342.00	500.00	0.17	0.08
Total by-products value				**0.34**	**0.16**
MARGIN (= product value + by-products value – raw materials cost)				**20.43**	**9.23**

Remarks

(1) Please refer to table 3.11 and appendix A2.1 for estimation and assumptions made for the prices of raw materials, product and by-products.
(2) Please refer to appendix A2.1 for more detailed calculation.
(3) Only cost of raw materials, product and by-products values are consider here.
(4) The conversion rate from Dfl to Euro is 2.2

The advantage of this plant is that no waste stream produced. All by products can be sold. The mixture from the top of distillation column (95% wt toluene) can be sold as technical grade toluene. Lanthanum hydroxide can also be sold to the manufacturers who need this catalyst.

From table 3.11, it can be seen that the cost for chemical catalyst (lanthanum isopropoxide) counts for the main cost of raw materials. Loss of activity of the catalyst should be extremely avoided. Therefore, important consideration in designing the plant is to ensure dry condition inside the reactor, it means that the nitrogen injection step is very essential.

It can be seen from the estimated margin, the process in very promising.

The margin is found to be 20.4 million Dfl/year or 204 millions for 10 working years. This margin is much higher compared to net present value of 26.4 millions found in economic evaluation in chapter 11. It is because the margin calculated in this chapter did not include the costs of utilities, labor, shipping and packaging, insurance etc. and also the interest was not considered.

3.4.2 Determination of maximum allowed investment

The following assumptions are made to determine maximum allowed investment:

- The economic plant life of project is 11 years
- The design/building period is 1 year and the working period is 10 years
- The productivity of the last year of this project is still 5000 kg/year.
- The interest rate (r) is 8% per year
- The margin is 22.43 millions Dfl (or 9.23 millions Euro) as from table 3.11

The following formulas are used to calculate maximum allowed investment

1) $$\text{Present margin} = \frac{\text{Margin}}{(1+r)^n}$$

2) $$\text{Cumulative of margin in working years} = \sum_{n=2}^{n=11} \frac{\text{Margin}}{(1+r)^n}$$

n is the year;
r is the interest rate

3)
$$\text{DCFROR} = \frac{\text{Cumulative net cash flow at the end of project}}{\text{Life of project} \times \text{Original investment}}$$

$$\text{DCFROR} = \frac{\text{Cumulative of margin in working years - Original investment}}{\text{Life of project} \times \text{Original investment}}$$

As DCFROR is 10% or 0.1:

$$\frac{\text{Cumulative of margin in working years - Original investment}}{\text{Life of project} \times \text{Original investment}} = 0.1$$

$$\rightarrow \text{Original investment} = \frac{\text{Cumulative of margin in working years}}{0.1 \times \text{Life of project} + 1}$$

Maximum acceptable investment is determined to be 60.62 millions Dfl (or 27.55 millions Euro) at DCFROR (Discount Cash Flow rate of Return) of 10% (please refer to appendix A2.2 for detailed calculation)

CHAPTER 4 THERMODYNAMIC PROPERTIES

4.1 Model for vapor/liquid equilibrium

There are three methods of calculating phase equilibrium: the equation-of-state method, the activity coefficient method and a special application method.

The equation-of-state method is used to describe both liquid and vapor phase behavior. This method is applicable for systems where the interaction of the components in the liquid phase is assumed to be minimal **[9]**. This is for most hydrocarbon systems at high and moderate pressure and temperature **[10]**. Since our system is mostly organic compounds at low pressure, hence the equation-of-state method is not applicable.

The activity coefficient method is a combination of two different methods: one to describe liquid phase behavior (γ_j in the unsymmetric form) and the other to calculate vapor phase properties (ϕ_j^v). This method should be used for highly non-ideal mixtures. This is for (chemical) systems with dissimilarity in size, shape and intermolecular forces **[9]**. Since the chemicals involved in the system are acetone, toluene, propene acetate, 3-chloro-1-phenylpropyl acetate (precursor of Prozac) and 3-chloro-1-phenyl-1-propanol (raw material), which are coming from different groups and they are of course, dissimilar in size, shape and intermolecular forces, hence the activity coefficient method should be chosen to model vapor/liquid equilibrium for this system.

The special application method is available for systems that for some reasons can't easily fall into one of the other two methods **[9]**. The models covered by this method are very dependent on the flowsheet simulator that is used. A typical model is for example the amines package for the removal of sour gases from hydrocarbon streams using MEA or DEA. This model falls for most simulators into the category of special applications **[9]**. Since our system can already be described by activity coefficient, then the special application method should not be chosen.

In activity coefficient method, typical models to describe liquid phase behavior are:

- Wilson
- NRTL
- Uniquac
- Van Laar
- UNIFAC

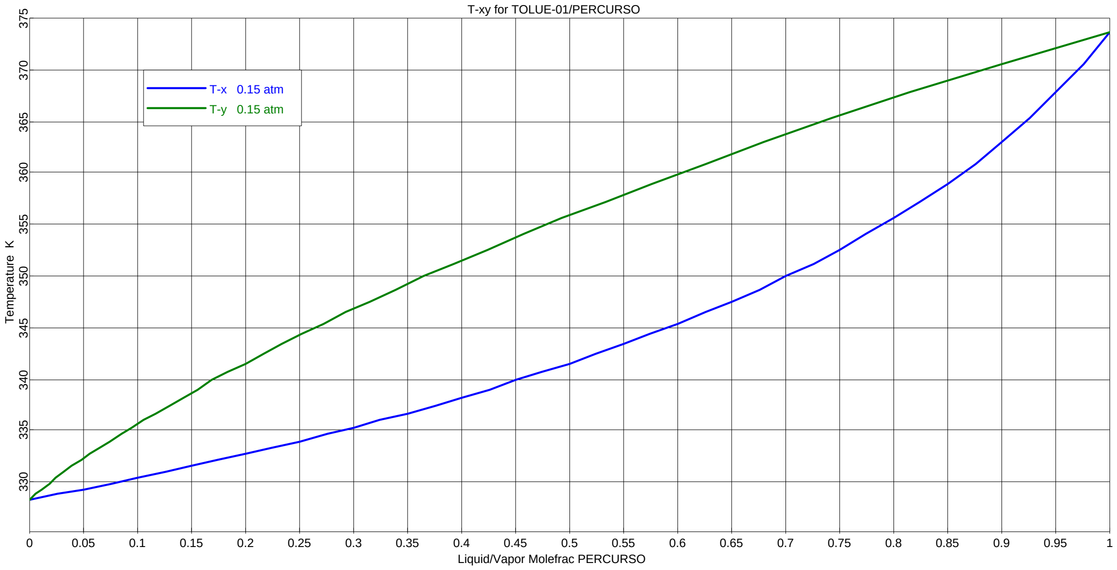
Wilson and Van Laar are only suitable for vapor-liquid systems, while NRTL and Uniquac can also be used in cases that there are two liquid phases present. None of these models should be used under critical conditions **[9]**.

A special activity coefficient model is UNIFAC. This method can predict phase equilibrium for systems for which no experimental data are available. It doesn't depend on binary interaction parameters, but is based upon the so-called group contribution method **[10]**. Since the thermodynamic data for propene acetate, 3-chloro-1-phenylpropyl acetate (precursor of Prozac) and 3-chloro-1-phenyl-1-propanol (raw material) is hardly available (even in ASPEN SIMULATION engine), therefore UNIFAC is chosen to predict vapor/liquid equilibrium for this system.

It is aimed to separate the precursor (3-chloro-1-phenylpropyl acetate) from the others (mainly toluene). Because the most volatile component is toluene then toluene is chosen as the light key component while the heavy key is the precursor since it has the highest boiling point among the others.

To give some idea about what kind of separation it’s going to be used, the T/x @p constant diagram is made for the key components. The graph is made for key components only because they’re the main components in the top and bottom of distillation column. The graph is obtained from ASPEN PLUS simulation engine.

Figure 4.1: T/x diagram at p constant for the key components (the product, 3-chloro-1 phenylpropyl acetate, and toluene)



From the figure, it can be seen that the separation of product from solvent can be done easily by distillation.

4.2 Thermodynamic data

4.2.1 Reaction enthalpy data

Since the reaction proceeds at 60°C, then the reaction enthalpy is calculated from the heat of formation of each component at 60°C. (*Note: Data of heat of formation at 60°C for each component is taken from ASPEN SIMULATION engine*)

Table 4.1: Heat of formation of the components at 60°C (from ASPEN)

Component	*$\Delta H_{f,\,60^\circ C}$ (kJ/kmol)*
Propene acetate	-380190.02
3-chloro-1-phenylpropyl acetate	-428370.02
3-chloro-1-phenyl-1-propanol	-228080.01
Acetone	-242540.01

The reaction is:
3-chloro-1-phenyl-1-propanol + propene acetate → 3-chloro-1-phenylpropyl acetate + acetone

Hence the heat of the reaction can be calculated as:

$$\Delta H_{\text{reaction at } 60^{o}\text{C}} = \Delta H_{\text{product}} - \Delta H_{\text{reactant}}$$

$$\Delta H_{\text{reaction at } 60^{o}\text{C}} = -428370.02 - 242540.01 - (-228080.01 - 380190.02)$$

$$\Delta H_{\text{reaction at } 60^{o}\text{C}} = -62.64 \frac{kJoule}{mol}$$

Hence, the reaction is exothermic.

4.2.2 Specific heat data

Typical constant pressure specific heat of each component can be obtained from ASPEN PLUS simulation engine. As an example of specific heat data of pure components is given below:

Table 4.2: Example of specific heat of the component at 1atm, 25°C (obtained from ASPEN)

Component	*Specific heat (kJ/kmol-K) at 1 atm*
Propenyl acetate	194.99
3-chloro-1-phenylpropyl acetate	253.82
3-chloro-1-phenyl-1-propanol	182.88
Acetone	131.40
Toluene	168.81
Water	73.53
Isopropanol	188.30

4.3 Validation of method

For separations Carlson (1996) [9] suggests to check boiling points of the pure components against values from literature. Since for 3-chloro-1-phenylpropyl acetate and 3-chloro-1-phenyl-1-propanol, there is no data available in the literature hence they can't be compared.

Table 4.3: Comparison the boiling points of the components obtained by using UNIFAC model and literature values

Component	*Normal boiling point (°C)*	
	Literature	*UNIFAC*
Toluene	110.6	110.68
Acetone	56.5	56.13
Isopropanol	81-83	82.35
Water	100	100
Propenyl acetate	94-97	95.4

As it can be seen from the above table, the boiling point of each component from UNIFAC model is not different from that in the literature.

For3-chloro-1-phenylpropyl acetate, the boiling point is only available at 0.1 atm, then the normal boiling point of 193°C is estimated from ASPEN.

CHAPTER 5 PROCESS STRUCTURE AND DESCRIPTION

5.1 Criteria and selections

In this section, all information from foregoing chapter will be explained to assess the various design criteria. Some of criteria, which determine the choice of design, are for example: productivity, product purity, safety, and cost. Based on those criteria, the designed elements, like selection of unit operation, sequence of process, specific type of equipment, final process conditions, etc, are determined carefully.

Please refer to the Process Flow Scheme (part 5.2, chapter 5) in order to follow the explanation below:

5.1.1 Toluene storage tanks (T101 and T104)

It's decided to place the storage tank outside the building (outdoor) since toluene is dangerously flammable material and toxic. Toluene will be stored to fulfill the needs of 20 batches (10.4 tons). Since this amount is considerably big, then outdoor storage can reduce the explosion potential of the unit and provide good ventilation in case of explosion occurs. This also applies for industrial grade toluene tank (T104). Hence, safety criteria determine this choice.

For other unit operations, they are placed inside the building since the risk of explosion is less than that of toluene storage tank.

5.1.2 Dissolving process

The catalyst lanthanum isopropoxide dissolves in toluene. It is desirable for the reaction to dissolve it first before it reacts. This dissolving process is also what is being done in the laboratory of Applied Organic Chemistry and Catalysis group (TOCK), TU.Delft.

5.1.3 Sequence of adding raw materials

Solid materials (catalysts) should be added after the liquid to make sure that the solid will not lump. The solid will also be distributed evenly if it's done in that way.

5.1.4 Precipitation process

The catalyst lanthanum isopropoxide is harmful and toxic therefore it should be removed from the mixture. The easiest way to separate it is by precipitating with water **[6]**. The lanthanum isopropoxide reacts with water producing lanthanum hydroxide (solid) and isopropanol.

5.1.5 Separation process (distillation column)

From Figure 4.1 in chapter 4 (Thermodynamics property), it can be seen that the separation can be done easily by distillation column since the boiling point different between those two components are relatively high (82.4°C).

To reduce the heat duty of distillation column, a vacuum evaporator is proposed to vaporize toluene first. However, after simulating with ASPEN, it seems impossible to do this way because some of the products (precursor of Prozac) will evaporate together with toluene. Since product lost should be prevented, using evaporator is not a good choice. If distillation column is used, such a problem can be prevented (see appendix A5.10).

So from the productivity criteria, the distillation column is chosen instead of evaporator.

5.1.6 Mesh and Filter operation chosen (F101)

First, it is thought to put mesh at the bottom of the reactor R101 in order to separate the mixture from lipase B. In this case, no extra unit operation is needed. However, the mesh at the bottom of the reactor might cause the lipase B adheres on the holes of the mesh, therefore the mixer will not work as expected. That will cause the productivity decreases. So from productivity reason it is decided to use filter instead of mesh at the bottom of the reactor.

5.1.7 Filter type chosen (F101, F102)

Micro-filters are used in the plant since the product is an intermediate for the production of pharmaceutical product (Prozac). High purity criterion is essential and it is a base for the decision to choose micro filters for the best separation result.

5.1.8 Mixing method in the tanks chosen (T102, R101, T103)

Internal impellers are chosen as the mixing device in the tanks because the cost of other devices or methods (bubble mixing and external pump) are much more expensive (for details please refer to part 8.2 chapter 8). Therefore, economic criteria determined the choice of mixing method for the tanks.

5.1.9 Heating method chosen for reactor (R101)

Since internal heat transfer surface and external heat exchanger will cost more than jacket heat exchanger, so jacket reactor is used (for details please refer to part 8.2 chapter 8). Hence, economic criteria determined the choice of heating method for the reactor.

5.1.10 Pumps chosen (P101-P108)

Pumps are used in the plant to transfer liquid through the whole process. Because the amount of liquid only depends on the requirement of productivity, so the choice of pump is determined by productivity criteria (refer to part 8.2, chapter 8 for details)

5.1.11 Heat exchangers chosen (E101-E104)

The same reason as explained in pump chosen part, productivity criteria also determined the choice of heat exchangers (refer to part 8.2, chapter 8 for more details)

5.1.12 Utility chosen

After considering the cost of different utilities and required amount of heat transfer in the plant (calculation is based on plant productivity criteria), the cheapest utilities are chosen from all possible choices (refer to appendix A4.3.2 and part 5.5,chapter 5 for detail calculation and selection). Therefore, the utilities selection here is determined by productivity criteria and cost criteria

5.1.13 Heat integration

In the plant, from the calculation of process heat needed and heat released (calculation is base on plant productivity criteria), it’s first considered all possibilities of heat integration. By using economic criteria, it can be found whether it is worth or not to apply such heat integration technology in the plant. Therefore, the heat integration is determined by productivity criteria and cost criteria. (The possibility of pinch technology is discussed in details in appendix A4.3.3)

5.2 Process flow scheme

1. Nitrogen injection to T102

Figure 5.1.1: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

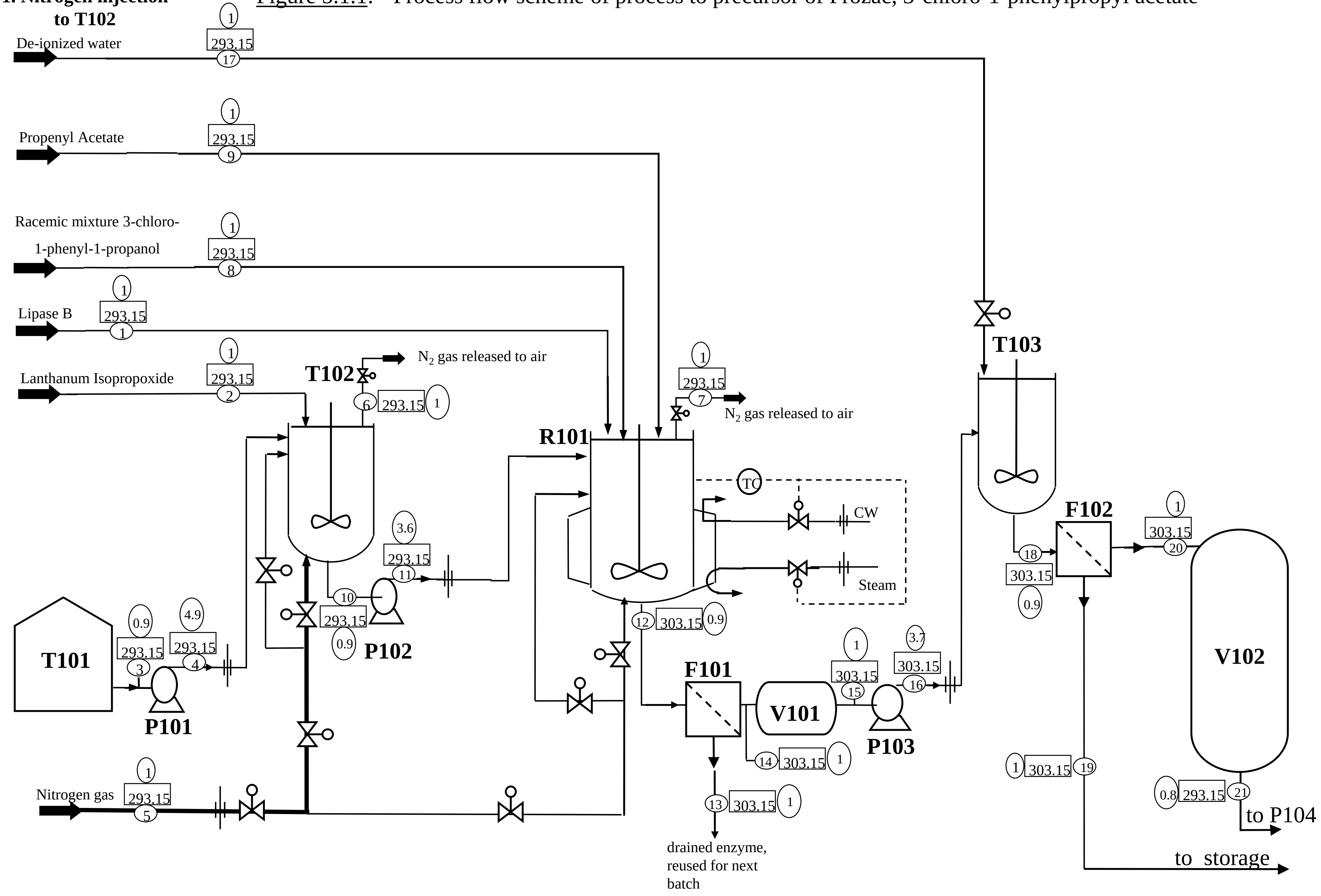


Figure 5.1.2: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

2. Fill T102 with toluene and nitrogen inject to R101

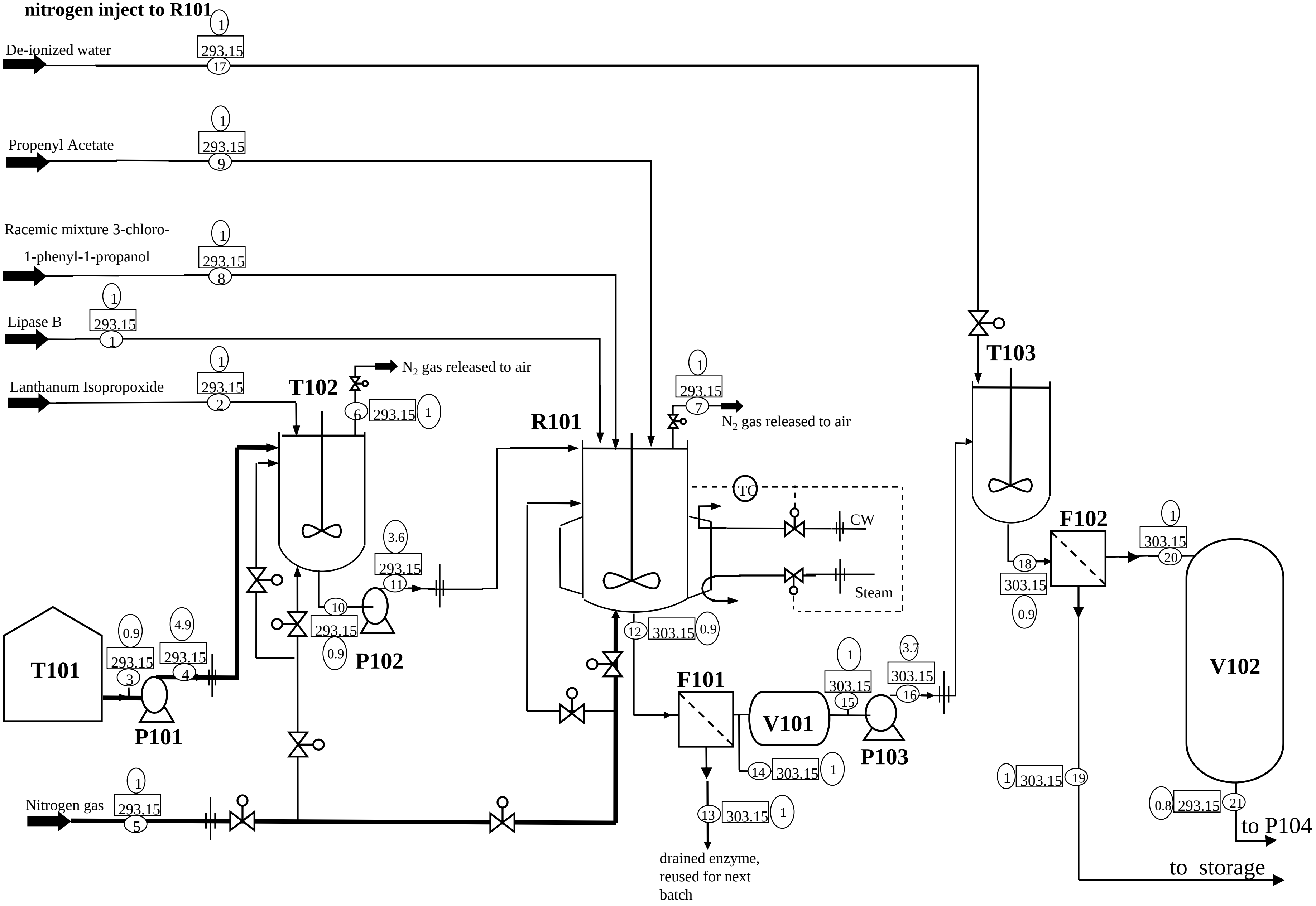


Figure 5.1.3: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

3. Add lanthanum isopropoxide to T102 and nitrogen inject to R101

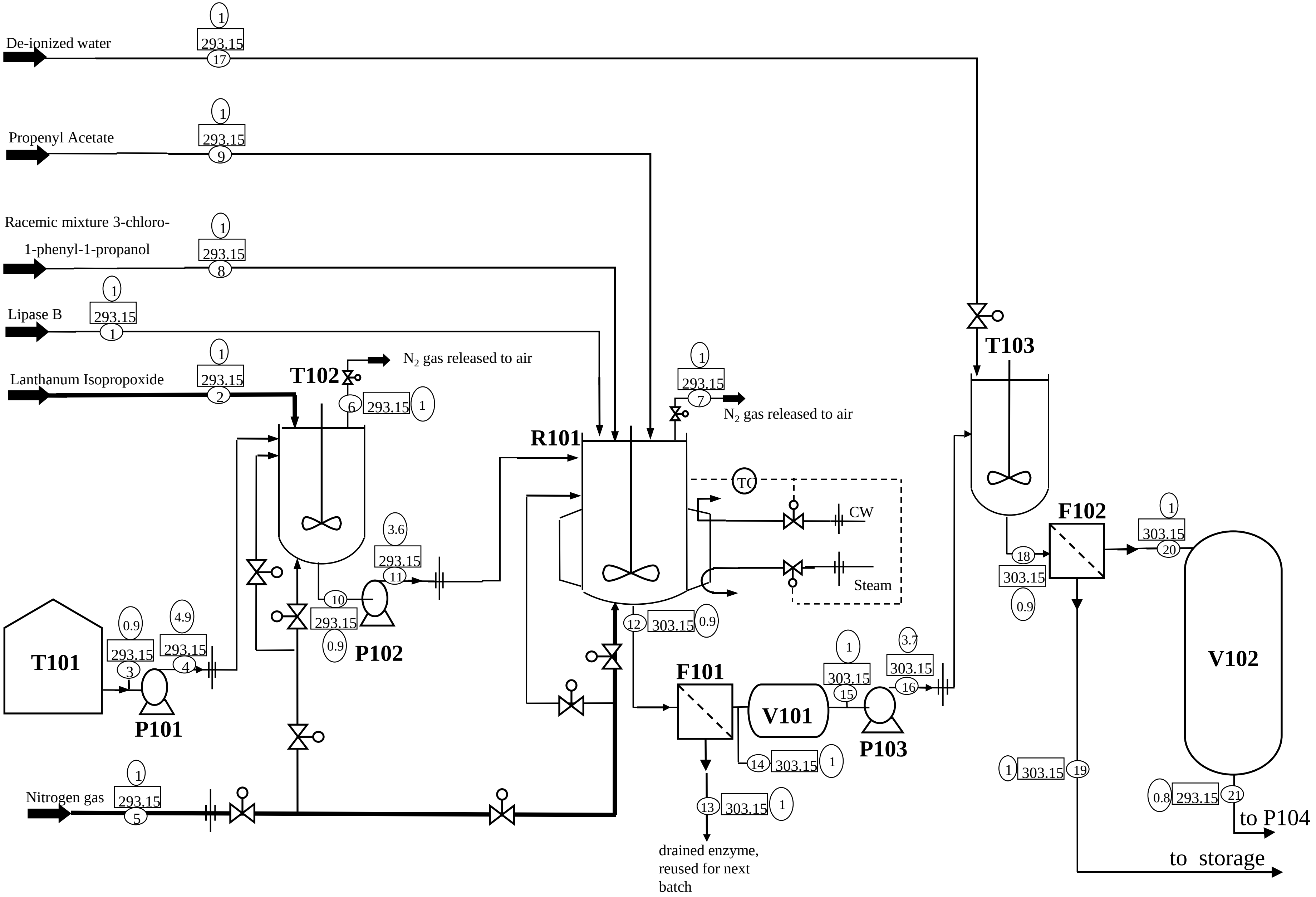


Figure 5.1.4: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

4. Nitrogen injection to T102

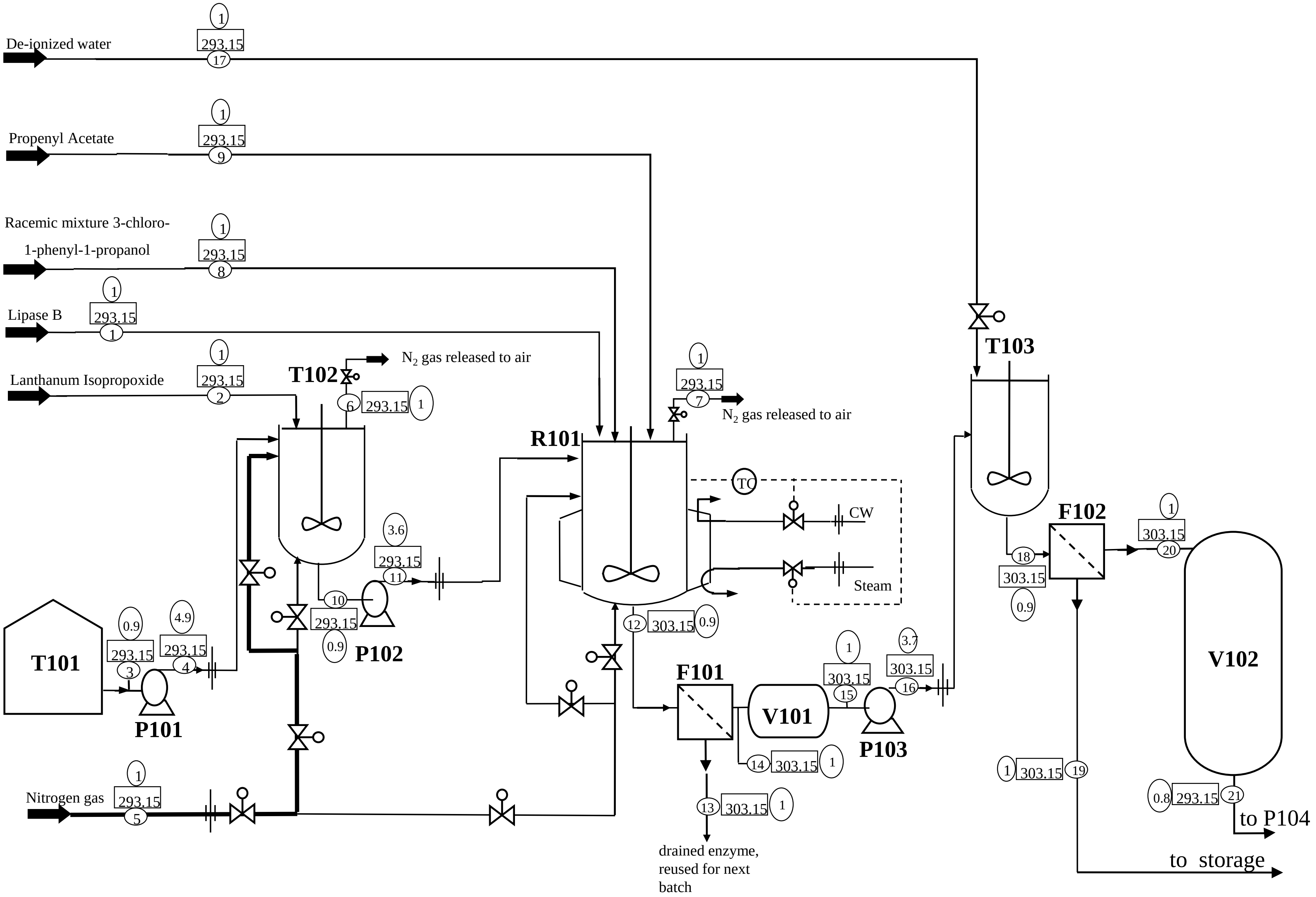


Figure 5.1.5: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

5. Discharge from T102 to R102

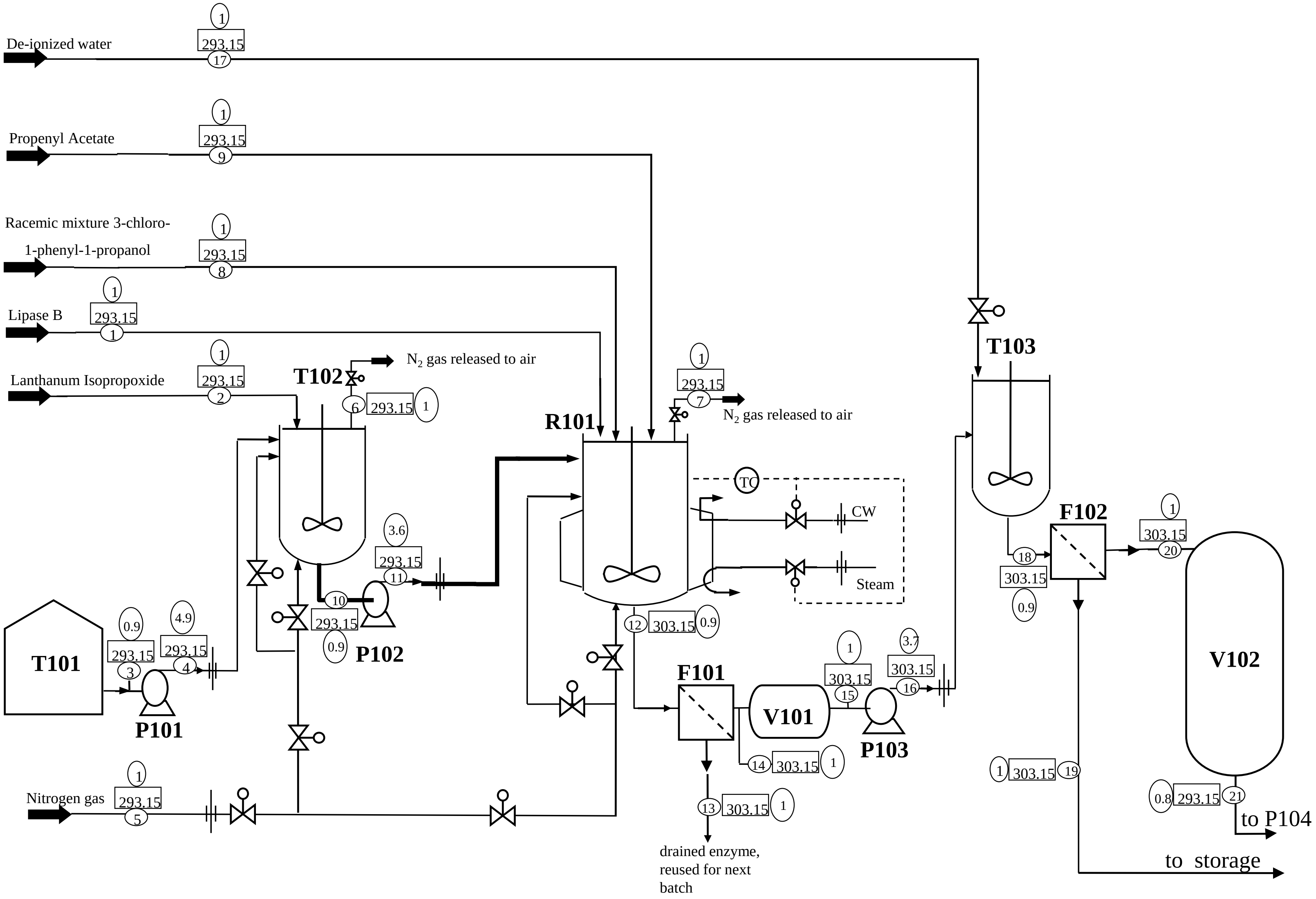


Figure 5.1.6: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

6. Feed R101 with racemic mixture

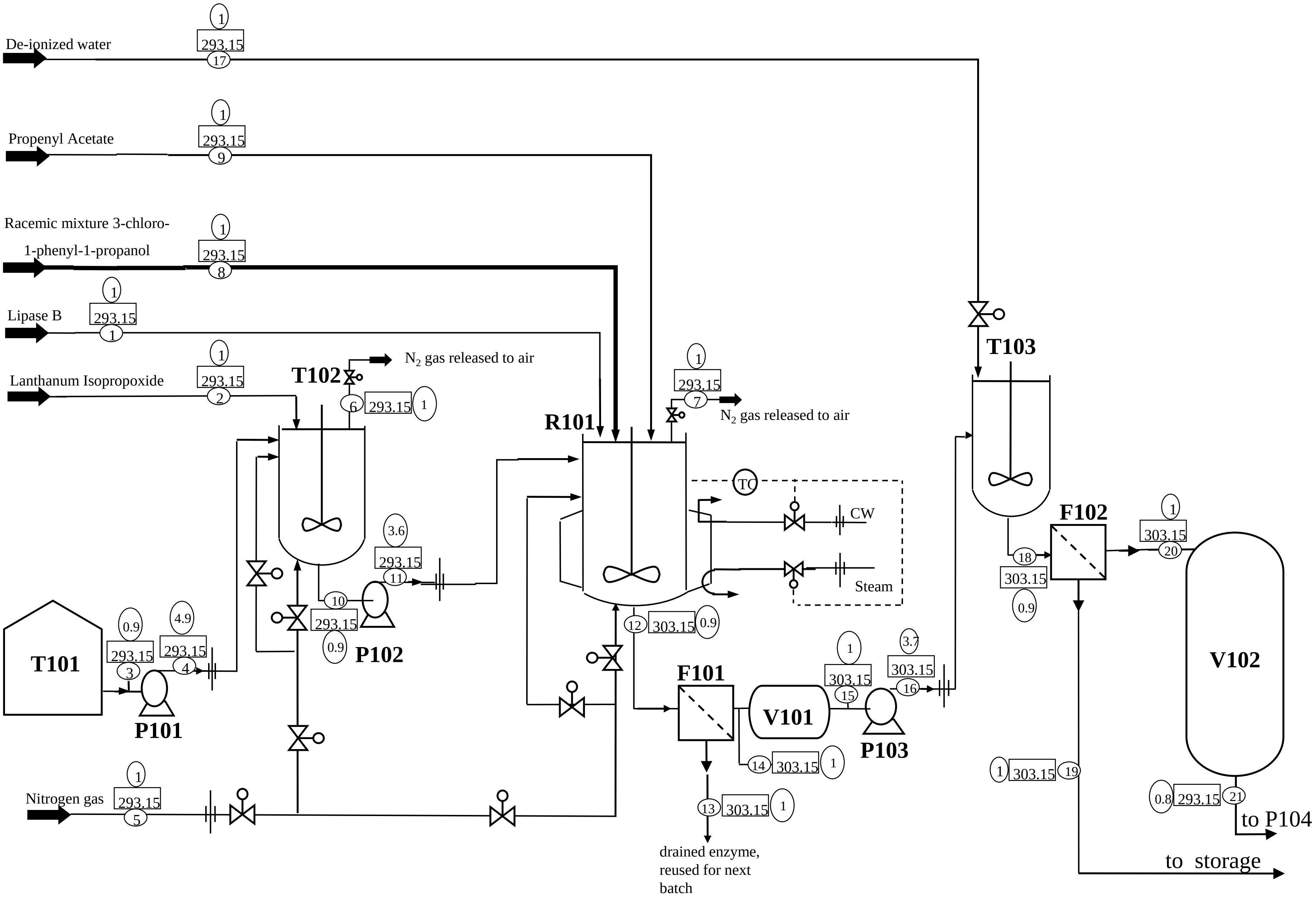


Figure 5.1.7: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

7. Fill R101 with propenyl acetate

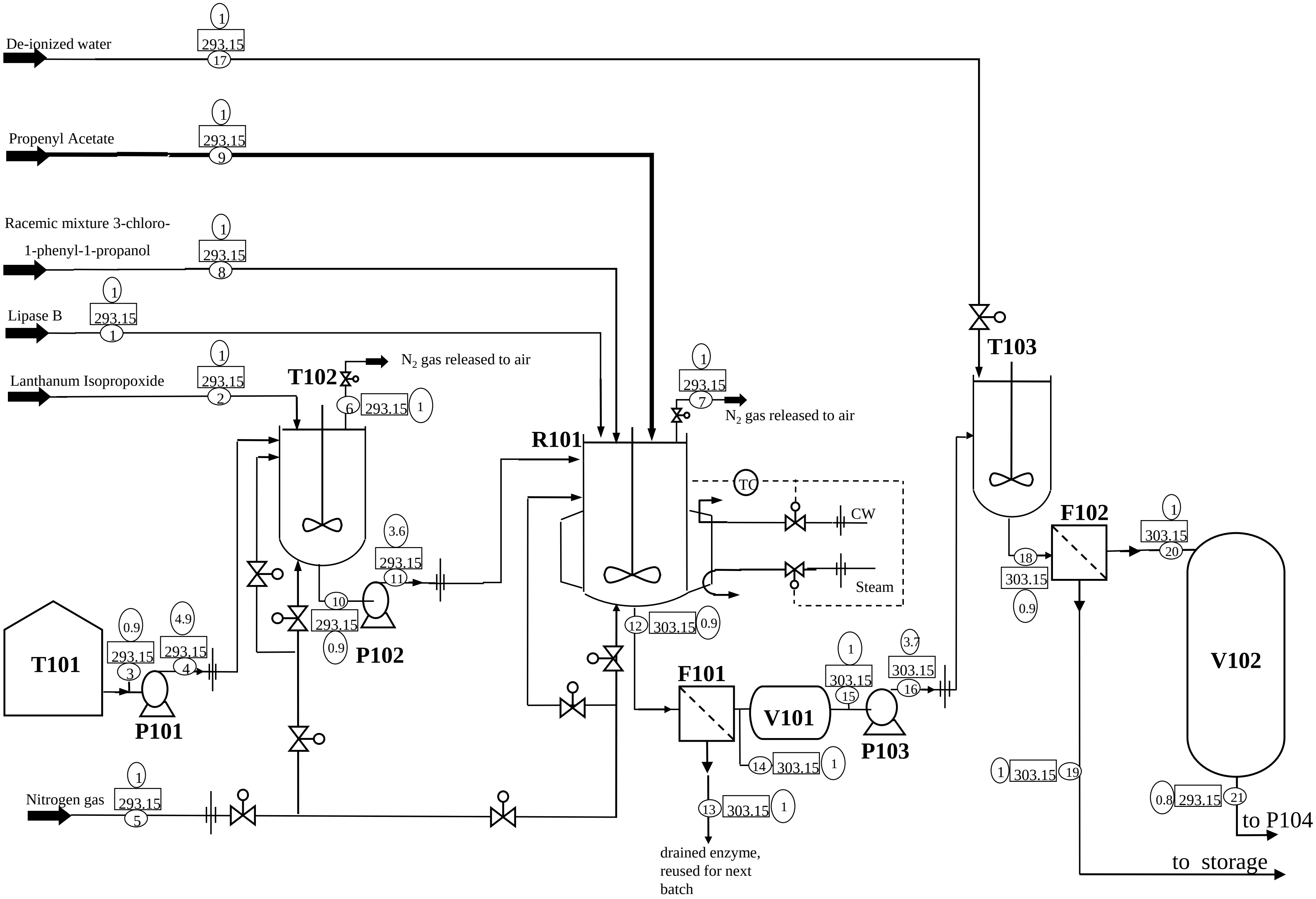


Figure 5.1.8: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

8. Add lipase B to R101

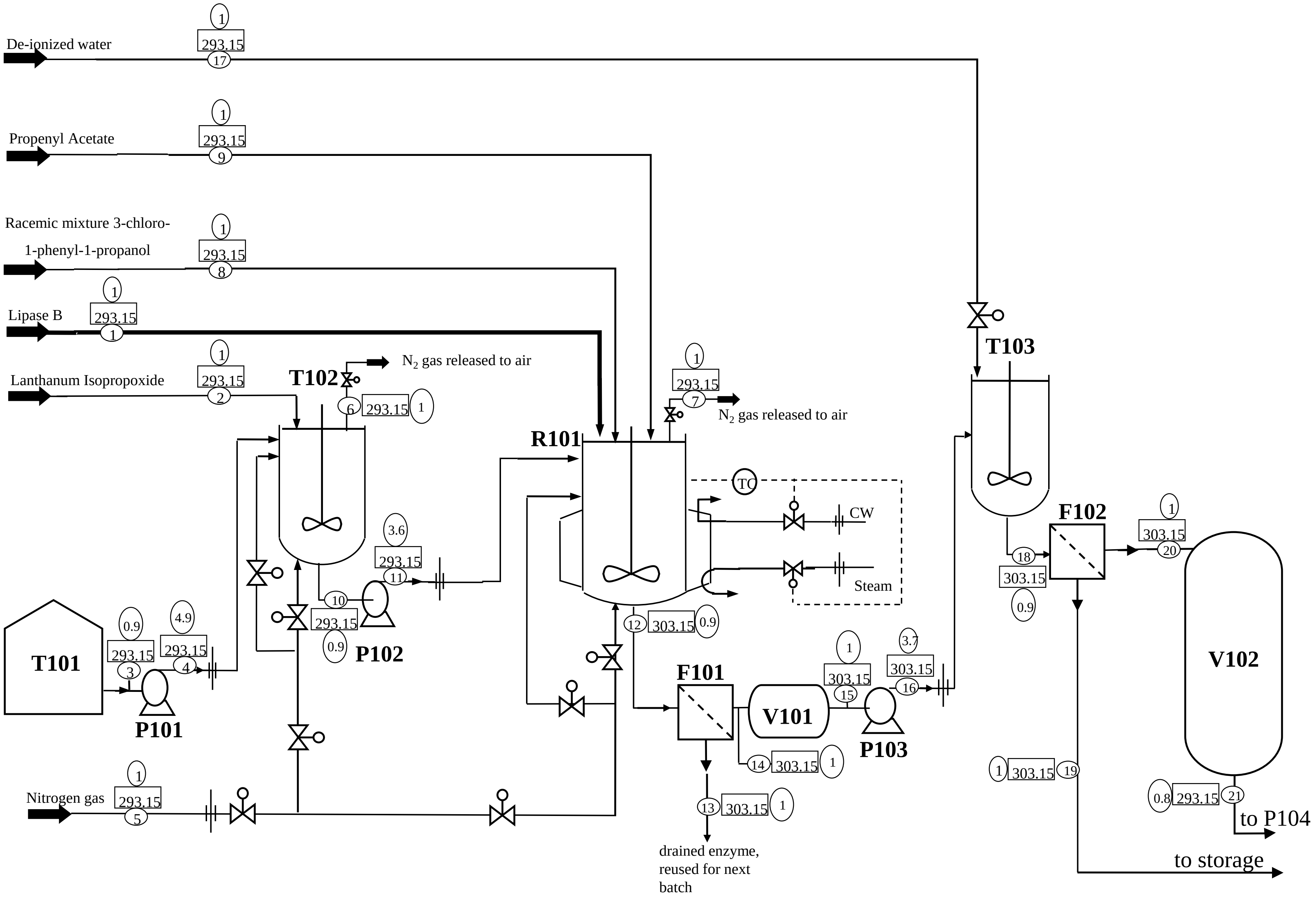
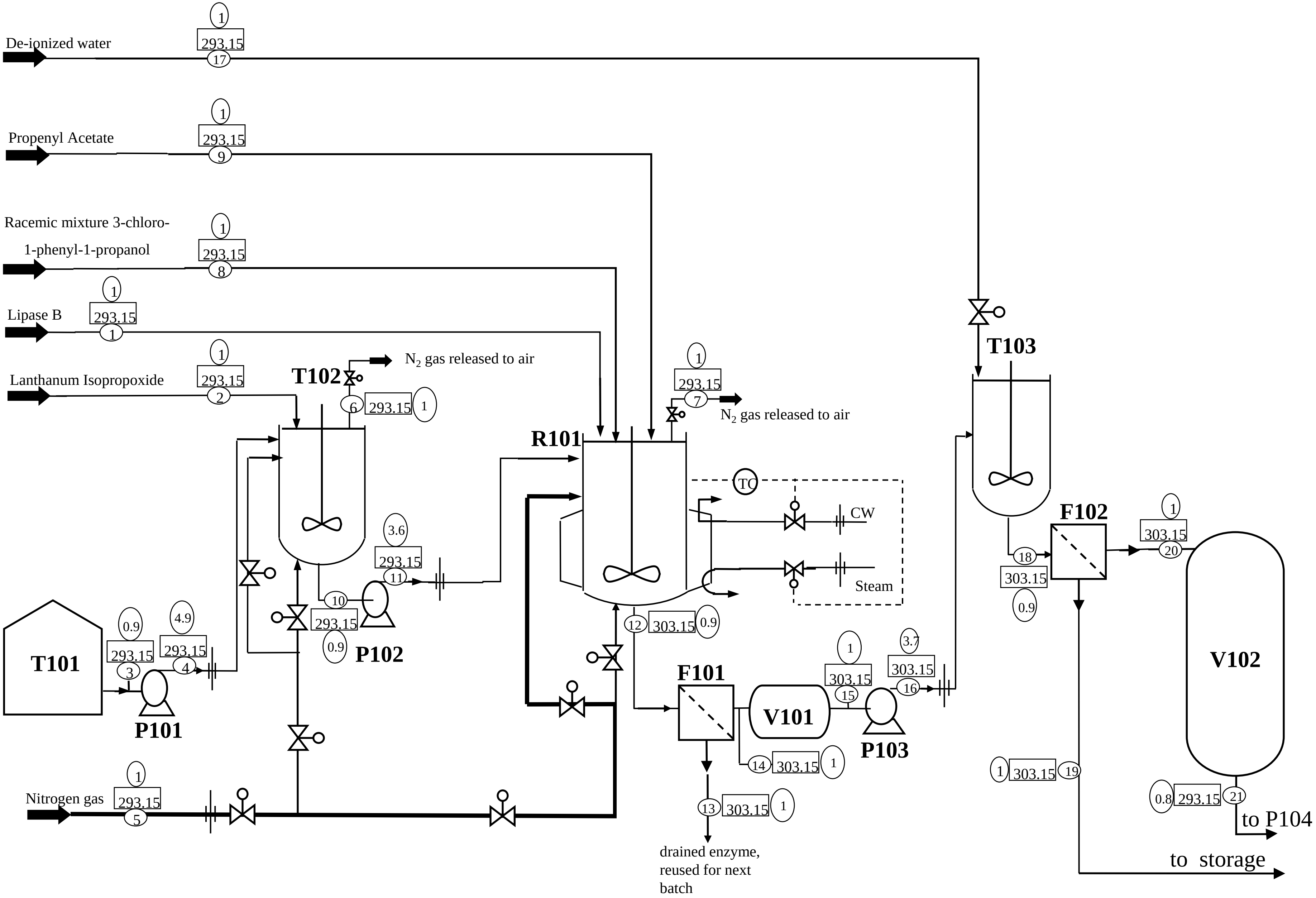


Figure 5.1.9: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

9. Nitrogen injection to R101



10. Heating up

Figure 5.1.10: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

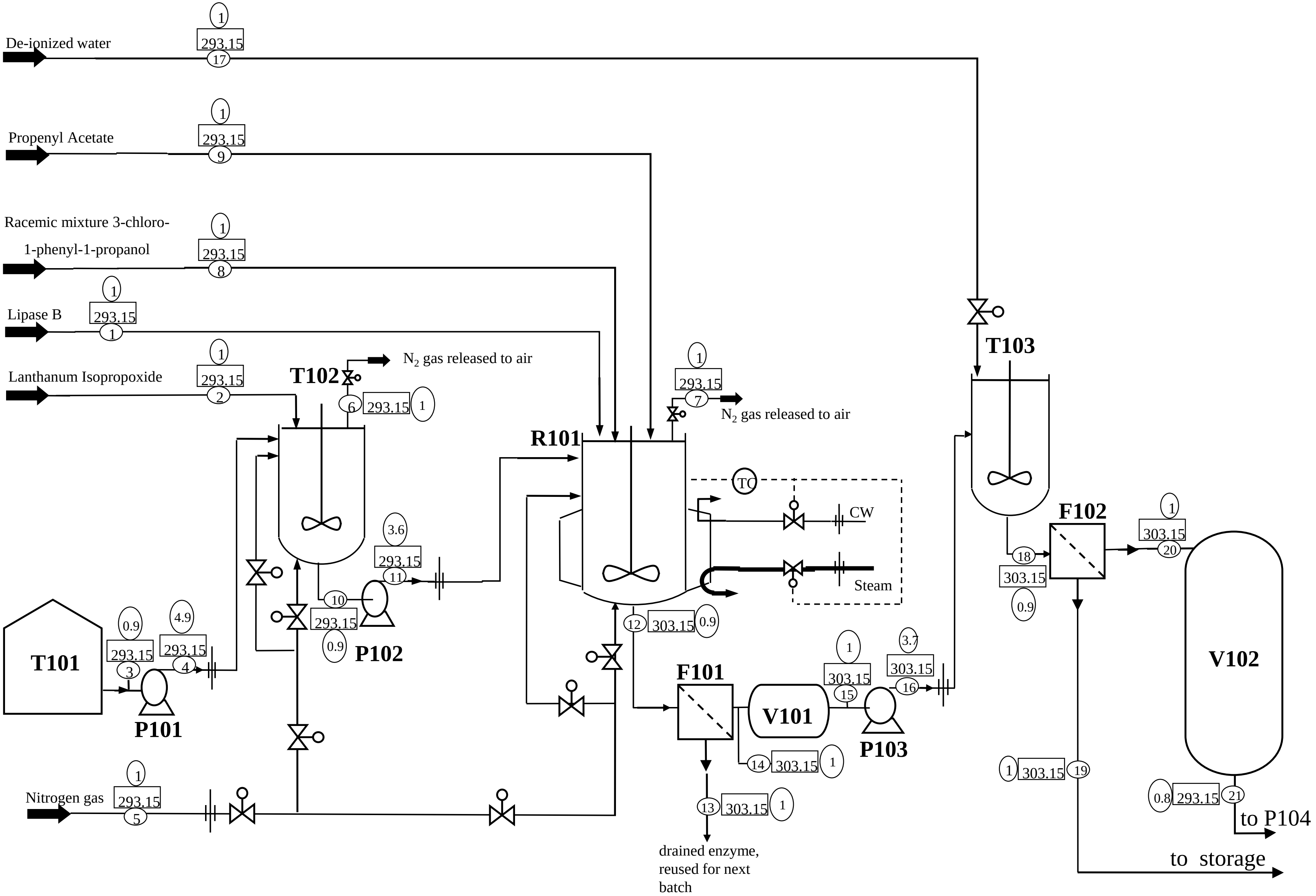


Figure 5.1.11: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

11. Reaction and cooling

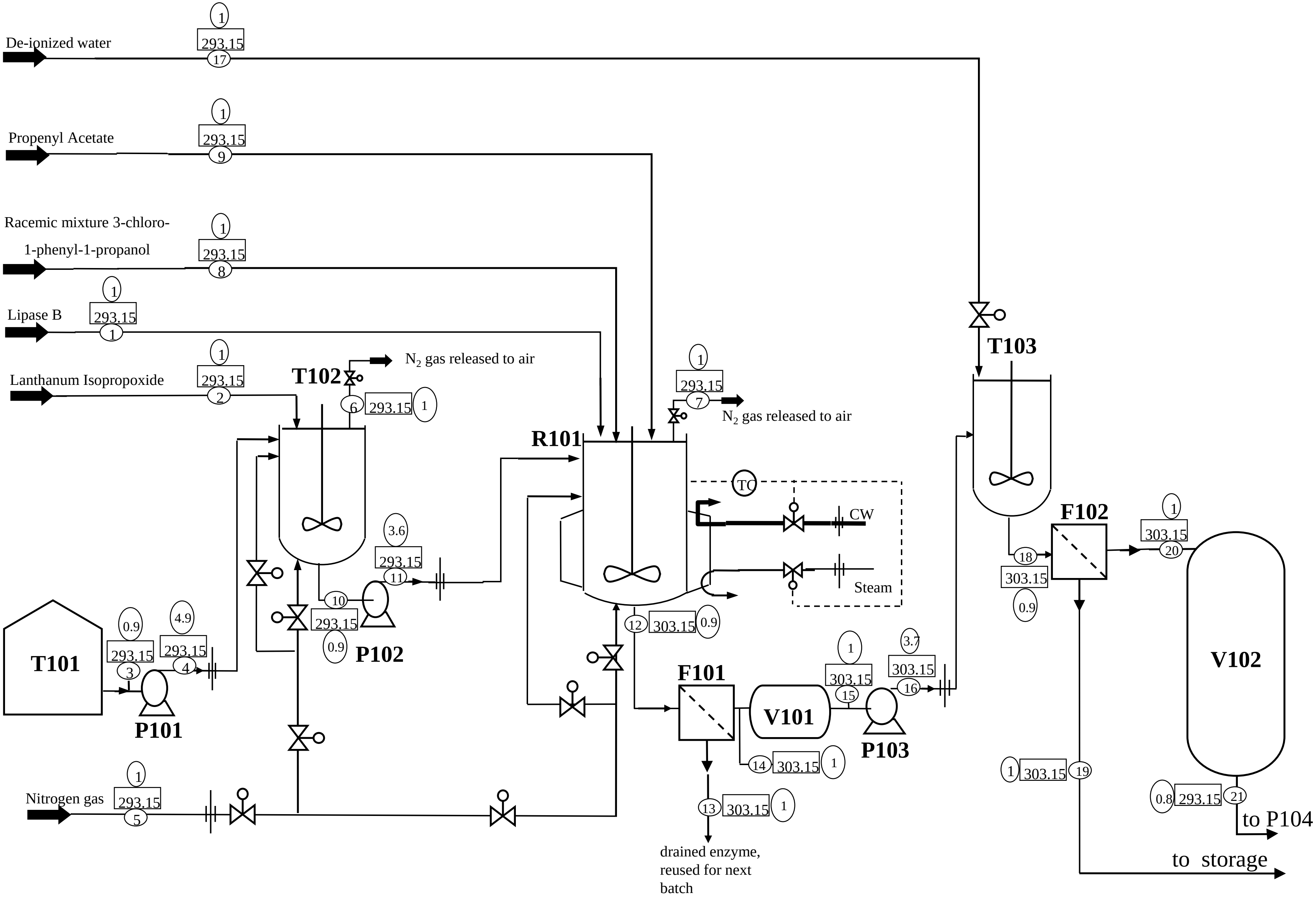


Figure 5.1.12: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

12. Cooling down

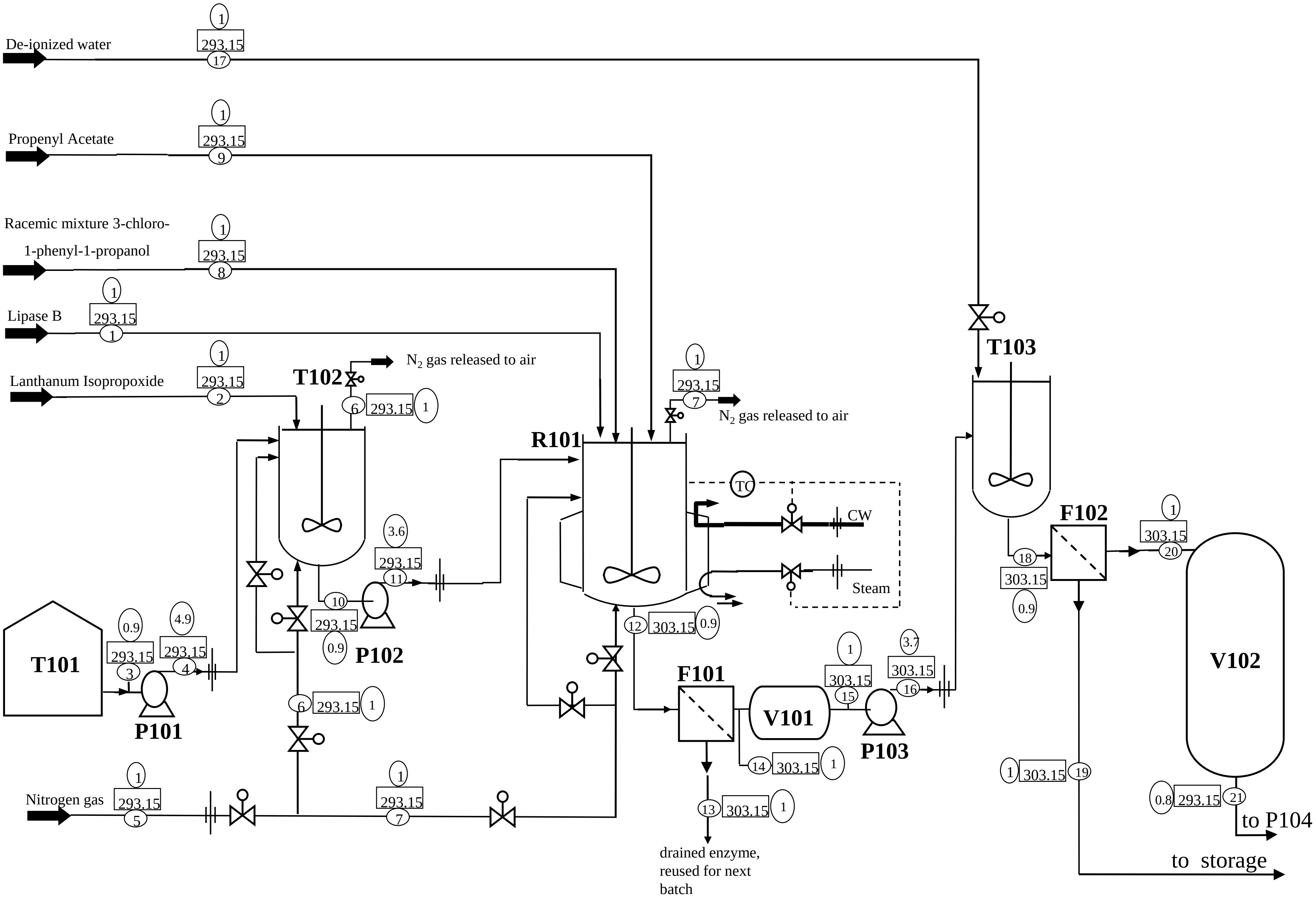


Figure 5.1.13: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

13. Discharge to F101 and filtration process

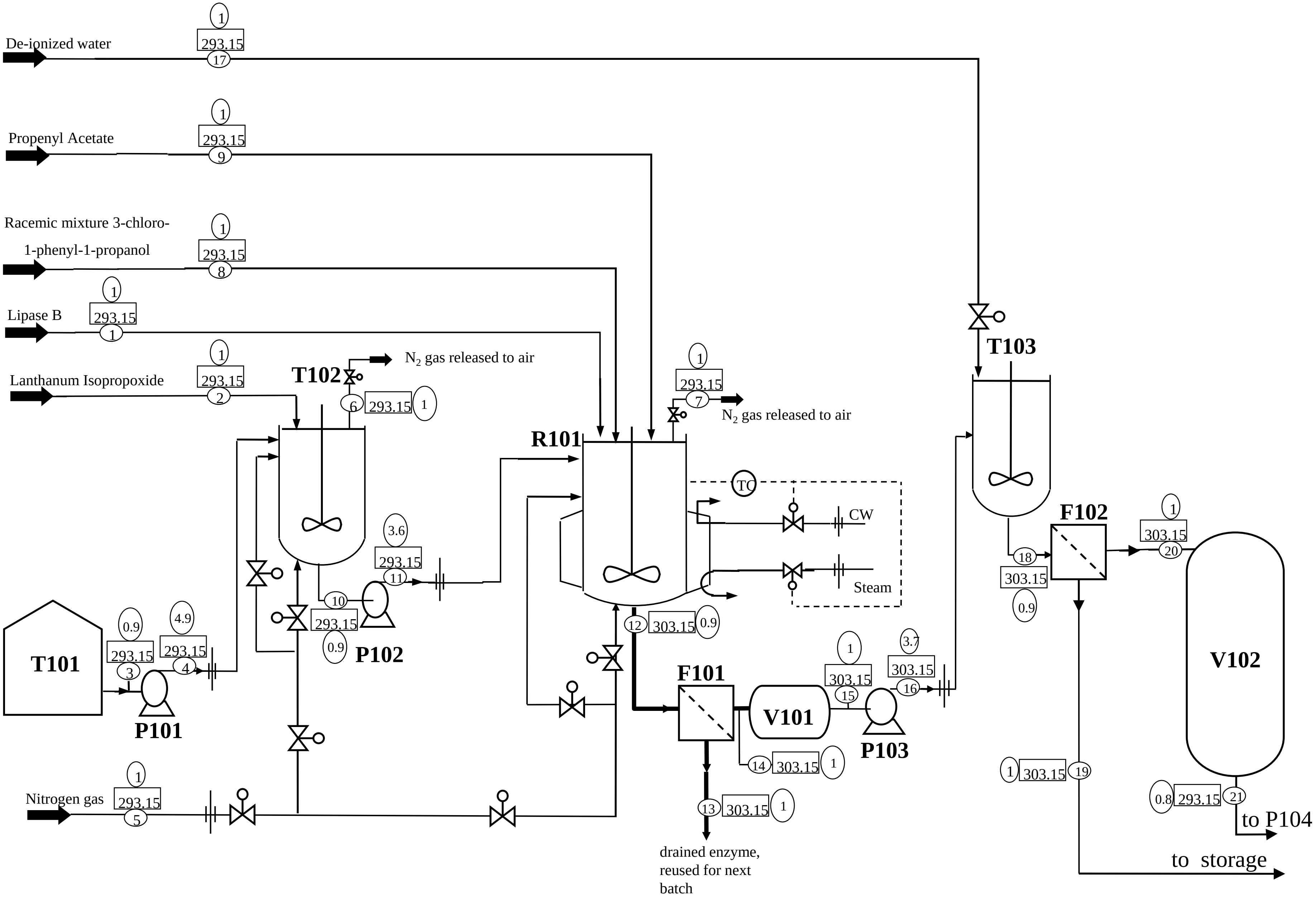


Figure 5.1.14: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

14. Discharge to T103 & feed de-ionized water to T103

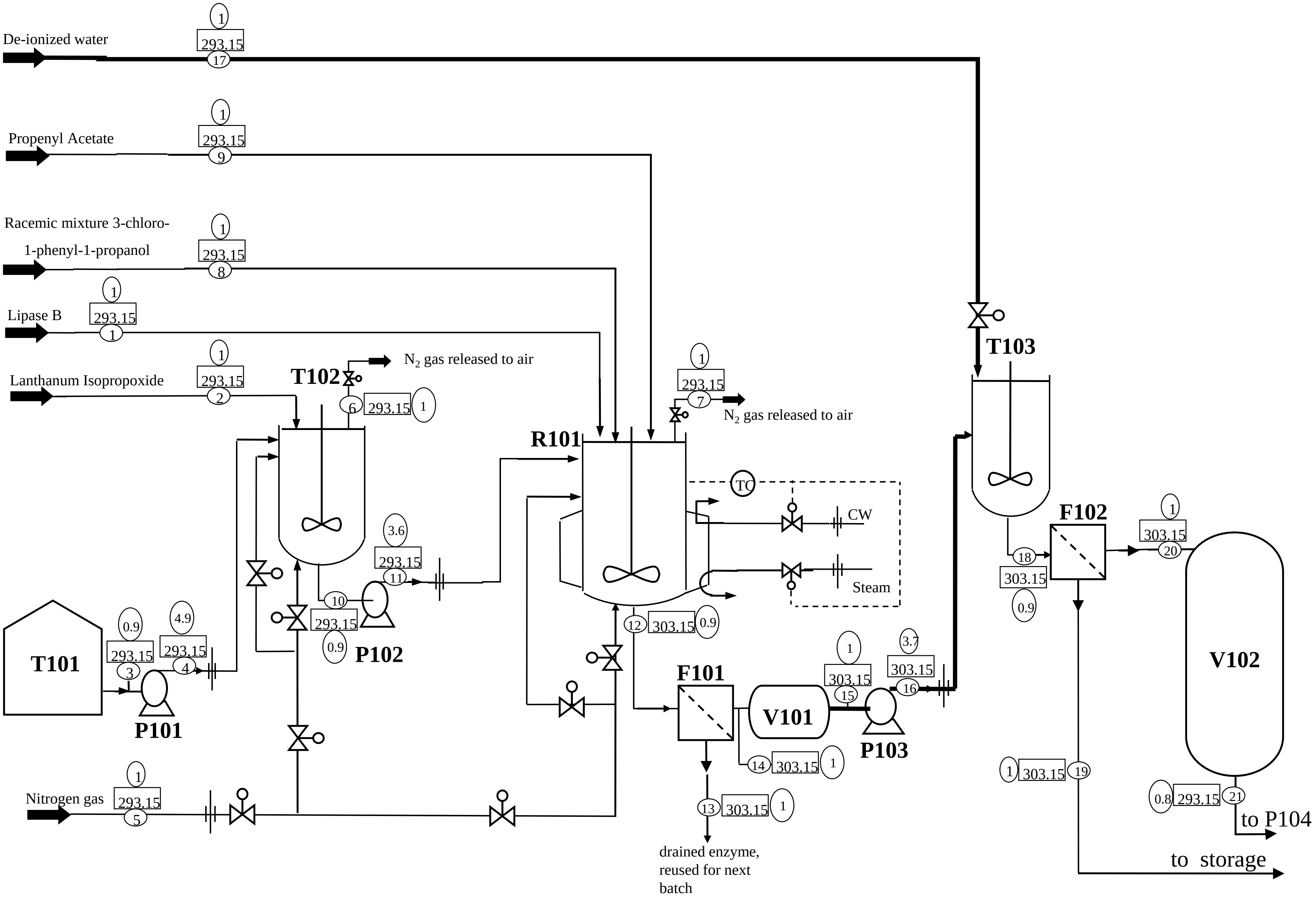


Figure 5.1.15: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

15. Discharge to F102, filtration process and discharge to V102 (intermediate storage tank)

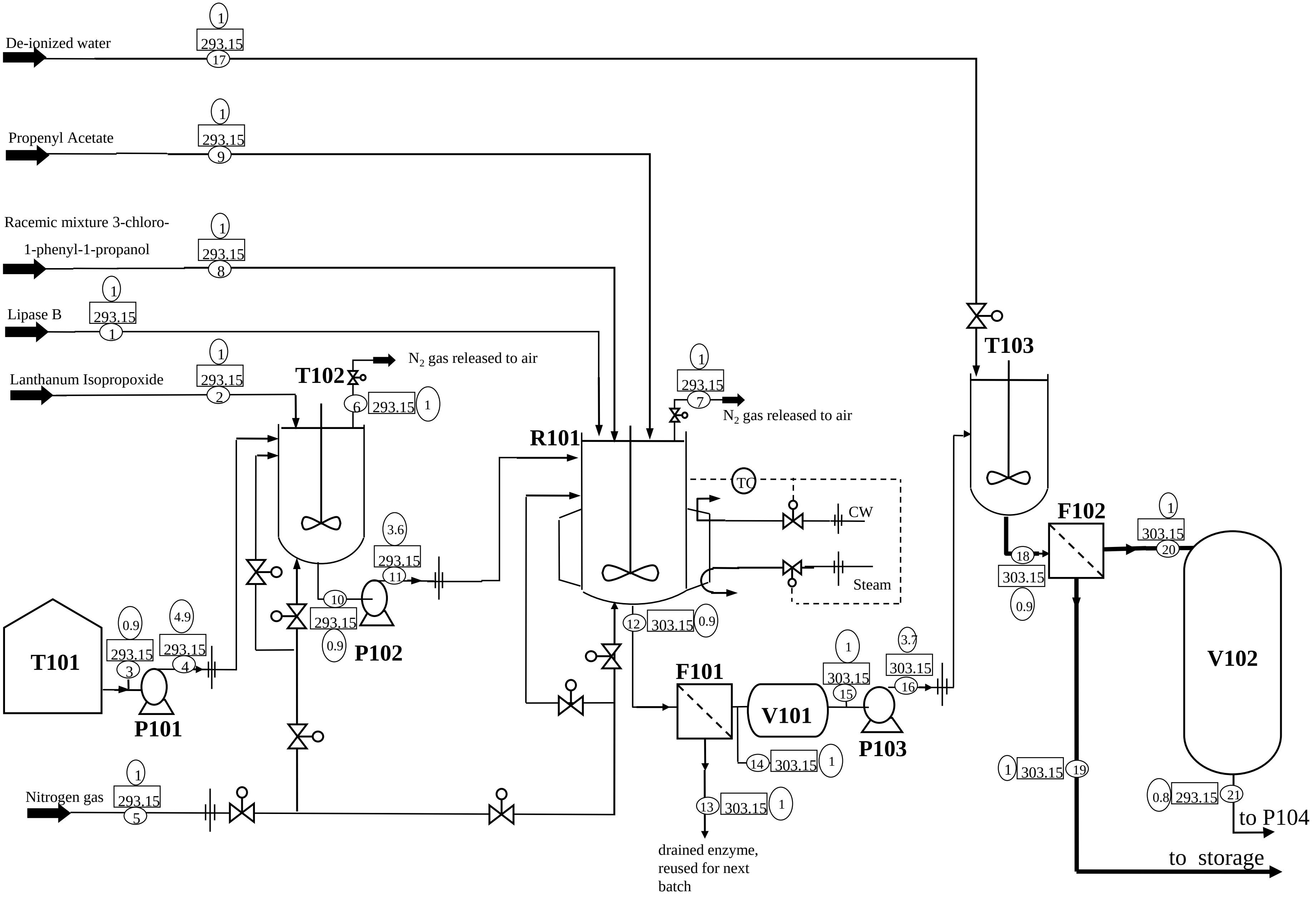


Figure 5.1.16: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

16. Idle until next batch

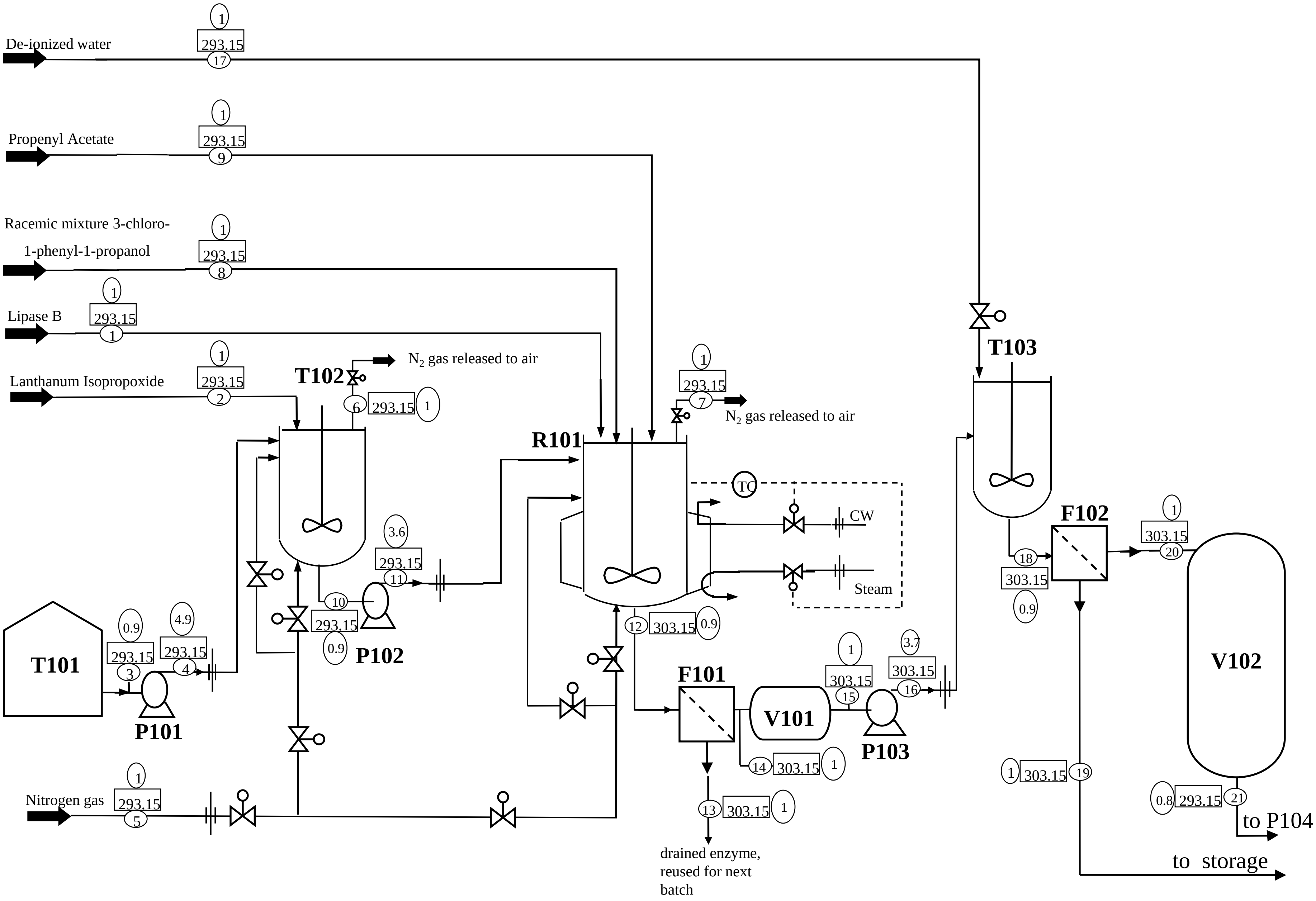


Figure 5.1.17: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

17. Discharge to P104 (after 20 batches)

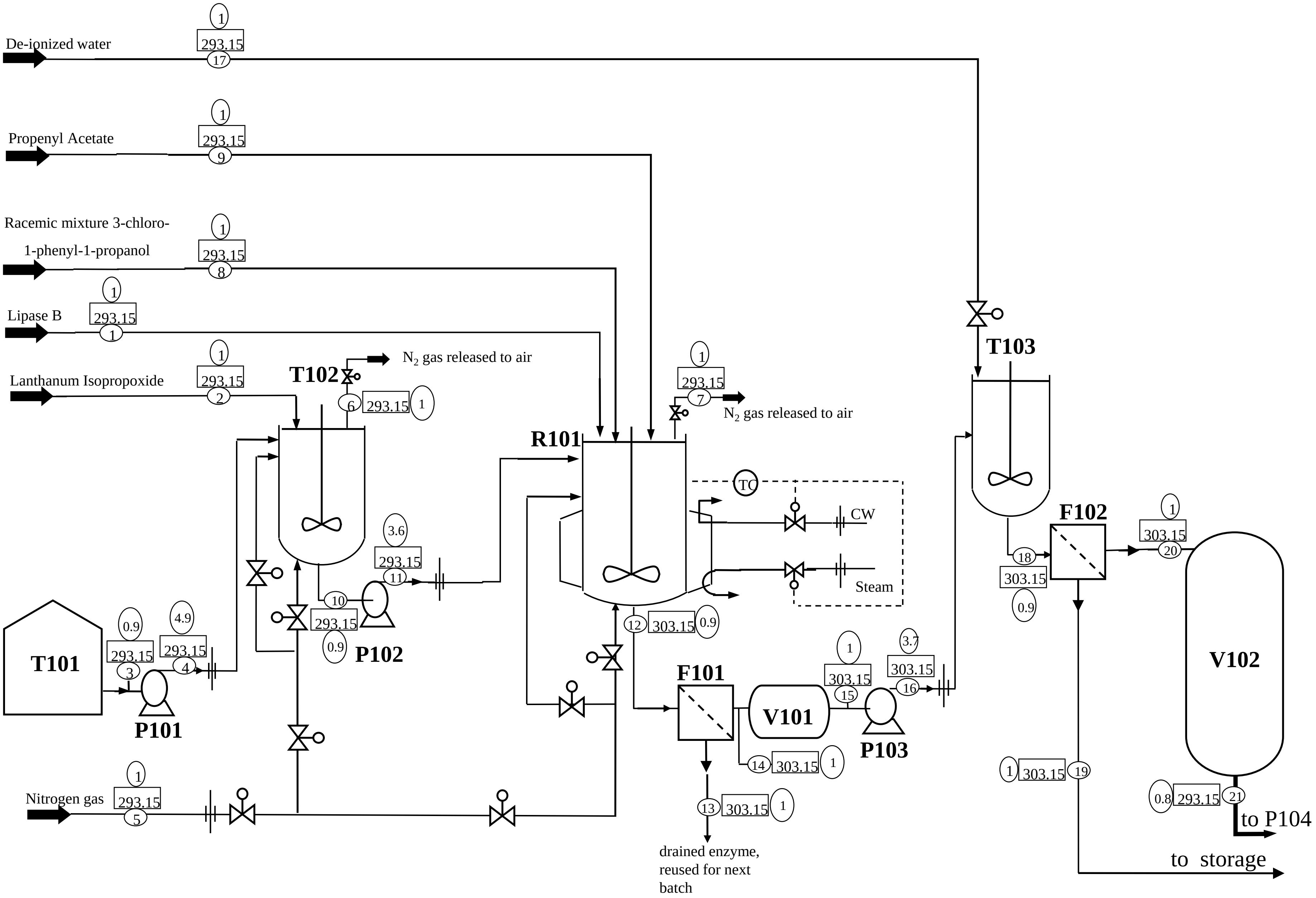
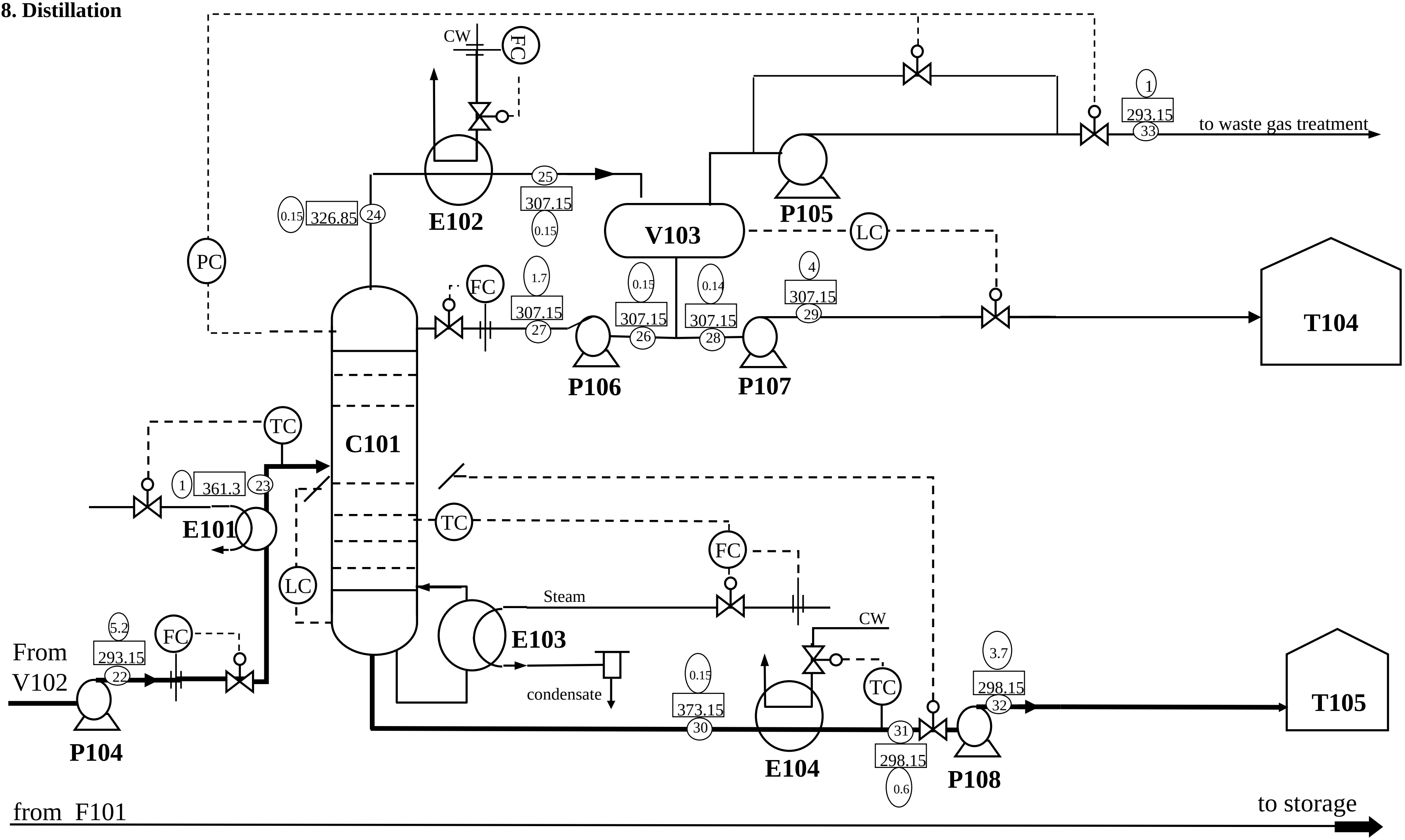


Figure 5.1.18: Process flow scheme of process to precursor of Prozac, 3-chloro-1-phenylpropyl acetate

18. Distillation



Process Equipment Summary

C101 : Distllation Column
E101 : Effl.Heater V102
E102 : Condensor C101
E103 : Reboiler C101
E104 : Product cooler
F101 : Microfilter R101
F102 : Microfilter T103

P101 : Toluene feed
P102 : Disolved catalyst feed
P103 : Effl. V101
P104 : Effl. V102
P105 : Vaccum pump C101
P106 : Reflux C101

P107 : Ovhd.C101
P108 : Bottoms C101
R101 : Reactor
T101 : Toluene
T102 : Catalyst Dissolving
T103 : Precipitation

T104 : Industrial grade toluene
T105 : Product
V101 : Buffer tank F101
V102 : Buffertank F102
V103 : Reflux accu C101

Process Flow Scheme

Project : A New Process Route to Prozac
Proj. ID Number : **CPD 3265**
Completion Date : December 21st 2001

○ Stream number
☐ Temp. (K)
○ Pressure (bar)

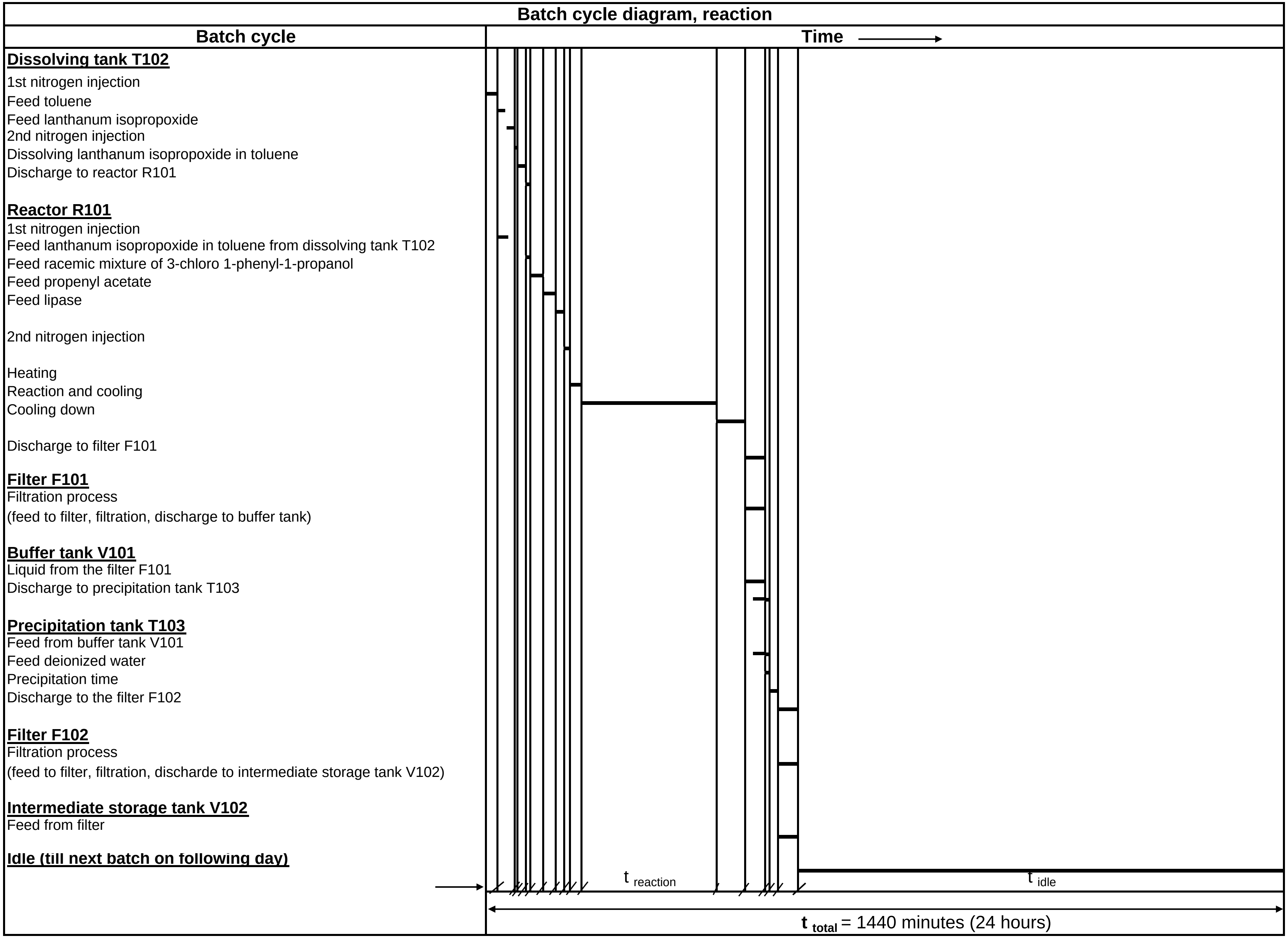
5.3 Batch cycle diagram

(please refer to figure 5.2 of batch cycle diagram)

Table 5.1: The cycle times of process

Cycle times			*Unit*	*Remarks*
$t_{\text{1st nitrogen injection to dissolving tank T102}}$		12	min	- refer to appendix A3.1
$t_{\text{feed toluene dissolving tank}}$		10	min	- refer to appendix A5.9.1
$t_{\text{feed lanthanum isopropoxide to dissolving tank T102}}$		10	min	- assumed time for adding solid)
$t_{\text{1st nitrogen injection to reactor R101}}$	13.3		min	- refer to appendix A3.1 - inject nitrogen to the reactor at the same time of pumping toluene and adding catalyst to the dissolving tank
$t_{\text{2nd nitrogen injection to dissolving tank T102}}$		4	min	- refer to appendix A3.1
$t_{\text{dissolving lanthanum isopropoxide in toluene}}$		10	min	- refer to appendix A5.2
$t_{\text{discharge from dissolving tank T102 to reactor R101}}$		5	min	= $t_{\text{feed lanthanum isopropoxide in toluene into the reactor}}$ - refer to appendix A5.9
$t_{\text{feed racemic mixture of 3-chloro-1-phenyl-1-propanol into reactor R101}}$		15	min	- assumption for adding manually
$t_{\text{feed propenyl acetate into reactor R101}}$		15	min	- assumption for adding manually
$t_{\text{feed lipase into reactor R101}}$		10	min	- assumption for adding solid
$t_{\text{2nd nitrogen injection to reactor R101}}$		4.5	min	- refer to appendix A3.1
t_{heating}	12.7			= t_{reaction} = 270 mins = 4.5 hours - refer to chapter 2 for the time of the reaction) - refer to appendix A4.3.1 for the heating time)
$t_{\text{reaction and cooling}}$	257.3	270	min	
$t_{\text{cooling down}}$		47	min	- refer to appendix A4.3.1for the cooling time)
$t_{\text{discharge from reactor R101 to the filter F101}}$		25		= $t_{\text{filtration process}}$ = $t_{\text{feed to buffer tank}}$ - refer to part 8.2.2, chapter 8 for filters chosen and filtration time)
$t_{\text{discharge from buffer tank V101 to precipitation tank T103}}$	15 +	5		- After 10 minutes of filtration process, the liquid in buffer tank is pumped to precipitation tank. The total time required for pumping from buffer tank to precipitation tank is 20 mins.
$t_{\text{feed deionized water to precipitation tank T103}}$	5			- Feeding water after 15min discharging the liquid from the buffer tank to the precipitation tank. The feeding time is an assumption
$t_{\text{precipitation time}}$		10		- refer to appendix A5.5
$t_{\text{discharge from precipitation tank T103 to the filter F102}}$		25		= $t_{\text{filtration process}}$ = $t_{\text{feed to intermediate storage tank V102}}$ (refer to chapter 8 for filters chosen and filtration time)
t_{idle}		962.5		Idle time till next batch on the following day
t_{total}		1440		1 batch/day

Figure 5.2: **Batch cycle diagram**



5.4 Batch process stream summary

Table 5.2: Batch process stream summary
(please also refer to appendix A4.1 for batch remarks and calculation)

Stream Nr.		<3> / <4>			<2>			<4>			<10>/<11>		
Batch Cycle		Feed toluene to T102		Start/End	Feed La-Isoprop to T102		Start/End	Dissolving in T102		Start/End	Discharge from T102 & feed to R101		Start/End
Component	Mwt	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.
Toluene	92.14	520.120	3120.720	21.672				520.120	3120.720	21.672	520.120	6241.440	21.672
La-Isopropoxide	316.2				5.697	34.182	0.237	5.697	34.182	0.237	5.697	68.364	0.237
R-, S- 3-chloro-1-phenyl-1-propanol	170.5												
Lipase B													
Propenyl Acetate	100.1												
(R)-3-chloro-1-phenylpropyl acetate	212.5												
Acetone	58.08												
Water	18												
Lanthanum Hydroxide	189.9												
Isopropanol	60.1												
Total		520.120	3120.720	21.672	5.697	34.182	0.237	525.817	34.182	21.909	525.817	6309.804	21.909
Enthalpy MJ - kW – kW		64.378	107.297	0.745	-0.035	-0.058	0.000	64.344	107.239	0.745	64.344	214.479	0.745
Phase L / S / S-L / L			L			S			S-L			L	
Pressure : bar			0.9 / 4.9			1			1			0.9 / 3.6	
Temperature : °C			20			20			20			20	
Cycle times [h]													
-Cycle&Process :			0.167	24.000		0.167	24.000		0.167	24.000		0.083	24.000

Stream Nr.		<8>			<9>			<1>			n/a (in R101)		
Batch Cycle		Feed Racemic to R101		Start/End	Feed Prop.Acetate		Start/End	Feed Lipase B to R101		Start/End	Heating Up		Start
Component	Mwt	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.
Toluene	92.14										520.120	2457.260	21.672
La-Isopropoxide	316.2										5.697	26.915	0.237
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	40.960	163.840	1.707							40.960	193.512	1.707
Lipase B								8.800	52.800	0.367	8.800	41.575	0.367
Propenyl Acetate	100.1				36.080	144.320	1.503				36.080	170.457	1.503
(R)-3-chloro-1-phenylpropyl acetate	212.5												
Acetone	58.08												
Water	18												
Lanthanum Hydroxide	189.9												
Isopropanol	60.1												
Total		40.960	163.840	1.707	36.080	144.320	1.503	8.800	52.800	0.367	611.657	2889.718	25.486
Enthalpy MJ - kW – kW		-71.138	-79.042	-0.823	-139.709	-155.232	-1.617				-146.502	-192.260	-1.696
Phase L / L / S / S-L			L			L			S			S-L	
Pressure : bar			1			1			1			1	
Temperature : °C			20			20			20			20	
Cycle times [h]													
-Cycle&Process :			0.250	24.000		0.250	24.000		0.167	24.000		0.212	24.000

Table 5.2: Batch process stream summary (cont'd)

Stream Nr.		n/a (in R101)			n/a (in R101)			n/a (in R101)			n/a (in R101)		
Batch Cycle		Heating Up		End	Reaction & Cooling		Start	Reaction & Cooling		End	Cooling Down		End
Component	Mwt	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.
Toluene	92.14	520.120	2457.260	21.672	520.120	121.287	21.672	520.120	121.287	21.672	520.120	663.983	21.672
La-Isopropoxide	316.2	5.697	26.915	0.237	5.697	1.328	0.237	5.697	1.328	0.237	5.697	7.273	0.237
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	29.591	139.800	1.233	29.591	6.900	1.233	0.041	0.010	0.002	0.041	0.052	0.002
Lipase B		8.800	41.575	0.367	8.800	2.052	0.367	8.800	2.052	0.367	8.800	11.234	0.367
Propenyl Acetate	100.1	29.403	138.912	1.225	29.403	6.857	1.225	12.050	2.810	0.502	12.050	15.383	0.502
(R)-3-chloro-1-phenylpropyl acetate	212.5	14.171	66.950	0.590	14.171	3.305	0.590	51.000	11.893	2.125	51.000	65.106	2.125
Acetone	58.08	3.873	18.298	0.161	3.873	0.903	0.161	13.940	3.251	0.581	13.940	17.796	0.581
Water	18												
Lanthanum Hydroxide	189.9												
Isopropanol	60.1												
Total		611.657	2889.709	25.486	611.657	142.632	25.486	611.657	142.631	25.485	611.657	780.827	25.485
Enthalpy MJ - kW – kW		-105.598	-138.580	-1.222	-105.598	-138.580	-1.222	-105.598	-6.871	-1.228	-134.744	-48.604	-1.586
Phase S-L / S-L / S-L /S-L		S-L			S-L			S-L			S-L		
Pressure : bar		1			1			1			1		
Temperature : °C		60			60			60			30		
Cycle times [h]													
-Cycle&Process :			0.212	24.000		4.288	24.000		4.288	24.000		0.783	24.000

Stream Nr.		<12>			<14>			<15> / <16>			<17>		
Batch Cycle		Filtration in F101		Start	Filtration in F101		End	Feed to T103		Start/End	Feed water to T103		Start/End
Component	Mwt	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.
Toluene	92.14	520.120	1248.288	21.672	520.120	1248.288	21.672	520.120	1560.360	21.672			
La-Isopropoxide	316.2	5.697	13.673	0.237	5.697	13.673	0.237	5.697	17.091	0.237			
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	0.041	0.098	0.002	0.041	0.098	0.002	0.041	0.123	0.002			
Lipase B		8.800	21.120	0.367									
Propenyl Acetate	100.1	12.050	28.920	0.502	12.050	28.920	0.502	12.050	36.150	0.502			
(R)-3-chloro-1-phenylpropyl acetate	212.5	51.000	122.400	2.125	51.000	122.400	2.125	51.000	153.000	2.125			
Acetone	58.08	13.940	33.456	0.581	13.940	33.456	0.581	13.940	41.820	0.581			
Water	18										1.460	17.520	0.061
Lanthanum Hydroxide	189.9												
Isopropanol	60.1												
Total		611.657	1467.955	25.485	602.857	1446.835	25.119	602.857	1808.544	25.119	1.460	17.520	0.061
Enthalpy MJ - kW - kW		-134.744	-91.375	-1.586	-134.744	-91.375	-1.586	-134.744	-114.218	-1.586	-23.181	-77.268	-0.268
Phase S-L / L / L /L		S-L			L			L			L		
Pressure : bar		0.9			1			1 / 3.7			1		
Temperature : °C		30			30			30			20		
Cycle times [h]													
-Cycle&Process :			0.417	24.000		0.417	24.000		0.333	24.000		0.083	24.000

Table 5.2: Batch process stream summary (cont'd)

Stream Nr.		n/a			<18>			<20>			<1> to <20>		
Batch Cycle		Precipitation in T103		Start	Filtra. in F102+feed to V102		Start	Filtration in F102+feed to V102		End	Idle till next batch		Start/End
Component	Mwt	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.	Cycle kg	Cycle kg/h	Process kg/h avg.
Toluene	92.14	520.120	3120.720	21.672	520.120	1248.288	21.672	520.120	1248.288	21.672			
La-Isopropoxide	316.2												
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	0.041	0.246	0.002	0.041	0.098	0.002	0.041	0.098	0.002			
Lipase B													
Propenyl Acetate	100.1	12.050	72.300	0.502	12.050	28.920	0.502	12.050	28.920	0.502			
(R)-3-chloro-1-phenylpropyl acetate	212.5	51.000	306.000	2.125	51.000	122.400	2.125	51.000	122.400	2.125			
Acetone	58.08	13.940	83.640	0.581	13.940	33.456	0.581	13.940	33.456	0.581			
Water	18	0.487	2.921	0.020	0.487	1.168	0.020	0.487	1.168	0.020			
Lanthanum Hydroxide	189.9	3.422	20.532	0.143	3.422	8.213	0.143						
Isopropanol	60.1	3.250	19.500	0.135	3.250	7.800	0.135	3.250	7.800	0.135			
Total		604.317	3625.859	25.180	604.317	1450.344	25.180	600.895	1442.131	25.037			
Enthalpy MJ - kW - kW		-161.911	-269.851	-1.874	-161.911	-107.940	-1.874	-161.911	-107.947	-1.874			
Phase S-L / S-L / L		S-L			S-L			S-L			L		
Pressure : bar		0.9			1			1			1		
Temperature : C		30			30			30			20		
Cycle times [h] -Cycle&Process :			0.167	24.000		0.417	24.000		0.417	24.000		16.01	24.000

Table 5.2: Batch process stream summary (cont'd)

Equipment name		Intermediate tank	
		Mass flow	
Component	Mwt	kg/h	kmol/h
Toluene	92.14	650.141	7.056
La-Isopropoxide	316.2	-	-
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	0.051	3.77E-04
Lipase B		-	-
Propenyl Acetate	100.1	15.063	0.15
(R)-3-chloro-1-phenylpropyl acetate	212.5	63.750	0.3
Acetone	58.08	17.424	0.3
Water	18	0.609	0.034
Lanthanum Hydroxide	189.9	-	-
Isopropanol	60.1	4.062	0.068
Total		751.100	7.908
Enthalpy : kW		-34.518	
Phase : L		L	
Pressure : atm		1	
Temperature : C		88.111	

Equipment		Distillation column					
		Mass flow					
Stream Nr. Name		<23> Feed to distillation column		<29> Toluene Product		<32> Precursor Product	
Component	Mwt	flow		flow		flow	
		kg/h	kmol/h	kg/h	kmol/h	kg/h	kmol/h
Toluene	92.14	650.141	7.056	650.048	7.055	0.093	0.001
La-Isopropoxide	316.2	-	-	-	-	-	-
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	0.051	0.000	0.000	0.000	0.051	0.000
Lipase B		-	-	-	-	-	-
Propenyl Acetate	100.1	15.063	0.150	15.063	0.150	0.000	0.000
(R)-3-chloro-1-phenylpropyl acetate	212.5	63.750	0.300	0.213	0.001	63.537	0.299
Acetone	58.08	17.424	0.300	17.424	0.300	0.000	0.000
Water	18	0.609	0.034	0.609	0.034	0.000	0.000
Lanthanum Hydroxide	189.9	-	-	-	-	-	-
Isopropanol	60.1	4.062	0.068	4.062	0.068	0.000	0.000
Total		751.100	7.908	687.381	7.608	63.719	0.300
Enthalpy : kW		-34.518		-18.652		-34.686	
Phase		L		L		L	
Pressure : atm		1		0.15		0.15	
Temperature : C		88.111		33.954		100.019	

5.5 Utilities

5.5.1 Utilities requirement

Table 5.3: The requirements of utilities

UTILITIES REQUIREMENTS

Name	*Function*	*Utility type*	*Load* (kW)	*Requirements*			
				CW (t/a)	*Steam* (t/a)	*Electricity* (kWh/a)	*Nitrogen* (m^3/a)
T102	Dissolving tank	Nitrogen					150.80
R101	Reactor	Nitrogen					168.00
T102	Stirrer of dissolving tank	Electricity	0.15			1.25	
R101	Stirrer of reactor	Electricity	0.17			88.76	
R101	Reactor (heating steam)	Steam	45.45		1.58		
R101	Reactor (cooling water during reaction + cooling down)	CW	11.04	76.88			
F101	Micro filter	Electricity	16.00			666.67	
T103	Precipitation tank stirrer	Electricity	0.17			2.80	
F102	Micro filter	Electricity	16.00			666.67	
E101	Column feed heater	Steam	25.20		3.30		
E103	Reboiler	Steam	100.20		13.38		
E102	Condenser	CW	121.02	833.84			
E104	Product cooler	CW	1.55	10.7			
P101	Pump	Electricity	1.50			25.00	
P102	Pump	Electricity	1.30			10.83	
P103	Pump	Electricity	0.70			23.33	
P104	Pump	Electricity	0.70			56.00	
P106	Pump	Electricity	0.10			8.00	
P107	Pump	Electricity	0.45			36.00	
P108	Pump	Electricity	0.013			1.04	
P105	Vacuum pump	Electricity	2.80			224.00	
Total				**921.4**	**18.24**	**1810.10**	**318.80**

Remarks:
- Please also refer to appendix A3.2 for the summary of utilities
- The volume of nitrogen needed is in appendix A3.1
- Power needed for a stirrer of dissolving tank is calculated in appendix A5.2
- Power needed for a stirrer of reactor is calculated in appendix A5.3
- Micro filter used as in Superpro design (refer to chapter 8 for equipment chosen)
- Steam and cooling water for heating and cooling the reactor are calculated in appendix A4.3
- Power needed for a stirrer of precipitation tank is calculated in appendix A5.5
- Column feed heater, reboiler & condenser are calculated in appendix A4.3
- Power for the pumps are calculated in appendix A5.9 of pump design

5.5.2 Options and selection

There are several options for choosing utilities. Cold utilities, which are CW and CA (cooling air), can be chosen. Hot utilities, which are LP, MP, HP and hot oil, are available. Nitrogen and other gases are available as drying utilities for the reactors and dissolving tank. Cooling water, low pressure steam and nitrogen are chosen as cold utility, hot utility and utility for drying because:

- *Cold utility*: CW is chosen as cold utility, because the mixture in the reactor needs to be cooled down to 30^0C after the reaction. It is also because the temperature of liquid should not be too high when it goes through the pipes. The temperature for air can be 30^oC (in hot summer day) so it is not sufficient to use air to cool the liquid in the reactor to 30^0C. Also for cooling water the heat capacity (4.18 kJ/kg K) and heat film coefficient (0.20) of water are higher than that of air (1.00 kJ/kg K and 0.10 respectively). It means that less amount of cooling water needed to achieve the same effect as air and the area needed is much less.

- Hot utility: LP steam is chosen as hot utility. All hot utilities available including hot oil (280-260^0C), HP steam (25bar 225^0C), HP steam (18bar, 205^0C), MP steam (4bar 140^0C) and LP steam (1.5 bar 110^0C) can be used as hot utility for both the reactor and distillation column. The reason to choose LP steam is because of economic reason. The price of LP steam is cheaper and the cost of equipment for LP steam needed is also cheaper than that for HP steam.

  Another reason for not using HP steam is the amount of steam needed is quite small so even after using heat integration to combine column feed and reboiler together only 41.03 kg/h LP steam can be saved. Based on the comparison of the prices between LP steam and HP steam, it is decided to use LP steam as hot utility in the process (please refer to appendix 4.3.2 for column heat balance)

- Dry utility: Nitrogen is chosen as dry utility to obtain the dry condition in the dissolve tank and the reactor. The reason for not using other gases but nitrogen is because nitrogen has many advantages such as inert, low cost and harmless to human and environment.

5.5.3 Major users and possibilities for future reduction

Table 5.4: The cost of the utilities

UTILITY COST (Dfl)			
Utility	*Unit*	*Cost per unit Dfl*	*Total cost Dfl/a*
Electricity	kWh	0.1016	184.0
Steam	ton	30.0	547.2
Cooling water	ton	0.1	92.1
Nitrogen	m^3	7,500	2,391,000.0
Total			**2.4×10^6**

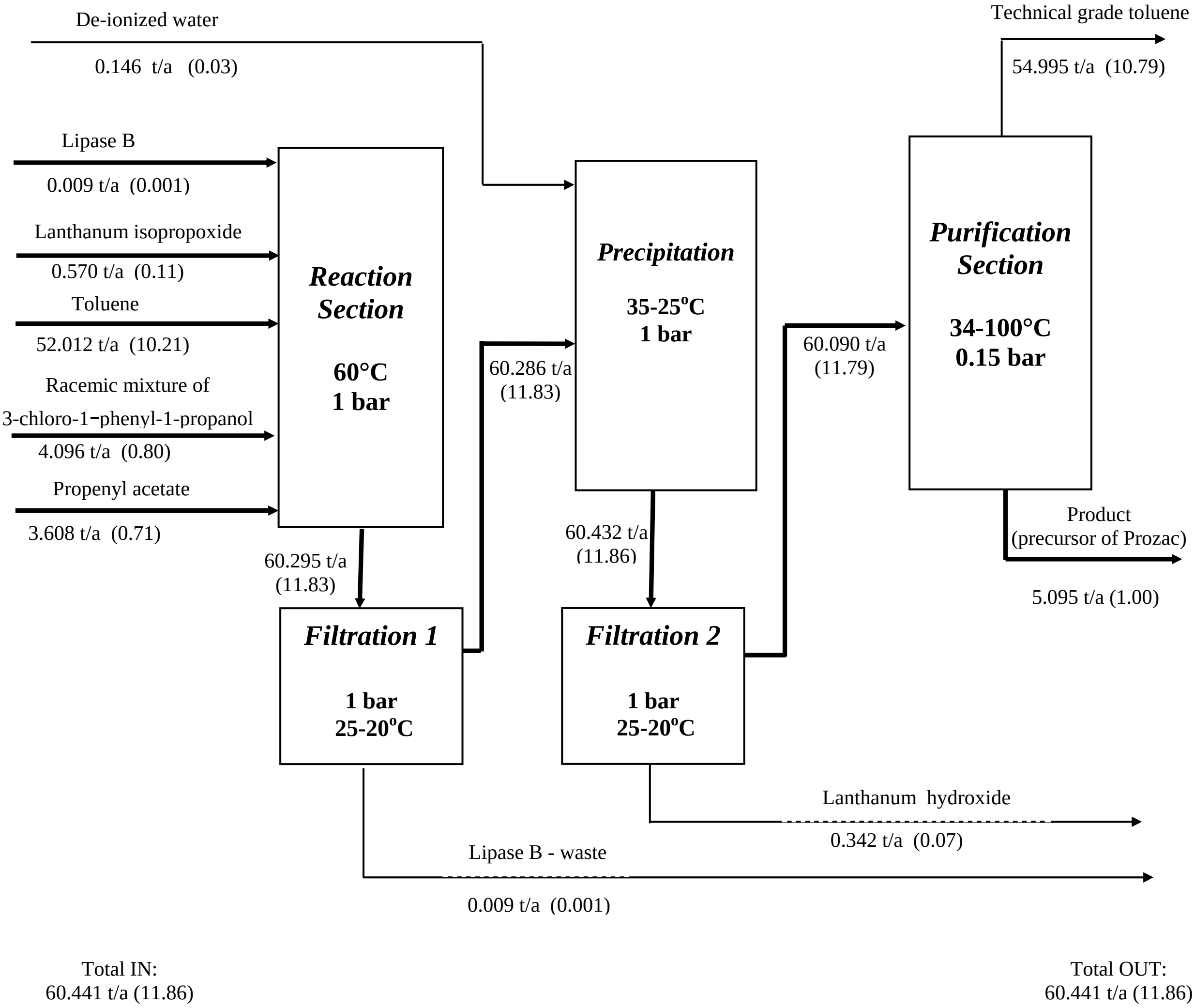
From the table 5.4 it is found that nitrogen counts for the major cost of utilities due to high price of nitrogen. Other utilities such as electricity, steam and cooling water the cost is not so high because the operating time is not long for each batch (please refer to table 5.1 of the cycle times). Electricity is only needed for the stirrers and mini pumps' power (the power needed for the pumps is relatively low). The cost for these utilities can be neglected in comparison to the cost for nitrogen. Therefore, only the possibility for reduction of nitrogen cost is discussed here.

The major users of nitrogen are dissolving tank T102 and the reactor R101.It is possible to reduce the amount of nitrogen use by reducing the amount of nitrogen inject each batch. Because during the reaction the reactors are enclosed, so that means the only chance for air can get into the reactors is when catalysts are fed in. Nitrogen can be just injected after catalysts are fed in to make sure there is no air present in the reactor. Originally, the total amount of nitrogen needed each batch is 2 times of the total volume of dissolving tank and reactor (or 200%). The amount of nitrogen injected after the materials added into the tank and the rector is equivalent to 50% of the total volume of these equipments (please also refer to part 3.2.2 for description of block scheme and appendix A3.1 for nitrogen injection). Therefore, the amount of nitrogen can be reduced to 25% of the original amount.

5.6 Process yields

Table 5.5a: The process yield (excluding the utilities)

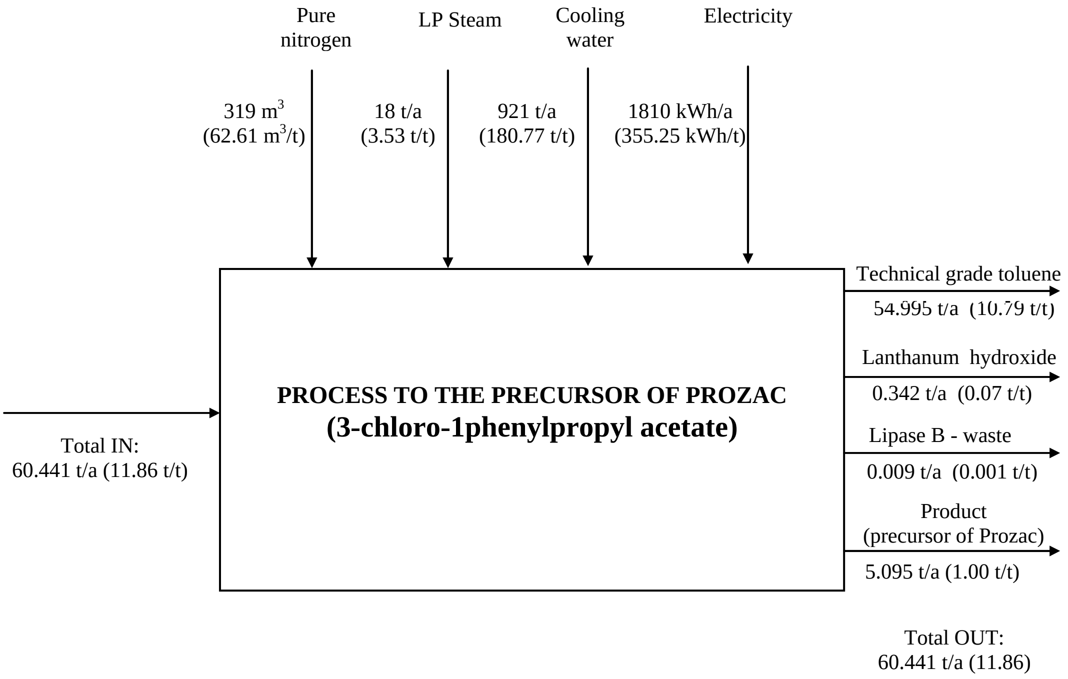
Process Streams					
Name	Ref. Stream	t/a		t/t product	
		IN	OUT	IN	OUT
Lipase B		0.009		0.001	
Lathanum isopropoxide		0.570		0.11	
Toluene		52.012		10.21	
R-,S-3-chloro-1-phenyl-1-propanol		4.096		0.80	
Propenyl acetate		3.608		0.71	
Deionized water		0.146		0.03	
3-chloro-1-phenylpropyl acetate=**Product**			5.095		**1.00**
Technical grade toluene = by product			54.995		10.79
Lanthanum hydroxide = by product			0.342		0.07
Lipase B (wastes)			0.009		0.001
Total		60.441	60.441	11.86	11.86



Notes: Figures between the brackets ( ) are t/t values

Table 5.5b: The process yield (the utilities)

Utilities							
Name	Ref. Stream	m^3/a	t/a	kWh/a	m^3/t product	t/t product	kWh/ t product
Nitrogen	-	319			62.61		
LP Steam	-		18			3.53	
Cooling water	-		921			180.57	
Electricity	-			1810			355.25



Comments:

- Above yields indicate no accountable loss on feed stock (11.87 t/t), i.e. neither the precursor of Prozac (1.00 t/t = reference) nor technical grade toluene (10.79 t/t) nor lanthanum hydroxide (0.07) nor lipase B (waste) (0.01 t/t). It can also be seen from the material balance. This is understandable because by-product generating reactions do not occur
- The process requires nitrogen (62.57m^3/t) to get all the air in the dissolving tank T102 and the reactor R101 out. It is essential to have dry condition in these equipments because the catalyst (lanthanum isopropoxide) is very sensitive to water. The volume of the nitrogen injected is equivalent to 2 times of the total volume of these equipments.
- The process requires minimal power just for the pumps and the stirrers

CHAPTER 6 PROCESS CONTROL

The process can be divided to two parts: reaction section and separation section.

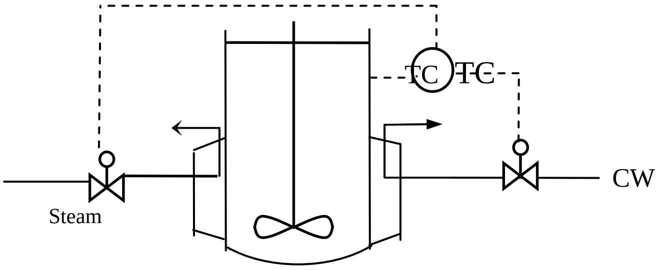
The reactor effluent stream is stored in an intermediate storage tank V102. After 20 batches in reaction section are finished, reaction mixture from the tank V102 is fed to the distillation column, where the desired product is separated from the other components. The storage tank decouples the two processing units (reactor and distillation column). Thus any variations in the composition, temperature, or flow of the reactor's effluent stream are 'damped' out in the tank and do not disturb the operation of the column. The decoupling between reactor and column allows synthesizing a control system for each unit independently.

6.1 Reaction section

6.1.1 Control of the reactor R101

The control of the reactor include three stages:

1. <u>Preheat</u>: to increase temperature to 60°C. The steam is introduced to increase the temperature. According to the process description, the reactor temperature will reache around 60°C in the preheat period (refer to part 3.2.2, chapter3). Because this period is to preheat the reactants and the process is dynamic, steam valve is adjusted according to the temperature difference between the measured temperature and the set temperature. When the temperature reaches 60°C, the steam valve will be closed and the cooling water valve will be opened and the controller will function to keep the temperature precisely at 60°C, in the coming reaction period. (See Figure 6.1)



<u>Figure 6.1</u>: The control configuration for the reactor

2. <u>Reaction</u>. The temperature of reaction is required to keep at 60°C for 4.5 hours from the process point of view. Because of the exothermal reaction, cooling water is used to move the reaction heat out of the system. The temperature can be measured and controlled by adjusting the flow rate of cooling water. In the batch reaction, the concentration varies and the process is dynamic, the temperature is controlled by adjust cooling water flow rate, according to the temperature difference between the measured temperature and the set temperature. If the reactor temperature increases, the cooling water control valve opens wider. If the reactor temperature decreases, the control valve opens less (see figure 6.1).

3. Cooling down: Cool down the reactor after the reaction time. After 4.5 hours of reaction at 60°C, the reactor needs to be cooled down to 30°C. Here, same cooling water is used. To make the temperature decreases to required value and avoid the sharp drop, the above controller in the reaction period is still used to make sure that the temperature can decrease smoothly. In this situation, the parameter in the controller should change automatically to make it work for the cooling down period (see figure 6.1).

6.1.2 Control of nitrogen injection

Before the reaction, nitrogen is used to "wash" the reactor to move all the air inside the reactor. But it should be noticed that it is not necessary to use controller to control the flow rate of nitrogen very precisely because it is only needed to make sure that there is enough nitrogen filled in the reactor and it is not so important whether nitrogen flow rate is exactly constant. After the flow measurement and valves are installed, the operation of nitrogen "wash" can be done manually. The worker only needs to open the proper valves until the measurement indicates the required value according to the time needed for the injection (as calculated in appendix A3.1) and then closes the valve and the "wash" process is finished.

6.2 Separation section

- The distillation column is operated in continuous way; so the feed flow rate should be kept at constant value. The flow controller here is necessary. Because the fluid may be flash a bit after control valve due to the pressure drop, which will make the measured value smaller than the actual flow rate. The measurement should be installed before the control valve, to measure the flow rate correctly. (see figure 6.2).

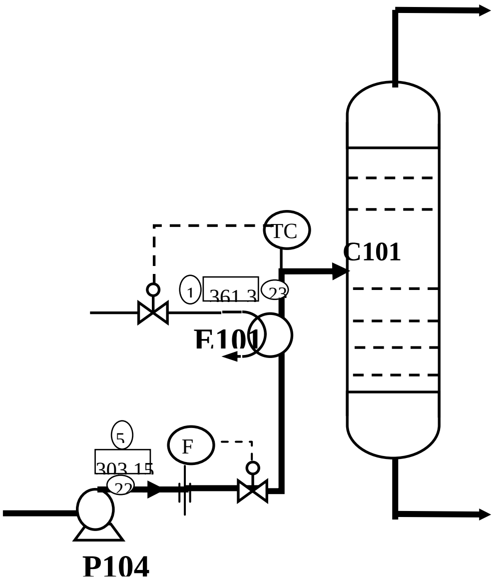


Figure 6.2: The control configuration for the feed stream to the distillation column

- The feed needs to be heated to 361.3K; a heat exchanger is used here to keep the temperature of feed stable. According to the measured temperature value, the temperature controller will adjust the flow rate of steam to control the temperature. If the temperature is higher than 361.3K, the steam flow rate will be adjusted to decrease to make the temperature to decrease. If the temperature is lower, the flow rate of steam will be increased to make the temperature to increase (see figure 6.2).

- The top stream will go through the condenser and the reflux drum. In the condenser, it is important to control the flow rate of cooling water to make sure that heat can be removed effectively and vapor can condense to liquid. If the follow rate of cooling water varies, the liquid level in the reflux accumulator will also vary. So the flow rate of cooling water should be controlled. It is obvious that a simple flow controller can fulfill this task. Before the cooling water flows through the control valve, the flow rate disturbance is measured and controller will adjust the valve accordingly to make the flow rate constant (see figure 6.3)

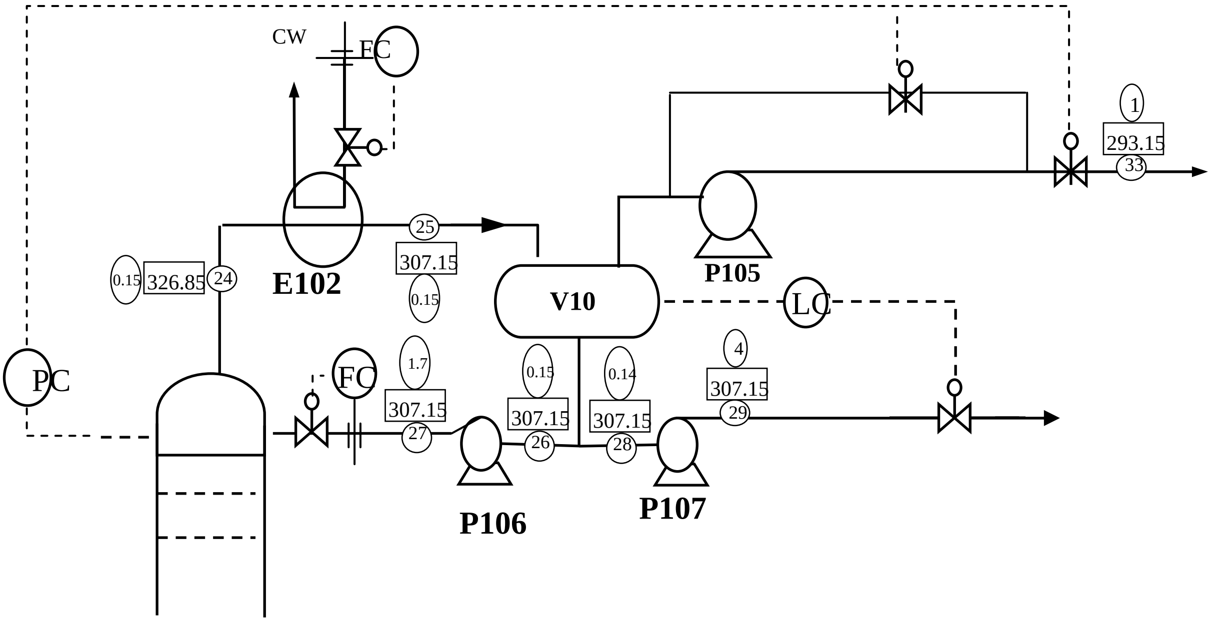


Figure 6.3: The control configuration for the top stream from the distillation column

- The pressure is 0.15bar as design requirement. The vacuum pump is connected to the vent of the reflux accumulator. To make the pump works in a continuous way, a branch of outlet of the pump is circulated back to the inlet to keep a certain amount of gas goes through the vacuum pump (see figure 6.3)

  To create the vacuum, the air first should be extracted until the pressure in column reaches 0.15bar by the vacuum pump. Then, the controller will open the circulation control valve and close the valve on the outlet stream 33. The remaining air just circulates inside the pump to keep the pump works. The column begins to startup and the vapor will pushes the air out of the column, the vacuum pump is still kept working in this period. When the pressure in the column becomes higher than 0.15bar, the control valve of stream 33 will open and the circulation valve will close, vacuum pump will begin to extract the vapor out to make the column pressure reduces to 0.15bar. After certain time, the column's pressure will be kept at 0.15bar, the control valve of stream 33 will approach to close and circulation valve open. Then, if the column's pressure is higher than 0.15 bar, the circulation valve will close and control valve of stream 33 will open; if the pressure is lower, the control valve will close until more vapor rising from the reboiler increases the pressure. In such a way, the vacuum can be created and kept at 0.15bar.

- The liquid level in the reflux accumulator should be taken care. If the level is too high or too low, the flow rate of the leaving stream and reflux stream will vary, and the balance of column system will be disturbed. The liquid level is designed to be 1m high and is controlled by the flow rate of leaving stream. If the level is too high, the leaving stream's flow rate will increase; if the level is too low, the leaving stream's flow rate will decrease. The liquid level can't be controlled by another stream, reflux stream. Otherwise, in the column the vapor-liquid equilibrium will be disturbed frequently (see figure 6.3)

- The reflux stream is critical for the operation of column. According to the process design, the reflux rate should be kept at 0.0855 kg/s. If the reflux flow changes, the whole column system will be disturbed. The flow rate of down-flow liquid will change and disturb the equilibrium of liquid and vapor on every tray. The whole operation and product quality will be affected. So the reflux stream flow rate is important. It is obvious that a flow controller can fulfill this task as shown in the figure (see figure 6.3)

- Inside the bottom of the column, there is also liquid, which should be kept at certain level. If there is no liquid, the column cannot be operated; if the liquid is too much, more heat is needed and efficiency decreases. To control the liquid level in the bottom of column, only the leaving stream can be controlled to keep the level. A liquid controller is used here. The stream, which enters the reboiler, cannot be controlled because it will affect the amount of vapor and further the system balance (see figure 6.4)

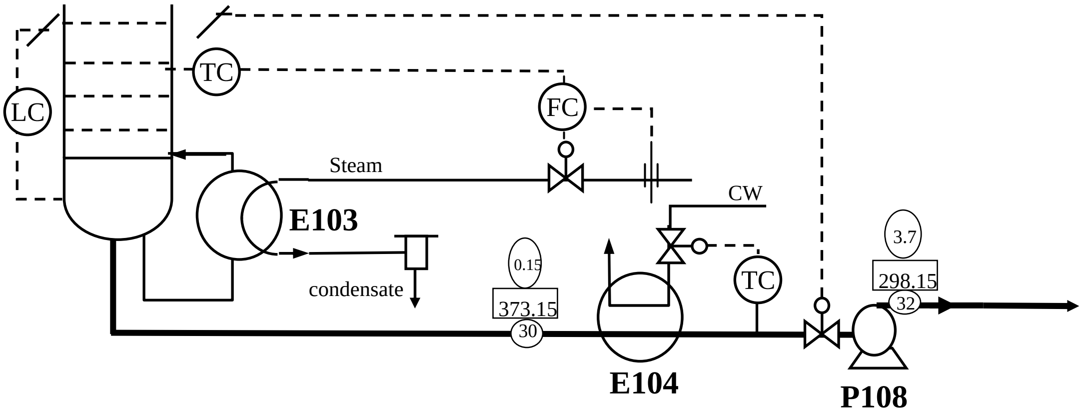


Figure 6.4: The control configuration for the bottom stream from the distillation column

- The temperature in the bottom of the column is important for the quality of the product. Because the source of heat is from the steam entering the reboiler, it is obvious that the temperature can be controlled by the steam flow rate. A controller is installed to control the temperature by adjusting the steam. Secondly, the reboiler should work in the stable condition, which means the flow rate of steam should be kept stable. If the steam flow rate increases, the amount of vapor in the reboiler will increase. The consequence is that the temperature in the bottom of the column will also increase. Of course the temperature controller will adjust the steam flow rate to control the temperature, but there is time lag and maybe some hot spots are formed and temperature even cannot be reduced. To avoid it, it is important to prevent such disturbance before the steam enters the reboiler. So the cascade controller is used here. If the steam flow rate changes a bit, the flow controller will first adjust it back to the required value. Then, the stable steam flow enters the column. If the temperature in the bottom varies, the temperature controller will control the flow rate more easily and effectively (see figure 6.4)

- The temperature of the steam leaving the column is about 100°C; it is necessary to cool down the stream to the environment's temperature of 25°C. The reason is that the product will be transported through the pipes and stored in the storage. If the temperature is higher than the required value, the liquid density will change and even flash to the vapor. Then, the pressure drop along the pipe will be smaller and the stream cannot be transported easily, even the pump cannot work properly. To get the low temperature, a heat exchanger is used to cool down the stream. The cooling water is the cooling source. It is important to make the flow rate of the cooling water constant to make sure the temperature of the stream can reach 25°C. So, a temperature controller is installed here to adjust the flow rate of cooling water to keep the temperature of bottom-leaving stream reach 25°C and stable (see figure 6.4)

CHAPTER 7 MASS AND HEAT BALANCES

7.1 Practical aspects

In the following section, the mass and heat balances for total stream and for stream components are made. The mass and heat balance in reaction part (batch section) is given in table 7.1, while in table 7.2, the mass and heat balance in separation part (distillation section) is shown. As it can be seen in the tables, no imbalances do occur. All mass and heat coming to the plant are the same as those going out from the plant.

In table 7.4, the overall component mass and stream heat balance is shown. It provides the difference between enthalpies of IN and OUT going streams. This difference should equal to the difference between heats "IN" and "OUT" as introduced or removed by heat exchanger equipment (steam, cooling water, air cooling, etc).

As it can be seen from table 7.4, imbalances do occur in mass balance. These imbalances are due to round-up factor. Since the calculation is done with both Microsoft Excel and Aspen Simulation, and the results are rounded-up to 3 decimal places, this round up might be carried on until the last calculation and causes imbalances at the end. However, the errors are just very small (0.002% for mass balance and 0.003% for mole balance) and they will not give any influence on the final result.

In checking the difference between enthalpies "IN" and "OUT" going stream in table 7.4 with the heat difference in Table 7.2 and 7.3, an error of 1.96% is founded. This also can be explained because of round-up factor of calculation. Since this error is considerably small, it will not give any effect on the final result.

7.2 Balance for total stream

Table 7.1: Heat and mass balance for streams total of reaction part

HEAT & MASS BALANCE FOR STREAMS TOTAL										
REACTION PART										
IN						OUT				
Plant		EQUIPMENT			EQUIPM.	EQUIPMENT			Plant	
Mass kg/batch	Heat MJ	Mass kg/batch	Heat MJ	Stream Nr.	IDENTIF.	Stream Nr.	Mass kg/batch	Heat MJ	Mass kg/batch	Heat MJ
5.697	-0.035	5.697	-0.035	<2>	**T102**	<10>	525.817	64.343		
520.120	64.378	520.120	64.378	<4>						
		525.817	64.343		Total		525.817	64.343		
		525.817	64.343	<10>	**P102**	<11>	525.817	64.343		
8.800	0.000	8.800	0.000	<1>	**R101**		611.657	-105.598		
40.960	-71.138	40.960	-71.138	<8>	**heating up**					
36.080	-139.709	36.080	-139.709	<9>	**period**					
		525.817	64.343	<11>						
	34.685		34.685		jacket					
	4.185		4.185		heat of react					
		611.657	-105.598		Total		611.657	-105.598		

Table 7.1: Heat and mass balance for streams total of reaction part (cont'd)

HEAT & MASS BALANCE FOR STREAMS TOTAL										
REACTION PART										
IN						OUT				
Plant		EQUIPMENT			EQUIPM.	EQUIPMENT			Plant	
Mass kg/batch	Heat MJ	Mass kg/batch	Heat MJ	Stream Nr.	IDENTIF.	Stream Nr.	Mass kg/batch	Heat MJ	Mass kg/batch	Heat MJ
		611.657	-105.598		**R101 during reaction**		611.657	-105.598		
					jacket			10.844		**10.844**
	10.844		10.844		heat of react					
		611.657	-94.754		Total		611.657	-94.754		
		611.657	-105.598		**R101 cooling down**	<12>	611.657	-134.74		
					jacket			29.146		**29.146**
		611.657	-105.598		Total		611.657	-105.598		
		611.657	-134.744	<12>	**F101**	<13>	8.800	0	8.800	0
						<14>	602.857	-134.74		
		611.657	-134.744		Total		611.657	-134.74		
		602.857	-134.744	<14>	**V101**	<15>	602.857	-134.744		
		602.857	-134.744	<16>	**T103**	<18>	604.317	-161.91		
1.460	-23.181	1.460	-23.181	<17>						
					heat loss			**1.95**		**1.95**
		604.317	-157.93		Total		604.317	-159.96		
		604.317	-161.91	<18>	**F102**	<19>	3.422	0.01	3.422	0.01
						<20>	600.895	-161.92	600.895	-161.921
		604.317	-161.91		Total		604.317	-161.91		
613.117	-119.972								613.117	-119.971
OUT-IN :									0.000	0.000

Table 7.2: Heat and mass balance for streams total of separation part

HEAT & MASS BALANCE FOR STREAMS TOTAL SEPARATION PART										
IN						OUT				
Plant		EQUIPMENT			EQUIPM.	EQUIPMENT			Plant	
Mass kg/h	Heat kW	Mass kg/h	Heat kW	Stream Nr.	IDENTIF.	Stream Nr.	Mass kg/h	Heat kW	Mass kg/h	Heat kW
751.104	-59.719	751.104	-59.719	<22>		<23>	751.104	-34.518		
	25.201		25.201		**E101**					
		751.104	-34.518		Total		751.104	-34.518		
		751.104	-34.518	<23>	**C101**	<29>	687.381	-18.652	687.381	-18.652
						<30>	63.723	-34.686		
					E102			121.022		**121.022**
	102.202		102.202		**E103**					
		751.104	67.684		Total		751.104	67.684		
		63.723	-34.686	<30>		<31>	63.723	-36.237	63.723	-36.237
					E104			1.551		**1.551**
		63.723	-34.686		Total		63.723	-34.686		
751.104	67.684								751.104	67.684
OUT-IN :									0.000	0.000

Note: please also refer to appendix A4.2 for the mass and heat balances of all streams of separation part

Some remarks related to the above tables:

Table 7.3: Remarks on heat and mass balances calculation

Equipment Identification	*Parameter*	*Description*	*Value*	*Unit*	*Remarks*
R101 heating	Reactor jacket	Heat added during heating-up period	**34.685**	MJ	See Appendix A4.3.1
up period	Heat of react	Heat released from exothermic reaction during heating up period	**4.185**	MJ	See Appendix A4.3.1
R101 during	Heat of react	Heat released from exothermic reaction during reaction time	**10.844**	MJ	See Appendix A4.3.1
reaction	Reactor jacket	Heat removed during reaction	**10.844**	MJ	See Appendix A4.3.1
R101 cooling down	Reactor jacket	Heat removed during cooling down period	**29.146**	MJ	See Appendix A.4.3.1
E101	heat in	heat added to preheat feed of distillation column	**25.201**	kW	See Appendix A4.3.2
E103	heat in	reboiler heat duty	**102.202**	kW	See Appendix A4.3.2
E102	heat out	condensor heat duty	**121.022**	kW	See Appendix A4.3.2
E104	heat out	heat released for cooling down product	**1.551**	kW	See Appendix A4.3.2

Notes:
- For mass data of each stream, please refer to table 5.2, chapter 5 (Batch Process Stream Summary)
- Heat data of stream is calculated from enthalpy of each element
(see table A.4.1 Batch Remarks and Calculation for enthalpy data of each element)

7.3 Balance for stream components

Mass balance per component inside battery limit is shown in the following table:

Table 7.4: Overall component mass and stream heat balance

Overall Component Mass and Stream Heat Balance							
Stream Nr.		<1>+<2>+<3>+ <8>+<9>+<17>	**IN**	<13>+<19>+ <29>+<32>	**OUT**		**OUT-IN**
Name		Total Plant		Total Plant		Total Plant	
Component	Mwt	ton/year	tmol/year	ton/year	tmol/year	ton/year	tmol/year
Toluene	92.14	5201.200	56.449	5201.200	56.449		
La-Isopropoxide	316.2	56.970	0.180	0.000	0.000		
R-, S- 3-chloro-1-phenyl-1-propanol	170.5	409.600	2.402	0.512	0.003		
Lipase B		8.800	0.000	8.800	0.000		
Propenyl Acetate	100.1	360.800	3.604	120.144	1.200		
(R)-3-chloro-1-phenylpropyl acetate	212.5	0.000	0.000	510.008	2.400		
Acetone	58.08	0.000	0.000	139.392	2.400		
Water	18.0	14.600	0.811	4.896	0.272		
Lanthanum Hydroxide	189.9	0.000	0.000	34.220	0.180		
Isopropanol	60.1	0.000	0.000	32.696	0.544		
Total		6051.970	63.446	6051.868	63.448	-0.102	0.002
Enthalpy GJ		-16.9685		-14.76			2.212

Checking the enthalpy difference in table 7.3 with the heat difference from table 7.2 and table 7.3:

Table 7.5: Heat difference in reaction part

Reaction part	**IN** MJ/batch	MJ/year	**OUT** MJ/batch	MJ/year
Steam jacket	34.685	3468.480		
Heat of reaction (heating)	4.185	418.494		
Heat of reaction (reaction)	10.844	1084.36		
Cooling water jacket (reaction)			10.844	1084.36
Cooling water jacket (cooling down)			29.146	2914.6
Heat loss			1.95	195.0
Total	(A) =	4971.334	(B) =	4193.96

Table 7.6: Heat difference in the separation part

Separation part	**IN** kW/batch	MJ/year	**OUT** kW/batch	MJ/year
Steam from E101	25.201	7258.0161		
Steam from E103	102.202	29434.176		
Cooling water from E102			121.022	34854.336
Cooling water from E104			1.551	446.688
Total	(C) =	36692.192	(D) =	35301.024

Comparison

Table 7.7: Comparison of net heat and net enthalpy

Total heat IN (A) + (C)	41.664	GJ/year
Total heat OUT (B) + (D)	39.495	GJ/year
Heat OUT-IN	-2.169	GJ/year
Enthalpy OUT-IN (from table 7.4)	2.212	GJ/year
Error	1.965	%

From table 7.7, it can be seen that the net heat is almost the same as the net enthalpy; the small error is just due to round-up factor.

CHAPTER 8 PROCESS AND EQUIPMENT DESIGN

8.1 Integration by process simulation

The calculation in distillation column is done in ASPEN PLUS simulation engine. Because there is not enough data for rigorous simulation model RADFRAC, DSTWU model should be used first to predict some basic parameter roughly (also refer to appendix A4.3.2 for more detailed explanation)

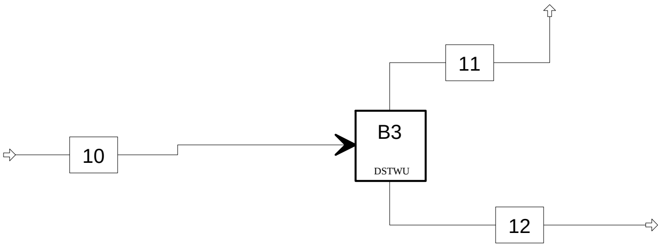


Figure 8.1: DSTWU simulation model in ASPEN PLUS

From the simulation model DSTWU, the reflux ratio of 0.45 and the number of stages of 22 (including condenser and reboiler) are obtained. With these data, the model RADFRAC is used to simulate again, the product purity is found to be 99.4%, which satisfies the requirements (refer to part 3.3, chapter 3 for basic assumptions). Therefore, this result can be used as the base of the column design. The details of distillation column are given in appendix A5.7

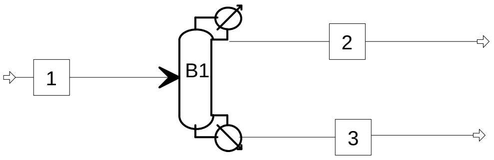


Figure 8.2: RADFRAC simulation model in ASPEN PLUS

The most important parameters of the distillation column design:

Number of stages:	22
Feed stage:	10
Reflux ratio:	0.45

Table 8.1: Operating conditions of distillation column

Pressure	top	0.15 atm
	bottom	0.15 atm
Temperature	top	307.1 K
	bottom	373.2 K
Heat duty	top	-121.022 kW
	bottom	102.202kW

8.2 Equipment selection and design

8.2.1 Selection

(Refer to figure 5.1, chapter 5 of process flow scheme for equipment names)
(Note: in this section *S denotes Selection*)

S1. Storage tank for toluene T101

T101 is designed as storage tank, which can contains the amount of toluene needed for 20 batches in the plant. The reason to choose 20 batches is to get good reactor size (refer to part 2.2 chapter 2 for more explanation).

S2. Dissolving tank T102

T102 is designed as a tank for dissolving catalyst lanthanum isopropoxide in toluene.

Mixing method chosen:
There are three normal ways to stir the contents in the tank:

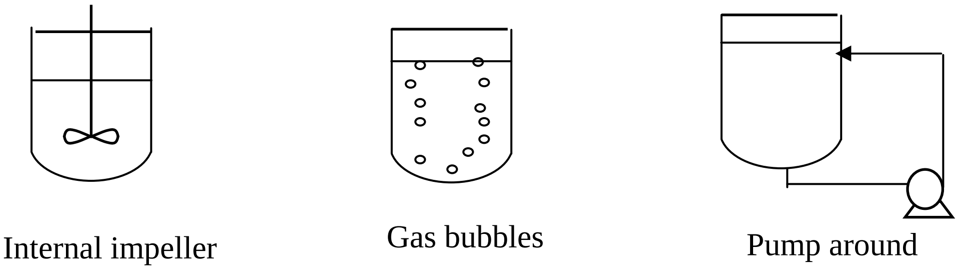
- using internal impellers;
- gas bubbles;
- pump around

(please refer to figure 8.3 bellow)

The reaction requires extremely dry condition, so it is impossible to use air bubbles as mixing bubbles because air bubbles always contain water, which comes from air). If pure nitrogen is used as mixing bubbles the cost will be high since the pure nitrogen is relatively expensive (The price is 7500 Dfl/m^3, refer to table 3.9, chapter 3)

The 'pump around' method is always used in big scale conditions and the external pump is required. The external pump will increase the cost of equipment purchase.

Therefore, internal impeller is chosen**.**



Internal impeller Gas bubbles Pump around

Figure 8.3: Different mixing methods

Inlet and outlet holes for T102:
(please also refer to part 3.2.2, chapter 3 of the discription of the block scheme for the need to design the inlet and outlet holes for T102)

There are four inlet holes on the dissolving tank (refer to figure 8.4 bellow)

- No1 is the hole, which connects T101 with toluene input stream
- No2 is designed in order to fit the hopper for adding solid (lanthanum isopropoxide) into the tank.
- No 3 and No 4 are designed as gas (nitrogen) inlet holes. The reason not to use only one hole for gas (nitrogen) input instead of two is to make sure that the air, which might be coming during feeding of lanthanum isopropoxide, is all

pushed out from the reactor. So the position of 2nd hole for gas inlet should be above the liquid level in the tank.

There are two outlet holes on the dissolving tank (refer to figure 8.4 bellow)

- No 5 is designed as the hole for gas outlet (for nitrogen and air)
- No 6 is designed as the hole for liquid outlet (lanthanum isopropoxide dissolved into toluene) to reactor R101

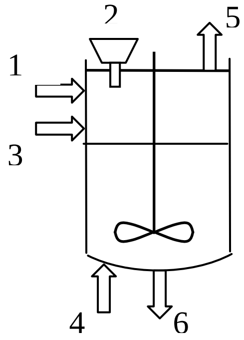


Figure 8.4: Dissolving tank T102

S3. Reactor R101

Reactor is the most important equipment in the plant. There are several steps need to be followed during the reactor design.

Type of reactor chosen

The batch reactor is chosen. (please refer to part 2.2 chapter2 for reasons of the type of reactor chosen)

Mixing method chosen

Internal impeller is chosen. (please refer to mixing method chosen in T102 selection for reasons).

Heat exchange equipment chosen

There are three kinds of equipment normally used for heat transfer, which are jacket, internal heat transfer surface and pump around through an exchanger (please refer to figure 8.5 bellow).

Since the amount of heat needs to be transferred is not very much (please refer to appendix A4.3.1) and also because the heat transfer surfaces is more expensive than normal surfaces. Therefore, pump around through an exchanger will not be chosen.

The system in the reactor is multiphase system, which has solid (catalyst lipase B) and liquid (mainly toluene). If internal heat transfer surface is used there might be a possibility in which the mixing condition is affected. Also internal heat transfer surface will increase the size of reactor, and leads to increase in the reactor's cost. Due to these reasons, internal heat transfer surface will not be chosen [12].

Therefore, a jacket is chosen as heat exchange equipment for the reactor.

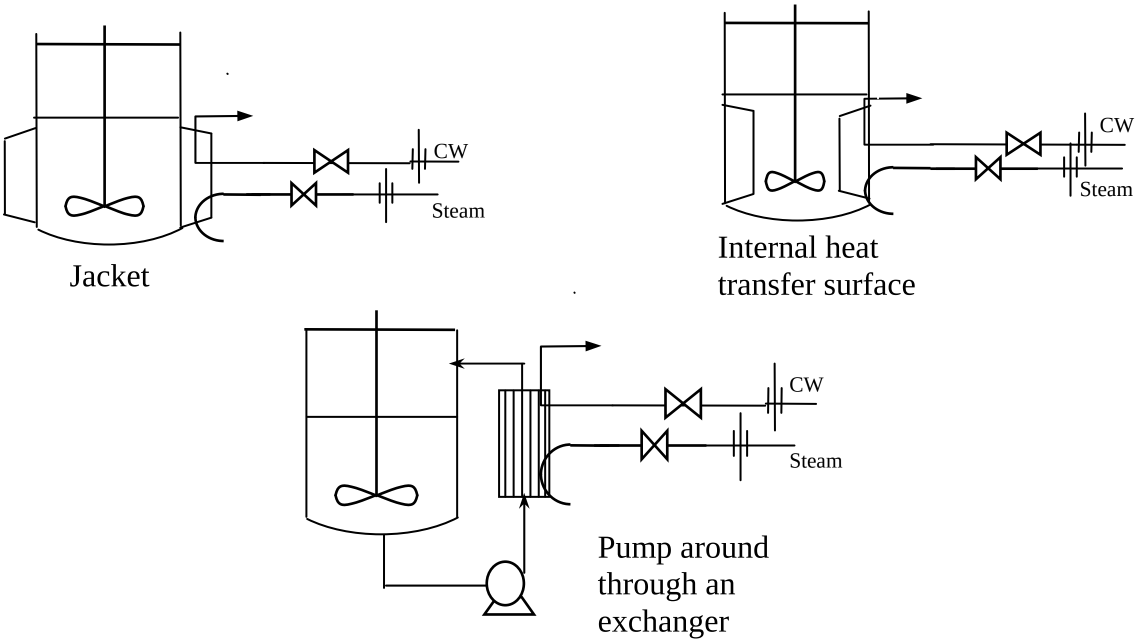


Figure 8.5: Different designs of reactor's heat transfer system

Inlets and outlet holes of reactor
(please also refer to part 3.2.2, chapter 3 of the discription of the block scheme for the need to design the inlet and outlet holes for the reactor)

There are four inlet holes on the reactor (please also refer to figure 8.6 bellow)

- No 1 is the hole, which connects with T102 for liquid (lanthanum isopropoxide dissolved in toluene) input stream.
- No 2 is designed in order to fit the hoppers for adding solid (lipase B)and liquid (racemic mixture of 3-chloro-1-phenyl-1-propanol and propenyl acetate), which are added manually into the reactor.
- No 3 and No. 4 are designed as gas (nitrogen) inlets. The reason for not designing only one hole for gas (nitrogen) inlet instead of two is the same as the reason used in T102 selection.

There are two outlet holes on the reactor (refer to figure 8.6 bellow).

- No 5 is designed as the hole for gas outlet (for nitrogen and air)
- No 6 is designed as the hole for reaction mixture outlet

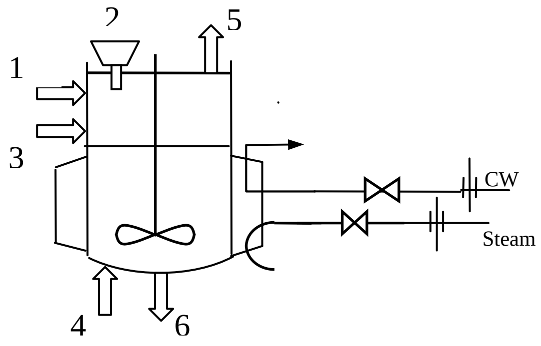


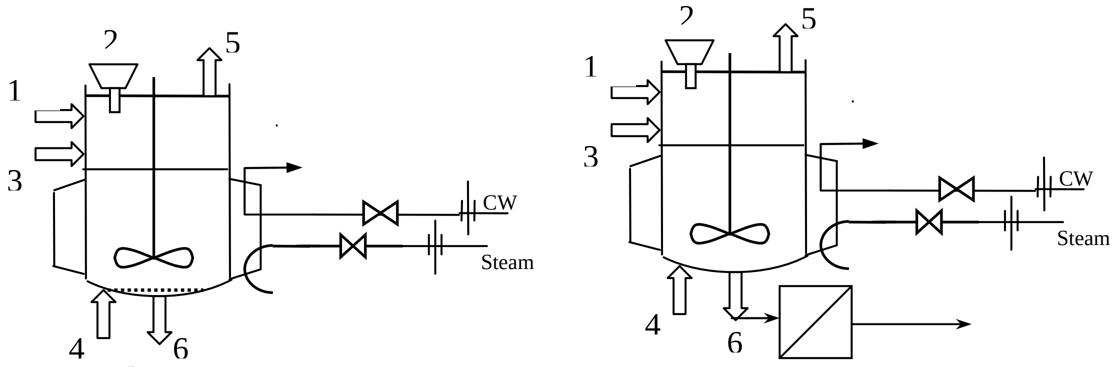
Figure 8.6: Reactor design

S4. Filter F101

Filter is used here to separate lipase B from liquid phase (reaction mixture)

Filter vs mesh
(please refer to figure 8.7 bellow)

By comparing 2 options of mesh and filter, it is found that the cost of mesh is much less, however the mesh might cause the solid particles (lipase B) adhere on the holes of the mesh. It later might affect the mixing condition in the reactor. Therefore, the filter is chosen to separate the solid (lipase B) from liquid phase (reaction mixture).



Mesh

Filter

Figure 8.7: Filter vs Mesh

Type of filter chosen

Table 8.2: Advantages and disadvantages for different types of filter

Type of Filters	*Disadvantage*	*Advantage*
Plate & frame filter	- Short replacement time, hence high replacement cost; - Can not separate micro-size particles	- High average filtrate flux (250l/m^2h). - Large maximum filter area (100m^2)
Rotary vacuum filter	- Short replacement time, hence high replacement cost; - Can not separate micro-size particles - Pressure drop: 2bar	- High average filtrate flux 250l/m^2h, - Cheap membrane cost
Micro-filter	- Expensive membrane cost 200$/$m^2$ - Low average filtrate flux 20l/m^2h.	- Can separate very small particles. - Long membrane replacement time (2000 operation hours), hence, low replacement cost

Note: The characters mentioned in the table are from SUPERPRO program

Micro-filter is chosen here for better separation result. The product (precursor of Prozac) is pharmaceutical product, so the key point in the separation part is to make sure the solid impurity will be separated completely. Therefore, micro-filter is chosen.

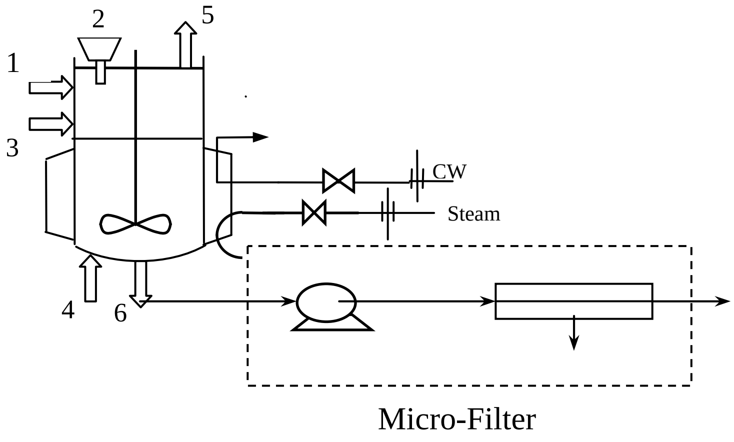


Figure 8.8: Micro-filter

S5. Buffer tank V101

V101 is designed as the buffer tank between F101 (filter) and P103 (pump). The fluxes for filter and pump P103 may be different so buffer tank is placed here to make sure that the process will run smoothly.

S6. Precipitation tank T103

T103 is designed as the tank for precipitation of the catalyst lanthanum isopropoxide to lanthanum hydroxide.

Type of reactor chosen

Batch reactor is chosen (the same reason as for R101 selection).

Mixing method chosen

Internal impeller is chosen (please refer to T102 selection for the same explanation)

Inlets and outlet holes of reactor

(please also refer to part 3.2.2, chapter 3 of the discription of the block scheme for the need to design the inlet and outlet holes for the precipitation tank)

There are two inlet holes on the reactor (refer to figure 8.8 bellow)

- No1 connects with V101 for liquid (reaction mixture) input stream
- No 2 is the hole for deionized water input stream

There is only one outlet for the precipitation tank (refer to figure 8.8 bellow)

- No 3 is designed as the outlet hole for liquid and solid ($La(OH)_3$) to F102.

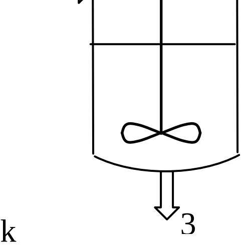


Figure 8.8: Precipitation tank

S7. Filter F102

Filter here is used to separate $La(OH)_3$ from liquid phase (reaction mixture)

Type of filter chosen

Micro-filter is chosen for better separation because the heavy-metal-salt like $La(OH)_3$ is very harmful to human, and the product of the plant is pharmaceutical intermediate. So the key point in separation part is to make sure that the harmful solid will be separated completely from the product (please refer to F101 selection for the same explanation)

S8. Intermediate storage tank V102

V102 is designed as intermediate storage tank, which can contains the liquid of reaction mixture of 20 batches coming from T103. The reason for choosing 20 batches is for designing good batch reactor size (please refer to part 2.2, chapter 2 for more explanation).

S9. Heat exchangers E101 – E104

Heat exchangers are used in distillation column, as heater for feed fed (E101), rebolier (E103), condenser (E102) and cooler for product (E104).

Type of heat exchangers chosen

The most commonly used type of heat-transfer equipment, which is shell and tube exchanger is chosen due to its many advantages such as:

- The configuration gives a large surface area in a small volume
- Good mechanical layout: a good shape for pressure operation
- Well-established fabrication techniques
- Can be constructed from wide range of materials
- Easily cleaned
- Well-established design procedures

Type of tube and shell heat exchangers chosen

There are different kinds of tube and shell heat exchanger are used in the industry, including baffle spacers and tie rods, fixed –tube plate, internal floating head without clamp ring, U-tube, single tube etc.

Because the temperature difference for flows in the plant is not very much and also the amount of flows is not much, which is only between 60-1000 kg/h (please refer to mass balance and heat balance in chapter 7), so total amount of heat needed to be transferred is not so much and heat transfer surface required is quite small. Therefore, single tube heat exchanger is chosen.

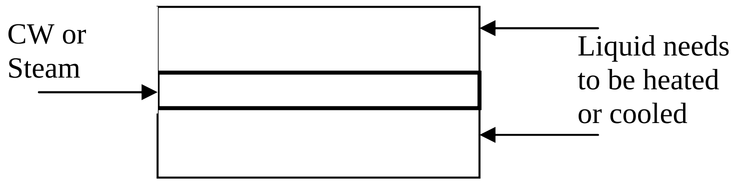


Figure 8.9: Single tube and shell heat exchanger

S10. Distillation column C101

There are 2 types of distillation column: plate and packed column. The choice for a particular application can only be made by costing each design. However, this will not always be worthwhile, or necessary, and the choice can usually be made based on experience. Normally, plate column can be designed with more assurance than packed columns. There is always some doubt that good liquid distribution can be maintained throughout a packed column under the operating conditions. In our case, the purity requirement for the product is quite high, more than 99%, and also because of the nature of the product, which is a pharmaceutical ingredient, hence the quantity of the product should be kept high and stable. So, hereby the plate column is chosen.

Cross-flow plates are the most common type of plate contactor used in distillation columns. In a cross-flow plate the liquid flows across the plate and the vapor up through the plate. The flowing liquid is transferred from plate and a pool of liquid is retained on the plate by an outlet weir. Three principal types of cross-flow tray are used which are classified according to the method used to contact to the vapor and liquid:

- sieve plates
- bubble-cap plates
- 3 valve plates

The principal factors to be considered when comparing the performance of bubble-cap, sieve and valve plates are: cost, capacity, operating range, efficiency and pressure drop.

Cost:
Bubble-cap plates are appreciably more expensive than sieve or valve plates. For mild steel the ratios of bubble-cap: valve: sieve are approximately 3.0:1.5:1.0

Capacity:
There is little difference in the capacity rating of the three types; however the ranking is sieve, valve, bubble-cap

Operating range:
Bubble-cap plates have a positive liquid seal and can operate efficiently at very low vapor rates. Sieve plates rely on the flow of vapor through the holes to hold the liquid on the plate, and cannot operate at very low vapor rates; Valve plates are intended to give greater flexibility than sieve plates at a lower cost than bubble-caps.

Efficiency:
The efficiency of the three types of plate will virtually the same when operating over their design flow range, and no real distinction can be made between them.

Pressure drop:
The pressure drop over the plates can be an important design consideration, particularly for vacuum columns. In general sieve plates give the lowest pressure drop, followed by valves, with bubble-caps giving the highest.

Therefore, from the point of view of cost and capacity, sieve plate is the first choice. In our case, distillation column is operated under vacuum condition, but the pressure is not very low: 0.15bar, so sieve plate can deal with it. According to the calculation, (see appendix A5.7) the pressure drop along the whole column is less than 0.01bar that is corresponding to the performance of sieve plate. In all, *sieve plate* is the choice in this case.

S11. Buffer tank V103

V103 is designed as a buffer tank between E102 and P106, P107. The use of this tank is to make sure there is enough liquid which has been condensed before pumping. This tank is also used as the place to connect with vaccum pump for vaccum pump to push the gas (air and little toluene vapor) out and to create vaccum condition in the column.

S12. Storage tank for technical grade toluene T105

T105 is designed as storage tank, which can contain produced technical grade toluene of all production year.

S13. Storage tank for product T106

T106 is designed as product storage tank before product is filled into 50L containers.

S14. Pumps P101-P108

Pumps can be classified into two general pumps:

- dynamic pumps, such as centrifugal pumps
- positive displacement pumps, such as reciprocating, diaphragm and rotary pumps

The single-stage, horizontal, overhung, centrifugal pump is the most commonly used in the chemical process industry. Other types are used where special process considerations are specified, such as vacuum.

Pumps selection is made based on the flow rate and head required, together with other process considerations, such as corrosion, etc.

- ♦ There are 4 pumps needed before separation part:

Pump P101: Toluene transport pump

This pump is designed to pump toluene from storage tank T101 to dissolving tank T102. The choice of pump will depend on the capacity and head requirement. Centrifugal pumps will normally be the first choice for pumping process fluids, the other types only being used for special applications, such as the use of reciprocating and gear pumps for metering. The capacity range of centrifugal pumps is 0.25-1000m^3/h and typical head is 10-50m of water for single stage, 300m water for multistage. In this case, the flow rate of toluene is 3.6m^3/h and maximum head required is 44.1m. So, centrifugal pump ca be used as toluene transport pump.

Pump P102: Liquid transport pump

This pump is designed to pump liquid from dissolving tank T102 to reactor R101. The flow rate of liquid is 7.2m^3/h and maximum head required is 36m so centrifugal pump can be used as liquid transport pump. (Please refer to selection of pump P101 for the choice of pump P102)

Pump P103: Liquid transport pump

This pump is designed to pump liquid from buffer tank V101 to precipitation tank T103. The flow rate of liquid is 1.6m^3/h and maximum head required is 38m, so centrifugal pump can be used as liquid transport pump. (Please refer to selection of pump P101 for the choice of pump P103)

Pump P104: Column's feed pump

This pump is designed to pump the liquid from storage tank V102 to distillation column C101. The flow rate of liquid is 0.85 m^3/h and maximum head required is 60m, so centrifugal pump can be used as column's feed pump. (Please refer to selection of pump P101 for the choice of pump P104)

- ♦ There are 4 pumps required in separation part:

Pump P105: Vacuum pump

To create vacuum, rotary pump or steam jet ejector can be used to create 0.15bar **[13]**. However, in the steam jet ejector, high-pressure steam is used, normally higher than 6bar. The steam is relieved through a converging and diverging nozzle and will give off part of its kinetic energy to the aspirated vapor so that the mixture of the two fluids goes through inverse transformation in which the velocity is converted into pressure at the diffuser discharge. So, if steam jet ejector is used, high-pressure steam, which is expensive is required. Secondly, the steam will contaminate the toluene vapor, which is not good because it is desired to sell toluene as technical grade of approximately 95% purity. Rotary pump has no such problem. In rotary pumps the liquid is displaced by rotation of one or more members within a stationary housing. The selection of materials for designing rotary pumps is critical. The materials must be corrosion-resistant and capable of some abrasion resistance. In our case, the vapor consists of air and toluene, which are not so corrosive, so mild steel is suitable for designing the rotary pump

Pump P106: Toluene reflux pump

In the distillation column, the top vapor is condensed. Part of it should be refluxed to the column. To transport the reflux stream, the pump is necessary. The capacity range of centrifugal pumps is 0.25-1000m^3/h and typical head is 10-50m of liquid. In our case, the flow rate of reflux is 0.36m^3/h and maximum head required is 27m, so centrifugal pump can be used as reflux pump (Please refer to selection of pump P101 for the choice of pump P106)

Pump P107: Toluene transport pump

After condensing the top vapor, another part of condensate should leave the column as the top stream. In our case, the flow rate is 0.8m^3/h and maximum head required is 46m. For the same reason as pump P106, centrifugal pump can be chosen as toluene transport pump.

Pump P108: Precursor transport pump

At the bottom of distillation column, the precursor stream will leave the column. To transport the precursor to the storage tank, the pump is needed here. The flow rate of precursor is very small, 0.054m^3/h, centrifugal pump can not operate in this capacity range. Only the diaphragm pump can operate in such low capacity for transportation. Also the typical head of diaphragm pump is 5-60m. The maximum head required is 36m of liquid. Therefore, diaphragm pump is used to transport the product to the storage tank T105.

8.2.2 Design

(Note: in this section *D denotes Design*)

D1. Storage tank for toluene T101

Approach: - Approximated amount of liquid is used to calculate design volume
- Chosen diameter (for good tank size) is used calculate the height

Table 8.3 Design parameters of storage tank T101

Volume (m^3)	15.1	*Remark*: refer to appendix A5.1 (storage tank design) for detailed calculation.
Diameter (m)	2.0	
Height (m)	4.8	

D2. Dissolving tank T102

Approach: - Liquid volume is calculated
- Liquid volume is used to calculate design volume
- Chosen diameter (for good tank size) is used to calculate the height
- Universal mixing time relation is used to calculate mixing time and power needed: $N_{mix} = \frac{t_m \varepsilon^{1/3}}{D^{2/3}} = \frac{\alpha}{\beta^{4/3}\gamma^{1/3}}\left(\frac{L_s}{H}\right)^2\left(\frac{H}{D}\right)^2$ **[14]**

Table 8.4 Design parameters of dissolving tank T102

Volume (m^3)	0.75	*Remark*: refer to appendix A5.2 (dissolving tank design) for detailed calculation.
Diameter (m)	1.00	
Height (m)	0.96	
Mixing time (s)	106.3	
Power (kW)	0.15	

D3. Reactor R101

Approach: - Liquid volume is calculated
- Liquid volume is used to calculate design volume
- Chosen diameter (for cheaper reactor cost) is used to calculate the height
- Universal mixing time relation is used to calculate mixing time and power needed: $N_{mix} = \frac{t_m \varepsilon^{1/3}}{D^{2/3}} = \frac{\alpha}{\beta^{4/3}\gamma^{1/3}}\left(\frac{L_s}{H}\right)^2\left(\frac{H}{D}\right)^2$ **[14]**

Table 8.5 Design parameters of dissolving tank T102

Volume (m^3)	0.84	*Remark*: refer to appendix A5.3 (reactor design) for detailed calculation.
Diameter (m)	1.00	
Height (m)	1.07	
Heat transfer surface (m^2)	3.33	
Mixing time (s)	115	
Power (kW)	0.17	

D4. Filter F101

Table 8.6 Design parameters of filter F101

Filtration area (m^2)	80	*Remark*: - default design in SUPERPRO program is chosen because it only influences the filtration time. The filtration time is equal to the volume of the liquid to be filtrated divided by the average flux. The filtration time is found to be 25 minutes (refer to appendix A5.3 for the volume of liquid in reactor R101 to be filtrated)
Average flux (m^3/h)	1.6	
Power (kW)	16	

D5. Buffer tank V101

Approach:
- Estimate the time needed for the liquid fed to the buffer tank
- Based on the time estimated above the volume of the buffer tank is calculated
- Chosen diameter (for good tank size) is used to calculate the height of the tank

Table 8.7 Design parameters of buffer tank V101

"Buffer" time (min)	10	*Remark*: refer to appendix A5.4 (buffer tank design) for detailed calculation.
Volume (m^3)	0.40	
Diameter (m)	0.60	
Height (m)	1.45	

D6. Precipitation tank T103

Approach:
- Liquid volume is calculated
- Liquid volume is used to calculate design volume
- Chosen diameter (for good tank size) is used to calculate the height
- Universal mixing time relation is used to calculate mixing time and power needed: $N_{mix} = \frac{t_m \varepsilon^{1/3}}{D^{2/3}} = \frac{\alpha}{\beta^{4/3}\gamma^{1/3}}\left(\frac{L_s}{H}\right)^2\left(\frac{H}{D}\right)^2$ **[14]**

Table 8.8 Design parameters of precipitation tank T103

Volume (m^3)	0.84	*Remark*: refer to appendix A5.5 (precipitation tank design) for detailed calculation.
Diameter (m)	1.00	
Height (m)	1.07	
Mixing time (s)	115	
Power (kW)	0.13	

D7. Filter F102

Table 8.9 Design parameters of filter F102

Filtration area (m^2)	80	*Remarks*: - default design in SUPERPRO program is chosen because it only influences the filtration time. The filtration time is equal to the volume of the liquid to be filtrated divided by the average flux. The filtration time is found to be 25 minutes (refer to appendix A5.5 for the volume of liquid in precipitation tank T103 to be filtrated)
Average flux (m^3/h)	1.6	
Power (kW)	16	

D8. Intermediate storage tank V102

Approach: - the same approach as for tank T101

Table 8.10 Design parameters of intermediate storage tank V102

Volume (m^3)	16.75	*Remark*: refer to appendix A5.6 (intermediate storage tank design) for detailed calculation.
Diameter (m)	2.50	
Height (m)	3.50	

D9. Heat exchangers E101 – E104

Approach: - Using known heat transfer power (refer to appendix A4.3.2) and mean temperature difference (calculated from temperature difference using equation: $\Delta T_{lm} = \dfrac{(T_1 - t_2) - (T_2 - t_1)}{\ln \dfrac{(T_1 - t_2)}{(T_2 - t_1)}}$ [15]) heat transfer surface is calculated

Table 8.11 Design parameters of heat exchangers E101-104

	E101 *Column feed heater*	E102 *Column condenser*	E103 *Column reboiler*	E104 *Column product cooler*
Hot utility	L.P. steam (110°C, 1.5bar)		L.P. steam (110°C, 1.5bar)	
Cold utility		Cooling water (20-30°C)		Cooling water (20-30°C)
Temperature range (°C)	20-88	53.7-34	98.2-100.02	98.2-25
Heat transfer surface (m^2)	2.1	26.27	37.63	0.26
Remark: - refer to appendix A5.8 for heat exchangers' design				

D10. Distillation column C101

McCabe-Thille method is the basic way to design distillation column. The dimensioning design procedure is given by J. M. Coulson & J. F. Richarson (1979) **[15]**. In Delft University of Technology, another effective method is used, so-called *Delft Method* **[16]**. In our design, integration by process simulation is done first for the calculation, which is shown in the appendix A5.7, then *Delft Method* is used for dimensioning the column.

Delft method is an iterative procedure:

- Internal flows and physical properties along the column
- Choice of column type, i.e. vapor/liquid contacting device
- Determination of column diameter and column height
- Check pressure drop and adjust all calculation accordingly.

Table 8.12 The key dimensioning result of distillation column

Diameter (m)	0.50
Total height (m)	14.55
Tray spacing (m)	0.45
Weir length (m)	0.275
Weir height (m)	0.025
Skirt clearance (m)	2.00
Remark: - refer to appendix A5.7 for detailed calculation	

D11. Buffer tank V103

Approach: - the same approach as for buffer tank V101

Table 8.13 Design parameters of buffer tank V103

"Buffer" time (min)	60	*Remark*: refer to appendix A5.4 (buffer tank design) for detailed calculation.
Volume (m^3)	1.44	
Diameter (m)	1.00	
Height (m)	1.84	

D12. Storage tank for technical grade toluene T105

Approach: - the same approach as for toluene storage tank T101

Table 8.14 Design parameters of technical grade toluene storage tank T105

Volume (m^3)	79.4	*Remark*: refer to appendix A5.1 (storage tank design) for detailed calculation.
Diameter (m)	3.0	
Height (m)	11.2	

D13. Storage tank for product T106

Approach: - the same approach as for toluene storage tank T101

Table 8.15 Design parameters of product storage tank T106

Volume (m^3)	4.2	*Remark*: refer to appendix A5.1 (storage tank design) for detailed calculation.
Diameter (m)	1.5	
Height (m)	2.4	

D14. Pumps P101-P108

♦ Transport pumps P101-P104 needed before separation part

Approach: - first, the suction pressure and discharge pressure are calculated separately.
- the pressure differential across the pump and power of centrifugal pump are calculated

Table 8.16.1: Design parameters of transport pumps P101-P104

Pumps	*Suction pressure* *(kPa)*	*Discharge pressure* *(kPa)*	*Pressure differential across the pump* ΔP *(kPa)*	*Flow rate* Q_p *(m^3/s)*	*Pump efficiency* η_p (%)	*Power* *(kW)*
P101 Toluene transport pump	93.88	490.6	396.7	10^{-3}	27%	1.5
P102 Liquid transport pump	93.72	359.4	265.6	2×10^{-3}	42%	1.3
P103 Liquid transport pump	90.71	370.8	280.1	5.5×10^{-3}	23%	0.7
P104 Column's feed pump	84.23	519.5	435.5	2.4×10^{-4}	17%	0.7
Remarks: - refer to figure 5.1, chapter 5 of PFS for the name and position of the pumps - refer to appendix A5.9 for detailed calculation of pumps - pump efficiency is determined according to J. M. Coulson & J. F. Richarson, 1979, *Chemical Engineering*, volume 6 (p435, figure 10.62)						

- Vacuum pump P105

To create the vacuum, the air should first be extract until the pressure in column reaches 0.15bar. Then the column begins to startup and the vapor will push the air out of the column, the vacuum pump will still work in this period. When the column reaches the balance condition, the vacuum pump will stop working. Only when the pressure in the column is above 0.15bar, the vacuum pump will begin to work to extract the toluene vapor. But it means the vacuum pump does not work continuously, which is not good for the maintenance. To avoid it, a branch of outlet of pump is circulated back to the inlet to keep a certain amount of gas goes through the vacuum pump to keep it working smoothly

Assuming it takes 5mins to extract air out of column, then

$$flow\,speed = \frac{volume}{time} = \frac{3.14 \cdot 0.25^2 \cdot 14.55 \cdot (1-0.15)}{5 \cdot 60} = 0.008\,m^3/s$$

$$Power = \frac{\Delta P \times Q_p}{\eta_p} \times 100$$

$$where\ \ \Delta P = pressure\ \ differential\ \ across\ \ the\ \ pump\,(N/m^2)$$

$$Q_p = flow\ \ rate\,(m^3/s)$$

$$\eta_p = pump\ \ effeciency\,(\%)$$

The key data result in the table below:

Table 8.16.2: Design parameters of vacuum pump P105

Pumps	*Suction pressure* *(kPa)*	*Discharge pressure* *(kPa)*	*Pressure differential across the pump* ΔP *(kPa)*	*Flow rate* Q_p *(m^3/s)*	*Pump efficiency* η_p (%)	*Power* *(kW)*
P105 Vacuum pump	14.4	326.5	312.1	0.008	90%	2.8

Remarks:
- refer to figure 5.1, chapter 5 of PFS for the name and position of the pumps
- refer to appendix A5.9 for detailed calculation of pumps
- pump efficiency is determined according to J. M. Coulson & J. F. Richarson, 1979, *Chemical Engineering*, volume 6 (p435, figure 10.62)

After extracting air out and pressure reaches 0.15bar, the column startup and the vapor will push the remaining air out. The controller will almost close the control valve to make the remaining vapor circulate around the pump, to keep the pump working.

If the pressure in the reflux accumulator is higher than the column's pressure, the controller valve will open to make the pressure in the reflux accumulator to decrease. Also, when the pressure of column is higher than 0.15 bar, the controller valve will adjust to make the column pressure drop to 0.15bar.

- ♦ Transport pumps P106-P108 needed in separation part

Approach: - the approach is the same as the one used for transport pumps P101-P104

Table 8.16.3: Design parameters of transport pumps P106-P108

Pumps	*Suction pressure (kPa)*	*Discharge pressure (kPa)*	*Pressure differential across the pump ΔP (kPa)*	*Flow rate Q_p (m^3/s)*	*Pump efficiency η_p (%)*	*Power (kW)*
P106 Toluene reflux pump	29.7	235.9	206.2	10^{-4}	20%	0.11
P107 Toluene transport pump	20.1	399.0	378.9	2.2×10^{-4}	20%	0.45
P108 Toluene transport pump	60.0	480.0	420.0	1.5×10^{-5}	50%	0.013

Remarks:
- refer to figure 5.1, chapter 5 of PFS for the name and position of the pumps
- refer to appendix A5.9 for detailed calculation of pumps
- pump efficiency is determined according to J. M. Coulson & J. F. Richarson, 1979, *Chemical Engineering*, volume 6 (p435, figure 10.62)

8.3 Special issues

The simulation model, Aspen plus, is described in this section.

Aspen is a chemical process flow sheet simulation, optimization and design package. Aspen provides a complete library of steady state models for a number of unit operations in the chemical process industries including petroleum, petrochemical, gas processing, polymer, mineral processing. It also provides a large physical properties and rigorous thermodynamic properties library.

Process R&D staffs use ASPEN PLUS in the early stages of process discovery for the rapid development, evaluation, screening and scale-up of process flow sheet alternatives. Unique ASPEN PLUS capabilities, such as property estimation, property and Kinetics data regression, shortcut equipment models and sensitivity analysis, allow the R&D engineers to build process models with minimal information.

8.3.1 Physical properties

Accurate physical properties representation is the key to generating meaningful simulation results. The ASPEN PLUS property system is generally regarded as the best commercially available in the industry. It includes state-of-the-art models for representing the thermodynamic and transport properties of:

- non-ideal mixtures using both equation of-state and activity-coefficient approaches
- petroleum assays and blends
- aqueous and non-aqueous electrolyte solutions
- systems containing solids, including multiple solid phases
- polymer systems (with the POLYMERS PLUS® module)

A comprehensive properties' databank system containing:

- data for over 5,000 pure components; approximately 40,000 binary parameters representing 5,000 binary mixtures; and reaction constants for almost 1,000 aqueous ionic reactions
- an interface to the DETHERM®databanks, the world's most-extensive compilation of experimental VLE, LLE and other property data for more than 250,000 mixtures
- interfaces to in-house databanks

8.3.2 Unit operations

ASPEN PLUS contains a comprehensive library of over 50 built-in unit operation models that cover the entire range of process equipment and operating conditions, including:

- the RADFRAC model for rigorously simulating distillation, absorption, stripping, extractive and azeotropic distillation. RADFRAC can handle a second liquid phase and solid phase anywhere in the column, as well as any number of chemical or electrolytic reactions on any or all stages;
- the PETROFRAC model for refinery applications, such as preflash towers, crude units, vacuum units, FCC main fractionators and delayed coker fractionators
- A variety of reactor models, including stoichiometric reactors, equilibrium reactors based on Gibbs free energy minimization, and kinetics-based CSTR, plug-flow and batch reactors.
- Rigorous equipment sizing and rating calculations for pressure relief, heat exchangers, pumps and compressors, pipes and pipelines, and columns with trays or random and structured packing.

The detail of the simulation in the process of producing precursor of Prozac, (3-choloro-1-phenyl-1-propanol) is in Appendix A5.10

8.4 Equipment data sheets

Equipment Data Summary Sheets and Equipment Data Specification Sheets are given in appendix A5.11

CHAPTER 9 WASTES

This chapter provides the information about the direct wastes produced and how they are handled in the design.

9.1 Direct wastes

Table 9.1 Wastes produced in the plant

Stream number	***Waste type***	***Phase***	***Amount of waste (kg/year)***
<13>	Lipase B	Solid	8.80 *(1)*
<33>	Toluene	Gas	18.25 *(2)*
<33>	Hazardous Air *(3)*	Gas	14.53 *(4)*

Remarks:

(1) Please refer to part 2.3, chapter 2 for amount of catalyst lipase B required

(2) Assume the pressure in the distillation column will be disturbed 5 times per year. Every time the pressure will increase from 0.15bar to 0.5bar, therefore to keep the pressure in the distillation column constant, the vacuum pump needs to pump out certain amount of toluene gas from the column. The amount of toluene is calculated by using ideal gas equation:
$\Delta PV = nRT$
$\Delta P = 0.5-0.15 = 0.35$bar = 35350pa
V = 2.86m^3 (please refer to appendix A5.11, table A5.11.14)
R=8.314J/Kmol
T=307.15K (please refer to appendix A4, table A4.4)
Calculated:
n = 39.59mol since MW of toluene is 92.14g/mol (please refer to table 3.2, chapter3), the amount of toluene is 3.648 kg/batch, hence 18.25 kg/year (5batches of separation part/year)

(3) The normal air should not be treated as waste gas. But the air here comes from column, which contains toluene therefore the concentration of toluene in the air is higher than the normal condition. Because toluene is a harmful gas, so the air in the column should not be released to atmosphere without any treatment.

(4) Every time before starting separation process it is required to have the vacuum in the distillation column from 1bar to 0.15bar, the amount of air needs to be pumped out from the column is calculate as the method used in remark (2).
$\Delta PV = nRT$
$\Delta P = 0.1-0.15 = 0.85$bar = 85850pa
V=2.86m^3 (please refer to appendix A5.11, table A5.11.14)
R=8.314J/Kmol
T=293.15K(taken 20^{o}C as air temperature)
Calculated:
n = 100.74mol since MW of air is 28.84g/mol (assuming the composition of air is 79mol% N_2 & 21mol% O_2), the amount of air is 2.91 kg, hence 14.53 kg/year (5batches of separation part/year)

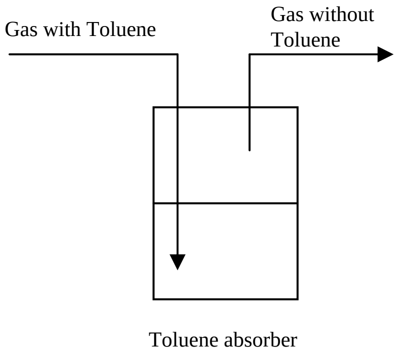
9.2 Methods of treatment

Table 9.2: Treatment of waste lipase B

Waste	*Lipase B (solid)*	
Effect	Bio-in-degradable compound because the carrier of the enzyme is plastic	
Treatment options		
Options	*Advantages*	*Disadvantages*
Burning	- Easy way, only furnace is needed; - Cheapest methods (If not considering about the penalty from government)	- Harmful smoke will be produced. In western Europe it is impossible to release this kind of smoke freely.
Dumping	- Most common way, no extra penalty.	- The expenditure is quite high. - Lipase B still exists and it sill might cause ground pollution.
Regeneration	- No pollution produced	- The cost is high.
Decision: - Regeneration option is chosen, because prevention of waste is the best remedy. - Assume the treatment cost for lipase B is 20% of purchasing cost		

Table 9.3 Treatment of waste gases

Waste	*Waste gases (Toluene + Air)*	
Effect	Toluene is flammable, hazardous compound.	
Treatment options		
Options	*Advantages*	*Disadvantages*
Burning	- Easy way, only furnace is needed; - No extra waste	- If the amount of toluene is high, it is not economical to treat it using this way
Through liquid absorber (1)	- Easy way, only suitable liquid absorber is needed - No extra waste.	- Quality of the treatment won't be met if the liquid absorber is not suitable
Condense and then add to T104 (2)	- Can deal with large amount of toluene.	- Extra equipment is needed
Decision: Burning option is chosen because the amount of toluene waste gas produced in the plant is not of high quantity (please refer to table 9.1)		
Remarks: (1) Please refer to Figure 9.1 (2) Please refer to Figure 9.2		



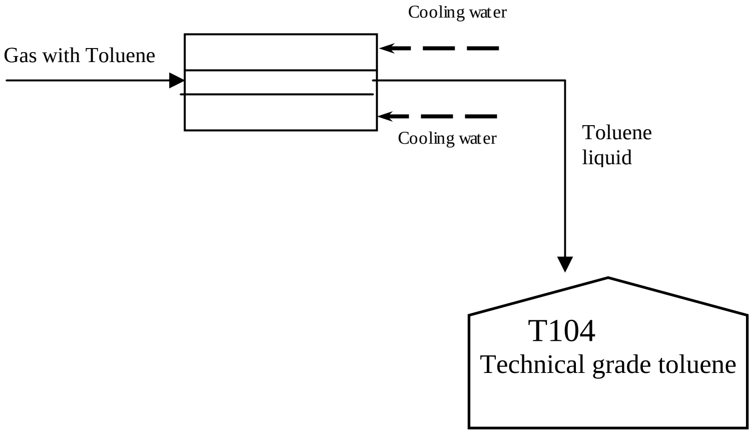


Figure 9.1: Waste gas treatment using toluene absorber leaving the gas without toluene

Figure 9.2: Waste gas treatment using using a condenser to condense toluene and add to storage tank

CHAPTER 10 PROCESS SAFETY

In this chapter, safety aspects vis a vis operating personnel from process design point of view by using two tools: *Fire and Explosion Index* (FEI) and *Hazard and Operability study* (HAZOP). Due to the nature of the product of the plant (pharmaceutical product), *Good Manufacturing Practices* (GMP) will be briefly mentioned.

10.1 Fire and Explosion Index (FEI)

The evaluation of the Dow Fire and Explosion Index for Prozac precursor plant is set out on the special form shown in table 10.1. Notes on the decisions taken and the factors used are explained as the following:

Unit: consider the total plant, no separate areas, including the main storages

Material factor: for Toluene MF = 16 **[15]** (p329)

Note: Toluene is chosen to determine material factor as it is the most dominant material in the plant. Other materials are too small and not as dangerous as toluene.

General process hazards:

A. Esterification reaction, factor = 0.5
B. Endothermic processes, not applicable
C. Material and handling and transfer
   Since for Toluene the flammability is equal to 3 (N_F = 3) **[17]**, hence a penalty of 0.85 is applied. This category includes drums and cylinders **[18]**
D. Enclosed or Indoor process units.
   All storage tanks are placed outdoor, hence this factor is not applicable.
E. Access, adequate access will be provided, factor = 0.0
F. Drainage and spill control, adequate drainage will be provided, factor = 0.0

Special process hazards:

A. Toxic material
   Toluene is highly toxic material, likely to cause serious temporary or residual injury on short exposure (N_H=3). A penalty of 0.2 × N_H is used. Hence, the factor is 0.6.
B. Sub-Atmospheric Pressure
   This penalty is not applicable since the absolute pressure is more than 500 mmHg (760 mmHg).
C. Operation In or Near Flammable Range
   This factor is not applicable since air can't be breathed into the tank during pump-out or sudden cooling of the tank.
D. Dust Explosion, not applicable
E. Pressure
   Using equation from Dow's Fire and Explosion Index Hazard Classification Guide **[18]** $Y = 0.16109 + \frac{1.61503 \cdot X}{1000} - 1.42879 \cdot \left(\frac{X}{1000}\right)^2 + 0.5172 \cdot \left(\frac{X}{1000}\right)^3$

   where: Y is penalty factor
   X is pressure in psig
   In this case, atmospheric pressure is used, then X= 0 psig

   It yields Y=0.16

F. Low temperature
Not applicable, since no unit operation is operated below ductile/transition temperature (10°C).

G. Quantity of Flammable/Unstable Material
The largest quantity of toluene in the process will be the liquid in the storage tank, which is 10.4 tons (the storage tank stores 20 batches of toluene, hence 20 × 520 kg/batch = 10.4 tons).
The heat of combustion = 31.3 MJ/kg **[15]** (table 9.3)
Hence the potential energy release = 10400 × 31.3 = 325,520 MJ = 0.30853×10^9 Btu.
Using equation from Dow's Fire and Explosion Index Hazard Classification Guide:

$$\log Y = -0.403115 + 0.378703(\log X) - 0.046402(\log X)^2 - 0.015379(\log X)^3$$

where: Y is penalty factor
X is potential energy release in 10^9 Btu.
It results the penalty factor = 0.25

H. Corrosion and Erosion
The corrosion rate is considered to be the sum of the external and internal corrosion rate. External corrosion is possible due to Lanthanum Isopropoxide material which is very corrosive, allow minimum factor = 0.1

I. Leakage-joint and packing
Welded joints will be used on toluene service and mechanical seals on pumps. Use minimum factor 0.1 as full equipment details are not known at the flow-sheet stage, factor = 0.1.

J. Use of Fired Heaters
There are no fired equipments in a process; hence this factor is not applicable.

K. Hot oil heat exchange system
Heat exchange system only uses steam as heating medium.

L. Rotating equipment
All pumps here are not used in excess of 75 HP, hence this factor is not applicable.

The index works out at 83: classified as "moderate". Toluene is considered a dangerously flammable material (MF=16); the danger of material handling and transfer, and internal explosion in the storage tank are the main process hazards. Toxicity of toluene and the corrosiveness of lanthanum isopropoxide also need to be considered in a full hazard evaluation.

Table 10.1: Dow's fire and explosion index analysis

FIRE AND EXPLOSION INDEX (FEI)		LOCATION The Netherlands	DATE 21-Dec-01
PLANT WAHX Chemicals	PROCESS UNIT Whole plant	EVALUATED BY HTN	REVIEWED BY XNL
MATERIALS AND PROCESS			
MATERIALS IN PROCESS UNIT Toluene, Lanthanum Isopropoxide, Lipase B, R-,S- 3 chloro-1-phenyl-1-propanol, Propenyl Acetate, R- 3-chloro-1-phenylpropylacetate, acetone, water, Lanthanum Hydroxide, Isopropanol			
STATE OF OPERATION [ ] START UP [ ] SHUT DOWN [ ] NORMAL OPERATION		*Basic Material For MF* TOLUENE	
MATERIAL FACTOR (MF)			16
1. GENERAL PROCESS HAZARD	*Penalty*	*Penalty Used*	
BASE FACTOR	1	1	
A. EXOTHERMIC CHEMICAL REACTIONS (FACTOR 0.3 to 0.125)		0.5	
B. ENDOTHERMIC PROCESSES (FACTOR 0.2 to 0.4)			
C. MATERIAL HANDLING AND TRANSFER		0.85	
D. ENCLOSED OR INDOOR PROCESS UNITS (FACTOR 0.25 to 0.90)			
E. ACCESS	0.35		
F. DRAINAGE AND SPILL CONTROL (FACTOR 0.25 to 0.50)			
GENERAL PROCESS HAZARDS FACTOR (F_1)		2.35	
2. SPECIAL PROCESS HAZARDS			
BASE FACTOR	1	1	
A. TOXIC MATERIALS (FACTOR 0.20 to 0.80)		0.6	
B. SUB-ATMOSPHERIC PRESSURE (<500 mmHg)	0.5		
C. OPERATION IN OR NEAR FLAMMABLE RANGE			
[ ] INERTED [ ] NOT INERTED			
1. TANK FARMS STORAGE FLAMMABLE LIQUIDS	0.5		
2. PROCESS UPSET OR PURGE FAILURE	0.3		
3. ALWAYS IN FLAMMABLE RANGE	0.8		
D. DUST EXPLOSION			
E. PRESSURE : OPERATING PRESSURE: 0 psig		0.16	
F. LOW TEMPERATURE (FACTOR 0.2 to 0.3)			
G. QUANTITY OF FLAMMABLE / UNSTABLE MATERIAL:			
QUANTITY : 10.4 tons Hc = 31.3 MJ/kg			
1. LIQUIDS, GASES AND REACTIVE MATERIALS IN PROCESS			
2. LIQUIDS OR GASES IN STORAGE		0.25	
3. COMBUSTIBLE SOLIDS IN STORAGE DUST IN PROCESS			
H. CORROSION AND EROSION (FACTOR 0.10 to 0.75)		0.1	
I . LEAKAGE-JOINTS AND PACKING (FACTOR 0.10 to 1.5)		0.1	
J. USE OF FIRED HEATERS			
K. HOT OIL HEAT EXCHANGE SYSTEM (FACTOR 0.15 to 1.50)			
L. ROTATING EQUIPMENT	0.5		
SPECIAL HAZARD FACTOR (F_2)		2.21	
UNIT HAZARD FACTOR (F_1 x F_2 = F_3)		5.194	
FIRE AND EXPLOSION INDEX (F3 x MF = F&EI)			83

10.2 Hazard and Operability study (HAZOP)

A limited Hazard and Operability study is carried out here for equipments, which are evidently critical, such as a dissolving tank, reactor and distillation column. Only deviations leading to action, and those having consequences of interest are recorded.

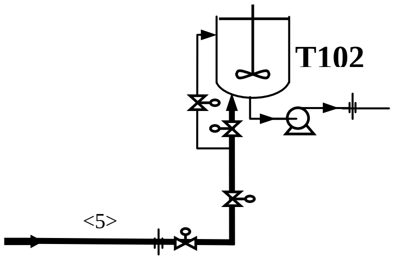


Figure 10.1: Dissolving tank section (Prozac's precursor plant)

T102 - Dissolving tank
Intention – to dilute lanthanum isopropoxide with toluene
Line <5> (nitrogen line)
Intention – to inject N_2 into T102

Table 10.2: HAZOP analysis for dissolving tank T102

Guide word	*Deviation*	*Cause*	*Consequences and action*
NO	No Flow	(1) No nitrogen at storage	(a) Damage for catalyst lanthanum isopropoxide, the catalyst will not react properly. Action: ensure good communication with operator.
		(2) Valves fail open	As for (a) Action: change the valve with the new ones

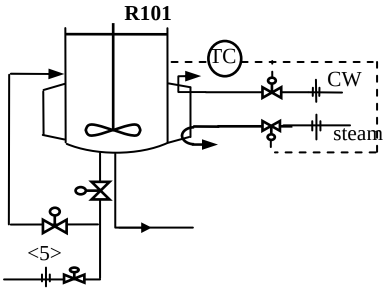


Figure10.2: Reactor section (Prozac-precursor plant)

R101 – Reactor
Intention – to react reactants into product and by product
Analysis for possible hazard in line <5> (nitrogen line) is the same as in table 10.1

Steam line
Intention – to heat reaction mixture up to 60°C

Table 10.3: HAZOP analysis for reactor R101, steam line

Guide word	*Deviation*	*Cause*	*Consequences and action*
NO	No Flow	(3) No steam at storage	(b) the reaction will still proceed but the conversion might not be 99.9%. Action: ensure good communication with operator.
		(4) Valves fail to open	As for (b) Action: change the valves with the new ones
MORE	More Flow	(5) Valves opens too wide	(c) It might bring to detonation since the flash point of toluene is very low. Action: -Ensure the temperature control is working properly. -Check the valves periodically to ensure that it works as expected.

Cooling water line

Intention – to maintain temperature in the reactor 60°C during the reaction
- to cool down the reaction mixture into 30°C after the reaction finishes

Table 10.4: HAZOP analysis for reactor R101, cooling waterline

Guide word	*Deviation*	*Cause*	*Consequences and action*
NO	No Flow	(6) No cooling water at storage	(d) the temperature in the reactor will increase slightly and it might lead to the detonation of toluene. (e) during the cooling down, if the cooling water is not supplied then the temperature of product flowing in the discharge pipe will be so hot and it might harm workers nearby. Action: ensure good communication with operator.
		(7) Valves fail to open	As for (d) and (e) Action: change the valve with the new ones
MORE	More Flow	(8) Valves opens too wide	(f) too much cooling water rate, then it will increase the operating cost. Action: -Ensure the temperature control is working properly. -Check the valves periodically to ensure that it works as expected.

For separation part (distillation column), everything is under control (please refer to chapter 6 of process control for explanation why a specific controller is put there). If the controllers are working properly then it will cause no damage. If some controllers are broken, then they should be replaced to keep the process running safely.

Recommendation
Basically, the main cause of hazard is whether or not the valve and controllers are working properly. Hence in order to keep the process inherently safe, checking those equipments regularly is recommended.

10.3 Good Manufacturing Practices (GMPs)

The product of this plant is a pharmaceutical intermediate of Prozac, an antidepressant drug. US Food and Drug Administration (FDA) provided the guidance on Good Manufacturing Practices for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality and safety. Within the world community, materials may vary as to their legal classification as an active pharmaceutical ingredient. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this guidance **[19]**.

Development and implementation of Good Manufacturing Practices can be a project itself and it is not included in the scope of this project. However, it is kept in mind of the designers of this plant that Good Manufacturing Practices is a “must” and once the plant is approved for installation, the development and implementation of GMPs should be put in action as one of the first steps.

However, the designers of this plant found that it is necessary to briefly mention the most important points of Good Manufacturing Practices for the manufacturing of active pharmaceutical ingredients according to the guidance provided by FDA. These issues are presented below and referenced from the abovementioned guidance.

10.3.1 Product quality review

Regular quality-reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results
- A review of all batches that failed to meet established specification(s)
- A review of all critical deviations or nonconformances and related investigations
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program
- A review of all quality-related returns, complaints and recalls
- A review of adequacy of corrective actions

10.3.2 Personnel hygiene

- Personnel should practice good sanitation and health habits.
- Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed, when

appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and APIs from contamination.

- Personnel should avoid direct contact with intermediates or APIs.
- Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.
- Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

10.3.3 Utilities and water

All utilities that could affect product quality (e.g., steam, gas, compressed air, heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded.

Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use. Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

Water used in this plant is de-ionized water and will be purchased from Alfa-Chemicals and it is potable.

10.3.4 Sanitation and maintenance

Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance.

Equipment used in this plant should be of appropriate design. Cleaning, sanitation and maintenance should be done appropriately

10.3.5 Documentation and records

Equipment cleaning and use record

Records of major equipment use, cleaning, sanitation, and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

Records of raw materials, intermediates, API labeling and packaging materials

Records should be maintained including:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
- The results of any test or examination performed and the conclusions derived from this
- Records tracing the use of materials
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specification
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials

Batch production record

Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used
- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- Actual results recorded for critical process parameters
- Any sampling performed
- Signatures of the persons performing and directly supervising or checking each critical step in the operation
- In-process and laboratory test results
- Actual yield at appropriate phases or times
- Description of packaging and label for intermediate or API
- Representative label of API or intermediate if made commercially available
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- Results of release testing

Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

Please refer to the following page for an example of the record form

Please refer to reference **[19]** for more details on Good Manufacturing Practices Guidance.

Table 10.5: Raw materials weighing record form

WAHX CHEMICALS **RAW MATERIALS WEIGHING RECORD FORM**					
PRODUCTION LINE:			BATCH NO:		
DATE:					
INGREDIENT		WEIGHT (g)	DEVIATION FROM SPECS	TIME	SIGNATURE
Name	Code				
LINE MANAGER: --					

CHAPTER 11 ECONOMY

This chapter provides economic evaluation of a conceptual process design of the plant producing the precursor of Prozac (3-chloro-1-phenylpropyl acetate)

11.1 Capital investment costs

The table below presents the capital investment costs of the plant

Table 11.1: Capital investment cost

Capital			
Description	%	IN (Dfl) ($\times 10^6$)	IN (Euro) ($\times 10^6$)
- Fixed Capital (FC)	89.0	4.63	2.10
- Working Capital (approximate as11% of total investment)	11.0	0.57	0.26
Total investment	100.0	**5.20**	**2.36**

Remarks:
- Refer to appendix A6.3 for details of fixed capital calculation
- The working capital is assumed to be 11% of total cost.
- The calculation is in Dutch gulden as well as Euro as standard currency. The ROE between Dutch gulden and Euro is 2.2.

11.2 Income (annual)

Table 11.2: Income (annual) of sales of products and sellable by-products

Products				
Description	OUT (kg/a)	*Sales* (Dfl/kg)	IN (Dfl/a) ($\times 10^6$)	IN (Euro/a) ($\times 10^6$)
Product (Precursor of Prozac ®)				
3-chloro-1-phenylpropyl acetate	5,095	10,000	50.95	23.16
By products				
- Technical grade Toluene	54,990	3.0	0.17	0.08
- Lanthanum hydroxide	342	500.0	0.17	0.08
Wastes				
- Lipase B	8.8	-6000	-0.05	-0.02
- Waste gas	-	-	-	
Total / Gross Income	60,427		**51.24**	**23.30**

Remarks:
- Refer to tables 3.6 and 3.7 (chapter 3) for the amount of product and by-products.
- Refer to table 3.11 (chapter 3) for the prices of products and by-products
- Assume the treatment cost for lipase B is 20% of purchasing cost (refer to chapter 9 of waste treatment)

The waste gas produces only when there are leaks in the distillation column. Assume the leaks in distillation column seldom found, and if there is some waste gas is produced, the treatment is to burn it to CO_2 and H_2O and then release them to the atmosphere. The cost of this treatment can be negligible (refer to chapter 9 for waste treatment).

11.3 Operation cost

11.3.1 Raw material costs

Table 11.3: Costs of raw materials

In going streams				
Description	IN (kg/a)	Purchase cost (Dfl/kg)	OUT (Dfl/a) $(\times 10^6)$	OUT (Euro/a) $(\times 10^6)$
Raw materials:				
- Racemic mixture (3-chloro-1-phenyl-1-propanol)	4,096.0	500.0	2.05	0.93
- Propenyl acetate	3,608.0	48.0	0.17	0.08
- De-ionized water	145.9	40.0	0.006	0.003
Catalysts:				
- Lipase B from Candida Antartica	8.8	30,000.0	0.26	0.12
- La-(-O-isopropyl)3	569.7	48,500.0	27.60	12.55
Solvent:				
- Toluene	52,012.0	15.0	0.77	0.35
Total	60,440.4		**30.86**	**14.03**

Remarks:
- The life for catalyst lipase B is 100 batches (refer to part 2.3, chapter 2)
- Refer to table A2.1 (appendix A2) for the amount of raw materials needed

11.3.2 Utilities costs

Table 11.4: Costs of utilities

Utilities					
Description	Units	IN (Units/a)	Cost (Dfl/Unit)	OUT (Dfl/a)	OUT (Euro/a)
- Steam	t	18.2	30	547.2	248.7
- Cooling water	t	921.4	0.1	92.1	41.8
- Electrical power	kWh	1,810.1	0.1016	183.9	83.6
- Nitrogen	m^3	319.0	7500	2,391,000	1,087,000
Total				**2,392,000**	**1,087,000**

Remarks:
- Refer to part 5.5, chapter 5 for the quantity of utilities

11.3.3 Summary of production costs

Table 11.5: Summary of annual production (manufacturing) costs

Summary of annual production (manufacturing) costs (kDfl/a)				
Cost type	kDfl/a	%		*Remarks*
Direct				
Variable				(A)
1 Raw materials	30,862	92.7%	65.8%	
2 Miscellaneous materials	46	0.1%	0.1%	(5): kDfl 463 10%
3 Utilities	2,392	7.2%	5.1%	Refer to part 5.5, chapter 5
4 Shipping & packaging				always negligible
Sub-total	*33,300*	*100%*	*71.6%*	
Fixed				(B)
5 Maintenance	463	19%	1.0%	Fixed Cap.: kDfl 4625 10%
6 Operating labour	600	24%	1.3%	3 oper.+2QC+1 for other job=6 operators
7 Laboratory	138	6%	0.3%	(6): kDfl 600 23%
8 Supervision	120	5%	0.3%	(6): kDfl 600 20%
9 Plant overhead	300	12%	0.6%	(6): kDfl 600 50%
10 Capital charges	694	28%	1.5%	Fixed cap.: kDfl 4625 15%
11 Insurance	46	2%	0.1%	Fixed cap.: kDfl 4625 1%
12 Local taxes	93	4%	0.2%	Fixed cap.: kDfl 4625 2%
13 Royalties	46	2%	0.1%	Fixed cap.: kDfl 4625 1%
Sub-total	*2,499*	*100%*	*5.3%*	
Total	*35,799*		*76.9%*	(A)+(B)
Other				(C)
14 Sales expenses 15 General overhead 16 Research & Dev.	10,740		23.1%	(A)+(B): kDfl 35,799 30%
Total Production Costs				
Annual [MDfl/a]	**46.5**		100%	(A)+(B)+(C)
Per ton P [Dfl/kg]	9,134			5095kg/a
Annual [Meuro./a]	**21.2**			
Per ton P [Euro/kg]	4,152			

Note:
- This table follows J. M. Coulson & J. F. Richarson's Chemical Engineering textbook (vol.6, p232, table 6.6)

There are 6 operators needed: 3 operators, 2 quality control engineers and one worker. The responsibility of the 3 workers is to operate the production line including batch reaction part and separation part. The reasons for having 3 operators are:

- Firstly, at the beginning of the process *propenyl acetate*, *racemic mixture 3-chloro-1-phenyl-1-propanol* and *lipase B* are added manually (refer part 3.2.2, chapter 3 for process description). It is supposed that this step requires two operators. At the same time it is still necessary to have at least another operator working in the control room. Therefore, the minimum number of operators required is 3.

- Secondly, after every 20 batches of reaction part the separation part (distillation column) will work continuously 16-24 hours. It is assumed that each batch of separation will take 24 hours in total (for heating the column at the beginning, cooling the column after 16 hours of operation, etc) (refer to part 3.3, chapter 3 for the basic assumptions). In Europe normal working hour is 8 hours per day, therefore for the separation part at least three operators are also required

Two quality control engineers' responsibility is to ensure the quality of the product is under control. Another worker is needed to do other jobs like cleaning or maintaining equipment.

11.4 Gross income, net cash flow and economic criteria

The following assumptions are made to determine maximum allowed investment:

- The economic plant life of project is 11 years
- The design/building period is 1 year and the working period is 10 years
- The interest rate (r) is 8% per year

Table 11.6: Gross income, net cash flow, economic criteria

Gross income, net cash flow, economic criteria

Item	*Unit*	*Value*	kDfl/a	kEuro/a	*Remarks*
Gross Income			51,233	23,288	
Production Costs			46,539	21,154	
Net Cash Flow, ***Before Tax***			**4,694**	**2,134**	= (A)
Economical Plant Life & Depreciation					
- Total Investment	kDfl	**5,197**			= (B)
- Econ. Plant Life, years:	years	11			Incl. 1 yrs Des.& Con.
- Annual Depreciation over 11 years			472	215	
Net Cash Flow, ***After Depreciation***			**4,222**	**1,919**	
- Income Tax @ 45%			1,900	864	
Net Cash Flow, ***After Tax***			**2,322**	**1,055**	
Pay-Out Time, ***Before Tax***	year	**1.1**			= (B) / (A)
Rate of Return, ***Before Tax***	%	**90.3%**			= (A) / (B)
DCF Rate of Return, ***Before Tax***	%	**90.2%**	**nil**	nil	DCFROR
Net Present Value, ***Before Tax***	%	**8.0%**	**26,302**	**11,955**	Appendix A6.4
Net Future Value, ***Before Tax***	kDfl		**41,745**	**18,975**	Interest = 0

Note:
- Refer to appendix A6.4 for the details of Discounted Cash Flow Rate On Return, Net Present Value and Net Future Value's calculation.

11.5 Cost review

Table 11.5 shows that variable cost is 71.6%, fixed cost is 5.3% and other cost is 23.1% because during the calculation other cost is calculated as 20-30% of the direct production cost **[15]**. It is also shown in table 11.5 that raw material costs 92.7% of total variable cost and it makes up 65.8% of total production cost.

Table 11.3 shows that catalyst - La-(-O-isopropyl)$_3$ costs nearly 90% of total raw materials' cost so the cost for purchasing La-(-O-isopropyl)$_3$ is the main cost for raw materials. There are three possibilities to reduce the cost of catalyst:

- Firstly, the possibility to reduce the cost of La-(-O-isopropyl)$_3$ is dependent on the progress of laboratory work. Better ratio between La-(-O-isopropyl)$_3$ and raw materials needed might be a solution. New catalyst, which has cheaper price can be studied as an alternative.
- Secondly, the reaction time can be prolonged to reduce the amount of catalyst needed. However, justification is needed for this reasoning. Also prolonging the time of the reaction might be not a wise solution since time is money.
- Thirdly, it is the method to separate La-(-O-isopropyl)$_3$ after the reaction. In this process La-(-O-isopropyl)$_3$ is precipitated out by adding water. The precipitate is separated from the reaction mixture by means of a micro-filter. As a result, it is impossible to recycle the catalyst. Other ways to separate the catalyst like extraction or distillation might be a solution, which might open the possibility to recycle the catalyst. However, the product is pharmaceutical product and La-(-O-isopropyl)$_3$ is very harmful so it is much safer to precipitate all the catalyst (it is possible because this catalyst is very sensitive to water) to solid La(OH)$_3$ and then to separate by using micro-filter as used in this process. Also, if there is a possible way, which can be used to recycle La-(-O-isopropyl)$_3$, the other costs might be increased such as the cost of extraction liquid or distillation column.

Table 11.7 below presents the gross income, cash flow and economic criteria calculated for the case if there is 20% reduction in the original amount of catalyst

Table 11.7: The impact of 20% reduction in the original amount of catalyst on economic criteria

Item	*Unit*	*Value*	kDfl/a	kEuro/a	*Remarks*
Gross Income			51,233	23,288	
Production Costs			39,363	17,892	
Net Cash Flow, ***Before Tax***			**11,870**	**5,395**	= (A)
Economical Plant Life & Depreciation					
- **Total Investment**	kDfl	**5,197**			= (B)
- Econ. Plant Life, years:	years	11			Incl. 1 yrs Des.& Con.
- Annual Depreciation over 11 years			472	215	
Net Cash Flow, ***After Depreciation***			**11,398**	**5,181**	
- Income Tax @ 45%			5,129	2,331	
Net Cash Flow, ***After Tax***			**6,269**	**2,850**	
Pay-Out Time, ***Before Tax***	year	**0.44**			= (B) / (A)
Rate of Return, ***Before Tax***	%	**228.4%**			= (A) / (B)

DCF Rate of Return, *Before Tax*	%	**228.4%**	**nil**	nil	DCFROR
Net Present Value, *Before Tax*	%	**8.0%**	**74,454**	**33,843**	Appendix A6.5
Net Future Value, *Before Tax*	kDfl		**113,506**	**51,594**	Interest = 0

<u>*Note*</u>:
- Refer to appendix A6.5 for the details of Discounted Cash Flow Rate On Return, Net Present Value and Net Future Value's calculation for 20% reduction in the original amount of catalyst

By comparing table 11.7 and table 11.6 it is found that the effect of reducing the main cost, which is the cost of La-(-O-isopropyl)$_3$, is remarkable especially for the rate of return and DCFROR. It is because in this case the investment is quite small compares to net cash flow and therefore, it really improves a lot of profit.

11.6 Sensitivities

<u>Table 11.8</u>: Sensitivity of economic criteria with respect to investment, operating costs (utilities, raw material costs), product's price with the variances of +/-10%

Variable	***Range*** (%)	***Total investment*** (Dfl) (× 10^6)	***Gross income*** (Dfl) (× 10^6)	***Operation cost*** (Dfl) (× 10^6)	**NCF** (Dfl) (× 10^6)	**ROR** (%)	**POT** (year)	**NFV** 0% int. (Dfl) (× 10^6)	**NPV** 8% int. (Dfl) (× 10^6)
Original value	**0%**	**5.197**	**51.233**	**46.539**	**4.694**	**90.3%**	**1.107**	**41.745**	**26.302**
Investment	10%	5.716	51.233	46.539	4.694	82.1%	1.218	41.227	25.783
								-1%	-2%
	-10%	4.677	51.233	46.539	4.694	100.4%	0.996	42.266	26.822
								1%	2%
Operation Cost Utilities	10%	5.197	51.233	46.850	4.383	84.3%	1.186	38.636	24.215
								-7%	-8%
	-10%	5.197	51.233	46.228	5.005	96.3%	1.038	44.855	28.388
								7%	8%
Operation Cost Raw materials	10%	5.197	51.233	50.551	0.682	13.1%	7.620	1.625	-0.619
								-96%	-102%
	-10%	5.197	51.233	42.527	8.706	167.5%	0.597	81.866	53.223
								96%	102%
Product's price	10%	5.197	56.328	46.539	9.789	188.4%	0.531	92.695	60.490
								122%	130%
	-10%	5.197	46.138	46.539	-0.401	-7.7%	-12.960	-9.205	-5.197
								-122%	-120%

As it is shown in table 11.8 the most sensitive factor is product price among investment, utilities cost, raw material cost (especially catalyst La-(-O-isopropyl)$_3$ cost) and product price. If the product price decreases 10% the plant will have deficit even NCF has negative value. The second sensitive factor is raw materials cost. When there is 10% of increase in the cost of raw materials the plant will have deficit, but the NFC still stays positive. For other factors fluctuations are less than 10% so they can be disregarded as sensitive factors.

There are still some other factors, which are not mentioned in table 11.8 like miscellaneous materials cost, fixed cost, by-products cost and waste cost. These costs can also be disregarded as sensitive factors.

11.7 Net cash flow

It is found from table 11.6 that if the prices of product and the catalyst La-(-O-isopropyl)$_3$ do not change, the Net cash Flow will be always positive unless the interest is more than 90.2%. However, it is not realistic if the interest goes as high as 90% in normal business environment.

It can be concluded that it is safe to invest this plant. The profits should be achieved as shown in table 11.6.

11.8 Discussion

As it shows in table 11.6, the net present value is 26.3 million Guilders with the interest of 8% and net future value is 41.7 millions. The total investment of the plant is 5.2 millions. The pay out time is only after 1 year. It can be seen that the process in very promising in term of profits and it is quick to get the money back. The values obtained for economic evaluation in this chapter can be said to be reliable because the highest costs for raw materials are taken for the calculation. Also, the low price for product (estimated only 20% of the price of a pure enantiomer which has similarities in chemical structure, refer to part 3.3, chapter 3 for more details) is used for the calculation. It is expected to have higher price for the product, hence more profit is also expected.

CHAPTER 12 CONCLUSION AND RECOMMENDATION

The plant of production scale of 5tons/year of the precursor of Prozac ((R)-3-chloro-1-phenylpropyl acetate) is successfully designed. The chemical route of the process is developed by Applied Organic Chemistry and Catalysis group (TOCK) of Delft University of Technology (chapter 2). This route is considered as a "break-through" in term of reaction time and yield (chapter 1). The plant in design consists of two parts: reaction part and a separation part for purification of the product (chapter 2, 3). The design of the plant is based on the assumptions, key data for the design (chapter 3), thermodynamic models and properties (chapter 4). It results in the process structure (chapter 5) and design of equipment of the plant (chapter 8).

The treatment methods for direct wastes produced in the plant are selected to make the plant environmental friendly. Although the cost for regeneration of the catalyst is high, this method is considered for the treatment of lipase B (chapter 9). The carrier of lipase B is plastic, which is non-biodegradable, therefore burning or dumping into the ground is not preferred. Small amount of other direct wastes, which are toluene vapor and the air containing toluene are burned using a furnace. The safety aspects are assessed (chapter 10) and the Dow's Fire and Explosion Index is found to be 83, which means that the degree of hazard of the plant is only moderate.

(R) enantiomer 3-chloro-1-phenylpropyl acetate, a precursor of Prozac is not yet available in the market, however, a big market for this precursor is expected to develop due to its medical and economical potential (chapter 1). It can be seen from the economic analysis (chapter 11) that total capital investment of this plant is 5.20 million guilders (2.36 million euros), and the rate of return is 90.3% with pay out time is equal to 1.1 year. In term of rate of return and pay out time, this project is very promising. It is believed that the product of the plant in the design will be able to compete in the market of Prozac and its precursors since the market of this antidepressant is expected to be very competitive after the patent protection on Prozac of Eli Lilly expires in 2003. Hence, it can be concluded that this plant is very potentially and economically feasible to implement.

Reliability of the design

The process can be considered robust and reliable because appropriate controllers are designed to maintain the desired process conditions (chapter6). However some deviations might occur during operation since perfect operation can be rarely achieved. From Hazard and Operability Study (HAZOP) analysis, checking valves and controllers regularly is recommended to ensure that the process is running safely.

Recommendation and suggestions

- Research on rate of reaction is recommended in order to validate the assumptions of first kinetic order (refer to part 2.4, chapter 2). Once the exact order of reaction is known, it will affect the heat balance in the reactor and consequently the required utility (cooling water and steam) in the reactor.
- As shown in chapter 11 (part 11.3.1 of raw material costs), the price of catalyst is the most expensive among other materials. Finding cheaper catalysts with the same performance as lanthanum isopropoxide could be an interesting research topic.

- Since the final product is one of pharmaceutical ingredients, hence the attention should be taken in complying with Good Manufacturing Practices. Even since the first stage of approval of the project, the development and implementation of Good Manufacturing Practice should be put into action.
- Toluene is used as a solvent in large amount. Since this material is considered dangerously flammable, appropriate instructions should be provided for workers handling this material.