



In Plant Training Report

Zydus Cadila



INDUSTRIAL INTERNSHIP REPORT

Zydus Dedicated to Life

Pharmaceutical Plant

B Tech (Pharmaceuticals Chemistry and Technology)

Batch: 2019-2023

Submitted By

Pratham K Lotia (19PHT110)

Submitted To

Institute of Chemical Technology, Mumbai

Internship Institution: Zydus Lifesciences Ltd./Cadila Healthcare Ltd.

Internship Period: 2nd May - 31st July 2022

Date Of Report Submission: 20th August 2022

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Acceptance Letter



Zydus Lifesciences Limited
(Formerly known as Cadila Healthcare Ltd.)



Date: May 02, 2022

To,
Internship Coordinator
The Principal / the Placement Coordinator/ H.O.D. | Institute Of Chemical Technology.
Reference: Industrial Training dated

Subject: Permission Letter

Dear Sir/Madam

We thank you for showing interest in our organization. We are in receipt of your letter requesting us to accommodate Mr. Pratham Lotia, student of Institute Of Chemical Technology, studying in B.Tech (Pharmaceutical Chemistry & Technology) branch of your good college to undergo vocational training in Process Engineering Department of our organization, commencing from May 02nd, 2022 to July 30th, 2022. For the said matter, we are glad to confirm the internship.

Further to this, we on behalf of the organization, specify that the students have to adhere to the following Do's & Don'ts while entering the company premises:

- During the training period no compensation/lodging/boarding facilities shall be provided.
- He has to mark his attendance at the security gate before entering the premises.
- He will not be allowed to carry any electronic gadgets like Pen drive, CDs, Mobile, Laptop, etc. inside the company or out from the company without prior permission from the concerned authorities. Also he shall not disclose or divulge any information that is concerned with the technical process/patents/transactions/financial/personal affairs of the company without the consent of the company.
- He will have to strictly follow the safety rules while entering the manufacturing site. Entering the manufacturing site would be his responsibility and the company will not be liable for any legal compliance thereof.
- He shall be bound by the decision of the company in regard to publications written or any work done with which he may be associated.
- At any point of time, if he is found dishonest/disobedient/intemperate/irregular in attendance, the company will be entitled to take strict action or even terminate his training with the company.

We are sure this training shall be of immense professional value to his first-hand exposure from the actual functioning of the organization.

We wish him all the success in his future endeavors.

For - M/s. Zydus Lifesciences LTD,


Jigneshsinh Gohil
Manager – Human Resources

API Division (Ankleswar - Unit 2) : Plot No. 5/1-B, G.I.D.C. of Ankleshwar, Taluka : Ankleshwar - 393 002, District : Bharuch, Gujarat, India

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Phone : +91-079-71800000, +91-079-48040000 www.zyduscadila.com CIN : L24230GJ1995PLC025878

Internship Certificate



Date: 05/08/2022

TO WHOMSOEVER IT MAY CONCERN

This is to certify that Mr. Pratham Lotia student of the **B.Tech (Pharmaceuticals Chemistry & Technology)**, Institute Of Chemical Technology, has completed his industrial training at our organization in **Process Engineering / Process Development Lab** from **02/05/2022 to 30/07/2022**.

During the course of **industrial training**, we found his conduct **Satisfactory**.

We wish him all the success in his career.

Zydus Lifesciences Limited
(Formerly known as Cadila Healthcare Limited)



05/08/2022

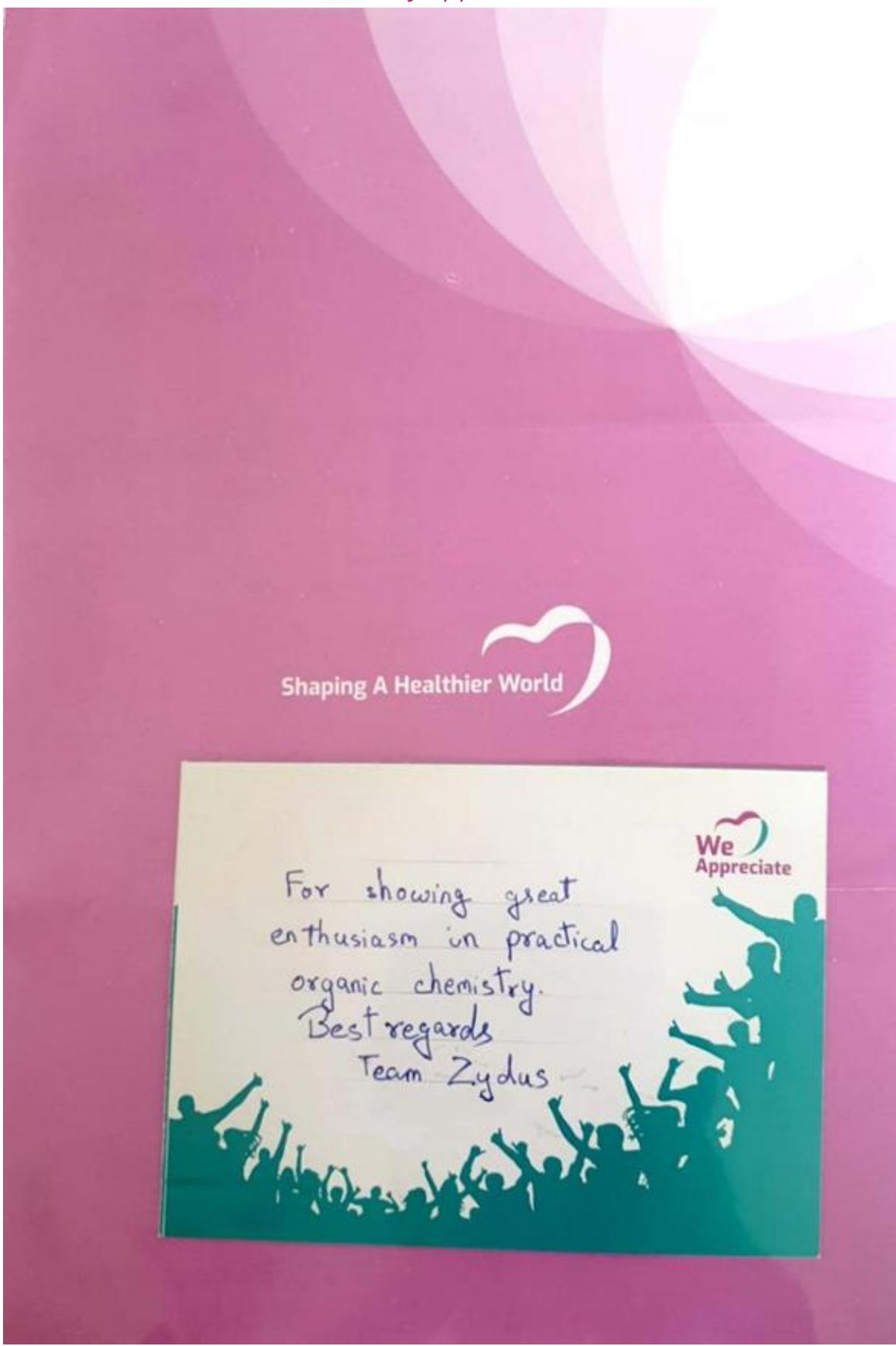
Human Resources

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website : www.zyduslife.com | CIN : L24230GJ1995PLC025878



Token of appreciation



Acknowledgements

Industrial Training – a vital part of the engineering curriculum provides engineers with a chance to work with cutting edge technologies and gives them knowledge of the practical aspects of their studies. I am immensely indebted to ZYDUS CADILA family for the invaluable help that they have rendered at every step of this training to achieve this goal.

We express our deep sense of gratitude to MR JIGNESH GOHIL for giving me permission for industrial training of the CADILA HEALTHCARE LTD.UNIT 1.

It gives me great pleasure to have completed my training at ZYDUS CADILA HEALTHCARE LTD. at Ankleshwar, and we are submitting the training report for the same.

My sincere thanks to the head of the department of process engineering, production and process development lab as mentors during training programs at CADILA HEALTHCARE LTD. Ankleshwar and for continuously guiding us throughout the various aspects, functioning and processes of the plant and their effective coordination in terms of allotting us the appropriate schedule to undertake the training.

Lastly, I am also thankful to all the staff members of the plant for their kind cooperation and valuable guidance throughout the process of work.

Introduction to the company

VISION AND MISSION: -

Zydus shall be a leading global Healthcare provider with a robust product pipeline; opening up new pathways through innovation and quality excellence, we shall be at research-based company by 2021-22.

Zydus Cadila is dedicated to life, in all its dimensions our world is shaped by a passion for innovation, commitment to partners and concern for people in an effort to create healthier communities globally.

THE BRAND: -

Zydus Cadila, a leading Indian Pharmaceutical company is a fully integrated, global healthcare provider. With in-depth domain expertise in the field of healthcare, it has strong capabilities across the spectrum of the pharmaceutical value chain. From formulations to active pharmaceutical ingredients and animal healthcare products to wellness products, Zydus has earned a reputation amongst Indian pharmaceutical companies for providing comprehensive and complete healthcare solutions.

One of the salient features of Zydus is its rich history and lineage. The origin of the company dates all the way back to the 1950s. The company was founded in the year 1952 by Mr. Raman Bhai B. Patel (late), a first-generation entrepreneur and a doyen in the field of Indian Pharmaceuticals.

In 1995, the group was restructured and thus was formed Cadila Healthcare under the aegis of the Zydus group. From a humble turnover Rs. 250 crores in 1995 the group witnessed a significant financial growth and registered a turnover of over Rs. 15,000crores in FY-21.

Adhering to its brand promise of being dedicated to life in all its dimensions, Zydus continues to innovate with an unwavering focus to address the unmet healthcare needs. Simultaneously it rededicates itself to its mission of creating healthier, happier communities across the globe.

IN THE COMMUNITY: -

Good health, happiness, joy, growth, togetherness, discovery, learning, exploration, evolution, transformation, aspirations, are all intrinsically linked with life. Zydus is dedicated to all these dimensions. Zydus Srishti, the group's CSR program, is about reaching out to make a difference in a myriad way in the areas of Health - Swasthya, Education - Shiksha, Research - Shodh and Outreach - Saath. Through these initiatives, the group reaches out to the community that it forms a part of, finding new expressions for its mission to create healthier communities globally. The group has forged meaningful partnerships with its key stakeholders both internal and external, partners in progress and the community at large. Ethical practices, accountability, robust governance and sustainable initiatives are at the very core of the group's business strategy, planning and operations which helps minimize risks and leverage opportunities to create value. The group's philosophy for community engagement is based on the principle of volunteerism and is an intensive, comprehensive and sustainable program.

AWARDS: -

The Overall India Pharma Excellence Award and the India Pharma Innovation of the Year Award from the Department of Pharmaceuticals, Government of India.

The CII Industrial Innovation Grand Jury Award of being the Most Innovative Company of the Year Declared the most Innovative Pharmaceutical Company by Thomson Reuters. Amongst the top 3 finalists at the Time India Awards 2017 in the 'Global Manufacturer for the Year" category.

Amongst the top five companies worldwide at the FT Arcelor Mittal Boldness in Business Awards 2014 in the Developing Markets category.

Declared as the "Emerging Company of the Year by the Economic Times Awards for Corporate Excellence 2010.

THE COMPANY: -

Driven by creativity and innovation, we strive for excellence and to make a difference in the world of pharmaceuticals and healthcare.

Abbreviations

SS-Stainless Steel

AL-Aluminium

SSR-Stainless steel Reactor

GLR-Glass lined Reactor

kg-Kilogram

GC-General cleaning

BBC-Batch to Batch Cleaning

QC-Quality Control

QA-Quantity Assurance

L-Length

KG-kilogram

PC-Personal Cleaning

BMR-Batch Manufacturing Record

EMR-Electronic Manufacturing Record

HDPE-High Density Polyethylene

ANFD-Agitated Nutsche Filter Dryer

R- Reactor, Reciever

SPF-Sparkler Filter

mm-Millimetre

DL-dry level

IL-initial level

CFG-Centrifuge

MEK-methyl ethyl ketone

MDC- Methyl Dichloride

ATN-Addition Tank

CTN-Charging Tank
ML-mother liquor
KL-kilolitre
MFG-manufacturing general
ATFD- Agitated thin film dryer
M-Meter
L-Litre
MEE- Multiple Effective Evaporator
ETP- Effluent Treatment Plant
SRP-Solvent Recovery Plant
RCVD- Roto-cone Vacuum type dryer
FBD-Fluidized Bed Dryer
STD-Steam Tray Dryer
ANF-Agitated Nutsche Filter
MTF-Multi Tubular Filter
SOP-Standard Operating Procedure
PCC-Product Change to Cleaning
min-Minute
SEC-Second
VL-vapour line
PL-Pressure line
SCT-Solvent Collection Tank
HWL-Hot-Water Line
CWL-Cooling-Water line
BWL-Brine-Water line
DL-Dumping line

IPA-isopropyl Alcohol

cm-centimetre

cP- centipoise

hr-Hour

K-Kelvin

RO-Reverse Osmosis

RM-Raw material

RPM-Rotation per minute

Th in- Hot water inside Temperature

Th out- Hot water outside Temperature

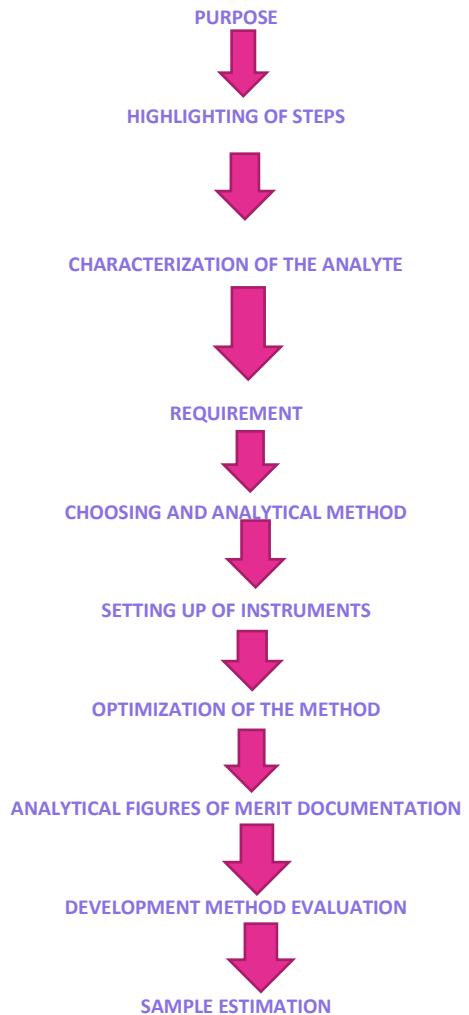
Tc in- Cold water inside Temperature

Tc out- Cold water outside Temperature

CP-Control Panel

INTRODUCTION

1.1 Steps involved in pharmaceutical Industry-



PIPE COLOUR AND CODE: -

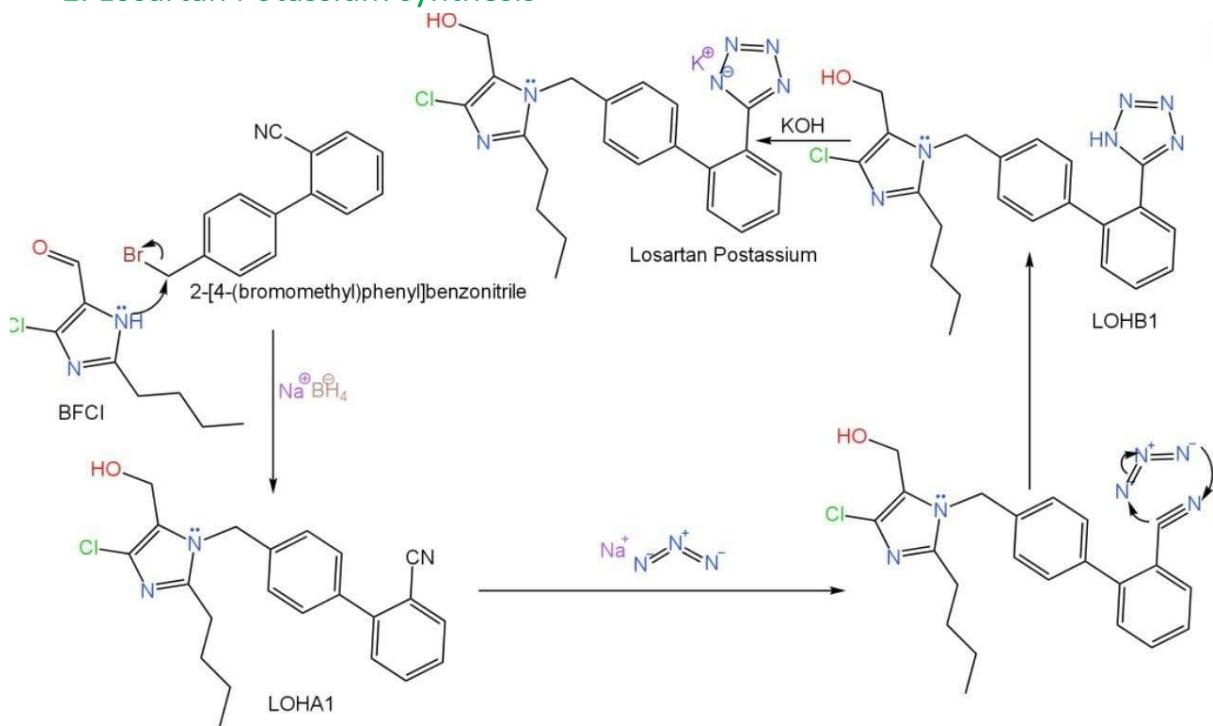
| PIPE COTENTS NAME | PIPE LINE COLOUR |
|---------------------|---|
| ➢ Portable water | Sea Green + 1 st band blue |
| ➢ Cooling water in | Light Green |
| ➢ Cooling water out | Dark Green |
| ➢ Steam | Aluminium + 1 st band black |
| ➢ Brine water | SS AL CLADDING + 1 ST band brown black |
| ➢ Chilled water | SS AL cladding + 1 st band black |
| ➢ Air | Sky blue |
| ➢ Vacuum | White |
| ➢ Nitrogen gas | Yellow + 1 st band black |
| ➢ Natural gas | Yellow |
| ➢ Fire hydrate | Red |
| ➢ Hot water | SS AL cladding + 1 st band dark violet |
| ➢ Hot oil | SS AL cladding + 1 st band orange |

Process and Reaction equipments

Process General Definition: - It is a series of action or steps taken in order to achieve a particular end.

RAW MATERIALS AND PRODUCTS: -

1. Losartan Potassium synthesis



Raw Materials: -

A) Stage 1: - Synthesis of LOHA1

- 1) BFCI (2, Butyl 4-chloro 5 formyl imidazole) $315\text{kg} = 315/171.604 \text{ kmol} = 1.83\text{kmol}$
- 2) NaOH for assisting in Nucleophilic attack (Sodium Hydroxide flakes) 74.16kg
- 3) Recovered Toluene 3000L
- 4) 2 Cyano,4 Benzyl Bromide Biphenyl $468\text{kg} = 468/272.15 \text{ kmol} = 1.72\text{kmol}$ (limiting)
- 5) Methanol 630L
- 6) Sodium Borohydride as reducing agent 25.6kg
- 7) Tetra Butyl Ammonium Bromide (TBAB) as Phase Transfer Catalyst 12.6kg
- 8) Potable Water 1845L

Theoretical Yield: 653.41kg; Practical yield: 597-604kg

B) Stage 2: - Synthesis of LOHB1

- 1) LOHA1 140kg=0.36853kmol (Limiting)
- 2) Sparkler filter with 32 meshes
- 3) Potable Water 60L
- 4) N-Methyl-2-Pyrollidone (NMP) Easily dissolves LOHA1 as well as miscible in water
- 5) TEA-HCl (Triethylamine Hydrochloride) Solubilizer
- 6) NaN₃ 59.9kg=0.9216kmol 
- 7) NaOH (Sodium Hydroxide) pH adjustment
- 8) Toluene as solvent
- 9) DCM (Dichloromethane) as solvent
- 10) Sodium Metabisulphite (Na₂S₂O₅) as antioxidant
- 11) Sodium Hydrosulphite as a synergizing compound to Na₂S₂O₅ and a decolourizer along with activated charcoal
- 12) Activated Charcoal as decolourising agent
- 13) AA (Acetic Acid) as a pH adjuster
- 14) Ethyl Acetate as a pH buffer
- 15) TPP (Triphenyl Phosphine) used in order to aid the nucleophilic attack
- 16) Methanol as solvent
- 17) Water as solvent

Theoretical Yield: 155.86kg; Practical Yield: 132-137kg

C) Stage 3: - Synthesis of Losartan Potassium by salt formation

- 1) LOHB1
- 2) KOH

Reaction quantity and ingredients not specified as it's a trade secret.

Losartan Potassium Reaction Stages: -

Stage 1: - Nucleophilic attack of nitrogen within imidazole ring (BFCI) to give nucleophilic addition product; reduction of formaldehyde by NaBH₄.

NaBH₄ is added step by step to reduce heat

Stage 2: - Sodium azide addition over the nitrile group for ring annulation

**Stage 3: - Potassium Base addition to give us the final product .It's
Operating Temperature is 90-110°Celsius.**

List of each equipment used: -

| NAME | MOC | CAPACITY(L) | AGITATOR TYPE |
|-------------------------------|-------|-------------------|-------------------|
| Glass line Reactor (GLR) | MSGL | 500,1600 | Anchor, Propeller |
| Stainless Steel Reactor (SSR) | SS316 | 1000,2000,2500 | Anchor, Hydrofoil |
| Sparkler Filter | SS316 | 18 inch 16 plates | NA |
| Stainless Steel Centrifuge | SS316 | 48 inch 36 inch | NA |
| Steam Tray Dryer | SS316 | 48 trays | NA |
| Receiver | SS316 | 500,1000,1500 | NA |
| ANFD | SS316 | 2000 | Propeller |

Procedure: -

- 1) Charge NaOH in reactor within temperature range of 25-40°C**
- 2) stir the reaction mass within a definite temperature.**
- 3) cool the reaction mass within 25-35°C**
- 4) charge std BFCI reaction at some quantity and then rinse reactor at some temperature range.**
- 5) Stir reaction mass in reactor for 30 min up to a certain temperature.**
- 6) Charge toluene mass for some min in reactor within temperature of 25-35°C**

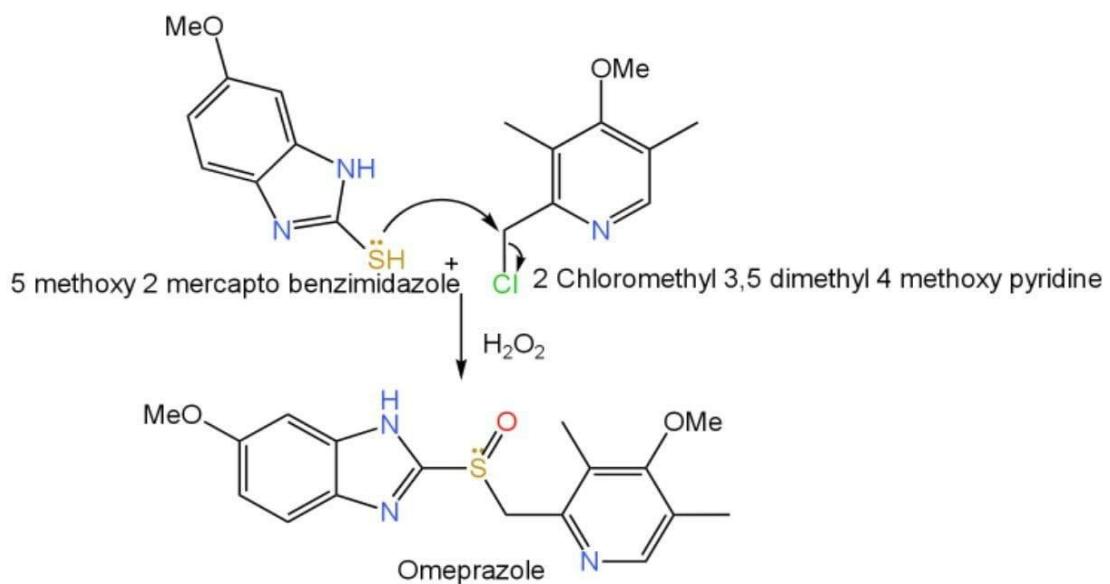
- 7) Hold material charging act in reactor for minimum 15 min to dissipate the static charge after solvent charging
- 8) Charge TBAB within some temperature range
- 9) Stir the reaction mass for some min in a reactor at a definite temperature range.
- 10) Charge toluene into reactor.
- 11) Hold the material charging act to dissipated static charge after solvent charging.
- 12) Charge some standard quantity of 2 cyano 4 benzyl bromide biphenyl in reactor at some temperature range
- 13) Heat the reaction mass by circulating the hot water.
- 14) Stir and maintain reaction mass in reactor within temperature range and record temperature at every time interval
- 15) Stop the stirrer of the reactor and allow the layer to settle within some temperature range
- 16) Separate lower aqueous layer from reactor to effluent tank maintaining a definite temperature range
- 17) Charge methanol of some quantity and portable water into reactor under stirring.
- 18) Charge sodium borohydride std quantity with ss scoop into reactor under stirring.
- 19) Stir for some minute within a temperature range.
- 20) Cool reaction mass up to a definite temperature range.
- 21) Charge some quantity with ss scoop into reactor under stirrer.
- 22) close the valve of nitrogen line(N2).
- 23) Heat the reaction mass using steam under some temperature range.
- 24) Stir and maintain the reaction mass for some minute in reactor within some temperature range and record temperature for every min interval.



25) Then our feed goes to ANFD where by giving vacuum and pressing feed the feed is cutting and drying until the mother liquor (ML) comes out.

In this way, our product, losartan potassium is made.

2. Omeprazole synthesis



Raw Materials: -**Stage 1: - Synthesis of Omeprazole**

- 1)2-chloromethyl-3,5-dimethyl-4-methoxy Pyridine HCl 425kg=2.2893kmol
- 2)5-methoxy-2-mercaptop-benzimidazole 344.9kg=1.914kmol (Limiting)
- 3)Caustic Soda flakes for pH adjustment (263.2kg)
- 4)50% Hydrogen Peroxide as oxidising agent (156kg)
- 5)Activated charcoal as a decolourant (10.6kg)
- 6)Methanol as a solvent (2006L)
- 7)Acetic acid for pH adjustment (167L)
- 8)Sodium Molybdate as a catalyst (2.6kg)
- 9)Sodium Thiosulphate (34kg) < 15°C after addition
- 10)MDC (Methylene Dichloride) (319kg)
- 11)Potable water (5296L)

Theoretical yield: 661.38kg; Practical Yield: 564-581kg

Omeprazole Reaction Stage: -

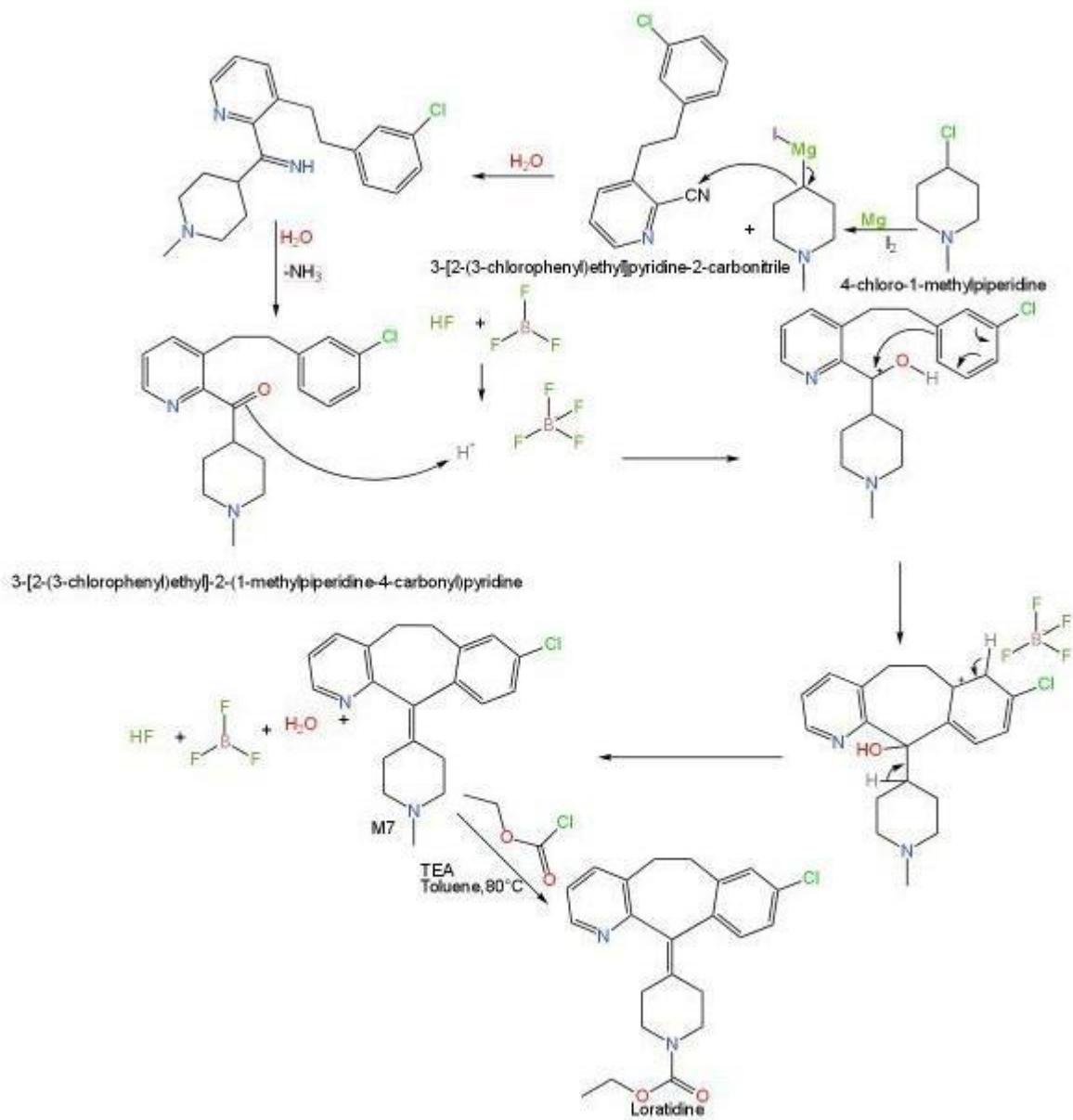
Nucleophilic attack of sulphur from the thiol group over methylene chloride of the pyridine moiety. Followed by oxidation of thioester group with the help of H₂O₂.

Procedure: -

- 1) Initially, Caustic soda flakes are charged manually (eyes are covered with protective eye wear while charging NaOH) along with MeOH. After MeOH charging, proper earthing is applied to dissipate any static charge present. Even while charging, earthing must be present along with N₂ purging
- 2) 5 methoxy 2 mercapto benzimidazole addition is endothermic. While adding it, if temperature falls below 25°C then the mixture inside the reactor will turn into a solid slurry. So temperature must be kept between 30-40°C. If it crosses 30°C then hot water from the utility must immediately be supplied to the jacket of the reactor and RM supply must simultaneously and immediately be demurred.

- 3) Following this, addition of 2-chloromethyl-3,5-dimethyl-4-methoxy pyridine, which is exothermic in nature, is carried out. It's carried out in parts to avoid temperature increment above 35°C as if it crosses this threshold, N-alkylated by-products start forming.
- 4) After a healthy amount of time dedicated to homogenous mixing, TLC tests are performed to calculate % unreacted pyridine moiety. If less than 1%, the test passes and the batch is ready for further process. If not, then the batch is further agitated and at regular intervals, QC tests are conducted unless the batch passes the test.
- 5) The batch is further centrifuged and MeOH washing is given while centrifuging. ML (Mothe Liquor) is removed and the wet cake is lifted by LBD system to reactor. pH is adjusted with the help of acetic acid in a glass pot for the product to be between 7.8 – 8.2 for H₂O₂ addition.
- 6) The mixture is cooled by brine/dry ice between -3°C to 3°C
- 7) Furthermore, if the mixture is not clear, then it is heated back to 35-40°C and then cooled slowly.
- 8) After maintaining temperature, first sodium molybdate is added in an addition tank along with water, this allows sodium molybdate to dissolve in water and then add to the mixture. Addition only takes place after the catalyst is completely dissolved. One might be in a shock to compare the amount of catalyst to the amount of product being formed.
- 9) MDC is added for dissolving any organic impurity and then layer separation takes place.

3. Loratadine synthesis:



Raw materials: -

Stage 1: - Grignard reaction

- 1) 3-(3-chlorophenyl ethyl)-2-cyanopyridine (M5) 100kg=0.412kmol (Limiting)
- 2) THF from BASF as a solvent (fresh/recovered) (504L)
- 3) Toluene (920L)
- 4) N-methyl-4-chloro piperidine 97.88kg=0.733kmol

- 5) Magnesium turnings for Grignard reaction (16.73kg)
- 6) I₂ (3kg)
- 7) HCl (200L)
- 8) Caustic Soda Flakes (13.33kg)
- 9) Ethylene Dibromide as a catalyst for synthesizing Grignard reagent and reducing by-products (1L)
- 10) Potable water (933L)
- 11) N₂ gas

Product formed: M6

Theoretical Yield: 141.263kg; Practical Yield: 123.5-125kg

Stage 2: - Ring Annulation with the help of Super Acids

- 1) HF
- 2) BF₃
- 3) M6

HF/ BF₃ is utilised at a concentration of 92%. This gas passes through PTFE pipes. As stage 2 was at a hydrogenation plant, interns are not authorized to visit such plants due to safety concerns.

Stage 3: - Ethyl Chloroformate addition

- 1) M7 1797kg=5.532kmol
- 2) Toluene (100L)
- 3) Hyflow Supercell 24L
- 4) Ethyl Chloroformate 110kg=1.014kmol (Limiting)
- 5) TEA (220mL) as a catalyst in this case
- 6) Toluene (720L)
- 7) NaCl IP (200kg) as a buffer
- 8) Sodium bicarbonate as the main buffer (50kg)
- 9) Activated Charcoal (10kg)
- 10) Acetonitrile (421L)

11)Potable water (11798L)

12)Methanol (30L)

Loratadine Reaction stages: -

Stage 1: - The first stage is nothing more than a known Grignard reaction. Here, the Grignard reagent is synthesized by adding Mg along with I₂ and Ethylene Dibromide to the piperidine moiety. A salient feature of this stage is the use of Ethylene Dibromide at a minimal quantity for aiding the Grignard reaction.

Stage 2: - The mechanism of the second stage is quite vivid from regular literature as it applies super acids, a method proposed by Prof. G. D. Yadav, Ex-Vice Chancellor of ICT, a college that I am proud to attend. Advantage is taken by the difference in electronegativities of Hydrogen and Fluorine allowing BF₃, a Lewis acid, to isolate the proton, in such a manner that by the laws of thermodynamics and kinetics, this proton is able to destabilise the benzene ring in such a way, that it allows annulation to take place also providing a sufficient yield simultaneously.

Stage 3: - In the 3rd stage, multiple reactions are happening at a single space, within a single reactor simultaneously. These reactions are, namely, demethylation, ethyl formylation, chlorination, acidification, acid dumping and neutralization. For all such reactions, a tremendous amount of water is required for obtaining a good quality of product as seen. TEA can be considered as a catalyst due to its tremendously less amount of usage. Its role is to dump any chlorinated by-product as it's a Lewis base. NaCl acts as a buffer, a neutralizer and so on, along with sodium bicarbonate, which enhances the capabilities of the former in this reaction.

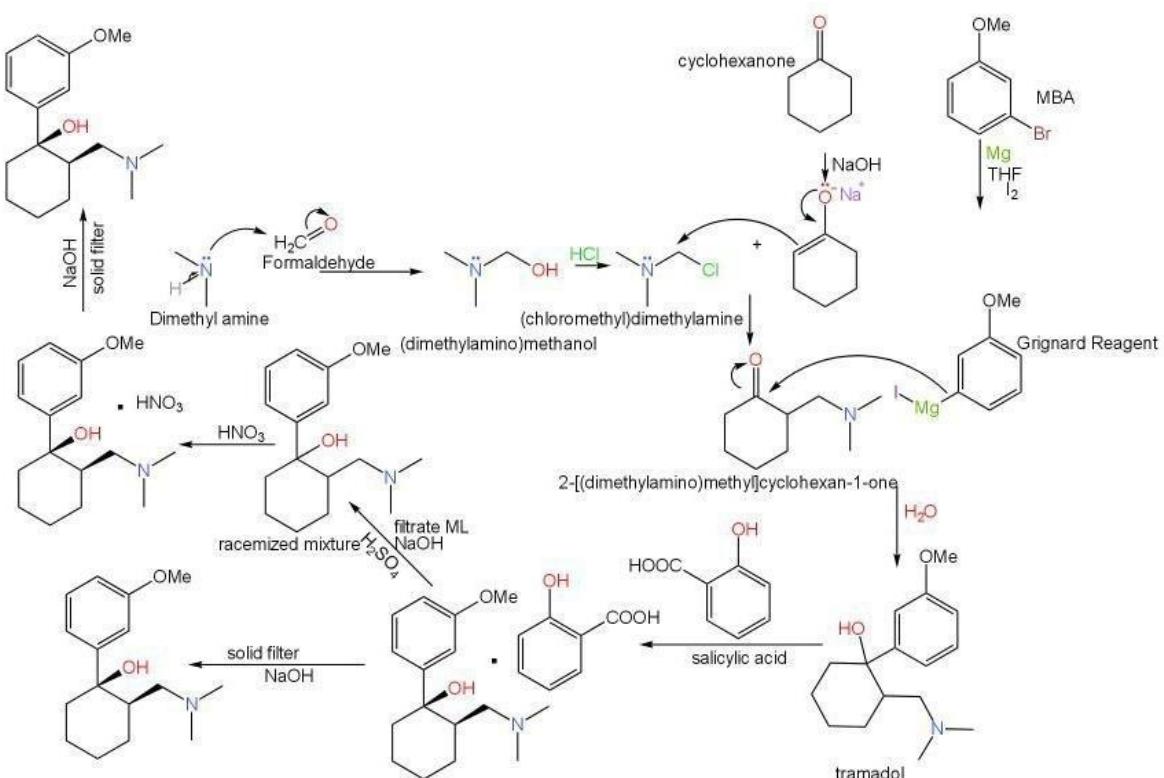
Procedure: -

- 1) Initially, the reactor is depressurised completely by providing vacuum. Later, Nitrogen is purged into this reactor. Again, vacuum is applied, but this time, half the initial negative pressure. This is done to ensure that the reactor is void of moisture, otherwise, in the presence of moisture, magnesium would get converted into magnesium hydroxide which does not help in synthesizing the Grignard reagent.
- 2) HF along with BF₃ is highly reactive and corrosive to human skin. It might easily corrode your skin and penetrate, further ionising your blood, hence, PTFE tubes are double coated to prevent leakage. After

every batch, they are checked for integrity and if faulty, they are replaced before the next batch.

- 3) The chloroformate moiety is quite reactive and hence, properly stored. Also, it is slowly added for the same reason.
- 4) Hyflow supercell along with activated charcoal are responsible for clearing any mottled colour appearing in the product. If the product remains black, i.e., some charcoal is still remaining and needs to be filtered.
- 5) Acetonitrile is fatal and hence, is added with a PPE kit.

4. Tramadol synthesis: -



Raw Materials: -

Stage 1: - Synthesis of Mannish Base

- 1) Cyclohexanone 380kg=3.878kmol
- 2) Potable Water (1695L)
- 3) Dimethyl amine HCl 315.63kg=3.872kmol
- 4) Paraformaldehyde 116.28kg=3.876kmol
- 5) Hydrochloric acid (36.5L)
- 6) Toluene (1710L)

- 7) Caustic Soda flakes (174.8kg)
- 8) NaCl (117.8kg)
- 9) Potable water (100L)

Theoretical Yield: 592.32kg; Practical yield: 480-498kg

Stage 2: - Synthesis of Tramadol Base (Racemised)

- 1) Mannish Base 216kg=1.412kmol
- 2) Potable water (100L)
- 3) THF (fresh/recovered) (1325L)
- 4) Magnesium Turning (40.65kg)
- 5) Iodine (2.34kg)
- 6) Meta Bromo Anisole 260.56kg=1.3931kmol (Limiting)

Theoretical Yield: 366.92kg; Practical yield: 288-311kg

Stage 3: - Synthesis of Tramadol Salicylate

- 1) Tramadol base 340kg=1.291kmol
- 2) Iso Propyl Alcohol (IPA) (6294L)
- 3) Salicylic acid 196.2kg=1.421kmol

Theoretical Yield: 518.3378kg; Practical yield: 496-512kg

Stage 4: - Resolution of Tramadol (along with second crop isolation)

- 1) NaOH
- 2) H₂SO₄
- 3) HNO₃
- 4) Racemic Tramadol
- 5) Toluene
- 6) HCl

No information is provided for this step as it is a trade secret

Tramadol Reaction Stages: -

Stage 1: - Dimethylamine attack carbonyl carbon of formaldehyde in an aqueous phase under basic conditions (caustic), after which, the mixture undergoes acid hydrolysis and chlorinates the hydroxy group. This provides us 1-(chloromethyl)-2,3-dimethylamine as the product. Cyclohexanone, on the other hand is dissolved in toluene under basic conditions.

Cyclohexanone, is then allowed to react with the amine where the alpha hydrogen of cyclohexanone is acidic and hence, under basic conditions, it leaves a lone pair, which conjugates with the double bond of the carbonyl group. This double bond further attacks the amine at the methylene chloride part, symbolising a nucleophilic addition reaction. Thus, Mannish Base is synthesized.

Stage 2: - Meta Bromo Anisole (MBA) is the key ingredients for synthesising the Grignard reagent. It is dissolved in THF. I₂ is added as Iodine is bulkier than Bromine and hence, it can easily form the Grignard reagent as it is a good leaving group. The Grignard reagent forms a phenyl anion, which is very reactive. This anion attacks the carbonyl group of Mannish Base to give a tertiary hydroxy group within the Tramadol Base.

Stage 3: - Synthesis of Tramadol Salicylate

The tramadol base has **2 chiral carbons**. Hence, a racemic base cannot be formulated. In order to obtain optical purity, Salicylic acid is added. Tramadol is a base, and as the name suggests, salicylic acid is an acid. By simple acid-base chemistry, a salt forms which is optically pure and precipitates out. The precipitated salt is acidified with HCl to provide Tramadol HCl. There is yet some amount of racemic tramadol base which is further isolated as ML and treated.

Stage 4: - Resolution of Tramadol (along with second crop isolation)

The racemised base is further treated with HNO₃ for the salt to precipitate out in the same way as with salicylic acid. This time, this optically pure salt is first isolated, followed by addition of caustic solution to isolate tramadol base in the aqueous solution and the salt NaNO₃ is precipitated out. This Tramadol is further treated with HCl to synthesize API of the second crop.

List of each equipment used: -

| Name | MOC | Capacity | Agitator Type | No. of equipment's |
|------------|-------|----------|------------------|--------------------|
| SSR | SS316 | 3KL | Tickler, Turbine | 4 |
| GLR | MSGL | 2KL | Anchor, Turbine | 2 |
| SSR | SS316 | 2KL | Pitch blade | 1 |
| Centrifuge | SS316 | 5KL | - | 2 |
| ANFD | SS316 | 5KL | propeller | 2 |

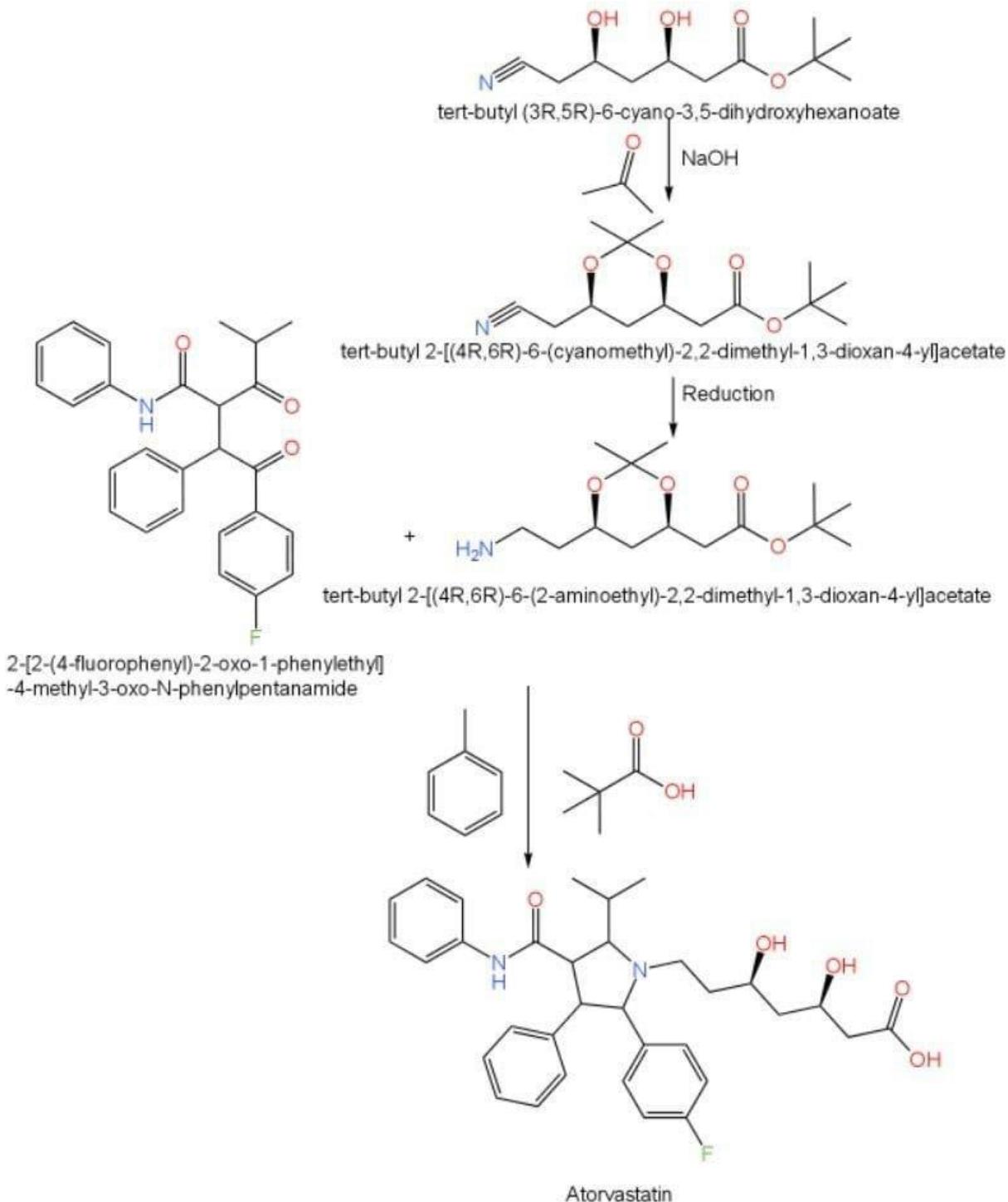
Procedure: -

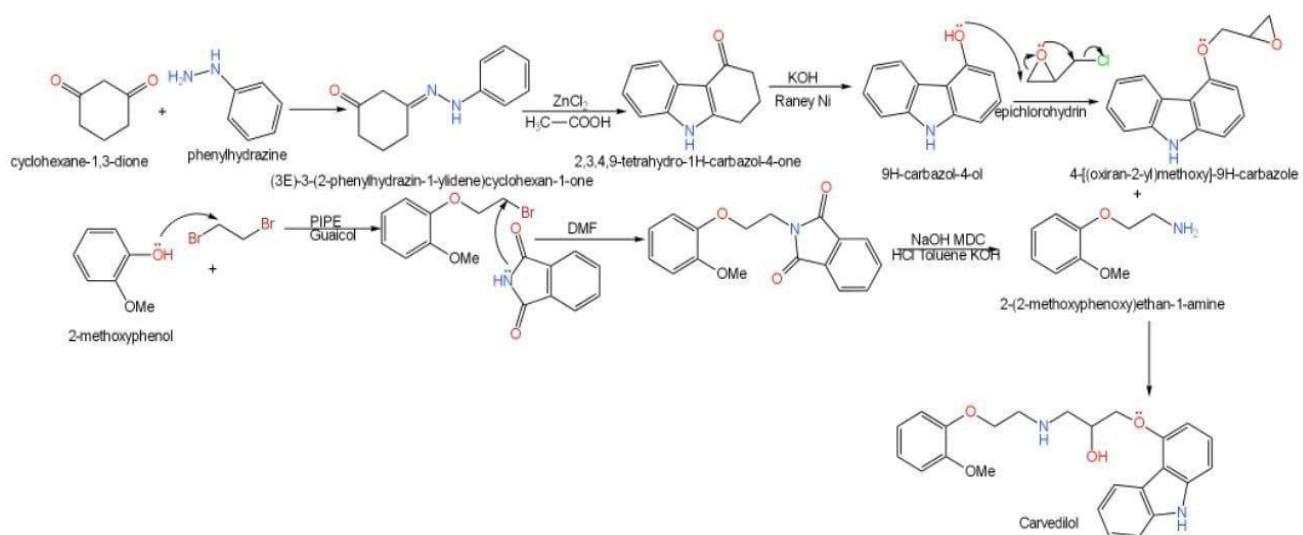
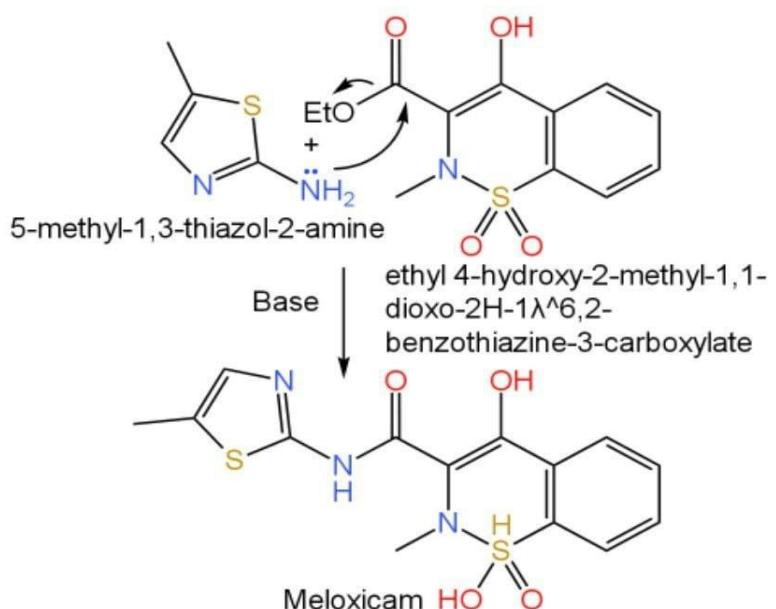
- 1) Before charging Paraformaldehyde, the reactor is purged with N₂ to prevent any oxygen present in the reactor from remaining, otherwise, while charging Paraformaldehyde, due to presence of static as well as oxygen, there are high chances of combustion.
- 2) After synthesizing 1-(chloromethyl)-2,3-dimethylamine, Toluene is added to this aqueous phase for solubilizing all organic impurities and by-products. After adding Toluene, layer separation takes place. Due to limited space of the reactor, toluene is added 3 times, each time after which layer separation takes place.
- 3) Toluene is charged into another reactor, followed by cyclohexanone charging. Finally, Caustic soda flakes are charged which increase the reactor temperature. To counter this, brine is circulated through the reactor jacket after caustic charging.
- 4) After layer separations, the aqueous phase containing 1-(chloromethyl)-2,3-dimethylamine is dumped into the organic phase containing cyclohexanone. The ionic nature of caustic cyclohexanone allows it to react with the amine in the aqueous phase.
- 5) For the reaction to provide us a sufficient yield of Mannish Base, temperature must be increased to 80-85°C. In order to obtain this, steam is continuously applied in the jacket until temperature reaches 67°C, and then the vessel is left for 5-10 minutes within which the desired temperature is achieved. If temperature does not increase due to exotherm., steam is reapplied till it reaches 80-85°C and then, temperature is controlled by cooling.
- 6) Now, we have our desired Mannish base in a biphasic system. Due to the hexane moiety present in it, it dissolves in the organic phase. Hence, layer separation takes place by first adding Potable water, and then isolating the organic phase. This happens twice to get rid of the aqueous impurities and by-products present.
- 7) A fresh reactor is taken for the next stage. First, vacuum is applied for half an hour to get -740mm Hg, followed by nitrogen purging to obtain a pressure up to 1.75kg/m². Nitrogen is released after this, to carry away remaining oxygen or moisture along with it. Magnesium turnings (breath=0.5cm, strips of Magnesium, one side smooth and the other side rough) are added to the reactor after this.

- 8) An addition tank is connected to the reactor. Within this tank, first THF is charged, followed by I₂ and lastly MBA. Once the addition tank is filled, a waiting period of 2 hrs is observed for the material within it to get solubilized into a single solution. After this, slow addition takes place along with agitation for 20-22hrs for the Grignard reagent to form.
- 9) Mannish base is added to the Grignard reagent to synthesize Tramadol base. This takes 2 days straight for a sufficient yield to form. After 2 days, due to presence of potable water and Magnesium salts, a biphasic layer is formed in which Tramadol base is in the organic phase. Hence, layer separation is carried out and the aqueous layer is dumped into a reactor containing NH₄Cl+H₂O in order to treat and dispose Magnesium salts properly.
- 10) THF along with Tramadol is present in the organic phase. THF is distilled out to obtain a racemic Tramadol Base.
- 11) This racemic mixture is dissolved in IPA to which salicylic acid is added. Most of the Tramadol Base forms an optically pure salt which precipitates. This mixture is further centrifuged to obtain the salt. The remaining ML is collected for the next stage. The salt is treated with concentrated HCl for synthesizing the API along with isolation of salicylic acid. (HCl is a stronger acid than salicylic acid)
- 12) The racemic ML is treated with concentrated HNO₃ to again form a salt. As a part of the second crop isolation, this salt is isolated, treated with caustic to form Tramadol Base and NaNO₃, of which the base is isolated and treated with HCl to synthesize API.

Some More APIs along with Routes of Synthesis:

Atorvastatin:



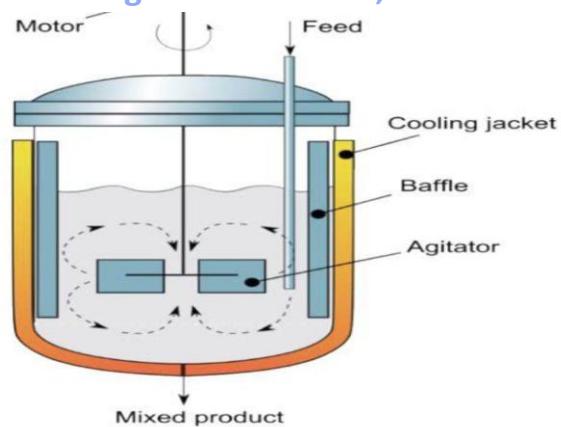
Carvedilol:**Meloxicam**

PROCESS ENGINEERING: -

1. Reaction Equipments: -

a) Batch Reactor

- A batch reactor is the simplest type of reactor vessels used for chemical or industrial processes.
- A typical batch reactor consists of a tank where chemical reactions occur.
- These tanks also have an agitator and an internal heating or cooling system.
- Tank sizes range from 1L to 15,000 L.



b) Stainless Steel Batch Reactor: -

- It is also known as an inox steel or inox from French i.e. inoxidable is a steel alloy with a minimum of 10.5% chromium by mass.
- SSR are used for reaction in basic or neutral Ph.
- These reactors are preferred for distillation and better heating and cooling.



c) Glass-Lined Reactor: -

- The glass line equipment is a pressure vessel whose main body is made of high carbon steel is lined with special silicate glass by fitting at a high temperature.
- This Reactors are suitable for reaction in acidic or neutral pH.



2. Agitators: -

It is something which is used to stir liquid or mix the two liquids.

It is mainly used in multiple operations in pharma industry

It consists of three main components: -

- 1) Impellers.
- 2) Baffles.
- 3) Outlet valve.

In simple words we can say that it is a process of mixing the two mixtures in a proper mixed state.

Types of Agitators: -

- 1) Paddle Agitators.
- 2) Anchor Agitators.

Mostly, these two agitators are used in the reactor.

- a) Paddle Agitators
- b) Low stirring speeds (20 – 200 rpm)
- c) Length = 60-80% of tank diameter
- d) 2-bladed / 4-bladed
- e) Width = 1/10th to 1/6th of blade length
- f) Ineffective for suspending solids
- g) Sweeps tank walls and sometimes tank bottoms



b) Anchor Agitators

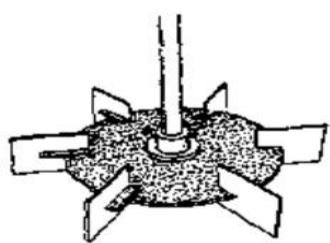
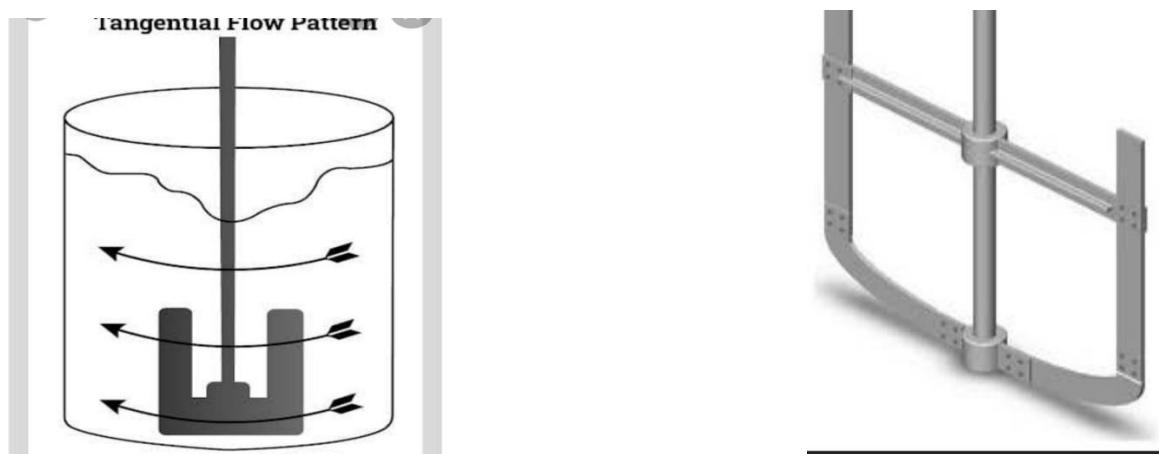
- It is a simple agitator which consists of a shaft and an anchor type propeller and can be mounted centrally or at an angle. It is mainly used in reactors.
- Application: - highly used in pharma industry for several operations (Mainly used in reactors).
- Pros: -

1) It increases possible heat transfer rate in reactors from reactor heat transfer surface to mass.

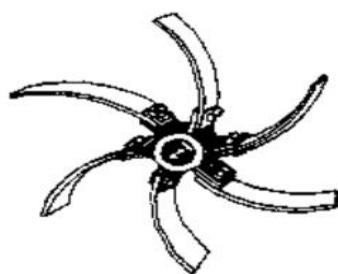
Cons: -

- 1) It required high power.
- 2) It required high efficiency gear box.
- 3) Agitator selection and viscosity ranges from $50 \text{ Pa.s} \leq \mu \leq 500 \text{ Pa.s}$ modified paddles such as Anchors / Gate
- 4) Flow patterns of Anchor Agitator is in tangential

Flow.



Disk Style Flat Blade Turbine
Commonly Referred to as
the Rushton Impeller



Sweptback or Curved Blade Turbine
(a Spiral Turbine)

3. Dryers: -

What is Drying?

- It is defined as the removal of small amounts of water or other liquid from a material by the application of heat.

It also includes removal of volatile liquids or water from another liquid or gas or a suspension, drying is possible when the environment is unsaturated with the water vapour.

Types of Dryers which are Available in Industry are as follows: -

- Steam Tray Dryer
- Fluidized Bed Dryer
- Roto-cone vacuum type Dryer

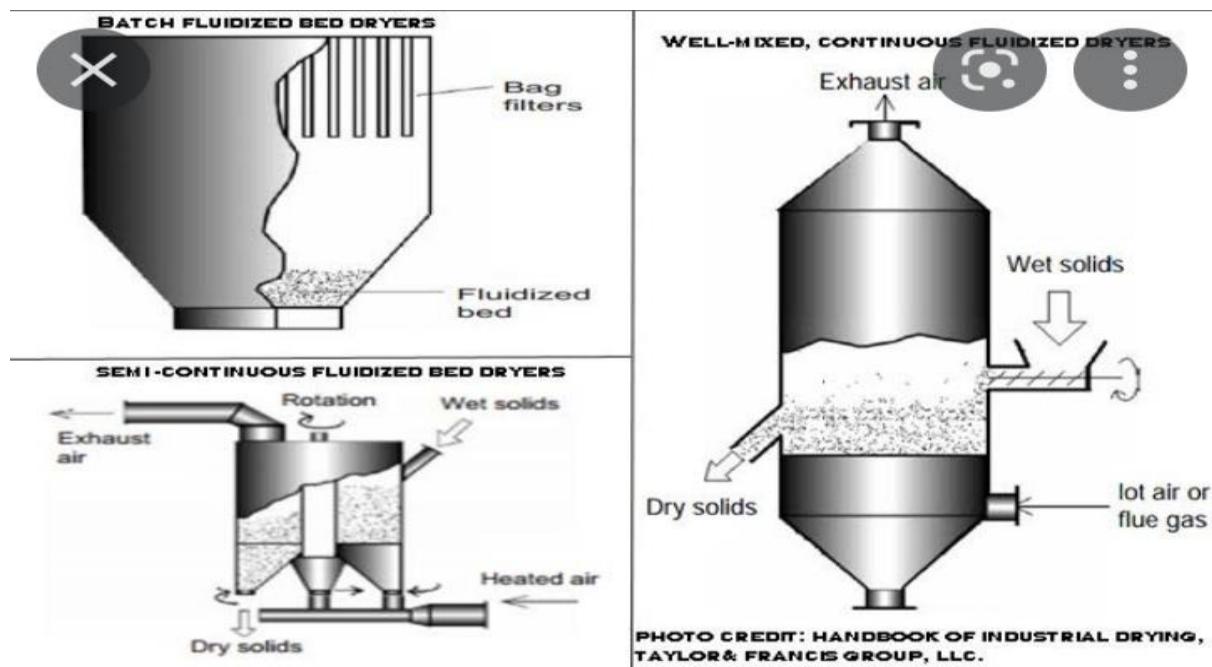
a) Steam Tray Dryer

- Tray dryer can be electrically heated, and Steam heated. Tray Dryer comes in 6 trays, 12 trays, 24 trays, 48 trays, 96 trays and 192 trays.
- The construction of the machine varies as per requirement of the customer, it can be inside outside MS or GMP model depending upon the product and industry requirement.
- Tray Dryer is the most conventional Dryer used very widely and still being used where the moisture content is more and where the product has to be dried at low temperature for long hours.



b) Fluidized Bed Dryer

- Good contact between the warm drying air and wet particles is found in fluidized bed drier.
- Principle of Fluidisation:- The particulate matter is contained in a vessel of which it is perforated, enabling a fluid to pass through the bed and increase gradually and the pressure drop through the bed is measured, the graph of the operation shows several distinct regions.



c) Roto-cone Vacuum Dryer

- It is a multipurpose drying unit which is extremely useful for uniform and low temperature drying of heat sensitive chemicals, pharmaceuticals, etc.
- It has a double conical vessel with rotating system and vacuum solvent recovery system.
- The dryer rotates at a very low speed (5-15 rpm) and thus it has a very low wear and tear and it requires very little maintenance.
- Here, loss of a material is very effective and controlled by a specially designed pilot filter fitted on vacuum side.



4. Filtration Equipment's: -

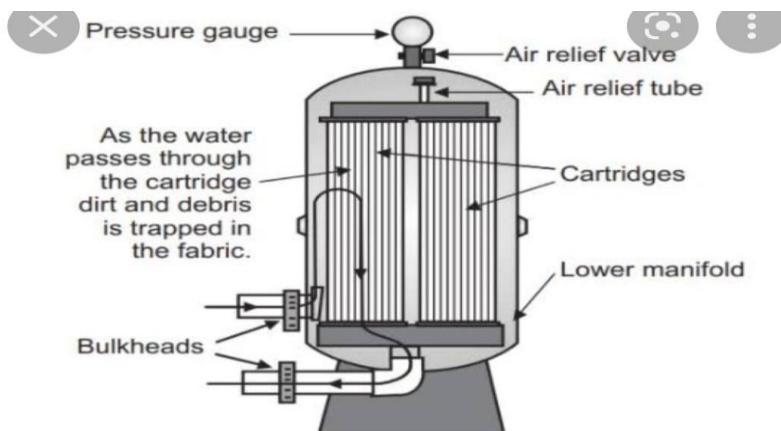
What is Filtration?

→ Filtration is a physical separation process that separates solid matter and fluid from a mixture using a *filter medium* that has a complex structure through which only the fluid can pass.

- **Types of Filtration methods that are used in industry are as follows: -**
- Cartridge filter
- Agitated Nutsche filter
- Sparkler filter
- Centrifuge

a) Cartridge filter

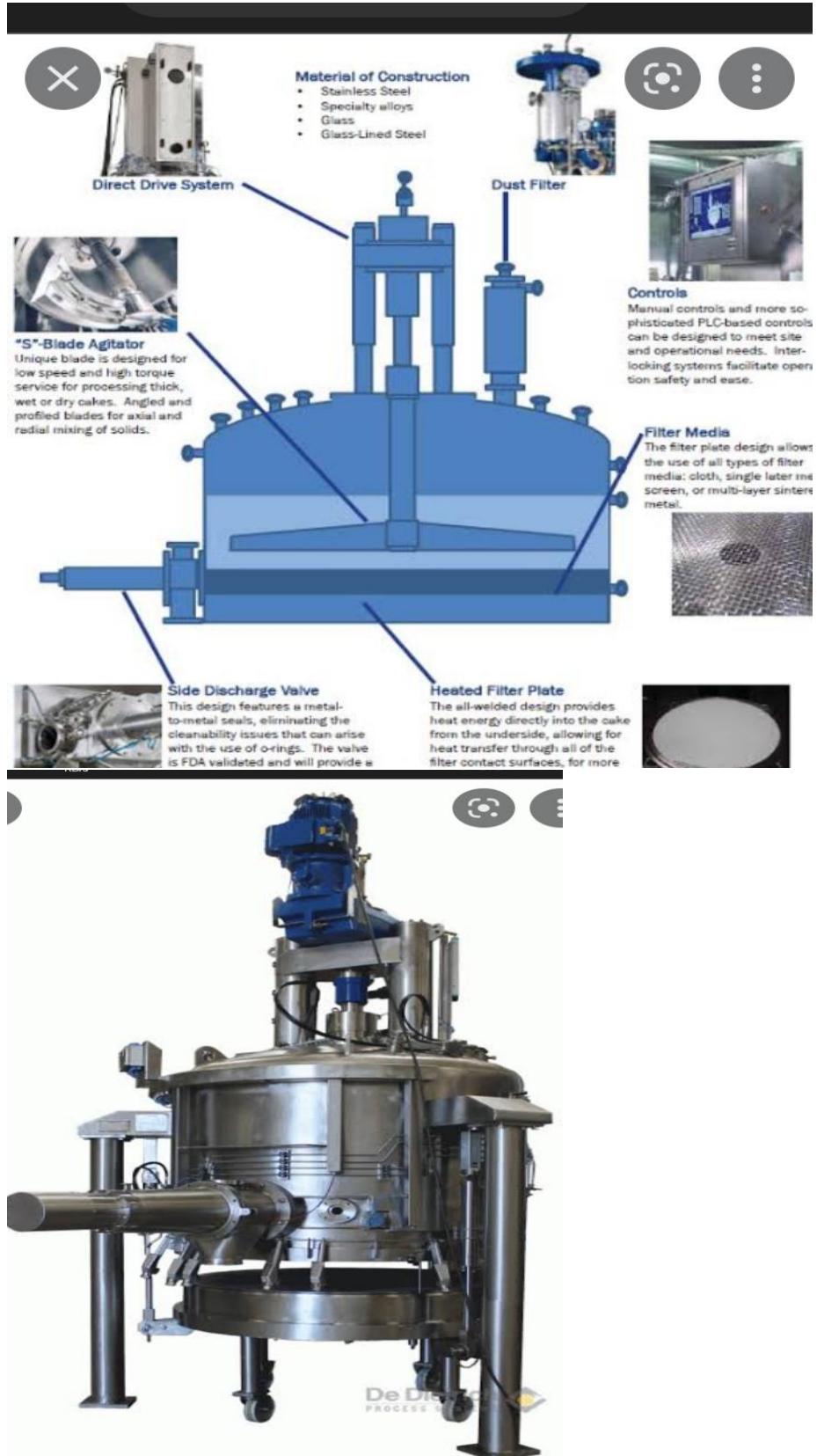
- It uses the filtration technology of removing the solid matter and suspended impurities from a fluid stream by passing it through a variety of microporous filter.
- These types of filters are actually made of a polyester or some other material that can provide a superfine filtering surface.
- The fabric catches and holds the impurities until you clean or replace the filter.
- The tight pleats or folds allow for a large amount of material to be used in a small container, the more material used the larger the surface area available to capture unwanted dirt or debris in the water.



b) Agitated Nutsche filter

- It is a closed vessel designed to separate solid and liquid by filtration under pressure or vacuum.
- It is extensively used in chemical, herbal, pharma industry.

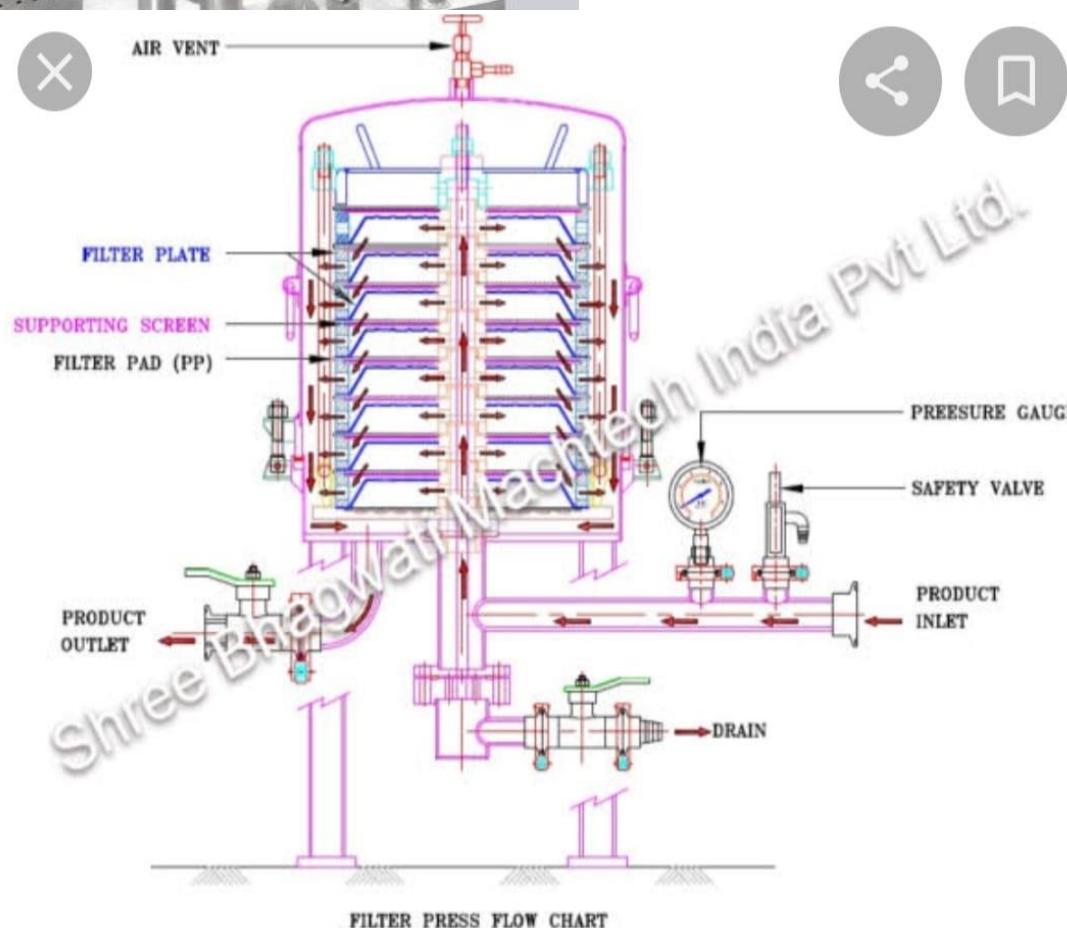
- It consists of a cylindrical shell with top dished and welded flat bottom.



- It works in both purpose as a filtration also and as a Dryer also.

c) Sparkler filter

- This type of filter is usually used for filtering a moderate quantity of suspended solids from the mixture.
- These filters are available from 4 plate to 22 plate in size with different plate diameter.
- Here, also external heating may be provided depending upon the process requirement.



d) Centrifuge

- It is a process of applying centrifugal force to separate the useful components in the mixtures of the solids and liquids.
- It is widely used in Chemical, oil, food, pharmaceutical industries.
- The principle of centrifuge is divided to centrifugal filtering and centrifugal sedimentation.



5. SIZE REDUCTION EQUIPMENTS: -

Types of size reduction equipment's used in our industry are as follows: -

- Multi Mill
- Jet Mill

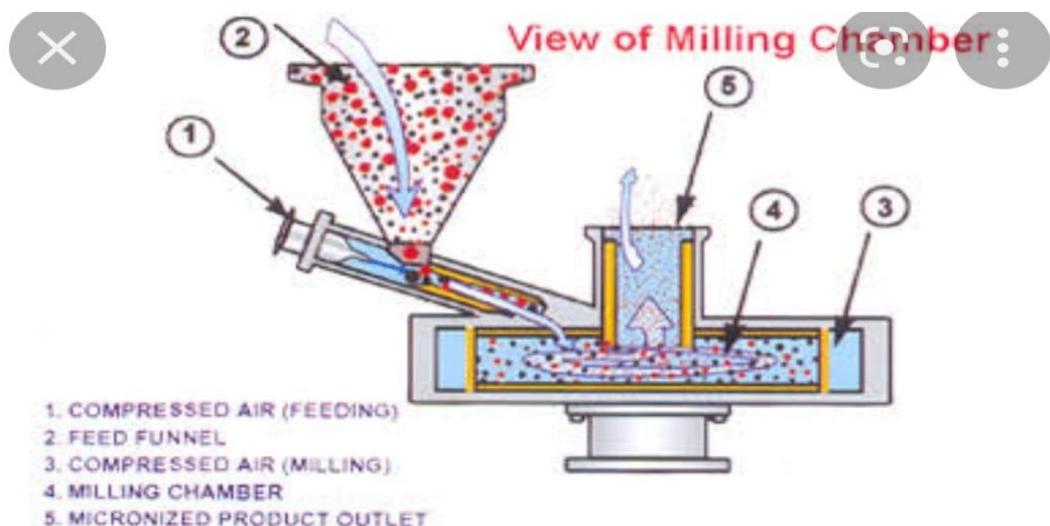
a) Multi Mill

- These mill machines are widely used for wet and dry granulation, pulverisation etc.
- These machines find their application in pharmaceutical, chemical, bulk drug, cosmetics, and food processing industries.



b) Jet Mill

- It takes place in central chamber of jet energy mill as the process material is driven at near sonic velocity around the perimeter of toroidal chamber by multiple jets of air or stream.
- A jet mill consists of a short cylinder, meaning the cylinder's height is less than its diameter.
- No grinding media is involved size reduction is the result of high velocity collisions between particles of process material itself.
- The interior of chamber is designed to allow recirculation of over-sized particles enhancing the incidence and the effect of these collisions.



6. Boiler: -

What is Boiler?

→ It is a closed vessel in which water is heated, steam is generated, superheated or any combination thereof under pressure or vacuum by direct application of heat.

- **Classification of boiler: -**

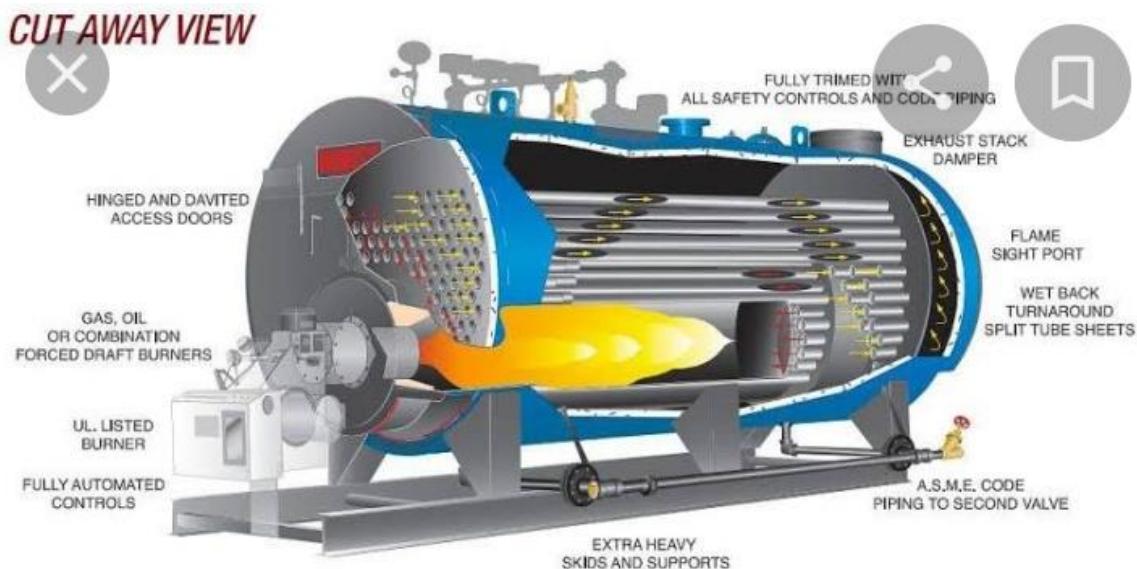
- High Pressure Boiler (HPB).
- Low Pressure Boiler (LPB).
- LPB are designed to withstand a maximum of 15 psig steam or a MAWP 160 psig water.
- HPB are designed to withstand a pressure about 15 psig steam or a 160 psig water.

In our Industry Gas type Boiler is used to Produce Saturated Steam: -

- **How Boiler works?**

→ Both Gas and Oil-fired boiler used controlled combustion of fuel to heat water. The key boiler components involved in this process are the burner, combustion chamber, Heat Exchanger and controls.

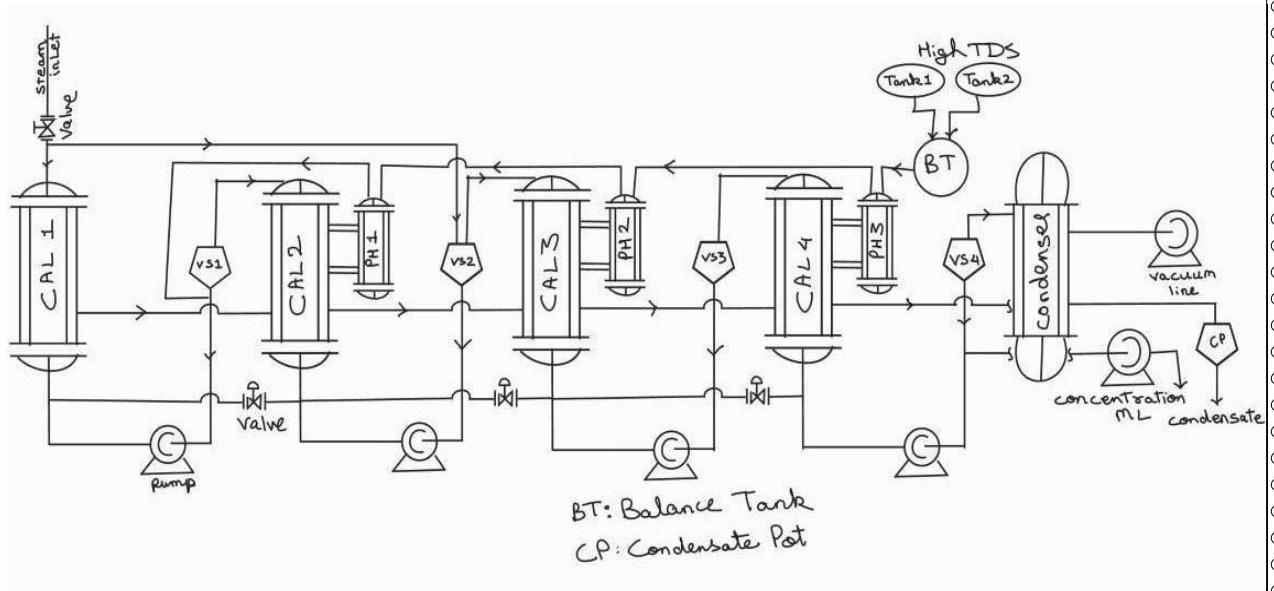
Diagram of Fire-Tube Boiler: -



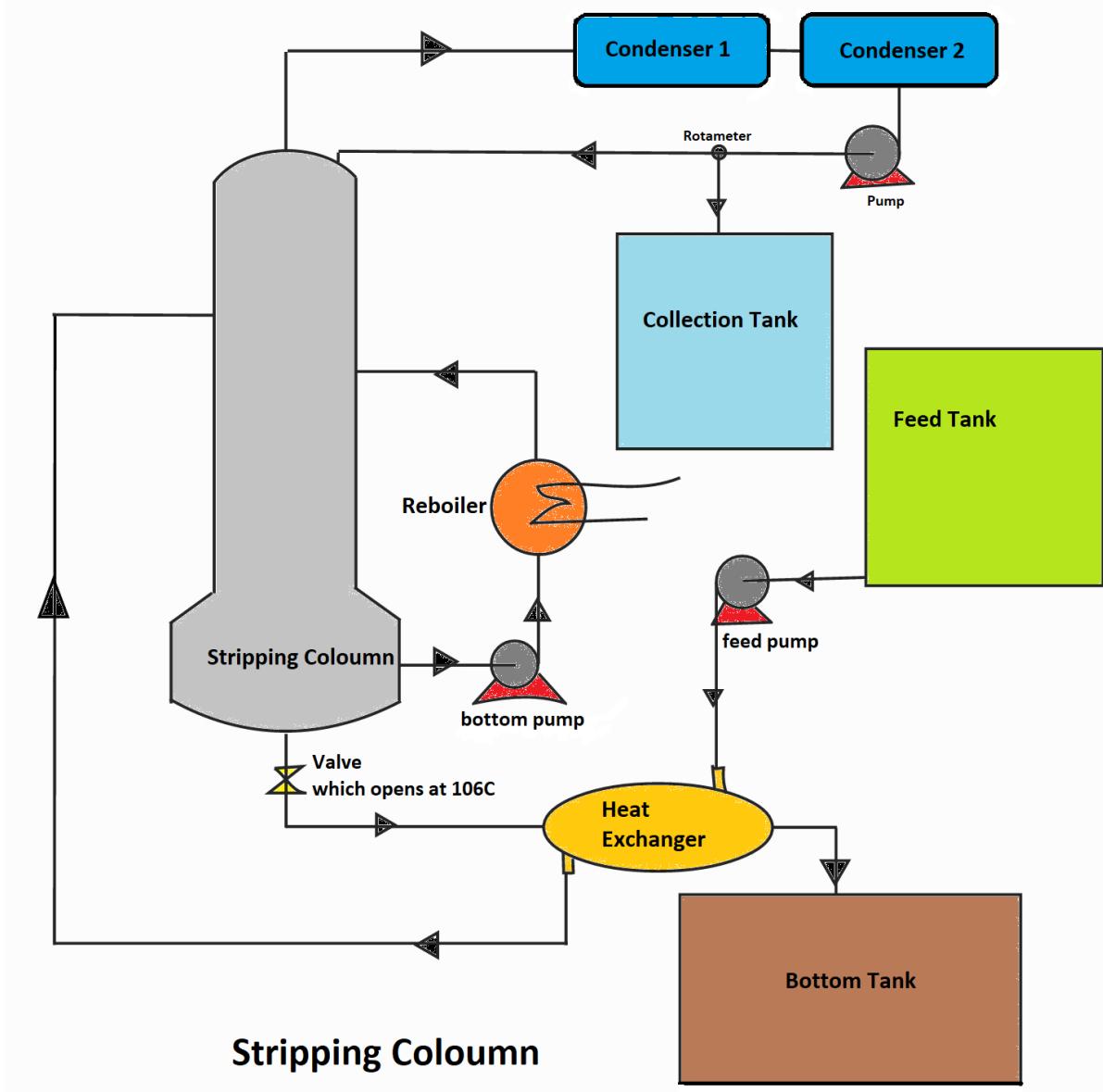
7. MEE (Multi Effective Evaporator) Plant: -

Main basic process of MEE Plant: -

- A multiple-effect evaporator, as defined in chemical engineering, is an apparatus for efficiently using the heat from steam to evaporate water.
- In a multiple-effect evaporator, water is boiled in a sequence of vessels, each held at a lower pressure than the last. Because the boiling temperature of water decreases as pressure decreases, the vapor boiled off in one vessel can be used to heat the next, and only the first vessel (at the highest pressure) requires an external source of heat.
- The RO rejects after passing through MEE turns into a viscous suspension which is then treated by ATFD.
- ATFD is used to dry and collect baggable solids from high TDS solution that comes out of Multi Effect Evaporator after water recovery.
- It consists of a tubular heat transfer area with an external heating jacket and a fast-revolving, inner rotor with flexible or rigid wiper elements.
- The feed product is evenly distributed by the rotor and its wipers over the heating surface, forming a thin liquid film of uniform thickness
- The output of ATFD is dried particles of toxic waste which is collected and dumped in a feasible dumping ground (possibly in regions like Kutch).



Stripper Column Procedure: -



- The feed for the stripper column is collected in a feed tank.
- This feed contains solvent waste from various plants and water containing extra materials such as its COD and BOD has high values.
- This feed is pumped into heat exchanger (HE-1) where the feed temperature rises by 30°C the initial feed temperature is 30°C and the feed temperature in the outlet of heat exchanger is 60°C .
- This feed now enters in stripping section.
- The feed passes through the stripping section which acts like a batch distillation column.

- A reflux is provided at the bottom of stripping section so that the bottom temperature can be increased, for the reflux to pass through reboiler a circulating pump is provided which has a header greater than feed pump and which is responsible for the increase in temperature at the bottom.
- At the top, a vapour outlet is provided where all the solvent vapour tends to release which then further condensed by condenser.
- The condensed liquid is then passes through a rotameter where an engineer can adjust the setting of rotameter as one outlet from rotameter is charged back into the top of stripper column whereas, the other outlet of rotameter goes to solvent collection tank (approx: 5.5% of feed is solvent collect).
- At the bottom a temperature specific valve is provided this valve determines the nature of stripper column.
- Below 106°C the bottom valve is closed allowing the stripper column to enter the batch distillation column.
- At and above 106°C the bottom valve opens and allowed the bottom to flow through heat exchanger (HE-1) and the outer temperature of the bottom is approx. 75-80°C.
- This bottom distillate is collected in a bottom collection tank at the rate of 1.9-2.1 kl/hr.
- Within the bottom collection tank one can find solvent free water which needs to be treated.

Reverse osmosis (RO): -

- The bottom distillate of stripper is filled in a container having one side connected to a semi-permeable membrane then hydraulic pressure is applied for the phenomenon of reverse osmosis to occur.
- The filtered water on the other side of membrane has a low COD but high BOD. Hence this water is treated by the ETP plant.
- The RO reject is a slurry which contains a high COD and hence it is then sent to ME plant for further treatment.

8. Solvent Recovery Plant

SRP Plant procedure (Solvent Recovery Plant): -

- ▶ Empty and clean the Equipment.
- ▶ Enter the (IPA and Water) as a feed in the reactor and start the agitator.
- ▶ Open the condenser cooling jacket valve.
- ▶ In the reactor Temperature could not exceed above 85-95°C.
- ▶ If the temperature exceeds above the given temperature, then cool in condenser.
- ▶ Take the First stage mixing in a storage tank for further use.
- ▶ Then our mixture goes in receiver reflux tank and work of reflux receiver tank is to maintain the reflux.
- ▶ Also open the steam valve jacket to maintain the temperature.
- ▶ After heating or after recovery cool the residue by continuously moving the agitator and then filled it in a receiver tank.
- ▶ After the whole procedure take the first 10 ml sample for testing that the chemicals inside it is recovered or not.
- ▶ This is the process of Solvent Recovery Plant (SRP).

Equipments used in SRP Plant: -

| NAME | Capacity | MOC | AGITATOR |
|--------------------------------------|----------|-------|----------------------------|
| Reactor | 8, 5 kL | SS316 | Hydrofoil +Tickler+ Anchor |
| Receiver | 2, 4 kL | SS316 | NA |
| Batch Distillation col | NA | SS316 | NA |
| Continuous Distillation col | NA | SS316 | NA |
| Hold up Receiver tank | 2 kL | SS316 | NA |
| Receiver reflux tank | 2, 4 kL | SS316 | NA |
| Decanter (to separate oil and water) | 2kL | SS316 | NA |

PROCESS DEVELOPMENT LAB



P. D. LAB

A lab that focuses on development of the process that results in
Cost Reduction and Error Minimization

X

Jayesh Ranpariya
PD Lab Manager

Mentor In charge

Cost Reduction

1. Route Selection

The most important and primary step for cost reduction is Route selection. The route of synthesis first needs to be decided as further it cannot be changed. Changes for a DMF route requires innumerable protocols as many tests are required to be performed over each step of the route of synthesis. A lot of preliminary data is required which is costly to conduct. Hence, Companies prefer to invest in route selection, to obtain a viable and a feasible Route of synthesis, rather than investing in route modification. Modification only takes place when there is a significant cost reduction. In order to understand route selection, one must first understand PMI. PMI is the abbreviation used for Purchasing Manager's Index. This index defines the weightage by cost of each element within the reaction. For example:



The above pie chart depicts the PMI for a certain reaction. It is observed that the KSM cost is unequivocal. In such cases, the route of synthesis must be different. If the labour cost has a greater weight like KSM in this case, then modern machinery must be applied to curb labour cost. In such ways, the PMI helps us understand where the focus of cost reduction must be.

2. Paper Costing

Every product has innumerable ways to be synthesized. Of these methods, only some are up to the category, which are feasible on a large scale. Of these, only some are cost effective. Paper costing involves the Raw Material Costing, Solvent usage, Isolation and recovery

costing, equipment, labour & utility costing. Before any reaction is put to work, paper costing is mandatory as it allows the industry to compare the routes, check for availability of Raw materials and Labour, and make the industry understand the net expense of a batch.

Nowadays industries also consider safety hazard costing which includes understanding how hazardous a reaction can be, what are the potential consequences of it, and how much losses would the industry have to bear if the consequences are existent in reality.

3. Mass balance

Mass balance is the concept of balancing the masses of the left-hand side (reactants, reagents, etc) and the right-hand side (products, by-products, impurities, unreacted reactants etc) of any chemical reaction. This helps us in understanding the yield of the reaction and how to optimize it. Once the mass balance is carried out, with the help of DOE, the reaction yield is optimized.

Example: A+B=>C. For this reaction, by taking 1 mol equivalent of both reactants, the expected outcome is 1 mol equivalent of C. Both A & B are solids and dissolve readily in a solvent X. C precipitate out of X by the addition of compound D in X. In actuality, 0.8 mol equivalents of C is precipitated out. Mass balance helps us in finding where the rest of C is present. If there is an increment of mass in solvent X, maybe the rest of C might be present out there. If the masses of C, D and X don't add up as the solvent, maybe the compound D was added early, in which case trace amounts of A & B are also present in solvent X. In such a way, mass balance helps us determine where the yield is lost. Once it is determined, to increase the yield is quite easy by changing parameters or using isolation techniques to achieve the requirements.

4. Solvent selection, Solvent Ratio

One of the most important criteria for reaction yield optimization is solvent selection. An appropriate solvent is essential for a respective reaction as it controls the parameters of reactant solubility and thus reactant - reactant interaction which leads to product formation. There are cases in which 2 or more solvents are appropriate for a reaction. In that case, solvent selection dictates to select among those solvents whichever solvent is greener, cost effective and less toxic/combustible. The amount of solvent is also essential as the quantity of the solvent must be adequate to dissolve the reactants at an optimum concentration, but also, it must not be in excess quantities such that its recovery becomes more costly and difficult. Optimum solvent quantity is dictated by solvent ratio.

Example: A compound X is organic in nature. Thus, it is soluble in THF as well as Toluene. Its solubility in THF is 10g/mL whereas its solubility in Toluene is 5g/mL. The difference in its solubility is accounted for by its molecular scaffold which has greater affinity towards THF. Thus, in this case, THF is an ideal solvent. The amount of solvent is determined by the ratio of mass of the compound to its solubility in its solvent.

5. Mole ratio study

Usually, for any given reaction, the reactants are taken in stoichiometric molar ratios to the limiting reactant which is usually taken as 1 mol eq. But in real life scenarios, sometimes due to vigorous reaction conditions, the reactants might degrade, some faster than the other, or, one reactant might react with the product or reagents as well to give an undesired byproduct. In such cases, the mole ratio study tells us that the reactants should not be taken in 1:1 ratio of mole equivalents, rather, by practical implementation of trial and error, the reactant which is liable to degradation (faster) or which is very reactive (with other compounds), must be taken in slight excess with respect to the limiting reactant.

Example: For the given reaction $2A + B \Rightarrow C$, ideally A should be taken in 2 mol equivalents and B should be taken as 1 mol equivalent to obtain 1 mol equivalent of C.

But practically, industries prefer a temperature at which the reaction rate doubles, but, along with this, A degrades even faster, thus resulting in reduced yields. In such cases, A is taken as 2.05 mol equivalents along with the same amount of B to obtain the same amount of C.

6. DOE Experiment

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7. Parameter changes

Any reaction is dictated by the parameters of time and temperature. Time dictates the duration of the energy and reagent utilization. More the duration, more the energy required. Most of the time, yield is directly proportional to the duration of the reaction. But to get maximum yield, more duration is required thus resulting in more utilization of energy which might not be efficient. So, by trial and error, an optimum reaction duration must be set up so that there is an efficient consumption of energy. Another leading parameter in the chemistry of reactions is temperature. Most of the reactions gain energy from the temperature. Adjusting the temperature is also a must as temperatures may lead to increase/decrease in yields as well as degradation product yields. Furthermore, temperature is designated as a critical parameter as lack of control over temperature may lead to combustion as well as loss of life.

Example:

Below, is a table which illustrates the yield of the same reaction at different temperatures and durations

| time\ temperature | 40 degrees | 50 degrees | 60 degrees |
|-------------------|------------|------------|------------|
| 1 hour | 35% | 47% | 53% |
| 2 hours | 56% | 84% | 76% |
| 3 hours | 69% | 77% | 67% |

8. Time cycle reduction

For any given reaction, the time cycle varies with the reaction conditions, particularly related to the temperature and pressure, composition of the reaction mixture, the quantity of the reactants and the agitation applied to the reaction. Reduction in time cycle duration for the same amount of yield that was previously achieved is always desired.

Example: Without the use of a catalyst in hydrogenation, synthesis of ammonia was a very daunting task as it took hours to get less than 10% of the yield. With the help of osmium catalyst, the time required has reduced to just 2 hours to synthesize 88% of the theoretical yield of ammonia.

9. 2nd crop isolation

Sometimes, within a purification process like separation, not much yield is attained as a quantifiable amount is within the reject of the separation. In order to increase the yield, a further separation process is carried out on the reject. This separated product along with the primary separated product have a combined increase in yield. This method is called the 2nd crop isolation. It is only feasible if isolation is cheaper in comparison to the increase in yield achieved. If isolation is expensive, and the yield, even if being more significant, is of an API which is cheap, 2nd crop isolation is not preferred.

Example: The yield of a reaction is 82% after centrifugation. The ML from the centrifuge contains the remaining 15% of the API as the rest 3% is lost to degradation. By Liquid-Liquid extraction, 8% of the total API is isolated from the ML. Thus, our new yield results in $82+8=90\%$. If that 8% is x kg which costs $\$y$ in the market and the isolation cost is $\$z$ where $y>z$, then only the isolation is performed. Even if $y=z$, isolation is not performed in most cases as the purity of the 2nd crop is lesser than the purity of the 1st in most cases.

10. Solvent Recovery (90%+)

Solvent recovery is only carried out for cost reduction when certain criteria are met. One of the major criteria is that solvent recovery cost should be less than the fresh solvent cost itself, otherwise, it's hardly of any use. The next parameter is that over 90% of solvent must be recovered otherwise the operation is not preferable. The 3rd criteria are that the solvent must not be explosive or toxic and that its recovery is hazardous to the people around it. Another parameter is that the solvent must be pure, i.e., there must not be an azeotrope along with it which may hinder its purity.

Example: The cost of the solvent has a 60% weightage in the PMI index. To reduce this cost solves most of the problems. For this, the recovery of the utilised solvent is a must. But the solvent, once recovered, contains many by-products and reactants, which are undesirable. Hence, if only there is a method to recover 90% or more of the solvent, then only solvent recovery is applied.

11. *In situ*

Any chemical reaction would consist of intermediates. The isolation of these intermediates would lead to decrease in yield as well as the cost of isolation would increase. Thus, where not required, isolation of the intermediate from the medium can be skipped and in the same medium, new reagents can be introduced.

Example: A+B=>C (92%/88% on isolation)

C+D=>E (96%/92% on isolation)

E+F=>G (90% on isolation)

The 3 given reactions occur in the same solvent. If we isolate the compounds C & E, the overall yield for G for 1 mol equivalent of A & B is $0.88*0.92*0.9*100\%=72.9\%$. If C & E are not isolated, then the overall yield for G is $0.92*0.96*0.9*100\%=79.5\%$. One must keep in mind that *insitu* should only be performed if the unreacted reactants do not react with the product or intermediate. If B reacts with D, E, F or G to give an undesired and a hazardous product, then compound C must be isolated or compound B must be isolated.

12. Back extraction

Sometimes, by layer separation, some amount of the product is within the layer which is not of interest to the reaction. If this amount were to be sizable, it would be a huge loss for the batch. But by back extraction, it is possible to extract a sizable amount of product from the undesired layer.

Example: Product X is present, 65% in toluene and 35% in water. Water is the undesirable layer and so water is isolated. From the information given, we understand that LogP of X is 13/7. Of the isolated water layer, if the same amount of

fresh toluene is to be added, 22.75% of X would be in toluene and 12.25% would remain in water. If this layer of toluene is to be added to the previous toluene layer, the net yield of X would be 87.75%. Further back extraction can be done to water, depending on the expense of toluene. If toluene is expensive, then to further go for back extraction is pennywise pound foolish.

13. CF ML Recycling (filtrate ML)

Centrifugation involves the process of washing with solvent while centrifugation is carried out. To use a new solvent every time would be expensive and washing reduces the yield as some of the yield of the product dissolves in the solvent while washing. After washing, the ML is thrown away to waste. Some industries, instead of wasting this ML, use it for further batches as the ML only contains the solvent, a trace number of by-products and the yield. By using this ML, we are not just recycling it but also as the ML is saturated with the product, lesser yield would leach out while washing.

Example: Batch 1 had a yield of 90% as it used Methanol as solvent for washing. The ML of Batch 1 contained 8% product 91% Methanol and 1% by-product. This ML was used by Batch 2 for washing. The yield of Batch 2 then turned out to be 92%. This shows that recycled CF ML could be used for washing.

14. Excess RM used → Recovery RM

Sometimes, for certain reactions, taking reactants in equivalent moles is not enough for the reaction to proceed or to give sufficient yields. Hence, some reactants are taken in excess to obtain sufficient yields. But after the reaction is complete, a good amount of the reaction ML contains the RM which was put in excess. This RM must be isolated for reuse or the same ML could be used for reaction by adding the limited RM. If isolated, the RM can be reused for any further reactions. This point is similar to RM isolation. But in RM isolation, unreacted RM is isolated for further use. Here, RM is deliberately added in excess.

Example: A+B=>C; C+D=>E; the latter is a RDS. Here, excess addition of external C will increase the reaction rate. Hence, along with A & B, C is also added in excess with D which is already present with A & B. Here, recovery of C is further required for the next batch.

15. Drying Elimination

In many reactions, the need for drying is not required at every step such as insitu reactions. In such cases, drying elimination leads to reduction in solvent recovery as well as steam utility for steam tray drying and vacuum utility in vacuum tray drying. Thus, drying elimination is a key step for cost reduction. Drying also causes degradation of the product. Thus, elimination of drying also increases the yield.

Example: A compound X contains trace amounts of solvents. Its application is in a reaction which is conducted in such a solvent which dilutes the trace amounts of solvents present within compound X. Thus, drying of compound X is not required for compound X to perform that reaction.

16. Bi-product Recovery

The by-products of any reaction can be isolated and could be used for some other reaction. But for this, the yield of the byproduct must be sufficient and the method of isolation must be cost effective.

Example: A=>D+B where D is the desired product and B is the byproduct. As B has a variety of uses as well, for reactions like B+V=>Z and even B+C=>A, B is isolated. As C is cheap, synthesizing A from B is also easy. Here, in such cases, byproduct recovery plays a vital role.

17. Raw Material Isolation

A chemical reaction can never reach completion unless it's a certain addition reaction like hydrogenation. There are always unreacted reactants left behind at minimal

concentrations. Sometimes, the unreacted concentration is more than it should be which tends the chemist to isolate it and reuse the unreacted reactant in future batches. This concept is called raw material isolation. RM isolation is preferred when the reaction is an equilibrium reaction.

Example: For the reaction $A \Rightarrow Z$, for 1 mol equivalent of A being charged into the reactor, only f mol equivalent of Z is formed (where f is a fraction), and $1-f$ mol equivalent of A is precipitated. If $3f > 1$ for bulk production of Z, if we isolate $1-f$ A and add it to the second batch, $2-f$ mol equivalents of A will be available for the second batch. As f is a fraction, $2-f > 1$, the 2nd batch will result in more yields of Z. By RM isolation at every batch, the amount of RM increases causing an increase in yield for Z.

18. Blending

Note: This technique is not practiced in the pharma industry.

It involves blending 2 batches to homogenize both of them so that if there is a batch that fails along with a batch that passes with flying colours, their homogenized mixture would allow both the batches to pass the required test.

Example: The minimum concentration required for HCl is 75%. There are 2 batches, one with a concentration of 69% and the other with 95%. Obviously, the first batch would fail if the batches are not homogenized. If homogenization takes place, each batch would have a concentration of 82%, thus allowing both batches to pass.

19. Impurity Isolation

In many cases, impurities are even more expensive than the desired products. The reason behind this is that the quantities of impurities synthesized are far less than the products synthesized. This makes the impurity rarer and more expensive and so its isolation is beneficial. The isolation of impurities does not reduce the cost of the reaction but rather the overall net reaction cost reduces if the impurity is valuable in the market and is put up for sale.

Example: Impurity K achieved while synthesizing compound X is of yield 0.02% of the theoretical yield of X and the probability of it occurring is 1/500. K has better efficacy than X and is potent in nature, hence, K is pretty expensive in the market. To isolate K would therefore be beneficial to the synthesizer of X.

Process Scale Up

Task: To scale up a lab process into a pilot plant

Given: Blade diameters, speed of the lab agitator, Volume of both vessels

To find: speed of agitator at pilot plant

By equating power per unit volume in both cases we could estimate the desired speed of the Pilot plant

$$\frac{P_L}{V_L} = \frac{P_P}{V_P}$$

$$\frac{P}{V} = \frac{N_p \times \rho \times N^3 \times d^5}{V}$$

P \in Power V \in Volume

N_p \in Power number which is same in both cases as both are same types of agitators (Propellers)

ρ \in density, again same

N \in speed

d \in diameter

$$\therefore N_L = 200 \text{ rpm}; d_L = 0.09 \text{ m}$$

$$\frac{V_P}{V_L} = 10^3; d_P = 1 \text{ m}$$

$$\therefore \frac{N_L^3 d_L^5}{V_L} = \frac{N_P^3 d_P^5}{V_P}$$

$$\therefore N_P = N_L \sqrt[3]{\frac{V_P}{V_L} \times \left(\frac{d_L}{d_P}\right)^5}$$

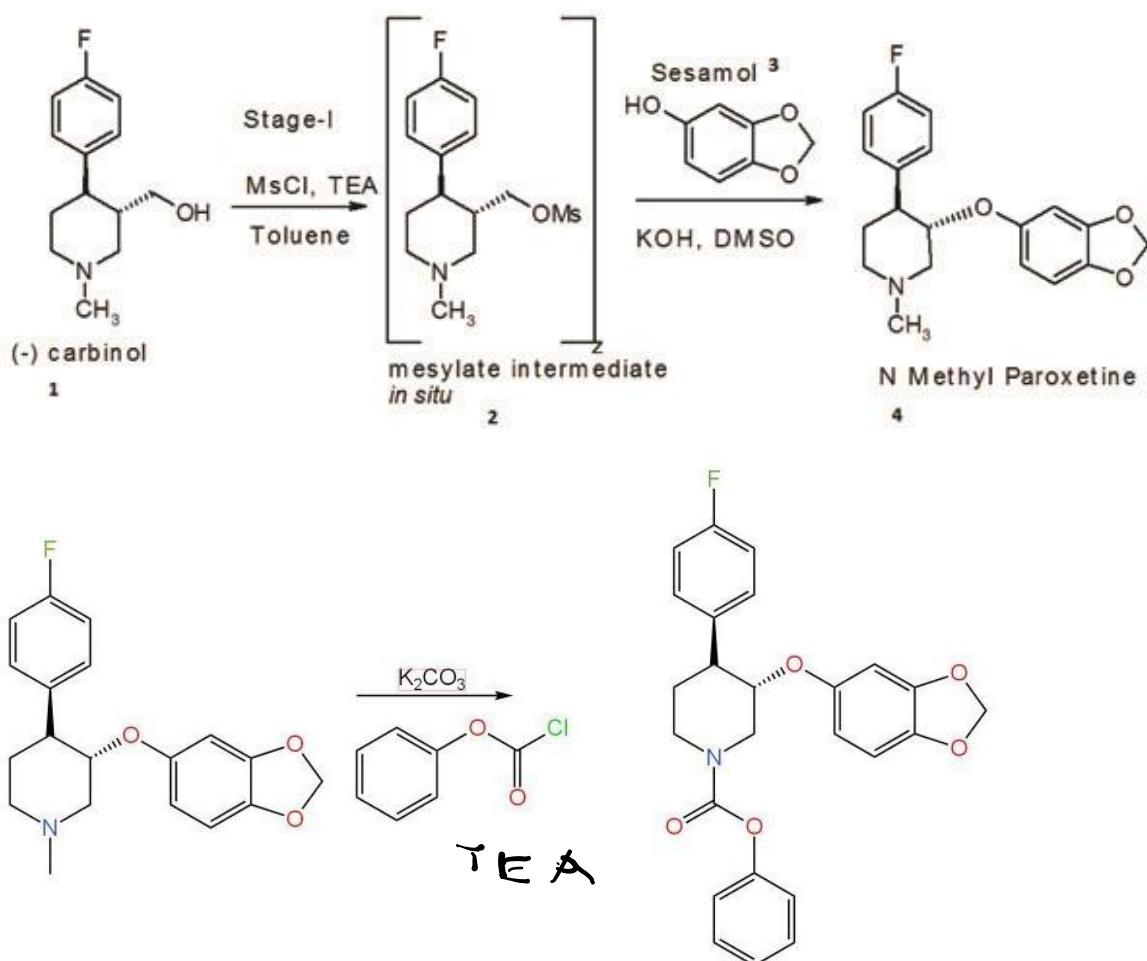
$$= 200 \text{ rpm} \times (10 \times 0.018)$$

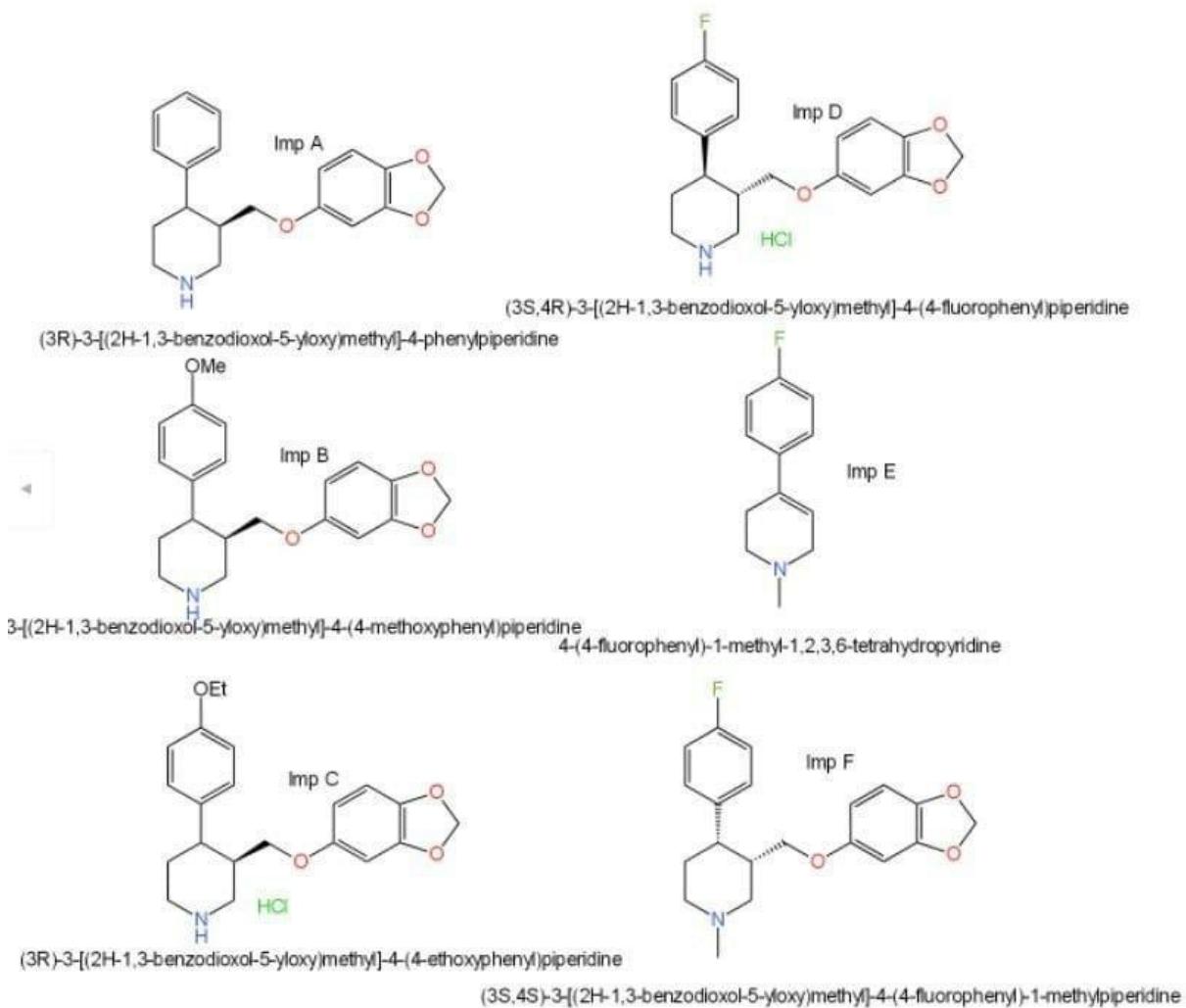
$$N_P = 36.149 \text{ rpm}$$

PAROXETINE

Paroxetine is an antidepressant sold in the form of Paroxetine HCl. Phenyl Paroxetine formate is the material to be synthesized as, in the form of formate, Paroxetine can be synthesized in a good quantity. For this, 3 stages are required. This process is completely *Insitu*. The best raw material available is Carbinol. An ether linkage needs to be established between sesamol and carbinol but by directly reacting both of them with each other, the yield is quite less. Hence, by addition of Methyl Sulphonyl Chloride, an activating group, to carbinol, we obtain a mesylate intermediate which easily reacts with sesamol to synthesize NMP. In this reaction, TEA absorbs all HCl generated to form TEA HCl. DMSO aids the sesamol salt which is partially lyophobic to react with Mesylate present in Toluene. PCF reacts with NMP to give us our desired product. Washing with K_2CO_3 reduce impurities in the solution. TEA forms a quaternary salt with the released methyl chloride and gets washed off by K_2CO_3 .

Route of Synthesis:



Impurities:

Such Impurities are generated while synthesizing Paroxetine.

Practical Synthesis of N-Methyl Paroxetine

The task was given to synthesize NMP without the use of DMSO, because as per PMI of reagents, DMSO is quite costly. Furthermore, DMSO is hazardous to the skin and can penetrate and damage cells of the body easily.

The approach taken was to use the benefit of azeotropes to substitute the role of DMSO as a solubilizer. The azeotrope chosen was THF+H₂O. Mesylate is soluble in THF as 1g:1mL ratio. 5gm Mesylate batch was decided.

- By mole equivalence, 2.4gm of sesamol was taken along with 1gm NaOH flakes in a beaker along with 4mL H₂O.
- In another beaker, 5gm Mesylate was added to 5 mL THF.
- A sonicator was used in both cases to solubilize the raw materials in respective solvents
- Both beakers were emptied in the 3rd beaker, followed by stirring for 45mins at 50°C in the 3rd beaker
- After stirring, Aqueous and Organic layers were obtained due to change in density
- By TLC it was determined that the bulk of NMP resided in Organic phase
- After layer separation, the organic phase was distilled out and 3.5gm product was obtained

Theoretical Yield: 5.5gm; Practical Yield: 3.5gm; %Yield = 63.63%

Conclusion: Less yield/ 2nd crop isolation from aqueous phase required

