

PROJECT REPORT



JULY 10

Nectar Lifesciences Ltd.
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Cefixime trihydrate

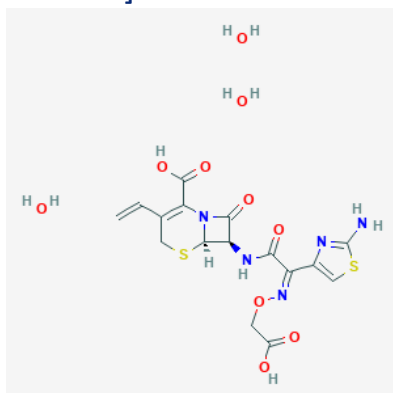
General information

Chemical name: (6R,7R)-7-[[[(Z)-2-(2-aminothiazol-4-yl)-2-[carboxymethoxy]imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trihydrate

Trade name: Suprax

CAS registry No. : [79350-37-1]

Structure:



Description: Almost white to light yellow powder

Molecular formula: C₁₆H₁₅N₅O₇S₂·3H₂O

Molecular weight: 507.5g/mol

Melting range: ~240°C

SOR: (-)75° to (-)88°

pH: 2.6 to 4.1

Hygroscopicity: Hygroscopic in nature

Partition Coefficient: The Octanol /water partition of cefixime trihydrate is 0.0029

Maximum Daily Dose: 400mg

Dissociation constant: Cefixime exhibits three ionization contents, which are characterized as follows:

1. pKa₁ 2.10 –COOH of the Cephem group
2. pKa₂ 2.69 –NH₂ of the amino group
3. pKa₃ 3.73 –COOH of the 7-side chain

Initial Raw Material: GCLE

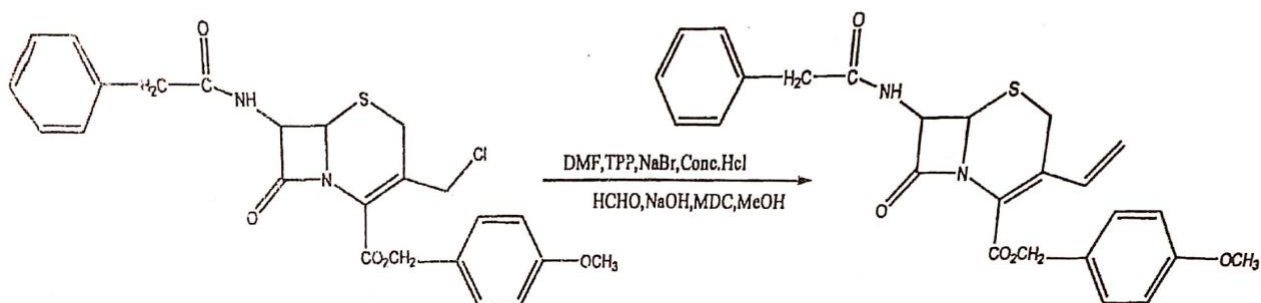
Description: It is an orally active third generation cephalosporin highly active against Enterobacteriaceae, H. influenzae, Strep. pyogenes, and is resistant to many β-lactamases. However, it is not active on Staph. aureus, most pneumococci and Pseudomonas. Stool changes and diarrhoea are the most prominent side effects

Intermediates

- **GVNE (7 – Phenyl acetamido - 3 - Vinyl cephalosporinic acid – p – methoxy benzyl ester)**
- **GVNA**
- **7-AVCA (7 – Amino – 3 – Vinyl – Cephalosporinic Acid)**
- **ACMV**

Reaction 1

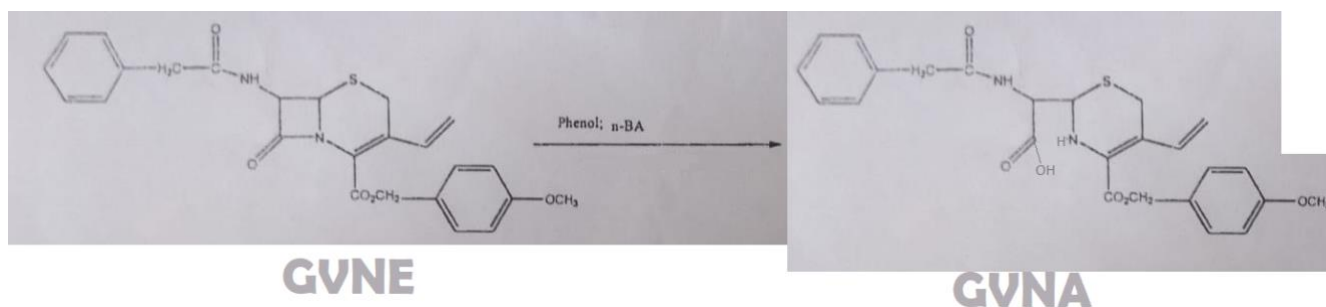
1). STAGE I: PREPARATION OF GVNE FROM GCLE



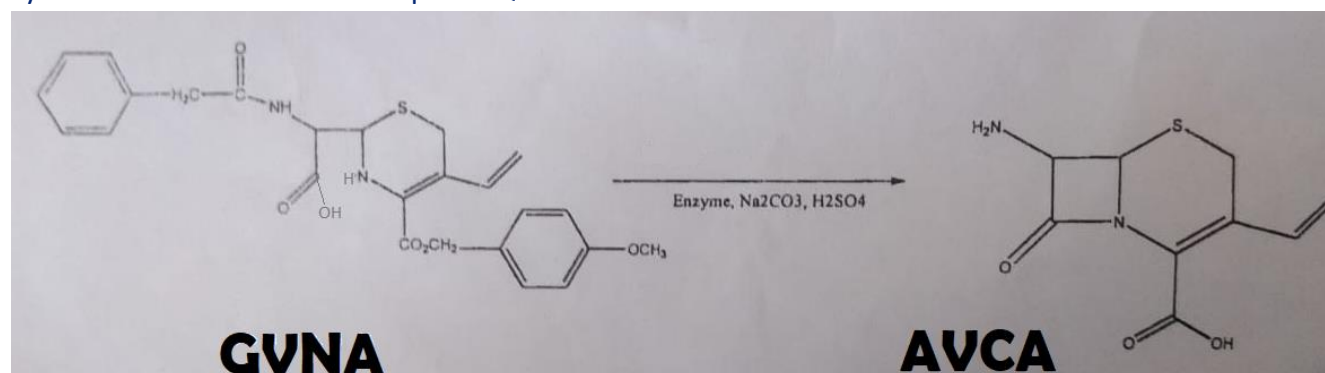
| | | | | | |
|---------------|---|-------------------------|---------------|---|-----------------------|
| Name | : | GCLE | Name | : | GVNE |
| Mol.wt | : | 486.95 | Mol.wt | : | 464.53 |
| M F | : | $C_{24}H_{23}O_5N_2SCl$ | M F | : | $C_{25}H_{24}O_5N_2S$ |

Observations:

As we are dealing with conc. HCl, it is advisable to use a Glass lined reactor (GLR) for HCl is highly corrosive but the GLR is made up of 85% silica, 15% lead and some other material if the prior materials are taken less, thus making the inner lining of the GLR highly resistant to corrosion. Both conc. HCl and NaOH are stored in their respective storage measuring tanks (SMTs) with labelling of toxicity and flammability of compound over SMT. The SMTs are at the top floor with a Spindle valve at the bottom for charging the compounds to the GLR. GCLE comes from the Raw Material pipe provided. Dimethyl formamide DMF is used out here as an aprotic solvent. NaBr is used as a buffer. First, a halogen substitution reaction occurs followed by a chain elongation reaction and finally, water is lost for double bond formation. Temperature is controlled by the utility header. It has got 4 valves namely cold water, hot water, treated water and brine. The user can easily and manually control the temperature by opening the respective valve required and the respective fluids will start flowing in the jacket allowing the reactor to exchange heat by the jacket with the help of heat transfer. The GVNE formed is then sent to GLR 01 for the next reaction. Send sample to QC



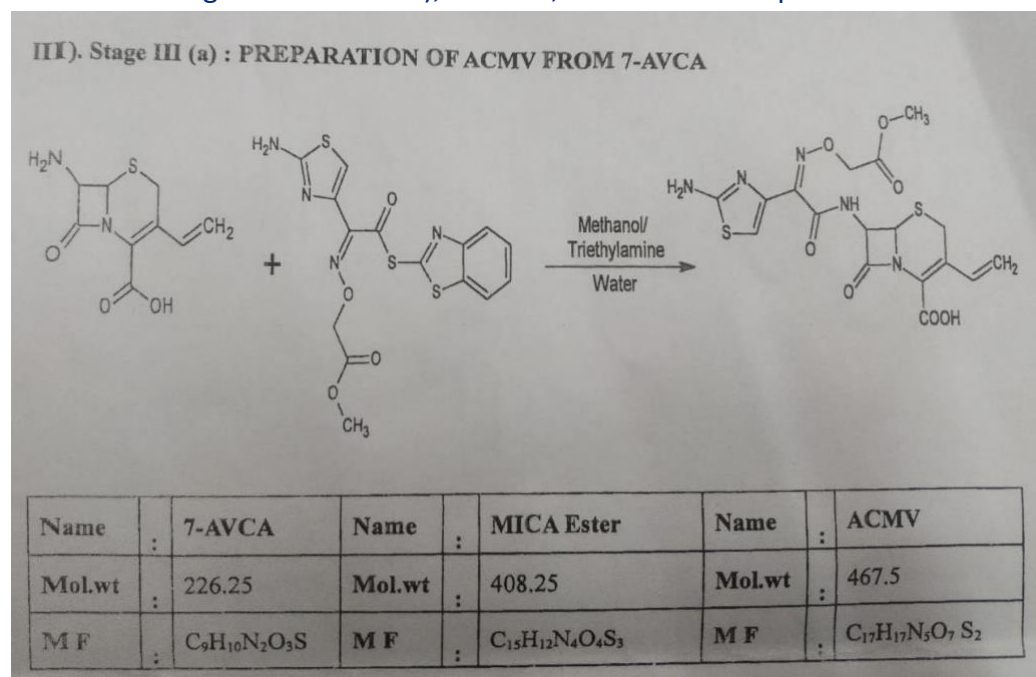
Observation: n-Butyl Acetate (n-BA) and treated water (having low TDS) are charged into GLR01 and then, the freshly prepared GVNE is charged from above by the spindle valve. Later Phenol which is stored in Storage Agitated Vessel (SAV) is charged is GLR01. Above the opening of every manhole of SSRs and GLRs there is a scrubber connected to scrubber line which prevents the escape of any gas into the plant by sucking it and processing it and then leaving it open via the exhaust to the atmosphere As phenol is highly corrosive in nature, hence GLR is used out here. The reaction is carried out for 5.5 to 6hrs until GVNA is formed. The manhole is kept open to prevent overflow by foaming. The only base purpose of the reaction is the cleavage of the peptide bond within the beta-lactam ring which will be reconfigured in the further reactions but for now it's cleaved for successful synthesis of 7-AVCA. Send sample to QC



Observation:

The freshly prepared GVNA is sent to the enzymator. The enzymator is a typical reactor used for handling enzymes. For this reaction, penicillin G-amydase is the enzyme which also acts as the catalyst. Fun fact out here is that this enzyme is eco-friendly and can be used for 100-200 cycles Tr. Water is charged in enzymator reactor (500-600L) and enzyme is dipped with appropriate quantity of treated water. Na_2CO_3 is used as pH maintainer and increases the pH drastically. If the pH has increased more than enough, H_2SO_4 decreases it until the pH is satisfied. Overall this is a hydrolysis step where the peptide bond that was broken in the last step is reformed and the ester bond is hydrolysed releasing the byproduct (6-methanol) Anisole. The AVCA received undergoes carbon treatment in GLR02. This is done by adding 2-2.5kg carbon in the form of charcoal into the reactor and stirring the reactor so that the adsorptive surface of carbon can adsorb all the dirt or any fine particles present in the solution. This carbon is later removed by Spray Dry filter SPF02. A spray dry filter is a cylinder consisting of Plates having mesh and a cloth layer over it. The number of plates vary from 15 – 25. The material to be filtered is sent from the bottom of the spray drier. When passing

through each plate, nitrogen is applied in the opposite direction as it assists with positive pressure as a vehicle for our material to pass through. The material of construction of the plates is 8S.C316. For SPF02 each plate has a filtration area of 3.9504 m². The filtration takes place between 1-1.5 hrs. There's a rod in between to keep all the plates intact which can be unloaded by manually rotating up. SPF02 had a max cake holding capacity of 91.2L and fine cake holding capacity of 50.4L, its max operating pressure is 3.5g (kg/cm³) The pores in the plate are of 5mm. After filtration, open the outer layer of SPF, unwind the rod and remove the carbon settled above the cloth over each plate. This charcoal can be reused after the waste is extracted. Each plate is cleaned properly before reuse. The filtered AVCA is sent to GLR04/09 where AVCA is crystallized for 4hrs at low pH (3.6) which is adjusted by H₂SO₄ temperature below 1°C. After crystallization the AVCA is further sent for centrifugation at CFG08/09 where the centrifuge rotates at 900 rpm with AVCA and acetone in it for 2hrs at 3.5°C. After centrifugation, semi dry AVCA will be found at the edges of the centrifuge whereas Acetone would form a component of the mother liquor and separate out in ML tank. The semidry AVCA is then loaded in trays of Steam Tray Drier STD. The door of the STD is shut and drying begins for 105-110 kg at 60°C within 30mins to 1hr. After drying, the AVCA powder is manually crushed and stored in HDPE containers, shifted to the storage room which is below 25°C, weighed properly(with respect to the tear weight of containers), labelled, and stored. Sample from each container is sent to QC.



Observation:

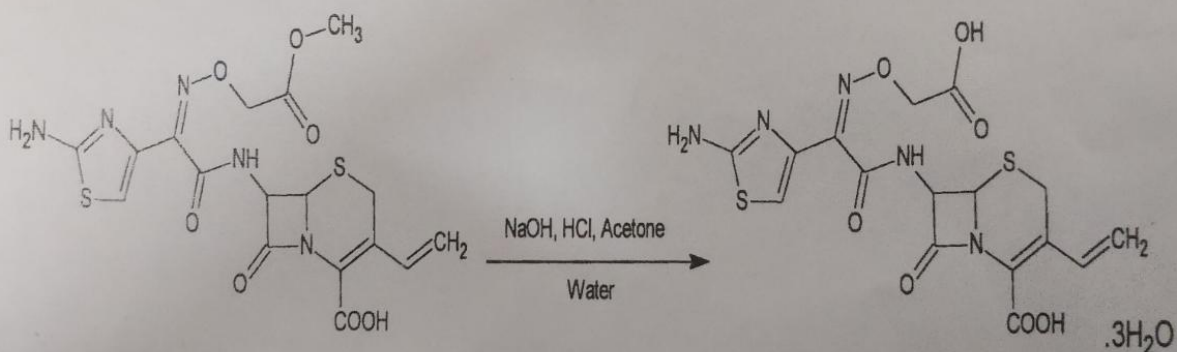
ACMV Stage

Methanol(45L) is charged from SMT to storage agitated vessel SAV06. Brine efficiency is calculated for SAV06 by the formula=Volumetric brine flow*Container Capacity/Initial brine temperature. Cool the mass between -1°C to -12°C. This chilled mixture of MeOH+H₂O is charged into SAV01. 90kg of dried 7-AVCA is charged from the manhole inlet into the reactor at 100RPM. After charging, the

reaction is stirred and cooled. The diluting agent, triethyl amine TEA + methanol solution (47.1kg+20L) is added between -9°C to -12°C. This reaction mass is then cooled to -5 to -10 with the help of the utility head. 168kg of the reagent, mica ester is charged in SAV01 for 20mins at 100rpm. Usage of treated water for hydrolysis is a must. MBT ML from previous batch + Treated water (950L+1200L) is charged from SAV03 to GLR05. Acetic acid is made 10% by stirring in HDPE container to make a homogeneous solution. The solution in SAV01 is then transferred to GLR05. Now the temperature of the mass is raised to 18°C to 20°C via utility head hot water in jacket. pH adjustments now take place with dilute acetic acid solution and the mass is now slightly acidic (ph 6.7-6.8). The mass in GLR05 is stirred for 20mins. This mass is then sent to centrifuge CFG03. CFG03 has dimensions diameter*height(1.22m*046m) and runs at 11kW power at 800rpm and its max capacity is 295kg. The aqueous ML solution is sent to SAV05. MBT slurry preparation is necessary. 1.3kg EDTA as chelating agent is charged into SSR02 having cleared filtrated of CFG03 between 18°C to 20°C for 5mins. ML from SAV05 is also charged into SSR02. Now, stirring occurs for 20-45mins at raised temperature 25°C to 28 . Again pH reduction is required till 2.2-2.4 and so 1:4 HCl solution is prepared. Its 1:4 for HCl is highly corrosive and so only 1/5th of HCl can only be taken with 4/5th of tr. Water which is sent to SSR02. After pH adjustment, stir at 25°C to 28°C for 30-35min. Cool reactor between 0-5°C by charging brine in jacket for 30 minutes. ACMV is synthesized. Samples need to be sent to QC for impurity checking.

Preparation of ACMV wet cake: Tr. Water is added to ACMV in GLR at 25rpm stirring and a sweary is formed. This sweary is cooled to 1°C with the help of brine from the utility header in SSR03

IV). STAGE-III (b) : PREPARATION OF CEFIXIME FROM ACMV



| | | | | | |
|--------|---|--|--------|---|---|
| Name | : | ACMV | Name | : | CEFIXIME |
| Mol.wt | : | 467.5 | Mol.wt | : | 507.5 |
| M F | : | C ₁₇ H ₁₇ N ₃ O ₇ S ₂ | M F | : | C ₁₆ H ₁₅ N ₃ O ₇ S ₂ .3H ₂ O |

Preparation of NaOH solution: NaOH 5kg is agitated with Purified Water of 614L and cooled to 0-3°C in SAV04

The ACMV wet cake (320kg) is already in SSR03. NaOH solution is added to limit pH to 12.5 to 13. Ethyl acetate is also added sometimes (0-5L) to prevent foaming. HCl (361L) and NaCl (100kg) are then charged into SSR03 to decrease the concentration of ACMV. EDTA (1.9kg) is added as Chelating agent. Currently, the product is hazy, but after adding Na hydrosulphite (5kg) we get a clearer solution as Na hydrosulphite is a clearing agent. Once again the carbon slurry 43L is filtered with the help of SPF (10-16kg). Cefexime trihydrate is prepared. This Cefexime is dried by vacuum tray drier VTD. It's heated by hot water (temperature 55°C -60°C). It is unloaded in double LDPE polybags and HDPE containers. After drying it is sent to multimill MML01 which consists of a cylindrical mesh and the pore size is (0.5mm, 1mm, 1.5mm, 2mm). After milling, it is sent to blender OBL02 where if 2 or more batches want to be merged together then they could be merged out there. For fine particle production, it is sieved in the sifter SFT01 with mesh size 40 microns for 3 to 4 plates. After sifting, the product is packed in LDPE bags and stored below 25°C. This cefixime trihydrate API is the finished good that can be sold.

Cefuroxime axetil

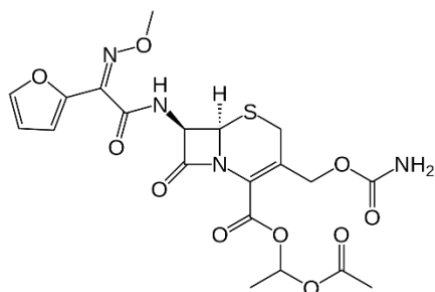
General information

Chemical name: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[[(aminocarbonyl)oxy]methyl]-7-[[[(2Z)-2-(2-furanyl)-2-(methoxyimino)acetyl]amino]-8-oxo-, 1-(acetyloxy)ethyl ester, (6R,7R)-

Trade name: Zinnat, Ceftin, Ceftum

CAS registry No. : [64544-07-6]

Structure:



Description: Almost white to light yellow powder

Molecular formula: $C_{20}H_{22}N_4O_{10}S$

Molecular weight: 510.47g/mol

Melting range: 175-180 °C

Density: 1.61±0.1 g/cm³ | **Condition:** Temp: 20 °C Press: 760 Torr

pKa: 8.31±0.60 | **Condition:** Most Acidic Temp: 25 °C

Maximum Daily Dose: 500 mg

Description: It is resistant to gram-negative β -lactamases: has high activity against organisms producing these enzymes including PPNG and ampicillin-resistant H. influenzae, while retaining significant activity on gram-positive cocci and certain

anaerobes, but not *B. fragilis*. It has been superseded by 3rd generation cephalosporins in the treatment of meningitis. The activity depends on in vivo hydrolysis and release of cefuroxime.

| Dust explosion properties | | Electrostatic properties | |
|--|-------------------|-------------------------------|--|
| Group | A | Charge relaxation time | 10405 seconds ≈ 3 hours |
| pMax (max explosion pressure) | 8.7 bar | Resistivity | $10^{15}\Omega$ Non conductive |
| dp/dt (rate of pressure rise) | 938bar/sec | Oxygen balance | -129 potential hazard |
| St Class (Explosion severity class) | 2 | | |
| LOC (Limiting oxygen concentration) | 12% | | |
| MIE (minimum ignition energy) | 3-4mJ | | |
| MIT (maximum ignition temperature) | 310°C | | |
| LIT (layer ignition temperature) | 400°C | | |

Crystalline synthesis

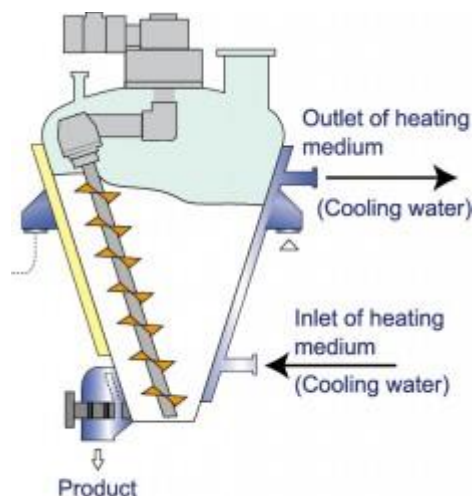
Major raw material: D-7-ACA (Des Acetyl-7-Amino Cephalosporinic Acid)

Intermediates:

- CFUH (Hydroxy Cefuroxime)
- CFUA (Cefuroximic acid)

CFUH Synthesis: Methyl Dichloride MDC (1.325g/cc & Moisture NMT 0.05%) is charged inside SSR01. NH_3 is applied at the jacket for cooling between (-20°C to -22°C) instead of LN_2 as it is a moisture absorbent. Before charging MDC, check if any layer is floating on the top, if not, then start the agitator. Now, wearing the safety precaution kit (breathing system) charge PCl_5 (360kg) into the reactor. Make sure that you don't expose yourself to PCl_5 as it may damage ones liver and kidneys. Even make sure that the reactor is moisture free as $\text{PCl}_5 + \text{H}_2\text{O} = \text{POCl}_3 + 2\text{HCl}$, which is an exothermic reaction. Cooling is continued upto -28°C to -30°C. Now, N,N-Dimethyl Acetamide (DMAc) (200L & moisture NMT 0.2%) is charged for 1hr as a catalyst (temp -5°C to -10°C). While adding DMAc, a highly exothermic reaction occurs (for which we had cooled for so long) so addition must be done under N_2 blanketing and the vents must be open and the reactor is maintained 70mins after addition. Cooling is done again but now till -18°C to -20°C. 300kg SMIA (Z)-2-methoxyimino-2 furyl acetic acid is charged for 150mins (moisture NMT 1%) while stirring at temperature -1°C to -5°C. Cooling again takes place upto -40°C. Charging of treated water (2kL) is now taking place at SSR02, this is further flushed into SSR01 before temperature reaches -40°C. After charging, agitation (68rpm) is stopped and the reaction mass is allowed to settle (30mins) for layer separation. The aqueous phase is sent to ETP effluent treatment plant. Solvent MDC is charged to SSR02. In SSR03 Methanol is charged (1300L reacted + 650L fresh) along with 1600L tr. Water and stirring takes place at 21rpm for homogeneity for 15-20mins (temp 35°C cooled down to 4°C). Now, its cooled by Ammonia upto -30°C. D-7-ACA is now charged in SSR03 upto 350kg in the form of solid powder. Caustic soda solution is prepared in SAV01 by charging 60kg NaOH in the form of flakes and 480L water and cooled between -5°C to 0°C. After solution preparation, 1st caustic soda solution addition begins

from SAV01 to SSR03. After addition, the solution gets clarity. The organic layer from SSR01 is now charged in SSR03. Now, the pH has to be maintained between 6.5 to 7 and so 2nd caustic soda addition takes place for 1hr and the sample is sent to QC. CFUH is prepared but now refining is required. Aqueous layer (MeOH+water) is separated by 34% HCl and the pH is lowered. This crystallizes after 30mins wherein HCl is again used for pH maintenance. This is proceeded in filtration in CFG (size 1600mm, capacity 822L, 850rpm) where wet cake is obtained at the surfaces and ML is extracted at the middle. The wet cake is sent in batches of 45 to 48kg each to Fluidized Bed Drier FBD where drying occurs partially with inlet temperature 48.6°C, outlet temperature 41°C to 42°C and bed temperature 40°C. From here, it is sent for complete drying to NAUTA dryer for 16 to 22hrs. The NAUTA drier consists of 2 motors namely the main motor at 4kW and the lump breaker. It is a pressurized vessel (3.5kL) containing a rotating drill that rotates between 1-100rpm. Pressure is maintained by vacuum (-ve pressure) and can be reduced by N₂ purging (+ve pressure). Hot water is applied at the jacket of the vessel when pressure is above 650mmHg (not below that). After complete drying, it is sent for milling, where after it is stored in LDPE and sample is sent to QC. CFUH is prepared.



NAUTA dryer

CFUA crude synthesis: Process begins with charging of acetonitrile CH₃CN, ACN (2300L) in SSR22 at 70-8-rpm. This is cooled from -40°C to -42°C. The charging of CFUH now commences manually by the manhole at 46rpm. Before charging, one must see to it that ACN and CFUH have moisture content NMT 0.1% & 2% respectively. After charging CFUH, the temperature breaks down to -35+/-1°C. Now, the maintenance of the temperature is very essential and one must take care that the product does not get hazy (freezes like curd formation). If it gets hazy, start adding CSI and maintain the temperature between -35°C to -37°C. Again, one must wear breathing suit and charge CSI Chlorosulphonyl isocyanate by vacuum into SSR22 from GLP01. The protocols must be handled with precaution for CSI is also like MIC Methyl Isocyanate, the gas responsible for innumerable deaths in Bhopal. Furthermore CSI is corrosive and hence stored in glass lined pot GLP. After addition is complete, chelation check is compulsory (material must be translucent/ clarity must be there). The ammonia cooling is stopped before chelating and the reactor is maintained for 1hr. Tr. Water (815L) is added to SSR05 at temperature 13-15°C. After maintenance is over in SSR22, the material is charged into SSR05 and SSR22 is flashed with ACN. Once charged at SSR05, the material is observed as thin as water and like diet coke in colour. Upon stirring for 5mins, it turns viscous and colour like orange juice and after 5 more minutes it becomes hazy like curd and colour like peach wherein the agitator stops. After 5mins, the agitator is restarted at max rpm wherein the curd like formation dissolves into a less viscous formation. This process is called scrapping. Scrapping helps in the freeing of the material from the surface of the reactor and breaks all the adhesive forces

between the reactor and the material. Before scrapping, brine cooling takes place for 3-4mins (till -10°C) in time with the colour and viscosity variation till the agitator shuts down. After scrapping, the temperature is maintained between -8°C to -11°C . After this, centrifugation takes place at 850rpm for 3-4hrs where ML is extracted and we get crude wet cake of CFUA.

CFUA pure synthesis: Crude CFUA wet cakes are manually charged by manhole into SSR06. Before batch charging, weight is checked. Purity of Acetone is checked, and acetone (3775-3780L) is charged into SSR06. Hot water is charged in the jacket with the help of utility header to increase reactor temperature upto 28°C . Tr. Water (205-210L) is added from SMT02 to SSR06. The previously prepared caustic soda solution is again added for maintaining pH between 2.6-2.8 and SSR06 is stirred for material clarity. Activated carbon (10kg) is charged into SSR06. This mixture is sent to SPF having 15 to 19 plates. Each plate is made up of stainless steel and has a diameter of 18 inches and has innumerable 3mm holes. Above every plate, there is a mesh and above the mesh, there is a cloth over which the filtrated carbon is collected. A centrifugal pump used to pass through the material through the plates from bottom to upwards. The filtration should not take more than 1-1.5hrs. The filtrated material is given sparkler washing by acetone solution (40-43L acetone+420-425L water agitated for 5mins) and the mass is collected in SSR07. Pure CFUA is synthesized.

Distillation: Once the mass is collected in SSR07, vacuum is applied to a pressure NLT 650mmHg and the mass is agitated for 1hr between 50 to 60rpm. Once the pressure reaches upto 650mmHg, hot water is applied at the jacket at $58-60^{\circ}\text{C}$ so that acetone (boiling point 56.7°C) is distilled out to RCV (recovery). Once distillation is done, haziness appears in the mass. The recovered acetone is sent to condenser for recovering it in the liquid form. Once distillation and later stirring is over, the vacuum is released by N_2 purging and the volume of the mass is determined by its depth. The depth is manually determined by dipping a rod inside the reactor via manhole and measuring the dipped length of the rod (usually 18-20cm). Once the volume is determined, the manhole is shut and the mass is stirred for 5mins at max rpm. MDC is then added via inlet valve at $10-18^{\circ}\text{C}$ in SSR07. Cooling proceeds with brine from utility between -2°C to 2°C . SSR07 also has a reflux line for solvent circulation. This mass is sent for centrifugation to CFG at 850rpm for 3-4hrs. ML is extracted and the wet cake of pure CFUA is sent to NAUTA drier at $45-50^{\circ}\text{C}$ drying. This semi dried material is sent to FBD.

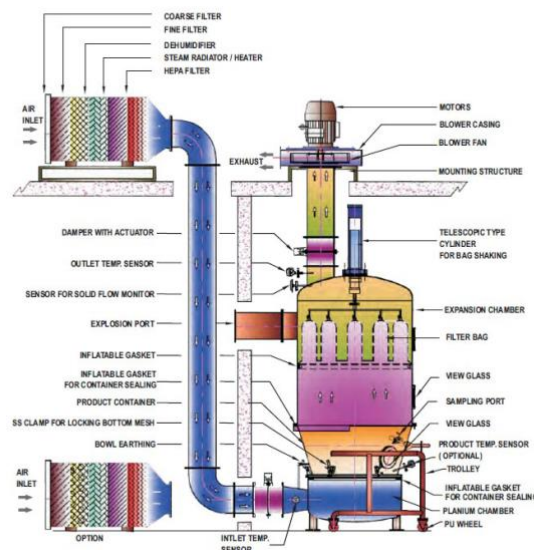
The FBD consists of a blower of 50horsepowers which sucks the air and makes it pass through:

1. Fine filter₁
2. Cooling coil cooled with brine
3. Fine filter₂
4. Heating coil heated with steam
5. HEPA filter
6. Fluidized bed
7. Filter bags
8. Via blower back to the atmosphere

There is a valve between the cooling coil and the ff₂ controlling the velocity of cooled air. The air does not take too much time at the heating coil and so the air is not overheated. The HEPA filter prevents the hot air from dissolving the cloth of the bag filter.

There are 37 finger bags in the bag filter, the hot air from bottom causes the material to rise but after certain elevation it falls due to gravity. This rise and fall goes on and on and causes the moisture in the material to leave with the hot air. The filter bag is tightly attached to the

SCHEMATIC DIAGRAM OF FLUID BED DRYING SYSTEM



FBD metal body causing no gap to form and there is also a gasket at the bottom loader keeping the FBD void of gaps so that no air escapes through the main body of the FBD. The FBD output is only 20%. The inlet and outlet temperature is set to 45°C whereas dew temperature is 20°C. The filter bag pressure is maintained at 250mmWC. After drying CFUA is loaded into double LDPE bags. CFUA refining is complete. Esterification and Cefuroxime axetil (crystalline) synthesis: Firstly, the GLR09 is checked for fractures and if there are no fractures, DMAc is charged (600L refined + 100L fresh) from SMT05 to GLR09. Temperature of the reactor is RT. After charge, the temperature is 20-22°C. Now, CFUA (175kg) is charged into GLR09 which turns the solution a bit hazy and yellow and increases the temperature to 28-29°C. The clarity must be checked and the mass must be kept untouched for 30mins. Then charge brine from utility to decrease the temperature to 10°C within 30-40mins. Then 28.1kg of NaHCO₃ is charged to increase the pH. After 3-4hrs, the temperature falls to -5°C. After those 3-4hrs, Acetoxy Ethyl Bromide AEB is charged (136.4L) and added for 30-45mins. As the addition reaches its completion, batch monitoring time begins for 4hrs in which the temperature is maintained between -0.5°C to -1°C. Cefuroxime axetil is prepared by esterification which is maroonish dark red in colour and a clear liquid. Sample is sent to QC. If QC approves then the batch is charged into SSR12 which already has ethyl acetate (2550L) and water (2100L) in the reactor. Stirring occurs for 45mins which is proceeded by settling for 45mins which would cause layer separation i.e. an organic layer would float over an aqueous layer which will be separated out by the bottom valve. The bottom valve consists of 2 valves, one is the primary bottom valve and the other is the secondary bottom valve. The former is always kept open during layer separation while the latter is under manual control. Between these 2, is a small cylindrical glass which allows the user to observe what is passing through. When primary valve is initially opened, we first observe the organic heavy particles settled below flowing which settle at the bottom valve cavity. Upon opening the secondary valve the aqueous layer starts flowing like translucent turbid yellow. After 15mins, once the emulsion appears, the secondary valve is shut and the emulsion also settles at the cavity proceeding the closing of the primary valve. Thus, the organic is stored in SSR12 whereas the aqueous layer is sent to SRP-B. Now, as we are dealing with final product instead of an intermediate, we would be using Purified water instead of tr. Water because of its low TLS rate. In GLR17, SMBS (Sodium meta bicarbonate solution i.e. 21 kg SMBC + 175L water) + HCl solution (HCl 5.2L + 175L water) is prepared. The mass in GLR17 is then charged into SSR12 along with 1865L purified water proceeded by 45min stirring and 45min settling after that for layer separation. Again aqueous layer is transferred to SRP-B whereas now organic layer is transferred to GLR15. This organic layer is like a mosambi juice in colour as well as viscosity and it also leaves a pungent odour. NaCl solution (35kg NaCl + 175L P. Water) is charged from GLR17 to GLR15 to reduced concentration of Cefuroxime. NaHCO₃ solution (17.5kg bicarbonate + 175L water) is also charged as a buffer. This is followed by 45min stirring at 90rpm followed by 45 min settling and layer separation. Aqueous layer is always transferred to SRP-B whereas organic layer is shifted GLR16 with the help of a centrifugal pump. NaCl solution (70kg NaCl + 175L P. water) (pH 6.8-7.1) is again formed in GLR17 and is charged into GLR16 followed by NaHCO₃ solution (2kg bicarbonate + 175kg water) charge in GLR16 in accordance to 30 min stirring at 90rpm and 30 min settling followed by layer separation. Steps are repeated so that no aqueous part is found in the organic layer. After layer separation organic layer is sent back to GLR15 where 800L water is added, after which 30min stirring, 30min settling and layer separation due to which organic is sent back to GLR15, repeating what it did in GLR16 but this time 400L instead of 800L and organic layer is sent back to GLR16. Now, the pH is between 4.5-5.5 of the organic layer. 11.5kg charcoal is charged into GLR16 after which 20min stirring occurs at GLR16 at 90rpm. After this, it passes through SPF and then, the

filtered mass is charged into SSR18 (5kL capacity) for distillation. Here the pH is checked along with the depth by rod and it comes out to be 55-56 inches. Vacuum pump is initiated to maintain the pressure of SSR18 between 650 to 670 mmHg. Hot water (80°C) is applied at jacket to evaporate ethyl acetate (boiling point 77.1°C) for 6 to 8 hrs as distillation time. This Ethyl acetate is condensed and liquefied and refined for reuse. Per batch 570-600L of ethyl acetate is recovered. The pH of the solution is now 4.5 pH. 970-1140L cyclohexane is then charged by inlet valve into SSR. After cyclo-addition, the remaining height in SSR18 must not be too thick or it might choke.

This cefuroxime is further sent to agitator nutsche filter dryer ANFD. This equipment not just filters the mass but also dries it with the help of the agitator. The filter plate is circular and has an area of 1.77m². ANFD continues till ML (1600-1700L) doesn't come out, which takes approximately 4-5 hrs. Washing takes place with cyclohexane 175L and ethyl acetate 175L.

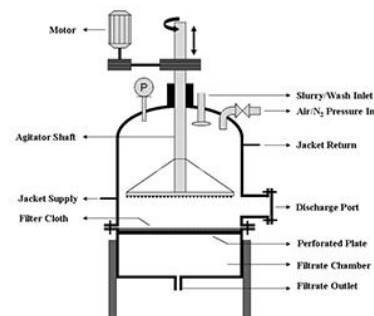
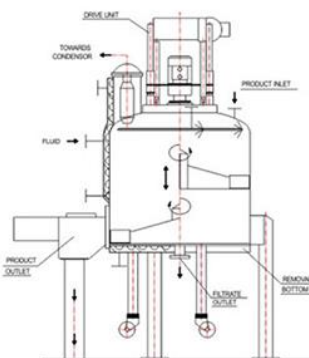
After 10-15 mins, N₂ positive pressure is applied for 4-5 hrs until complete ML sucking takes place. Still, big lumps are formed, so hot water is applied to break the lumps. The mass temperature should be 35°C. Once lumps are destroyed, the crystalline cefuroxime is stored in LDPE bags and sent to RCVD. If distillation columns are not free, the mass can directly be sent to Centrifuges where ethyl acetate will be removed as liquid as a part of ML, drying will occur and then it can go to RCVD. But it's not advisable as big lumps will form and for milling 3-5mm mesh size will be required.

Rotocone Vacuum Dryer (RCVD) can handle 2 batches at a time. It contains a chopper (1600rpm) and a filter bag. It is air tight 700 mmHg and has a capacity of 300kg. It itself rotates at its own axis within 20 seconds for 1 rotation. The inlet temperature is 56°C whereas output is in double LDPE bags.

From here, the mass is sent for milling by the multimill.

The mesh of the multimill is cylindrical and pore size is 1.5mm.

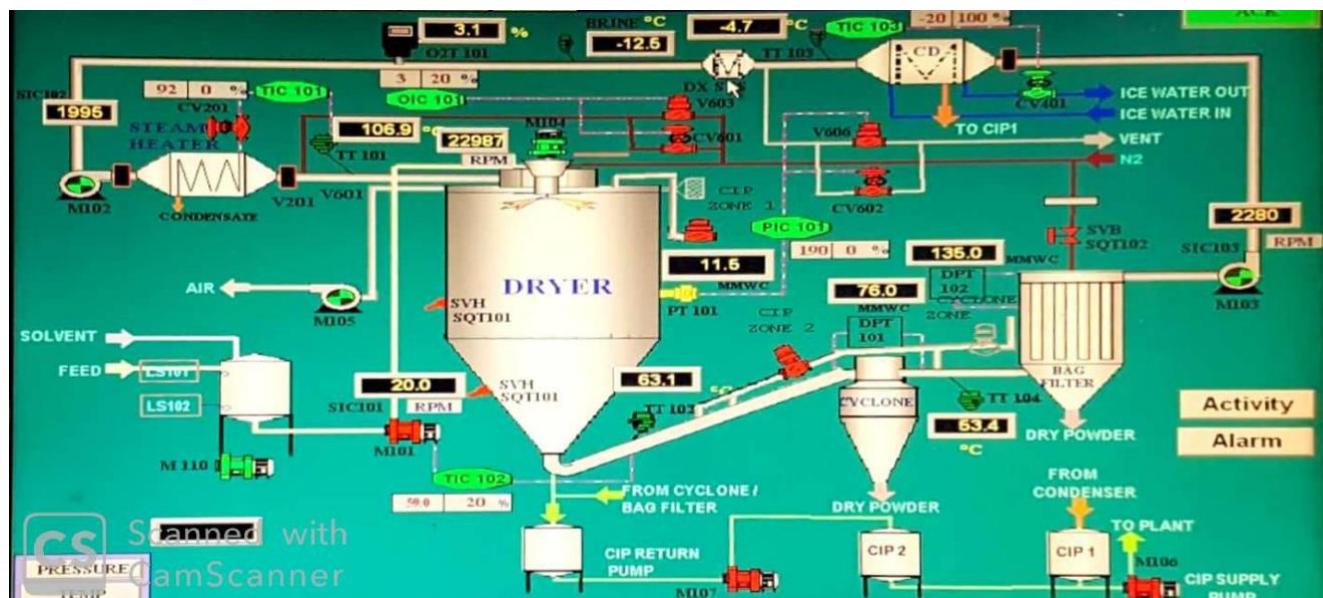
From here, it is sent to blender if 2 or more packages need to be mixed. After blending it is sent to the sifter having 3 cylindrical porous stainless steel plates and pore size is 0.5mm. The finished good is collected from the sifter and stored in LDPE bags, labelled and sample is sent to QC. Crystalline Cefuroxime axetil is white in colour and turns mild yellow if close to heat or sunlight. It is stored below 25°C



Multimill mesh



Spray Drying



Spray drying is done to prevent crystalline API from showing polymorphism, and so it is converted into an amorphous form which is viable. 60 kg crystalline cefuroxime axetil is charged into SSR01 where it is dissolved in 450L acetone until we get a clear solution. Acetone here acts as the solvent. Note that cefuroxime is always charged after acetone so that dissolution is better. The mass of SSR01 is then charged into SMT to measure the volume of the mass. This mass is further charged into the atomizer via the peristaltic pump. The peristaltic pump is a typical pump that rotates rollers around the outlet of the inlet feed pipe between 20-35rpm. In each rotation, the roller presses the pipe and then releases it causing vacuum to form and later this vacuum sucks up the liquid. Before reaching the feed, it goes through damper which prevents air entrapment and candle filter to filter out insolubilized matter. Once the feed reaches the atomizer, by computer control, the rpm of the atomizer is increased every 5 seconds by 10 rpm till we reach 100 rpm, then after every 5 seconds, it is increased by 50 rpm till 250 after which increment is by 100rpm till 1000rpm, later increment is by 500 rpm till desired rpm is not achieved. In the spray drying chamber, along with our feed, we have hot N_2 which acts as our carrier and also maintains the temperature of the spray drying chamber at 58-60°C so that acetone (boiling point 56.7°C) evaporates. The upper spray dryer pressure is 150-350mmWC whereas Cyclone pressure is less comparatively (40-50mmWC). This causes the semidried Cefuroxime to pass through the U tube at the bottom of the spray drier and enter the cyclone. The U tube is a very delicate pathway as it may get choked due to several pressure factors or even if the acetone concentration is more within the feed. One of the major facilities of the spray drying chamber is the automated hammer which strikes the chamber every 10 to 15 seconds weakening the adhesive force between the semidried powder and the inner chamber surface and also allowing the powder to circulate in the process. Before entering the cyclone, the gas is stopped at the valve before the inlet of the cyclone. When this valve opens, the valve at the cyclone outlet and the valve at the Spray drying chamber outlet closes, not allowing any new gas to enter the cyclone. Within the cyclone, heavy particles of high bulk density settle whereas the hot N_2 gas carries away all the light particles to the bag filter. When the bag filter inlet valve i.e. the cyclone outlet valve is opened, the cyclone inlet valve automatically shuts down causing no new gas to enter from the pray drying chamber and the unidirectional flow of gas. The pressure of the bag filter is balanced along with the pressure of the cyclone to the pressure of the spray drying

chamber. The bag filter consists of 25 polypropylene bags which help in the separation of fine materials of size 0.25 microns. The filter is used at 70% efficiency. The powder from cyclone and that from bag filter are separately sent to RCVD for further drying with the help of PTS powder transport system. After drying at the RCVD, the moisture content within the product is NMT 1%. The product is Cefuroxime axetil in amorphous form as finished good FG which is packed in HDPE containers. This finished good is sent to QC for checking moisture content. If it's less than 1 then it's approved. The finished good is vendor specific. If the vendor wishes a fine particle FG then he'll get that of bag filter, but if the size hardly concerns his needs, he would go for FG synthesized from cyclone. The hot air from the bag filter is then pulled up by the exhaust. The exhaust pulls up 80-90% of the feed and sends it to the pre HEPA. The pre HEPA ensures that before the air gets inside the condenser, there is no particle entry that may choke the condenser. The condenser consists of a primary coil having chilled water and a secondary coil consisting of brine. Temperature can be adjusted by adjusting the 2 coils. The chilled water (8-15°C) and brine after use is circulated back to the utility from where it came. This then passes through DX (-12°C to -15°C) for more cooling. DX consists of industrial gas 404A which is a set of fluorochemicals used for cooling. The acetone used, is cooled out here and liquefied for reuse. The gas then passes through oxygen measuring meter which measures % of oxygen in the feed. The oxygen measuring meter is connected to a short circuit system in which if the % of oxygen in the gas is more than 3, then the plant shuts down automatically. The plant cannot operate with oxygen content more than 3% or else if the oxygen comes in contact with the hot nitrogen, heat transfer may occur resulting in combustion and thus, a massive plant blast. Hence, this is a preventive measure. This gas is pulled up by the supply fan running at 1267rpm and pushes it into the heater towards the chamber. It now passes through the 4 coil heater where N₂ is reheated to be sent back to the spray drying chamber. After this, the heated N₂ passes through the 5 to 6 layers of the HEPA filter so that this hot gas does not corrode or disintegrate the inner lining of spray drying chamber or the crystalline Cefuroxime axetil. This hot gas finally passes through the candle filter which only allows the particle size below 0.2-0.3 microns after which the cycle restarts. Overall N₂ is ecofriendly as it is a one-time purchase. There is also a rupture disk in the short circuit system which is connected to the spray drying chamber. If the pressure increases over safety limits, the rupture disk opens up all vents and releases the extra pressure to the atmosphere thus shutting down the system and preventing a fatal accident of life and property. This is the spray drying mechanism.