RESEARCH PAPER

Manufacturing Process for EDC-HCl used in Pharmaceutical Industry

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ABSTRACT

EDC-HCl or EDAC Hydrochloride (1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide which is use as a coupling agent in pharmaceutical industry. This work done with help of various pharmaceutical industry processes, various research papers, literature study. The important factors like Residence Time, Temperature and pH are affected on yield of EDC·HCl. EDC·HCl has less toxicity to health than DCC. EDC·HCl is a smooth powdery crystal and very easy to treat. As per literatures review, observation and data collected from the industry, we got the product manufacturing process, various raw materials, and various unit operations. By using such data we find optimum values of various parameters that affected on the yield of products. EDAC Hydrochloride is odourless white crystalline product which is highly soluble in water. Ethyl Isocyanate, Dimethyl Propylene Amine, Chloroform, Calcium Carbonate, Potassium Hydroxide, Acetonitrile and HCl is the major raw material use for production of EDAC Hydrochloride.

Keywords - EDC·HCl, pH, Residence time, Temperature, reactors, vacuum distillation, yield.

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INTRODUCTION

EDC-HCl is a carbodiimide derivatives used for the coupling of primary amines. EDC-HCl activates carboxylic acid to form amides and ester which is act as a carboxyl activating agent on amide. It is a popular choice for peptide synthesis through a reactive carbodiimide (EDC-HCl) and Sulfo-NHS as a catalyst. The scientist in crosslinking proteins or creating protein: protein conjugates. Additives such as N-hydroxyben zotriazole (HOBt) are widely used for the generation of active esters capable of efficient acylation of amino groups, especially in the case of amino acids & peptides. [2] By using EDC·HCl the formation of EDC-urea is easy to dissolve into almost all solvents. The synthesis of macromolecules, high performance reagents and medicines are increased. EDC·HCl is very useful because of its solubility in solvents, especially in water. EDC·HCl has less toxicity to health than DCC. EDC·HCl is a smooth powdery crystal and very easy to treat, whereas DCC is an oily solid. EDC·HCl will come to be used more and more in the near future. [3]

MATERIALS AND METHODS

Physical and Chemical Properties

Molecular formula – $C_8H_{17}N_3.HCl$
Molecular Weight – 191.70
Melting Point – 112-116 ^{O}C
Purity – 98 %
Solubility – soluble in water, ethanol, methanol
CAS No- 25952-53-8
Physical state: Solid
Appearance: Solid.
Colour: White to off-white
Odor: Odourless
Specific gravity / density: 1044 kg/m³
Solubility: Soluble in water. Water: > 100 g/100ml (20 °C)
Decomposition temperature: >= 125 °

Raw Materials

For production of EDC-HCl the major raw materials are EITC (Ethyl Isocyanate), Dimethyl Propylene Amine (N, N Dimethyl-1,3-Propane diamine) , Chloroform, Calcium Carbonate ($CaCO_3$), Potassium Hydroxide, Acetonitrile (Fresh) and HCl (Gas).

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Preparation of EDC-HCl:

EDC-HCl prepared by coupling ethyl isocyanate with N, N-dimethylpropane-1, 3-diamine to give a urea, followed by dehydration and treatment with HC. [3]

$C_2H_5N=C=O + H_2N (CH_2)_3N (Me)_2 = C_2H_5NHCOHN (CH_2)_3N (Me)_2$

Process Description

Ethyl isothiocyanate treated with N, N-Dimethyl-1,3-propanediamine in presence of sodium hypochlorite, potassium hydroxide in calcium carbonate treatment in chloroform as solvent, after completion of reaction, reaction mass is quenched with water and isolated product 1-ethyl-3-(3- dimethylaminopropyl) carbodiimide. 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide further treated with anhydrous hydrochloric acid in acetonitrile solvent to give 1-ethyl-3- (3-dimethyl amino propyl) carbodiimide hydrochloride. [2, 3]

1. Ethylenediamine solution (0.25 mol/L) prepared by dissolving 15 g of ethylenediamine in 500 ml of water.
2. The solution was adjusted to pH 7 with hydrochloric acid and diluted to 1000 ml with water.
3. After 40 g of pyridine dissolved in 500 ml water, adjusted to pH 7 with hydrochloric acid and was diluted to 1000 ml with water (0.5 mol/L).
4. as a carrier solution (CS), 0.1 mol/L HCl used. For a reagent solution (RS), 0.25 mol/L ethylenediamine and 0.5mol/L pyridine solutions mixed 1 to 1 by volume: final concentrations 0.125 mol/L ethylenediamine and 0.25 mol/L pyridine

1. Condensation Reaction - Condensation process carried out for reactant Ethyl isothiocyanate, Chloroform, Calcium Carbonate, Dimethyl 1,3 Propane Diamine, Potassium Hydroxide to obtained condensate of the reactant.

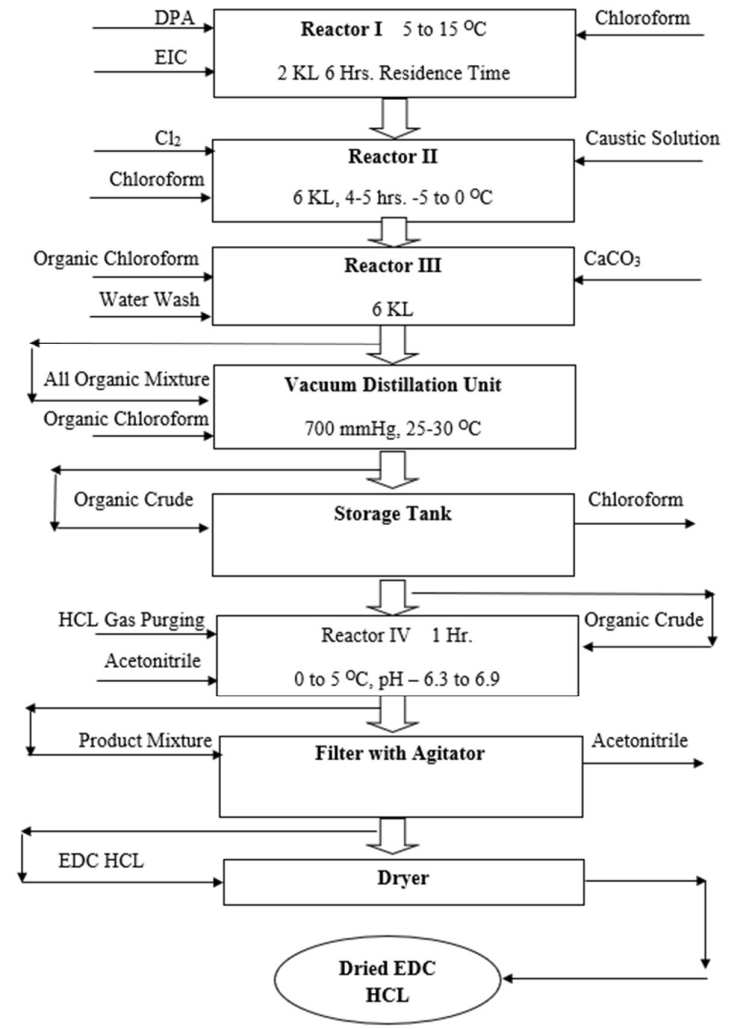
2. Separation and Distillation – In this step with help of water separation and distillation process carried out. After this process chloroform produced as a distillate and dissolved salt to be separated as a bottom product.

3. Reactions and Salt Formation – Reaction of dissolved salt, acetonitrile and HCL carried out again salt formation taking place and H_2 gas release.

4. Filtration Process – Acetonitrile, Mother Liquor and EDC-HCL to be separated with help of filtration process.

5. Drying and Storage- After filtration final product to be sent for drying process and finally for storage.

Process Flow Diagram



Process Diagram for Production of EDC-HCL

Quantitative requirement of Raw Materials

The following requirement of material as per actual plant manufacturing process. For production of 145-150 kg of EDC-HCl, Requirements as follows,

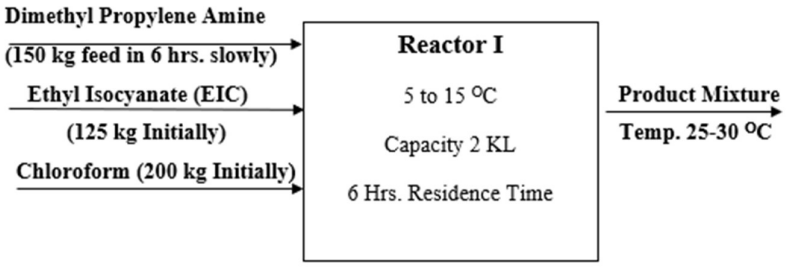
Sr. No.	Name of Material	Quantity in kg
01	EIC (Ethyl Isocyanate)	125
02	DPA (Dimethyl Propylene Amine)	145-150
03	Chloroform	1600
04	$CaCO_3$	90
05	Acetonitrile (Fresh)	1650
06	HCL	72
07	Cl_2	3500
08	Water	2000 KL

Table of Quantitative requirement of Raw Materials

Above raw material quantity shows with recycle stream balance. The raw material quantity based on the actual process run in plant. The actual yield of product depends the processes conditions like temperature, pressure, flow rate, amount of material, catalyst. In the production of EDC-HCL the measure parameter impact on the yield of product is temperature.

Process Description

1. Reactor I

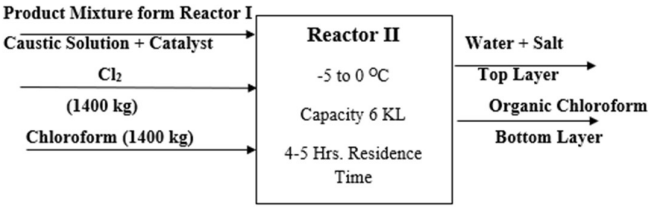


Initially EIC and Chloroform feed to reactor. Reaction is exothermic and temperature maintained at 5-15 ^{O}C with help of brine solution feed to chilling process for 6 hrs. By maintaining this condition third reactant DPA feed continuously (add slowly). Reaction completed within 6 hrs. and then product mixture sends to be next reactor after maintaining the temperature between 25-30 ^{O}C.

Chemical Reaction

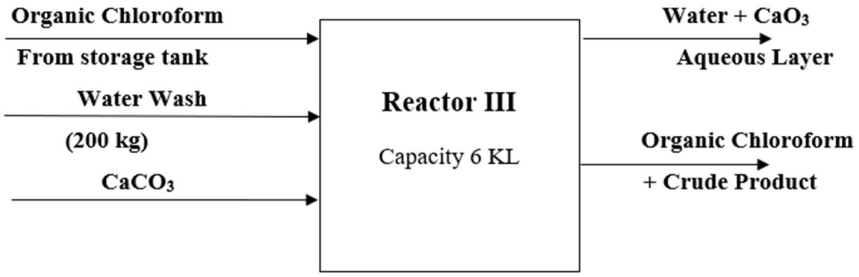
Dimethyl Propylene Amine + Ethyl Isocyanate = (Dimethyl Amino) Propyl] - N'-ethyl carbodiimide

2. Reactor II



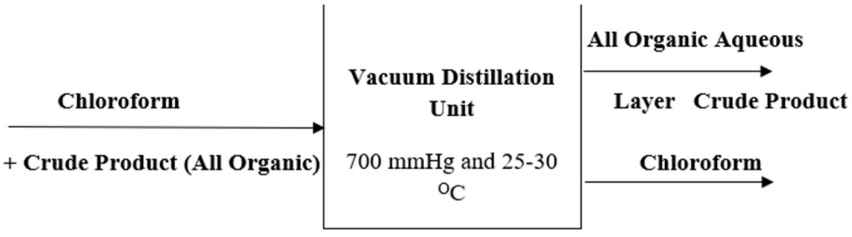
Initially product mixture, caustic soda, catalyst, Cl_2 and chloroform feed to reactor II. Temperature maintained between -5-0 ^{O}C for 4-5 hrs. After completion of reaction two layers are form top layers contains water and salt, bottom layer contains organic chloroform. Organic chloroform is sent to storage tank and further sent to reactor III.

3. Reactor III



Organic chloroform with product mixture is introduced to reactor III where water wash and $CaCO_3$ feed to removal of impurities from product mixture and also maintaining the product pH. From reactor III top layer separated as water, CaCO3 and impurities. Bottom layer contains organic chloroform and crude product.

4. Vacuum Distillation Unit



Organic chloroform and crude product are introduced to vacuum distillation unit. This unit operation is important for separation of organic chloroform and crude product. The temperature is important factor for separation of product mixture. As temperature of system increase to above 30 ^{O}C product will be melt and reduce below 25 ^{O}C impact on separation process. As temperature increase or decreases the amount of product will be reduce that will impact on yield of final product.

5. Reactor IV

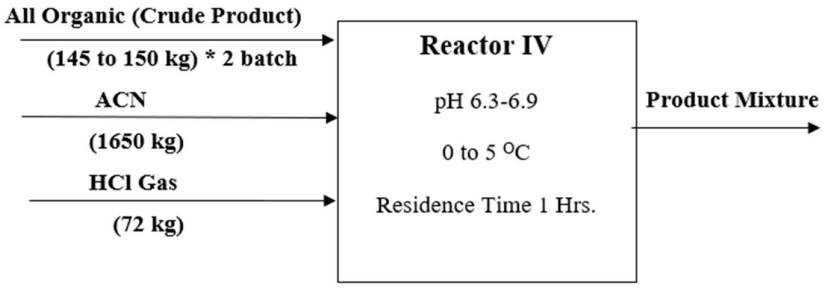


Fig. Process block Diagram for Reactor IV

Crude product, ACN and HCl gas is introduced to reactor IV where the reaction carried out at pH 6.5-6.9 and temperature 0 to 5 ^{O}C. In reactor IV final reaction is carried out in which Dimethyl Amino Propyl-ethyl carbodiimide reacted with HCl to gives EDC-HCl is the final product. Temperature and pH are the important factor which impact on yield of reaction. Optimum value of temperature and pH are 6.5-6.9 and 0-5 ^{O}C resp.

Chemical Reaction

(Dimethyl Amino) Propyl] - N'-ethyl carbodiimide + HCl == N- [3- (dimethyl amino) propyl] - N'-ethyl carbodiimide. Hydrochloride or (EDC.HCl)

6. Filtration and Dying Process

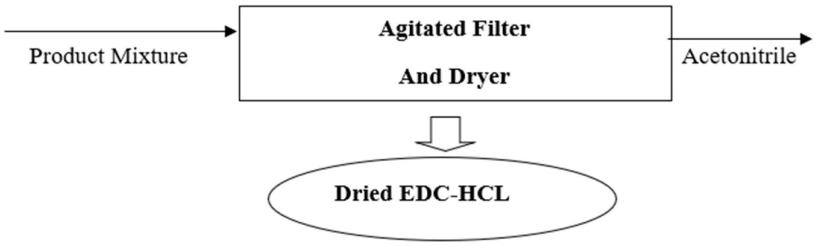


Fig. Process block Diagram for Filtration and Drying Unit

Filtration and Dying Process carried out simultaneously. In agitated filtration process acetonitrile removed and product send for drying unit. Final product sent for storage after drying process.

RESULTS AND DISCUSSIONS

Effect of Temperature on EDC HCl Production

Sr. No.	Temperature in ^{O}C	Kg of EDC:HCL
01	-10 to -5	90
02	-5 to 0	110
03	0 to 5	150
04	5 to 10	90
05	10 to 15	80

Effect of Temperature on EDC HCl Production

Table shows the effect of temperature on production of EDC·HCl. Temperature at 0 to 5 ^{O}C gives the maximum yield of EDC-HCL. As the value of temperature increases and decrease which can directly impact on yield of product. Temperature at 0 to 5 ^{O}C gives the highest yield of (150 kg) product which is the optimum value.

Effect of pH on EDC HCl Production

Sr. No.	pH	Kg of EDC:HCL
01	5 to 5.5	95
02	5.5 to 6	115
03	6 to 6.5	140
04	6.5 to 7	150
05	7 to 7.5	110
06	7.5 to 8	90

Effect of pH on EDC HCl Production

Table shows the effect of pH on production of EDC·HCl. pH at 6 to 7 gives the maximum yield of product (140-150 kg) which is maximum. As the value of pH increases or decreases which can directly impact on yield of product. The value of pH 6 to 7 produce maximum yield of (150 kg) product which is the optimum value.

Effect of Residence Time on EDC HCl Production

Sr. No.	Residence Time in Hrs.	Kg of EDC:HCL
01	0.25 to 0.5	90
02	0.5 to 0.75	110
03	0.75 to 1	140
04	1 to 1.25	150
05	1.25 to 1.5	120
06	1.5 to 2	115

Effect of Residence Time EDC HCl Production

Table shows the effect of Residence Time on production of EDC·HCl. Residence Time range between 0.75 to 1.25 hrs. Gives the maximum yield of product (140-150 kg). As the residence time increases or decreases which is directly impact on the product yield.

CONCLUSION

As per observation reaction between EIC and Chloroform temperature should be maintained at 5-15 ^{O}C which gives highest yield for production of Dimethyl Amino Propyl-ethyl carbodiimide important material used for production of EDC-HCl. For reaction between EDC and HCl temperature should be maintained at 0 to 5 ^{O}C which gives highest yield for production of final product of EDC-HCl. For reaction between EDC and HCl value of pH should be maintained between 6.3-6.9 which can give highest yield for production of final product of EDC-HCl. In reactor IV final reaction is carried out in which Dimethyl Amino Propyl-ethyl carbodiimide reacted with HCl to gives EDC-HCl is the final product. For reaction between EIC and Chloroform residence time should be maintained 6 hrs. Which gives highest yield for production of Dimethyl Amino Propyl-ethyl carbodiimide important material used for production of EDC-HCl. For reactor II optimum value of residence time is 4-5 hrs. For reaction between EDC and HCl residence time should be maintained between 1 hr.

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