

## **CHAPTER II**

### **THEORY AND LITERATURE REVIEW**

#### **2.1 Process of Amoxicillin Trihydrate [3,4]**

##### **a) Preparation of Mixed Anhydride**

D(-) parahydroxyphenylglycine danc salt potassium methyl is added to anhydrous methylene chloride and the suspension is cooled. Dimethylacetamide is added and the mixture is cooled. 2,6-Lutidine is added followed by pivaloyl chloride at such a rate to maintain the temperature around  $-30^{\circ}\text{C}$ . The reaction mixture is stirred further for 1 hour.

##### **b) Preparation of 6-APA Solution**

A suspension of 6-APA in methylene chloride and water is cooled and treated with triethylamine at such a rate to the temperature below 12 to  $15^{\circ}\text{C}$ . A pale yellow solution forms.

##### **c) Preparation of Amoxicillin Trihydrate**

The 6-APA solution above is added over 30 minutes to the mixed anhydride preparation keeping the temperature below  $-65^{\circ}\text{C}$ . The reaction mixture is stirred further for 3 hours. The mixture is allowed to warm to  $-33^{\circ}\text{C}$ , and water is added. The temperature rises to  $0^{\circ}\text{C}$  to  $8^{\circ}\text{C}$ . Concentrated hydrochloric acid is added and the mixture is stirred for 8 minutes. The layers are separated, and acetone is added. The pH of the aqueous phase is adjusted with sodium hydroxide keeping the temperature at  $2^{\circ}\text{C}$  to  $5^{\circ}\text{C}$ . The resulting precipitate is stirred for 10 minutes keeping the pH at 1.8 by further addition of sodium hydroxide. Finally the mixture is brought to pH 5.0 with sodium hydroxide and stirred for 1 hour. Amoxicillin trihydrate is centrifuged, washed with cold water and acetone and dried. Process of Amoxicillin trihydrate is shown in Figure 2.1.

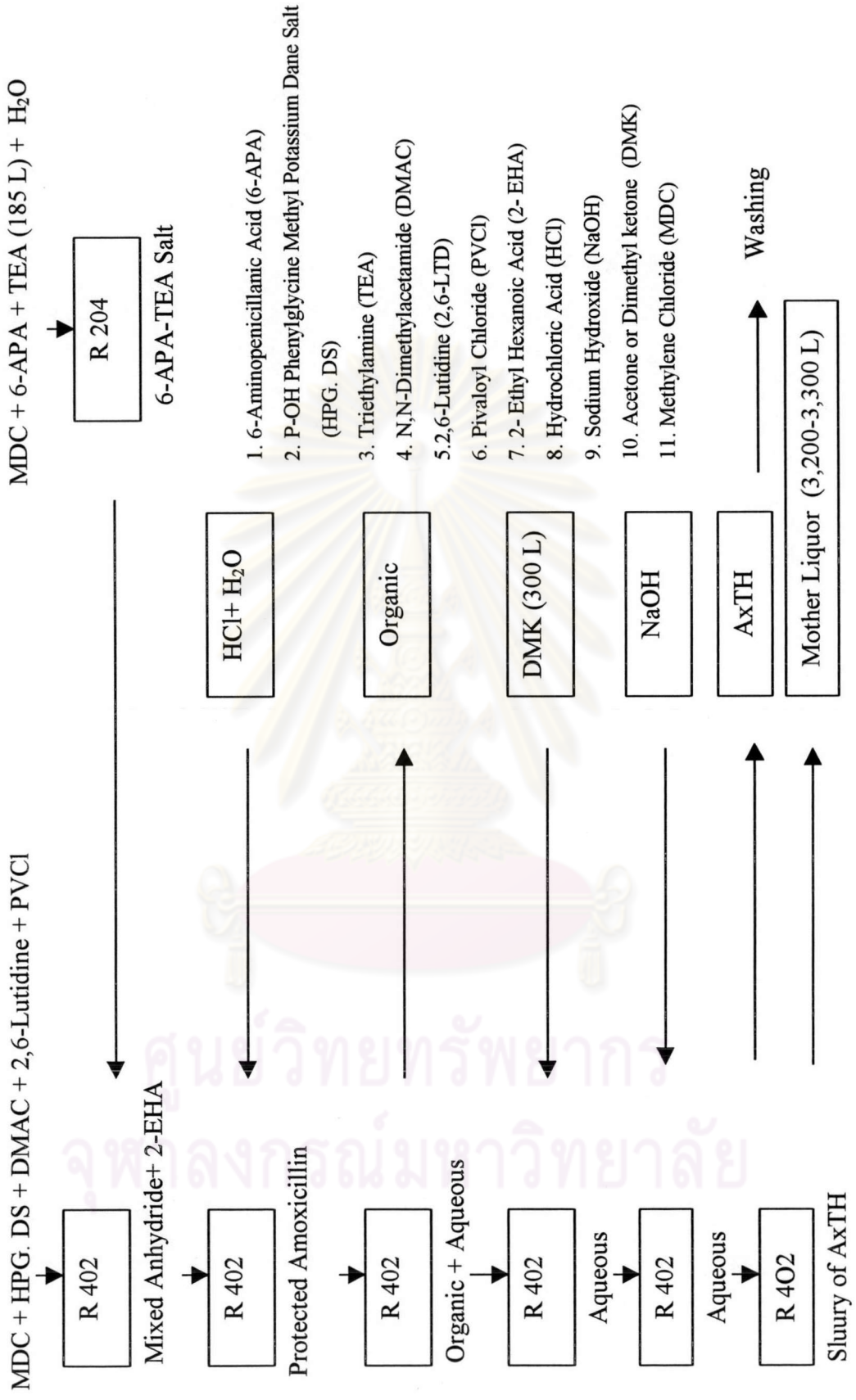
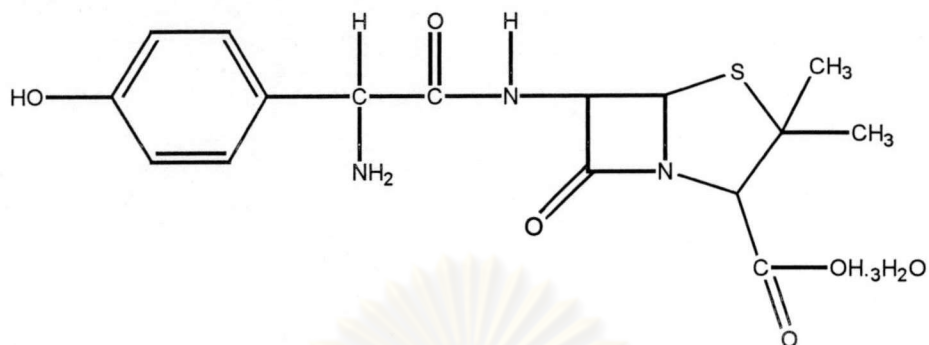
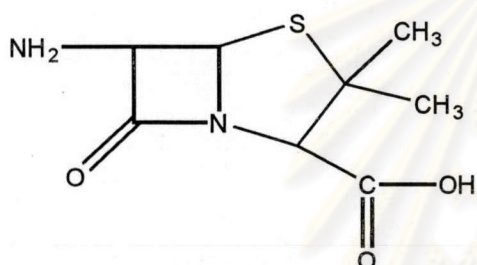


Figure 2.1 The overall schematic of amoxicillin trihydrate process.

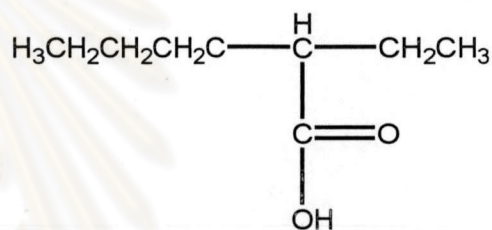
## 2.2 Structure of Chemicals



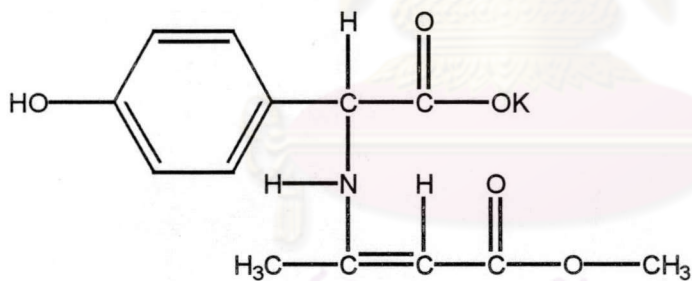
Amoxicillin Trihydrate



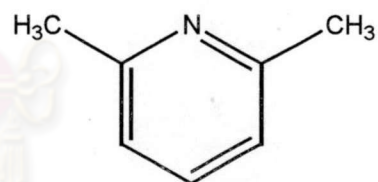
6-Aminopenicillanic acid



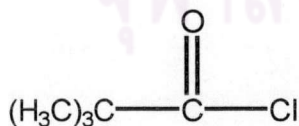
2-Ethyl hexanoic acid



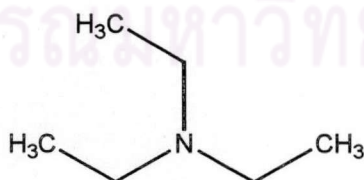
P-OH Phenylglycine methyl potassium salt



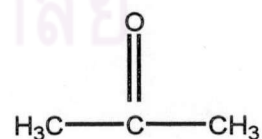
2,6-Lutidine



Pivaloyl chloride



Triethylamine



Acetone

## 2.3 Typical Physical and Chemical Properties [5]

Table 2.1 shows typical physical and chemical properties of triethylamine, 2,6-lutidine and solvents used in process of amoxicillin trihydrate.

## 2.4 Fraction of Non-Ideal Solutions

### 2.4.1 Minimum-Boiling Mixtures [6]

A low-boiling azeotrope is distilled through a column, no change in composition occurs, either in boiler, column, or condenser. On the other hand, if the mixture of these particular components does not have the azeotropic composition, the column causes more or less change in composition. It is then customary to state that “fractionation occurs”.

For example (Figure 2.2), if 100 g of aqueous ethyl alcohol (50%) should be distilled through an ideal, highly efficient column, 96% alcohol would be steadily received in the condenser until the boiler was completely stripped of alcohol. The temperature at the top of the column would remain constant 78.15°C during the distillation. Approximately 2 g of water would by this time have come over with the 50 g of alcohol, with yield of about 52 g of the azeotrope. Further attempt to distill would, after momentary interruption, cause about 48 g of water to come over at 100°C.

### 2.4.2 Maximum-Boiling Mixtures [6]

Mixtures in which negative deviation from Raoult's law occurs may also be fractionated, provided that they are not of azeotropic composition. This time the first distillate will be of one single component. This is illustrated in Figure 2.3, which should be examined along with the corresponding boiling point-composition diagram of Figure 2.4.

Table 2.1 Typical physical and chemical properties [5].

Properties	Acetone	Methylene chloride	Triethylamine	2,6-Lutidine
physical and chemical				
from	liquid	liquid	liquid	liquid
colour	colourless	colourless	colourless	colourless
odour	fruity	sweetish	amine-like	unpleasant
pH value	5-6 @395g/l H <sub>2</sub> O (20°C)	neutral (20°C)	12.7@100g/l H <sub>2</sub> O (15°C)	
melting point ( °C)	-95.4	-97	-115	-6
boiling point (°C)	56.2	39.5-40.5	88-90	144
density @ 20 °C (g/cm <sup>3</sup> )	0.79	1.32	0.73	1.92
solubility in				
water @ 20 °C (g/l)	soluble	20	133	soluble
organic @ 20 °C	soluble		soluble	soluble
decompose (°C)		>120		

Suppose a mixture of chloroform (40 g) and acetone (40 g) is distilled through an idea fractionating column. At first pure acetone passes over until just 30 g has left the boiler. The balance is of the azeotropic composition, acetone (10 g) and chloroform (40 g). Fractionation ceases, and the entire residue, which is the azeotrope, will distill uniformly at 64.7°C to the end.

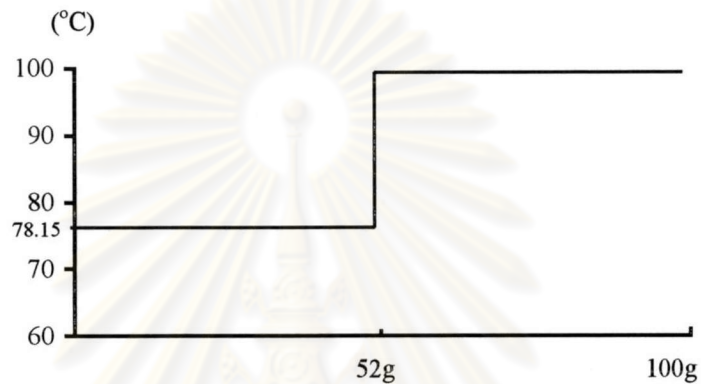


Figure 2.2 Distillation of 100 g of a 50% solution of ethyl alcohol through an efficient column [6].

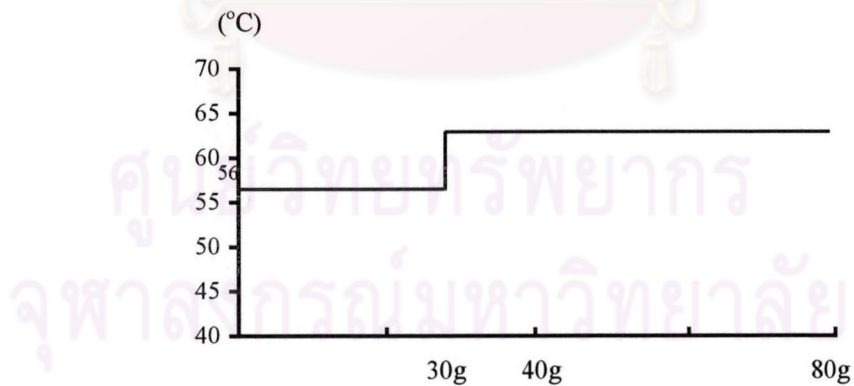


Figure 2.3 Distillation of acetone-chloroform mixture through a column [6].

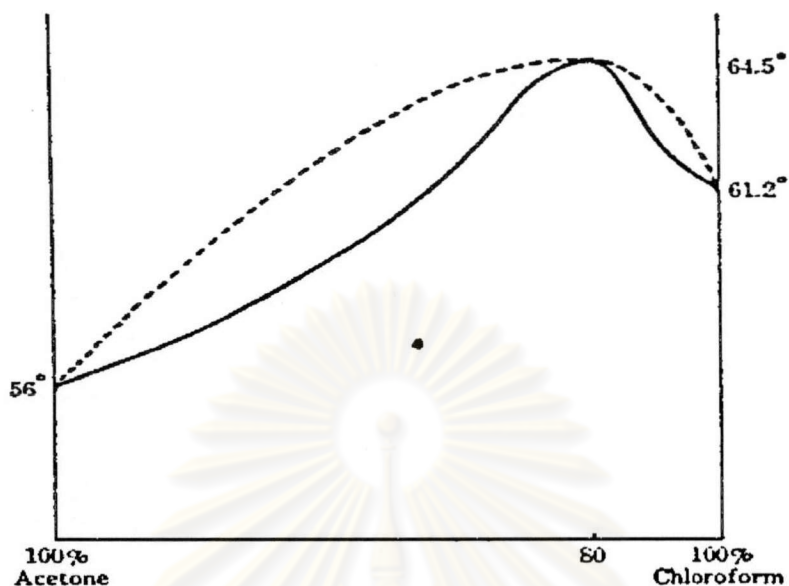
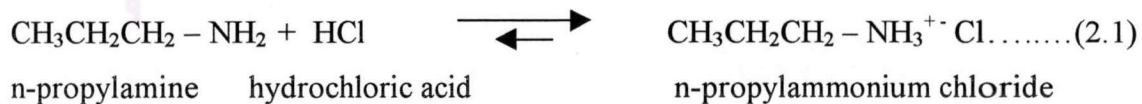
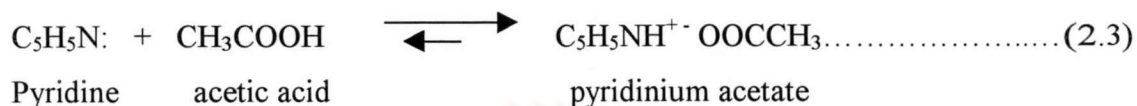
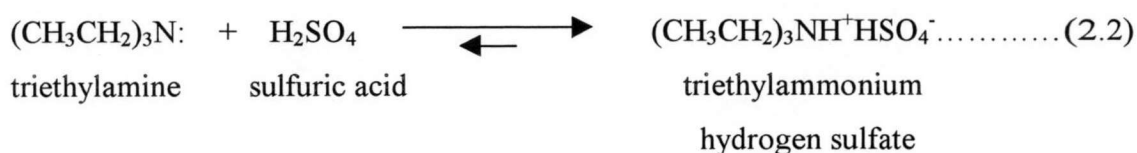


Figure 2.4 Negative deviation [6].

## 2.5 Salts of Amines [7]

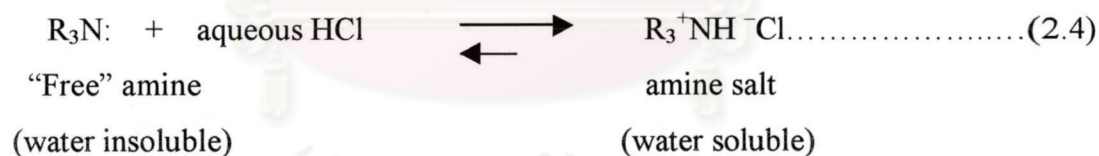
When an amine is protonated by a strong acid, the product is an amine salt. The amine salt is composed of two types of ions: the protonated amine cation (an ammonium ion) and the anion derived from the acid. Simple amine salts are named as the substituted ammonium salts. The salts of more complex amines are named using the names of the amine and acid that make up the salt.





Amine salts are ionic, high-melting, nonvolatile solids. They are much more soluble in water than the parent amines, and they are only slightly soluble in nonpolar organic solvents.

The formation of amine salts can be used to isolate and characterize amines. Most amines containing more than six carbon atoms are relatively insoluble in water. In dilute aqueous acid these amines form their corresponding ammonium salts and they dissolve. The formation of a soluble salt is one of the characteristic functional group tests for amines.



The formation of amine salts is also used to separate amines from less basic compounds. The amine forms a salt and dissolves in dilute acid. When the acidic solution of the amine salt is made alkaline by the addition of NaOH, the amine is regenerated. The purified free amine either precipitates out of the aqueous solution or is extracted into an organic solvent.

Many drugs and other biologically important amines are commonly stored and used as their salts. The amine salts are much less prone to decomposition by oxidation



and other reactions, and they have virtually no fishy odor. The salts are soluble in water, and they are easily converted to solution for syrups and injectables [7].

## 2.6 Phase-Transfer Catalysis [8]

Charles M. Starks has summarized the catalytic cycle as shown in Figure 2.5. Everything hinges on the fact that the alkyl groups of the quaternary ion make it lipophilic, and hence capable of entering the organic phase. But it cannot go alone; to balance its positive charge it must take an anion along. This anion will occasionally be its original counter-ion, bisulfate; this weakly basic anion has virtually no nucleophilic power, and does nothing.

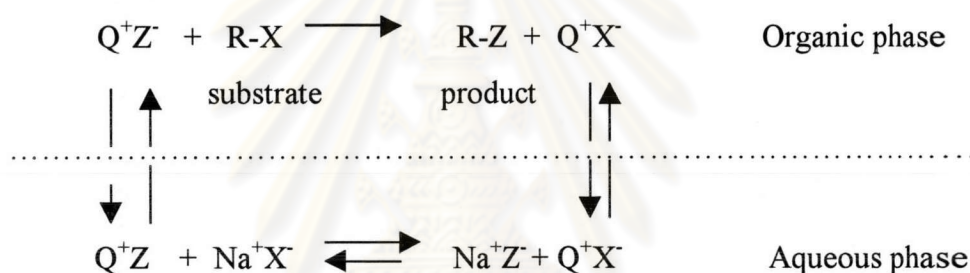


Figure 2.5 Phase-transfer catalysis

From Figure 2.5, for phase-transfer catalysis [8], the quaternary ammonium ion ( $\text{Q}^+$ ) is both hydrophilic and lipophilic. It shuttles back and forth between the aqueous phase and the organic phase taking an anion with it: the nucleophile is ( $\text{Z}^-$ ) or the leaving group is ( $\text{X}^-$ ). In the organic phase, the nucleophile is virtually unsolvated and reacts rapidly with the substrate ( $\text{R-X}$ ).

## 2.7 Drying Agents [9]

Drying agents fall into two broad categories, those used for preliminary drying and the drying extracts, and those used for rigorous drying. The pre-drying agents are largely interchangeable with each other and the choice is usually limited only by the

chemical reactivity of some of the reagents. Preliminary drying of solvents, prior to rigorous drying, is essential unless the solvent already has a low ( $< 0.1\%$ ) water content. Of necessity the reagents used of thorough drying are very reactive and they must be treated with great care. In particular, it is important to make the right choice of drying agent for the solvent in question, in order to avoid dangerous or undesirable reactions between the solvent and the drying agent, and care must be taken to ensure the safe destruction and disposal of excess reagent remaining in solvent residues [9].

a) Barium oxide, BaO. The commercially available anhydrous product is an inexpensive drying agent which is useful for amines and pyridines (30-50 ppm after standing for 24h over 5% w/v). It is strongly basic and is ineffective for alcohols and dipolar aprotic solvents [9].

b) Calcium hydride, CaH<sub>2</sub>. The reagent of choice for rigorous drying amines, pyridines, and HMPA, and effective also for hydrocarbons, alcohols, ethers, and DMF. It is available in powdered or granular form; the granular is preferable if it is to be stored for any length of time. The granules should be crushed immediately before use and residues should be destroyed by careful addition of water (H<sub>2</sub>O evolution) [9].

c) Molecular sieves. These are sodium and calcium aluminosilicates which have cage-like crystal lattice structures containing pores of various sizes, depending on their constitution. They can absorb small molecules, such as water, which can fit into the pores. The most commonly used types 3A, 4A, and 5A have pore sizes of approximately 3°A, 4°A, and 5°A respectively, and they are available in bead or powder form. After activation at 250 to 320 °C for a minimum of 3 h they are probably the most powerful desiccants available. They can be stored in a desiccator or in an oven at  $>100$  °C for a few weeks but they are rapidly hydrated in the air. If you are doubtful about the effectiveness of an old batch, place a few beads in the palm of your hand and add a drop of water if the sieves are active you should feel a distinctly exothermic reaction. In most cases extremely dry solvent can be obtained simply by

batchwise drying over sieves, i.e. allowing the solvent to stand over 5% w/v of sieves for 12 h, decanting, adding a second batch of sieves etc. Sieves absorb water reversibly so a solvent should always be decanted from the sieves prior to distillation. 4A Beads are recommended for thorough drying of amines, DMF, DMSO, and HMPA, and almost all rigorously dried solvent are best stored over 5% w/v of 4A sieves. Provided that they are not discoloured, sieves can be reused by washing well with a volatile organic solvent, allowing to dry, drying at 100°C for several hours, and then reactivating at 300°C [9].

d) Sodium and potassium hydroxide, NaOH and KOH. The use of these efficient reagents should usually be confined to the drying of amines (soda lime, barium oxide or calcium oxide may also be employed), potassium hydroxide is somewhat superior to the sodium compound, These bases react with many organic compound (e.g. acid, phenols, esters and amides) in the presence of water, and with some common solvents (e.g. chloroform) so that their use as desiccants is very limited [10].

e) Anhydrous potassium carbonate,  $K_2CO_3$ . This drying agent possesses a moderate efficiency and drying capacity (the hydrate is formed). It is applied to the drying of nitriles, ketones, ester and some alcohols, but cannot be employed for acids, phenols and other acidic substances. It also sometimes replaces sodium hydroxide or potassium hydroxide for amines, when a strongly alkaline reagent is to be avoided. Potassium carbonate frequently finds application in the salting-out of water-soluble alcohols, amines and ketones, and as a preliminary drying agent. In many cases it may be replaced by the desiccant magnesium sulphate [10].

## 2.8 Adsorption and Absorption [6]

Solids adsorb materials from solution as a result of van der Waals' forces. Such intermolecular forces operate only at very short distances and hold materials on a surface as a monomolecular layer. Competition for positions on the surface exists

between the various kinds of molecules in the solution, including solvent molecules. The amount of a solute that will be adsorbed from solution in a solvent will depend on the nature of both solute and solvent as well as on the concentration of solute and the amount of surface available. Adsorbents differ in their relative adsorptive power for various molecules, so that the amount of solute held also depends on the adsorbent used. If a weakly adsorbed compound has saturated a surface, and a solution of a substance that will adhere more strongly is brought into contact with that same surface, the more weakly adsorbed compound will be displaced. Similarly, if one capable of being held more strongly replaces the original solvent, the amount of solute remaining on the surface will be decreased by a similar displacement. This usually permits easy recovery of adsorbed materials [6].

Adsorption may serve in various ways as a basis for purification of compounds and separation of mixtures. A discussion of decolorizing procedures will be deferred until chromatography has been described and the factors involved in adsorption have been discussed [6].

Absorption and adsorption are two different things. For absorption, a chemical change occurs as this kind of desiccant, absorbent, attracts and retains water vapor [11].

## **2.9 Literature Review**

Phelps et al. [1] studied the adsorption process for organic base recovery from aqueous brine solutions. An adsorption process uses a non-ion-exchangeable adsorbent polymeric resin of a monoethylenically unsaturated monomer such as styrene and polyvinylidene monomer such as divinylbenzene for the adsorption of organic base, such as amines, amine salts and guanidinium salts, from high ionic strength aqueous solutions.

Timothy et al. [12] studied the solvent extraction technology. The Basic Extractive Sludge Treatment (B.E.S.T.) process is a patented solvent extraction system that uses triethylamine to separate organic contaminants from slugs, soils, and

sediments. Organics are concentrated in an oil phase, thereby reducing the volume of waste requiring further treatment. Multiple extractions are conducted and are followed by solvent recovery, oil polishing, solids drying, and water stripping. Triethylamine exhibits a property known as inverse miscibility, in which it is miscible with water below 60°F and immiscible with water above 60°F. Solids can be dewatered and organic contaminants extracted simultaneously during “cold extractions”; and any remaining organic contaminants can be removed during “warm” and “hot extractions”. The process was demonstrated at the Grand Calumet River in Gary, Indiana in July of 1992. Sediments collected from two locations in the river were treated separately. Contaminant reductions of 96% or greater for total PAHs and greater than 99% for total PCBs were achieved.

Bohrer et al. [13] studied the process for treating byproduct of optical fabrication. It has been found that in sol-gel processes utilizing tetramethylammonium hydroxide, it is possible to treat a trimethylamine-containing solution with hydrogen peroxide to form trimethylamine oxide, a water soluble compound which is less volatile and less odorous than trimethylamine, and which is capable of being sent to a standard wastewater treatment plant. The hydrogen peroxide is generally added to the trimethylamine-containing solution in a peroxide:trimethylamine ratio of at least 3:1, advantageously at least 10:1. Because of the resultant trimethylamine oxide solution ability to be sent to a standard wastewater treatment facility, improved productivity and lowered expense of the overall fiber fabrication process are obtained. The invention is also suitable for treatment of triethylamine.

Holtzaple et al. [14] studied the recovery of fermentation salts from dilute aqueous solution. Extracting water using low-miscibility, low-molecular-weight secondary and tertiary amine may concentrate dilute solutions of fermentation salts, e.g. triethylamine (TEA), diisopropyl amine (DIA), N,N-diethylmethylethylamine (DEMA), and mixtures thereof. At 30°C - 50°C., which corresponds to typical fermentation temperatures. These low-molecular-weight amines or their mixtures can

extract large amounts of water from dilute aqueous solutions containing fermentation salts. Thus, dilute fermentation salt solutions can be concentrated by selectively removing water. At these low temperatures, the amine phase contains 20-35% water and a much reduced quantity of fermentation salt. When the temperature is raised, water phases out of the amine, allowing the amine to be recycled and reused to extract additional water. Using this approach, about 82.5% of water can be removed from a 3% dilute solution using conventional multistage, countercurrent extraction, thus providing a 15% concentrated fermentation salt solution.

Martin et al. [15] studied the use of aqueous triethylamine/phosphoric acid salt solution to extract water and triethylamine from solutions thereof in organic solvents. Triethylamine and water are simultaneously removed from solutions in organic solvents, by liquid/liquid extraction with concentrated aqueous solutions of  $(C_2H_5)_3NH_3PO_4$  which preferably contain free phosphoric acid as well. Upon heating of the resulting extract, the water and amine taken up are boiled off and the extracting regenerated. The method is of particular value in the preparation of aqueous coating compositions comprising reaction products of polyether epoxides and  $H_3PO_4$  in organic media. The reaction product is salified with triethylamine in excess, in the presence of added water. The organic solution is boiled off, together with the excess amine and some of the water, to form an aqueous dispersion of the salified product and a distillate which can be processed by the method of the invention. The recovered solvent, water and amine may be recycled.