PART 2

Process Development and Industrialization

Chapter 4

Chemical Engineering and Process Engineering

4.1. History of chemical engineering and process engineering

From time immemorial, man has tried to transform substances found in mines or agriculture, into a variety of materials, consumer objects, and manufactured objects, in order to meet his basic requirements, to protect himself or conquer, to communicate, and to embellish his living space.

However, it was only in the 16th Century that what could be called the embryo of the chemical industry began to appear, which saw the Venetian Republic import, produce and export chemical products: aqua fortis (nitric acid), spirits of salt (hydrochloric acid), dyestuffs, and so on. The end of the 18th Century marked the rise of this industry, especially with the development of the manufacturing of sulfuric acid by the "lead-chamber" process and then with that of soda ash by the Leblanc process in 1791, who set up the first soda ash plant in Saint-Denis close to Paris.

The notion of *process*, without being explicitly used, gradually became established. It refers to the interaction of raw materials by using production facilities, purification of the resulting product, and disposal of residues. This process requires human and financial resources ... and customers. An industrial process is usually represented on paper by what is called a process flow diagram.

The diagram shown in Figure 4.1 represents the concept of a latex plant for construction in China along the Yangtze River. It implements the copolymerization

Chapter written by Jean-Pierre DAL PONT.

of butadiene with styrene monomer. The latex produced is used in paper coating and also in the manufacture of paints.
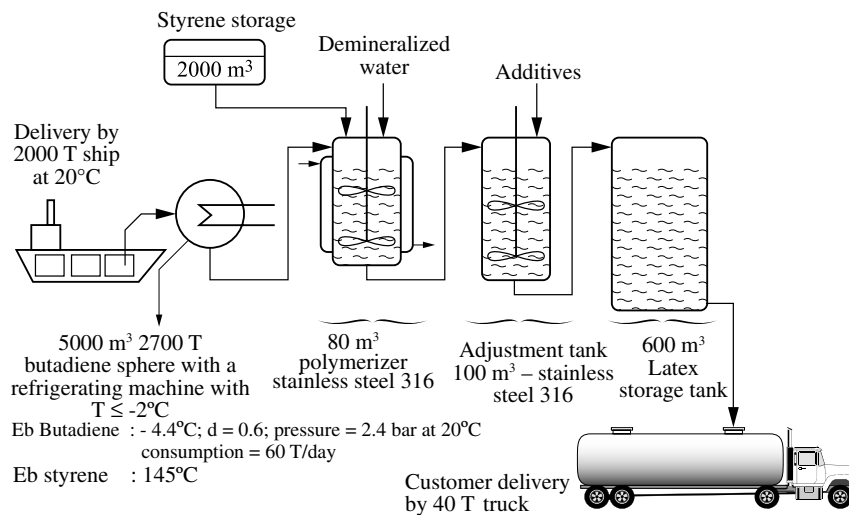

Figure 4.1. *Simplified diagram of a latex plant (capacity: 300 T/day)*

Gradually, as the demands for inorganic and organic products continued to increase and diversify, engineers were faced with equipment problems; equipment is necessary to make the products interact and to purify the products resulting from the reaction. Materials resistent to corrosion also had to be found. The same product started to be produced by different chemical means. This was how Ernest Solvay introduced the Solvay process, also known as the ammonia-soda process, in 1867. This process being more economical, gradually replaced the Leblanc process, which finally disappeared in 1915.

4.1.1. *Chemical engineering*

At the beginning of the 20th Century, in the United States, chemical engineering was born. More precisely, at MIT (Massachusetts Institute of Technology) with the arrival of Professor William H. Walker in 1902, as the head of the Chemical Engineering Department. Chemical engineering was no longer just the combination of industrial chemistry with mechanics. It began to shape itself as a specific discipline. Soon, the profession was organized and the AIChE (American Institute of Chemical Engineers) was founded in 1908. The formulation by Arthur D. Little of the concept of "Unit Operation" in an internal MIT report in 1915 represented the

last big step in these beginnings, a decisive step for the development of the field: "*Any chemical process, in whatever scale conducted, may be resolved into a coordinated series of what may be termed "unit actions", as pulverizing, mixing, heating, roasting, absorbing, condensing, lixiviating, precipitating, crystallizing, filtering, dissolving, electrolyzing, and so on. The number of these 'basic unit operations' is not very large and relatively few of them are involved in any particular process ...*".

The book *Principles of Chemical Engineering*, published by Walker, Lewis, and McAdams in 1923 can be considered to be the first basic book of the new discipline. Canadians translated *Chemical Engineering* into "génie chimique" in French. This term "génie chimique" was again used by Professor Cathala during the foundation of the "Institut du génie chimique" in Toulouse, France in 1949. Chemical engineering emerged as a major technology, in equal terms with electrical, civil, and mechanical engineering.

The prodigious development, in the early 20th Century, of the petroleum industry and the parachemical industry, which used the raw materials coming from refineries, gave chemical engineering an unprecedented boost. It also played a major role in the development of American chemical companies by following in the footsteps of DuPont.

The company founded in 1802 by Eleuthère Irénée DuPont along the banks of the Brandywine River (Delaware), started by manufacturing gunpowder by improving the process used in the powder mill of Essonnes near Paris. Most of DuPont's managers were graduates from MIT.

The chemical engineers had calculation methods to size the pieces of equipment such as distillation columns, pumps, and heat exchangers. At that time, many operations were more of an "art than science". This was true, for example, in the case of solution crystallization, which started to be studied in depth in the 1940s. The crystallizers were then progressively calculated and used on a scientific basis furthering the chances of success.

Chemical engineering grew enormously in the United States between the two World Wars (balance science, mathematical tools, applied thermodynamics) with the support of a very rich literature with the publication, for example, of the first edition of "Perry" (*Chemical Engineering Handbook*) in 1934 and the book *Principles of Chemical Engineering* by Hougen and Watson in 1937.

However, we should not forget the role played by some French in the 19th Century, for example, Eugène Péclet (*thermal effects*) or Jean-Baptiste-Cellier Blumenthal and Ernest Sorel (*distillation*).

In the 1940s, chemical engineering effectively contributed to the American war effort which saw the construction of factories in record time to produce synthetic

rubber and fuel, and huge factories for the production of fissile materials: uranium 235, plutonium, with methods never used before.

Other technological revolutions would follow. In 1960, the book by Bird, Stewart, and Lightfoot, *Transport Phenomena*, discussed the aspects of material, energy, and momentum transfer in detail. Meanwhile, Octave Levenspiel's patents of nobility on chemical reaction engineering constituted the discipline of study of reactors. This discipline aimed at characterizing reactors and thereby improving the efficiency and selectivity of reactions. The second half of the 20th Century saw the emergence of biotechnology and agri-food engineering.

At the same time, the skills of engineering firms responsible for the design and construction of the plants was completely changed by the emergence of information technology. Equipment calculations that had taken days, or even weeks, were done in minutes. Physical (plastic and wood) plant models were replaced with virtual computer models; Indian ink disappeared from the engineering and design department.

The chemical industry moved closer toward the customer: the concept of the *product* was distinguished from *commodities* such as sodium hydroxide, sulfuric acid, *specialty* chemicals with valuable use; high-quality shampoo contains up to 20 components and must meet sophisticated specifications.

The term *product engineering* refers to the techniques involved in the design and manufacturing of products. Thus, nanotechnologies deal with extremely refined products, be it solid particles used in cosmetics or textile fibers imitating natural silk.

The production techniques that gained a new impetus in Japan after World War II created the concept of flows: material flow, information flow, and human and financial resource flow. The production units, whether continuous and dedicated to the manufacture of a single product, or discontinuous and multipurpose – that is, manufacturing many products – were automated. The control system used sophisticated sensors, online analysis, and programmable logic controllers. The factory, whether it produced a few products of 10,000 tons per year or several hundred products, ranging from a few kilos to several hundred tons, per year, used administrative data processing to manage the operations and maintenance.

The 1960s saw an awareness from the general public regarding the chemical industry in general. The first oil crisis in 1973 and major industrial disasters like Flixborough (1974), Seveso (1976), Bhopal (1984), and AZF, Toulouse (2001) had a significant impact and continued to attract media attention. The concepts of health, safety, and the environment, denoted by the acronym HSE, began to influence the operating mode of industrial companies, whether in developing new products, designing or managing new production tools, or storing, transporting, and supplying the manufactured products to the customer.

4.2. Process engineering

4.2.1. *Objectives of process engineering*

By 1980, particularly in France, a federal concept slowly emerged based on the fact that many industries used the techniques and methods of chemical engineering.

The petroleum and parachemical industries, coals chemistry, pharmaceutical and healthcare industries, steel industry, basic chemicals, specialty chemicals, cosmetics, electronics, agri-food, cement, paper, glass, fertilizers, ores, plastics, energy, water purification, and environmental protection industries, just to mention the largest ones all use the concepts developed by chemical engineering over a century.

Process engineering is "the set of knowledge necessary to design, analyze, develop, construct, and operate, in an optimal way, the processes in which the material changes":

– its shape, state of aggregation, or dispersion;

– its physical state or physico-chemical properties;

– its chemical nature [VIL 83].

Process engineering, is therefore involved in industrial sectors whose economic significance is considerable. It should not be confused with industrial chemistry whose purpose is to study the properties of chemical products and their manufacturing processes.

What has just been discussed clearly shows the knowledge-savvy reader the wide variety, extreme complexity and enormous scope covered by process engineering. What follows is not exhaustive! We only hope that it will show that chemistry, which is present everywhere today cannot act alone. Any chemical reaction, either beneficial or harmful, is a link in a chain of physical processes that we will discuss briefly.

4.2.2. *The scientific bases and basic tools of process engineering*

Process engineering is built from a set of basic scientific disciplines, including:

– *mathematics and computer science* to equate, model, and simulate the processes;

– *thermodynamics* for all energy aspects, chemical thermodynamics for phase equilibria, interfacial phenomena, and so on;

– *chemical kinetics*;

– *fluid mechanics* (mixing, transportation, and flow of fluids);

– *transportation phenomena* – "physical kinetics" (transportation of materials and energy);

– *the mechanics of porous and dispersed media.*

The interaction of these disciplines led to specific developments like for example in:

– the domain of "mixing" (single- and multiphase);

– the domain of reactors (chemical and biochemical reactor engineering);

– the "traditional unit operations" that have already been mentioned, that is, distillation, crystallization and solid line (filtration, drying), solvent extraction, and so on;

– chromatographic techniques;

– membrane separation techniques;

– the engineering of material development and products with complex structures, and so on.

Process engineering commonly uses the notion of *driving force*, which can be compared with a voltage responsible for *transfers*, by analogy with electricity:

– a difference in temperature: a hot fluid heats up a cold fluid (see Figure 4.8);

– a difference in concentration: under the effect of temperature, methanol, which is more volatile, will enrich the gaseous phase of a water–methanol solution; this is the basic principle of distillation.

Process engineering has also developed tools and concepts specific to it, such as the concept of the *theoretical stage* or *counter-current* to ensure systematic contact between phases.

The engineer draws the process flow diagram, which is a *visualization* of the industrial process and will be documented, that is how one tries to determine for each line, that is, physically for each pipe, the temperature, pressure, flow rate, and chemical composition of the corresponding flow; this task is sometimes difficult because one needs to know "what is happening", and therefore be able to analyze chemically the flow and to have the appropriate measuring instruments.

This list would have been incomplete if the prodigious progress of process engineering in the 20th Century had not introduced specific technologies besides chemical engineering that could be described as classic. These include, among others, the following disciplines:

– electrochemical engineering (e.g. electrolysis of sodium chloride – table salt – to produce chlorine and sodium hydroxide);

– metallurgical engineering (extraction of metals from ores then refining);

– photochemical engineering (processes using light energy as a means of activation of the reaction);

– biochemical engineering including industrial fermentation, which is of considerable importance (brewing, vitamins, enzymes, drugs, food additives);

– agri-food engineering (freeze-drying, pasteurization, freezing, etc.).

A special place must be given to product engineering which covers all the know-how that enables us to develop and manufacture these products with specific functions. The active ingredient(s) are associated with formulation auxiliaries. For example, a herbicide is suspended in water using surfactants in order to be sprayed effectively.

The vast majority of installations in developed countries are now instrumented and automated. The *control system* is inseparable from the process.

It should also be noted that process engineering is currently being developed in a highly competitive economy in which the majority of disciplines require multidisciplinary teams. In addition to being a good technician, one must have a strong background in economics, particularly to determine the justification of certain investments, process modifications, and the launch of technical research.

Project management, the ability to work as a team and to communicate are techniques, sometimes described as "soft" skills, which, in addition to the "hard" skills, work toward making process engineering a discipline in itself.

4.3. The chemical reactor

A reactor is any piece of equipment where a chemical, biochemical, or nuclear reaction occurs. This reaction transforms molecules into other molecules. This is at the heart of the material transformation processes.

There are many classifications of reactors. This is the very broad domain of reaction engineering which is based on chemical and physical kinetics.

4.3.1. *Classification of reactors based on the method of feeding*

The first criterion for classification is whether it uses the *continuous or discontinuous operating mode*:

– the *continuous mode* is well adapted to the typical large tonnages of the inorganic industry (sodium hydroxide, sulfuric acid, fertilizers), petrochemical industry (ethylene), basic chemicals industry (phthalic anhydride, phenol), agri-food industry (confectionaries), and so on;

– the *discontinuous mode* (closed reactor) and semi-continuous mode (semi-continuous reactor) are suitable for tonnages limited to a few hundred or few thousand tonnes per year, especially when it is necessary to manufacture many products in the same workshop in successive *campaigns*. This holds true for the pharmaceutical, fine and specialty chemical (cosmetics, agricultural chemistry, etc.) industries.

A stirred reactor, equipped with a double jacket is shown in Figure 4.2. This reactor is also said to be closed, because the reactants are loaded at the beginning and they remain in the reactor until the end of the reaction. This is the simplest device; it reproduces the round bottom flask on a larger scale.
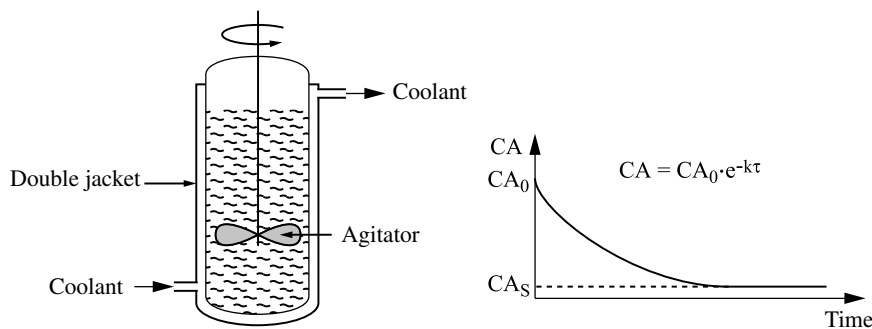

Figure 4.2. *(Discontinuous) closed reactor*

From now onward, we should note that another classification criterion relates to the nature of the system involved: we could talk about a *single-phase system* or a *multiphase* or *heterogeneous system*.

Real reactors often have complex reactive configurations, but they can sometimes be represented by a typical configuration called an "ideal" configuration, or by a combination of several of these ideal configurations.

In the case of continuous reactors, there are two types of ideal configuration:

– *continuous stirred tank reactor*, where the composition of the reactive mixture is uniform throughout the volume (Figure 4.3);

– *plug-flow reactor*, where the reactive mixture in the reactor progresses through sections perpendicular to the direction of flow, like a piston in a cylinder (Figure 4.4).
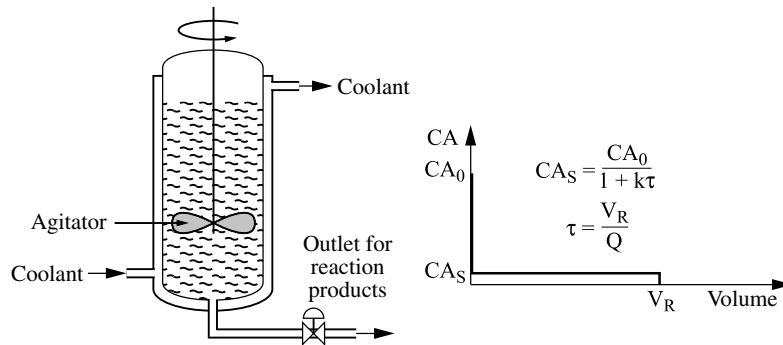
$$CA_S = \frac{CA_0}{1 + k\tau}$$

$$\tau = \frac{V_R}{Q}$$

Figure 4.3. *Continuous stirred tank reactor*

$$CA = CA_0 \cdot e^{-k\tau}$$
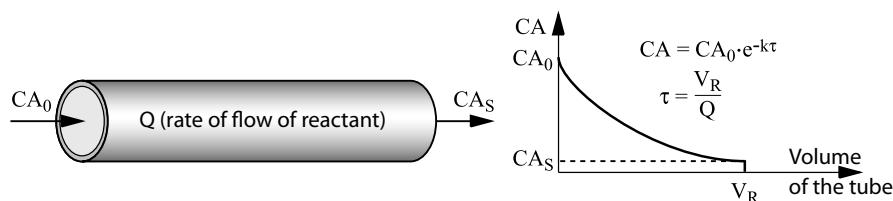
$$\tau = \frac{V_R}{Q}$$

Figure 4.4. *Plug-flow reactor*

This type of reactor is well adapted to the continuous mode and large tonnages. A very important application relates to the production of ethylene by steam cracking. The tube of about 8 cm in diameter is placed in a furnace which is heated by gas or fuel. The residence time, defined as the ratio of tube volume to the rate of flow of reactants, is less than 1 second.

4.3.2. *Classification according to the phases present*

4.3.2.1. *Gas/liquid system*

The reactor can be semi-continuous or continuous. The gas is brought into contact with the liquid by means of mechanical agitation (by injection in a turbine or self-priming using a suitable moving body), by recirculation through ejectors, or simply by dispersion at the bottom of the reactor in the absence of mechanical agitation (bubble columns, gas-lift reactors).

The continuous oxidation of cumene by air into the corresponding hydroperoxide, an intermediate of *phenol*, uses this type of reactor (Figure 4.5). The reactor, whose volume can exceed 100 m^3 provides a wide fluid retention.

In column scrubbers, the gas which is to be purified passes through some contacting devices by means of counter-current, where the gas and scrubbing solution come into contact.

The scrubbing is *systematic*: the higher the gas rises in the column, the more impurities are removed from it and the more it interacts with "strong" scrubbing solution, because the solution has not reacted much. The washing solution flows toward the bottom from tray to tray. This is the very important principle of *counter-current*.
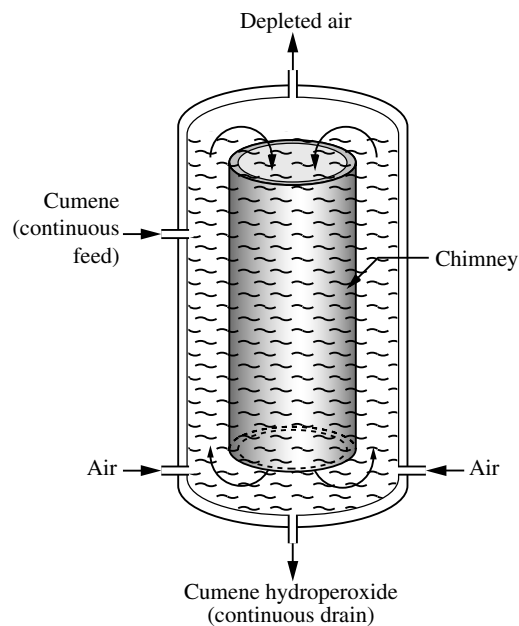

Figure 4.5. *Gas-lift or G/L reactor*

4.3.2.2. *The fluid/fluid/solids system*

The solid can act as the catalyst whose role is to increase the rate of the reaction. The solid(s) can either be the *reactants* alone, or the *reactants* or *products of transformation*. Examples include the rotary kilns used in cement works or continuous reaction of ore with sulfuric acid to produce phosphoric acid in stirred tanks.

The so-called catalytic or even heterogeneous reactors in the case where the catalyst is a solid, have to take into account the diffusion process. The reactants should have access to "*active sites*", located mostly within the *pores* of the catalyst.

For this reason, it is necessary to consider the morphology of the catalyst (balls, cylinders, etc.), its porosity, means of connecting fluids/catalyst, which must be strong enough so that the *diffusion process* is not the *limiting process*.

The reaction rate, removal, or supply of calories are factors that are to be considered in the design of reactors. Figure 4.6 represents a multitubular reactor in two-phase flow (trickle bed). In this case, the reactor is in fact a fixed *tube sheet* exchanger; a coolant flowing through the shell provides the calories needed to raise the temperature of the system at startup, and *removes* the heat of reaction in at a steady-state.
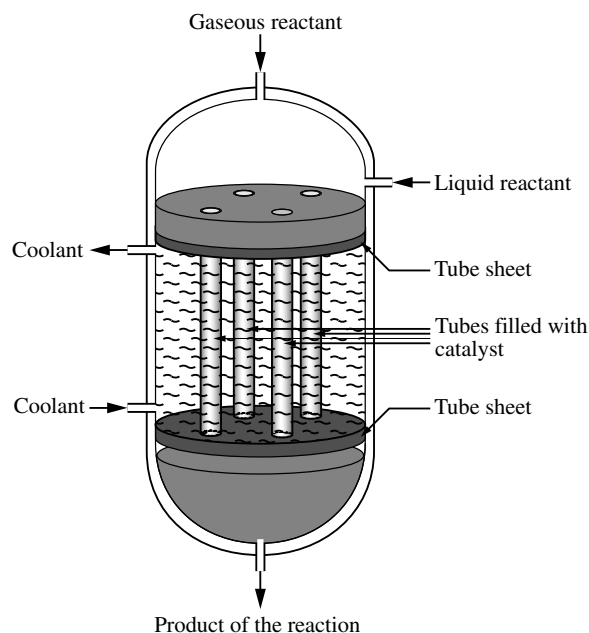

Figure 4.6. *Multitubular catalytic reactor*

We have already mentioned that the reactor is the heart of the process. The characteristics of the purification systems, systems for the extraction of marketable products, for the separation of by-products, the disposal of products with no market value (residues), the amount of wastewater to be treated, and the amount of unreacted reactants to be *recycled* will all depend on its efficiency and selectivity.

The reactor design must consider the thermal aspects. The removal of the heat from the reaction often poses a difficult problem. The addition of coils inside the

stirred tanks, an external circulation system through heat exchangers requires process studies that are sometimes difficult.

The reactor is often the most dangerous part of the production plant. It must be properly instrumented to control the flow rates as an increase in temperature may cause thermal runaway. It is necessarily equipped with safety devices, such as relief valves, blowdown, and an additional system of reaction blockers. Very often, the control devices are doubled or even tripled; this is called redundancy.

The reactor can also use very advanced construction techniques in the following cases, which are far from being restrictive:

– implementation of high temperatures or increased pressures;

– use of *exotic* materials such as metal alloys, which are difficult to process, graphite and enameled steel;

– very large volumes (several hundred m^3).

All these examples once again illustrate the complexity and scope of chemical reaction engineering (CRE).

4.4. Bioreactors

Bioreactors differ from conventional reactors by the nature of the catalyst, which is an *enzyme* and most often a *set of enzymes*. Apart from this, the basic principles stated above remain the same.

Let us recollect that an enzyme is a protein endowed with a special catalytic power. Enzymes may come from animals, plants, and especially microbes.

The enzyme is therefore a *biological catalyst* which, as such, is specific to a molecule. It quickens the transformation of the molecule without undergoing any transformation itself. It reacts only in pre-determined pH and temperature ranges.

There are two major classes of *bioreactions*.

4.4.1. *The enzymatic bioreactions*

Enzymatic bioreactions involve making one or more enzymes act on one substrate in order to transform it. The most classical example is starch hydrolysis using *amylase* that can hydrolyze it in glucose. This is how sugar syrups are manufactured from corn for confectioneries and cakes. It is also the reaction which,

in brewing, converts the starch from malt into fermentable sugars in the presence of yeast. The corresponding bioreactors differ a little from chemical reactors, except that they operate at moderate temperatures (less than 70°C in general), because of the heat sensitive enzymes.

Bioreaction, which is undoubtedly the most significant reaction in terms of tonnage, is the curdling of milk under the action of *rennet*, which is the starting point for cheese making. Rennet is a protease which causes the coagulation of casein: that is the formation of "curd".

The enzymes are never pure, despite undergoing purification operations. It follows that the reactions generated by the enzymes are many in number and complex.

4.4.2. *Bioreactions using microorganisms*

Bioreactions that employ microorganisms are also enzymatic reactions by the fact that the living cell functions through enzymatic systems that are specific to it.

These microbiological bioreactions, also known as *fermentations*, are even more widespread than the previous ones and have been since the dawn of time. Indeed, the fermentation of sweetened juices in order to produce alcohol, has been used (for the happiness and misery of humanity ...) probably, since man first picked fruits and squeezed them to extract its juice. Many food technologies at present use these food fermentation processes: wine making, brewing, distilling, cider making, and so on. These latter bioreactions are carried out in relatively simple devices, which are open to the air and where the temperature and sometimes pH may be controlled. However, they require some amount of industrial hygiene.

The same will hold true for the bioreactions for the synthesis of molecules, for the pharmaceutical industry (e.g. antibiotics or certain vitamins) or food for humans (flavorings, thickening agents, rennet, etc.). These reactions are carried out in completely controlled sophisticated reactors where sanitization must be strictly maintained.

Figure 4.7 represents a laboratory bioreactor.

Thus, the production of penicillin in a 50 m^3 reactor will pose a number of problems for the process engineer. All these problems must have a suitable technical solution, after the biochemist has defined the *nutrient medium* and selected an efficient *strain*.
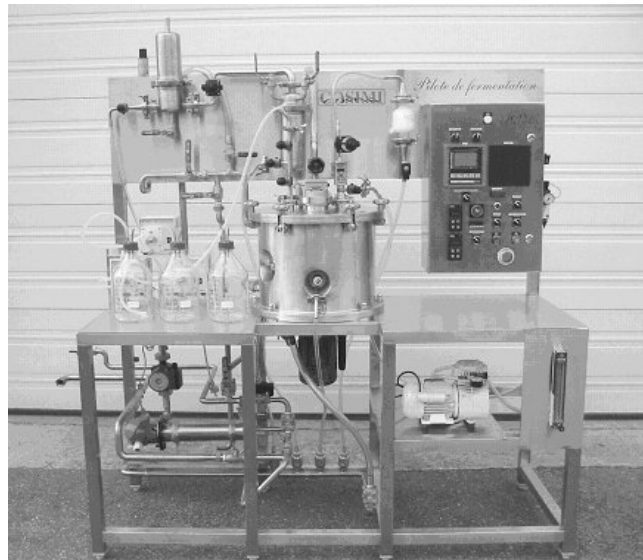
Figure 4.7. *Laboratory bioreactor used to test the raw materials and new production methods*

One must:

– define the feeding conditions of the fermenter in nutritive substances;

– specify the agitation to maintain the homogeneity of temperature and concentration;

– remove the heat of the reaction by using double jackets or coils immersed in the device;

– bring in filtered air under pressure and distribute it properly at the base of the fermenter;

– select and build material that can be sterilized with steam from the isolating valves up to the pipes and reactor.

Bioreactions or, more generally, biochemical reactions do not only occur in industrial reactors. A pot of yogurt, a cake in the oven, steak roasted in a pan, good wine aging in a barrel or a bottle, a "risen" bread (these are beer yeasts which, by producing CO_2, form holes in the dough), are the media where reactions associated with heat and material transfers (sugar, water, oxygen, etc.) take place.

Still closer to us, we can consider that every living organism is an extremely complex and efficient bioreactor!

4.5. Transportation and transfers

4.5.1. *Transportation and handling of fluids*

Fluids must be carried in pipes, compressed and mixed in the vessels. Liquids and suspensions have a flow rate of a few cm^3/h to several thousand m^3/h; the pressure can reach hundreds of bars; the temperature can be cryogenic or rise to hundreds of degrees. Fluids may be Newtonian or non-Newtonian and have high viscosities. To solve these problems, equipment manufacturers offer various *pump* models: conventional centrifugal, peristaltic, gear, multistage centrifugal, vortex, piston, lobe, vane, and so on.

Similarly, *compressors* can be piston, rotary, centrifugal, or axial compressors. Fans, especially in aeraulics, deal with high flow rates and low heads.

Mixing is a discipline of considerable importance, since reactants should be brought into contact, solids should be maintained in suspension, and dye pigments should be dispersed in viscous solutions.

Impellers can be fitted within tanks of several hundred cubic meters capacity (fermenters, mineral industry) and can be driven by engines of a power of several hundred kilowatts.

4.5.2. *Heat transfer; power, cooling, and heat generation*

Heat *exchangers* are a tool common to all industries. They are used to heat, cool, conserve energy, evaporate, and condense.

Figure 4.8 shows the simplest heat exchanger, the double pipe heat exchanger, used here with counter-current.
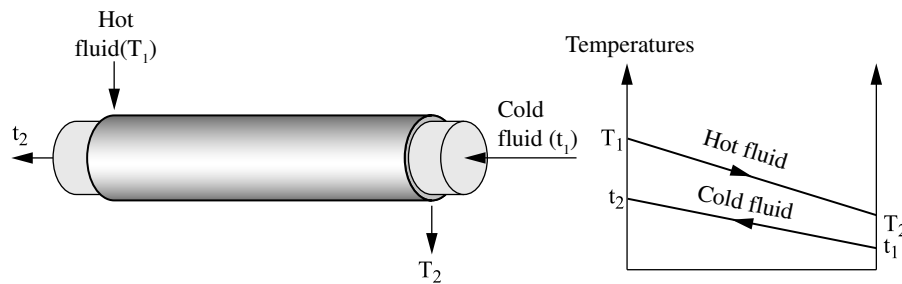

Figure 4.8. *Double pipe heat exchanger*

The amount of heat exchanged Q (kcal/h) obeys the following equation:

$$Q = U.\ A.\ \Delta t$$

with U, the transfer coefficient in $kcal.h^{-1}.m^2.\ °C^{-1}$, A, the exchange area in m^2, and Δt, the *mean* temperature difference between hot and cold fluids.

Chemical engineering is now used to calculate U and Δt in a few minutes, due to computer programs. Here again, exchangers can vary from a few square meters to several hundred square meters in surface area. They may be tubular heat exchangers, plate heat exchangers, spiral heat exchangers, cross flow heat exchangers, and so on.

Figure 4.9 illustrates the resistances to transfers: through the film of the warm and cold sides and through the metal of the tube wall.

Steam generation in oil-fired, gas-fired, and coal boilers, cold production in *refrigerating machines,* and *turbo-alternators* driven for the production of electricity come under the *energy* domain and obey the laws of thermodynamics.

Any plant needs *utilities*: steam, cooling water, nitrogen, brine, and so on. Station *utilities* are important for large tonnage products, such as chlorine, sodium hydroxide, and so on. They are less important for specialty chemicals.
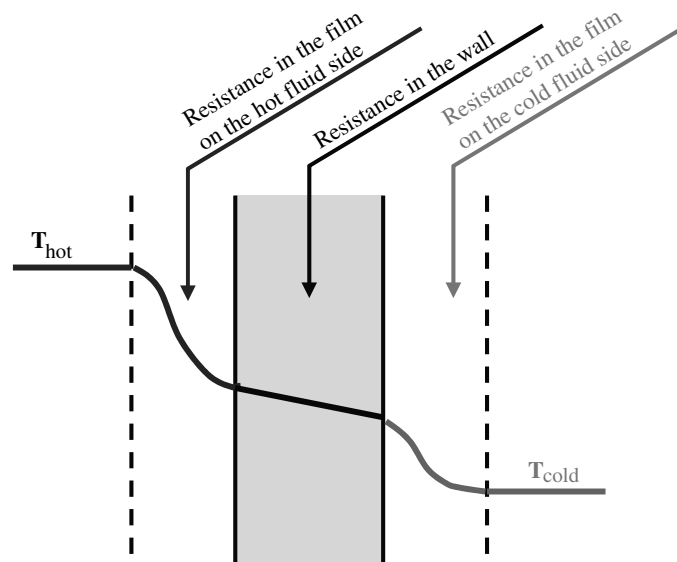

Figure 4.9. *Resistance to heat transfer in a heat exchanger*

4.5.3. *Transfer between two immiscible liquids*

Liquid–liquid extraction is an important operation in fermentation to extract the active ingredient from the broth, in the inorganic and rare earth industries.

The principle is based on the *difference in solubility* (driving force) of a solute contained in a solvent, such as water, and an *extractant* insoluble in water, such as IPE (isopropyl ether).

At the laboratory scale, IPE can be added to the solution in a settler tank that is stirred and then allowed to settle down: the solute passes through into the IPE. We can repeat the process several times with fresh solvent. The solution is often separated from the extractant by distillation.

Industrially, the operation is performed in columns similar to distillation columns.

4.6. Unit operations

The examination of a standard unit of crystallization, represented in Figure 4.10, shows a chain of operations and techniques that we will find in many chemical processes. In this case, the installation uses crystallization, filtration, drying, evacuation and transportation of a suspension. It is from this finding that Americans have named each block a *unit operation*.

The block, which consists of separating the crystals from the mother liquor, can be achieved by filtration as shown in the diagram, by sedimentation (using natural gravity), or by centrifugation.

Filtration as a unit operation can use a significant number of different filters: rotary vacuum, filter press type, band filter, and so on.

We see that we cannot separate the process from the equipment. There is no chemistry without equipment. The process and equipment must adapt themselves to each other.

Unit operations are extremely numerous and varied; they have accompanied the exponential development of the process industry, as stated in the section concerning the scientific bases of process engineering. It is impossible to list them all, as there are various classifications.

In the following sections, we will just examine crystallization and distillation in a little more detail and cite the principal unit operations. The membrane technologies and those whose applications are now becoming more and more important will be the subject of a special section.

4.6.1. *Crystallization in solution*

Crystallization in solution consists of forming a *crystalline* solid phase, that is *appropriated* from a solution containing a *solute,* which is to be extracted, and the solvent.

Crystallization in solution can be designed either to purify the solute, where the impurities remain in the solvent (mother liquor), or to obtain it in a solid form so as to avoid transportation when the solute is far from the production unit.

The *driving force* is the solubility. Experiments show that many products can be dissolved at a greater concentration than in equilibrium, for a time which can vary from a few seconds to several hours or even several days. This is called *supersaturation*.

The industrial crystallizer in Figure 4.10 is fed with a *supersaturated solution* at concentration C1. It works by vacuum flashing at temperature T2 at which the solubility is C2, C2 is less than C1; there is thus the formation of a solid.
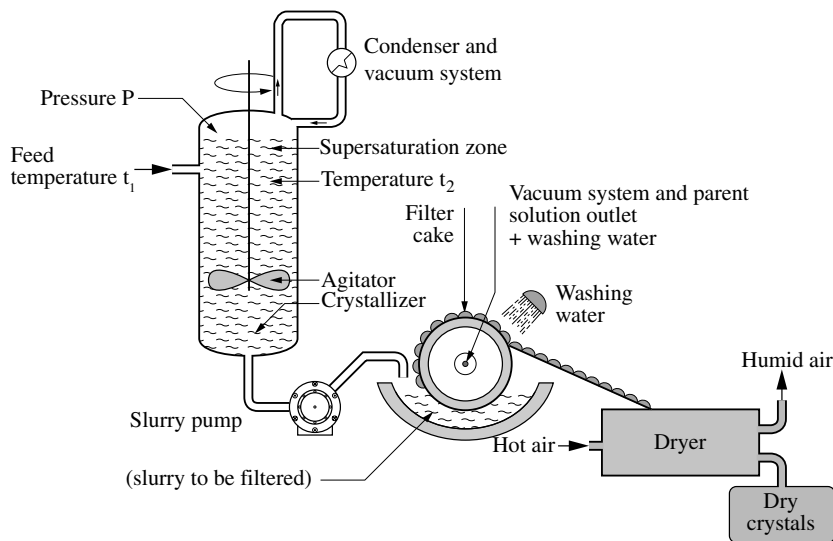

Figure 4.10. *Crystallization-filtration-drying typical unit*

Crystallization in solution is based on two essential phenomena:

– *nucleation*: the small crystals, or nuclei, which are formed first, serve as a support to the crystallizing solute;

– *growth*: to obtain large crystals, it is necessary to limit the nucleation, that is the number of nuclei and to have them grow by bringing the crystals already present in the tank into the supersaturation zone, in this case, at the surface of the *boiling* suspension. The role of the *agitator* is to perform this operation.

Some salts, for example table salt, have a solubility that varies little with temperature. From a practical point of view, crystallization is obtained by solvent evaporation in steam-heated evaporators. Salt marshes use natural evaporation due to the combination of wind and solar energy.

Crystallization is now a well-controlled process. Specialist companies offer various types of crystallizers for specific applications.

4.6.2. *Drying and gas/solid contact*

Drying implements heat transfer and material transfer, simultaneously. There are many types of dryers: tunnel, fluidized, rotating drum, spray (milk powder), and so on. The operation can be either continuous or discontinuous (*ovens*).

Adsorption uses the properties of *divided* and *porous* bodies to adsorb organic compounds contained, for example, in air. A widely used adsorbent is *activated carbon* that makes up the *cartridge* of gas masks.

The solids are essentially a "separate material", as they tend to create lumps, agglomerate together, clog pipes and pick up mass in the silos. They often generate dust and devices dealing with them are noisy.

The following operations are "mechanical" and do not involve any significant material transfer: grinding, agglomeration, extrusion, sedimentation, transportation by screw conveyor, air conveying or hydraulic transport, and sifting.

Fluidization consists of maintaining particles in suspension in a gas stream; this property is used to dry, to agglomerate particles and to make them react with other components. The fluidized bed acts as a pseudofluid for which the coefficients of material and heat transfer are high.

Solid-fluid separation is also a major operation. The *removal of dust* in *bag filters*, *cyclones*, and *electrostatic filters* comes under the air treatment processes. Solid–liquid separation can be accomplished by *filtration, centrifugation*, and *sedimentation*.

4.6.3. *Distillation*

Distillation is a basic operation in organic chemistry and the petrochemical industry. The distillation column forms an integral part of the chemical industry landscape.

Distillation is one of the oldest separation techniques as it was already known in the first centuries AD by Arabian alchemists who used it for the preparation of perfumes. For a long time it was empirical and it was only in the 19th Century that the bases of calculation and design of *stage equipment* were developed.

Distillation separates components with different volatilities, that is with different boiling points. Pure water, at atmospheric pressure, boils at 100°C; *at this temperature, water and its vapor are in equilibrium*.

Assume that we have to separate the water–methanol mixture. Methanol boils at 64.7°C at atmospheric pressure. Figure 4.11 shows the isobaric vapor–liquid equilibrium data of the water–methanol mixture.
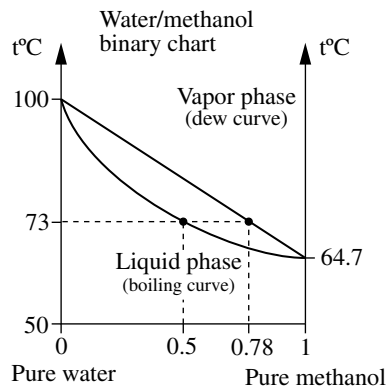

Figure 4.11. *Vapor–liquid equilibrium data of water–methanol mixture*

A mixture containing 50 mol% of methanol will boil at 73°C. *The vapor in equilibrium* with the liquid phase (liquidus) will have a molar composition of 78% in methanol. It is therefore richer in methanol than the liquid. This property is used in distillation *by putting* liquid and vapor into contact by means of *counter-current*.

The contacting device of the column in Figure 4.12 is a bubble tray. The bubble cap forces the vapor emitted by the reboiler located at the bottom of the column to *bubble* in the liquid. The liquid flows over the lower tray by an overflow (*weir*);

there is heat transfer and material transfer, simultaneously; part of the water in the vapor condenses and part of the methanol in the liquid vaporizes. If this tray was in perfect *thermodynamic equilibrium*, we would have what is called a *theoretical stage* or *tray*. The condenser installed at the column head condenses the vapors of pure methanol: part of the condensate is refluxed to provide counter-current.
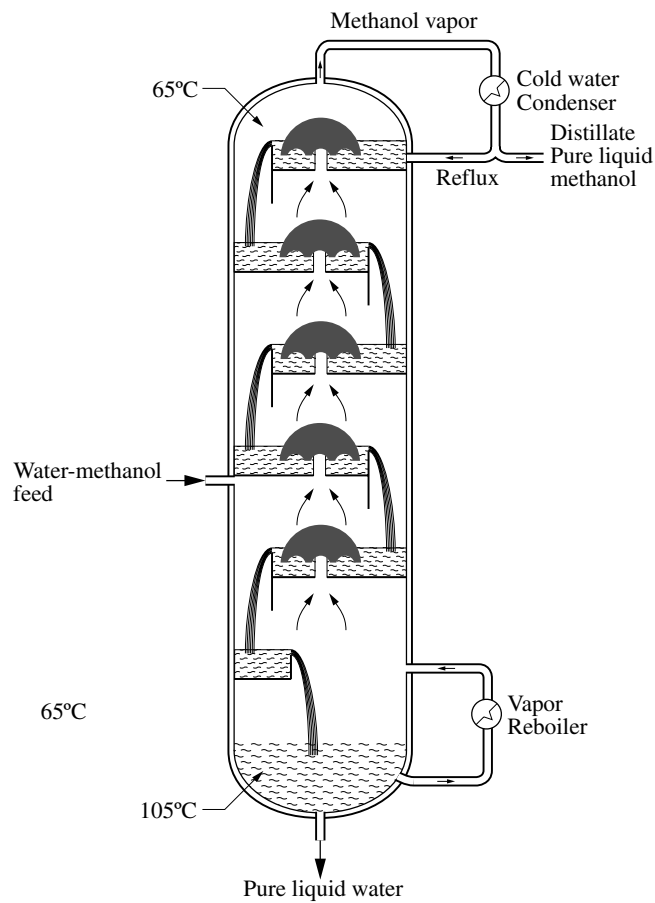

Figure 4.12. *Water-methanol separation by distillation*

The distillation operation is now well-known and lends itself to computer calculation. There are methods to calculate the number of theoretical plates required to perform a given separation and to size the trays (diameter, number of caps, etc.).

Various types of contacting trays exist: valve trays, sieve trays, bubble cap trays. There are also many types of packings of the dumped or arranged type.

4.6.4. *Other operations*

We have deliberately omitted many of the operations and chemical techniques, such as: absorption, stripping, evaporation, humidification, melting, solidification, molten crystallization, extractive distillation, azeotropic distillation, sublimation, dissolution, leaching, flotation, wastewater treatment, and so on.

As an example, we will discuss in a little more detail the development of operative techniques that were developed in the last decades of the 20th Century, namely membrane technologies, and we will conclude by discussing examples of challenges that process engineering has to face in the life sciences domain.

4.6.5. *An example of development: membrane technologies*

Membranes that help to separate molecules at an industrial level were invented in the 1960s by the Americans, Loeb and Sourirajan. Over the last 30 years or so, these techniques have emerged in many industries as a powerful means for fine separation of components. They form the basis of many applications in food processing, chemistry, and water treatment. Examples are the retrieval of proteins in milk by-products, water purification for the electronics industry, the treatment of machining fluids in the manufacturing industry, and the reverse osmosis of seawater to produce fresh water.

4.6.5.1. *Operating principle*

The ability of membranes to perform separations is based on the principle of "semipermeability". In fact, we know how to manufacture membranes containing thin skins of a few tenths of a millimeter thickness which, by playing on complex phenomena such as absorption, dissolution, porosity, and so on, "sort" the molecules that can pass through them. In fact, it is only an imitation of nature: without the semipermeability of our intestinal walls and kidneys, our life would be impossible. The same holds true for all living organisms: fish let in oxygen through their gills, plant roots "choose" what is necessary for the plant from the ground.

Semipermeability to water, given its importance, was the first to be studied for industrial applications (Figure 4.13).

In the schematized case in Figure 4.13, the membrane represented is semipermeable to water: the salt molecules are prohibited from passing through the membrane. This condition is essential for a spontaneous establishment of pressure in the closed compartment where the solution is found: this is the *osmotic pressure* of the solution, which is as high as the solution is concentrated. *Reverse osmosis*

consists of reversing this phenomenon by subjecting the solution to a pressure above the osmotic pressure, which leads to its concentration.
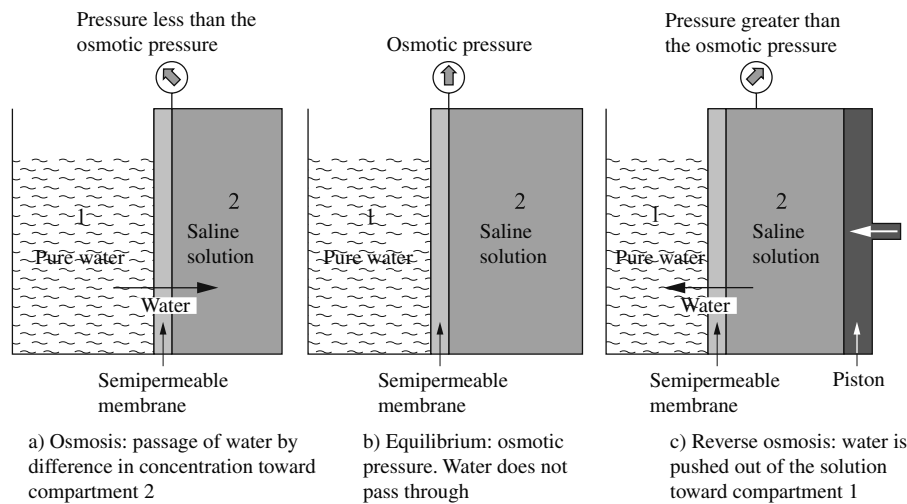

a) Osmosis: passage of water by difference in concentration toward compartment 2

b) Equilibrium: osmotic pressure. Water does not pass through

c) Reverse osmosis: water is pushed out of the solution toward compartment 1

Figure 4.13. *Osmosis, osmotic pressure, and reverse osmosis: in the case of a saline solution*

Other types of semipermeable membrane correspond to the sorting of dissolved molecules. This is true in the case of *ultrafiltration*, *nanofiltration*, and *electrodialysis*. The sorting of molecules is performed based on their *molecular weight*, *shape* (linear or globular), or their *ionic charge*. The phenomena involved are complex; they depend on the porosity of the membrane, affinities between the solute and membrane, and attractions/repulsions.

Finally, some membranes are capable of sorting "particles" that can be compared to macromolecules. They may be "micelles" (clusters of molecules often having a "skin" with particular electrochemical characteristics), bacteria, fat globules, microfibers, and so on. This operation is no longer considered to come under semipermeability; it is in fact a very fine filtration primarily based on the size of the pores of the membrane. This is the principle of *microfiltration*.

4.6.5.2. *The implementation of membranes*

Compared with the conventional filtration of liquid–solid and gas–solid suspensions, which is also known as "frontal" filtration, membranes, at the macroscopic level, have a special operating mode (Figure 4.14): the *tangential mode*.
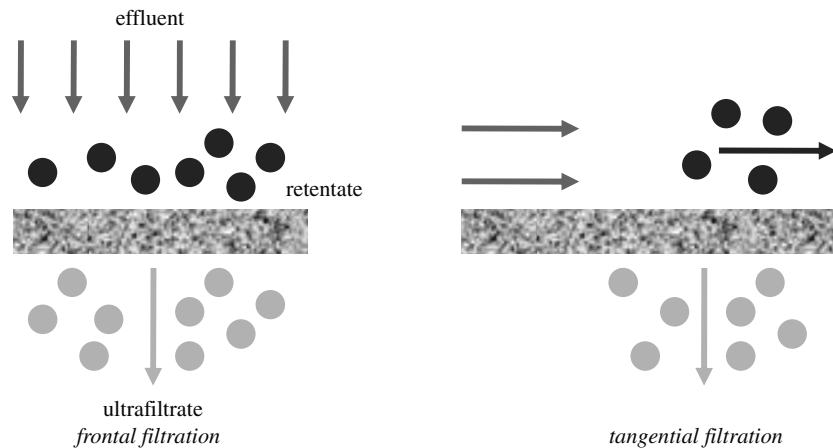
Figure 4.14. *Frontal filtration and tangential flow filtration*

Instead of bringing the suspension perpendicular to the filtering wall and making the entire carrier phase (liquid or gas) pass through the wall, the medium to be separated is circulated, at the necessary pressure, *parallel* to this wall. A part of this medium, the "filtrate", passes through the membrane whereas the "retentate" is still circulated. This slows down the accumulation of molecules or particles against the membrane, which is an inevitable phenomenon in frontal filtration. This process avoids clogging.

The materials of the first membranes were cellulosic by nature. The membrane material at present is of either *organic* or *inorganic* in nature. They are walls with a complex structure: generally, a very thin active part with a thickness of about 1/100th of a millimeter rests on a thicker part constituting the support. The total thickness is of the order of 1/10th of a millimeter for organic membranes and one millimeter for inorganic membranes. Electrodialysis membranes are still organic.

From a *practical* point of view, membranes can be *flat* (as in the case of organic membranes resting on grooved supports that can withstand applied pressures), flat but spirally wound, more often tubular (tubes of a few millimeters in diameter) or "hollow fiber" (microtubes less than a millimeter in diameter). The assembly of these basic elements into "modules", with an area of about 1 m^2, represents a part of the know-how of equipment manufacturers.

An *installation for membrane separation* thus consists of modules and pumps for pressurizing and circulating the liquid and various tanks (Figure 4.15).

Figure 4.15. *Industrial plant for desalination of seawater*

Temperature control systems, for example with the help of a heat exchanger, must be prepared to maintain the overall temperature at 50°C. It should also provide for means of declogging (often by reversing the direction of liquid flow in the membranes) and cleaning (by alkaline and acid solutions, and sometimes by enzymes that can break down the proteins constituting the clogged layer).

These installations operate either *in cycles*: the liquid is treated by tank loads one at a time, or *continuously*. Periodic stops are however needed to unclog and clean the membranes.

4.6.5.3. *Description and use of various membrane techniques*

The oldest membrane technique is *reverse osmosis*, whose principle has been stated above and which is used to separate the water from a solution. The usual procedure used in industry to concentrate solutions is based on evaporation. But in the case of products sensitive to heat, this process has the disadvantage of deteriorating the product (in the case of sugar solutions, the heat causes them to brown). A workaround is to operate in vacuum in order to lower the boiling temperature, which complicates the operation. One can use the same process to make pure water from brine. But the energy cost is high. Reverse osmosis does not have these problems ... but it has others: membranes are fragile, susceptible to clogging and unusable with concentrated solutions, as in this case, the osmotic pressures is very high, which can lead to operating pressures in the order of 60–80 bars, which in turn complicates the installation and results in high operating costs.

Other types of membranes are capable of carrying out sorting of different types. The most commonly used are *ultrafiltration* membranes, which allow small molecules including water to pass through, but retain the "large" molecules.

The most important application concerns the separation of serum (or "whey") from cheese. In the conventional manufacturing of cheese, the coagulation of casein can cause it to separate, in order to make cheese from it, from the solution (serum)

containing the other constituents of milk: lactose, salts, non-coagulated proteins, and some fat. This liquid was once discharged into a river, which had serious environmental drawbacks such as excessive growth of algae that consume oxygen to the detriment of fish. The industrialists, aware of the richness of this serum, strived hard to put it to good use rather than to throw it out. One of the methods put forward was to extract the proteins in order to use them as an ingredient for butchers and bakers. The technique that gained significance was *ultrafiltration*. The membranes retain these proteins in aqueous solution: this "retentate" can be dried under sufficiently mild conditions to retain its use value qualities: binding properties, emulsifying agent, and so on.

The other major dairy use of ultrafiltration is to question the process of cheese-making itself. This process involves coagulating casein, as described above, to make curd, which is drained in order to separate the serum. The draining phase is relatively long and difficult to control. Hence, the idea of ultrafiltering the milk itself, which allows us to extract the serum, and then to curdle the retained fraction that contains casein. Draining is no longer necessary, or its duration is greatly reduced since the serum has already been withdrawn. This technique, called "MMV", named after its inventors Maubois–Mocquot–Vassal, who were INRA (*Institut national de la recherche agronomique*) researchers, is now used in France and many other countries. However, it should be noted that the cheese produced, after the ripening phase that remains essential, does not have exactly the same characteristics as cheese manufactured by traditional processes, especially since incoagulable proteins are partly retained in the curd instead of being filtered out in the serum.

The automotive industry also uses the ultrafiltration technique for treating liquids resulting from machining. These are oil emulsions in the water used to lubricate and cool the metal cutting tools. The separation of the oil phase of these liquids after use allows the discharge of clean water and sometimes reuse of the oily portion.

Ultrafiltration also has applications for treating electrophoretic painting solutions used in the automotive and mechanical industries. This painting technique involves immersing the metal part in a bath containing the emulsion paint and using an electric field to exert a pull on the paint on the metal part. Here again, ultrafiltration can separate the "painting" phase from the aqueous phase before setting the latter aside.

In these examples, the potential of membrane technology for environmental protection can be noted.

In the biotechnology domain mentioned above, ultrafiltration modules can be coupled with biological reactors to extract from the reaction medium, the molecule

produced while leaving the catalyst cells and/or enzyme of this reaction. The efficiency of the reactor is improved, as the product of the reaction, when it accumulates, inhibits the reaction itself.

Nanofiltration is a recent technique: one uses new membranes that enable small molecules to be sorted from one another, by playing on both their size and electrical charge. For example, they enable us to separate monovalent ions (such as the chloride ion, Cl^-) from divalent ions (such as the sulfate ion, SO_4^{2-}) or sugars from salts. Their early applications include the simultaneous concentration and demineralization of milk to make yoghurt.

The principle of *electrodialysis* is based on the combination of membranes semipermeable to anions or cations subjected to an electric field. These membranes contain organic polymers comprising fixed groups and groups little related with the previous groups, which can move under the influence of an electric field and can be replaced with other groups. On the basis of the cationic or anionic nature of the mobile groups, the membrane lets the anions or the cations pass through it. A setup combining these two types of membranes can deionize a solution.

This technique is also one of the means to distinguish fresh water from salt water. The various techniques listed here: evaporation, reverse osmosis, and electrodialysis, are often used together to improve the competitiveness of the process.

4.7. Separation processes: process engineering and the new challenges for life sciences

The life science industries witnessed a true revolution at the beginning of the 21st Century: transformation of the pharmaceutical industry toward biomolecules, changes in the agri-food industry toward the development of more specific natural substances, and so on.

To illustrate these developments, let us consider two examples that play a prominent role. We can first quote the concept of biorefinery, born in the 1980s, and which is giving rise to growing interests. By analogy with oil refinery, it consists of developing all or part of plant fractions. Owing to the complexity of the media obtained at the end of extraction processes, the purification strategy proves to play a vital role. The same holds true in the case of biodrugs, designed and produced from living matter, and which are taking an active role in therapeutic innovation. The target molecules are thus extracted from extremely complex media, where they can be highly diluted. In both the cases, these molecules can be fragile, heat sensitive, and so on.

Given the complexity of the media considered, an initial feature of the purification processes is often the large number of unit operations required to isolate the relevant molecules. This finding leads to the first challenge: the need to implement processes with a reduced number of steps. For example, to develop purification methods that allow us to dispense with too many pretreatment steps. As an example, in ion exchange processes in a fluidized bed or expanded bed, the fermentation broth is injected directly into a column. The relevant molecules are retained on the resins, thereby avoiding a preliminary separation.

The concept of integrated process then calls for a global reflection on the entire process. An interesting illustration of this approach is the conversion of organic acid salts produced by fermentation. Indeed, during the fermentations, a base is used for pH control. The relevant form being the acid form, it was traditionally obtained by adding an acid. These processes led to the consumption of a base for the fermentation stage and an acid for the conversion stage, and to the generation of effluents. The use of electrodialysis with bipolar membranes (EDBM) can simultaneously convert salt in acid form and recycle the base for the fermentation stage. By considering the process as a whole, EDBM can help to limit the consumption of reactants and generation of effluents.

Many hybrid processes, bringing together the combination of several unit operations are presented in the literature. The idea is not just to juxtapose two operations, but to perform a coupling that contributes to raising the deadlocks of at least one of these operations. Membrane bioreactors, which allow a reaction with an integrated purification step, thus present a special advantage when a reaction inhibitor can be removed as and when it is produced.

Finally, various studies aim at designing separation processes that combine several types of driving forces, such as voltage, a difference in concentration, and so on. These processes simultaneously make use of multiple separation criteria such as differences in charge, size etc. New electro-membrane hybrid processes are thus the object of scientific publications. They particularly highlight the potential of electrodeionization (EDI) and electrodialysis combined with the use of ultrafiltration membranes (ED/UF).

This list is not exhaustive, of course: the potential pool of unit operations to be coupled offers vast possibilities to the imagination of researchers!

Let us now consider the impact of the large number of purification steps on solvent consumption. Indeed, crystallization, liquid–liquid or liquid–solid extraction, preparative chromatography, and so on, are all associated with the use of solvents. A strategy on the choice of solvents and optimization of their use thus proves to be a key element. To address this challenge, several approaches are used.

The first way is to set up a means for recycling the solvent, which is already quite a common practice in preparative chromatography. The quality control of the recycled solvent plays an essential role.

The problems associated with the consumption of solvent can also guide the selection process in advance. The resurgence of supercritical fluid chromatography (SFC), using a supercritical fluid as the mobile phase, is certainly related to its performance due to the low viscosity and high diffusivity of these media, but it is certainly also due to the ease of recycling this solvent. The development of crystallization processes, where supercritical CO_2 is used as an anti-solvent (SAS), helps, in addition to obtaining interesting properties of use, facilitates the removal of residual solvents. Similarly, extraction by supercritical CO_2 has the advantage of resulting in a spontaneous separation of substances extracted by simple depressurization.

Figure 4.16. *Picture of an installation of continuous separation by chromatography; this installation is used in the pharmaceutical industry to purify active ingredients, typically optical enantiomers. In the background, the installation for solvent recycling. Photo credit: NovaSep*

Finally, a third approach aiming to reduce the environmental impact of solvents is the use of solvents from "green" chemistry and to minimize their consumption by increasing, for example, the extraction using microwave heating, ultrasound heating, and so on.

Now let us consider the impact of the dilution of relevant molecules in a complex medium that includes many molecules with properties similar to that of the

target molecule, that is, the molecule that one wishes to extract. The challenge related to the selectivity of the separation step comes up here. For chromatography, a challenge is to synthesize phases that have specific affinities for the considered molecules and to select the best adsorbent/eluent couple in terms of selectivity and solubility. The development of such phases plays a vital role in the purification of monoclonal antibodies. Materials and processes should complement each other. Owing to the cost of phases involved, the choice of method should help to optimize the productivity, which is relative to the immobilized phase quantity. It is this objective that the development of continuous and sequential multicolumn processes is trying to achieve.

The performance evaluation of the processes implemented leads to another challenge: the development of analytical techniques. In fact, the analytical tests are essential to knowing the quality of the product obtained. To illustrate this key role, we can cite many analytical tests in the chromatographic operations of fractionation of blood plasma proteins. Analysis, however, is usually a major problem since the composition of matrices is unknown. In the case for example, of the purification of a molecule derived from a juice obtained from the leaves of a plant, the nature and concentration of other species present in the medium may not always be known and may vary from one crop to another. The components of these media are also not always available in pure form. It is therefore necessary, in each case, to develop methods that enable the detection and quantification of the relevant molecules. Moreover, the lack of sensors to perform online analyses can be an additional difficulty for process control because of the delay between the sampling and obtaining the test results.

All these evolutions happen in a binding regulatory context. In order to more effectively control the risks of cross contamination, there is a rise of single-use technologies.

Therefore, the mutations involved in life sciences have an impact on the manner of developing and industrializing the processes. A knowledge base in the domain of biological sciences is required to address these issues. The tools of process engineering can then respond to these new needs.

4.8. Acknowledgments

This chapter is largely inspired by the article "Génie Chimique génie des procédés" published by Editions Clartés[1] in 2002. It was written by Alain Storck, Jean-Jacques Bimbenet, Michel Auroy and coordinated by Jean-Pierre Dal Pont.

---

1 These items are available for reference exclusively at the *Bibliothèque nationale de France*.

4.9. Bibliography

[VIL 83] VILLERMAUX J., DAVID R., HOUZELOT J.-L., SCHWEICH D., "Vous avez dit génie des procédés", *L'actualité chimique*, p. 19, May 1983.