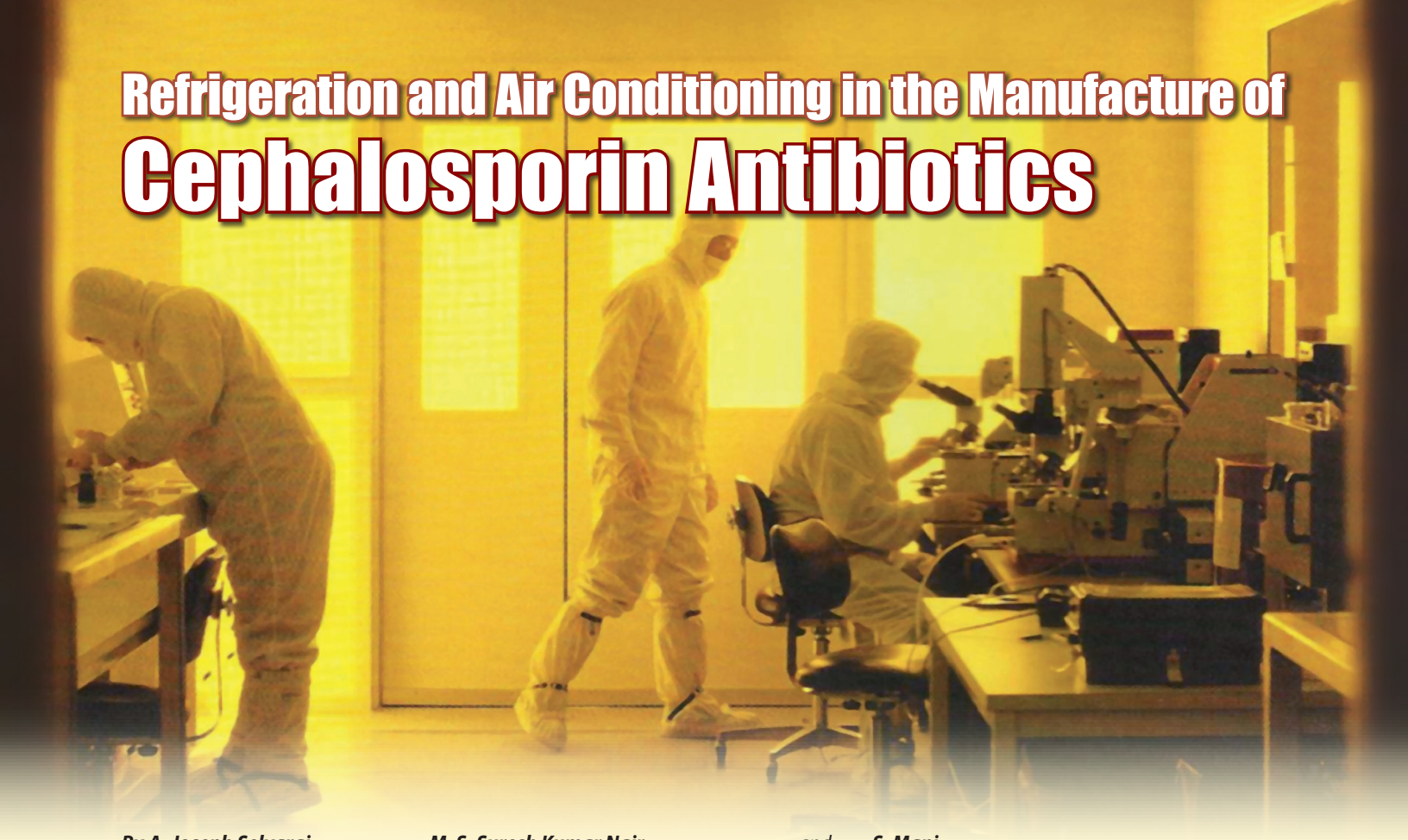
Refrigeration and Air Conditioning in the Manufacture of Cephalosporin Antibiotics



By A. Joseph Selvaraj
Deputy General Manager – Utilities

M. S. Suresh Kumar Nair *and* ***S. Mani***
Deputy General Manager - Process Development *President – Process Research, Corporate SHE and CSR*

Orchid Chemicals & Pharmaceuticals Ltd., Chennai

Raghavendra Rao, the promoter of Orchid Chemicals, Chennai, says, "We were born with an agenda to be in Cephalosporins (an antibiotic) and reached a position of eminence in that field", until selling this bread-and-butter business to Hosvira, a foreign pharma manufacturer in 2009 for $ 400 million. These words were the inspiration behind this article.

Introduction

Cephalosporin is a broad class of bactericidal antibiotics that have the ability to kill bacteria by inhibiting essential steps in bacterial cell wall synthesis, which in turn results in breakdown and death of the bacterial cell. These antibiotics are widely used because of their clinical efficiency and desirable safety profile.

Cephalosporin compounds were first isolated from cultures of Cephalosporium Acremonium from a sewer in Sardinia in 1948 by the Italian scientist Giuseppe Brotzu.

Cephalosporin Chemistry and its Need for Low Temperature Reactions

The thermo-chemistry of Cephalosporin indicates a higher adiabatic temperature for the reaction carried out but, in order to ensure process safety and product quality, most of the processes are carried out at lower temperatures. For example, in the Cefuroxime Axetil manufacturing process, the chemical reaction shown in *Figure1* needs to be carried out at -40°C.

It is necessary to carry out the chemical reaction at a low temperature so as to have a control on safety and to get better product quality.

All the cephalosporin intermediates are multifunctional in nature; due to this, multiple impurities are formed at the reaction stage. These products are identified as impurities of the final Active Pharmaceutical Agent (API). The magnitude of impurity formation depends on the reaction temperature. Low temperature reaction ensures and improves the quality of Cephalosporin API. Stringent impurity levels warrant controlled low temperature reactions.

To give another example, the Cefixime manufacturing process needs to be

About the Authors

A. Joseph Selvaraj is a mechanical engineer from Madurai Kamraj University (1998) and an Energy Manager from Bureau of Energy Efficiency. He has worked with Dr. Reddy's Labs and Nicholas Piramal, and is now Deputy General Manager – Utilities at Orchid Chemicals & Pharmaceuticals Ltd., Chennai.

M. S. Suresh Kumar Nair completed his master's in organic chemistry from Calicut University in 1991, worked with RPG Life Sciences and Sekhsaria Chemicals, and is now Deputy General Manager – Process Development at Orchid, Chennai.

S. Mani is President – API Process Research, Corporate SHE and CSR at Orchid, Chennai with an experience of 31 years. He is a mechanical engineer from REC Allahabad, and worked in BHEL before joining Orchid.

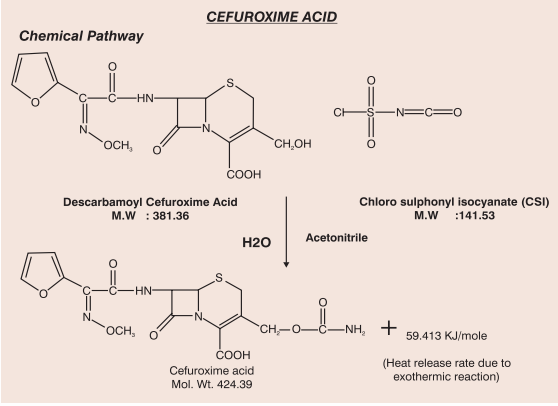


Figure 1: Cefuroxime Axetil chemical reaction

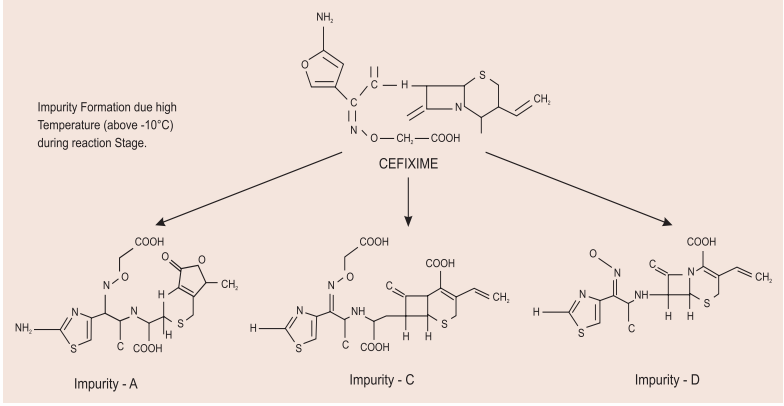


Figure 2: Chemical reaction of Cefixime

maintained below -10°C in order to avoid impurities A, C and D in the final API product, as shown in *Figure 2*.

Hence, low temperature refrigeration plays a vital role in the Cephalosporin manufacturing process.

Pharmaceutical Manufacturing Process

In general, a pharmaceutical manufacturing process has the following steps:

1. Bulk drug manufacturing.
2. Formulation.

A bulk drug is any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug.

Formulation is the process in which different chemical substances including APIs are combined to produce a final medicinal product.

Active Pharmaceutical Ingredients

APIs include substances manufactured by processes such as chemical synthesis, fermentation, recombinant DNA or other biotechnology methods, isolation/recovery from natural sources, or any combination of these processes. A typical API manufacturing process flow diagram is shown in *Figure 3*.

Reactors

These are large stainless steel or glass lined vessels installed with the top of the vessel at a workable height above the floor level. Raw materials are charged in these reactors at various stages and chemical reactions take place at the desired conditions, particularly temperature, pH and pressure.

There are certain chemicals that, by nature, liberate heat during their reaction (exothermic reaction) with one another. This heat needs to be removed continually so that a specified low temperature is maintained to achieve the desired product quality, yield and safety.

If the desired low temperature condition is not maintained, it may lead to product quality failure and, in some cases, it may even lead to a chain polymerization reaction at a high temperature, resulting in an unsafe condition.

Since Cephalosporin drugs are vulnerable at high temperature, the temperature of the process mass must be reduced to a sub-zero temperature (ranging from 0°C to -90°C) so that the reaction is carried out at this temperature.

Figure 3: API manufacturing process flow diagram

Centrifuge/ Drying and Milling

The product formed at the end of the reaction process is separated in centrifuges and further drying is carried out in various dryers, after which it is processed through multimills or jet mills to obtain the desired particle size.

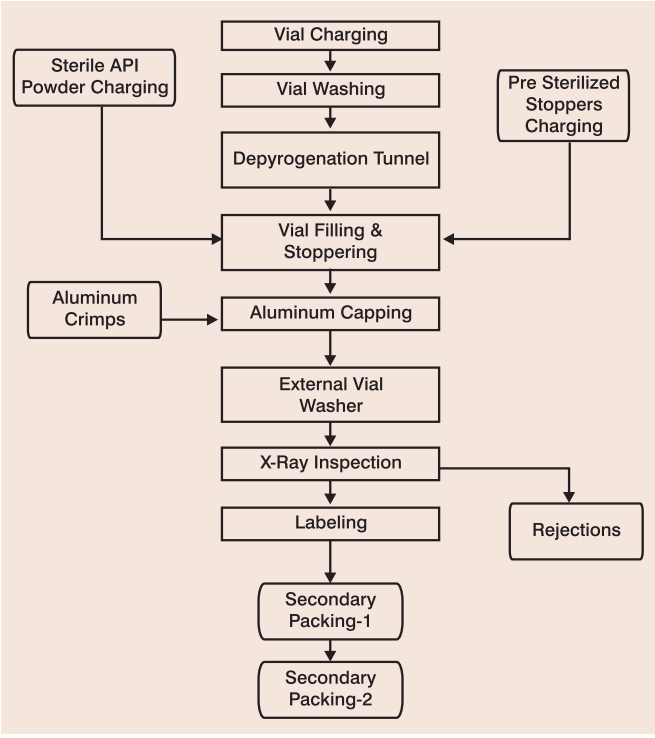


Figure 4: API-injectable process flow diagram

Packing and Storage

The product meeting total quality requirements is packed in clean rooms and stored in cold storage.

Formulation

A formulation is a mixture or a structure such as a capsule, tablet, or an injectable medicine prepared according to a specific procedure (called a formula). Competently designed formulations for particular applications are safer, more effective, and more economical than any of their components used individually.

A typical process flow diagram of a sterile API injectable drug formulation system is shown in *Figure 4*.

All the above mentioned processes in the diagram need to be carried out in a clean room.

Clean Rooms

Since pharma products (oral and injectable) finally get in touch with blood cells, the final processing area needs to meet the temperature, relative humidity, particulate count and total bacterial count in the area as stipulated by pharmaceutical guidelines or a Standard. An uncontrolled environment can lead to product degradation, or even complete loss of product.

The area where all these conditions are maintained is called a clean room. A clean room is defined as a room in which the concentration of airborne particles is controlled. Clean rooms have a defined environmental control of particulate and microbial contamination and are constructed, maintained, and used in such a way as to minimize the introduction, generation, and retention of contaminants. Generally class 100 to 100,000 rooms are used in the pharmaceutical industry.

A typical clean room is installed as shown in *Figure 5*.

The particulate count for various types of clean rooms is shown in *Table1*.

Table 1: Particulate count

Clean room Class Particle size	Particulate count limits per ft³	
	0.5 microns	5 microns
100	100	-
1,000	1,000	7
10,000	10,000	70
100,000	100,000	700

Clean room conditions like temperature, relative humidity, particulate and bacterial count are achieved through a clean room HVAC system.

What Differentiates Clean Room HVAC from Conventional HVAC Systems?

Clean room design encompasses much more than traditional temperature and humidity control. The design must consider aspects such as control of particulates, microbes, electrostatic discharge, gaseous contaminants, airflow pattern control and pressurization.

A clean room differs from an ordinary ventilated or conditioned room mainly in three ways:

1. *Increased Air Supply:* The increased air supply is an important aspect of particle control. Normal air-conditioning systems are designed for 0.5 to 2 air changes per hour, essentially based on the occupancy level or as determined from the building exhaust levels.

   A clean room would have at least 10 air changes per hour, and could have as high as 600 for absolute cleanliness. The large air supply is mainly provided to eliminate the settling of particulate contamination and dilute any contamination produced in the room to an acceptable concentration level.
2. *Use of High Efficiency Filters:* High efficiency filters are used to filter the supply air into a clean room to ensure the removal of small particles. The high efficiency filters used in clean rooms are installed at the point of air discharge into the room.

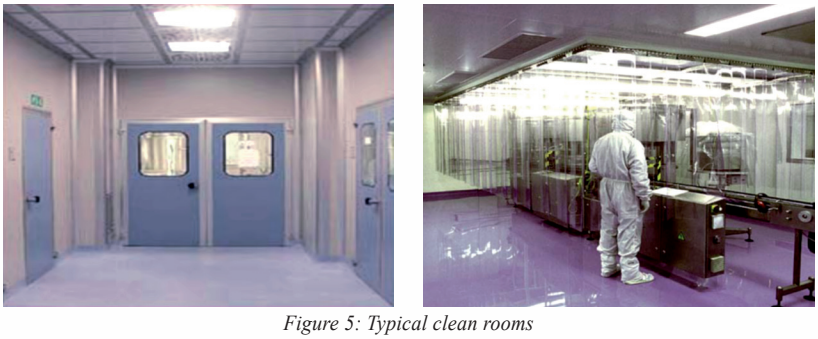


Figure 5: Typical clean rooms

continued on page 38

continued from page 36

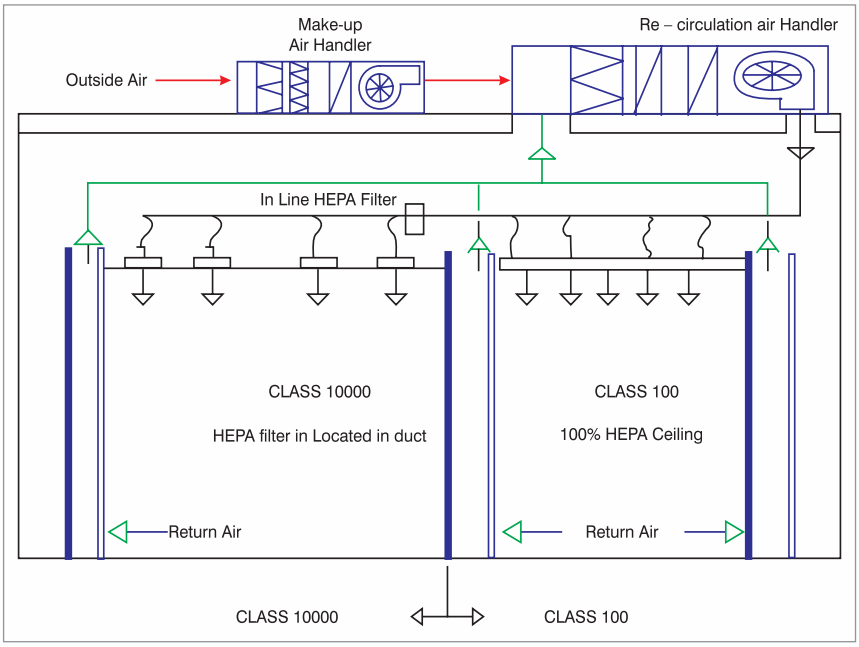


Figure 6: Air distribution system in a clean room

3. *Room Pressurization:* It is mainly provided to ensure that untreated air does not pass from 'dirtier' adjacent areas into the clean room. The clean room is positively pressurized with respect to the adjacent areas. This is done by supplying more air and extracting less air from the room.

There are more differences – the type of filtration, efficiency, airflow distribution and patterns, amount of pressurization, redundancy, noise issues etc.

Filtration

Filtration is an important aspect of clean rooms. Most of the filters are defined by their particle removal efficiency and airflow rate. Clean rooms require very high efficiency filters and for Class 100 and below, 100% HEPA filter coverage is recommended.

High Efficiency Particulate Air (HEPA)

HEPA filters are replaceable extended-media dry type filters having a minimum particle collective efficiency of 99.97 to 99.997% for a 0.3 micron particle, and a maximum clean filter pressure drop of 2.54 cm (1") water gauge when tested at the rated airflow capacity.

Airflow Distribution and Control

Depending on the degree of cleanliness required, it is common for air systems to deliver considerably more air than would be needed solely to meet the temperature and humidity design condition. Airborne particles can be organic or inorganic. Most contamination control problems concern the total contamination within the air. Particles of different sizes behave differently as air moves through a room. Selection of the airflow patterns is a major step in clean room design. While the number of air changes brings in a quantitative measure to the volume of air changed, airflow pattern considers the need to avoid pockets of stagnation that would otherwise permit accumulation of contaminants.

Room Pressurization

A clean room facility may consist of multiple rooms with different requirements for cleanliness. Rooms in a clean facility should be maintained at static pressures higher than atmospheric to prevent infiltration by wind. Positive differential pressures should be maintained between the rooms to ensure airflows from the cleanest space to the least clean space. The only exception to using a positive differential pressure is when dealing with specific hazardous materials where the statutory health and safety agencies require the room to be at a negative pressure.

The basic principle of pressurization is to supply air to areas of least contamination (greatest cleanliness) and stage this air to the areas of progressively greater contamination potential. Pharmaceutical operations are generally arranged in suites, with clearly defined operations in each space. The highest quality core room is generally placed at the center, which is separated from the lesser quality rooms by differential pressure using air locks. For example, the Class 100 area (filling area) is located in the innermost room space in a building plan area. The highest room air pressure is maintained in this area. It is surrounded by areas of descending pressures.

Clean Room Arrangement

The common HVAC clean room design has the filtered air distributed via the ceiling void area into the controlled room area and is taken out via the floor void or low wall return. The main reason is to keep the contaminants directed downwards as a result of unidirectional flow.

In the scheme in *Figure 6,* the Class 100 room arrangement is shown with 100% HEPA filter coverage. In practice, the make-up air handler (MAH) is a fresh air unit that provides room pressurization. MAH is designed for latent and sensible load of outside air. This unit feeds to single or multiple recirculation air handlers that are designed for the internal sensible heat load from the process machinery and personnel.

Levels of Protection

Based on the clean room class requirements, various 'Levels of Protection' have to be created, including:

1) Correlation between process operations and clean room classes
2) Type of operation permitted in each Level of Protection
3) Definition of clean room class (parameters, building materials, room requirements, HVAC systems)
4) Requirements for personnel and material in the different classes (clothing, training, type of materials, etc.)
5) Requirements on entry conditions for personnel and material (change procedures)

continued on page 40

continued from page 38

Parameters Influencing Levels of Protection

- Number of particles in the air
- Number of micro-organisms in the air or on the surface
- Number of air changes for each room
- Air velocity
- Airflow pattern
- Filters (type, position)
- Air pressure differentials between rooms
- Temperature and humidity

HVAC systems for clean rooms should be designed to ensure the level of protection. The working environment must be sufficiently well-controlled to minimize process defects, assure product quality, and to provide for worker safety and health.

Regulations mandate manufacturers to establish and maintain procedures to adequately control environmental conditions. Lighting, ventilation, temperature, humidity, air pressure, filtration, airborne contamination and static electricity are among the many conditions to be considered for control. National and international health authorities carry out periodical inspections to ensure that manufacturers comply with current regulations as laid out in EU-GMP and/or FDA.

In order to maintain the relative humidity and temperature in clean rooms, desiccant type dehumidifying systems are used instead of the conventional heating and cooling systems, in order to reduce the overall energy required for dehumidification process *(see Table 2)*. The schematic diagrams for both the systems and their comparison are shown in *Figure 7 and 8*.

Table 2: Comparison of conventional AHU and DHU + AHU

Comparison of Conventional AHU & DHU + AHU			
Description	**Conventional AHU**	**DHU + AHU**	**Total energy saving**
Cooling load	78.9 TR	52.8 TR	26.1 TR
Heating load	103957 kcal / hr	26775 kcal / hr	77182 kcal / hr
Process motor load	-	2.2 kw	-
Reactivation motor load	-	1.1 kw	-
Fan and motor load	-	-	-
Total energy	397 kw	219 kw	181 kw

Cold Rooms

Cold rooms are used to maintain the temperature of raw material, intermediates and finished products as they require low temperature storage conditions. The cold room temperature is maintained based on the product requirement. Generally cold rooms are designed to maintain the temperature range of +2°C to +8°C and +20° to 25°C. Separate DX refrigeration systems are used to maintain the temperature in the cold rooms. At our Alathur Plant, there are 17 cold rooms in different locations of the plant to meet various product requirements.

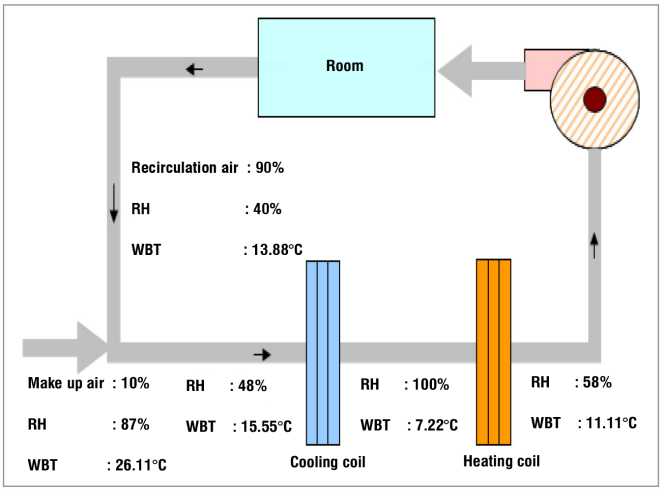


Figure 7: Conventional system

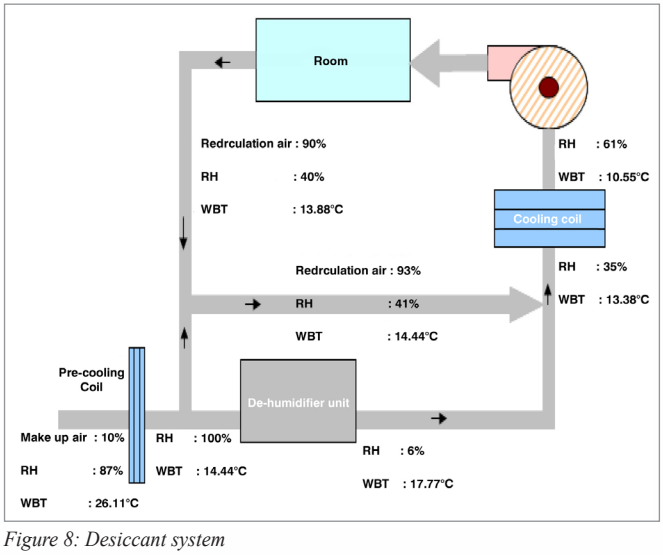


Figure 8: Desiccant system

Vent Gas Condensing System

Apart from using low temperatures in the manufacturing process, there is a pioneering usage of an environmental initiative at our plant.

The solvent vapour that is generated during the various stages of pharmaceutical production process needs to be contained in order to reduce the emissions to air. A Vent Gas Condensing System has been installed at the Alathur Plant – the first of its kind in the Indian pharmaceutical industry. It condenses the solvent vapour using -70°C ultra-low temperature brine as the cooling medium. An additional benefit of this system is that the condensed solvent vapour is re-used in the production process.

The typical vent gas system which is installed and being operated is shown in *Figure 9*.

Plant Capacities Required for Different Temperatures

The heat load removal rate and temperature conditions of cooling medium have been determined with the help of a

continued on page 42

continued from page 40

reaction calorimeter for process application, based on which suitable refrigeration plant capacities have been determined. A summary of the temperature conditions and plant capacities that have been selected for the ultimate output of Cephalosporin required are shown in *Table 3*.

Table 3: Temperature and plant capacity

S. No.	Utility services	Capacity
1	+7°C	2400 TR
2	-10°C	360 TR
3	-25°C	358 TR
4	-40°C	189 TR
5	-70°C	158 TR

Refrigeration Plants for Chilled Brine

In order to meet the process cooling requirements for the -10°C, -25°C and -40°C systems, eco-friendly ammonia is used as the refrigerant with the following safety precautions:

- Dual safety valve with three way isolation arrangement in order to have better flexibility to check/ replace the safety valve any time.
- All the refrigeration plant safety valve vents are connected to a dilution tank.
- The dilution tank drain passes through a static mixer with chemical dosing arrangement in order to minimize ammonia exposure to atmosphere while draining the ammonia contaminated water.
- Water sprinkler and fire alarm arrangement.
- Necessary interlocking system in SCADA to avoid failure.

Economizers, intercoolers, online air purger, oil drain pot and two stage compressor (wherever possible) are used for all the plants to obtain higher plant efficiencies and save on energy costs.

A single-stage ammonia refrigeration system for -40°C operating temperature would normally consume 4.0kW/TR whereas a two stage system consumes 2.85kW/TR only.

The following on-line monitoring system has been installed to verify equipment performance kW/TR for each refrigeration plant with totalizer in order to get both instantaneous and average performance of the plant:

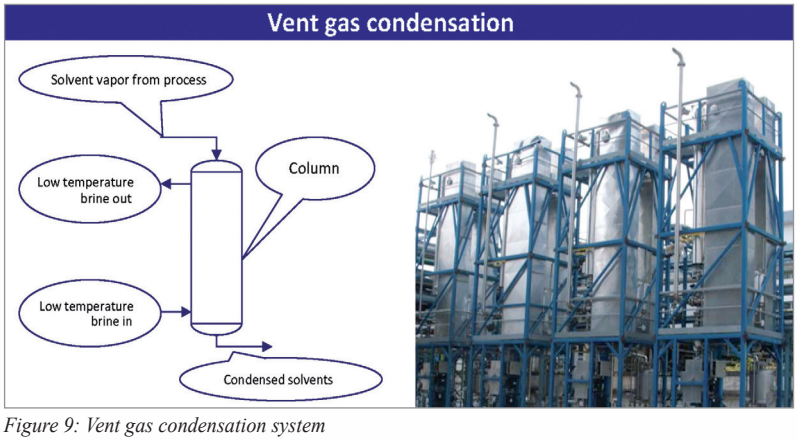


Figure 9: Vent gas condensation system

- Suction super heat, sub cooling of the refrigerant
- Pressures and temperatures at various stages for both refrigerant and oil

Details about the various ammonia refrigeration systems are given in *Table 5*.

Table 5: Various ammonia refrigeration systems

Temperature	-10°C	-25°C	-40°C
Chiller type	Open type screw	Open type screw	Open type screw
Installed Capacity	100 TR – 3 nos. 75 TR – 1 no.	100 TR – 2 nos. 158 TR – 1 no.	40 TR – 5 nos. 55 TR – 1 no.
Standby units capacity	100 TR	100 TR	40 TR – 2 nos.
No of stages	Single stage	Single stage	Two stage – 4 nos. Single stage – 2 nos.
Secondary refrigerant	Methanol brine (15% Weight)	Methanol brine (30% Weight)	Methanol brine (40% weight)
Application	Process cooling	Process cooling	Process cooling

The typical energy efficient two stage compound compressor installed is shown in *Figure 10*.

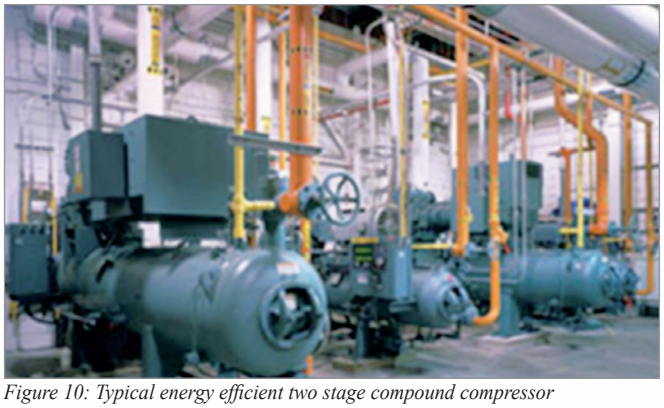


Figure 10: Typical energy efficient two stage compound compressor

Refrigeration Plants for Chilled Water

To handle the 2400 TR requirement of chilled water at 7°C for the clean rooms and solvent distillation column cooling requirement, initially roof top air-cooled screw chillers were installed, due to non-availability of make-up water required for the cooling towers. Later, when effluent water generated from the API process was reclaimed after treatment, the air-cooled chillers were replaced with water-cooled centrifugal chillers with special cupro nickel condenser tubes to prevent tube corrosion. There was a two-fold advantage in carrying out this change:

- Recycling of the effluent water and using this for makeup to the cooling towers was an effective way to utilize this water resource.
- The specific power consumption for the water chillers was reduced from 1.2 kW/TR for the air-cooled units to 0.60 kW/TR for the water-cooled units, saving a huge amount of electric power of around six million units/year.

continued on page 44

continued from page 42

Figure 11: Energy efficient centrifugal chiller

- Installed capacity of the system is shown in *Table 6.*

Table 6: Plant capacity

Chiller type	Semi-hermetic centrifugal chiller	Semi-hermetic screw chiller
Installed capacity	350 TR – 5 nos. 250 TR – 1 no.	200 TR – 2 nos.
Standby units capacity	350 TR	200 TR
Refrigerant	R-134a	R-134a

The typical energy efficient centrifugal chiller that is installed is shown in *Figure 11.*

Refrigeration for -70°C System

Two systems were considered for this ultra-low temperature requirement:

1. Use of liquid nitrogen, and
2. Mechanical refrigeration using a cascade system.

The benefits of mechanical refrigeration outweighed the use of liquid nitrogen, the main reason being that the operating cost of mechanical refrigeration is one-tenth of liquid nitrogen (Rs.45/TR as against Rs.450/TR).

Refrigerants used in the cascade system were R-23 and R-22. The disadvantage of mechanical refrigeration system was the difficulty in readily obtaining R-23 from the market and having to import and stock the item. The second disadvantage was the high initial investment required.

Need for a Convenient Chilled Brine Network

The API Ceph reaction processes are exothermic reactions in nature; the heat release would be instantaneous. In order to remove the instantaneous heat release, a DX (direct expansion) system would not be suitable. So, a chilled network was selected for installation.

In the past, brine consisted of salt solutions such as calcium or sodium chloride, which are seldom used now because of their corrosivity. Instead, we use methanol, which also helps to reduce pumping power that is 2% lower than calcium chloride brine. But methanol also has some demerits – it is flammable and not easily available in the market.

Monitoring and Control

All the refrigeration systems together consume around 50% (0.1 million units/day) of the total power consumption for API production. Hence, the performance of all the refrigeration systems (kW/TR as well as other critical parameters) is critically monitored through online trending, and deviations are addressed from time to time.

Insulation

Polyurethane foam (PUF) is used as the insulating medium, both for the chilled water as well as the low temperature and ultra-low temperature refrigeration systems. Heat loss on account of the insulation used for the ultra-low refrigeration system alone is estimated at about 20%. Vacuum insulated pipes are recommended for future upcoming low and ultra-low temperature systems.

Conclusion

Although low-temperature chemistry poses unique challenges to the process chemist and the refrigeration engineer, careful study and planning of cryogenic system design and operations can provide high value chemical products.

Energy-efficient design of the refrigeration and HVAC system can optimize the overall cost of manufacturing for the API pharma, with the added benefit of increased emphasis on safety and environmental care.

Technologies are constantly developing in the HVAC sector with increased attention to the Triple Bottom Line – Profits (Cost), People (Safety) and Planet (Environment). Thorough joint discussion between the user industry and the HVAC industry holds the key to selection of appropriate technology. ❖