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CRITICALITY OF VACCUM IN LYPHOLISATION-1

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ABSTRACT

Lyophilization process is used in many different fields in pharmaceutical it is used for preserving thermolabile material. Lyophilization success depends upon refrigeration system hydraulic system and vacuum system. Vacuum plays major role in successful lyophilization. this article describes criticality of vacuum in Lyophilization process.

Lyophilization processes are widely employed in the industrial field to preserve several kinds of substances, such as foods and drugs. In some cases, e.g., during the process optimization, the real-time measurement of mass and temperature is important to monitor drying rate and to prevent product damages because of unsuitable temperatures. In these cases, sensors and measurement instruments have to be installed inside the vacuum chamber of the freeze dryer, where temperature and pressure can reach -60^{0}C and 1 Pa respectively. This paper deals with the problems related to the measurement of mass and temperature inside freeze dryers and describes a measurement system that has been specifically designed to monitor lyophilization processes.

Lyophilization is the common, but cost-intensive process. Freezing is an equally important step in Lyophilization, as it affects both process efficiency and quality of the product. However simple concept, freezing is probably the most complex step in lyophilization. Therefore, to get a more comprehensive understanding, the lyophilization methods and application are first summarized. The different techniques or method that can be used in lyophilization are also reviewed.

KEYWORDS: Theory of Lyophilization, lyophilization Principle, The lyophilization process steps, Excipient in lyophilization, critically of vacuum in lyophilization.

INTRODUCTION

Lyophilization is the one of the greatest innovations in pharmaceutical industry for enhancing the long-term safety of drug products and simplifying the shipping and handling of drugs. It is a 3-stage process involving freezing, primary drying (ice sublimation), and secondary drying (unfrozen desorption of the water). It is a time-and energy-intensive process that can take days to complete, where A large part of the cycle time is spent on primary drying. During primary drying, the product temperature must be kept below the critical product temperature of the formulation, such as collapse temperature (Tc) for crystalline structures with amorphous or eutectic temperature (Te), So as to guarantee that the application is applied. Freezedrying is commonly used to gain long term stability in the processing of biopharmaceutical products, and is a time and energy-consuming process. Is a time and energy-consuming process which can allow day or went week finish when most cycle time is spent during primary drying. The optimization first stage therefore has become an important focal point for process development scientists to reduce operating costs and increase production throughput. The objective during stage 1 to minimize drying time (PDT) while keeping the product temperature (TP) below the critical product temperature of the formulation, such as collapse temperature (Tc) for amorphous system or eutectic temperature (Te) for crystalline systems. The formulations describe the critical product temperature to be the optimum primary drying TP, which is used as the Upper limit to identify process parameters that typically produce a primary drying temperature below that critical product temperature below 1-2 degree Celsius. The longest primary drying process is period of the Lyophilization cycle, during which ice sublimation takes place under conditions of vacuum and low temperature. During primary drying the product temperature is controlled by changing Temperature on shelf and the pressure of the room. An increased in product temperature above a critical temperature will adversely affect product quality, likely resulting in collapsed, so that measurement of the material of the temperature during stage 1 important. Using thermocouples, which has several significant limitations, is the standard approach to product temperature calculation on a commercial dryer.

THEORY OF LYOPHILIZATION

Freeze Drying- Freezing Is In the pharmaceutical industry, freezing is often used to ensure long-term safety of the parenteral products which are sensitive to moisture. There are three main processes of lyophilization: During the freezing process, freezing, primary drying, and secondary drying phase transition from liquid to solid state takes place.

PRINCIPLE

It also called sublimation in important principle involved in freezing drying, where water transfers directly from the solid state (ice) to vapor state without going through the liquid layer. Water sublimation can occur at pressures and temperatures below the triple point i.e. 4,579 mm Hg and 0.0099 degrees Celsius. The drying material freeze then Heated under a high vacuum, to leave only solid, dried components of the original liquid. The water vapor concentration gradient between the drying front and the condenser is the driving force for water removal during Lyophilization.

THE PROCESS STEP

- **Freezing:** Frozen goods, this provides the necessary condition for drying at low temperatures.
- **Vacuum:** The substance is then put under vacuum after freezing. It helps the freezing substance to vaporize without going through the liquid phase, which is a process called sublimation.
- **Heat:** Heat is added to frozen product in order to speed up sublimation.
- **Condensation:** The vaporized liquid is removed by low-temperature condenser plates from the vacuum chamber by transforming it back into a solid. It completes process of separation.

Heat Transfer in a Shelf Freeze Dryer

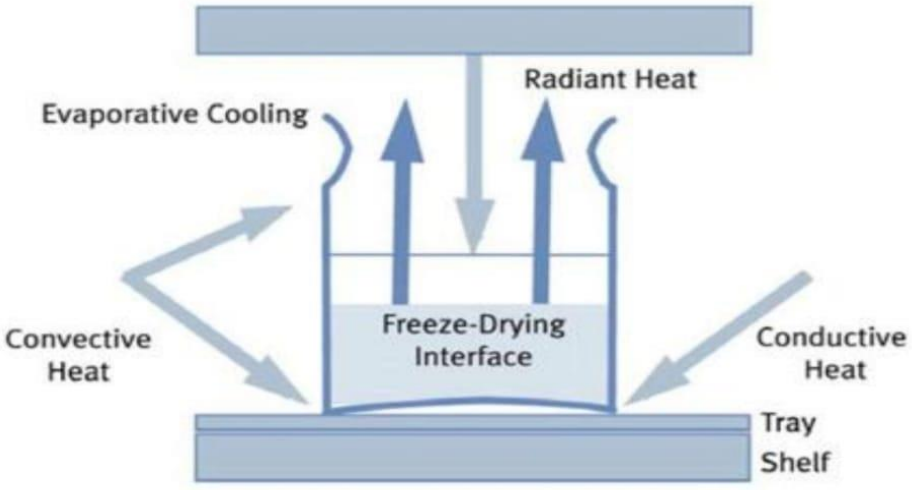


Figure 1.0: The process steps.

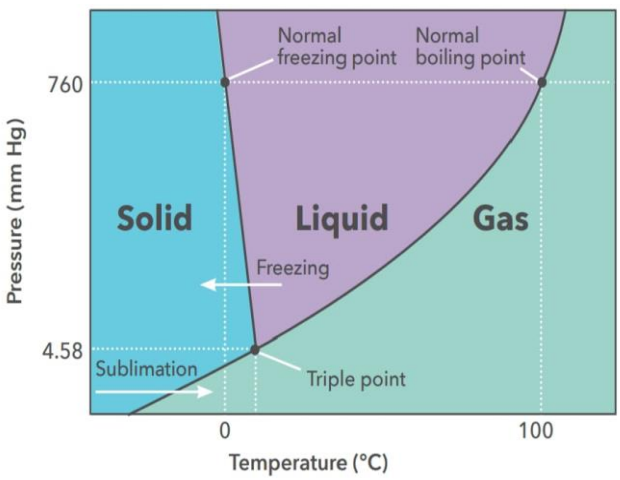


Figure 1.1: Phase Diagram of water.

Excipient in Lyophilization

- **Bulking agent:** Bulking agents make up bulk lyophilized substance and give the cake a proper structure. These are commonly used for low-dose (highpotency) drugs that do not have the bulk needed to support their own structure
- **Buffering Agent:** PH regulation is important to prevent product degradation during reconstitution, manufactured and storage requiring the Added buffering agent to lyophilized formulations.
- **Stabilizers:** lyophilization system in addition being a disaccharide, bulking agent form amorphous glass of sugar and has proved to be the most efficient in stabilizing materials such as proteins and liposome during lyophilization
- **Tonicity adjusters-** [Lyophilization system] in a number of cases, an isotonic formulation may be required. The need for such a formulation can be calculated either by the needs of quality of the bulk solution or by those for the route of administration.

Formulating Products for Lyophilization

While cycle development is critical for lyophilization, formulation and excipient selection play an equally important role in ensuring a successful product is obtained. In pharmaceutical development, the goal of any lyophilization process is to obtain a stable drug product, but API characteristics and the desired route of administration can affect how that is achieved. Additionally, lyophilization is often applied to already complex formulations such as microparticles and liposomes, each of which bring their own set of development challenges.

Lyophilization Equipment and Components: Pharmaceutical lyophilization typically takes place in a tray or shelf lyopholizer, which contains a series of temperature-controlled shelves that hold product during the freeze-drying process. Inside a lyopholizer, there are various components that allow for precise control over temperature and pressure and drive the steps of the process.

CRITICALITY OF VACCUM IN LYPHOLISATION

Success of Lyophilization depends upon application of vacuum to required magnitude. Lyophilization is applied to thermo labile compounds which are temperature sensitive products. Application vacuum to boil and vapors lyopholizer contains.

- Drying chamber with temperature-controlled shelves to supply the heat needed for sublimation of ice.
- Ice condenser to condense the water vapor evacuated from the drying chamber to ice. The condenser can be separated from the drying chamber by a vapor port.
- Vacuum pump to supply the vacuum needed to decrease pressure below the triple point.
- Refrigeration system to cool the ice condenser and shelves in the drying chamber.

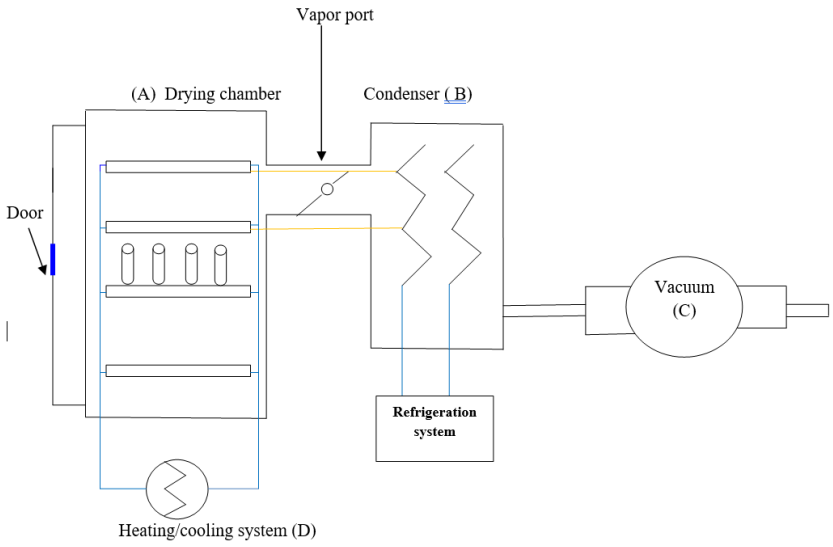


Figure 1.2: Schematic representation of the main part of freeze-dryer.

Fundamental Lyophilization Steps Are

a) Freezing
b) Primary drying
c) Secondary drying

1. **Freezing:** - In this step liquid is frozen to freezing temperature which depends upon nature of material.
2. **Primary drying: -** After freezing the product to required temperature vacuum is applied to remove water component from product from product. Water component from product is removed by going below triple point. Once we approach triple point plz. see the below diagram sublimation of the liquid takes place. Where solid is sublimated to vapor without passing this liquid phase.

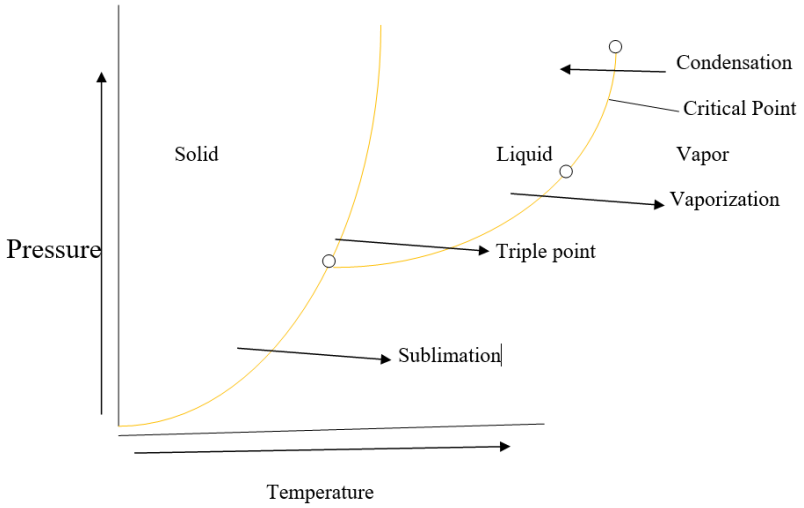


Figure 1.2: (a) Sublimation.

To bring the boiling point below triple point vacuum is applied to reduce pressure above liquid and as system pressure goes below. As the vapor pressure equals system pressure liquid will boil and vapor will migrate to condenser. This process of lowering boiling point depends upon vacuum application. If magnitude of vacuum is not achieved then water removal will not take place.

Note: - Each formulation has its unique triple point or collapse temperature according to its combined chemical formula. This indicated that magnitude of vacuum varies according to formulation.

a) During lyophilization vacuum is applied to condenser only difference is refrigeration system cooling is different chambers area cooled by silicone oil cooling system which flow through chamber shelves. And in case of condenser cooling system it is direct cooling system

with expansion valve with same refrigeration system both areas cooled direct expansion system in condenser and chamber cooling system is indirect cooling system.

Due to different method of heat transfer, there is temperature difference in between and this temperature difference creates vapor pressure difference and vapor starts migrating to condenser. Refrigeration system and vacuum system is very important.

Imagine while in operation vacuum pumps stop due power cut here chamber and condenser will act as storage of vacuum and on that moment vacuum pump oil can be sucked back and this can cause product contamination.

To Avoid such incidence vacuum pumps are fitted with quick closing valves. These valves need to close instantaneously.

As all are aware in third world countries power cuts area common phenomenon and in 24 hrs of the day there will be power cut from few minutes to few hrs every time there is power out rages there is risk of contamination. Hence in our country we should make practice of checking (Preventive maintenance or pre-checks before operation) those valves of lyophilizer.

One type valve operation given pictorially describing operation. The quick closing valve is fitted on top of vacuum pump.

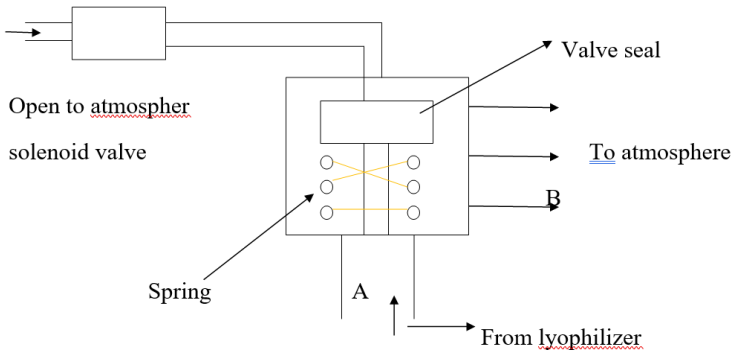


Figure 1.2 (b) Schematic representation.

In case of normal operation port A to port B but what happens When power interruption takes place

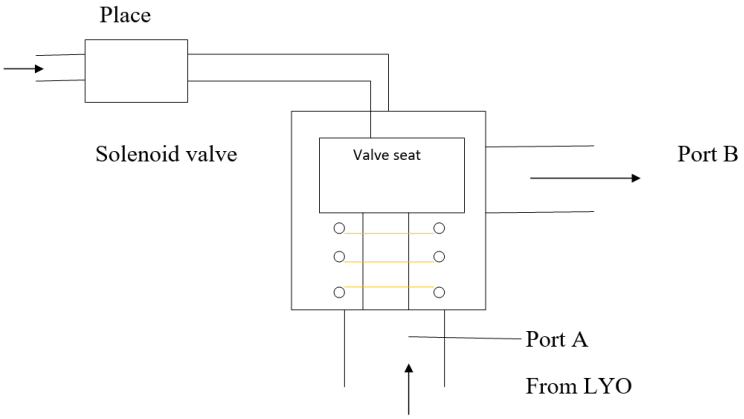


Figure 1.2 (c) Schematic representation.

Solenoid valve has same power supply as vacuum pump so as soon as power supply is interrupted Solenoid valve will open and allow outer atmospheric air and close the out let any pump. This closing time is 30 miliseconds (ms) to 40ms.

This quick closing valve malfunction can cause oil to suck back hence checking after every batch can assure proper functioning of the valve.

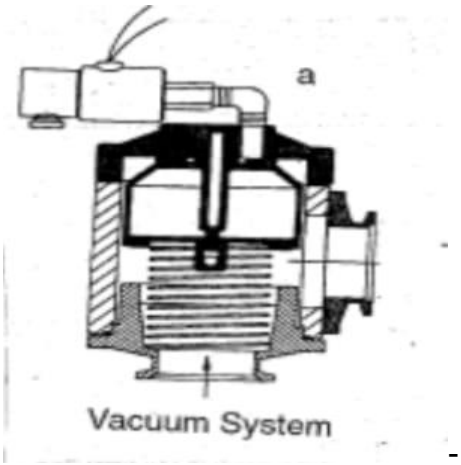


Figure 1.3(a): Normal Operation - Operation Sequence.

Figure 1.3(a): Normal Operation - Open Position Power is on to the mechanical pump and the VPI valve. The mechanical pump, inlet side of the VPI valve, and the VPI valve are all under vacuum at approximately the same pressure. The spring is holding the VPI valve open, and the vacuum system is exposed to the mechanical pump's full pumping speed.

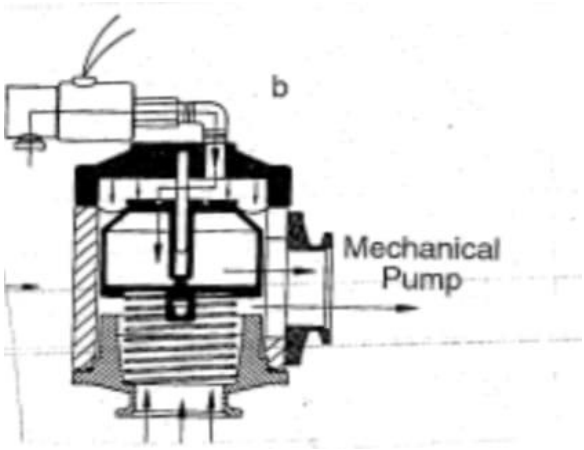


Figure 1.4 (b): Power Interruption.

Figure 1.4 (b): Power Interruption the VPI valve solenoid loses its power, since it is connected in parallel to the mechanical pump. The solenoid opens to the atmosphere. Air. enters the VPI valve through the solenoid and creates a higher pressure above the piston than exists below it. The piston closes rapidly (30 ms). During this time only the inside of the piston (buffer volume) is being filled, isolating the vacuum system from any introduction of air. This figure shows the piston in transit downward.

In case of power failure where Vacuum pump stops and due to application vacuum before power cut chamber will have more than Vacuum pump is Oil-cooled and sealed then back suction of oil is possible which can be very ethical as lyophilized Injectable product will have traces of oil normally there is quick closing Valve in the discharge of pump quick closing Valve malfunction or does not close properly can led to contamination of Injectable Products. Question in how of quick for time quick closing valve to close and how do you calibrate? Normally quick closing valve take 30 miliseconds to close.

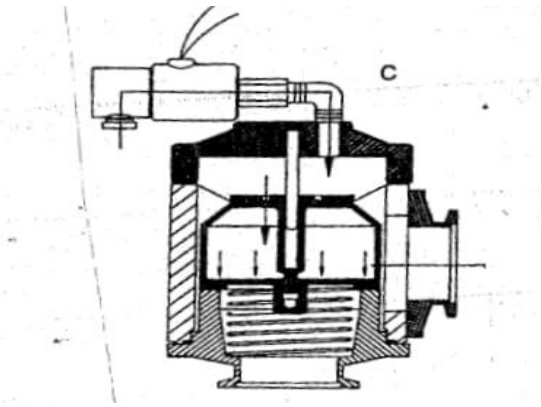


Figure 1.5 (c): Valve Closed.

Figure 1.5 (c): Valve Closed - Mechanical Pump Vented The piston is fully down and the VPI valve is fully closed. The higher pressure above the piston forces it-against the valve seat, where the Viton® O-ring makes a vacuum tight seal. Air from the higher-pressure area above the piston continues to flow through the small orifice in the top of the piston into the inside of the piston, and through a second small orifice in its side into the mechanical pump's inlet port. This vents the mechanical pump to atmospheric pressure gradually. When the pump is fully vented, the pressure above the piston, inside the piston, and in the mechanical pump are the same (atmospheric). The pressure below the piston, in the vacuum system, is still lower and the piston remains down (closed), maintaining the vacuum system under vacuum.

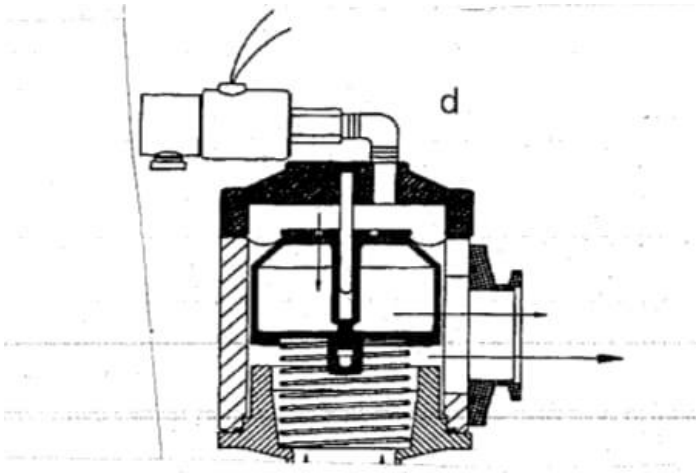


Figure 1.5(d): Power Restored.

NOTE: *Given enough time, the pressure in the vacuum system will rise due to outgassing, leaks, etc., or venting by the operator, and when the pressure is high enough, the spring will open the piston and the vacuum system will be at the same pressure as the mechanical pump (atmospheric).*

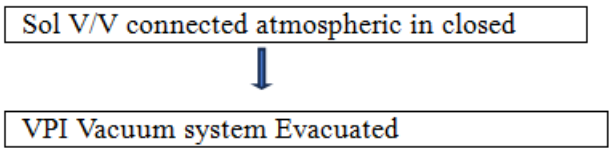
Figure 1.5(d): Power Restored The solenoid coil is energized causing the solenoid to close, isolating the inside of the VPI valve from the outside atmosphere. The mechanical pump evacuates the inside of the piston through the small orifice in its side and the area above the piston through the small orifice in the top of the piston via the inside of the piston. When the pressure above the piston is approximately equal to that in the vacuum system, the spring pushes the piston upward, fully opening the VPI valve. The vacuum system is now back in normal operation and exposed to the full pumping speed of the mechanical pump.

NOTE: In Figure 1.2 a,b &c, the mechanical pump is connected to the port on the right side and the vacuum system to the bottom port.

Quick closing valve is also named as vacuum isolation valve (VPI) this operates in the event of power failure by isolating the vacuum system and venting the mechanical pump. This is done to avoid oil backup.

VPI (Vacuum pump isolation valve) has ISO KF flange valve operates with atmospheric pressure it has advantage became as power failure takes place is closed by atmospheric pressure.

Fast acting vacuum pump isolation valve is designed for 100,000 cycles are normal i.e. Operating principal of vacuum pump isolation valve in normal operation when power is available.



When power failure takes places, valve closes due to atmospheric pressure and when power resumes Solenoid valve closes.

Specification of quick closing valve.

Leak rate

Body - $1x10^{-9}$ at mcc/sec

Seal - $1x10^{-9}$ at mcc/ sec

Closing time=30milli second

Normally material of construction is aluminium in seals of viton.

Venting line 10 to 60 sec/ litres.

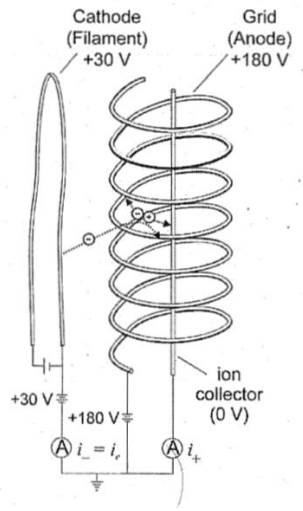


Figure 1.6: Diagram of a Bayard-Alpert type HCIG." The electron path shown is one possible trajectory.

As vacuum play's critical role in lyophilization quality of product. Instruments which are fitted needs to be calibrated trace able to NIST Std. normally calibration ranges of 10^{-7} Pa to Ipa Vacuum gauges calibration: These gauges are working 'in ionization principal to measure below. pressure below 10^{-5} Pa. ionization gauges are two types Hot cathode ionization gauges (HCIG) and Cold cathode ionization gauges (CCIG). Both gauges sense presses me by detecting Ions resulting and gas ionized by election bombardment.

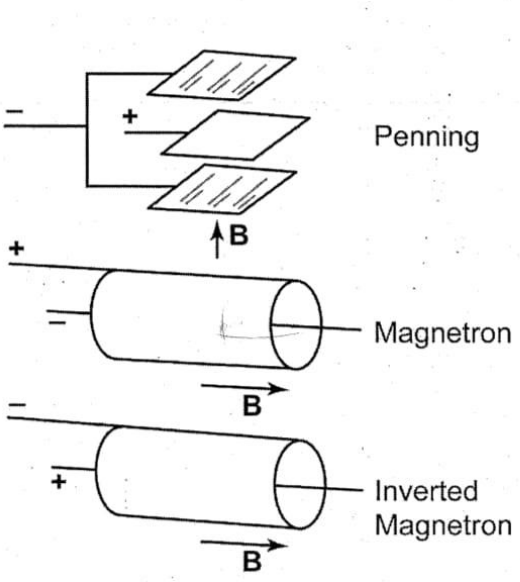


FIGURE 1.7: Diagram of typical cold-cathode electrode geometries.

Hot cathode Ionization gauges (HCIGS): Electrons are thermionically emitted from heated cathode element. These electrons are accelerated. into an Ionization Volume, typically in form of a cylindrically shaped a node - the grid or electron collector (anode) Ion Current is directly proportional gas density.

Cold-cathode ionization gauges (CCIGS): Indirectly the determine the press me by gas density from ion current. There are three common Configuration

(A) Penning

(B) Magneton

(C) Inverted magneton

See the figure Commonly used are Inverted magneton High Vacuum Calibration

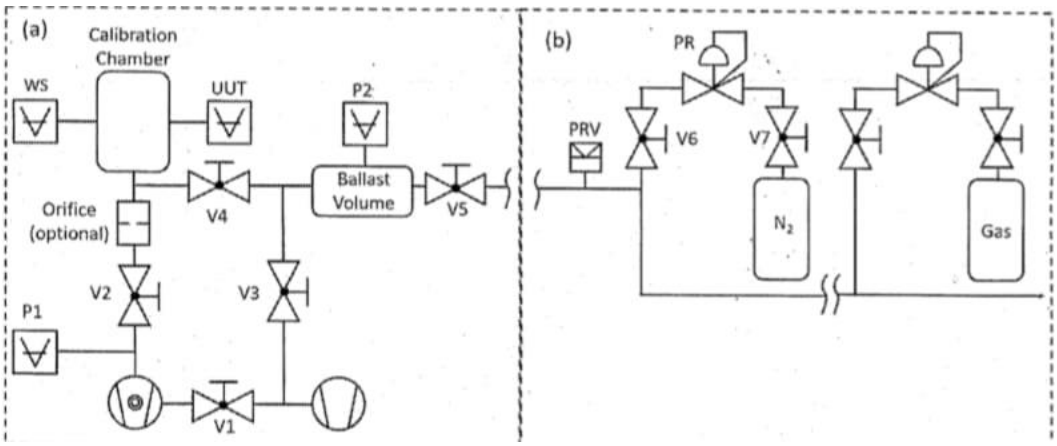


Figure 1.8 Calibration vacuum system (a) and gas admission system (b) for the calibration of ionization gauges using the comparison method. The unit under test (UUT) is compared to the working standard (WS); P1- gauge to read inlet pressure of the high vacuum pump; 12-gauge to read buffer volume pressure (optional), VI-V7 are valves; V4 is a leak valve; PRV is a pressure relieve valve; PR is a pressure regulator.

Calibrations chambers are typically Constructed stainless steel with flanges and fittings sealed with metal-gaskets high vacuum ionization gauges are calibrated by comparative method

Ref- NIST published vac Sci Technology 2018 10.1116/1.5025260

Vacuum leak testing for high Vacuum system no Vacuum device is absolutely vacuum tight and every Vacuum equipment leak but leakage rate has to be in accepted range as the pressure raise as function of time there are three curves.

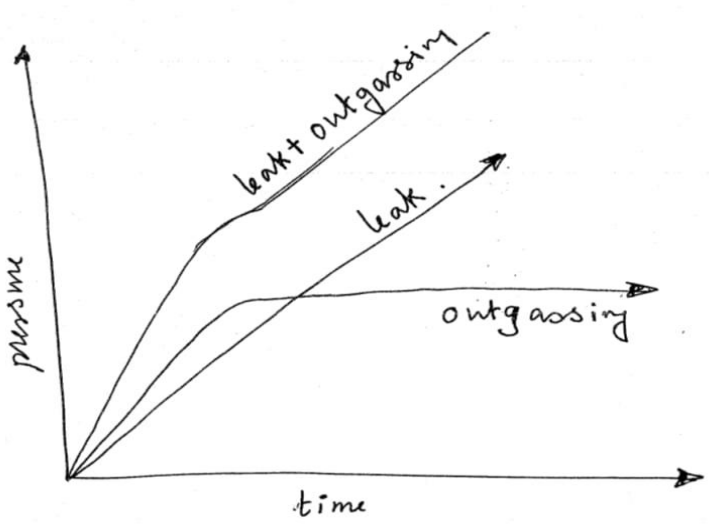


Figure 1.9: Three different Indication.

In practice it is impossible to build a completely leak-tight system. this is not even required. leak rate must be small enough to allow the required pressure level is reached.

Conversion factors for leak rates in various. System units.

	Mbar -1/s	**Torr -1/s**	**Pa m^8/s**	**Cm^3/s**
Mbar 1/s	1	0.75	0.1	0.99
Torr 1/s	1.33	1	0.133	1.32
Pa m^3/s	10	7.5	1	~ 10
Cm^8/s	1.01	0.76	0.101	1

Very tight system- $Q1<10^{-6}$ mbar 1/s

Tight system- $Q1<10^{-5}$ mbar 1/s

Leaky system- $Q1<10^{-4}$ mbar L/s

Ultra Sonic method of leak detection This detector can measure leak up to 10^{-2} mbar l/s bubbles water of soap to detect leak has sensitivity of 10^{-4} mbar 1/s

These methods are simple and cost effective in detecting leaks.

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