FREEZE-DRYING
Basic Concepts and principles

Telstar
Life Science solutions

Did you know…?

Lyophilisation technology has began with INCA civilization, in which the potatoes were freeze-dried to obtain "chuño". The product was freezed during the night and it was freeze-dried during the day in the high mountains…

Freeze-Drying

Also called **lyophilisation**, is a drying process where the wet product is first frozen to a solid phase and subsequently dried to vapour phase through sublimation, that is, without passing through the liquid phase, by exposing it to a low partial pressure of water vapour.

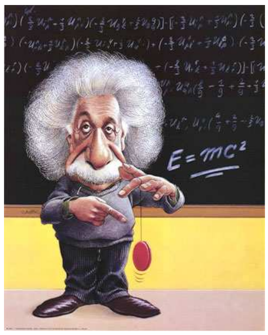
Lyo = Solvent	Philo = Friend

The lyophilisation process makes the dried product "solvent loving".

Basic Concepts

The basic concepts that we will cover in this session are:

- Heat/Cold
- Conduction, convection and radiation
- Sensible heat/latent heat
- Physical states of matter
- Phase diagram. Triple point
- Absolute/relative pressure
- Vapour pressure.
- Vacuum
- Vacuum pump mechanism
- Eutectic point
- Glass transition temperature
- Collapse



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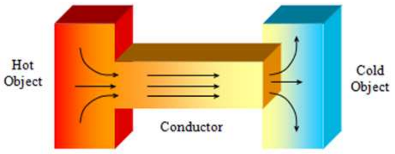
Heat and Cold

When two bodies come into contact, each with a different temperature – that is with different levels of molecular agitation – a flow of energy is transferred from hotter body, or rather the body with the greater internal energy, to the colder body. This continues until both bodies are of an equal temperature, known as balance temperature. At this point, the energy flow stops. This means one of the bodies will have reduced its internal energy, while the other will have increased.

This energy is called heat when it passes from the hotter to the colder body, and cold when it passes from the colder to the hotter body. Therefore, heat travels, is absorbed, transferred, lost, etc but it is not possessed. A body has internal energy, not heat. It could be said that the terms he and cold refer to quantity, while the term temperature refers to quality. Heat/cold are manifestations of energy, while temperature is the intensity of the form of energy.

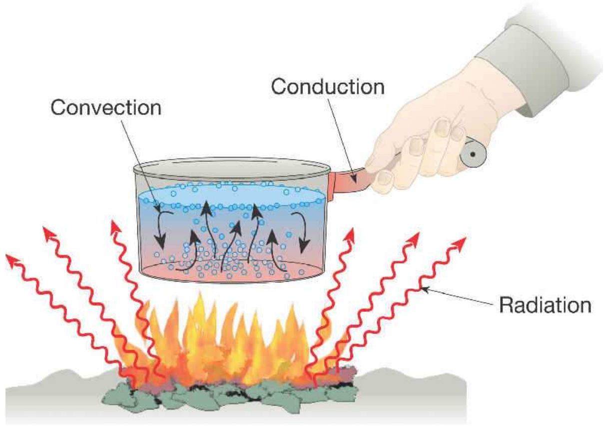


HEAT FLOWS FROM AREAS AT HIGHER TEMPERATURE TO AREAS OF LOWER TEMPERATURE

Units used for Temperature and Heat/Cold

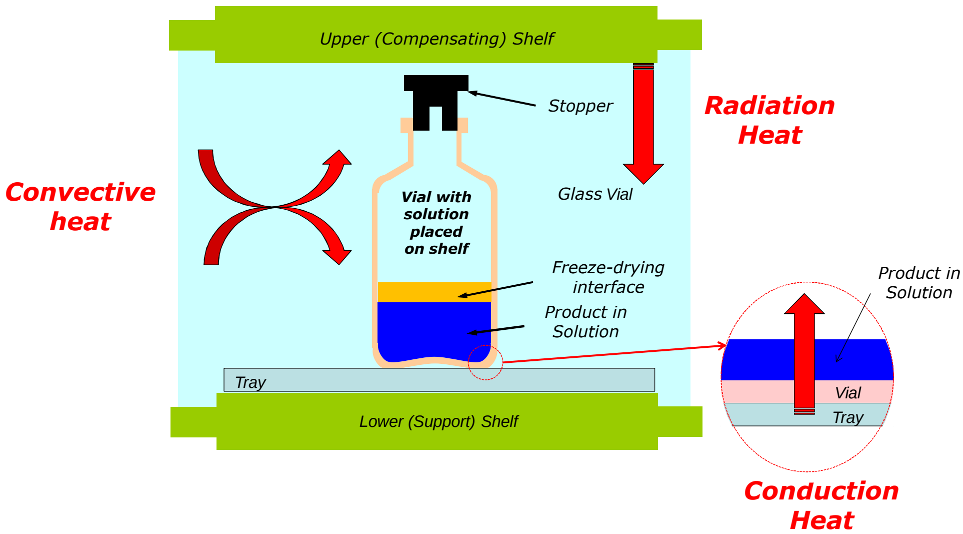
- **Temperature** is measured in degrees centigrade or Fahrenheit
- **Heat** is measured in calories and **cold** in negative calories.
- **Calorie** is defined as the heat necessary to raise the temperature of one gram of water from 14,5ºC to 15,5ºC.
- **Negative** calorie is defined as the amount of heat that must be removed from a gram of water for its temperature to drop from 1ºC to 0ºC.

Conduction, Convection, Radiation… in real life.



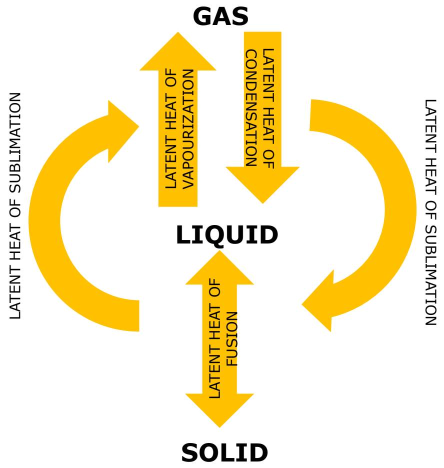
- **Conduction:** The most efficient method of heat transfer
- **Convection:** A slower method of heat transfer
- **Radiation:** The least efficient method of heat transfer

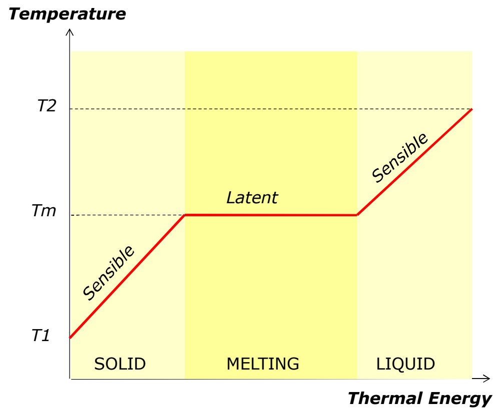
Conduction, Convection and Radiation… in freeze-drying process



Sensible heat/latent heat

If a body transfers heat to another causing its temperature rise to rise, this is called **sensible heat**, since it produces an effect that can measured with a Thermometer.
If heat is transferred to a liquid body at its evaporation temperature, the only effect this has it to change its physical state, from liquid to gas – it does not increase the temperature. This is **called latent heat.**





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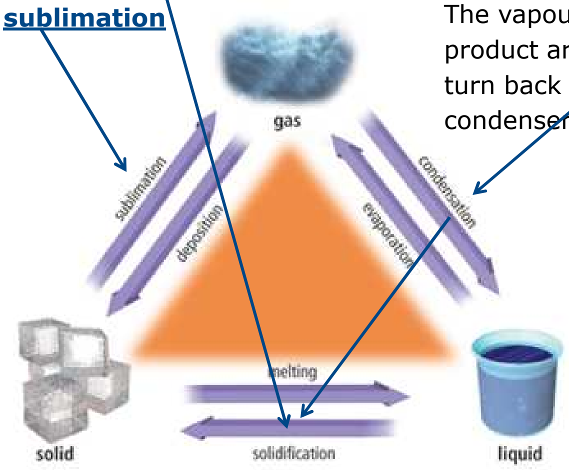
Physical states of matter

In a lyophilisation process, the wet product is first **frozen** to a solid phase and subsequently dried to vapour phase through **sublimation**

The vapours being sublimed of the product are **condensed** and turn back into solid form (ice) in condenser.



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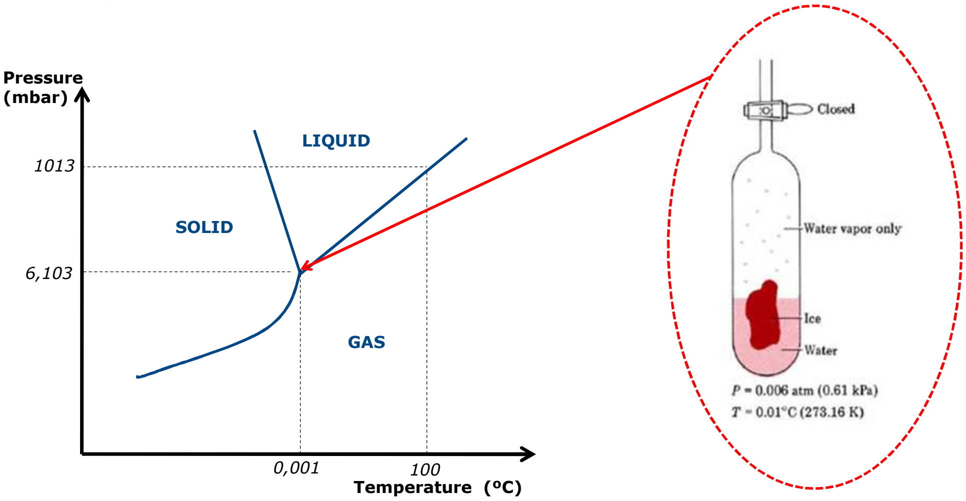
Phase Diagram /Triple point

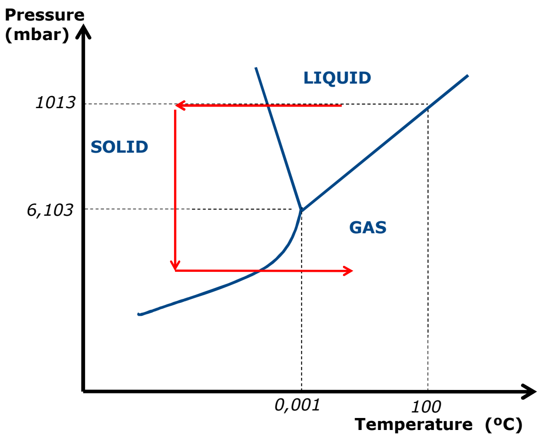
In triple point all three phases gas (vapour), liquid (water) and solid (ice) are in equilibrium



Phase Diagram and Freeze-drying

In a lyophilisation process, the wet product is:

- First frozen at atmospheric pressure.
- Then pressure is reduced
- and temperature is raised to promote sublimation from ice to vapour.
- Vapour travels to the ice condenser where it is trapped as ice.
- When drying is finished, trapped ice is melted and drained.



Vacuum

Given that is not possible for a space to exist completely free from matter, which would be the academic definition of vacuum, in practice vacuum is defined as a space filled with a gas at a pressure lower than the atmospheric pressure (0<P<1013 mbar).

Vacuum is generally divided into:

- Rough/Low vacuum : 101 to 1mbar
- Medium vacuum: 1 to 10-3 mbar
- High vacuum 10-3 to 10-7 mbar
- Ultra high vacuum<10-7mbar

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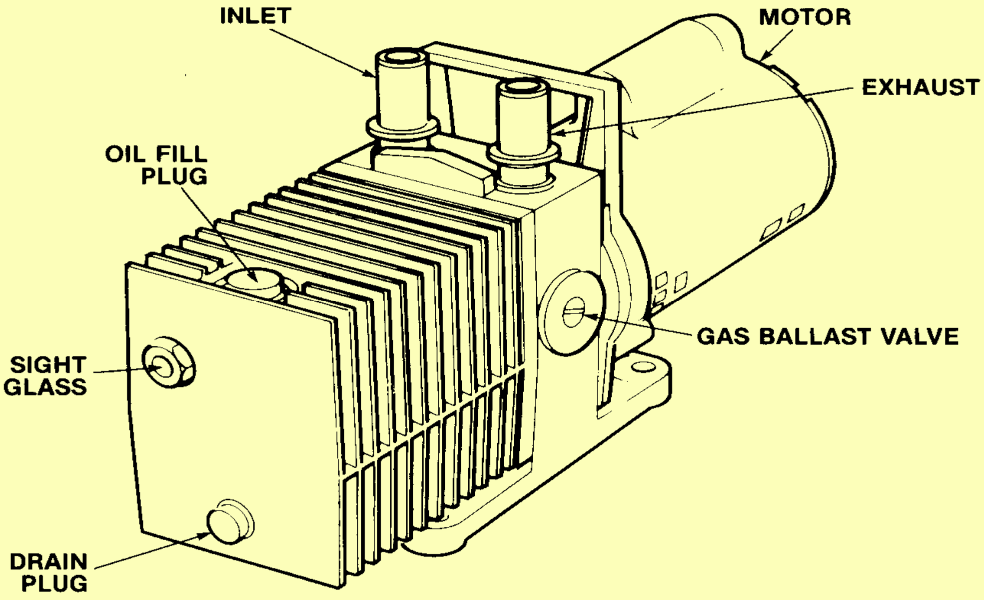
Telstar Expertise - Space simulation

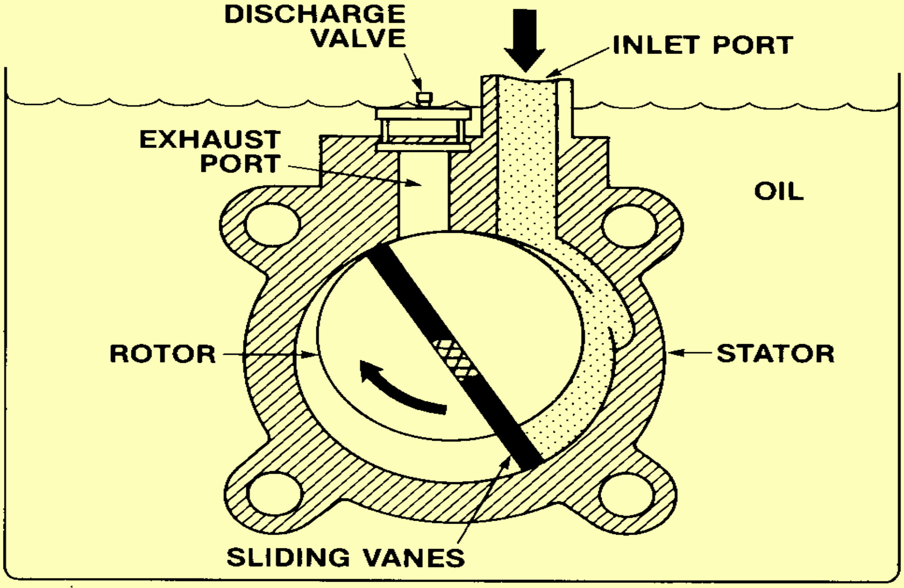
The extreme environmental conditions to which space equipment is exposed throughout its working life demands the highest available standards of materials and systems reliability. Ensuring the ongoing survival of space hardware requires that very thorough and detailed testing processes are conducted. The main aim of such exhaustive testing is to minimize the risks, since the value of a medium size satellite is of the order of hundreds of millions of euros/dollars

The simulation of such complex and environmentally variable conditions is technologically non-viable therefore the space simulation chambers are usually restricted to the **vacuum simulation up to 1. 10^{7-}mbar, cold and visible and infrared radiation (-190ºC/+180ºC).**

Vacuum Rotary vane, oil- sealed mechanical pump

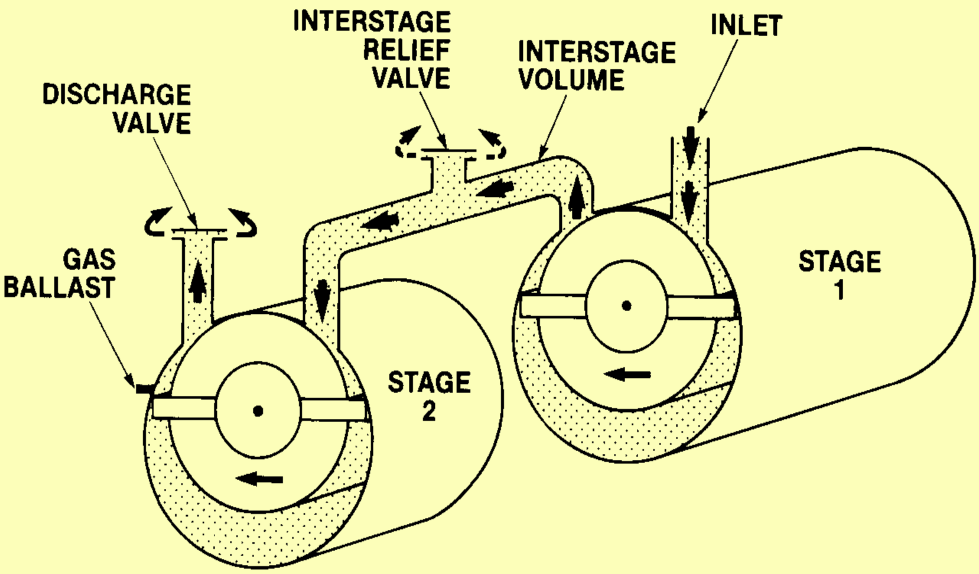


Vacuum Pump mechanism

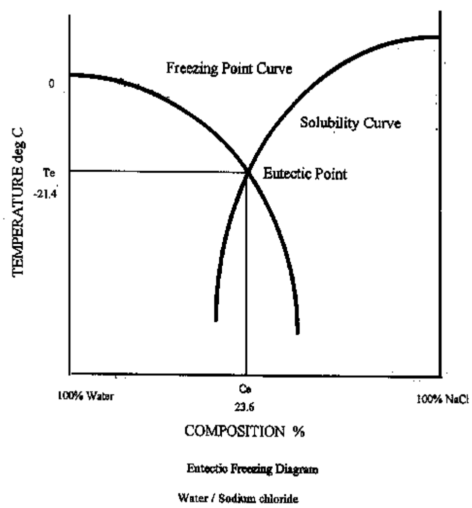


ROTARY OIL-SEALED MECHANICAL PUMP MODULE

How the pump works?



Eutectic point



- Above the freezing curve the solution has only one phase and it is liquid
- Below the freezing curve there are two phases: pure ice + more concentrated solution
- Below the crystallization curve there are two phases: NaCl solid and concentrated solution
- Below the eutectic, there is no liquid phase: everything is solid.
- A similar curve is obtained with amorphous materials: eutectic is replaced by glass-transition temperature

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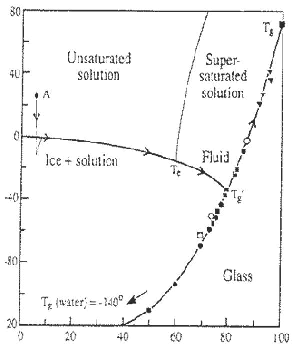
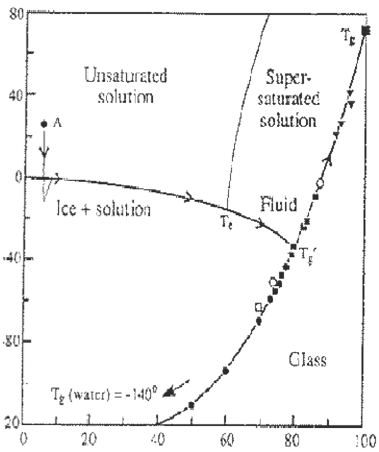
Glass Transition Temperature *(Tg)*



The glass transition temperature is the temperature below which the physical properties of amorphous materials vary in a manner similar to those of a solid phase (glassy state), and above which amorphous materials behave like liquids (rubbery state). A material's glass transition temperature, Tg, is the temperature below which molecules have little relative mobility. Tg is usually applicable to wholly or partially amorphous phases such as glasses and plastics. Thermoplastic (non-crosslinked) polymers have a Tg (lower than pure melting) below which they become rigid and brittle, and can crack and shatter under stress.

Above Tg, the bonds between the polymer chains become weak in comparison to thermal motion, and the polymer becomes rubbery and capable of elastic or plastic deformation without fracture. This behavior is one of the things which make most plastics useful. But such behavior is not exhibited by crosslinked thermosetting plastics which, once cured, are set for life and will shatter rather than deform, never becoming plastic again when heated, nor melting.

Glass Transition temperature



Solutions "frozen" with an amorphous structure show a certain mobility above its glass transition temperature Tg'.
This mobility may collapse the already dry phase.

The "dry" product may exhibit a glass transition Tg.

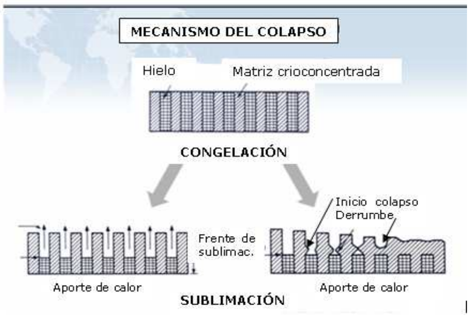
It is extremely dangerous when this Tg is close to ambient (storage) temperature. The product can collapse after a certain time.

Collapse

If pressure at sublimation front rises

- due to excessive heat supply because the difficulty increase of vapors to pass through the dry phase
- Or by an ice condenser overload

Sublimation front temperature also rises:



It may happen that the frozen temperature is above its Tg', so the interstitial phase may behave "rubbery", and may even become less and less viscous exhibiting certain mobility.

Then the already dry structure may collapse. The chimneys become clogged.

Further temperature rise may lead to melting.

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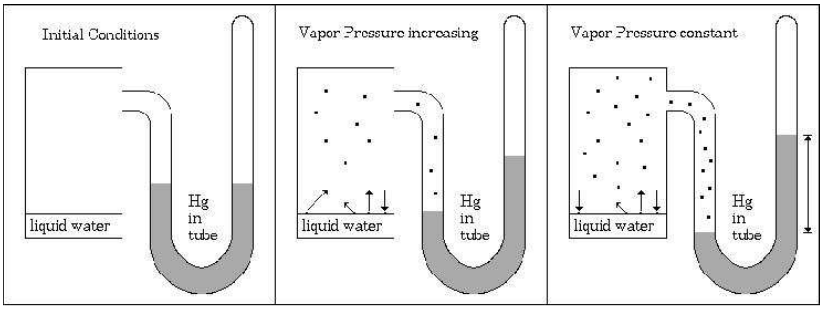
Vapour Pressure

- The vapour pressure of a liquid is the pressure exerted by its vapour when the liquid and vapour are in dynamic equilibrium.
- If a substance is placed in an evacuated, closed container, some of it would vaporise. The pressure in the space above the liquid would increase from zero and eventually stabilise at a constant value: the vapour pressure.
- This equilibrium pressure is a function of the temperature of the substance



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Examples vapour pressure in substances

SUBSTANCE	Vapor Pressure (SI units)	Vapor Pressure (Bar)	Vapor Pressure (mmHg)	Temperature
Tungsten	100 Pa	0.001	0.75	3203 °C
Ethylene glycol	500 Pa	0.005	3.75	20 °C
Xenon difluoride	600 Pa	0.006	4.50	25 °C
Water (H_2O)	2.3 kPa	0.023	17.5	20 °C
Propanol	2.4 kPa	0.024	18.0	20 °C
Ethanol	5.83 kPa	0.0583	43.7	20 °C
Methyl isobutyl ketone	26.48 kPa	0.2648	198.62	25 °C
Freon 113	37.9 kPa	0.379	284	20 °C
Acetaldehyde	98.7 kPa	0.987	740	20 °C
Butame	220 kPa	2.2	1650	20 °C
Formaldehude	435.7 kPa	4.357	3268	20 °C
Propane	1.013 MPa	10.133	7600	25.6 °C
Carbonyl sulfide	1.255 MPa	12.55	9412	25 °C
Carbon dioxie	5.7 MPa	57	42753	20 °C

In following training you will learn…

Types of freeze-dryers

LABORATORY FREEZE-DRYER specially suitable for the R&D centres in industries, universities, hospitals and scientific institutes. I has been designed according the GLP principles in order to comply with strictest international standards.

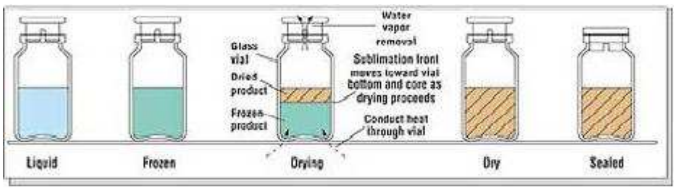
R+D FREEZE-DRYER has been equipped with the appropriate components, devices and sensors to control processing conditions: temperature, pressure and time. This allows defining the the process variables to achieve adequate control and reproducibility.

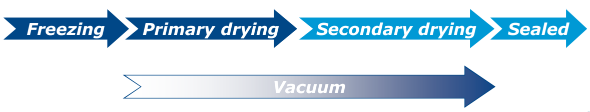
CUSTOMIZED GMP FREEZE-DRYING SOLUTIONS to cover a complete range of vial and bulk applications from manual trough semi-automatic to fully automatic systems to meet the requirements of each project. Technologies include the use of anthropomorphic robots for handling of trays, vacuum-based bulk powder unloading systems, tray-less “fixed” row-by-row or “ flexible shelf-by-shelf vehicle systems.

Lyophilisation Steps

The steps required to freeze-dry a product can be summarized as follow:

1. Pre-treatment /Formulation
2. Dosing product (Bulk, Flask, Vials)
3. Freezing at atmospheric pressure
4. Primary drying (sublimation) under vacuum
5. Secondary drying (desorption) under vacuum
6. Backfill & stoppering (for product vials) under partial vacuum
7. Removal of dried product from freeze-dryer





…And much more!

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Thanks for your attention
Questions & Answers