

# PHARMA*process*

Innovation Forum in Pharmaceutical Process

## CONTINUOUS FREEZE DRYING

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Barcelona, 28/10/15

[www.pharmaprocessforum.com](http://www.pharmaprocessforum.com)



## WHAT FREEZE DRYING IS?

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.

The ice in the product is converted into vapour, without passing through the liquid phase, if the ambient partial water vapour pressure is lower than the partial pressure of the ice at a suitable temperature.

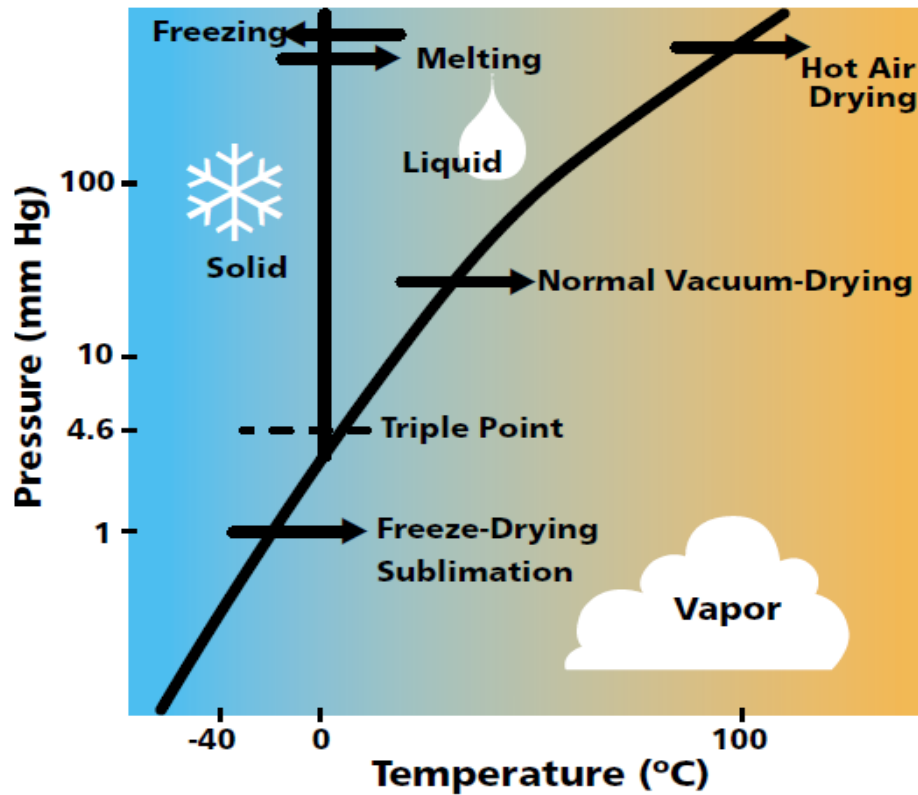
From Greek, **Lyo** means **Solvent** and **Philo** means **Friend**

The lyophilisation process makes the dried product “solvent loving”



## WHAT FREEZE DRYING IS?

### Phase Diagram for Water





## WHAT FREEZE DRYING IS?

Lyophilization technology has suffered many advances since the Incas, many centuries ago, prepared “chuño” from potatoes. The cold mountain temperatures froze the food and the water inside slowly sublimated under the low humidity of the high altitudes. Machu Picchu.

1906 – Physical principles of sublimation applied to the conservation of serums and vaccines (Bordas and D´Arsonval)

1909 – Rudimentary freeze dryer (Shackell)

1937- Nestle starts to freeze dry the excess of coffee in Brazil



## WHAT FREEZE DRYING IS?

1939-1945 – Second World War. Preservation of blood plasma (Flosdorf, Greaves, Mudd)

1945 – Discovery of penicillin. Lyophilization was used for antibiotics preservation (Chain)

XXI Century – Applications in Biotechnology, Nanotechnology, Liposome, Proteins





## WHAT FREEZE DRYING IS?

The freeze drying process is divided into two different physical process steps:

*Step one* is the freezing of the material below its solidification temperature (below its eutectic or its collapse temperature).

*Step two* removes the ice crystals at very low temperatures.

This last step can be divided in two additional steps:

*Primary drying* with removal of water by sublimation

*Secondary drying* with removal of remaining water by desorption



## FOOD INDUSTRY MANUFACTURING . CONTINUOUS PROCESS

### **EXTERNAL FREEZING TRAYS LOADING**

Product is frozen in external chamber.

Example of coffee.

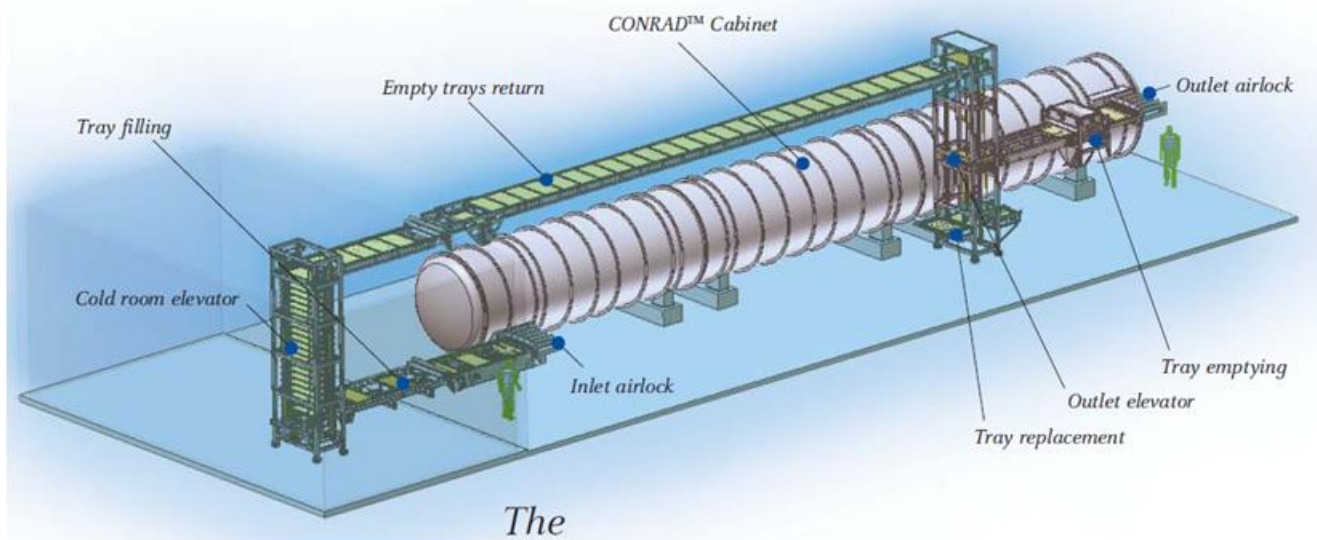
The coffee extract follows different steps of freezing process

The frozen product is continuously loaded onto trays that are then placed into an automated air lock.

The drying vessel is a long cylinder chamber designed to operate under vacuum.



## FOOD INDUSTRY MANUFACTURING. TRAYS LOADING



Source GEA Niro Inc.

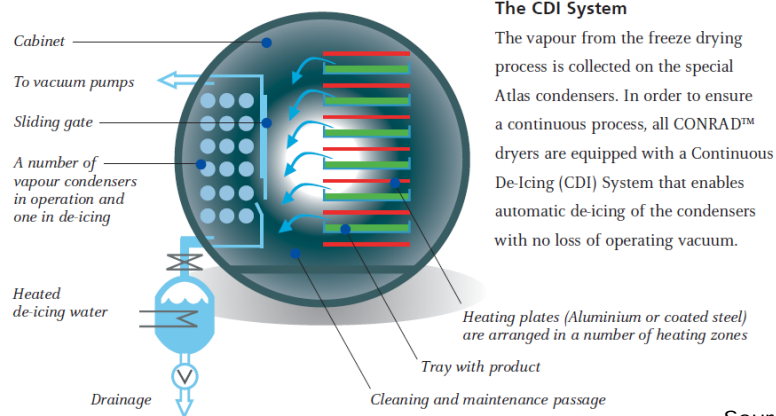
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## FOOD INDUSTRY MANUFACTURING. CONTINUOUS PROCESS



Source GEA Niro Inc.

The internal vapor condenser with built-in de-icing system compared with external condenser systems saves not only space. It is more reliable does not cause product loss and it uses less energy and thus ensures the best overall equipment efficiency.

## FOOD INDUSTRY MANUFACTURING . BELT PLANTS

### BELT DRYING PLANT

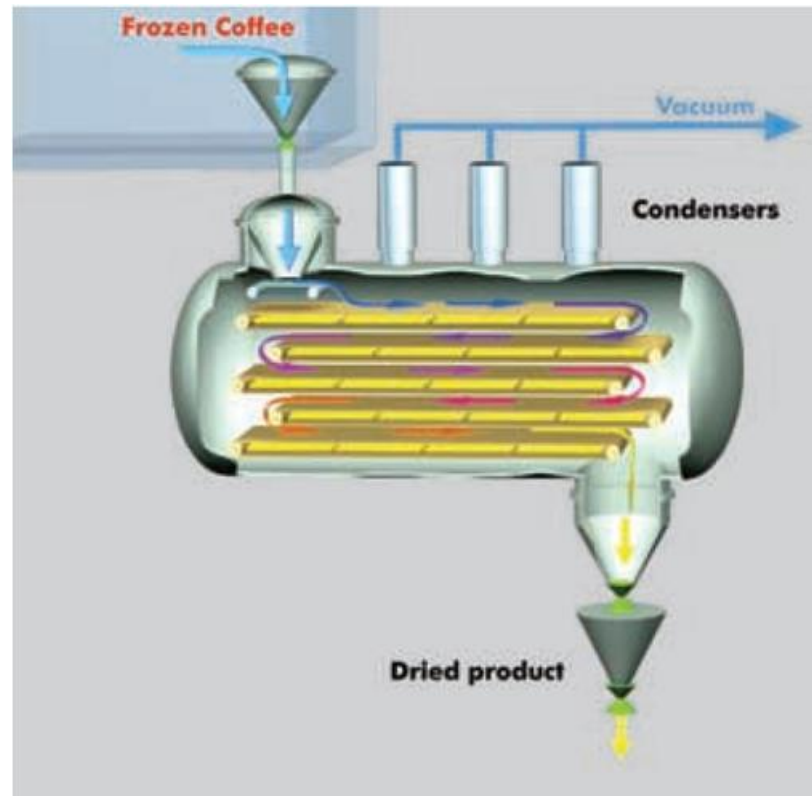
In addition to the freeze-drying method with trays (static freeze-drying) some manufacturers offers the so-called "Dynamic Freeze-Drying

This drying method is used for fluid/free-flowing products. In this "trayless systems", the products are in direct contact with the heating surface.

Quick frozen products are fet onto the dryer's belt through a vacuum tight rotary valve.

## FOOD INDUSTRY MANUFACTURING . BELT PLANTS

### BELT DRYING PLANT



Source ALD Vacuum Technologies.

## FOOD INDUSTRY MANUFACTURING. BELT PLANTS

Inside the drying tunnel, the product is uniformly distributed by a special distribution device to the first belt of the belt transport system.

Drying is controlled through a combination of belt speed and plate-temperatures (heating and cooling) as the product travels through the drying chamber



Source SPX GmbH

## FOOD INDUSTRY MANUFACTURING. BELT PLANTS

### INTERNAL FREEZING

Cuddon offers a unique answer to dry concentrated liquids by direct injection into the drying chamber.

The spray nozzle provides a method to spray and freeze in one action that allows a consistent product application onto the conveyor belt

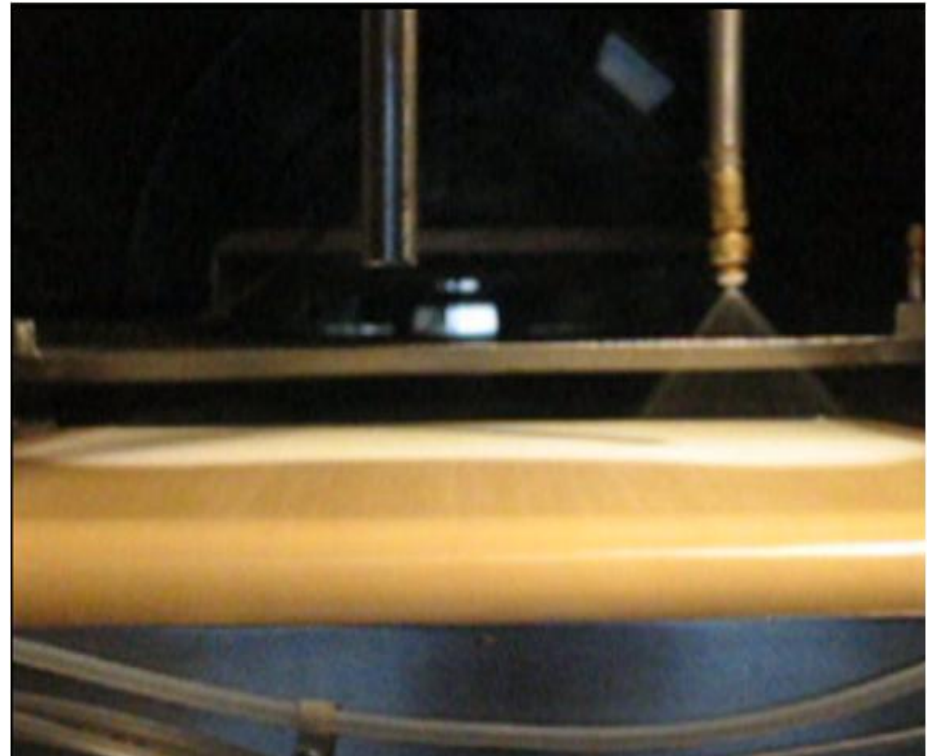


Source Cuddon.



## FOOD INDUSTRY MANUFACTURING. BELT PLANTS

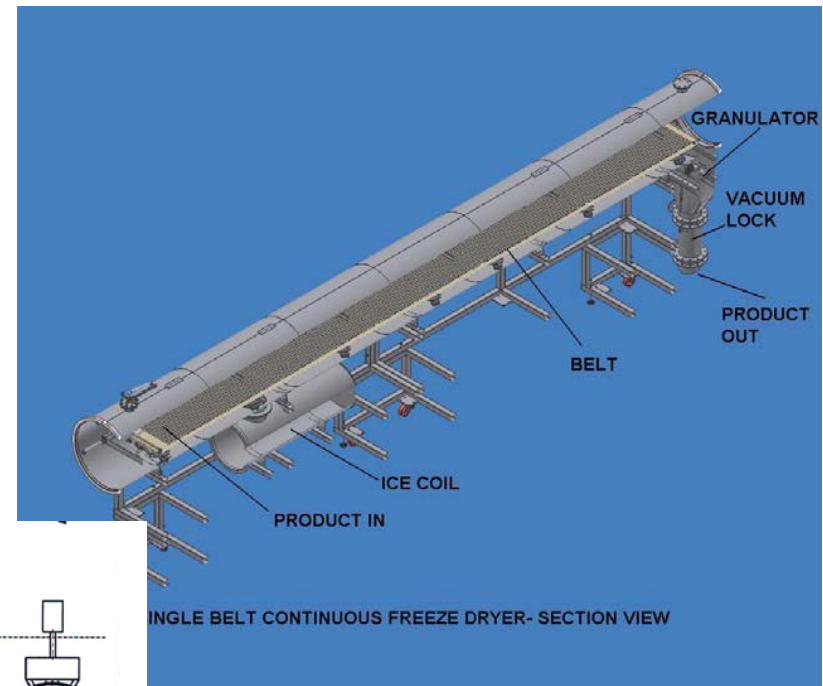
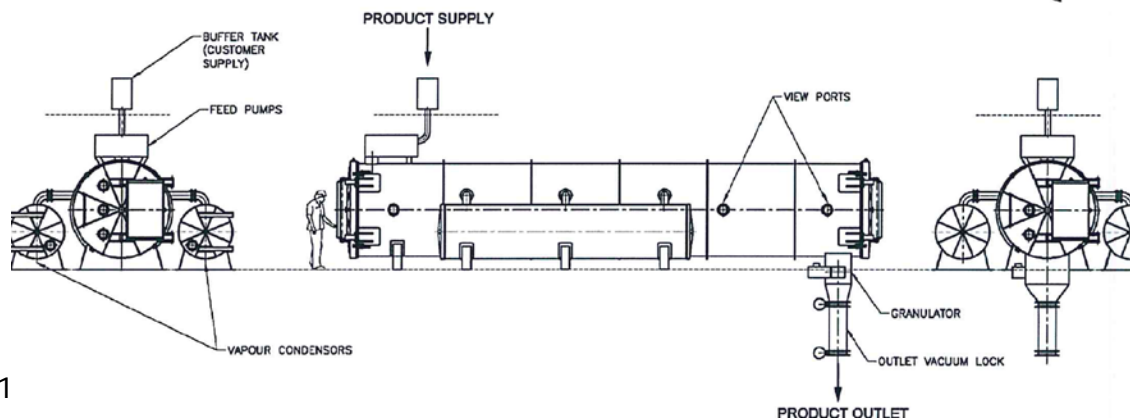
Liquid product is sprayed over the internal belt under vacuum. Sudden evaporation of a part of the water froze the solution by him shelves. Some radiation plates contribute the necessary energy for sublimation



Source Cuddon.

## FOOD INDUSTRY MANUFACTURING. BELT PLANTS

Dry product is unloaded at the end of the tunnel and it exits through a vacuum lock into the product bagging point.



Source Cuddon.

## FOOD INDUSTRY MANUFACTURING. BELT PLANTS

Continuous freeze-drying plants can manipulate up to 60 tons of fresh product per day per unit.

Continuous freeze-drying technology is well developed and it is growing.

The continuous freeze-drying tunnels are manufactured among others by GEA, ALD, BUCHER, DEVEX, SSP, SPX, CUDDON, ...

On the contrary, pharmaceutical industry has done only timid approaches to the continuous plants.

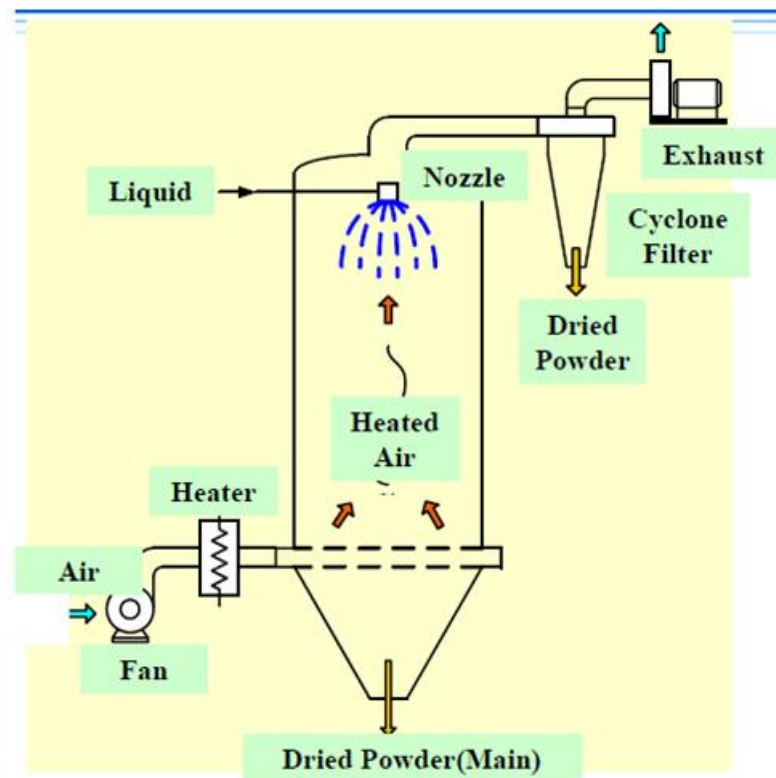
International organizations push the industry to implement the continuous process but several issues must be solved.

## PHARMACEUTICAL MANUFACTURING. CONTINUOUS SPRAY FREEZE DRYING

### CONTINUOUS SPRAY FREEZE-DRYING

Spray freeze drying (SFD) is a method in which a solution containing dissolved material is sprayed into a cold phase to form frozen and solid particles. After that this particles will be dried using lyophilisation technique. The powder produced by SFD differ from those obtained by other methods. SFD powders show a larger mid particle size as the droplet shrinkage during drying is low. The size of droplets could be controlled by choosing an appropriate

17 spray condition.



Source Ulvac

## PHARMACEUTICAL MANUFACTURING. DYNAMIC FREEZE-DRYING FOR BULK

### DYNAMIC FREEZE-DRYING

The following technology is not a continuous technique but it is closed to it.

MERIDION uses the same technology of spray to get frozen particles. In that case particles are freeze-dried in a rotary drum.

It allows the generation of sterile lyophilised microspheres as bulk.



Source Meridion



## PHARMACEUTICAL MANUFACTURING. DYNAMIC FREEZE-DRYING FOR BULK

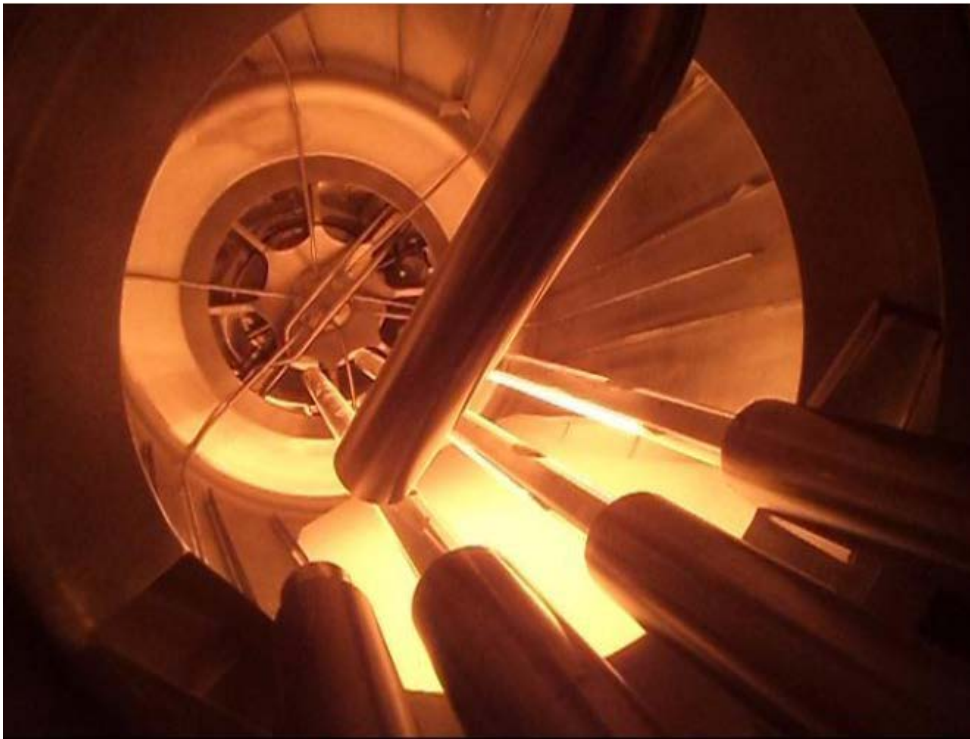


The resulting bulk product is homogeneous, free flowing and dust free. It therefore allows for an intermediate storage of the sterile bulk product.

The technology addresses new formulation strategies including option like combination products or personalized medication, as well as manufacturing logistics strategies.

Source Meridion

## PHARMACEUTICAL MANUFACTURING. DYNAMIC FREEZE-DRYING FOR BULK



The containment properties shows benefits in pharmaceutical applications.

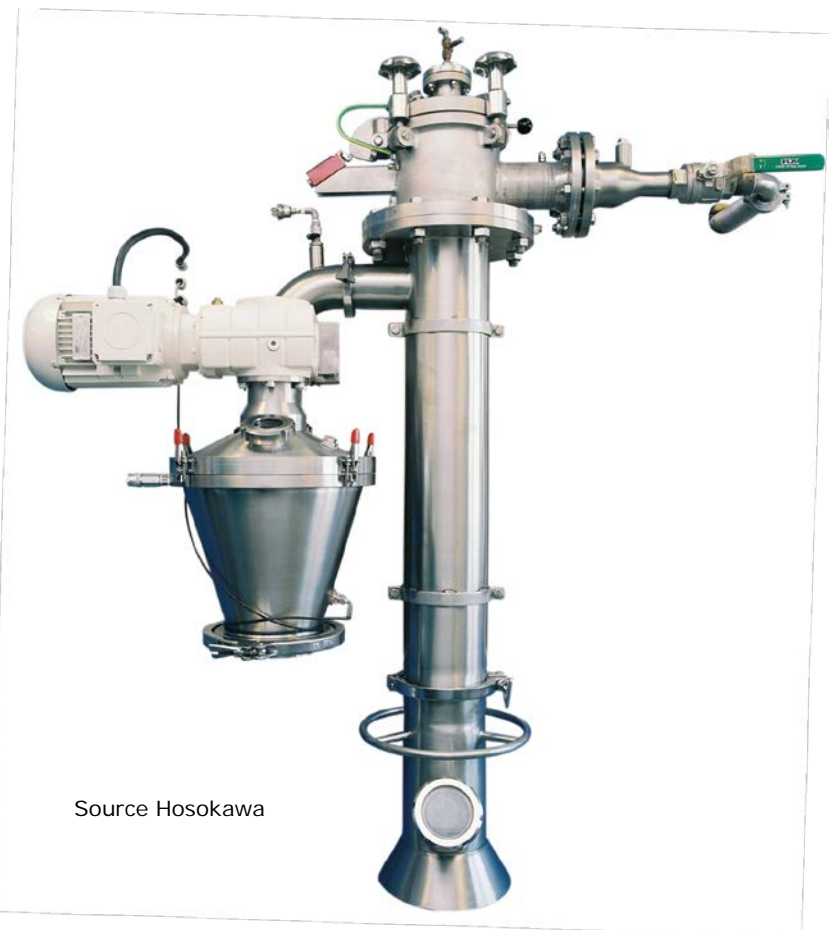
Solid dosage form technologies are applicable.

Source Meridion

## PHARMACEUTICAL MANUFACTURING. STIRRED FREEZE DRYING

### STIRRED FREEZED-DRYING

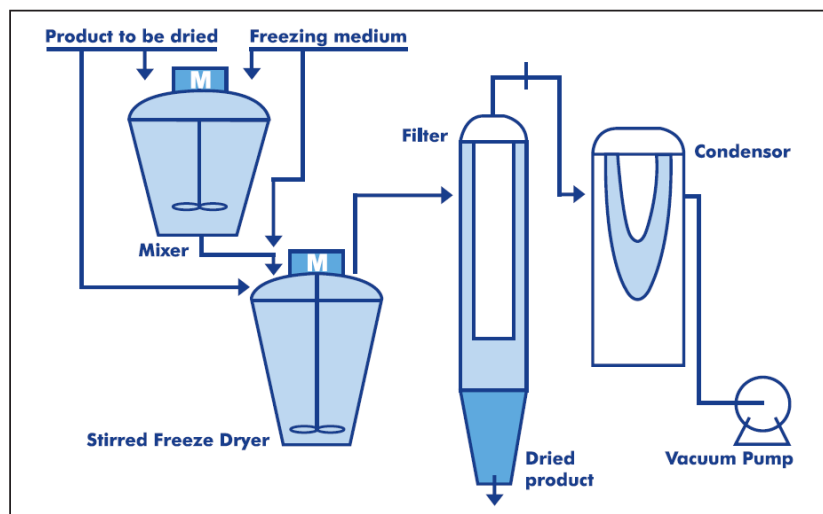
Hosokawa states that it is possible to operate a freeze dryer under stirred conditions. Hosokawa Micron's stirred freeze drying technology which incorporates the use of a jacketed and stirred Vrieco-Nauta, conical vacuum dryer operated at low temperature and pressure, produces a lump free, free-flowing, freeze dried product.



Source Hosokawa

## PHARMACEUTICAL MANUFACTURING. STIRRED FREEZE DRYING

Stirred freeze drying can be operated continuously with dry particles released from the frozen material during the drying process collected in a filter alongside the actual dryer.



Source Hosokawa

The main application of stirred freeze drying is found in the pharmaceuticals, macromolecules, electrolytes, probiotics...

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

### FINE SPRAY FREEZE-DRYING

ULVAC has developed a whole new freeze-dry process, by which a liquid is sprayed directly into a vacuum chamber to form micro particles. In addition, they have established an integrated mass-production system for sterile formulation that facilitates the processes from powder filling to rolling.

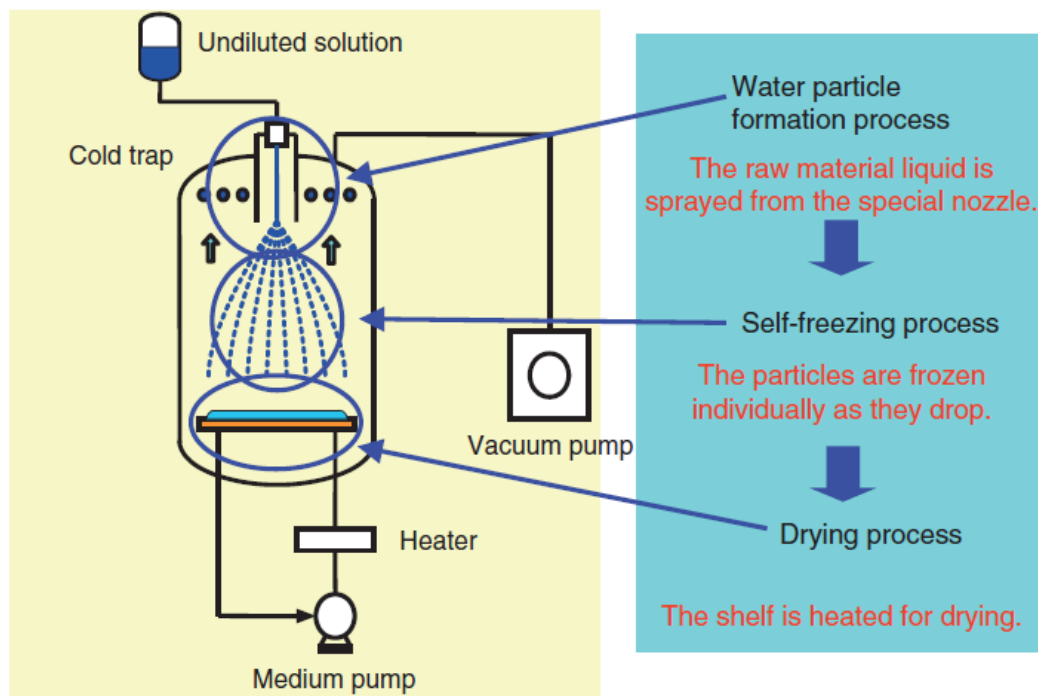
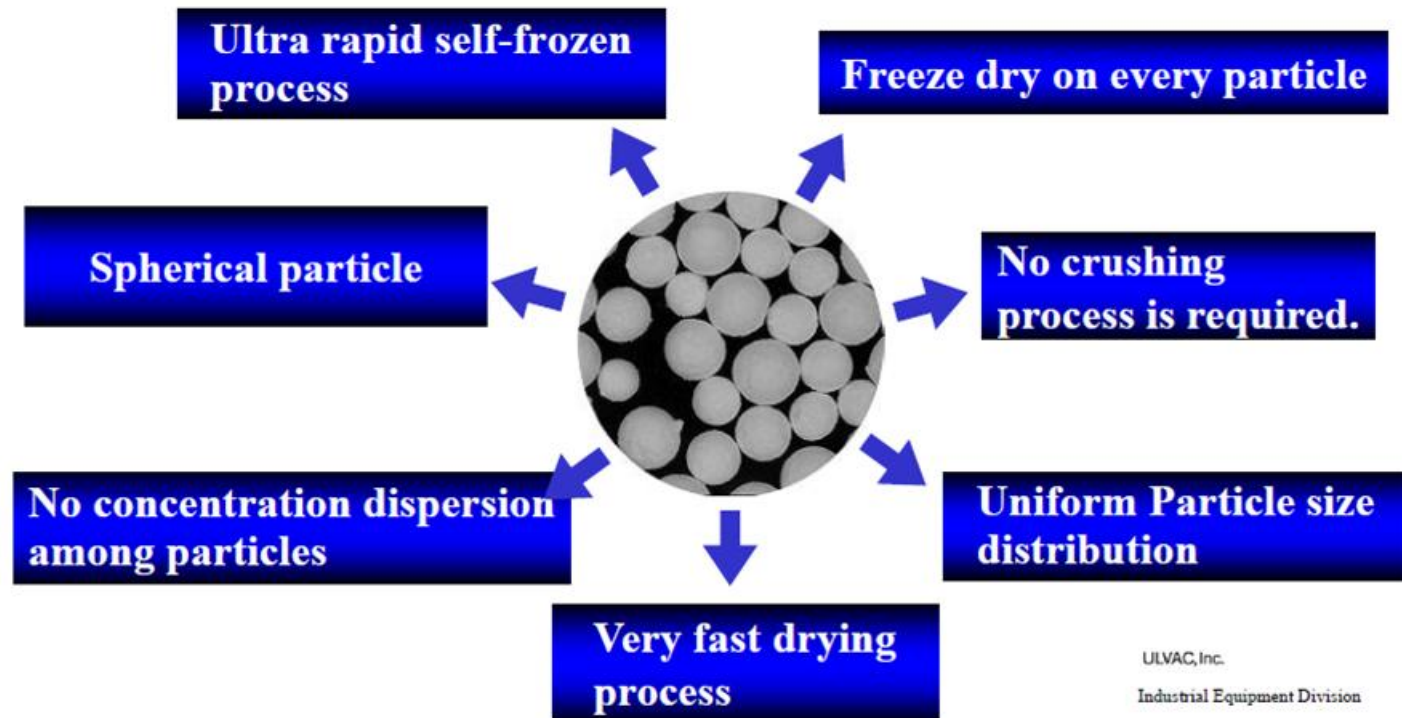


Figure 1 Principle of fine-spray freeze drying (µPD)



## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY



## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

### Micro powder dry system

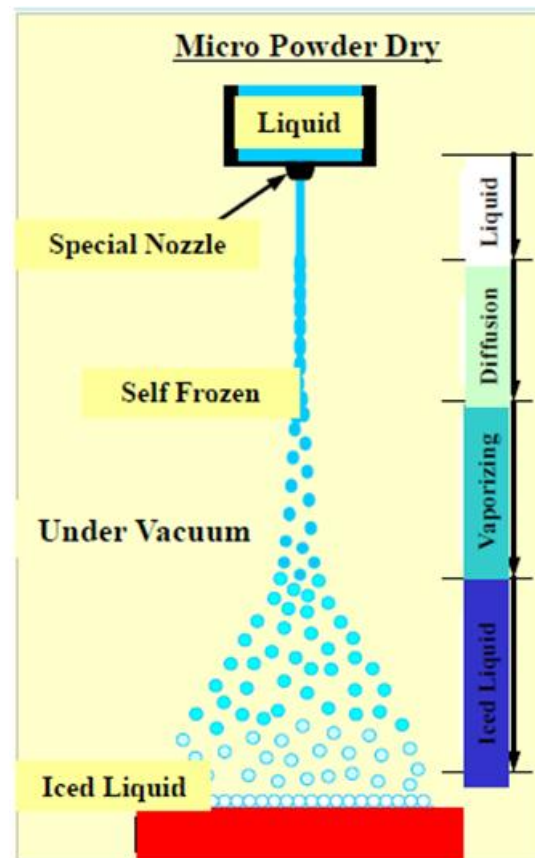


Source Ulvac

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

Water particle formation process

When a liquid is sprayed into the vacuum chamber, it is first in a liquid column state, but the specimen gradually disperses to form water particles. The particles of the dispersed specimen form uniform round particles because it is not subject to air resistance in a vacuum.



Source Ulvac

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

### Self-freezing process

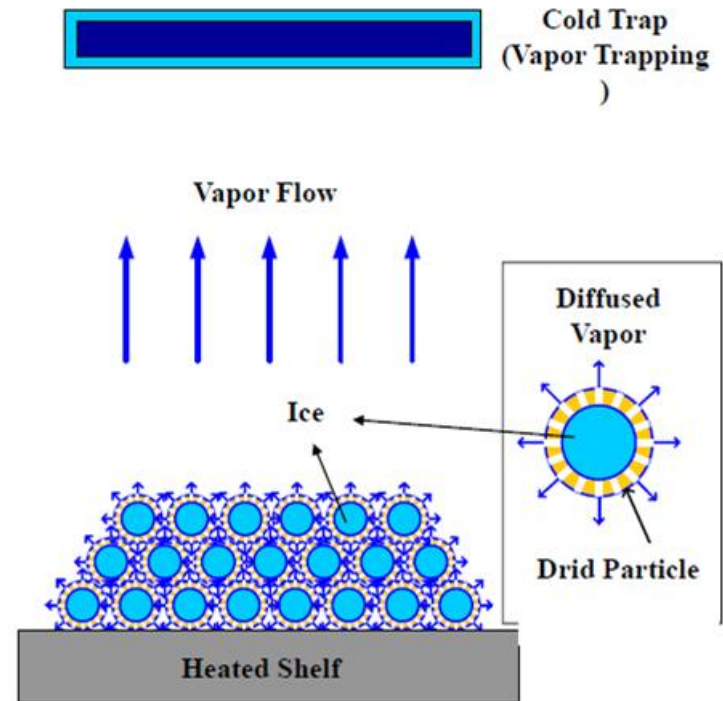
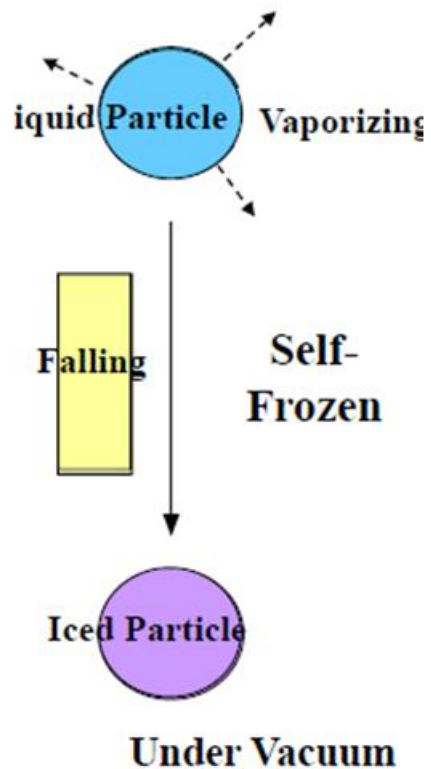
The particles are cooled down and they self-freeze to form frozen particles. The self-freezing and frozen particle formation takes place instantaneously in the vacuum chamber.

Evaporation latent heat  $L_{ws}=2,500$  kJ/kg (water  $\rightarrow$  vapor)

Solidification latent heat  $L_{wi}=330$  kJ/kg (water  $\rightarrow$  ice)

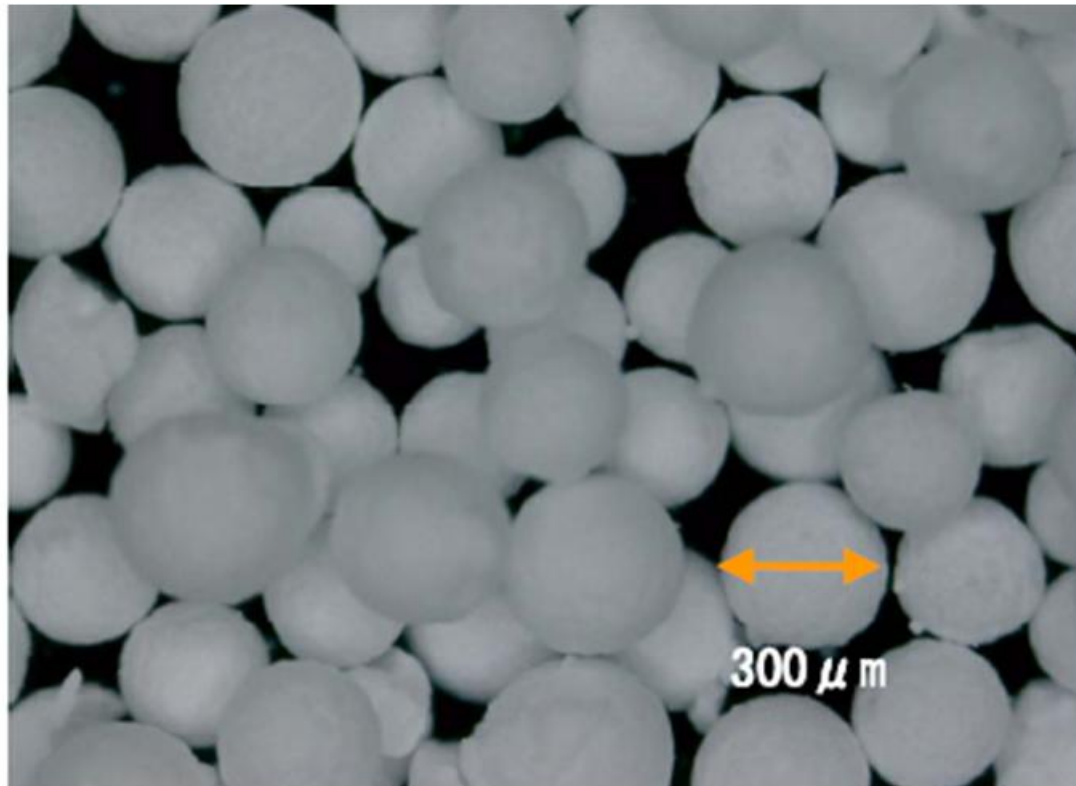
$L_{wi}/L_{ws}\approx 1$ . (Self-freezing takes place when about 13% of the water evaporates)

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY



Source Ulvac

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY



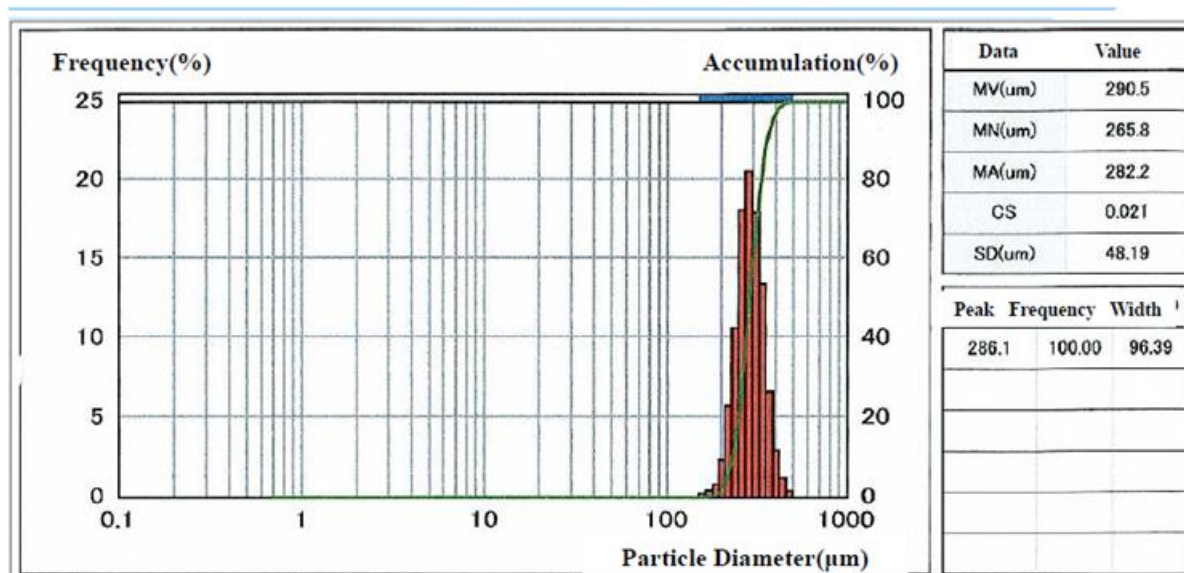
Source Ulvac



## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

### Drying process

The frozen particles formed by self-freezing are deposit on the heating/cooling shelf in the system. After spraying ends, the shelf is heated to dry the specimen.



Source Ulvac

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

### Advantages of fine-spray freeze drying

Fine-spray freeze drying is superior to conventional freeze drying and spray drying in the following ways:

- (1) Uniform concentration distribution
- (2) Uniform particle size distribution
- (3) Excellent solubility
- (4) Shorter drying time
- (5) Particle size of the dried powder is controllable

## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

Fully-closed freeze drying sterile formulation system  
In combination with the development of fine-spray freeze drying technology, Ulvac has established a fully closed system for sterile formulation.

This system uses fine-spray freeze drying equipment and covers the processes from the drying process to the rolling process after chemical preparation.



## PHARMACEUTICAL MANUFACTURING. FINE-SPRAY FREEZE DRYING TECHNOLOGY

Particles of different products are generated and frozen in a continuous way.

Frozen particles are collected in a device and water sublimates at a high velocity.

Process is well controlled and it is very stable

Different particles sizes are collected depending on the size of the spray nozzle

Product concentration and spray pressure are very important from the point of view of the particle quality.

## CONTINUOUS PROCESSING IN PHARMACEUTICAL INDUSTRY. CONCLUSIONS

As quoted by: Continuous Processing in Pharmaceutical Manufacturing. Matthew J. Mollan Jr. Ph.D. and Mayur Lodaya Ph. D. Pfizer Inc.

*Pharmaceutical processing is synonymous with batch processing*

*Food industry has steadily moved to continuous processing technologies driven mainly by cost and quality considerations.*

*The same cost and quality drivers are forcing pharmaceutical industry to look for ways to improve quality while maintaining or reducing manufacturing costs.*

*Continuous processing technologies provide one possible path forward.*



## CONTINUOUS PROCESSING IN PHARMACEUTICAL INDUSTRY

*FDA has issued a guidance to the pharmaceutical industry: PAT a Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance. (1)*

*Quality must be built by design*

*The guidance document states “Facilitating continuous processing to improve efficiency and manage variability”*

## CONTINUOUS PROCESSING IN PHARMACEUTICAL INDUSTRY

*Some very interesting concepts on continuous or semi-continuous lyophilisation technology were described by Rey.*

*The pharmaceutical industry is poised to change radically in the next years in response to a changing marketplace.*

*The design of new production facilities utilizing new technology and implementing continuous processing strategies will be one way to remain competitive.*

# PHARMAprocess

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