

Application note: N° F015

November 2011

## Freeze drying

### Facts & figures:

Maxwell House first introduced freeze dried instant coffee to the market in 1963.

Secondary drying lasts 1/3 or 1/2 of the time that primary drying lasts.

Some freeze dried products can be stored for up to 25 years without any issues at all!

### Freeze drying in general

The freeze drying method can be traced back to prehistoric times and was used by the Incas who stored their crops on the mountain heights above Machu Picchu: the cold mountain temperatures froze the food and the water inside slowly vaporised under the low air pressure of the high altitudes.

#### How freeze drying works.

Freeze drying involves the removal of water or other solvent from a frozen product by a process called sublimation.

Sublimation occurs when a frozen liquid goes directly to the gaseous state without passing through the liquid phase.

The freeze drying process consists of three stages: pre-freezing, primary drying and secondary drying.

#### Prefreezing:

Material intended to be freeze dried must first be pre-frozen below its eutectic temperature.

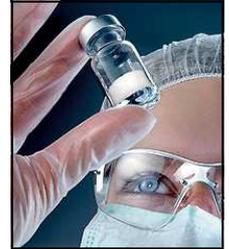
#### Primary drying:

After prefreezing the product, conditions must be established in which ice can be removed from the product via sublimation. This requires very careful control of two parameters: temperature and pressure (the pressure is controlled with a vacuum pump). The rate of sublimation of ice from a frozen product depends upon the difference in vapour pressure of the product compared to the vapour pressure of the ice collector. Molecules migrate from the higher pressure sample to the lower pressure sample. Since vapour pressure is related to temperature, it is also necessary that the prod-

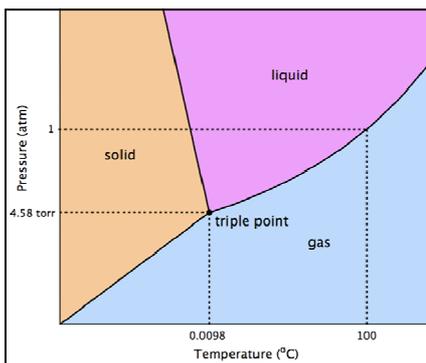
uct temperature is warmer than the ice trap temperature.

#### Secondary drying:

After primary freeze drying is complete and all ice has sublimated but bound water is still present in the product! Continued drying is necessary at warmer temperatures to remove the residual water. This process is called isothermal desorption as the bound water is desorbed from the sample. During secondary drying, the product temperature is higher than ambient. All of the other conditions, such as pressure and ice trap temperature remain the same.



Freeze dried drugs



The sublimation line is the line separating the solid phase from the gas phase.

#### Discussed in this edition:

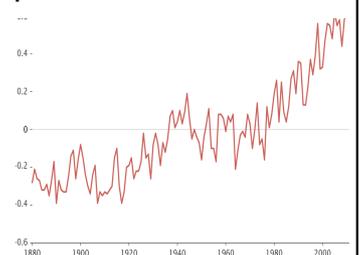
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### Eutectic temperature

#### What is eutectic temperature?

The majority of products that are subjected to freeze drying consist primarily of water, the solvent, and the materials dissolved or suspended in the water, the solute. Most samples that are to be freeze dried are eutectics which are a mixture of substances that freeze at lower temperatures than the surrounding water. Although a product may appear to be frozen because of all the ice present, in

actuality it is not completely frozen until all of the solute in the suspension is frozen. Only when all of the eutectic mixture is frozen is the suspension properly frozen: this is called the **eutectic temperature**.



## Why the need to measure the relative humidity?



Fresh raspberries



Frozen raspberries



Freeze dried raspberries

### Advantages and inconvenients

People use freeze drying to **preserve material**, such as pharmaceuticals. Many pharmaceuticals will degrade pretty quickly when exposed to water and air, for the same basic reason that food degrades. Chemists can greatly **extend pharmaceutical shelf life** by freeze-drying the material and storing it in a container free of oxygen and water. Similarly, research scientists may use freeze drying to **preserve biological samples for long periods of time**. Freeze dried biological samples are also big in the florist world. The freeze drying process has also been used to **restore water-**

**damaged materials**, such as rare and valuable manuscripts.

Freeze dried material can be **stored at warmer temperatures without suffering degradation**.

Freeze dried products can be **stored without cryogenic or freezing facilities**, the energy cost and the risk of product loss from power failure is greatly reduced.

As the product is dried out without excessive heating, **proteins and other products that would be thermally denatured can be successfully preserved without loss of activity**.

As products are much lighter when they are dry, freeze drying offers the **benefit of reducing transport costs**.

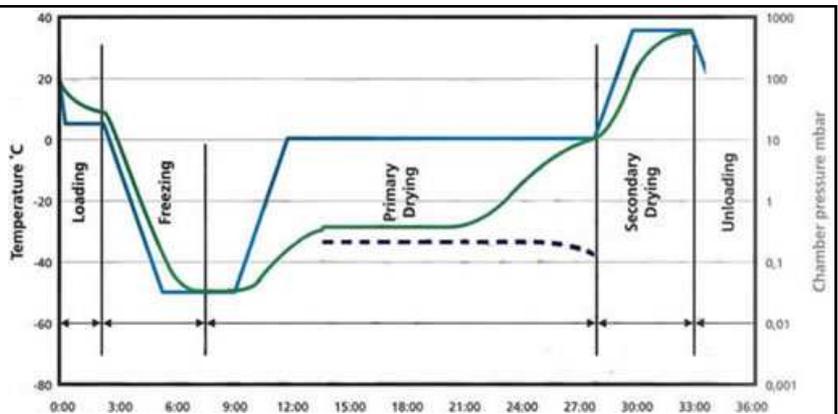
Compared to advantages, the only disadvantage is that freeze drying is **very a expensive process in terms of high investment and maintenance costs** and the production capacity is limited due to the long process time.

As freeze drying is an expensive process, once the product is freeze dried, it is important that it is monitored during the rest of the life span of the product.

### Freeze drying cycle

During the lyophilisation (freeze drying) process, the freezing is very important: rapid cooling results in small ice crystals, useful in preserving structures to be examined microscopically, but resulting in a product that is more difficult to freeze dry. Slower cooling results in larger ice crystals and less restrictive channels in the matrix during the drying process.

- Environment temperature
- Product temperature



### Optimising the process

**Air inlets:** During the freeze drying process the air inlets must be monitored. The dryer the air entering the room, the better.

By their nature, freeze dried products are hygroscopic and exposed to water during storage can destabilise the product. This means that the freeze dried products can “never” leave a controlled

zone.

The control of the **storage area** where freeze dried products are placed is compulsory.

The freeze drying process never comes alone, once the product is dry, there is then a need to **pack the product**: there are always filling machines that are placed in a

sterile areas or isolators where humidity must be controlled and can be sterilized with hydrogen peroxide.

**Residual humidity in elastomeric stoppers** can cause degradation of freeze dried products. Prior to packaging the product, stoppers are typically washed, steam sterilised and dried. The steam sterilisation process

drives humidity into the stopper. If the drying conditions for the stopper are not optimised, residual humidity can transfer into the freeze dried product over time.

**Packaging** used for freeze dried materials must be impermeable to relative humidity.

## What solutions can Rotronic offer?

Rotronic attests that the validated version of the Rotronic HW4 software and the associated devices fulfil the requirements defined in the Rotronic ERES white paper based on the following paragraphs:

- 21 CFR 110,
- 21 CFR 210,
- 21 CFR 211,
- EU Annex 11 to the EU guidelines of good manufacturing practice for medicinal products.



HF5 transmitter with a HC2-S probe

## Rotronic products:

### Humidity and temperature probes:

- **HC2-S**  
Standard humidity sensor,  
-50...100°C,  
0...100%rh,  
±0.8%rh and ±0.1K...
- **HC2-IM**  
Chrome nickel steel Industrial probe,  
-100...200°C,  
0...100%rh,  
±0.8%rh and ±0.1K...
- **HC2-P05**  
Insertion probe,  
-40...85°C,  
0...100%rh,  
±1.5%rh and ±0.3K...

### Transmitters:

- **HF5 series**  
For interchangeable probes,  
2 or 3/4 wire configuration,  
Various analogue and digital outputs,  
Display,  
All psychrometric calculations available...
- **HF7 series**  
Stainless steel probe,  
-100...200°C,  
3/4 wire configuration,  
Various analogue outputs,  
Display...

### Dataloggers:

- **HL-NT range**  
For interchangeable probes  
(up to 7 probes with docking station)  
32MB flash card,  
Display,  
Conform to FDA21 CFR Part 11 and GAMP4...
- **HL-20**  
20'000 measurement pairs,  
Display,  
±0.8%rh and ±0.2K,  
Conform to FDA21 CFR Part 11 and GAMP4...



HL20 datalogger

## Customer benefits:

### Interchangeability:

The Rotronic product range is setup around the interchangeability feature of the HC2 probes. Be it with loggers or transmitters, there is always the possibility of interchangeable probes.

When calibration is required, it is easy to remove a probe from a transmitter rather than removing the entire transmitter from the wall.

On the same level, it is possible to test a system loop

with using a Rotronic simulator probe that gives fixed outputs. Plug this into the transmitter and see if the loop works correctly!

### Calibration and adjustment:

Calibration and adjustment is very easy with the Rotronic product range. As all of the communication is digital, the whole calibration procedure can be done via a PC, or directly from the device with the help of the Rotronic humidity standards. Rotronic

can also offer a factory calibration (certified or not).

### Communication:

With all of the different communication methods, from RS-485, Wireless to Ethernet RJ45, Rotronic can provide the solution for each installation.

### Long term stability:

A long term stability with a drift under 1%rh per year (depending on the environment).



HL-NT datalogger

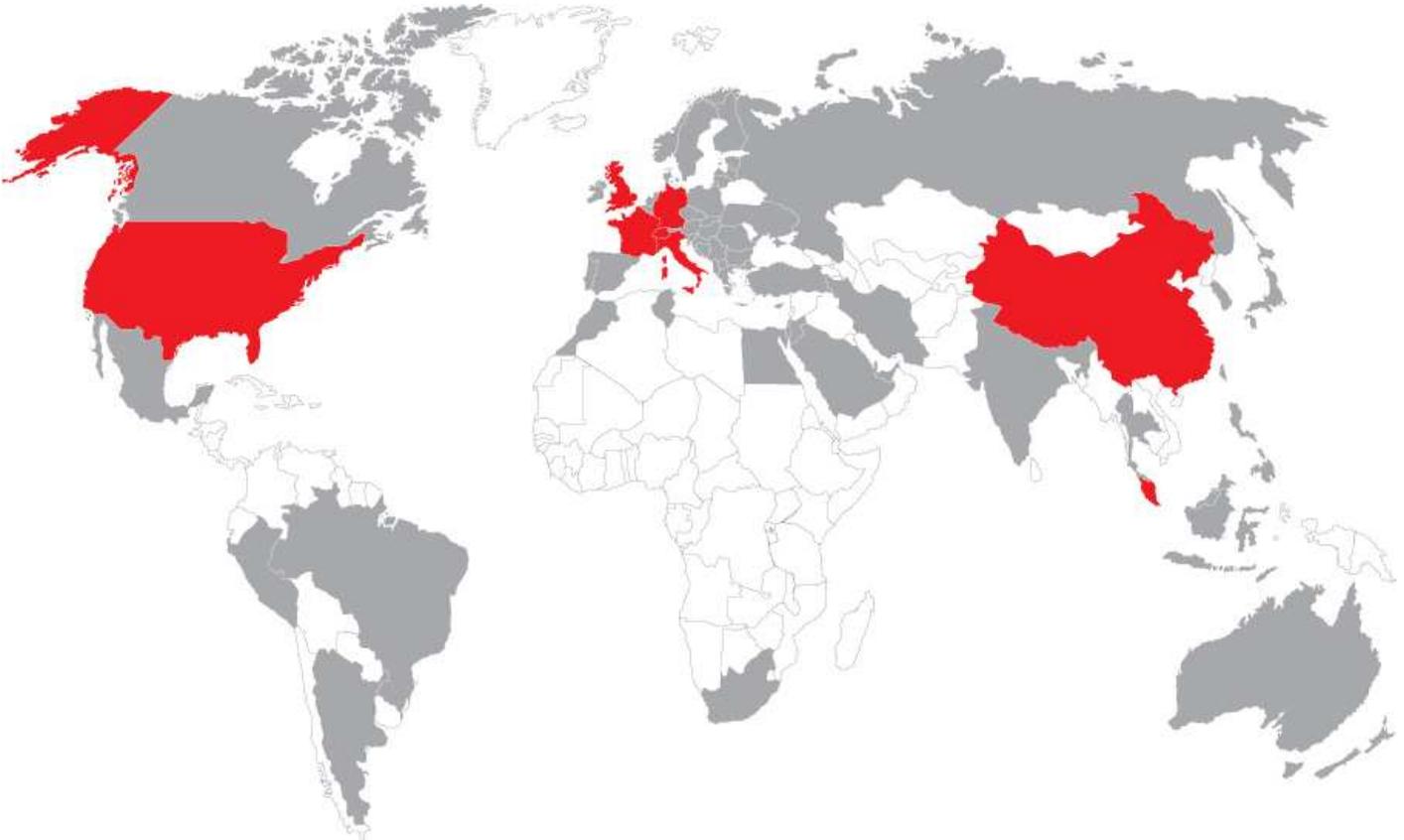


HF7 transmitter

## Contact us:

Rotronic is represented in over 40 countries around the world. An up to date list of all our partners is available on our website:

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