

Drastic reduction in drying times for pharmaceutical active ingredients in vials with microwaves.



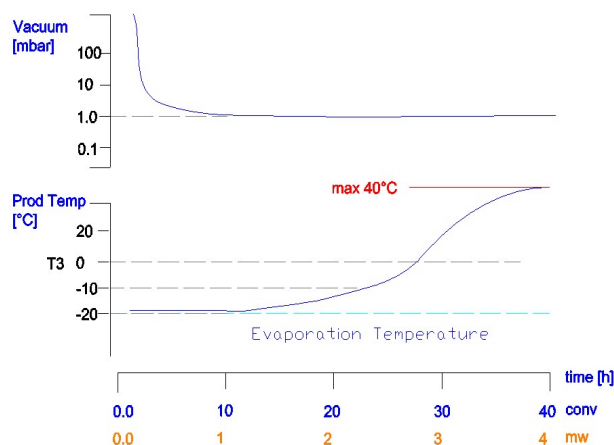
Pueschner Microwaves has been developing, manufacturing and distributing industrial microwaves worldwide for 50 years now. As a specialist for microwave applications and special plant manufacturer, Pueschner is constantly developing into new process areas and started in 2008 with microwave freeze drying, initially for ceramic products, and then expanded this into the areas of Food & BioTec. The latest developments are lab and production plant concepts for pharmaceutical products.

Freeze-drying has so far been the usual process for actively drying and stabilizing active pharmaceutical ingredients.

More and more active ingredients are based on biotechnological processes. Their molecular structure is becoming increasingly complex and drying times in conventional freeze-drying are becoming more critical. Common drying times in conventional multi-opening freeze dryers are in the range of 50-70h.

There is significant interest in alternative freeze-drying processes to reduce drying time and to dry more gently.

In active ingredient development, protein solutions are currently being developed whose mode of action can intervene highly selectively in metabolic processes. However, these new generations of active ingredients are also much more sensitive to drying, so that drying temperatures above 20-40°C should be avoided for longer periods. Conventional dryings of 50-70h imply a long dwell time in the end drying at temperatures above the freezing point, typically at about 20-40°C and above. The prolonged thermal stress in the end drying process, among other things, significantly impairs the survival rates of this new generation of active ingredients. There is great interest in alternative freeze-drying processes to reduce drying time and to dry more gently.



Picture 1. Comparison conventional and microwave freeze drying

Innovative leap in the freeze-drying of pharmaceutical vials

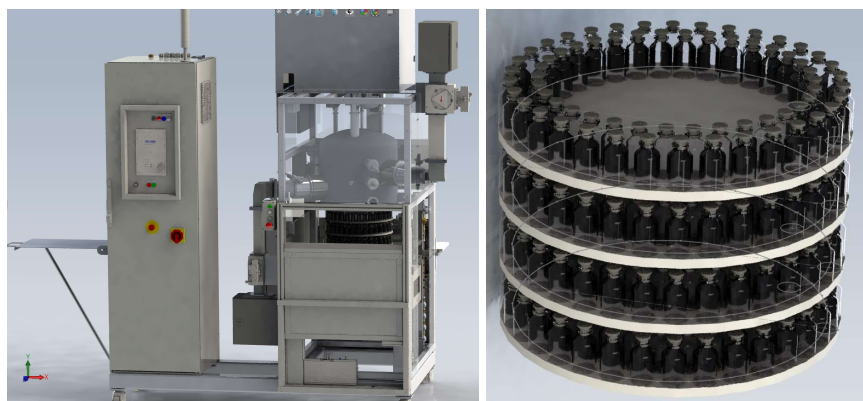
With microwave freeze drying, these drying times can be drastically reduced (factor 5-10). Thus, microwave freeze-drying is not only more economical, but also more gently on the product for the new generation of active ingredients. In publication 1) evidence of shortened drying times for "Monoclonal Antibodies" with Pueschner equipment technology is shown in the Journal of Pharmaceutical Science, where also the stability after 12 weeks is comparable to conventionally freeze-dried products.

Batch wise today and continuously tomorrow

Basically, two plant concepts are available:

1. Batch carousel microwave freeze dryer
2. Continuous microwave freeze dryer

The Batch carousel Mw freeze dryers are currently being tested in the market and will be presented in this article. These are designed for laboratory use in R&D and can be scaled up automatically operated parallel batch systems. In addition to Mw freeze-drying, these systems also can perform the freezing step and can also close the vials after drying.

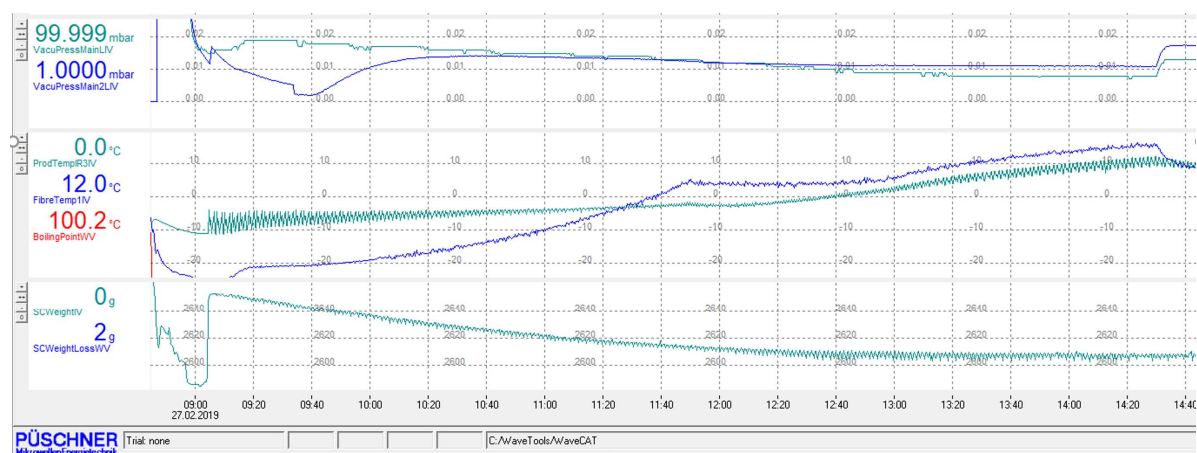


Picture 2. Mw Freeze Dryer μ WaveVac0163ly with Four Carousel Levels with 10R Vials

The system concept shown in the picture above is a bottom loader. The vials are arranged in a circle on several levels and are placed on a turntable with a load cell. The turntable is

integrated in the vacuum sealing disc in the base. After loading, the vacuum sealing disc moves up with the load and seals the vacuum containers. The freezing process first begins atmospherically until the nucleations are complete and the sugar solutions have crystallized accordingly. After that, the freezing process is still supported by a deep vacuum atmosphere.

Now the actual microwave freeze drying starts. The drying process is monitored by the online load cell as well as by non-contact temperature measurement of the sugar solution in each individual vial (see Fig. 3).



Picture 3. Vacuum pressure, temperature measurement (fiber optic and infrared) and weight loss over a drying of 120 vials in approx. 5.6h



Picture 4. Pharmaceutical elegance of the microwave dried product cake

After the temperatures have risen to approx. 20°C, the sugar solutions are at a residual moisture content of < 2%. Depending on the individual formulation, there is still a short post-drying phase at temperatures up to 30-40°C with a maximum of 30min.

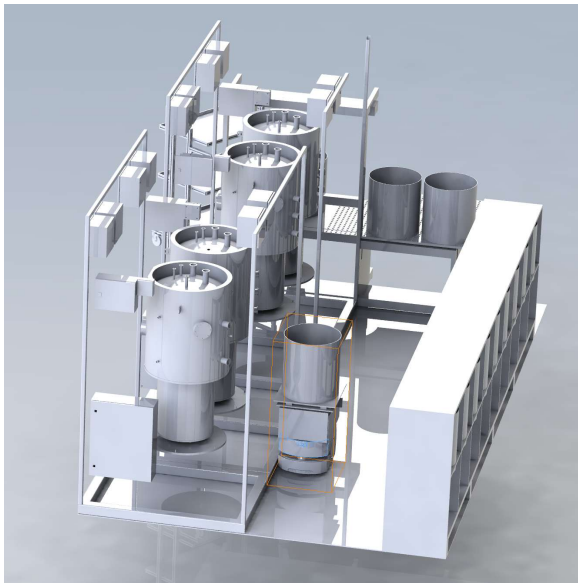
After this, the vials are sealed in the system under N₂ atmosphere. The vacuum sealing disc with the sealed vials opens and can be removed as a sealed unit.

Different batch unit sizes are available.

The smallest laboratory system **μWaveVac0163ly** consists of a maximum of three levels with a maximum of 3x120 (total 360) 2R vials.

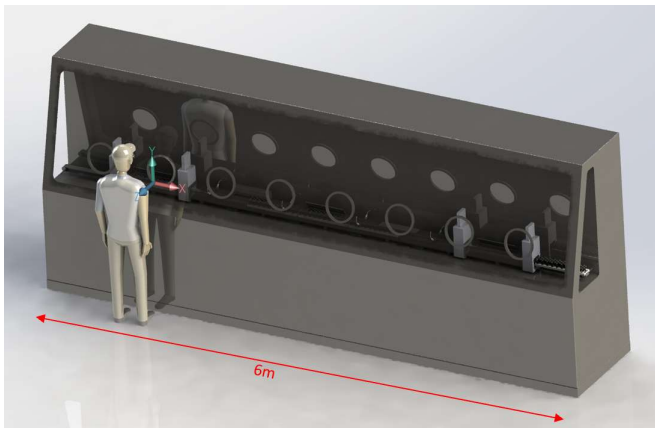
The next larger system type is a **μWaveVac0273ly** with 4x160 (total 640) 2R vials. Assuming approx. 2.5h freezing and 5.0h drying plus 0.5h for product handling, 3 batches can be run in 24h (1,920 2R vials). Four lines in a network, as shown in the picture below, can produce

approx. 7,680 2R vials in 24h. The automated loading is done by autonomous Lynx robots (Omron / Adaptec). One robot can load and unload four lines autonomously. The area shown in the picture below is 3.5 x 6.5m.



Picture 5. Four μ WaveVac0273ly microwave freeze dryers in compound with 640 batch size related to 2R vials loaded and unloaded via autonomous robot.

Continuous concepts are also currently under development. Here, so-called single mode systems are used, which have a homogeneous field distribution. These continuous systems are operated in isolators via appropriate airlock technology and allow a completely continuous process from the filling of the vials to the dried product.



Picture 6. μ WaveVac0353ly continuous microwave dryer designed for 100 to 200 2R vials per hour

It is possible to further increase the throughput by extending and widening the drying channel.

Outlook

Conventional freeze drying has been improved incrementally over the last decades. However, due to the limited conductive energy input, hardly any major performance improvements have been achieved lately. Microwaves introduce the sublimation energy directly into the volume and can deliver a dramatic reduction in drying time with better quality. Microwave

freeze-drying offers enormous advantages, especially for the new sensitive drug generations, and will establish itself as a new freeze-drying technology alongside conventional ones in the next few years.

References:

1. Significant Drying Time Reduction Using Microwave-Assisted Freeze-Drying for a Monoclonal Antibody, Journal of Pharmaceutical Sciences 107 (2018) 2538-2543
2. Paper von James Dolan (Use of Volumetric Heating to Improve Heat Transfer During Vial Freeze-Drying vom September 1998) Dissertation submitted to the Faculty of the Virginia Polytechnic Institute and State University