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Freeze drying with enhanced process control in the Glass Oven B-585: A comparison with a laboratory scale freeze dryer

Authors: Dr. Cordin Arpagaus, Sabine Kleinhaus, Nina Schafroth, BÜCHI Labortechnik AG, Flawil, Switzerland,  
Dr. Henning Gieseler, Silja von Graberg, Prof. Geoffrey Lee, Department of Pharmaceutics, Friedrich-Alexander  
University, Erlangen, Germany

# Freeze drying with enhanced process control in the Glass Oven B-585

## Introduction

Freeze drying (also known as lyophilization) is a well known technique to improve stabilization of active pharmaceutical ingredients (API) during long term storage. It is known as an expensive process due to initial investments of highly specialized equipment. Moreover the procedure is time and energy consuming [1].

Freeze drying works by freezing an aqueous solution, reducing the surrounding pressure and adding enough heat to allow the ice in the material to sublime directly from the solid phase to the gas phase. In pharmaceutical and biotech companies freeze drying is used to increase the self life of products, such as vaccines and injectables. The food industry uses the freeze drying process to reduce weight and to improve reconstitution of solutes. It is a very gentle drying method for maximum conservation of volatile ingredients, i.e. flavors. In bioseparation, freeze drying is used as a late stage purification procedure to effectively remove solvents. It is capable to concentrate molecules with low molecular weights that are too small to be filtered by membrane filtration. Moreover, the method is often applied for heat-sensitive materials, such as proteins, enzymes, microorganisms and blood plasma.

To successfully dry an API, a minimum of process control during primary and secondary drying is mandatory. This requires to control the product temperature ( $T_p$ ) and the chamber pressure ( $P_c$ ) in the freeze dryer. However, the collapse temperature of an amorphous system is usually much lower than the eutectic temperature of a crystalline system.

Recently, the new multi purpose laboratory Glass Oven B-585 (Fig. 1) system was introduced by BÜCHI Labortechnik AG, offering an option to freeze dry small quantities of a product in up to 6 vials. The containers are placed in a temperature controlled glass tube. The goal of this

study is to directly compare the freeze drying performance of the modified Glass Oven B-585 with a commercial laboratory scale freeze dryer from the company Martin Christ Freeze-Dryers (Osterode, Germany) in terms of drying time and final moisture. To enhance process control in the Glass Oven B-585 a new custom made process control accessory is applied.

and fractionated distillation. This method allows to separate components with a boiling point of more than 20°C below the next higher boiling point component. The distillations can be carried out under vacuum conditions while rotating the glass bulbs.

With its high operating temperature of up to 300°C, the Glass Oven B-585 can vaporize small amounts of high-boiling solvents where a rotary evaporator comes up against its limitations [2].



Fig 1: Glass Oven B-585 from Büchi Labortechnik AG with freeze drying option

## Glass Oven B-585

The Glass Oven B-585 is a versatile product and opens up a wide range of applications. Depending on the configuration, substances can be dried, freeze dried, distilled and sublimated. A glass tube with an electrical conductive coating serves as heating element up to 300°C. This allows quick and simple direct drying of small sample volumes. With the rotary drying option, a hard surface layer is avoided by extension of a drying surface. Temperatures are rapidly achieved and the time for drying is significantly reduced.

Bulb to bulb distillation enables the separation of multiple component mixtures

With a sublimation accessory inserted into the Glass Oven B-585, the frozen solvent is sublimated directly from solid phase to gaseous phase.

With the freeze drying insert it is possible to lyophilize small product samples, which is in particular suitable to dry temperature sensitive API formulations. For the freeze drying procedure, a chiller or a cold trap filled with dry ice or a dewar tank with liquid nitrogen is applied.

## Experimental Methods

In this study, the **Glass Oven B-585** system was connected by a short tube (1m length, 1cm diameter) to an external cold trap (coolant: LN<sub>2</sub>, 20l Dewar) and a vacuum pump (Vacuum Pump V-700). The principle configuration is shown in Fig. 2.

To enhance process control, a custom built stainless steel extension of the drying chamber was developed and connected by a flange ring to the Glass Oven system (Fig. 3). The alignment features a pressure gauge (Pirani type) as well as two thermocouples (T-type, Omega, Newport, CT, USA, 40AWG) at the outer side. The thermocouples are used to instantaneously determine the product temperature ( $T_P$ ) and the glass wall temperature ( $T_{GW}$ ), which delineate the impact of radiative heat transfer (Fig. 4).

The **freeze drying procedure** was conducted as follows. Aqueous mannitol and trehalose solutions (50 and 100mg/ml total solids, 1ml fill volume,  $L_{ice}$ : 0.49cm in 5ml vial) were frozen by immersing the vials into liquid nitrogen and subsequent placing in the drying chamber. Vacuum was applied to the lowest achievable pressure in the Glass Oven B-585 system. The same set points were used in the reference laboratory freeze dryer (Christ Delta 24-KD). For the primary (1<sup>st</sup>) drying time, predefined intervals of 5h to 24h were used at a shelf temperature or glass inner wall temperature of 25°C (recorded by a four channel data logger over time, Omega). The secondary (2<sup>nd</sup>) drying was conducted at 40°C. The vials in the reference laboratory freeze dryer were suspended to eliminate the contribution of heat transfer through the shelf by thermal contact.

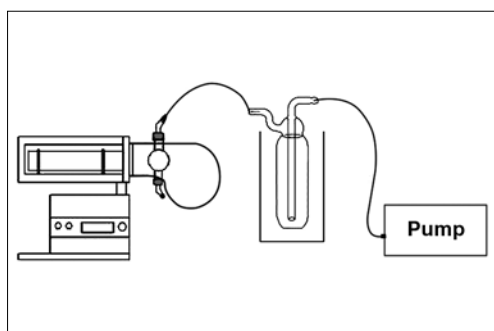


Fig 2: Principle drawing of the Glass Oven B-585 system in freeze drying configuration



Fig 3: Customized extension of the drying chamber providing process control of product temperature and chamber pressure



Fig 4: Placement of the two thermocouples monitoring the product temperature and glass wall temperature in the Glass Oven B-585

The residual moisture was determined by **Karl-Fischer Titration** using a water vaporizer (Mitsubishi CA-06, VA-06). 80 to 100mg of the solid samples were heated to 160°C, followed by calorimetric determination of the evaporated water. Dry N<sub>2</sub> was used as carrier gas.

The alteration in the physical state of mannitol was examined immediately after freeze drying by **X-ray powder diffraction (XRD)** using a Philips model Expert MPD with Cu K $\alpha$  radiation at 40kV/40mA and 25°C. Scans were measured in the range  $2\theta = 5^\circ$ -40° with a step size of 0.02° (time/step = 1s).

The morphology of freeze dried samples was analyzed by **Scanning Electron Microscopy (SEM)**. The samples were carefully broken, fixed on Al stubs (Model G301, Plano) and Au sputtered at 20mA / 5kV (Hummer JR Technics) for 1min. Cake morphology was then examined using an Amray 1810T Scanning Electron Microscope at 20kV.

## Scanning Electron Microscopy

The trehalose samples show a fine lamellar and porous structure due to the high initial cooling rate (Fig. 10). After drying in the Glass Oven B-585, 5% samples show minor structural loss (Fig. 11). The 10% trehalose solute reveals structural change and a slight collapse in the crystalline matrix (Fig. 12). The 5% mannitol samples show a rigid crystalline matrix after drying (Fig. 13). Sum-

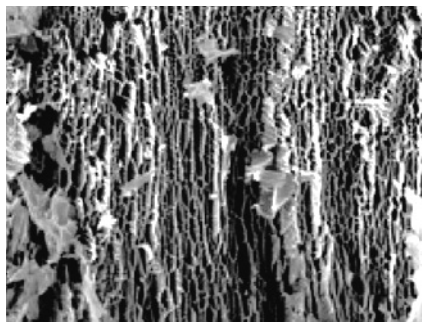


Fig 10: 5% trehalose solution, Freeze Dryer, magnification x 33

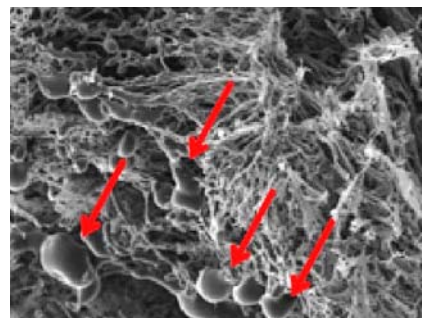


Fig 12: 10% trehalose solution, Glass Oven B-585, magnification x 100

marizing, controlled drying conditions in the Glass Oven B-585 leads to a product with no or little indication of partial collapse found in the product morphology.

## Conclusions

The Glass Oven B-585 shows its overall practicability in freeze drying of small quan-

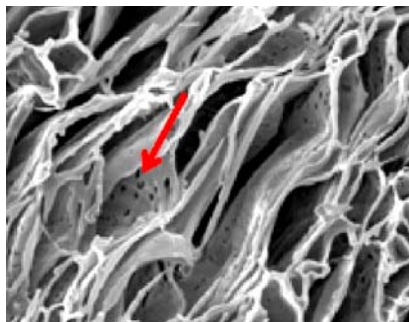


Fig 11: 5% trehalose solution, Glass Oven B-585, magnification x 500

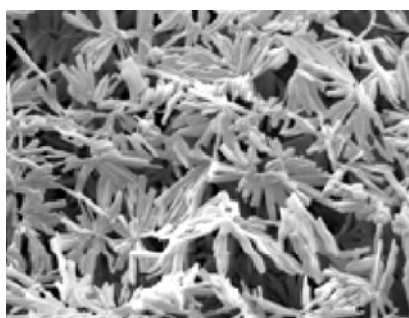


Fig 13: 5% Mannitol, Glass Oven B-585, magnification x 1000

ties. The enhancement of process control by additional pressure and product temperature measurement in the modified B-585 enables drying of amorphous substances at low concentrations and provides a good estimation of the primary drying time. The residual moisture of the product depends on concentration of the solution, fill depth and total number of vials. After approximately 10h drying time, the B-585 and the laboratory large scale freeze dryer achieve comparable residual moisture contents. The drying time increases with higher solute concentrations. Elevated heat transfer decreases the water content down to <1% for amorphous systems. The secondary drying time does not further reduce the residual water content. Final residual moisture values down to 0.4% are achieved with the B-585 (for 5% mannitol).

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- [3] Kim AI et al. The Physical State of Mannitol after Freeze-Drying: Effects of Mannitol Concentration, Freezing Rate and a Noncrystallizing Cosolute. J. Pharm. Sci., Vol. 87, No. 8 (1998)

BÜCHI Labortechnik AG  
Postfach  
9230 Flawil 1  
Schweiz  
T +41 71 394 63 63  
F +41 71 394 65 65  
buchhi@buchhi.com  
www.buchhi.com

BÜCHI Labortechnik GmbH  
Postfach 10 03 51  
45003 Essen  
Deutschland  
Freecall 0800 414 0414  
T +49 201 747 490  
F +49 201 237 082  
deutschland@buchhi.com  
www.buechigmbh.de

BÜCHI Labortechnik GmbH  
Branch Office Netherlands  
Postbus 142  
3340 AC Hendrik-Ido-Ambacht  
The Netherlands  
T +31 78 684 94 29  
F +31 78 684 94 30  
netherlands@buchhi.com  
www.buchhi.nl

BÜCHI Italia s.r.l.  
Centro Direzionale, Milano Fiori  
Pal. A-4, Strada 4  
20090 Assago (MI)  
Italia  
T +39 02 824 50 11  
F +39 02 57 51 28 55  
italia@buchhi.com  
www.buchhi.it

BUCHI (Thailand) Ltd.,  
77/175, Sin Sathon Tower,  
39th FL, Unit F  
Krunghthonburi Rd.  
Klongtong, Klongsan  
Bangkok 10600  
Thailand  
T +66 2 862 08 51  
F +66 2 862 08 54  
bacc@buchhi.com  
www.buchhi.com

BUCHI SMP  
Services Private Ltd.  
201, Magnum Opus  
Shantinagar Industrial Area  
Vakola, Santacruz (East)  
Mumbai 400 055,  
India  
T +91 22 66 98 94 50 / 51  
F +91 22 66 98 94 52  
smp@buchhi.com  
www.buchhi.com

BUCHI Corporation  
19 Lukens Drive, Suite 400  
New Castle  
Delaware 19720  
USA  
T +1 302 652 3000  
F +1 302 652 8777  
Toll Free: +1 877 692 8244  
us-sales@buchhi.com  
www.mybuchhi.com

BUCHI Hong Kong Ltd.  
1810 Fortress Tower  
250 King's Road  
North Point, Hong Kong  
China  
T +852 2389 2772  
F +852 2389 2774  
china@buchhi.com  
www.buchhi.com

BUCHI Shanghai Trading LLC  
21/F Shanghai Industrial  
Investment Building  
18 Caoxi Bei Road  
200030 Shanghai  
China  
T +86 21 6468 1888  
F +86 21 6428 3890  
china@buchhi.com  
www.buchhi.com

BUCHI UK Ltd  
5 Whitegate Business Centre  
Jardine Way  
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Chadderton  
Oldham OL9 9QL  
United Kingdom  
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www.buchhi.co.uk

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5, rue du Pont des Halles  
Z.A. du Delta  
94656 Rungis Cedex  
France  
T +33 1 56 70 62 50  
F +33 1 46 86 00 31  
france@buchhi.com  
www.buchhi.fr

Nihon BUCHI K.K.  
3F IMON Bldg.,  
2-7-17 Ikenohata, Taito-ku,  
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## Results and Discussion

The chamber pressure readings indicate much higher values compared to the cold trap (condenser) side providing a sufficient driving force for drying. However, the lower pressure limit is found to depend upon the cold trap installation (Fig. 5, upper chart) and the tubing between chamber and cold trap. A smaller tubing diameter imposes a higher resistance and reduces the total mass flux. Increase of the product temperature up to approximately glass wall temperature is a good indication of the end of the primary drying stage for all samples.

The vials were equipped with two thermocouples, one in the bottom center and the other in the center position. Towards the end of primary drying, the temperature readings confirm, that the last remaining ice is to be found at the bottom center of the vial.

## Heat and Mass Transfer in the Glass Oven B-585

Heat transfer  $dQ/dt$  in the oven system is dominated by radiation from the glass wall to the product and is calculated by the following equation [1]:

$$\frac{dm}{dt} \cdot \Delta H_s = \left( \frac{dQ}{dt} \right)_{\text{radiation}} - A_{\text{rad}} \cdot \epsilon_{\text{glass}} \cdot 1.0 \cdot 10^{-4} \cdot (T_{\text{wg}} - T_p)$$

where  $dm/dt$  is the mass transfer,  $\Delta H_s$  the sublimation enthalpy and  $10^{-4} \text{ W/m}^2\text{K}$  the heat transfer coefficient of glass. For a 5% trehalose solution in a 5ml vial ( $\epsilon=0.94$ ) the heat transfer is calculated to  $dQ/dt = 3.4 \times 10^{-3} \text{ cal/g}$  and the mass transfer to  $dm/dt = 0.18 \text{ g/h}$ . This is in the order of the experimentally measured primary drying time of about 200 min for 1ml water (0.3g/h) for this run (Fig. 6, lower chart).

## Comparison with conventional freeze dryer

The comparison of the drying pattern between the B-585 and the conventional freeze dryer revealed similar results for tested excipients with 5% solute concentration. After approximately 10h drying time, both systems achieved comparable residual moisture contents of about 0.4%. At higher solute concentrations (10% mannitol solution) the moisture content is higher when using the Glass Oven B-585. This is attributed to the pressure reduction in the Glass Oven compared to the larger scale laboratory freeze dryer from Christ. However, the impact of the chamber pressure reduction speed on product temperature is found to be slight (Fig. 6, green line).

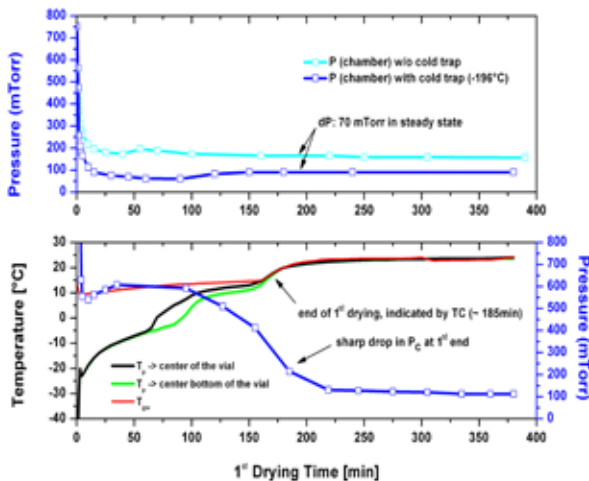


Fig 5: Impact of the cold trap on the chamber pressure limit (upper chart) and drying behaviour of a 5% mannitol solution in the Glass Oven B-585 (lower chart)

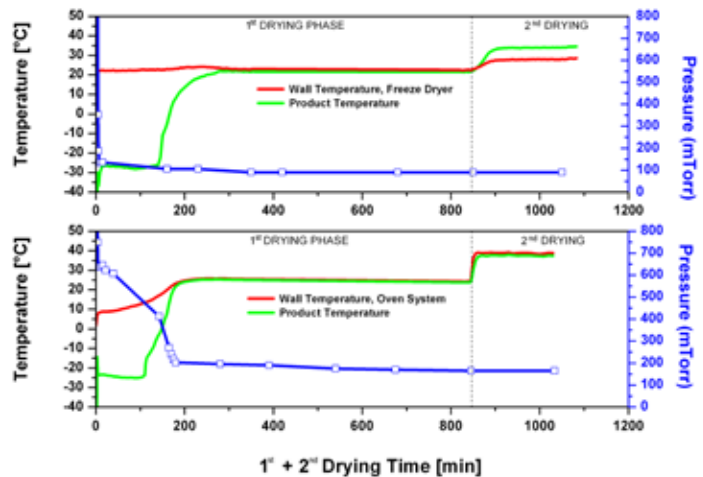


Fig 6: Drying behaviour of a 5% trehalose solution in the Christ freeze dryer (upper chart) and the Glass Oven B-585 (lower chart) with 25°C primary drying temperature and 40°C secondary drying temperature

## Residual Moisture Measurements

The residual water content for freeze dried 5% mannitol solution is in good agreement (deviation smaller than 5%) at any drying interval for both freeze drying systems. The secondary drying time at constant product and glass wall temperature does not further reduce the amount of residual moisture in the final product (Fig. 7). 10% Mannitol solutions dried in the Glass Oven B-585 show a higher residual moisture content if freeze dried for less than 10 hours than samples freeze dried in the laboratory scale freeze drier. This is attributed to the small chamber size of the Glass Oven, which allows lyophilizing of only small amounts of substance. Elevated heat transfer ( $T_{GW}$  of 40°C during secondary drying time) is beneficial to decrease the water content to <1% for the amorphous system in the laboratory large scale freeze dryer as well as in the Glass Oven B-585 system. After approximately 10h drying time both systems achieve comparable residual moisture contents. The moisture in both systems does not further decrease with extending secondary drying time at constant temperature. Similar results were obtained for a 5% trehalose solution, where the residual moisture is around 1% after 24h drying time.

## Physical state with XRD results

A mannitol concentration of 5% and rapid freezing forms a distinct  $\beta$ -polymorph during drying in both systems (Fig. 8). In contrast, for the 10% mannitol solution an alteration from the  $\beta$ - (5h) to  $\delta$ -polymorph (18h) is detected in the Glass Oven system. In the laboratory scale freeze dryer  $\delta$ -polymorph is observed at any drying time (Fig.9) [3].

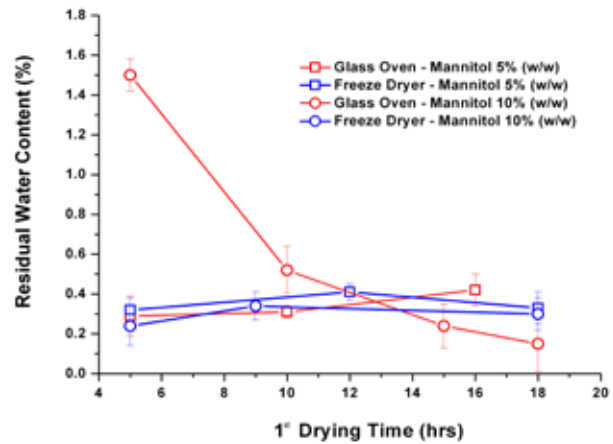


Fig 7: Comparison of the residual moisture content (3 measures) after drying 5% and 10% mannitol solution in the Glass Oven B-585 and laboratory freeze dryer

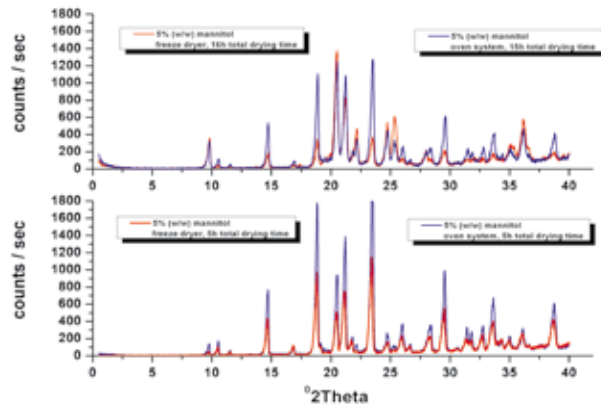


Fig 8: XRD results of freeze dried 5% mannitol solution in the reference freeze dryer (upper chart) and in the Glass Oven B-585 (lower chart). The data indicate mainly  $\beta$ -polymorph structure.

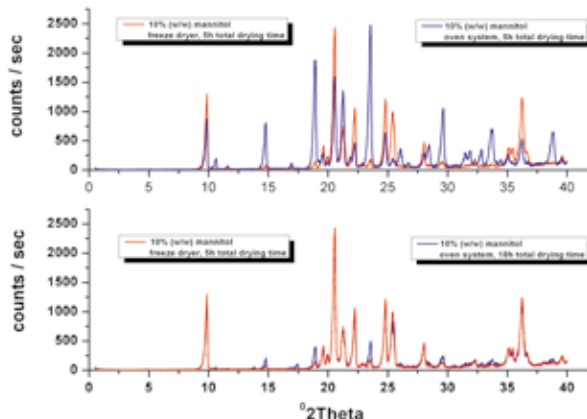


Fig 9: XRD results of freeze dried 10% mannitol solution in the reference freeze dryer (upper chart) and in the Glass Oven B-585 (lower chart). In the Glass Oven B-585 a distinct change from the  $\beta$  to the  $\delta$ -polymorph is stated.