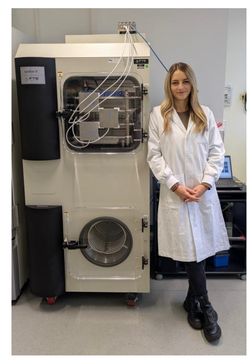
Improved Product Quality in Freeze Drying by Applying Live Statistics and Closed-Loop Control

Johanna Herzog[1]*, Anton Mangold[2], Oliver Bartels[3], Henning Gieseler[1]

[1]**FAU Erlangen-Nuernberg,** Division of Pharmaceutical Technology and Biopharmacy, Cauerstraße 4, 91058 Erlangen
[2]**Tempris GmbH**, Industriestraße 25, 83607 Holzkirchen [3]**Oliver Bartels F+E,** 80935 München, Germany



Introduction

Tempris Technology

Tempris is a single vial Tp measurement system for live control of freeze-drying processes from lab to pilot and production scales. The battery-free wireless sensors receive their power by excitation of the passive transponder by means of an amplitude-modulated electromagnetic signal in the internationally available 2.4-GHz ISM band, with evaluation of the back-scatter response[4], without requiring a battery. Their sterilizability and easy placement by e.g. automatic loading systems are a major improvement to current Tp measurement systems.

Material and Methods

Freeze-drying was performed on a LyoStar II pilot scale freeze dryer. Per shelf, 260 10R serum tubing vials were filled with 4 mL of 5% (w/v) trehalose solution. The following cycle was applied with no 2° drying and a 1° drying stopped when Pirani indicated a 50% drop*[1]:

Phase	Step	T_s [°C]	RR [°C/min]	T_{hold} [min]	P_c (CM) [mTorr]
Freez-ing	1	5	1	30	-
	2	-5	1	30	-
	3	-40	1	120	-
1° Drying	1	-20	1	*1	60

Tabl. 1: Applied freeze-drying cycle

Closed Loop Control

The newly developed algorithm presented in this poster proposes to predict the end of primary drying by detecting the inflection of the exponential function of the temperature rise curve of TEMPRIS-equipped vials. But is an equipped vial at all representative of other, non-equipped vials? The sensor volume can increase the liquid level in the vial, thereby extending the primary drying time.[5] To evaluate the influence on drying behavior, a freeze-drying run was performed and the residual moisture of each vial in question was determined to see in which range the influence runs. „Do the sensor-equipped vary? And how much?“ are main question followed.

Sensor Positioning

A total of two shelves was fully loaded and instrumented with ten TEMPRIS probes per shelf. Since the center vials represent the majority of all vials, 70% of the sensors were positioned in these vials such that the overall representation of the temperature distribution was as complete as possible. Each equipped vial was then compared to two neighboring vials as shown in the illustration.

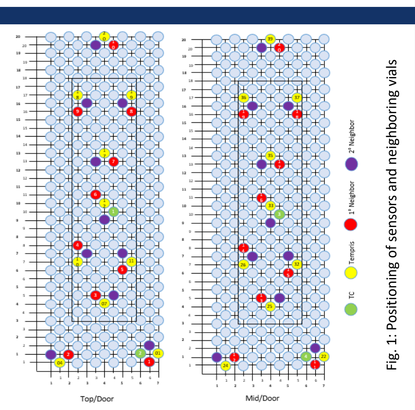


Fig. 1: Positioning of sensors and neighboring vials

Residual Moisture Bias

Karl Fischer Determination

Each residual moisture [%] of equipped and non-equipped neighboring vials was determined with standard coulometric Karl Fischer titration (oven sampler 130 °C). Product vials are essentially free of ice at 50% of the Pirani signal. As expected, moisture in edge and center vials was found to differ. However, the scattering of moisture values for every position and the deviation of the means was in a very small range:

$\bar{x}$(Tempris)=6.5755%; $\bar{x}$(1°)=6.6135%;
$\bar{x}$(2°)= 6.4384%

Distribution

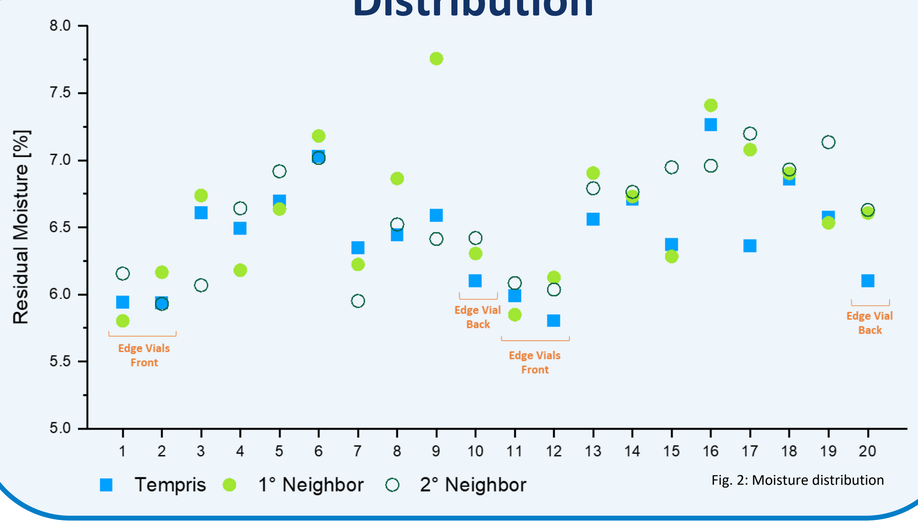


Fig. 2: Moisture distribution

Statistical Evaluation

To check if the sensor vial residual moisture deviates from the neighboring vials a statistical test, the ANOVA test, was applied. It compares the three groups to determine if there are statistically significant differences and assesses if the variation originates from actual differences between the groups or if they are of random nature. Requirements like normal distribution (Kolmogornov-Smirnov) and homogeneity of the group's variances (Levene test) had to be checked.

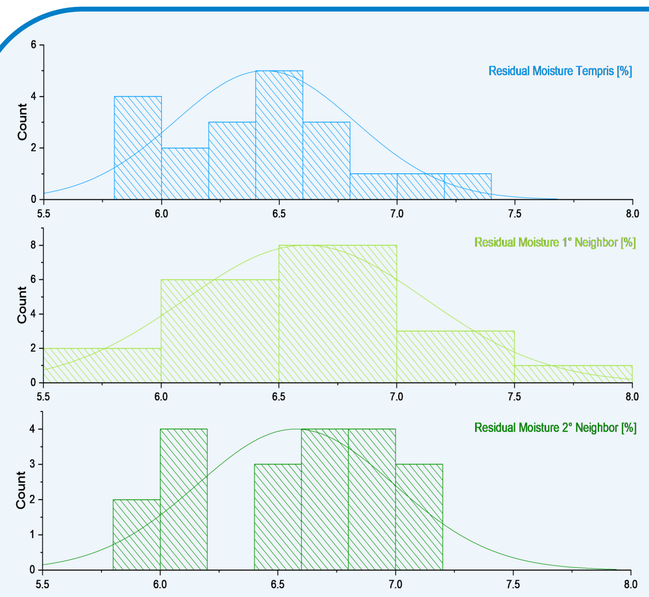


Fig. 3: Histogram of considered groups

ANOVA Test Results Kolmogorov-Smirnov test confirmed normal distribution (Fig. 3) and the Levene test showed no significant difference in variances (Fig.4). Data is permitted for ANOVA test: **F-value: 0.8735; p-value: 0.423; Level of significance: 0.05**; Null hypothesis maintained: No significant difference between the groups. The F-value is very small. This indicates that the variability between the groups is much smaller than within the groups. There is hardly any difference between the TEMPRIS group and the neighboring vial groups. The p-value is well above the typical significance level of 0.05. The probability of obtaining this or a more extreme F-value under the null hypothesis (no difference between groups) is very high. There is no evidence that the independent variable (Tempris-equipped *vs.* non-equipped) has an influence on the dependent variable (residual moisture). So yes, in this study a TEMPRIS instrumented vial is representative for other non-equipped vials, but of course other circumstances, e.g. variation of the size of the vials, fill level, formulations, solid contents, temperature and pressure, need to be evaluated.

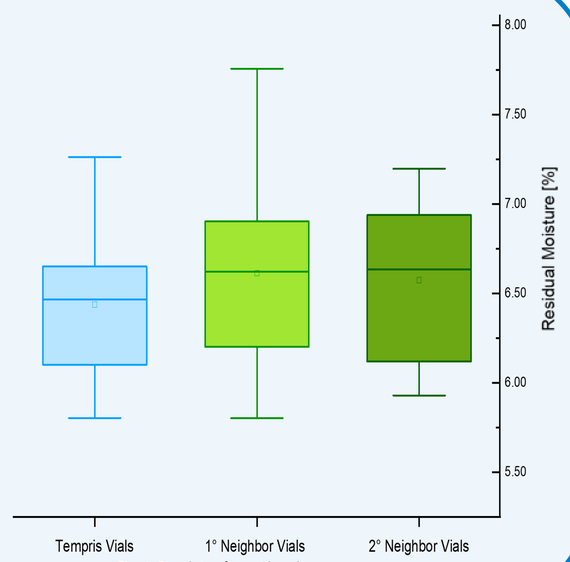


Fig. 4: Boxplots of considered groups

Closed Loop Algorithm Development

A new algorithm was proposed to determine the individual shelf temperature under each instrumented vial (Fig. 5). The new scientific approach is that at known shelf temperatures and temperatures in a vial, heat transfer may be assessed. With knowledge about the heat transfer for each individual vial, we can derive information about the residual moisture, which can lead to shorter freeze-drying cycles and better product quality. A key advantage of the algorithm is that it operates entirely independent of the formulation, size and fill volume of the vial. As a result, the process can be flexibly applied to different product types without the need for extensive pre-experiments for each new formulation.

Heat transfer (Q, A, K_v) simplified:

$$T - T_b = k_1 \frac{dm}{dt}$$

End of sublimation negative exponential section:

$$\frac{dm}{dt} = -k_2 m$$

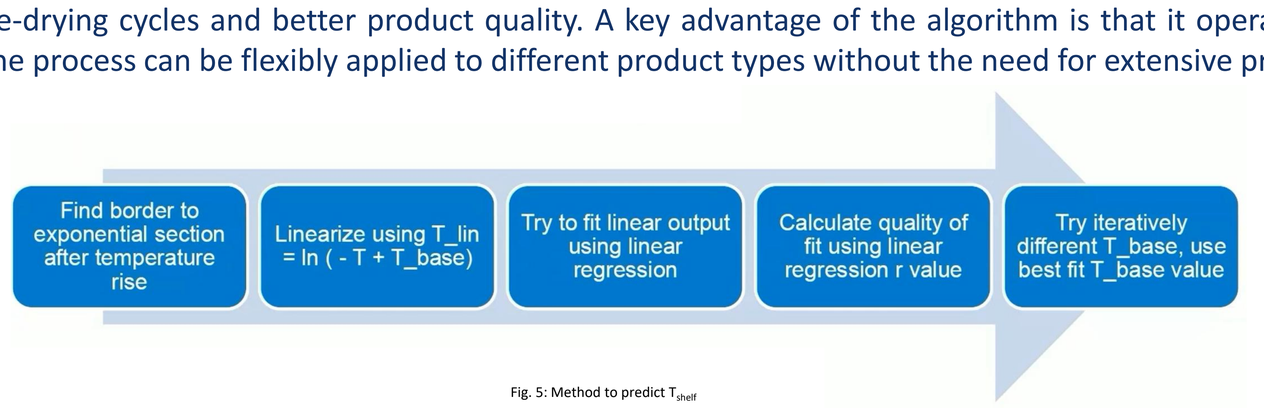


Fig. 5: Method to predict T_{shelf}

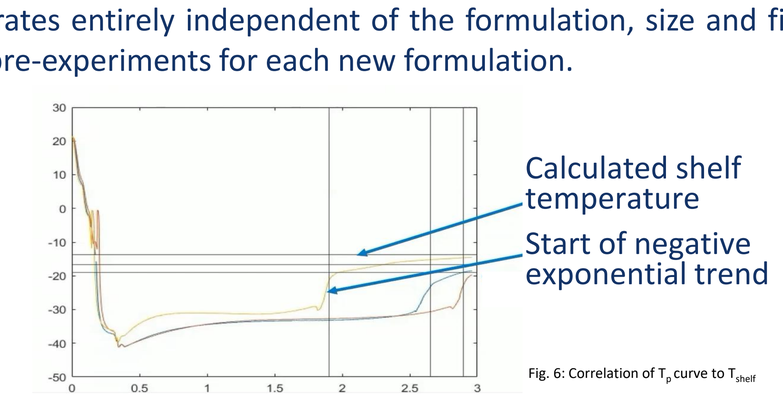


Fig. 6: Correlation of T_p curve to T_{shelf}

References:
[4] Schneid S., Gieseler H., Evaluation of a New Wireless Temperature Remote Interrogation System (TEMPRIS) to Measure Product Temperature During Freeze Drying. AAPS PharmSciTech 9(3):729-739 (2008).
[5] Steven Nail *et al.*: Recommended Best Practices for Process Monitoring Instrumentation in Pharmaceutical Freeze Drying—2017. AAPS PharmSciTech 18(7):2379-2393 (2017).

*Corresponding author: Johanna Herzog
Email: johanna.herzog@fau.de