GILYOS®

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TEMPRIS® Wireless Temperature Sensors – New Generation

- Initial Evaluation Tests -

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Abbreviations and Definitions

Abbreviation	Definition
Avg.	Average
AWG	American Wire Gauge
C	Center
CM	Capacitance Manometer
Max.	Maximum
PAT	Process Analytical Technology
P_c	Chamber pressure
TC	Thermocouple
RR	Ramp Rate
t_{hold}	Hold time at target T_s
T_n	Ice nucleation temperature
T_p	Product temperature
T_s	Shelf temperature
tbd	to be determined
V_{fill}	Fill volume
WFI	Water for Injection

1. Introduction

TEMPRIS® wireless temperature sensors are an established PAT tool for freeze drying applications. Due to their known advantages compared to other temperature measurement systems (passive, truly wireless, sterilizable, real-time monitoring), they can be used in all scales and cover the entire life cycle of a pharmaceutical product, from early development to routine production. By using only one single measurement technology, optimum comparability of data can be ensured.

Sensor design and ease of application has been continuously improved over the years. The latest generation of sensors is characterized by a slim design, including the thermo-sensitive area integrated into the sensor body. The results of an initial evaluation of the new sensor design for freeze drying applications are presented in this report.

2. Material and Methods

2.1. Equipment

Two prototypes of new generation TEMPRIS® sensors have been tested in comparison to the current design and thin wire thermocouples. Figure 1 illustrates the differences of the used TEMPRIS® sensors. In the new design A, the tip size has been reduced. Design B does not have a tip at all. Design C reflects the current design which differs from the new designs in terms of sensor body size and shape, as well as the size of the tip. The overall sensor volume was reduced by 20% in the new designs. However, the thermo-sensitive area has remained the same. In addition, a QR code was integrated in the sensor body. These changes facilitate automated sensor handling and traceability in the commercial freeze-drying process.

The thermocouples (TCs) used were Type T, AWG 36 (Omega Engineering GmbH, Deckenpfronn, Germany).

The tests were conducted on a 3-shelf Lyostar 3 freeze dryer (SP Scientific, Gardiner/Stone Ridge, NY, USA), with the top shelf latched and the vials positioned on the middle shelf.

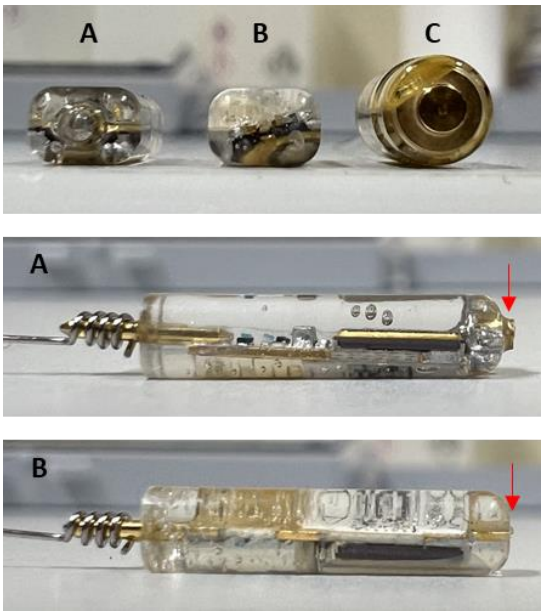

Figure 1: TEMPRIS® sensors used for the evaluation.
A: new design, tip; B: new design, no tip; C: current design.

2.2. Material

D-Mannitol (> 98%) was purchased from Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany). Trehalose dihydrate (Emprove® Expert) was obtained from Merck (Darmstadt, Germany), WFI (Ecoflac® plus) from B. Braun SE (Melsungen, Germany).

2 ml tubing vials (Fiolax Clear, Schott Pharma AG & Co. KGAA, Mainz, Germany) and 13 mm bromobutyl stoppers (Datwyler, Altdorf, Switzerland) were used as primary packaging materials.

2.3. Methods

50 mg/mL solutions of mannitol and trehalose dihydrate were prepared. Per cycle, one bottomless tray was loaded with vials in hexagonal packing. V_{fill} was 1 mL per vial. The outermost row of vials remained empty for radiation shielding (dummy vials). After loading, the tray bottom was removed for the vials to directly sit on the shelf.

The TEMPRIS® sensors were positioned in the vial array as follows (Table 1).

	Mannitol			Trehalose		
Sensor No.	Sensor Design	Channel No.	Array Position (column/row)	Sensor Design	Channel No.	Array Position (column/row)
1	C	08	C 6/15	C	08	C 7/15
2	C	09	C 9/13	C	09	C 9/14
3	C	23	C 8/16	C	23	C 8/16
4	C	26	C 10/16	C	26	C 10/15
5	C	01	C 11/17	C	01	C 11/16
6	C	03	C 12/15	C	30	C 12/14
7	C	06	C 9/19	A	13	C 12/15
8	C	02	C 11/11	A	14	C 11/14
9	A	16	C 10/15	A	16	C 10/14
10	A	24	C 12/16	A	24	C 9/17
11	A	28	C 7/14	A	28	C 7/14
12	A	29	C 07/16	A	29	C 7/16
13	A	05	C 8/14	A	05	C 8/14
14	A	13	C 9/17	B	15	C 9/16
15	A	14	C 11/13	B	07	C 11/15
16	A	30	C 8/18	B	12	C 10/16
17	B	22	C 8/15	B	22	C 8/15
18	B	04	C 13/17	B	04	C 12/16
19	B	27	C 7/17	B	27	C 7/17
20	B	32	C 8/12	B	32	C 8/13
21	B	15	C 09/15	-	-	-
22	B	07	C 11/15	-	-	-
23	B	12	C 10/18	-	-	-
24	B	33	C 10/13	-	-	-
25	B	36	C 12/13	-	-	-
26	B	37	C 6/13	-	-	-
27	B	39	C 6/19	-	-	-

Table 1: TEMPRIS® sensor information and position within vial array.
Blue: TEMPRIS®, current design (C); red: TEMPRIS®, new design, tip (A); green: TEMPRIS®, new design, no tip (B).

In addition, the instrumentation schemes are illustrated in Figure 2. Note that, for the TEMPRIS® sensors, the numbers mentioned in the map reflect the channel numbers.

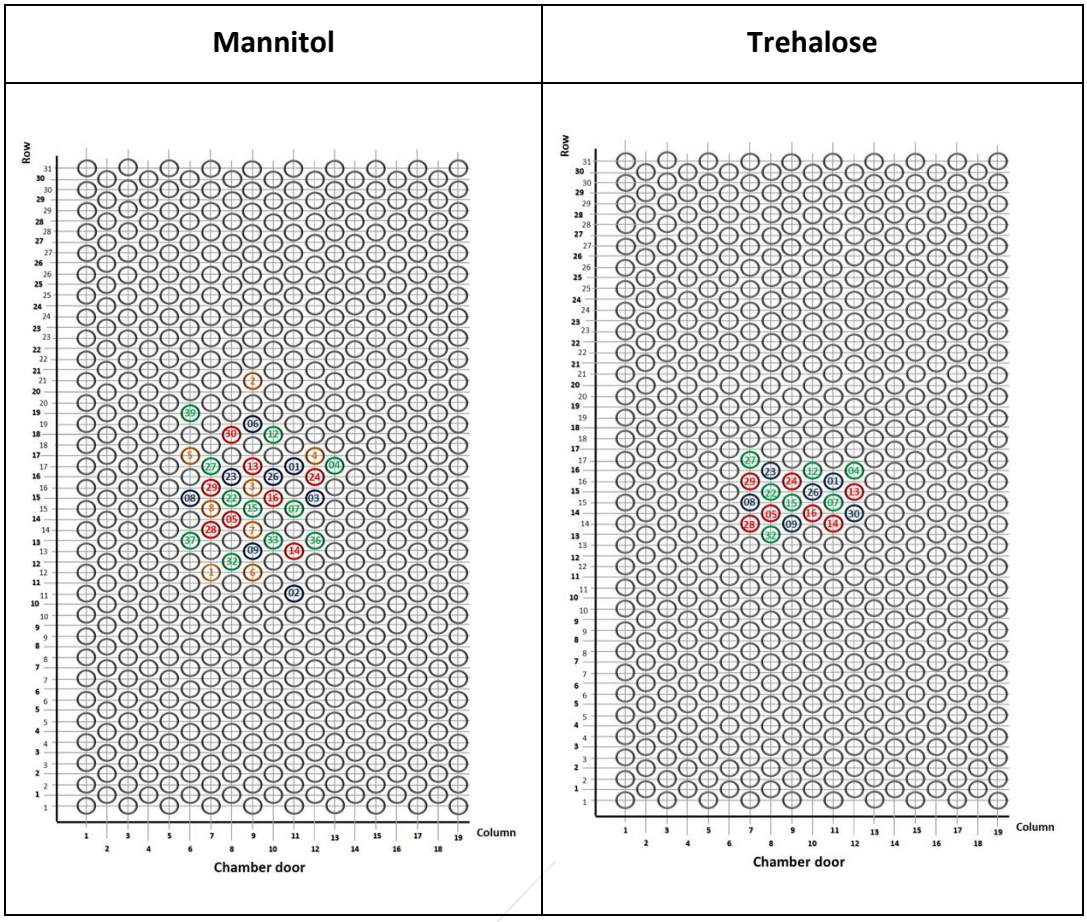

Figure 2: Instrumentation set-up of the test cycles.
Blue: TEMPRIS®, current design (C); red: TEMPRIS®, new design, tip (A); green: TEMPRIS®, new design, no tip (B); orange: TC.

Only center vials were used for product temperature measurement to avoid impact from edge vial effects. The number of sensors and their position within the array differed slightly between the two test cycles. The latter was for reasons of data transmission. TCs were only used in one cycle to re-confirm the already known comparability of product temperature profiles with the ones obtained with TEMPRIS® sensors [1].

The process conditions applied were as follows (Table 2). For mannitol, an annealing step was included to facilitate crystallization.

Phase	Step	Mannitol				Trehalose			
		T_s [°C]	RR [°C/min]	t_{hold} [min]	P_c (CM) [mTorr]	T_s [°C]	RR [°C/min]	t_{hold} [min]	P_c (CM) [mTorr]
Freeze	1	5	1	30	-	5	1	30	-
	2	-5	1	30	-	-5	1	30	-
	3	-40	1	120	-	-40	1	120	-
	4	-18	1	240	-	-	-	-	-
	5	-40	1	90	-	-	-	-	-
Primary drying	1	5	1	tbd[1]	100	-20	1	tbd[1]	60
Secondary drying	1	40	0.3	240	100	40	0.1	300	60
	2	50	0.3	60	100	-	-	-	-

Table 2: Freeze drying process conditions.

[1]Endpoint criterion: ≤ 5 mTorr by comparative pressure measurement (Pirani / CM differential).

The two cycles reflect different products requiring / suitable for conservative and more aggressive process conditions, respectively.

Average primary drying product temperatures were calculated from temperature values within the time range starting 60 minutes after T_s target was reached until the product temperature profile started the steep increase (indicating the end of sublimation for the respective vial). Maximum product temperatures were also determined from this time range.

3. Results and Discussion

3.1. Sensor Handling and Positioning

By using the TEMPRIS® piercing tool, the stopper is pierced centrally, and centering cross and antenna can be connected to the sensor easily. This allows to position the sensor “center-bottom” (center of the vial, sensor touching the bottom) in the vial (Figure 3). Correct positioning is important for representative temperature measurement over time and primary drying end point detection.

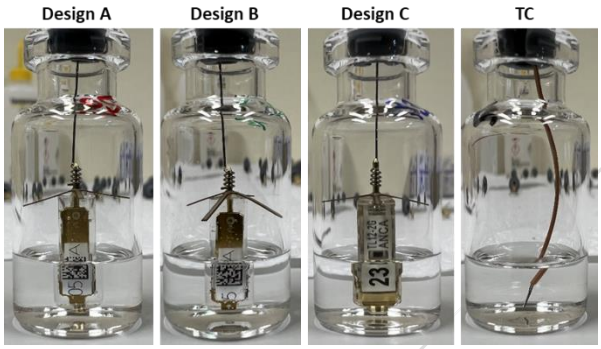

Figure 3: Instrumented vials.

No differences with regard to handling were observed for the different sensor designs.

Due to the reduced sensor volume, the displacement of liquid is also reduced (Figure 4).

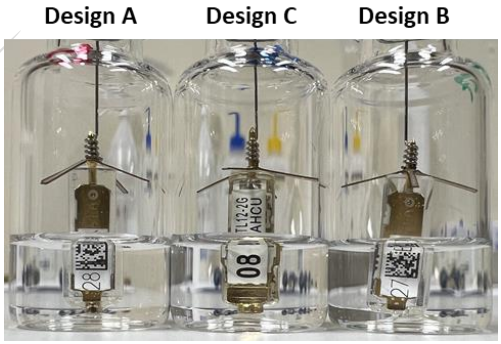

Figure 4: Volume displacement.

3.2. Process Data

3.2.1. Nucleation Temperatures

The nucleation temperatures (start of ice crystal formation during the freezing phase) and the respective process times when nucleation started are illustrated in Figure 5. Note that for single sensors T_n could not be determined for data transmission reasons. These sensors are not included in the graphs below.

T_n ranged from -7.8°C to -16.7°C. Since nucleation in a standard freeze dryer is of random nature, scattering of T_n values is expected. The observed values are within the expected range for standard laboratory conditions (non-sterile environment) and comparable for all probe types. Time of nucleation was at 1.6 to 2 hours of total process time. Again, no relevant differences between the probe types could be observed.

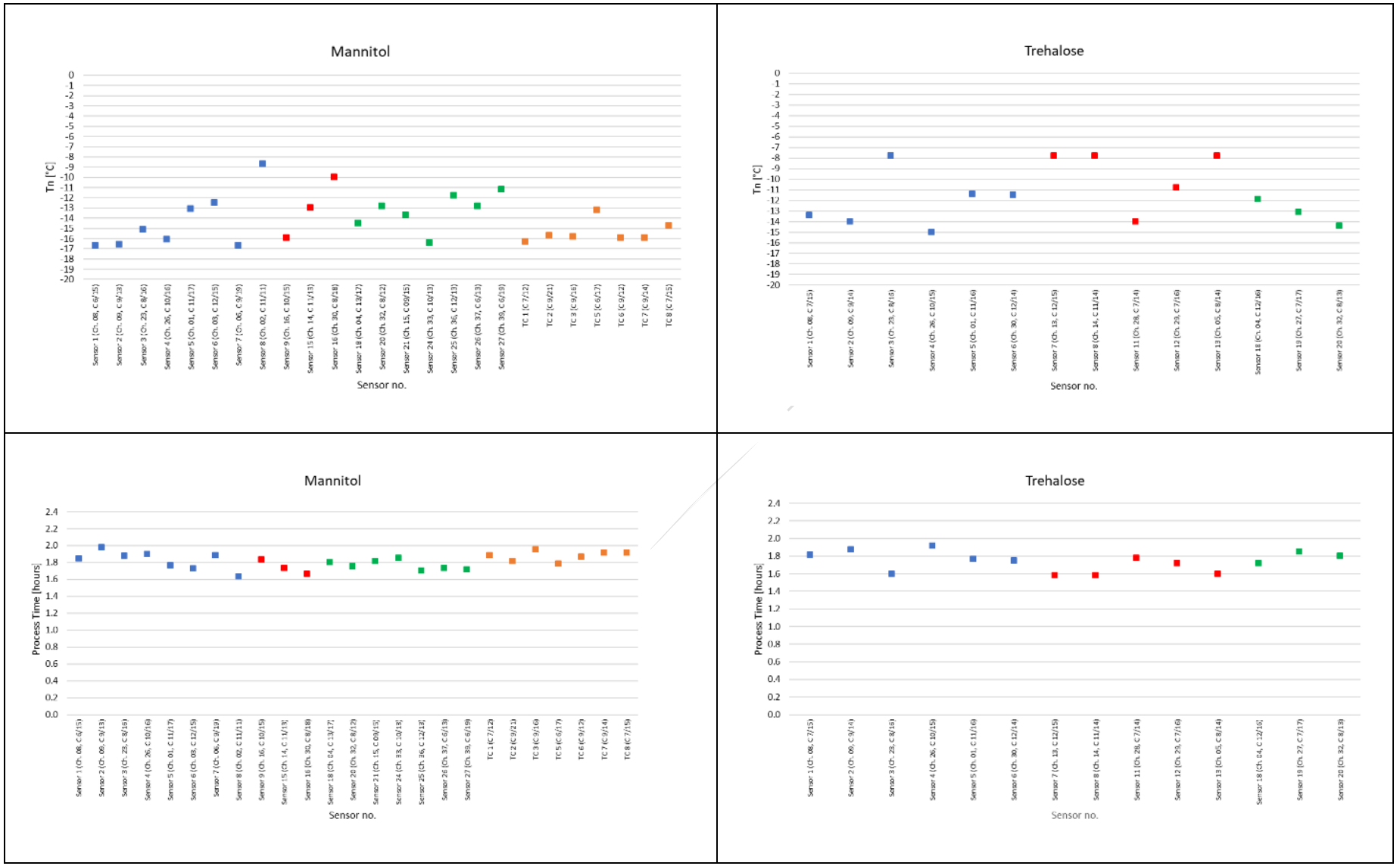

Figure 5: Nucleation temperatures and process times at T_n.

3.2.2. Product Temperatures

Cycle data of both runs are illustrated in Figure 6 (mannitol) and Figure 7 (trehalose).

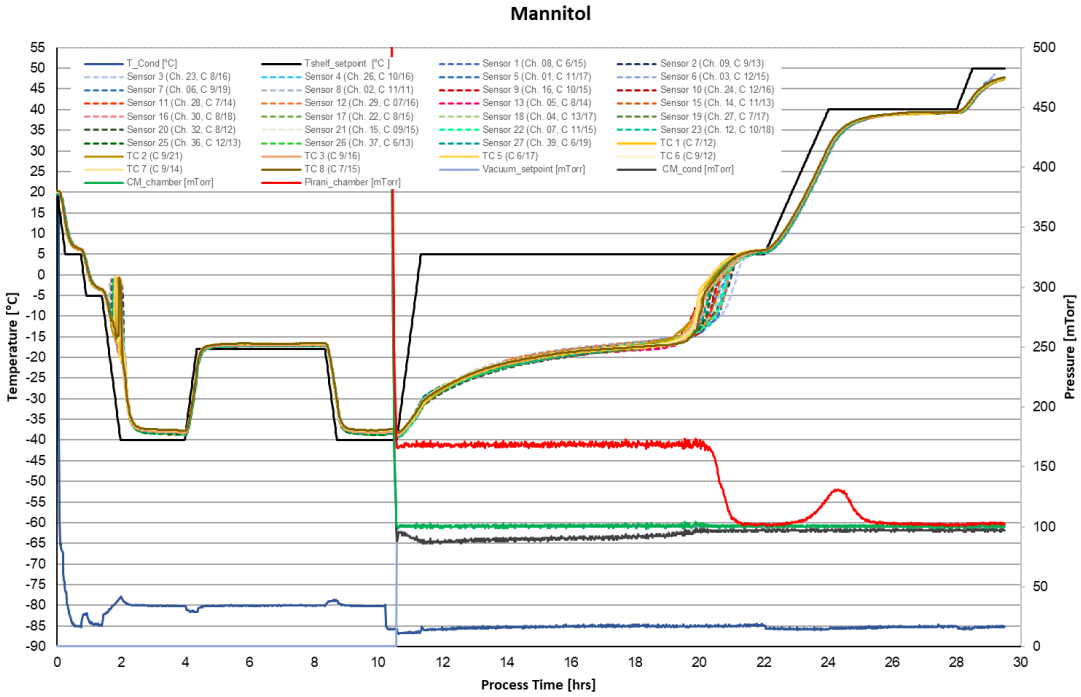

Figure 6: Freeze drying cycle plot of mannitol 50 mg/mL.

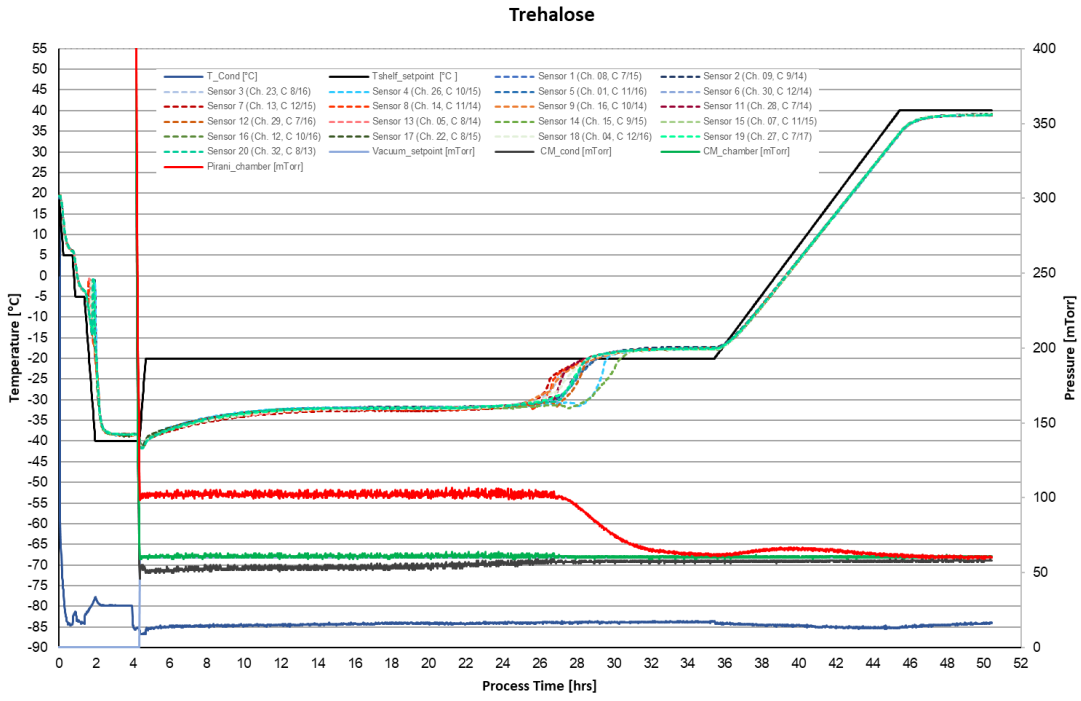

Figure 7: Freeze drying cycle plot of trehalose dihydrate 50 mg/mL.

The temperature curves show excellent comparability of all probes for both formulations and process conditions as indicated by the superimposable profiles during both primary and secondary drying. In agreement with earlier studies [1], the TEMPRIS® sensors showed a slight delay in temperature increase compared to the thermocouples (Figure 6). This may be explained by the larger thermo-sensitive area of the TEMPRIS® sensors which allows to detect remaining ice present. The endpoint of primary drying (T_p reaching T_s) was comparable for all sensor types in the mannitol cycle (within 0.5 hours). For the conservative cycle, the variability was increased (time interval: 1.8 hours), but no trend for differences in performance of the different sensor types could be observed. It is in agreement with the Pirani signal which showed a less steep decline compared to the mannitol cycle. The larger variability may be correlated to the conservative drying conditions, the different formulation, and the missing annealing step which facilitates not only crystallization but also homogeneity of ice crystal size by Ostwald ripening, which impacts the sublimation rate [2].

Average as well as maximum product temperatures obtained during primary drying were calculated (Figure 8). Similar to the nucleation temperatures, single sensors were excluded. The average product temperatures show comparable values and variations (note: statistical analysis was not conducted). Based on these results, the different sensor types may be considered comparable.

Figure 8: Average and maximum primary drying product temperatures.

4. Summary and Conclusion

Two new TEMPRIS® sensor designs were evaluated for their performance in comparison to the current design and thermocouples. Two different formulations at suitable freeze drying process conditions were tested. The results indicate comparability of all sensor types.

5. References

[1] Schneid S, Gieseler H. Evaluation of a New Wireless Temperature Remote Interrogation System (TEMPRIS) to Measure Product Temperature During Freeze Drying. AAPS PharmSciTech, Vol. 9, No. 3, September 2008.

[2] Searles J A, Carpenter J F, Randolph T W. Annealing to Optimize the Primary Drying Rate, Reduce Freezing-Induced Drying Rate Heterogeneity, and Determine Tg' in Pharmaceutical Lyophilization. J Pharm Sci, Vol. 90, No. 7, July 2001.