Innovative approaches for lyophilization process, equipment and drug product characterization

Peptalk 2017

Ahmad M. Abdul-Fattah

Coriolis Pharma Research GmbH, Am Klopferspitz 19, 82152 Martinsried, Germany

10th January 2017

Coriolis Pharma
Biopharmaceutical Research and Development Service

Acknowledgments

Andrea Hawe

Ilona Vollrath

Alexandra Mikolijka

Michael Wiggenhorn

Thomas Bosch

Angelika Freitag

Victoria Pauli/Laura Benz

Gerhard Winter

T.N. Thompson

Todd Reihbandt

Coriolis Pharma
Biopharmaceutical Research and Development Service

LMU
LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

MILLROCK TECHNOLOGY
millrocktech.com

PAT tools for freeze drying

	Method	Measurement principle	Primary drying end point	Product temp.	Product solid-state	Product moisture	Feasible scale-up	Sterilizability	Compatible w/ autom. loading system
Batch techniques	CM	Absolute pressure of the chamber	-	-	-	-	+	+	+
Batch techniques	Pirani gauge	Nitrogen pressure of the chamber	-	-	-	-	+	+	+
Batch techniques	Comparative CM vs. Pirani	Absolute vs. nitrogen pressure of the chamber	+	-	-	-	+	+	+
Batch techniques	PRT (e.g. MTM, DPE)	Rise of the absolute chamber pressure	+	+[1]	-	+[1]	-[2,3]	+	+
Batch techniques	Condenser pressure	Increase in nitrogen pressure	+	-	-	-	-[3]	+	+
Batch techniques	TDLAS	Flow and composition of the gas	+	+[1]	-	+[1]	-[3]	+	+
Batch techniques	Lyotrack	Composition of the chamber gas	+	-	-	+[1]	+	+	+
Batch techniques	RGA	Composition of the chamber gas	+	-	-	+[1]	+	+[4]	+
Batch techniques	Dew point	Dew point temperature of H_2O	+	-	-	-	+	+[4]	+
Batch techniques	Windmill	Water vapor flow	+	-	-	-	-[3]	+	+
Vial techniques	Raman	Inelastic scattering of radiation by product	-	-	+	-	-[5]	-	-
Vial techniques	NIR / FT-IR	Absorption of radiation by product	+	-	+	+	-[5]	-	-
Vial techniques	TC	Product temperature	+	+	-	-	-	-	-
Vial techniques	RTD	Product temperature	+	+	-	-	-	+	-
Vial techniques	TEMPRIS	Product temperature	+	+	-	-	+	+	+
Vial techniques	OFS	Product temperature	+	+	-	-	-	+	-
Vial techniques	Soft-sensor	Product temperature	+	+	-	-	+	+	+
Vial techniques	Dielectric spectroscopy	Polarizability of the product	+	+	+	+	-	-	-
Vial techniques	XRPD	Diffraction of the radiation by the product	-	-	+	-	-[5]	-	-
Vial techniques	Microbalance	Loss of mass of the product	+	-	-	+	-[5]	-	-
Vial techniques	Heat transfer monitor	Heat flow from the shelf to the product	+	-	-	-	-	-	-
Vial techniques	NMR spectroscopy	Relaxation of the magnetic moments of the product	+	-	+	-	-[5]	-	-
Vial techniques	Photographic observation	Position of the sublimation interface in the product	+	-	-	-	-[5]	+	-

[1]Average value. Only applicable in freeze-dryers with [2]fast closing valve, [3]external condenser chamber, [4]additional isolation system or [5] 'line of sight' to the sample.

Coriolis Pharma
Biopharmaceutical Research and Development Service

Raman and Near-Infrared Spectroscopic Methods for In-Line Monitoring of Freeze-Drying Process. **Ari Kauppinen Dissertation, 2015, University of Eastern Finland.**

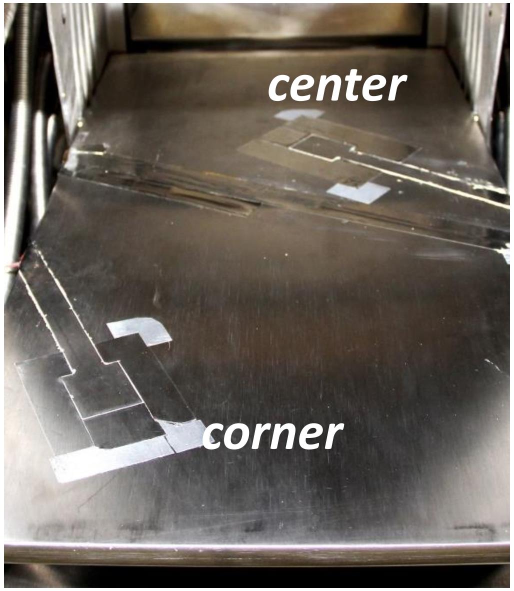
Outline

- PAT in the Laboratory: Case Studies in evaluating the heat flux sensor technology
  - Summary and conclusions
- PAT in the Laboratory: Case Studies in evaluating head space moisture
  - Summary and conclusions

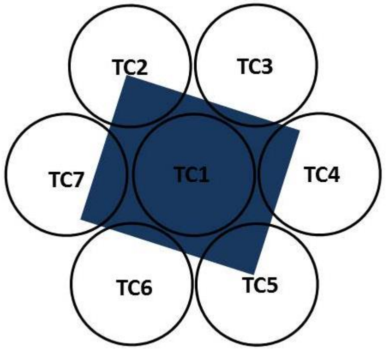
PAT in the Laboratory: Case Studies in evaluating the heat flux sensor technology

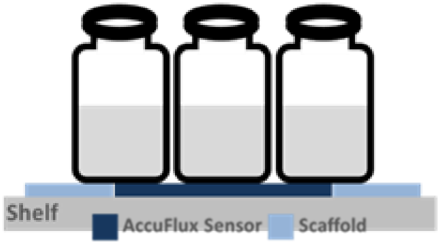
Heat flux sensor Concept

Heat flux sensor (Accuflux™) introduced by Millrock Technology Inc. (Kingston, NY) as a new monitoring PAT tool for freeze drying.



- Differential thermocouple sensor
- Mounted directly on freeze-dryer shelf
- Measures 3.6 x 3 cm
- Equipped with a built-in thermocouple to measure shelf temperature (ANSI Type T)
- Equipped with 2 cm of stainless steel tape (scaffold) mounted around the sensor → even standing of monitored vials
- Sensors fixed on shelf with electrically conductive silver filled epoxy
- Records data every 30 sec
- Heat flux output: W/m^2
- Experiments performed on a Millrock Magnum® Series freeze dryer

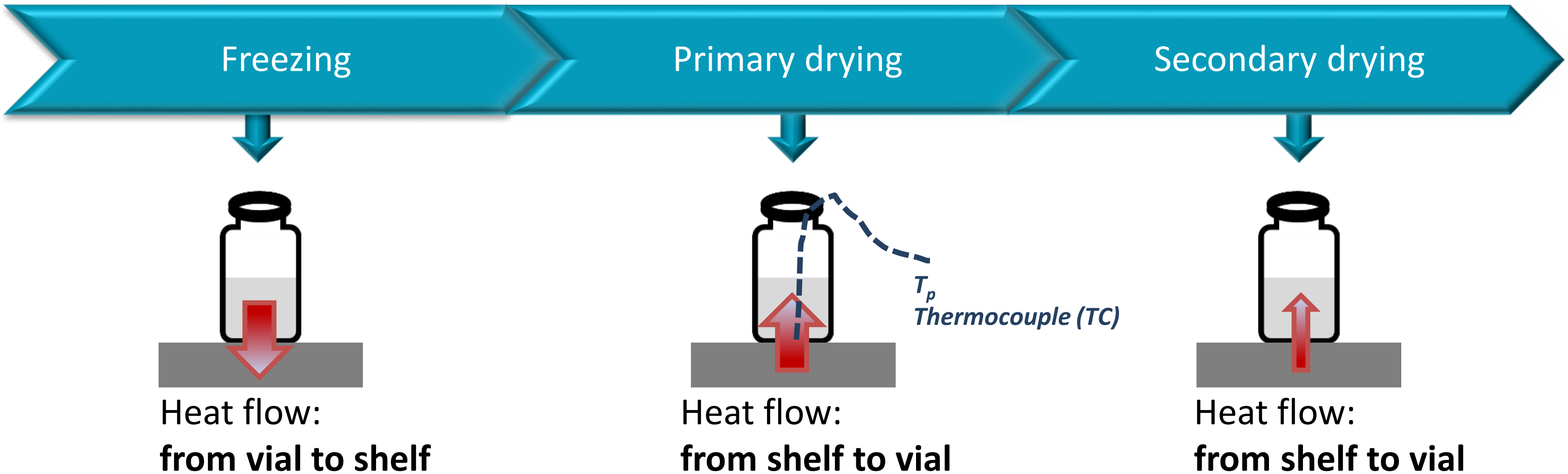




Coriolis Pharma
Biopharmaceutical Research and Development Service

Heat flux measurements in freeze drying

- **Heat flux (W/m^2) and shelf temperature T_s (°C) measured by the Accuflux™ sensor.**
- Product temperature T_P (°C) is measured via thermocouples located on the top of the sensor.



- LyoPAT™ software calculates vial heat transfer coefficient (K_v) [$W/m^2.°C$]:

$$K_v = \frac{heat\ flux}{(T_s - T_p)}$$

- LyoPAT™ software also calculates an estimated product temperature $T_{P,\ est}$ (°C), when K_v of a given process is known.

$$T_{p,\ est} = \frac{heat\ flux - Kv * Ts}{-K_v}$$

LyoPAT™ User Interface

A heat flux sensor offers a closed loop control of the whole process

<u>**Required input parameters**</u>

1) Vial characteristics

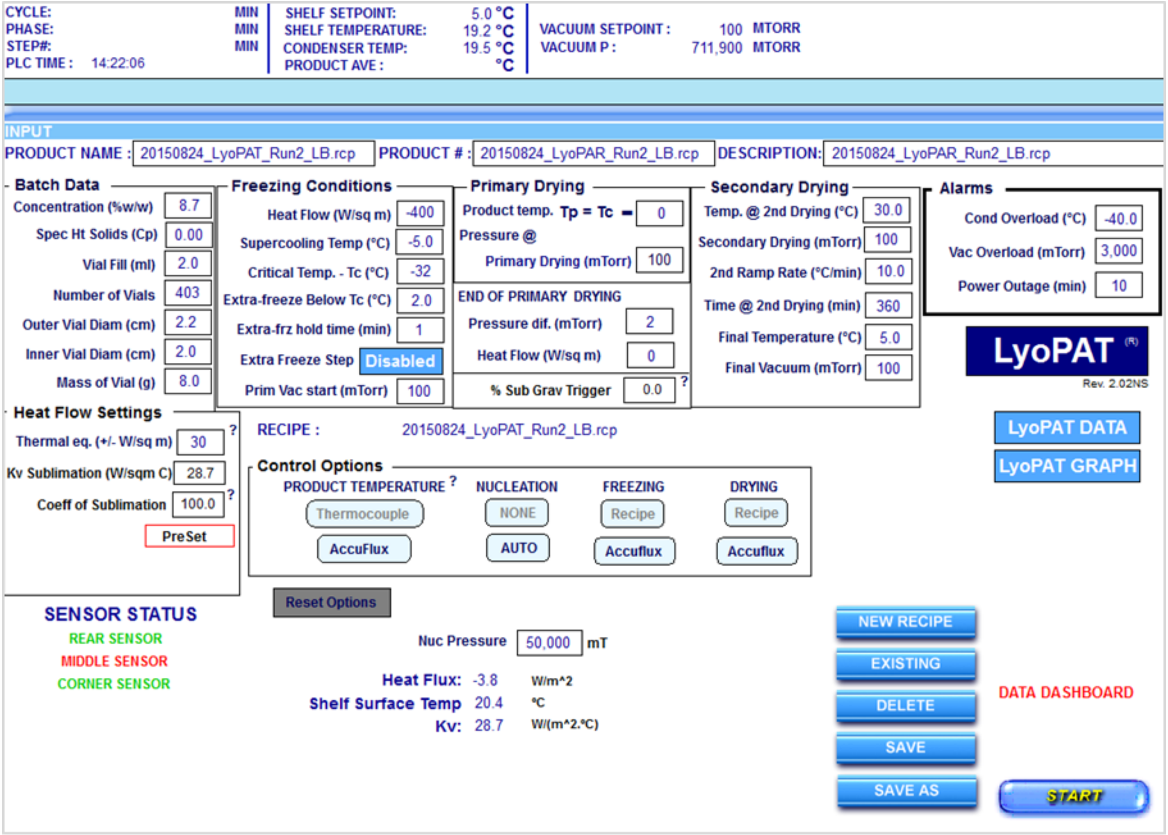
⇒ number of (product) vials
⇒ Mass of vial
⇒ vial inner surface area
⇒ vial outer surface area
⇒ K_v (predetermined)

2) Product characteristics

⇒ Concentration (g/g)
⇒ Critical temperature of the product (Tg`, Tc or Te)

3) Fill characteristics

⇒ Fill volume (ml)
⇒ Fill weight (mg)



Note: Need to determine critical temperature of product (e.g. DSC, FDM)

Heat flux sensor testing procedure

Basic tests: verification of procedure and evaluation of basic parameters

- Linearity (Heat flux vs. ΔT)
- Repeatability
- Robustness (vial position, moisture between shelf and vials)
- Sensor position (corner vs. center)
- Comparability of results obtained from Accuflux™ & LyoPAT™ to other PAT tools (e.g. $T_{P, est}$ vs. measured T_P (TC), end of primary drying by comparative pressure measurements)
- Comparability of K_v determined from Accuflux™ & LyoPAT™ vs. K_v gravimetric

Vollrath et al. J Pharm Sci (2017), in press

Basic tests: Potential applications of Accuflux™ (heat flux measurements)*

- A robust, repeatable PAT tool for measurement and process monitoring
- Reliable estimation of important parameters (T_p, K_v)
    - Estimated product temperature in good agreement with thermocouple (TC) readings
- Kv determination and product temperature estimation
    - K_v(LyoPAT) < K_v(gravimetric)
- Detection of nucleation events
    - Monitoring freezing step in random and controlled nucleation
- Monitoring of progress of primary drying
    - Determination of end point of primary drying by Accuflux™ in good agreement with TC and ΔT
    - Not as batch representative as comparative pressure measurements
- Quantification of radiation effects
    - Typical radiation
    - Atypical radiation

Vollrath et al. J Pharm Sci (2017), in press

Heat flux sensor testing procedure

Case studies: test of heat flux sensor performance under a variety of different conditions

- Solids content
- Fill volume
- Cycle parameters: Freezing protocol, P_c, T_s
- Study secondary drying kinetics in amorphous formulations: sucrose and sucrose/BSA mixtures
- In progress: Preliminary studies on design space creation

- different vial size:
  ⇒ 1cc, 3cc, 5cc
- different shelf load
  ⇒ full / partial load

In progress: other primary packaging, other product types

Factors affecting heat flux measurements

Heat flux sensor testing procedure

Case studies: test of heat flux sensor performance under a variety of different conditions

- Solids content
- Fill volume
- Cycle parameters: Freezing protocol, P_c, T_s
- Study secondary drying kinetics in amorphous formulations: sucrose and sucrose/BSA mixtures
- In progress: Preliminary studies on design space creation

- different vial size:
  ⇒ 1cc, 3cc, 5cc
- different shelf load
  ⇒ full / partial load

In progress: other primary packaging, other product types

Factors affecting heat flux measurements

Container

Heat flux sensor testing procedure

Case studies: test of heat flux sensor performance under a variety of different conditions

- Solids content
- Fill volume
- Cycle parameters: Freezing protocol, P_c, T_s
- Study secondary drying kinetics in amorphous formulations: sucrose and sucrose/BSA mixtures
- In progress: Preliminary studies on design space creation

- different vial size: ⇒ 1cc, 3cc, 5cc
- different shelf load ⇒ full / partial load

In progress: other primary packaging, other product types

Form./Process

Factors affecting heat flux measurements

Case studies with heat flux sensor: Experimental set up

Process setup

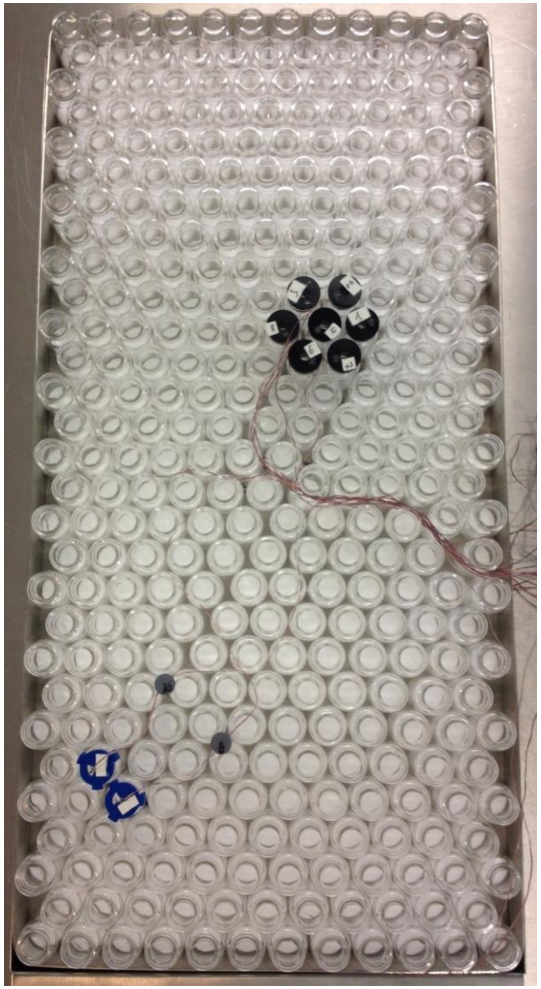
Freezing:
Controlled nucleation :at -5°C (Millrock FreezeBooster®)
Random nucleation: -1 °C/min → -50 °C
Primary drying setup:
Shelf temperature: -25 °C
Chamber pressure : 100 mTorr
Secondary drying setup:
Shelf temperature: 30 °C
Chamber pressure : 100 mTorr

Formulations/vial size

- Sucrose solutions (at different concentrations) with/without 10 mg/mL protein (BSA)
- 10R vials
- Fill volume: variable

Shelf setup

TC vials

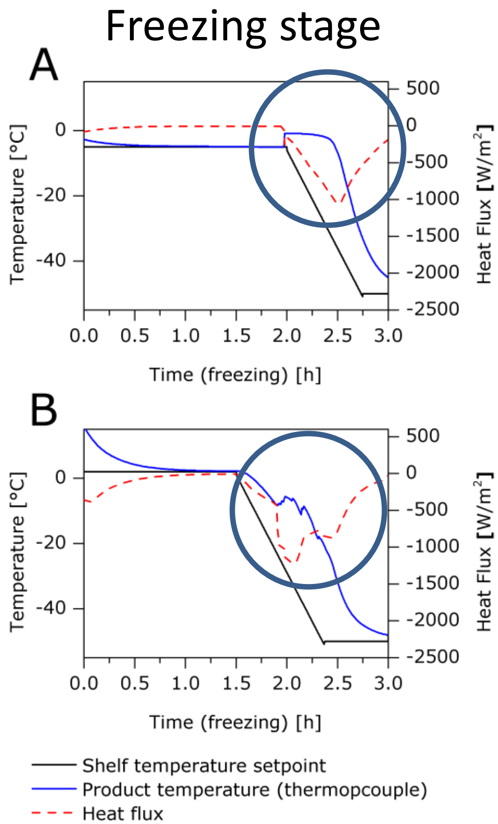


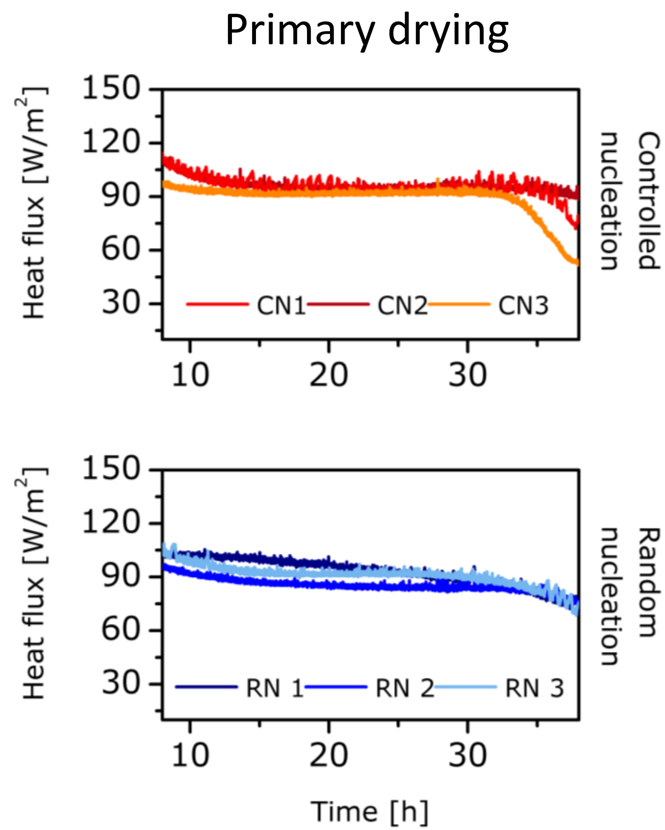
TC vials

Vollrath et al. J Pharm Sci (2017), in press

Coriolis Pharma
Biopharmaceutical Research and Development Service

Case study I: Impact of freezing protocol





- Freezing: Heat flux measurements give more insights into degree of homogeneity in freezing behavior of vials.
- Primary drying: no impact of freezing protocol on heat flux measurements

Coriolis Pharma
Biopharmaceutical Research and Development Service

Vollrath et al. J Pharm Sci (2017), in press

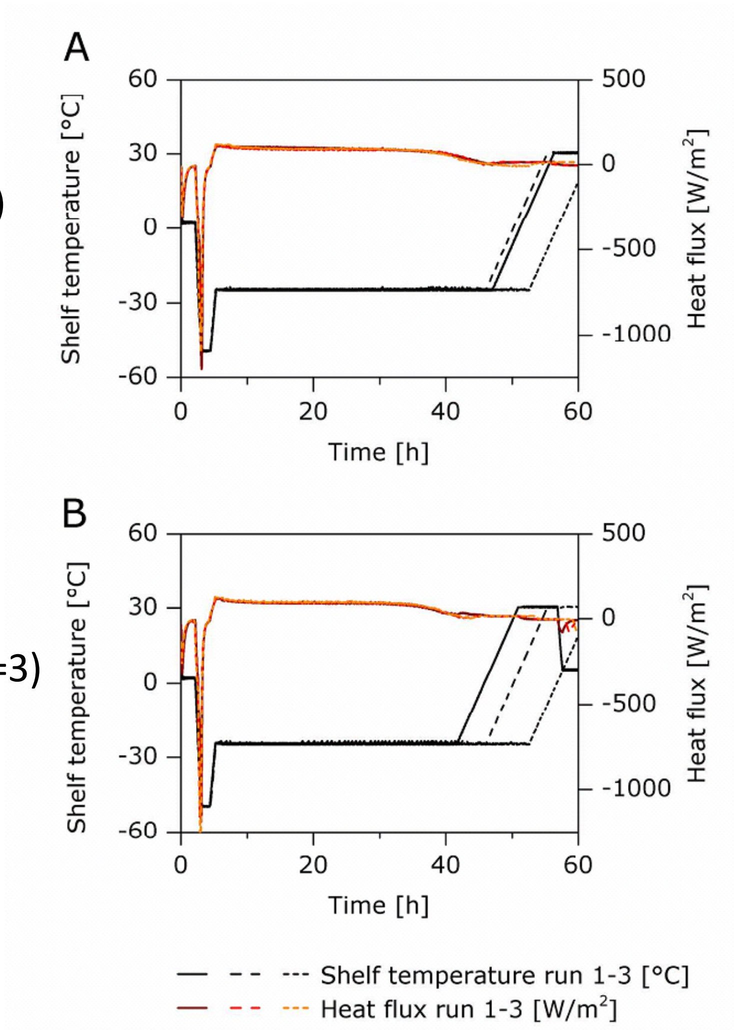
Case study II: Impact of degree of shelf loading

Fully loaded shelf (n=3)

772 vials

Partially loaded shelf (n=3)

150 vials

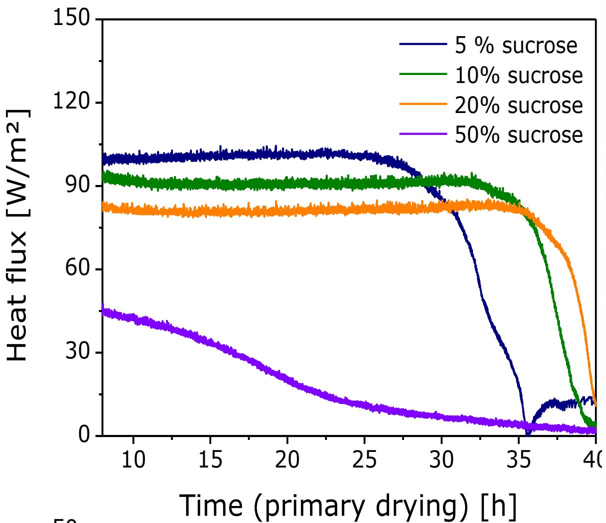


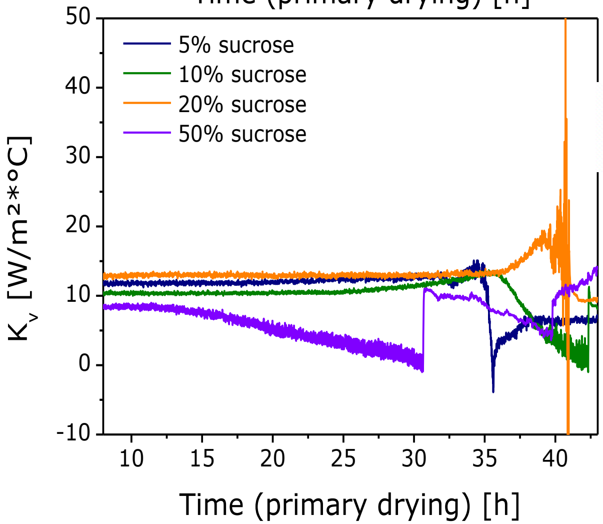
- No apparent impact of degree of shelf loading on heat flux measurements.
- Potential to design a cycle filling only a small number of vials

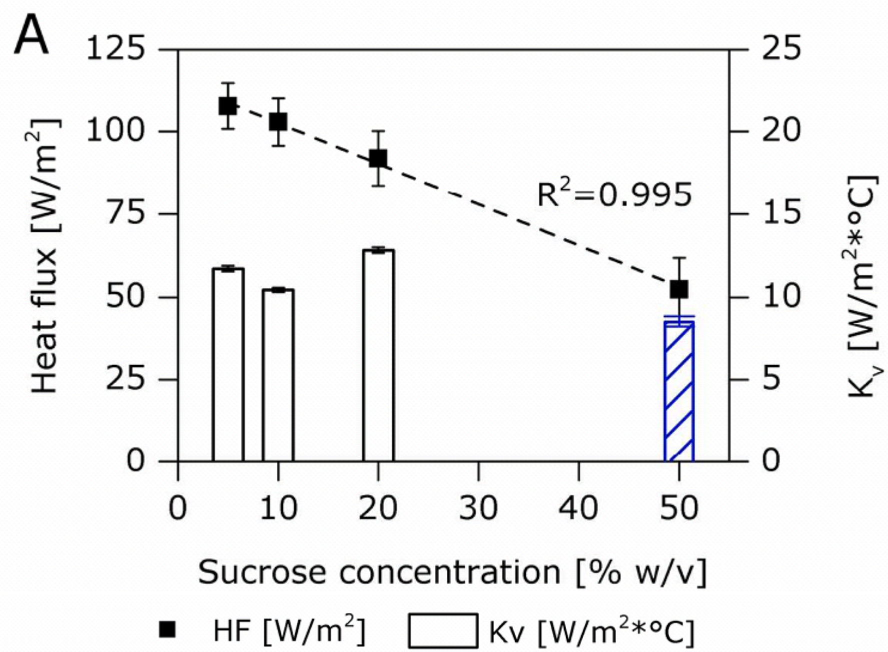
Coriolis Pharma
Biopharmaceutical Research and Development Service

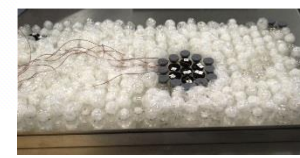
Vollrath et al. J Pharm Sci (2017), in press

Case study III: Impact of solids content







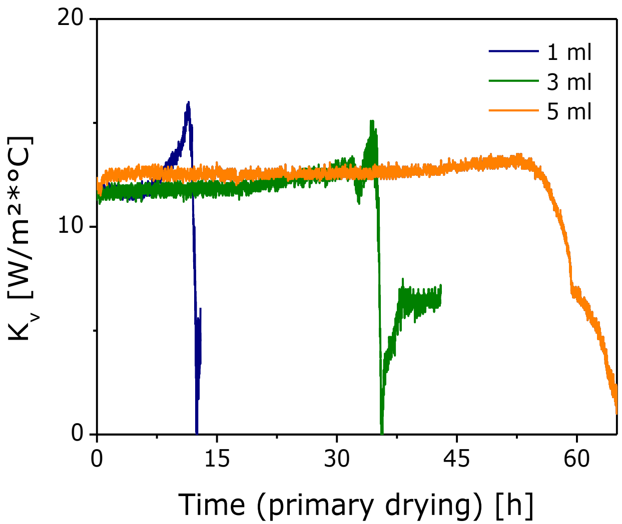


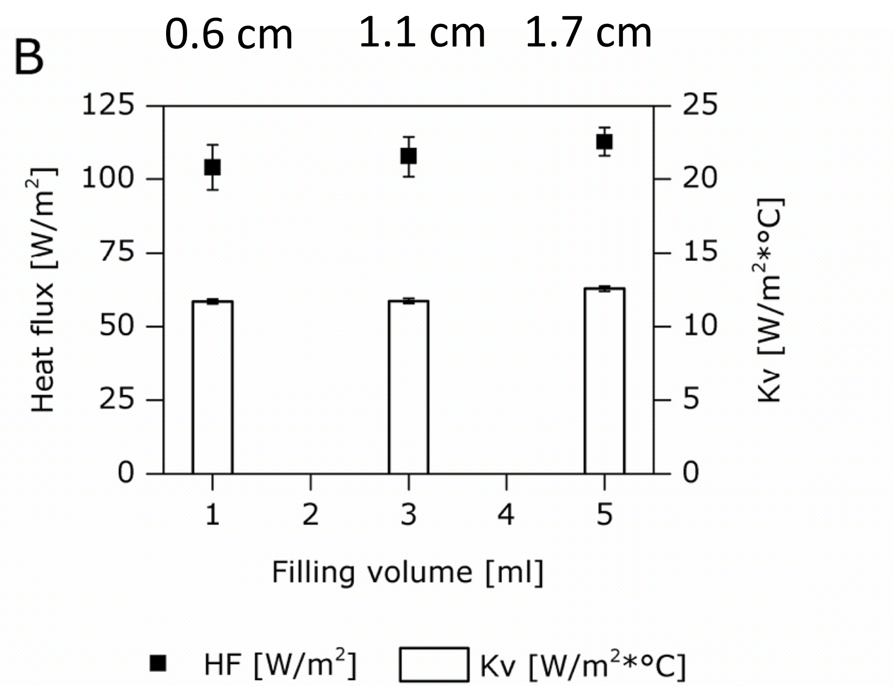
- Decrease in heat flux with increase in product concentration
  - → higher product resistance leads to lower sublimation rates
- K_v stayed constant for product concentrations 5 – 20 %
  - → T_p increases with lower sublimation rates
- Linear correlation between heat flux and product concentration
  - → facilitates process adjustment for different product concentration

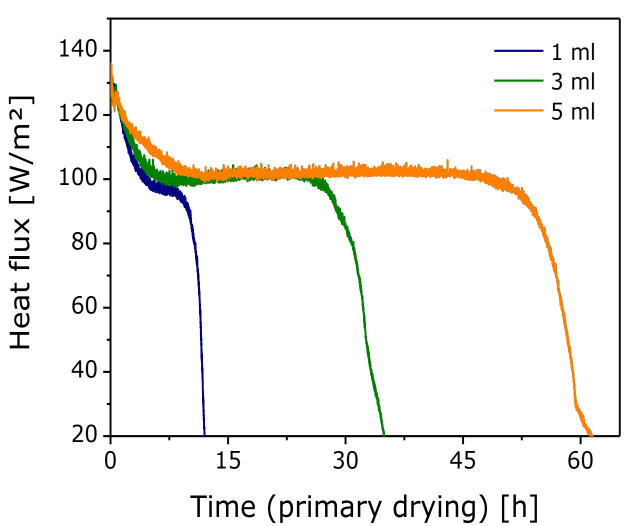
Vollrath et al. J Pharm Sci (2017), in press

Coriolis Pharma
Biopharmaceutical Research and Development Service

Case study IV: Impact of fill volume







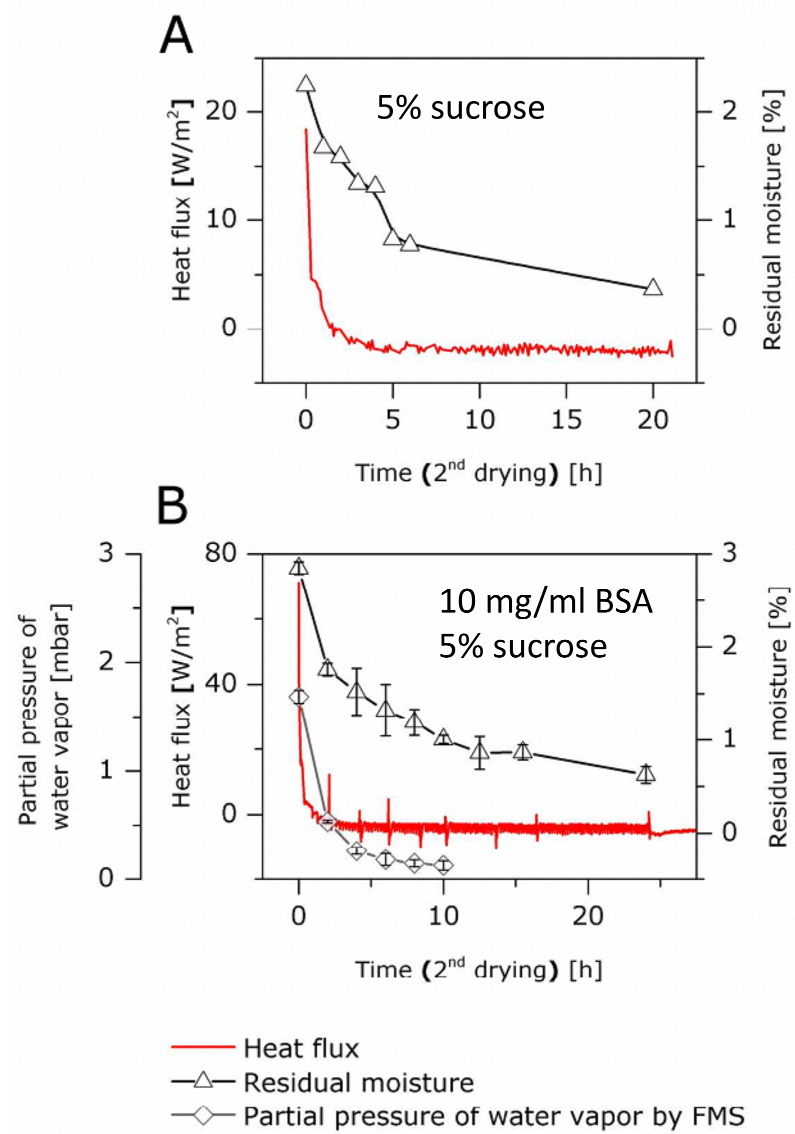
- Fill volume/fill height has no influence on heat flux and K_v
- heat flux limited by vial bottom not ice thickness
- P_c and T_s adjustment not necessary for higher fill volumes, only longer primary drying times needed

Coriolis Pharma
Biopharmaceutical Research and Development Service

Vollrath et al. J Pharm Sci (2017), in press

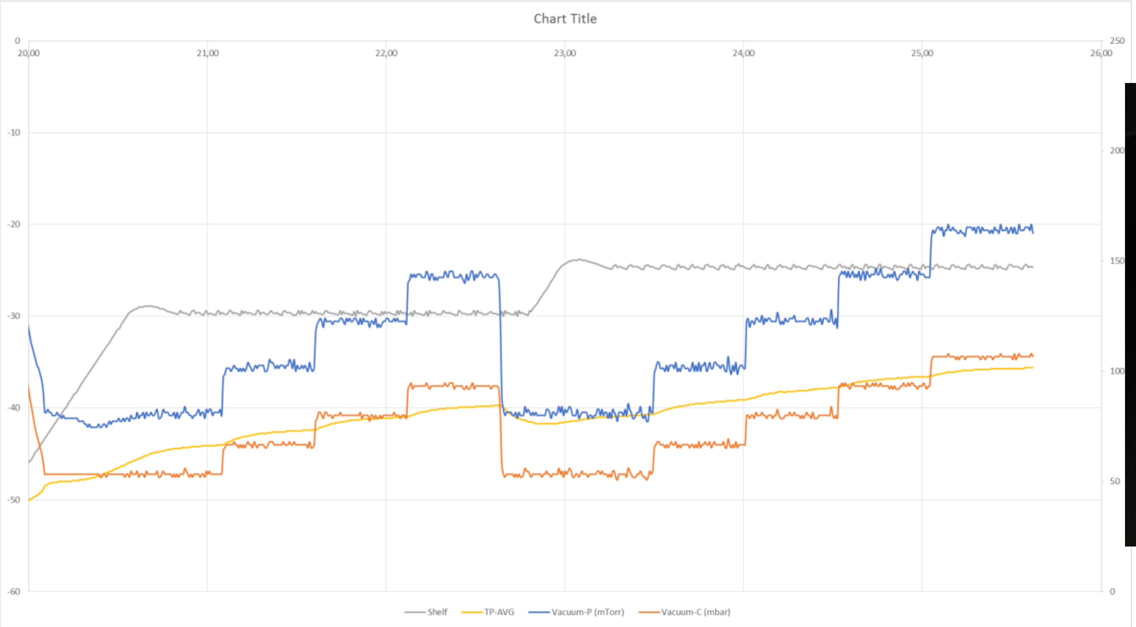
Case study V: Studying kinetics during secondary drying

- Correlation of heat flux during secondary drying to residual moisture (r.m.) content of the samples
- Heat flux decreased asymptotically in a similar way as compared to the water loss over time up to appr. 1.5% w/w
- Currently the sensitivity is not yet good enough to detect end of secondary drying.



Vollrath et al. J Pharm Sci (2017), in press

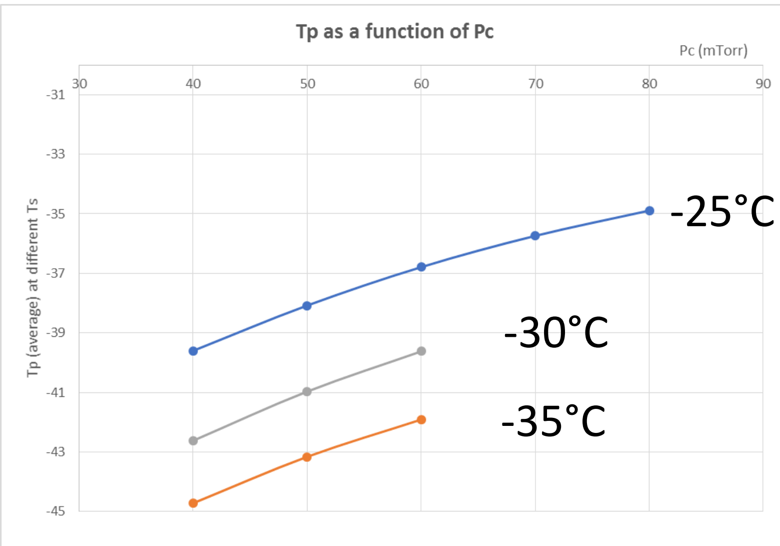
Case study VI: Feasibility of design space creation with more parameters

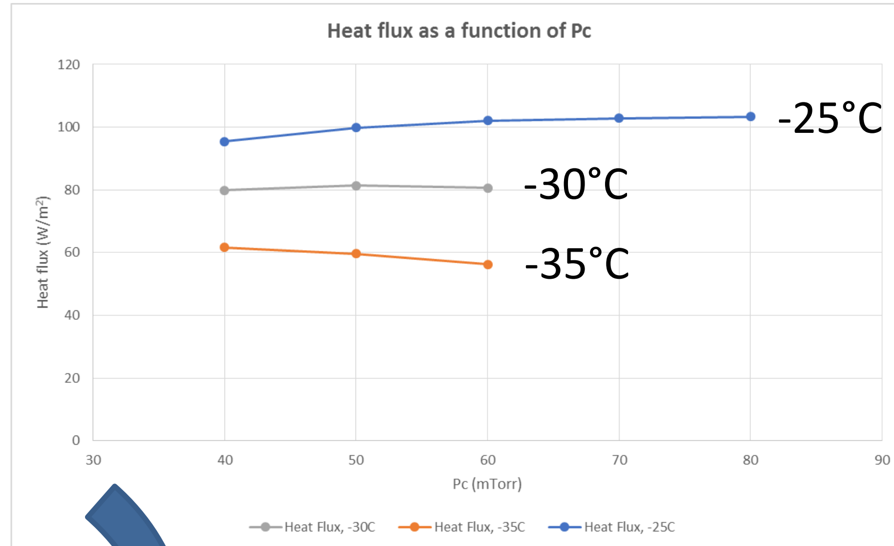


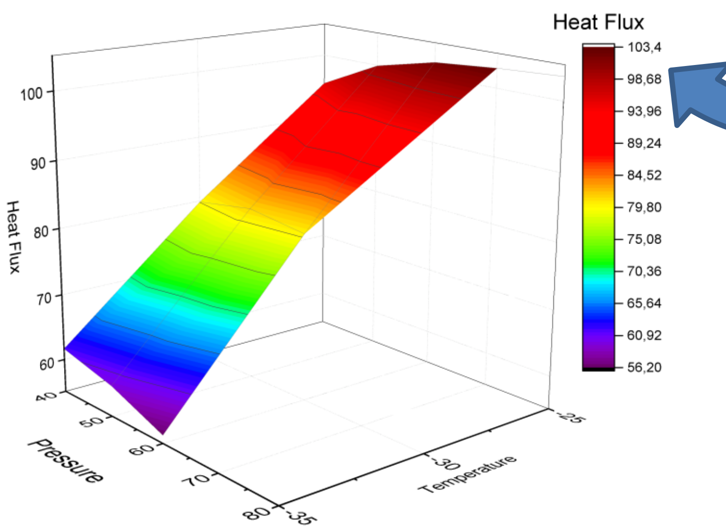
- Measure heat flux under different conditions (Ts and Pc) within 1 run and create a preliminary design space with multiple parameters

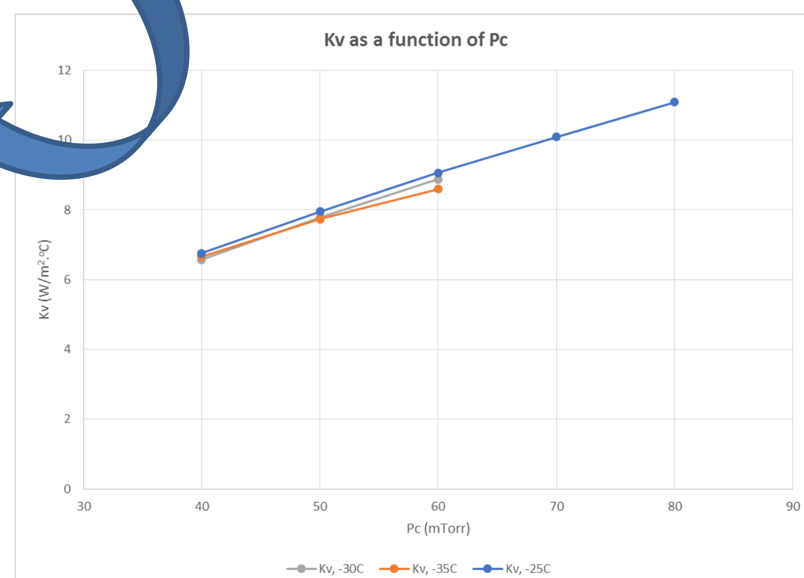
Coriolis Pharma
Biopharmaceutical Research and Development Service

Case study VI: Feasibility of design space creation with more parameters









Summary

- Factors affecting heat flux measurements
  - Solids content: Higher concentration = lower heat flux
  - Freezing protocol: freezing stage

- Factors with no significant impact on heat flux measurements
  - Freezing protocol: primary drying stage
  - Degree of shelf loading
    - Potential to use smaller batch sizes - ≤7 vials in cycle development (application of micro freeze dryer)
  - Fill volume/fill height (1-5 mL/0.6-1.7 cm)

- Accuflux™ sensitive enough to monitor secondary drying progress up to a residual moisture level of ~ 1.5% w/w.

- Feasibility to create a preliminary design space with multiple parameters in one run, further investigations needed.

PAT in the Laboratory: Case Studies in evaluating head space moisture

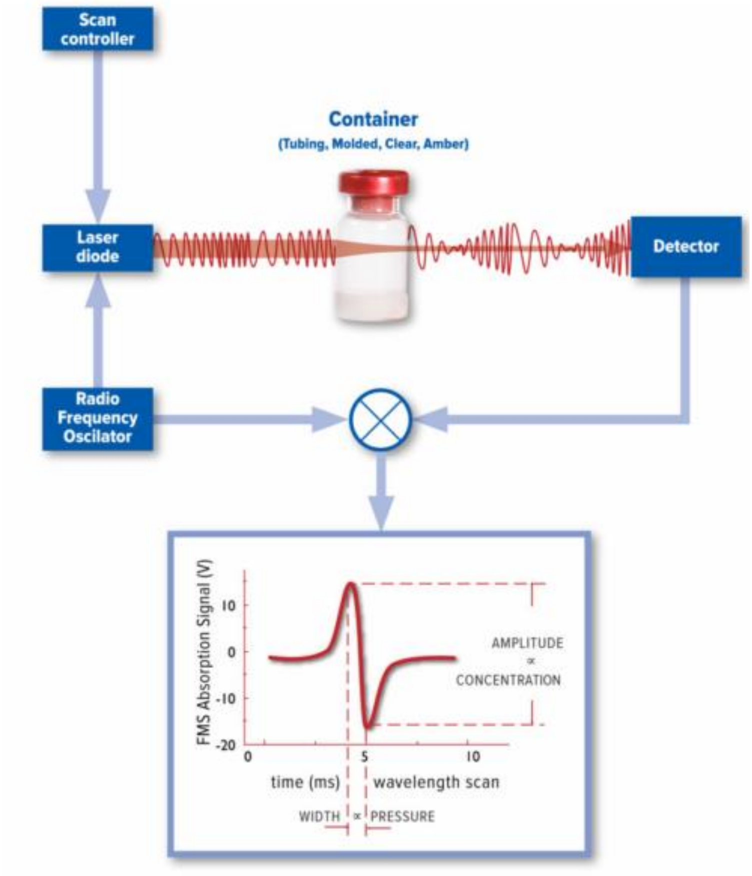
Aim

- Evaluation of application as non-invasive high throughput method for product and process characterization
  - Product characterization (e.g. batch homogeneity after freeze drying)
  - Process characterization

- Lighthouse FMS-1400 headspace moisture system
  - 6R vials used for all studies
  - Comparison against golden standard method (Karl-Fischer)

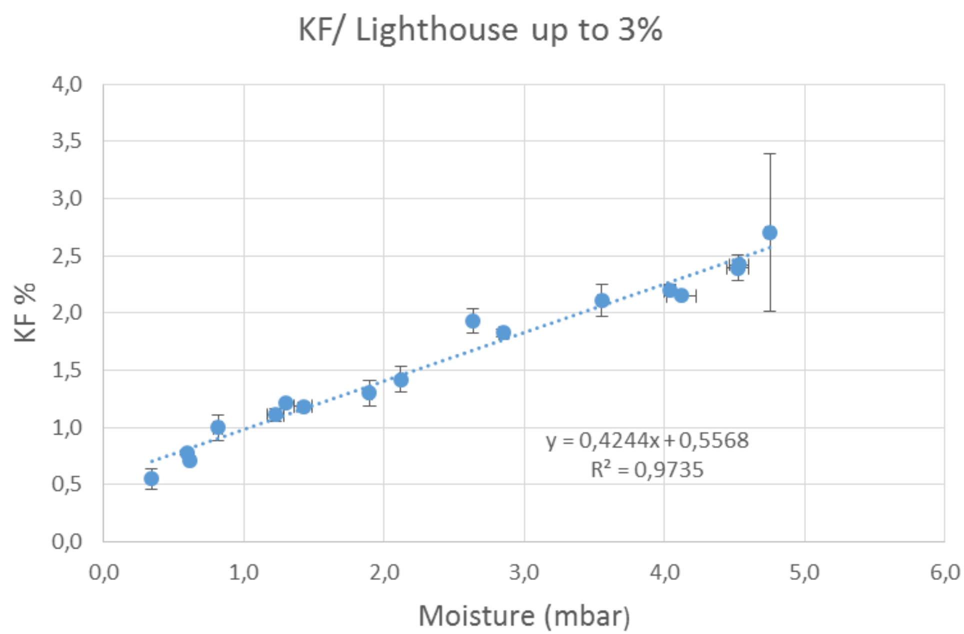
Frequency Modulation Spectroscopy (FMS)

- Principle: Determination of residual moisture
  - None-destructive and fast method, 100% control possible
  - Suitable for complete shelf mapping and identification of "hot" and "cold" spots on the shelves[1]
  - Quick characterization of drying efficiency and homogeneity as a function of the cycle (temperature and time)[1]
- Possible applications:
  - Information about product homogeneity including influence of different formulations on drying homogeneity
  - Characterization of product, indirect characterization of drying process
  - Stability study concerning vials with different residual moistures



[1] Cook I a., Ward KR. Headspace Moisture Mapping and the Information That Can Be Gained about Freeze-Dried Materials and Processes. PDA J Pharm Sci Technol. 2011;65(5):457-467. doi:10.5731/pdajpst.2011.00760

Establishing a correlationship between headspace moisture and direct moisture measurements



- Linear correlation between moisture measured by headspace analysis (FMS) and by Karl Fischer (KF)
  - Valid for 5% sucrose up to ~3% cake residual water content

Case study I: Using FMS to study moisture distribution as a function of formulation

- Conservative cycle used: Cake appearance acceptable, minor shrinkage in some vials
- Significant inhomogeneity in moisture distribution with sucrose
- Addition of protein improved homogeneity in moisture distribution

FD02 5% sucrose

Sh2 5% w/v sucrose solution, 6R vials, 2.5 ml fill

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0,958	0,811	0,812	0,848	0,852	0,859	0,844	0,876	0,849	0,868	0,831	0,897	0,995	1,032	1,106
0,843	0,866	0,764	0,911	0,807	0,825	0,832	0,853	0,91	0,98	0,831	0,88	0,918	0,868	1,01
0,731	0,895	0,865	0,802	1,126	0,837	0,823	1,062	1,061	0,914	1,221	0,83	0,981	0,967	0,945
0,783	0,825	0,818	1,065	0,808	0,868	1,09	0,93	0,901	1,446	0,837	0,952	0,843	0,929	0,898
0,719	0,847	1,06	1,132	0,821	1,116	0,954	1,141	0,976	1,137	1,027	0,888	1,087	0,835	0,807
0,986	0,791	0,845	0,774	1,6	1,43	0,941	1,236	0,966	0,888	1,05	0,899	0,997	0,837	0,771
0,718	0,766	0,839	0,794	0,817	1,135	0,921	0,767	1,504	0,892	2,035	1,109	0,921	0,77	0,689
0,71	0,72	0,917	0,845	1,461	0,988	1,238	1,323	1,073	1,373	1,107	0,949	0,75	0,801	0,683
0,704	0,922	0,946	0,724	1,647	1,015	1,308	1,466	1,213	0,787	0,881	0,797	0,855	0,687	0,752
0,681	0,709	0,747	0,84	0,705	1,097	1,165	0,982	1,868	1,265	1,213	1,099	1,083	0,742	0,677
0,76	0,879	0,734	1,399	1,297	0,808	1,351	1,31	1,007	0,93	1,093	1,275	1,014	0,762	0,743
0,706	0,724	0,823	0,79	0,767	1,087	1,431	1,277	1,081	0,789	1,44	0,965	0,76	0,717	0,657
0,69	0,725	1,015	1,073	1,471	0,735	1,331	1,126	0,999	1,016	1,155	0,918	0,662	0,785	0,721
0,649	0,724	0,719	0,755	1	1,226	1,686	0,723	0,991	0,702	1,087	1,017	0,877	0,809	0,859
0,677	1,165	1,158	0,835	0,832	1,394	0,846	1,432	1,314	0,903	0,774	0,987	0,792	0,747	0,684
0,657	0,808	0,769	0,878	0,806	1,108	1,27	1,313	0,829	0,714	1,261	0,832	1	0,709	0,703
0,692	0,902	0,756	0,921	1,156	0,846	0,933	0,928	0,766	0,749	0,835	1,265	0,748	0,685	0,726
0,654	0,699	0,721	0,886	0,884	0,723	0,832	0,785	1,173	0,775	0,837	0,745	0,745	0,734	0,764
0,695	0,672	0,783	0,754	0,799	0,876	0,765	0,81	0,986	0,728	0,69	0,771	0,678	0,843	0,813
0,656	0,711	0,665	0,737	0,853	0,729	0,772	1,037	0,827	0,733	0,764	0,781	0,725	0,758	0,769
0,707	0,695	0,659	0,698	0,657	0,754	0,746	0,813	0,797	0,67	0,736	0,794	0,791	0,787	0,69
0,746	0,713	0,844	0,758	0,773	0,7	0,699	0,793	0,814	0,733	0,718	0,728	0,802	0,693	0,755

Min.	0,65
Max.	2,04
Aver.	0,91
SD	0,22

FD02 5% sucr 25 mg/ml BSA

Sh3 25 mg/ml BSA, 5% w/v sucrose solution, 6R vials, 2.5 ml fill

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0,321	0,319	0,343	0,345	0,342	0,366	0,349	0,331	0,333	0,396	0,438	0,376	0,387	0,590	0,541
0,355	0,334	0,333	0,336	0,386	0,353	0,353	0,409	0,385	0,464	0,354	0,389	0,421	0,396	0,312
0,346	0,396	0,346	0,493	0,371	0,346	0,436	0,367	0,509	0,449	0,355	0,353	0,408	0,426	0,427
0,405	0,325	0,328	0,432	0,357	0,554	0,398	0,477	0,483	0,408	0,439	0,396	0,396	0,354	0,346
0,309	0,457	0,348	0,392	0,386	0,434	0,388	0,459	0,531	0,474	0,536	0,401	0,377	0,380	0,340
0,457	0,344	0,341	0,355	0,347	0,524	0,414	0,389	0,507	0,396	0,467	0,376	0,371	0,372	0,292
0,353	0,388	0,345	0,406	0,398	0,454	0,374	0,433	0,415	0,495	0,411	0,419	0,384	0,365	0,357
0,411	0,371	0,375	0,525	0,351	0,382	0,450	0,451	0,572	0,408	0,384	0,369	0,367	0,352	0,329
0,351	0,375	0,354	0,399	0,508	0,458	0,375	0,374	0,425	0,541	0,381	0,386	0,474	0,314	0,280
0,305	0,335	0,423	0,348	0,399	0,603	0,383	0,369	0,423	0,402	0,379	0,444	0,327	0,295	0,314
0,300	0,318	0,333	0,344	0,366	0,390	0,649	0,606	0,418	0,657	0,467	0,454	0,344	0,313	0,270
0,306	0,460	0,346	0,342	0,379	0,402	0,470	0,374	0,449	0,591	0,415	0,316	0,321	0,260	0,293
0,295	0,323	0,431	0,511	0,554	0,536	0,347	0,436	0,376	0,385	0,355	0,329	0,415	0,293	0,287
0,391	0,446	0,314	0,507	0,421	0,371	0,441	0,397	0,624	0,435	0,467	0,331	0,291	0,297	0,307
0,371	0,334	0,310	0,474	0,362	0,457	0,650	0,374	0,438	0,499	0,422	0,333	0,297	0,298	0,298
0,370	0,411	0,410	0,339	0,413	0,599	0,427	0,485	0,445	0,553	0,344	0,440	0,341	0,297	0,262
0,393	0,339	0,340	0,464	0,384	0,475	0,432	0,339	0,438	0,340	0,375	0,325	0,301	0,289	0,299
0,349	0,451	0,432	0,568	0,375	0,515	0,586	0,375	0,479	0,459	0,489	0,349	0,301	0,290	0,258
0,344	0,284	0,351	0,341	0,387	0,335	0,409	0,509	0,502	0,429	0,404	0,393	0,337	0,304	0,305
0,327	0,313	0,411	0,349	0,385	0,384	0,389	0,305	0,363	0,316	0,318	0,384	0,322	0,305	0,251
0,283	0,325	0,339	0,276	0,313	0,263	0,304	0,318	0,325	0,311	0,287	0,303	0,271	0,276	0,258
0,265	0,272	0,267	0,302	0,349	0,299	0,281	0,274	0,314	0,288	0,309	0,258	0,356	0,353	0,253

Min.	0,25
Max.	0,66
Aver.	0,38
SD	0,08

Coriolis Pharma
Biopharmaceutical Research and Development Service

Case study II: Using FMS to study moisture distribution as a function of cycle

5% sucrose solution, 6R vials, 2.5 ml fill

Conservative cycle

FD02 5% sucrose

Sh2

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0,958	0,811	0,812	0,848	0,852	0,859	0,844	0,876	0,849	0,868	0,831	0,897	0,995	1,032	1,106
0,843	0,866	0,764	0,911	0,807	0,825	0,832	0,853	0,91	0,98	0,831	0,88	0,918	0,868	1,01
0,731	0,895	0,865	0,802	1,126	0,837	0,823	1,062	1,061	0,914	1,221	0,83	0,981	0,967	0,945
0,783	0,825	0,818	1,065	0,808	0,868	1,09	0,93	0,901	1,446	0,837	0,952	0,843	0,929	0,898
0,719	0,847	1,06	1,132	0,821	1,116	0,954	1,141	0,976	1,137	1,027	0,888	1,087	0,835	0,807
0,986	0,791	0,845	0,774	1,6	1,43	0,941	1,236	0,966	0,888	1,05	0,899	0,997	0,837	0,771
0,718	0,766	0,839	0,794	0,817	1,135	0,921	0,767	1,504	0,892	2,035	1,109	0,921	0,77	0,689
0,71	0,72	0,917	0,845	1,461	0,988	1,238	1,323	1,073	1,373	1,107	0,949	0,75	0,801	0,683
0,704	0,922	0,946	0,724	1,647	1,015	1,308	1,466	1,213	0,787	0,881	0,797	0,855	0,687	0,752
0,681	0,709	0,747	0,84	0,705	1,097	1,165	0,982	1,868	1,265	1,213	1,099	1,083	0,742	0,677
0,76	0,879	0,734	1,399	1,297	0,808	1,351	1,31	1,007	0,93	1,093	1,275	1,014	0,762	0,743
0,706	0,724	0,823	0,79	0,767	1,087	1,431	1,277	1,081	0,789	1,44	0,965	0,76	0,717	0,657
0,69	0,725	1,015	1,073	1,471	0,735	1,331	1,126	0,999	1,016	1,155	0,918	0,662	0,785	0,721
0,649	0,724	0,719	0,755	1	1,226	1,686	0,723	0,991	0,702	1,087	1,017	0,877	0,809	0,859
0,677	1,165	1,158	0,835	0,832	1,394	0,846	1,432	1,314	0,903	0,774	0,987	0,792	0,747	0,684
0,657	0,808	0,769	0,878	0,806	1,108	1,27	1,313	0,829	0,714	1,261	0,832	1	0,709	0,703
0,692	0,902	0,756	0,921	1,156	0,846	0,933	0,928	0,766	0,749	0,835	1,265	0,748	0,685	0,726
0,654	0,699	0,721	0,886	0,884	0,723	0,832	0,785	1,173	0,775	0,837	0,745	0,745	0,734	0,764
0,695	0,672	0,783	0,754	0,799	0,876	0,765	0,81	0,986	0,728	0,69	0,771	0,678	0,843	0,813
0,656	0,711	0,665	0,737	0,853	0,729	0,772	1,037	0,827	0,733	0,764	0,781	0,725	0,758	0,769
0,707	0,695	0,659	0,698	0,657	0,754	0,746	0,813	0,797	0,67	0,736	0,794	0,791	0,787	0,69
0,746	0,713	0,844	0,758	0,773	0,7	0,699	0,793	0,814	0,733	0,718	0,728	0,802	0,693	0,755

Min.	0,65
Max.	2,04
Aver.	0,91
SD	0,22

Optimized cycle

Sh2

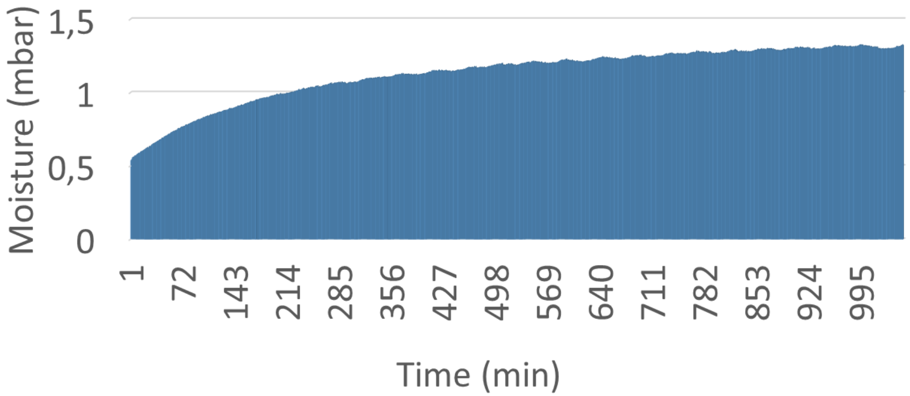
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0,466	0,571	0,566	0,683	0,591	0,599	0,605	0,639	0,574	0,662	0,589	0,674	0,586	0,598	0,721
0,598	0,564	0,599	0,575	0,624	0,582	0,569	0,576	0,657	0,581	0,581	0,628	0,813	0,659	0,613
0,533	0,593	0,596	0,581	0,609	0,55	0,556	0,55	0,586	0,609	0,588	0,811	0,565	0,609	0,602
0,551	0,559	0,553	0,608	0,587	0,532	0,581	0,573	0,594	0,643	0,645	0,531	0,6	0,602	0,61
0,733	0,62	0,597	0,565	0,469	0,543	0,47	0,609	0,51	0,559	0,578	0,59	0,762	0,55	0,571
0,549	0,533	0,492	0,564	0,571	0,514	0,478	0,582	0,584	0,509	0,605	0,79	0,442	0,55	0,479
0,904	0,559	0,505	0,455	0,559	0,517	0,521	0,415	0,473	0,677	0,567	0,517	0,546	0,511	0,619
0,568	0,558	0,524	0,588	0,551	0,554	0,57	0,555	0,521	0,593	0,502	0,665	0,516	0,548	0,49
0,491	0,563	0,567	0,583	0,653	0,427	0,745	0,46	0,555	0,644	0,66	0,413	0,606	0,464	0,549
0,771	0,549	0,567	0,523	0,451	0,565	0,458	0,605	0,541	0,456	0,494	0,525	0,537	0,519	0,477
0,531	0,543	0,444	0,531	0,529	0,518	0,507	1,02	0,528	0,557	0,668	0,531	0,54	0,535	0,586
0,603	0,557	0,599	0,419	0,529	0,57	0,479	0,574	0,602	0,49	0,554	0,529	0,474	0,474	0,496
0,541	0,452	0,53	0,494	0,567	0,594	0,489	0,582	0,528	0,537	0,547	0,557	0,506	0,585	0,512
0,467	0,558	0,538	0,488	0,881	0,525	0,528	0,503	0,498	0,433	0,574	0,492	0,394	0,446	0,472
0,454	0,569	0,611	0,55	0,57	0,622	0,543	0,496	0,439	0,536	0,597	0,561	0,548	0,49	0,53
0,492	0,519	0,514	0,52	0,521	0,543	0,598	0,527	0,521	0,506	0,481	0,535	0,461	0,529	0,618
0,486	0,595	0,521	0,55	0,5	0,465	0,538	0,517	0,576	0,438	0,645	0,523	0,51	0,525	0,544
0,583	0,535	0,512	0,554	0,476	0,544	0,524	0,537	0,558	0,713	0,541	0,555	0,592	0,452	0,843
0,482	0,546	0,516	0,557	0,516	0,553	0,536	0,533	0,572	0,582	0,571	0,583	0,467	0,558	0,571
0,497	0,506	0,492	0,455	0,555	0,587	0,57	0,603	0,649	0,5	0,623	0,529	0,528	0,581	0,418
0,464	0,781	0,652	0,527	0,499	0,534	0,516	0,532	0,606	0,623	0,555	0,519	0,541	0,516	0,714
0,474	0,452	0,501	0,577	0,514	0,574	0,486	0,429	0,509	0,537	0,586	0,473	0,526	0,677	0,691

Min.	0,39
Max.	1,02
Aver.	0,56
SD	0,08

- With a less conservative/more optimized cycle: More uniform moisture distribution (batch homogeneity)
- More radiation effects with more conservative cycle

Coriolis Pharma
Biopharmaceutical Research and Development Service

Challenges with headspace measurements



- Still not a high throughput method
  - But much quicker than KF!

- Equilibration time needed before measurements are performed on the day of the measurement

→ Need for product specific method development and validation (against KF)

Summary

- Headspace moisture is high(er) throughput tool for moisture measurement (as compared to traditional KF method)
  - Method needs to be developed and validated for each formulation/container closure configuration

- Headspace moisture is a versatile tool in product and process characterization
  - Application during equiment characterization?

- Factors affecting batch homogeneity
  - Formulation: Higher batch inhomogeneity with no protein
    - Minimum protein conc. for improvement of homogeneity?
  - Optimizing freeze drying cycle
    - Conservative vs. Optimized cycles
    - Impact of more aggressive cycles, as studied by FMS?

Questions?

company

privately held,
independent service provider
established in 2008

people

interdisciplinary team of highly qualified scientists
~ 60 FTE (all academic, 70% with PhD)

science

expert scientific board:
Prof. Dr. G. Winter
Prof. Dr. W. Friess
Prof. Dr. W. Jiskoot
Prof. Dr. J. Carpenter
Prof. Dr. C. Schöneich

techniques

innovative analytical and technical equipment,
focus aggregate and particle characterization

research

cutting edge research in the field of protein sciences with top publications

service

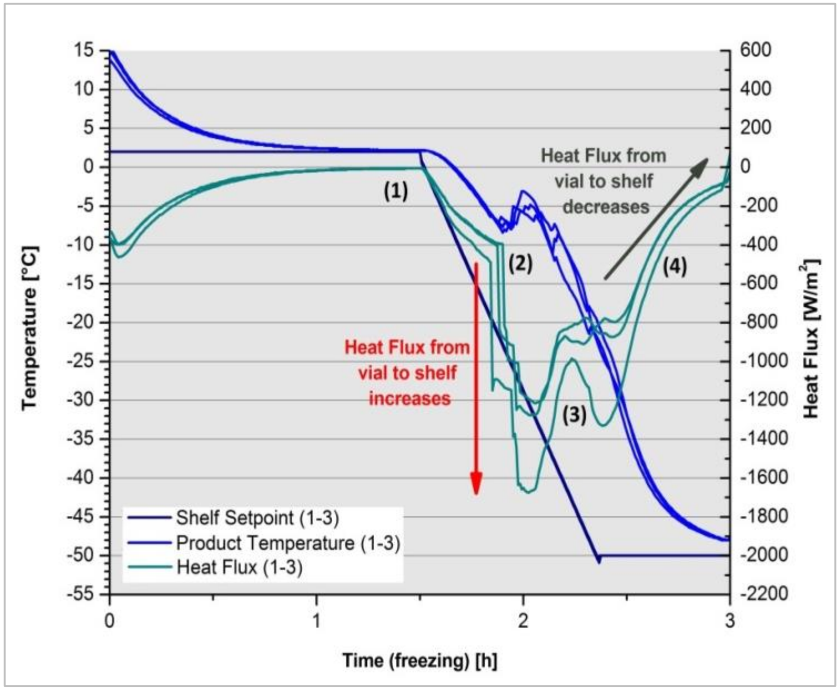
formulation development
lyophilization development
GMP analytics for biopharmaceuticals

Coriolis Pharma
Biopharmaceutical Research and Development Service

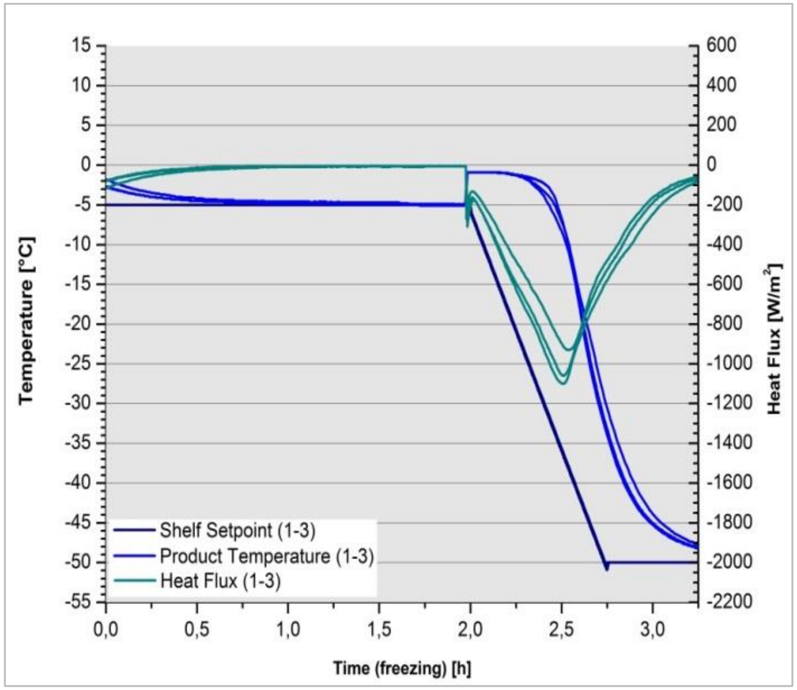
Back up slides

Employing the heat flux sensor as a PAT tool in freeze-drying: Freezing (CN vs. RN)

Random Nucleation (RN):

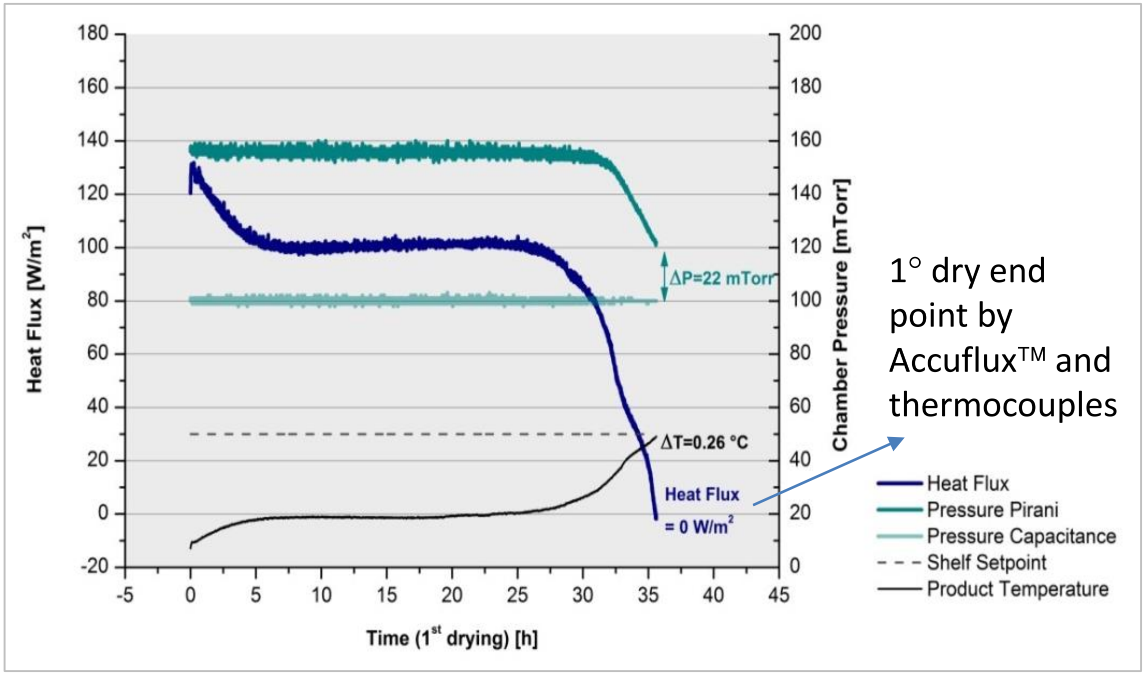


Controlled Nucleation (CN):



Heat flux sensor can reliably indicate nucleation events
Difference between RN and CN visible
→ thermodynamic evidence that freezing with CN is more repeatable than with RN

Employing the heat flux sensor as a PAT tool in freeze-drying: Primary drying



% sucrose/ Fill volume	1^{ry} drying [h]	ΔP_c [mTorr]	$\Delta T(T_s\text{-}T_p)$ [°C]
5%/3ml	35.6	22	0.3
20%/3ml	40.9	16	0.0
5%/1ml	22.5	7	-0.1
5%/5ml	65.9	13	1.2

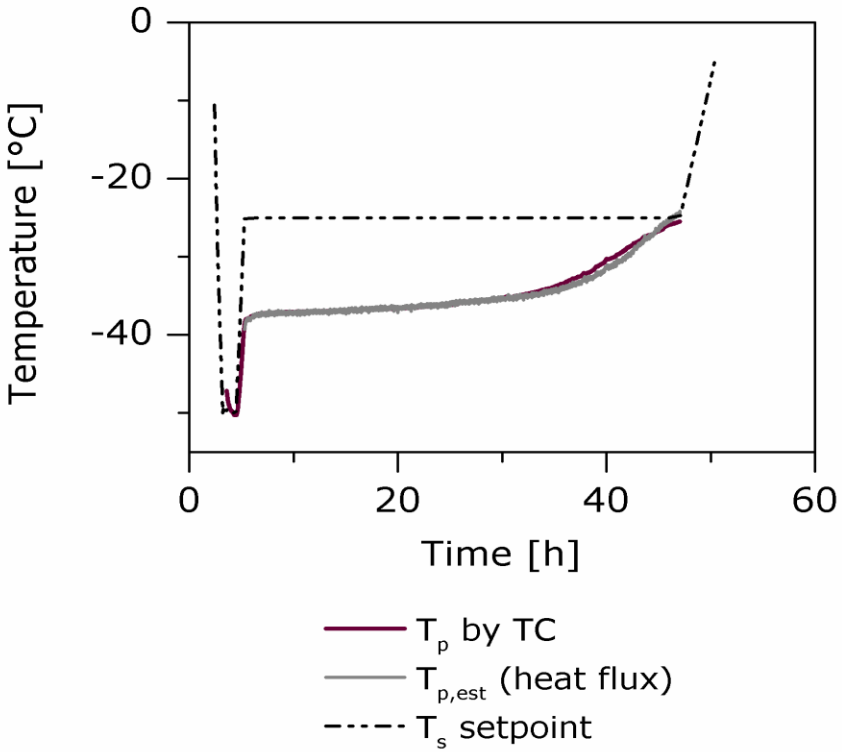
- Determination of end point of primary drying by Accuflux™ in good agreement with T_p and *ΔT*.
- Accuflux™ detected end of primary drying before pressure difference between the pirani & capacitance gauge reached 0.
- Not as batch representative as comparative pressure measurements.

Coriolis Pharma
Biopharmaceutical Research and Development Service

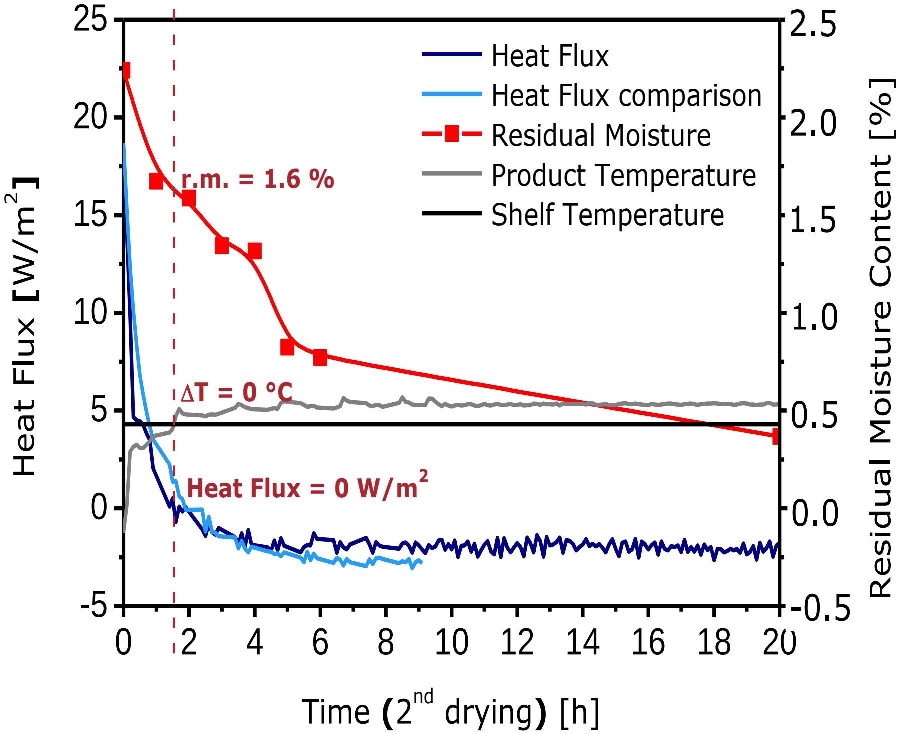
Product temperature estimation by heat flux measurements

$$T_{p,\,est} = \frac{heat\ flux - Kv * Ts}{-Kv}$$

- Although the heat flux measurements do not take all heat transfer effects into account, the result is in good accordance with the thermocouple readings
  - Simplified handling: no Thermocouple needed
  - Non invasive tool: no impact on drying behavior!



Employing the heat flux sensor as a PAT tool in freeze-drying: Secondary drying

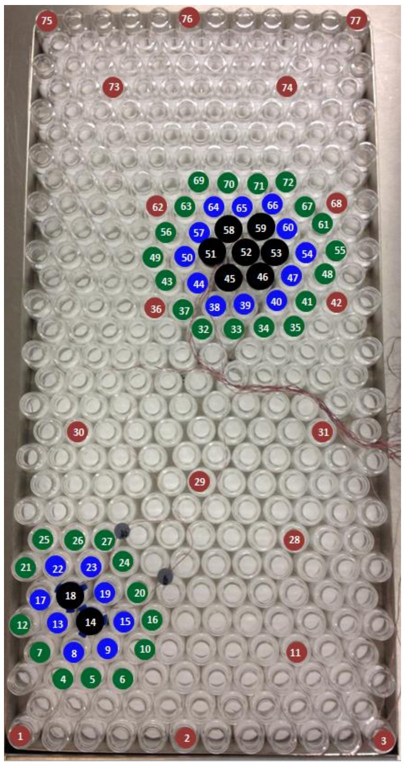


- Heat flux and residual moisture curve show the same course
- Further time points between 6 and 20 h are necessary to define if heat flux measurements can indicate the end of secondary drying

Coriolis Pharma
Biopharmaceutical Research and Development Service

Determination of mass and heat transfer coefficients by heat flux

Shelf setup



Process setup

Product: Water

Freezing:
- Controlled nucleation at -5 °C
- Freezing to: -50 °C (1 °C/min)

Primary drying:
- Shelf temperature: 0 °C;
- Chamber pressure: 100 mTorr

Secondary drying:
- Shelf temperature: 30 °C (0.1 °C/min)
- Chamber pressure: 100 mTorr

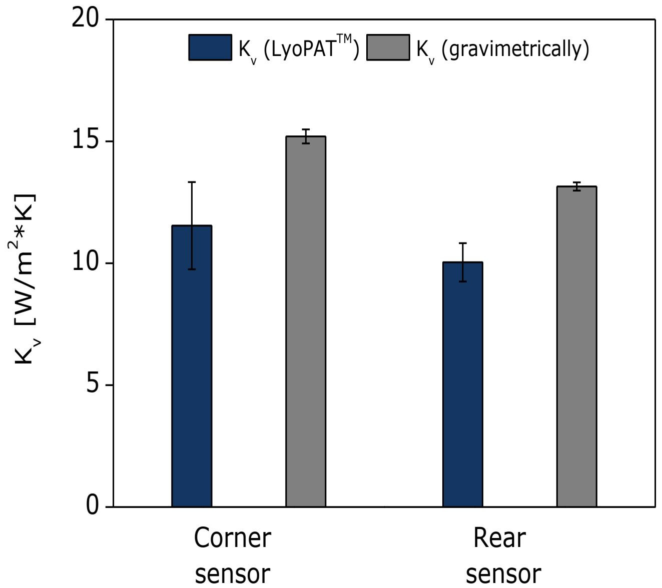
Calculations

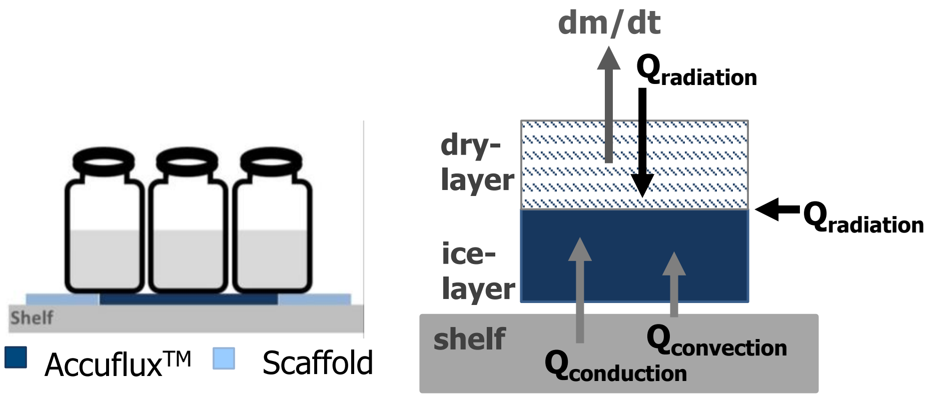
$$K_{v(LyoPAT)} = \frac{heat\ flux}{(Ts - Tp)}$$

$$K_{v(grav)} = \frac{\frac{dm}{dt} * \Delta H_s}{A_v * (Ts - Tp)}$$

With shelf temperature (T_s); product temperature (T_p); ΔH_s is the heat of sublimation (2594.4 J/g). dm/dt corresponds to the mass loss over time.

Determination of mass and heat transfer coefficients by heat flux measurements (ctd)





- In all cases the $K_{v(grav)}$ value was higher than the $K_{v(LyoPAT)}$ values.
- The corner K_v values for LyoPAT^{TM} and the gravimetrical method are higher → sensor is affected by radiation effects
- Next software version comes with calibration/adjustment function