Laser-Based Headspace Inspection

Moisture Mapping across Freeze Dryer Shelves

PDA Pharmaceutical Freeze Drying Conference
29th of September, 2009
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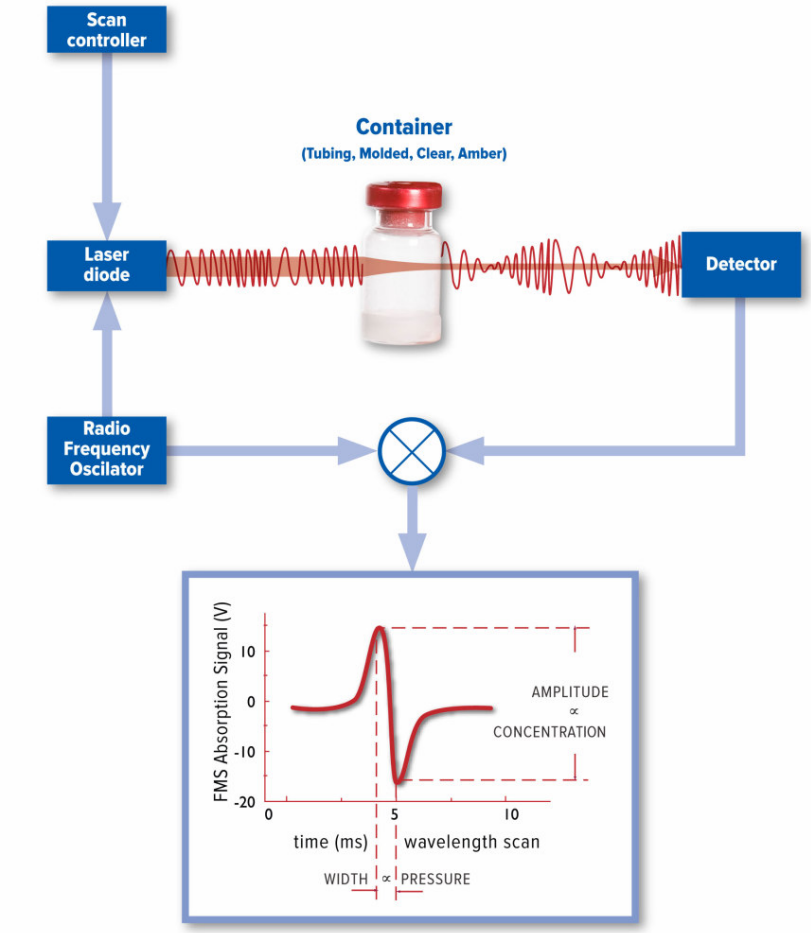
The Science of Pharmaceutical Manufacturing

Agenda

- Introduction to headspace method & systems
- Headspace moisture analysis of sterile freeze-dried vials
- Case study: Moisture mapping for lyo cycle development
- Case study: Moisture mapping for freeze dryer performance characterisation

Frequency Modulation Spectroscopy



Headspace Method

Modulation techniques result in 10,000x increase in sensitivity compared to first order absorption techniques such as NIR

LIGHTHOUSE Headspace Inspection Platforms

Initially developed with FDA funding

Automated systems:

VISTA/THC: Oxygen, pressure, moisture

VISTA/O: Oxygen

VISTA/P: Pressure, moisture

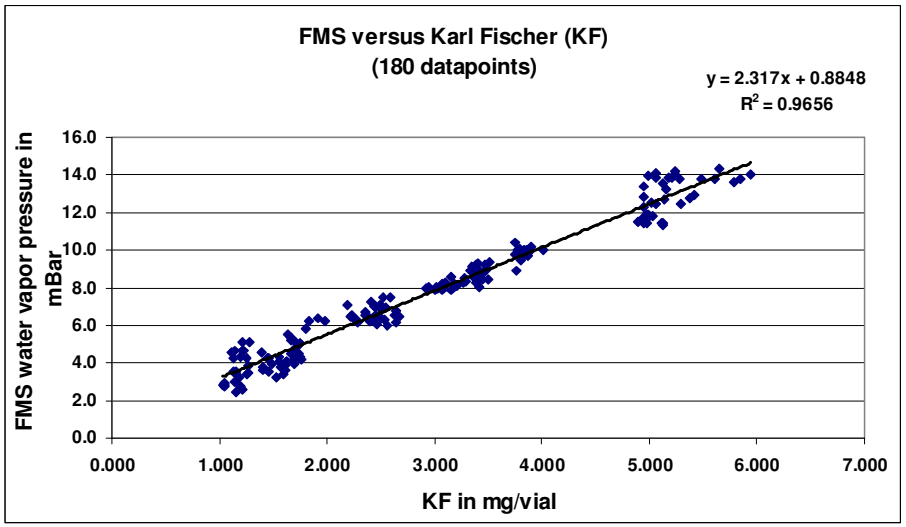
At-/Off-line systems:

FMS-760: Oxygen

FMS-1400: Pressure/Moisture

Implementing Headspace Moisture Analysis

- Correlate to existing standard method
  - Karl Fischer titration
  - Loss on drying
- Headspace moisture as primary method
  - Define product stability in terms of headspace moisture
  - Specify and control headspace moisture

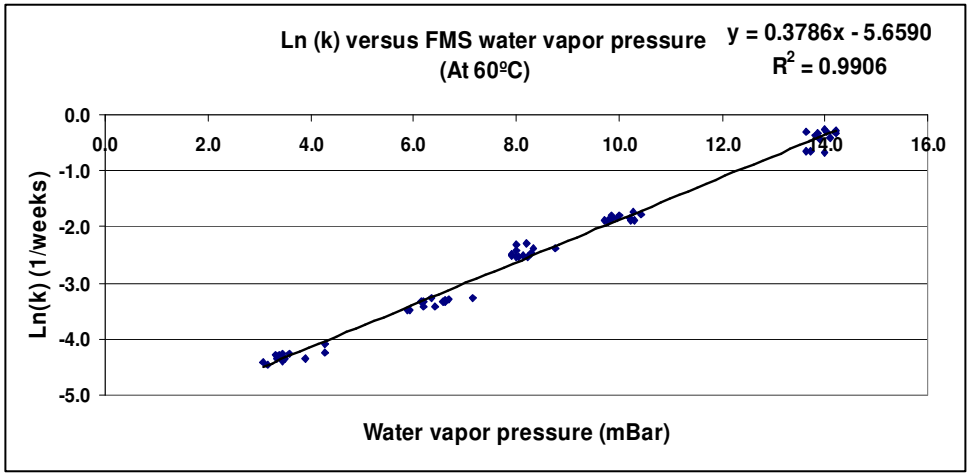


Data courtesy of Schering-Plough

Headspace moisture correlated to standard method

$$k = \frac{-(\mathrm{Ln}(\frac{[At]}{[Ao]}))}{t}$$

Headspace moisture directly correlated to product stability



Data courtesy of Schering-Plough

Headspace Moisture Ratios

Where is the water?? "Free water" vs. "Bound water"

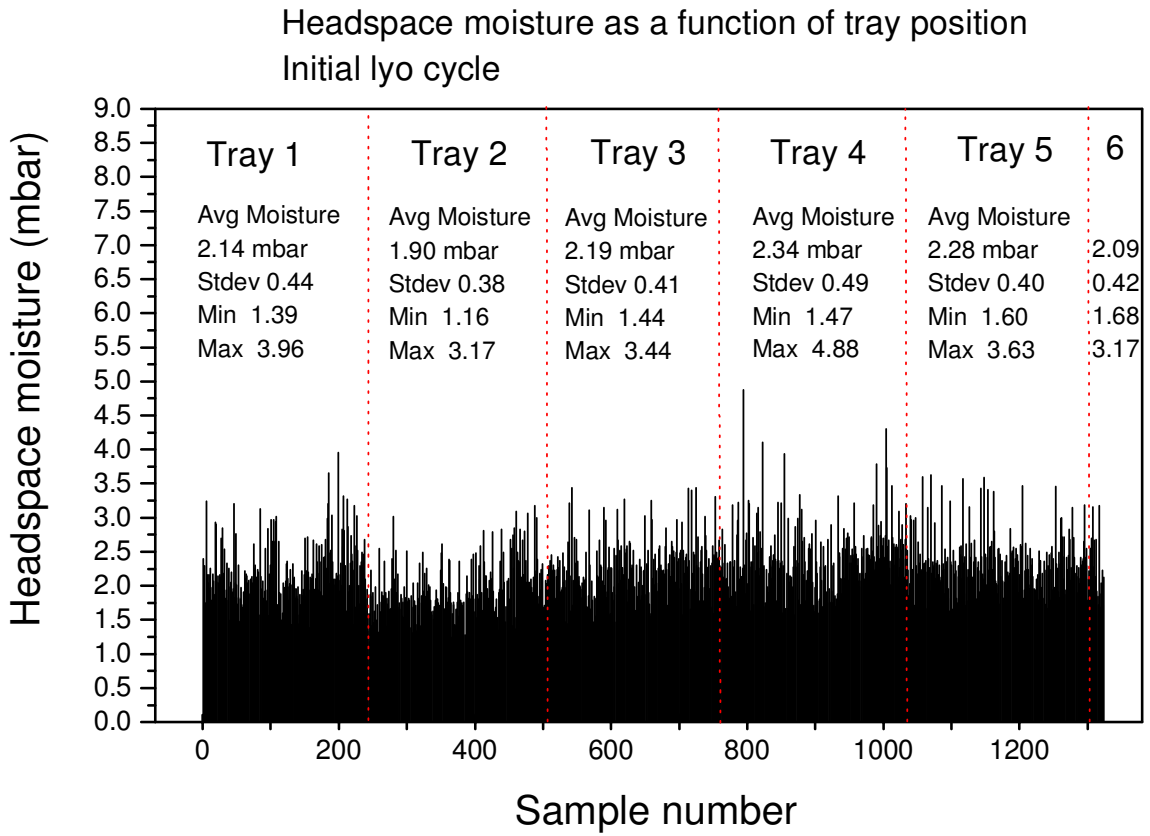
	Sucrose 4%	Mannitol 2% + Glucose 1%	Mannitol 2%	NaCl 5%
Karl Fischer Total Water (% w/w)	2.87	3.9	5.04	1.03
FMS Headspace Moisture (Torr)	2.03	3.3	6.32	6.13
FMS:KF Ratio	0.71	0.85	1.25	5.95

Data courtesy of Biopharma Technology Ltd

Moisture Mapping Case Study:

Lyo cycle development

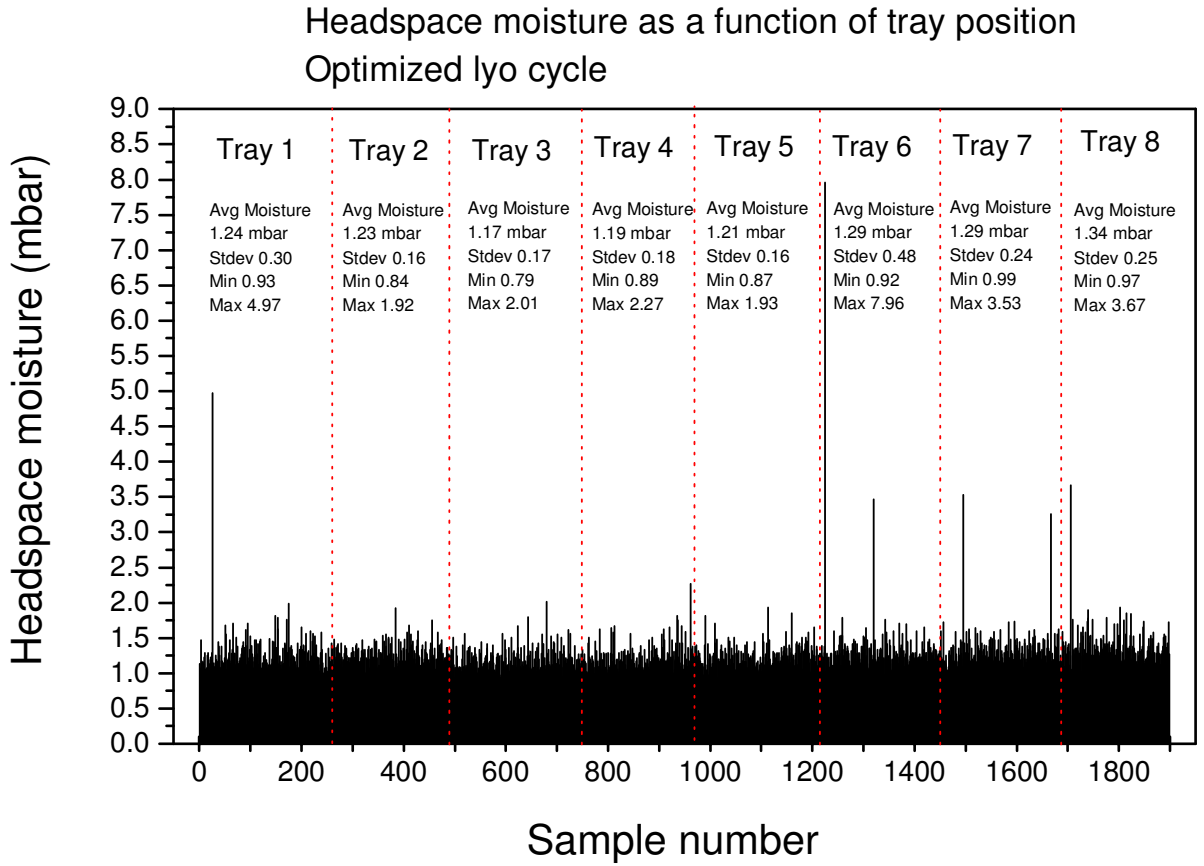
- Perform 100% headspace inspection on batch produced with a defined commercial lyo cycle.
- Headspace moisture results showed inhomogenous, location dependent drying.
- Results motivated client to optimise the lyo cycle.



Moisture Mapping Case Study:

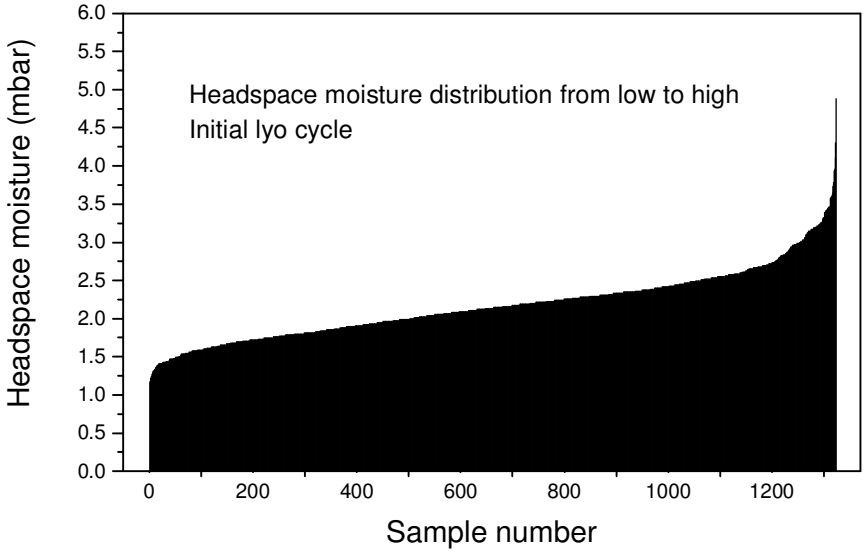
Lyo cycle development

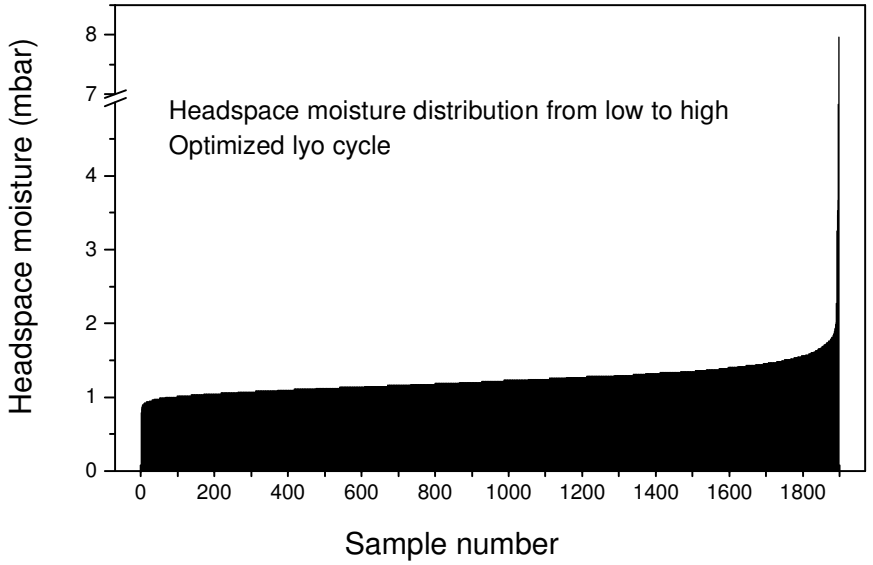
- Headspace moisture inspection helped optimise the lyo cycle for more homogenous drying.
- Even in the optimised process there are random high moisture vials.



Moisture Mapping Case Study:

Lyo cycle development





Plotting the headspace moisture values from low to high clearly shows a high moisture tail in the distribution even for the optimised lyo cycle

Moisture Mapping Case Study Conclusions

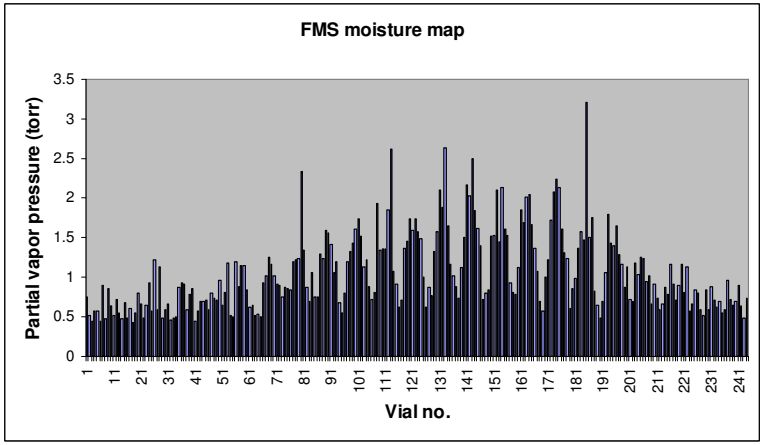
Rapid non-destructive headspace method enables:

- Quick characterisation of the drying efficiency, homogeneity as a function of the cycle
  - Primary and secondary drying temperature & time
- Insight into the number and frequency of moisture 'outliers'
  - Potential moisture control of stability samples
  - Minimise risk of losing batches due to an outlying quality sample

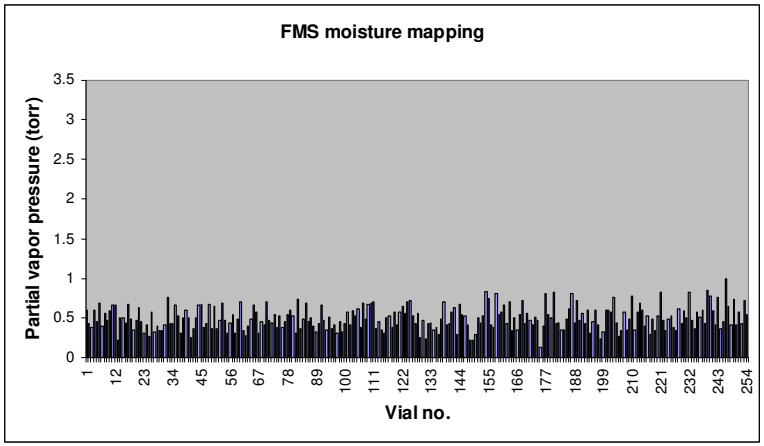
Moisture Mapping Case Study:

Freeze Dryer Characterization

- Formulation 4% sucrose, KF / FMS correlation gave R^2 of 0.989
- When using steel bottomed tray, headspace moisture mapping shows inhomogeneous drying
- High moisture values in center of tray



- Identical lyo cycle run with vials in direct contact with freeze dryer shelf
- Headspace moisture mapping shows better drying and a more homogeneous distribution



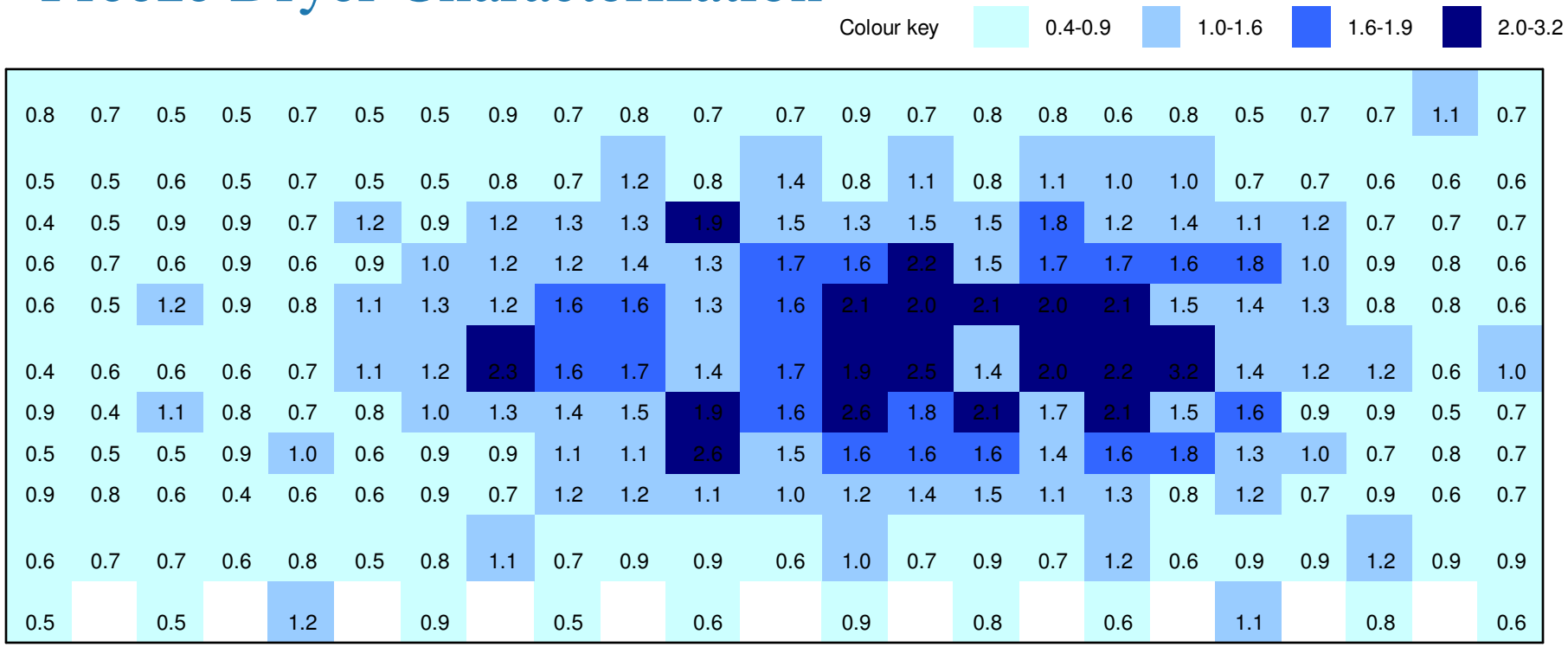
Data courtesy of Biopharma Technology Ltd

Moisture Mapping Case Study:

Freeze Dryer Characterization

Low value 0.4 torr = 1% KF

High value 3.2 torr = 4% KF



Data courtesy of Biopharma Technology Ltd

When using steel bottomed tray, headspace moisture plot shows high moisture samples in center of shelf

Moisture Mapping Case Study:

Freeze Dryer Characterization

Low value 0.2 torr = 1% KF

High value 1.0 torr = 1.8% KF

Colour key 0.1-0.4 0.5-0.6 0.7-1.0

0.6	0.7	0.5	0.4	0.5	0.5	0.5	0.5	0.7	0.4	0.4	0.7	0.2	0.5	0.4	0.8	0.5	0.6	0.3	0.5	0.8	0.8
0.4	0.2	0.3	0.4	0.7	0.3	0.7	0.4	0.4	0.3	0.6	0.4	0.2	0.6	0.6	0.4	0.6	0.6	0.6	0.3	0.5	0.4
0.4	0.5	0.4	0.7	0.7	0.4	0.6	0.5	0.5	0.5	0.2	0.4	0.3	0.7	0.5	0.4	0.4	0.8	0.7	0.5	0.4	0.5
0.6	0.5	0.3	0.5	0.4	0.5	0.3	0.5	0.4	0.3	0.5	0.6	0.5	0.4	0.4	0.4	0.6	0.4	0.6	0.5	0.6	1.0
0.5	0.4	0.6	0.3	0.4	0.3	0.5	0.6	0.3	0.4	0.2	0.6	0.4	0.7	0.5	0.4	0.3	0.3	0.4	0.4	0.5	0.6
0.7	0.7	0.3	0.5	0.7	0.5	0.4	0.5	0.4	0.6	0.4	0.3	0.5	0.3	0.5	0.5	0.4	0.3	0.5	0.3	0.6	0.4
0.4	0.5	0.4	0.6	0.4	0.7	0.7	0.3	0.7	0.4	0.4	0.7	0.8	0.5	0.1	0.6	0.6	0.6	0.3	0.6	0.4	0.7
0.6	0.3	0.3	0.5	0.6	0.3	0.5	0.7	0.5	0.6	0.3	0.5	0.8	0.4	0.4	0.8	0.4	0.4	0.5	0.4	0.8	0.4
0.5	0.5	0.3	0.2	0.4	0.3	0.4	0.4	0.4	0.5	0.4	0.5	0.4	0.5	0.8	0.4	0.2	0.5	0.3	0.6	0.8	0.6
0.6	0.6	0.4	0.4	0.5	0.4	0.5	0.5	0.5	0.6	0.3	0.4	0.4	0.7	0.5	0.7	0.3	0.8	0.5	0.5	0.6	0.4
0.7		0.8		0.7		0.4		0.4		0.5		0.8		0.5		0.6		0.8		0.4	

Data courtesy of Biopharma Technology Ltd

When samples have direct contact with shelf, headspace moisture plot shows homogeneous drying across the shelf

Moisture Mapping Case Study Conclusions

Freeze Dryer Characterization

Rapid non-destructive 100% headspace moisture inspection enables:

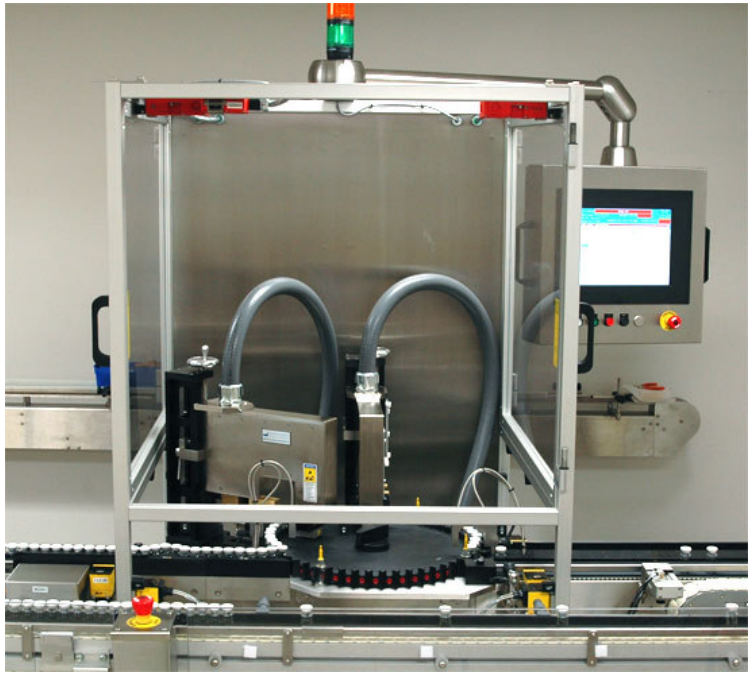
- Insight into freeze dryer specific effects on final product:
  - Thermal properties of shelves, trays
  - Loading conditions
  - Container used
  - Freeze dryer capacity

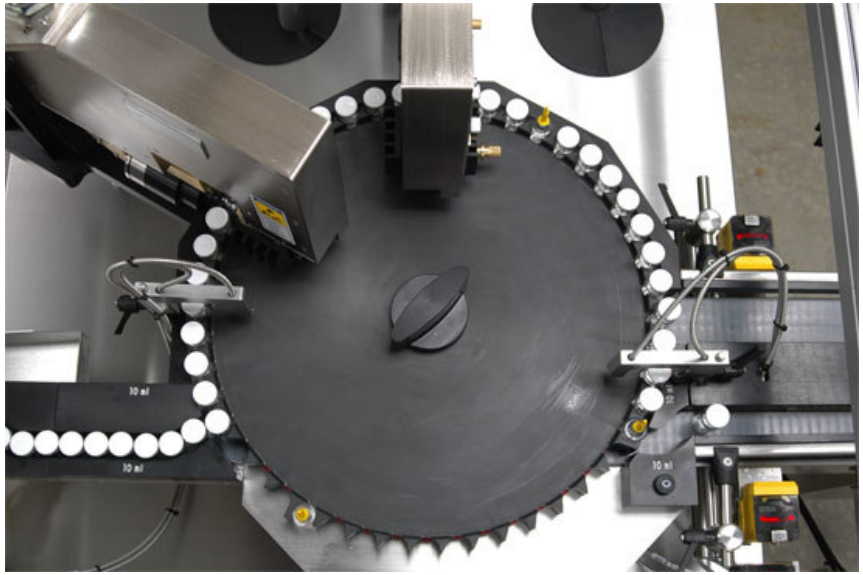
Automated Headspace Inspection

- Trend towards in-line process monitoring and 100% control of finished product
  - Regulatory drivers
  - Better process understanding enables a better risk-based approach
- Automated Headspace Inspection implemented since 2003
  - Primary application has been 100% container closure inspection
  - Current headspace implementations now being validated for 100% lyo moisture inspection

Total Headspace Characterization™

- Quantifying the physical headspace conditions
- Headspace oxygen, nitrogen pressure, & moisture



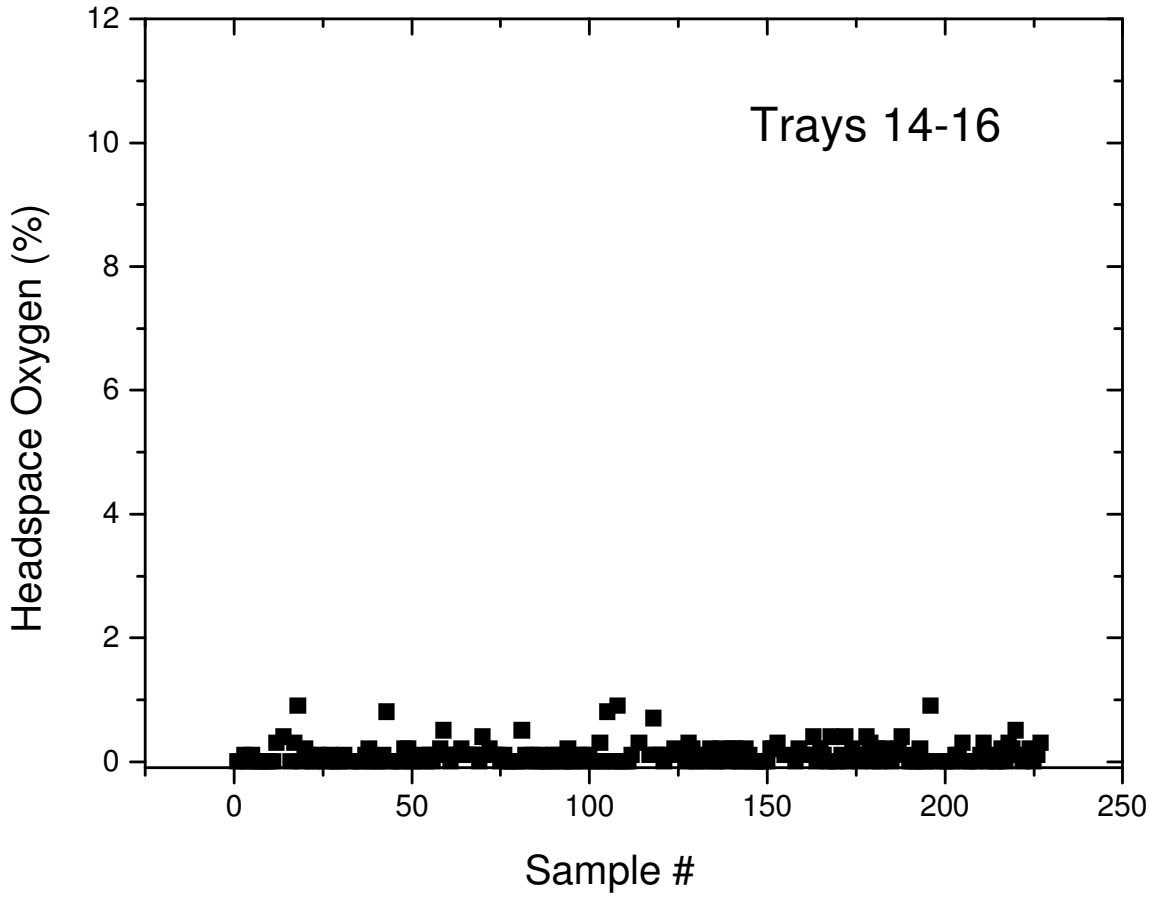


Inspection case study: Investigation of commercial batch

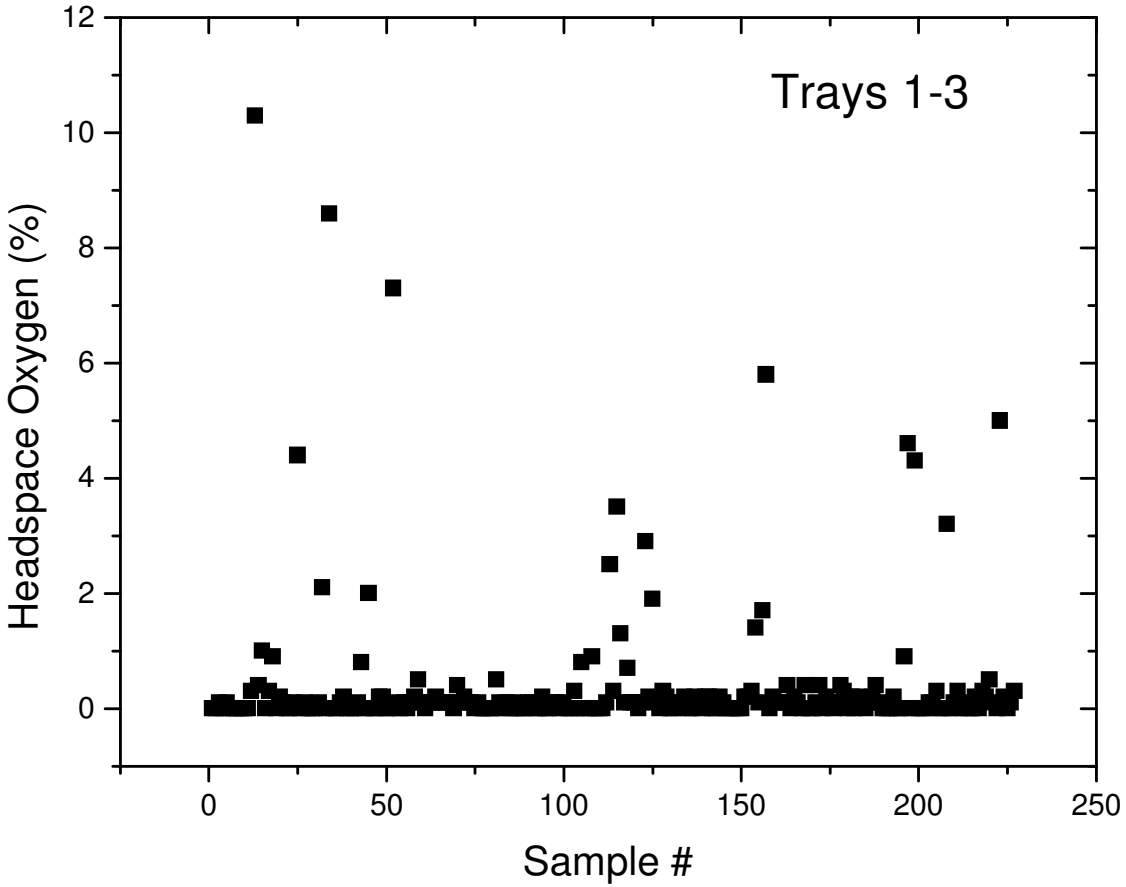
Evaluation of O2% for Oxygen-Sensitive Lyo Product

- The Objective:
  - Test for headspace oxygen in a commercial batch of oxygen-sensitive lyo product (10ml vial stoppered at 800 mbar nitrogen).
  - QC release tests showed high O2 content in statistical sampling of vials.
- The Inspection Activity:
  - Measure headspace oxygen on trays of product segmented by location in freeze dryer
  - Reject product with >1% oxygen

Inspection Results 'Good' trays



Inspection Results 'Bad' trays



Inspection Results: Failures as a function of tray position

Specified stoppering pressure:
800 mbar nitrogen

Reject limit: > 1% O2

Tray	Fail %	Tray	Fail %
1	12.8	9	0
2	6.7	10	1.1
3	7.7	11	6.3
4	1.6	12	0
5	0	13	0
6	1.1	14	0
7	2.2	15	0
8	0	16	0

Failures were in trays at the shelf edges - mechanical issue?

Inspection case study: Conclusions

- Non-destructive headspace inspection enabled 100% inspection of the batch.
- Analysis showed that four trays had a significant percentage (> 5%) of closure failures.
- Mapping of the container closure failures showed problems in trays located at the shelf edges in the lyo chamber.
- Results indicated a possible mechanical issue with the stoppering process.