Headspace Moisture and Water Activity Applications for Lyophilized Product

Rapid non-destructive moisture determination using headspace analysis

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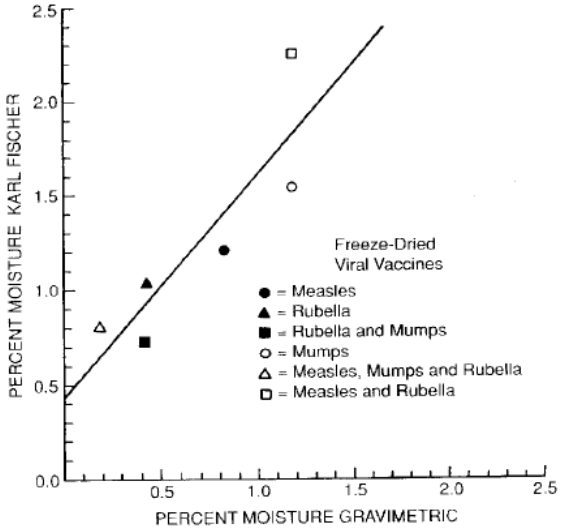
Moisture determination – a short history

- Thirty years ago the gravimetric or loss-on-drying method was the standard moisture determination method for freeze-dried pharmaceutical product.
  - Karl-Fischer (KF) titration used more frequently as a new method starting in the early 90's.
  - Total moisture content measured by both methods was different – so people started with correlation studies.



[Ref.] *Measurement of Final Container Residual Moisture in Freeze-Dried Biological Products,* Internatioal Symposium on Biological Product Freeze-Drying and Formulation, Bethesda, USA, 1990; Developm. biol. Standard., Vol. 74, pp. 153-164 (Karger, Basel, 1991)

Moisture determination – a short history

- Disadvantages of the standard moisture determination methods:
  - Risk of moisture contamination is high - methods dependent on operator skill
  - Methods are time & resource intensive
  - Methods are destructive meaning high value samples are lost

Very difficult (impossible) to analyze statistical sample sets of finished product:

- **Insight into the drying process is limited**
- **Accuracy of moisture stability specifications also limited** due to destructive analysis and assumptions about identical stability samples

Loss on drying → **KF Titration** → **NIR?** → **Find a better method?**

Why? Regulator- understand your process & product, 'statistical confidence in the process'

Agenda

- Headspace moisture analysis - Introduction
  - Comparison to standard moisture methods
  - Relation to water activity
- Application examples / Industry case studies
  - Formulation development
  - Process optimization and scale up
  - Manufacturing & QC
- Q & A

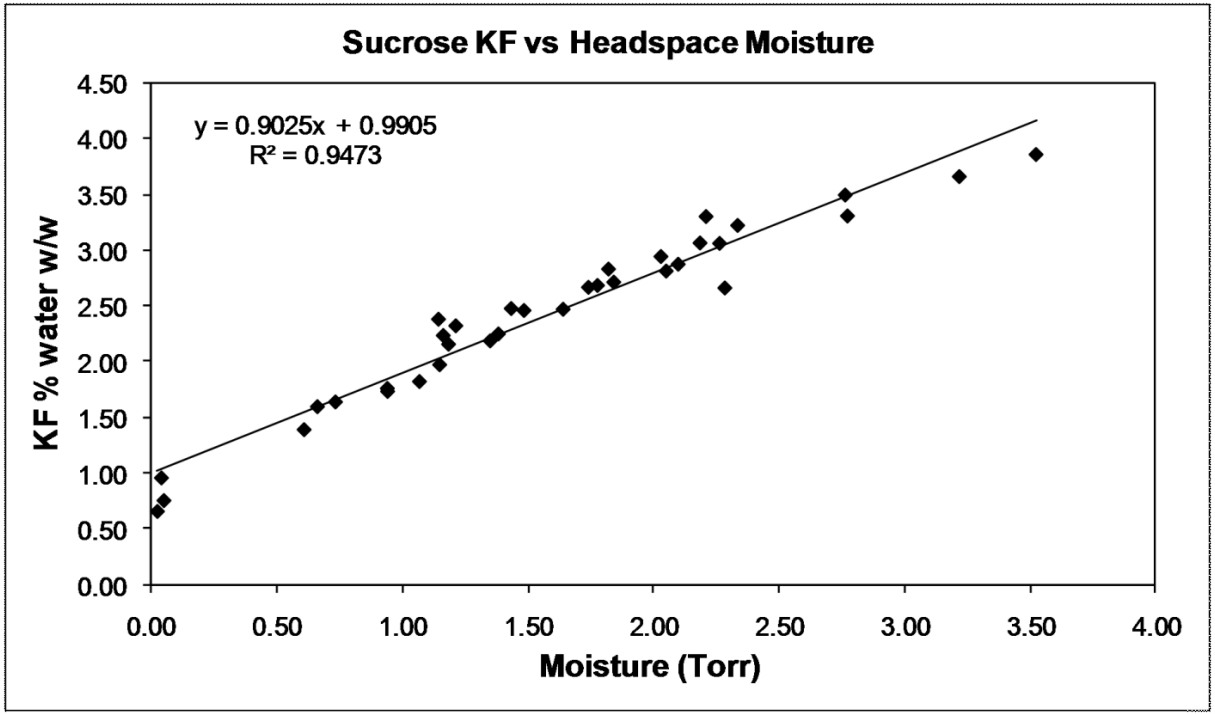
Headspace Moisture

Total moisture (Karl-Fischer)

Headspace moisture (laser-based headspace)

Cake moisture (loss on drying, …NIR)

Headspace Moisture – correlation with total moisture content



[Ref.] Isobel Cook and Kevin Ward (2011), Headspace Moisture Mapping and the Information That Can Be Gained about Freeze-Dried Materials and Processes PDA J Pharm Sci Technol September/October 2011 65:457-467

Water activity definition – thermodynamic property

- **Water activity,** or a_w is the **partial vapor pressure of water** in a substance divided by the standard state partial vapor pressure of water.
  - Indicates how much ‘free’ water is available for chemical reaction
  - A water activity of 0.80 means the vapor pressure is 80% of that of pure water

Introduction to USP<922> Water Activity Chapter

USP<922> Water Activity implemented in Q1 2021.

- "Total water content is an important quality attribute…However, water may be allocated in more than one compartment within these materials. Some of it may be tightly bound and not available to participate in chemical, biochemical, or physicochemical reactions (e.g., as hydrate salts), whereas some of the water may be more loosely bound and more freely available to participate in reactions... It is important to establish what fraction of the total water is contained in the latter category, and the determination of water activity (a_w) provides this information."

- "The determination of a_w aids in decisions during ingredient and product processes design, ingredient selection, packaging selection, and product storage. These include:
  - …
  - Reducing the degradation of active ingredients within product formulations, especially those susceptible to chemical hydrolysis
  - …
  - Providing a complementary method to the Karl Fischer titration for monitoring changes in water content
  - Controlling and monitoring physical, chemical, and microbial product stability
  - …"

Headspace moisture analysis = water activity determination

Non-destructive (product not lost, sample can be re-measured)
Rapid (~1 sec)

- Measurement of the water vapor pressure in a sealed container at a defined temperature is a water activity determination.
- Measurement concept can be applied to general containers containing dry material.
- **There will be a trend to replace some total moisture measurements with a water activity determination – USP <922>.**

Example Headspace Platforms for Non-destructive Lyo Moisture Analysis

Benchtop instruments: Laboratory and At-line Instruments & accessories

Inspection Machines: Automated, compact and flexible

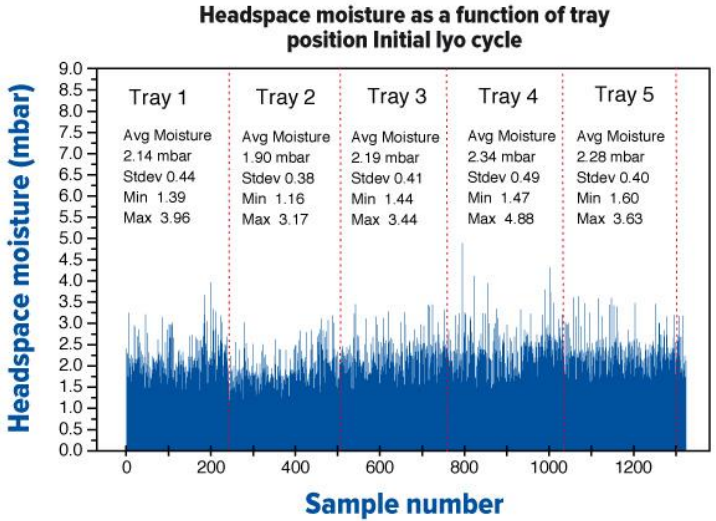
Moisture determination – need for a better toolbox

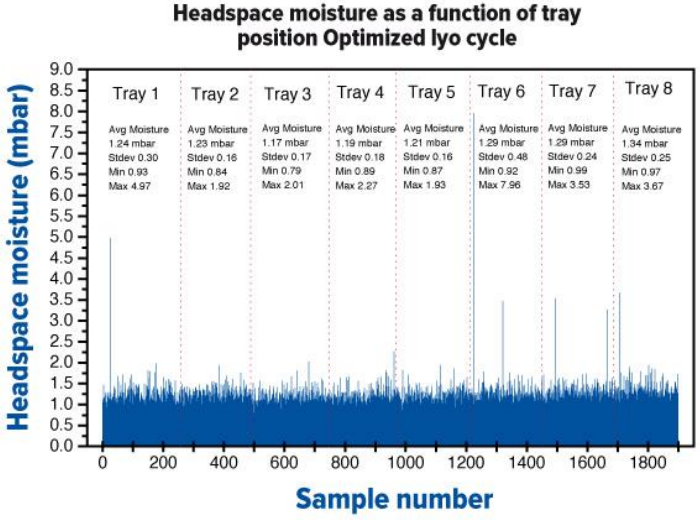
For process development and scale-up

- Driving quality in the pharma industry:
  - Regulators asking for more analytical data (QbD, validation, monitor & control)
  - **FDA** process validation guidance: **'Statistical confidence in the process'**
  - 'Collection and evaluation of data, from the process design phase throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.'
- Analysis of **statistically relevant sample sets of finished product** gives insight enabling decisions that are justified by science-based data
- There is no 'gold standard' moisture method – need broader toolbox!

Example: Robust efficient lyo cycle optimization

- Headspace water vapor correlates to product dryness
- 100% headspace moisture determination to characterize and optimize freeze drying cycle



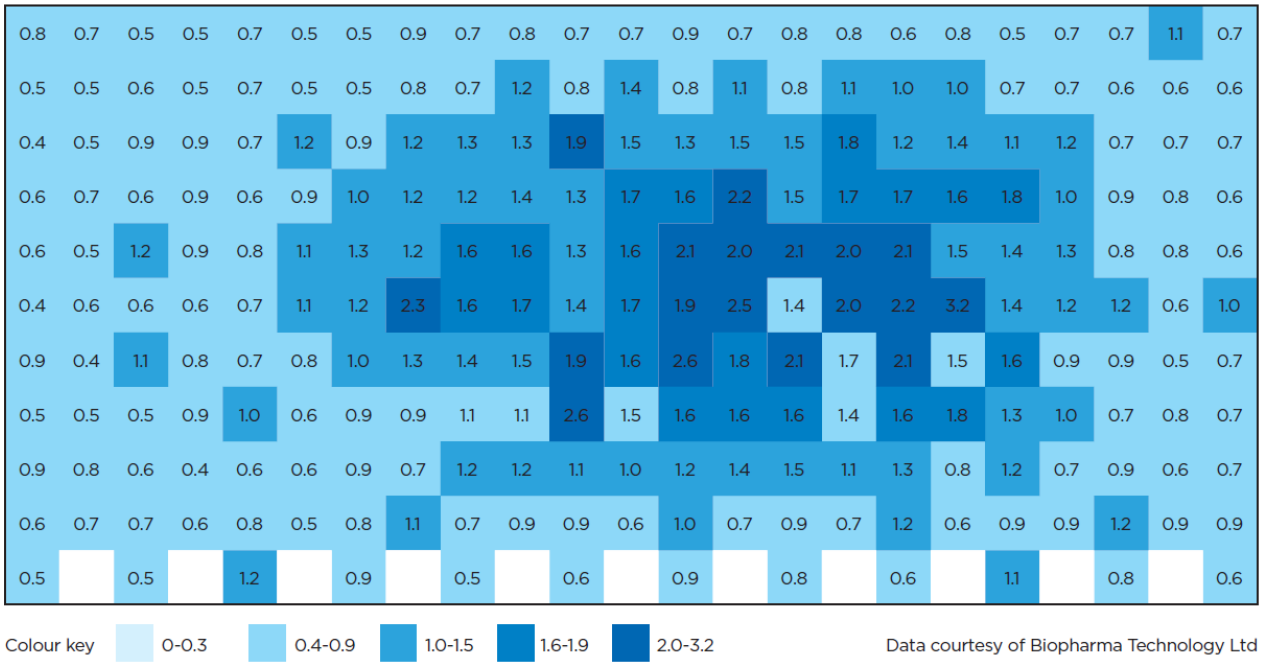


Total analysis time (both batches): ~ 1 day!

Example: Accurate lyo shelf moisture mapping

Low value 0.4 torr = 1% KF
High value 3.2 torr = 4% KF

- Track vial location on the shelf
- Perform 100% headspace moisture analysis to produce shelf moisture map

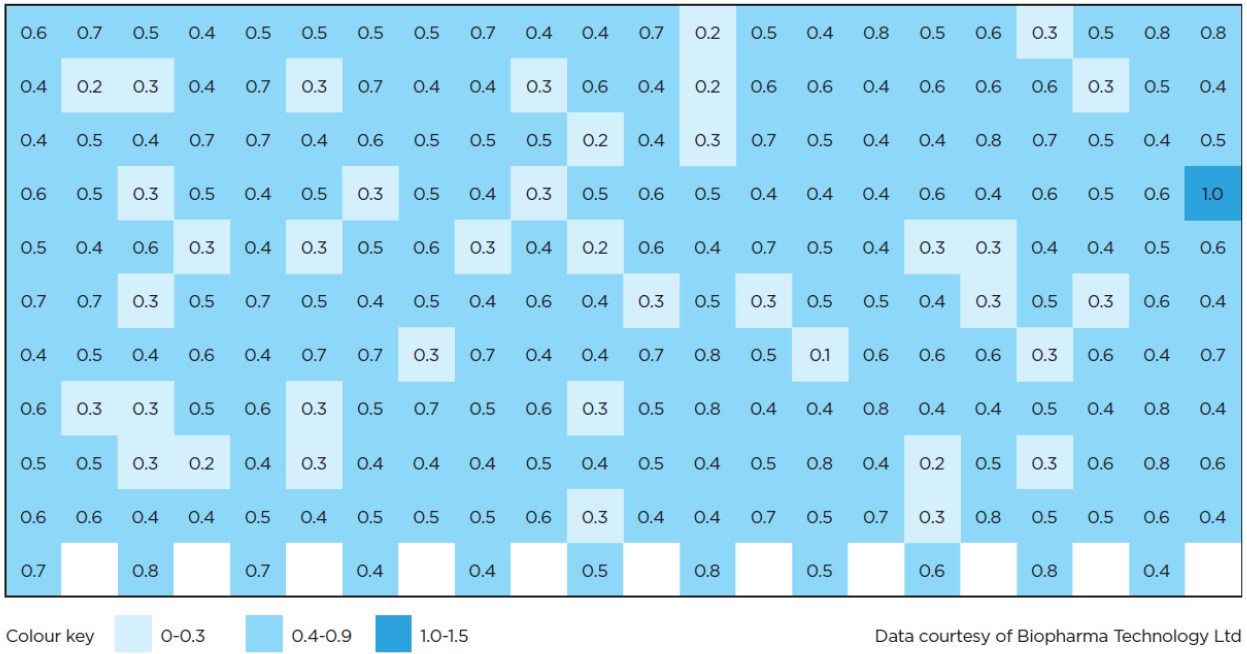


Headspace moisture plot shows ‘wet spot’ in center of shelf

Example: Accurate lyo shelf moisture mapping

Low value 0.2 torr = 1% KF
High value 1.0 torr = 1.8% KF

- Same cycle produced 2nd batch
- Improving heat transfer to the vials resulted in homogenous moisture distribution.



Total analysis time per shelf of pilot freeze dryer < 1 hour!

Industry case study: Demonstrating freeze dryer equivalence

- Model: 5% sucrose solution, 6R vials, 2.5 ml fill
- Full headspace moisture analysis of shelf:
  - Water vapor range of 0.65 to 2.04 mbar correlated to 0.8 to 1.4 % (KF)
  - Headspace results clearly show an inhomogeneous batch
- Edge effects front and side result in lower values at front and side positions (acrylic door, covered with stainless steel plate)

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

Industry case study: Demonstrating freeze dryer equivalence

- Model: 5% sucrose solution
- Full headspace moisture analysis of shelf:
  - 0.18 to 3.79 mbar, i.e. 0.6% to 2.2% KF
  - More inhomogeneous batch
- Cake appearance acceptable, minor shrinkage in some vials
- Edge effects front, back and side result in lower values (stainless steel door)

FD04 5% sucrose

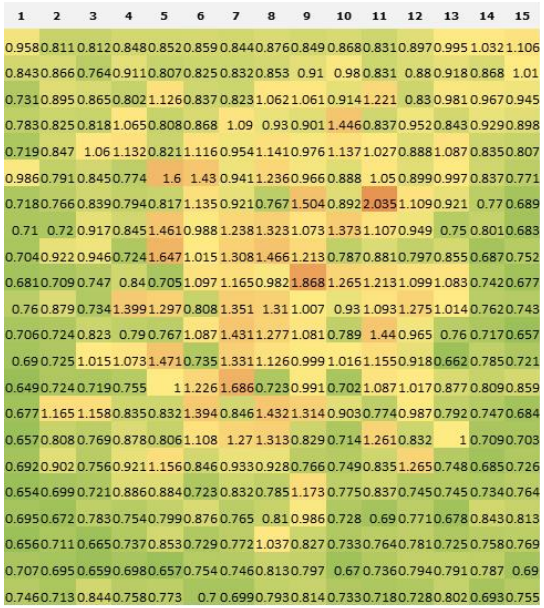
SH2

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0,379	0,358	0,434	0,389	0,361	0,378	0,366	0,357	0,184	0,465	0,37	0,366	0,38	0,388	0,399
0,362	0,342	0,481	0,361	0,724	0,401	0,483	0,433	0,369	0,647	0,369	0,433	0,483	0,469	0,339
0,321	0,514	0,411	1,765	0,691	0,556	0,942	1,684	1,448	0,867	1,779	0,76	1,103	0,398	0,369
0,414	1,166	2,279	0,701	0,936	1,52	1,245	1,912	0,644	0,599	0,944	1,194	0,734	0,627	0,351
0,314	0,434	1,781	2,45	1,222	0,978	1,355	0,609	2,214	1,23	2,338	1,149	1,935	0,746	0,448
0,435	0,851	1,363	0,657	1,437	0,727	1,364	2,411	1,397	2,607	2,705	1,178	1,808	0,552	0,32
0,39	0,439	0,515	2,332	1,569	2,863	3,314	0,796	0,815	0,671	2,009	2,124	0,806	0,435	0,356
0,419	1,044	1,344	0,868	2,009	2,887	2,36	1,791	2,045	2,154	1,073	0,881	0,738	0,548	0,343
0,324	0,51	2,236	1,741	0,861	1,579	3,786	2,423	0,558	2,298	0,857	3,309	1,881	0,669	0,408
0,408	0,421	1,537	2,209	2,348	0,604	3,19	1,626	1,831	2,212	0,795	2,845	1,278	0,493	0,325
0,305	1,504	1,257	1,083	1,698	1,799	2,104	1,63	1,624	2,199	2,284	0,896	2,069	1,529	0,395
0,488	0,804	0,504	3,424	0,602	3,228	1,459	2,468	2,233	1,008	1,876	0,701	2,491	0,747	0,483
0,336	0,694	0,935	1,43	1,388	2,623	0,913	1,828	2,009	0,793	1,93	1,001	2,921	1,918	0,443
0,4	0,515	2,229	1,095	1,452	2,353	2,917	2,318	2,467	2,45	0,804	2,731	1,434	0,53	0,357
0,437	0,4	0,481	1,381	1,302	2,294	2,495	3,326	3,278	0,658	2,368	1,241	0,785	0,504	0,39
0,366	0,906	3,334	3,688	1,201	2,144	1,051	1,202	2,837	1,399	2,307	2,965	1,256	0,384	0,363
0,301	0,369	2,257	1,301	1,004	2,114	1,919	2,571	2,187	2,045	0,63	2,032	0,707	0,751	0,355
0,335	0,45	0,519	2,507	1,388	1,109	1,045	1,202	0,615	2,912	1,841	2,991	1,494	0,455	0,359
0,305	0,359	0,782	1,541	1,199	0,578	1,669	0,49	1,303	2,892	0,815	2,355	1,55	0,416	0,424
0,34	0,378	0,675	0,483	0,584	0,657	0,667	0,705	0,97	0,792	1,29	0,398	0,591	0,417	0,431
0,338	0,399	0,452	0,34	0,388	0,395	0,36	0,353	0,516	0,473	0,38	0,394	0,378	0,374	0,486
0,342	0,393	0,356	0,379	0,376	0,351	0,38	0,367	0,361	0,392	0,363	0,401	0,352	0,364	0,358

Industry case study: Demonstrating freeze dryer equivalence

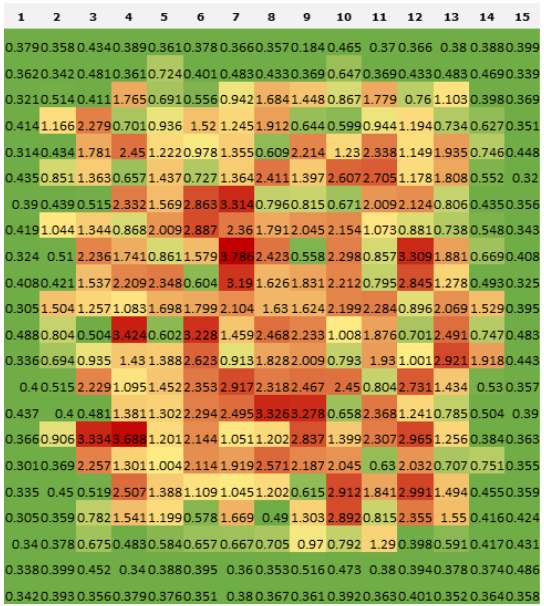
5% sucrose, lyophilized with **non-optimized cycle** on two different freeze-dryers

Freeze-dryer Nr 1



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

Freeze-dryer Nr 2



1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.379	0.358	0.434	0.389	0.361	0.378	0.366	0.357	0.184	0.465	0.37	0.366	0.38	0.388	0.399
0.362	0.342	0.481	0.361	0.724	0.401	0.483	0.433	0.369	0.647	0.369	0.433	0.483	0.469	0.339
0.321	0.514	0.411	1.765	0.691	0.556	0.942	1.684	1.448	0.867	1.779	0.76	1.103	0.398	0.369
0.414	1.166	2.279	0.701	0.936	1.52	1.245	1.912	0.644	0.599	0.944	1.194	0.734	0.627	0.351
0.314	0.434	1.781	2.45	1.222	0.978	1.355	0.609	2.214	1.23	2.338	1.149	1.935	0.746	0.448
0.435	0.851	1.363	0.657	1.437	0.727	1.364	2.411	1.397	2.607	2.705	1.178	1.808	0.552	0.32
0.39	0.439	0.515	2.332	1.569	2.863	3.314	0.796	0.815	0.671	2.009	2.124	0.806	0.435	0.356
0.419	1.044	1.344	0.868	2.009	2.887	2.36	1.791	2.045	2.154	1.073	0.881	0.738	0.548	0.343
0.324	0.51	2.236	1.741	0.861	1.579	3.786	2.423	0.558	2.298	0.857	3.309	1.881	0.669	0.408
0.408	0.421	1.537	2.209	2.348	0.604	3.19	1.626	1.831	2.212	0.795	2.845	1.278	0.493	0.325
0.305	1.504	1.257	1.083	1.698	1.799	2.104	1.63	1.624	2.199	2.284	0.896	2.069	1.529	0.395
0.488	0.804	0.504	3.424	0.602	3.228	1.459	2.468	2.233	1.008	1.876	0.701	2.491	0.747	0.483
0.336	0.694	0.935	1.43	1.388	2.623	0.913	1.828	2.009	0.793	1.93	1.001	2.921	1.918	0.443
0.4	0.515	2.229	1.095	1.452	2.353	2.917	2.318	2.467	2.45	0.804	2.731	1.434	0.53	0.357
0.437	0.4	0.481	1.381	1.302	2.294	2.495	3.326	3.278	0.658	2.368	1.241	0.785	0.504	0.39
0.366	0.906	3.334	3.688	1.201	2.144	1.051	1.202	2.837	1.399	2.307	2.965	1.256	0.384	0.363
0.301	0.369	2.257	1.301	1.004	2.114	1.919	2.571	2.187	2.045	0.63	2.032	0.707	0.751	0.355
0.335	0.45	0.519	2.507	1.388	1.109	1.045	1.202	0.615	2.912	1.841	2.991	1.494	0.455	0.359
0.305	0.359	0.782	1.541	1.199	0.578	1.669	0.49	1.303	2.892	0.815	2.355	1.55	0.416	0.424
0.34	0.378	0.675	0.483	0.584	0.657	0.667	0.705	0.97	0.792	1.29	0.398	0.591	0.417	0.431
0.338	0.399	0.452	0.34	0.388	0.395	0.36	0.353	0.516	0.473	0.38	0.394	0.378	0.374	0.486
0.342	0.393	0.356	0.379	0.376	0.351	0.38	0.367	0.361	0.392	0.363	0.401	0.352	0.364	0.358

Industry case study: Demonstrating freeze dryer equivalence

5% sucrose, **2.5% BSA**, lyophilized with an **optimized cycle** on the two different freeze-dryers

Headspace moisture analysis of statistical sample sets enabled efficient cycle optimization and clear demonstration of freeze dryer equivalence

Freeze-dryer Nr 1

FD02 5% sucr 25 mg/ml BSA

Sh3

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.32	0.32	0.34	0.35	0.34	0.37	0.35	0.33	0.33	0.40	0.44	0.38	0.39	0.59	0.54
0.36	0.33	0.33	0.34	0.39	0.35	0.35	0.41	0.39	0.46	0.35	0.39	0.42	0.40	0.31
0.35	0.40	0.35	0.49	0.37	0.35	0.44	0.37	0.51	0.45	0.36	0.35	0.41	0.43	0.43
0.41	0.33	0.33	0.43	0.36	0.55	0.40	0.48	0.48	0.41	0.44	0.40	0.40	0.35	0.35
0.31	0.46	0.35	0.39	0.39	0.43	0.39	0.46	0.53	0.47	0.54	0.40	0.38	0.38	0.34
0.46	0.34	0.34	0.36	0.35	0.52	0.41	0.39	0.51	0.40	0.47	0.38	0.37	0.37	0.29
0.35	0.39	0.35	0.41	0.40	0.45	0.37	0.43	0.42	0.50	0.41	0.42	0.38	0.37	0.36
0.41	0.37	0.38	0.53	0.35	0.38	0.45	0.45	0.57	0.41	0.38	0.37	0.37	0.35	0.33
0.35	0.38	0.35	0.40	0.51	0.46	0.38	0.37	0.43	0.54	0.38	0.39	0.47	0.31	0.28
0.31	0.34	0.42	0.35	0.40	0.60	0.38	0.37	0.42	0.40	0.38	0.44	0.33	0.30	0.31
0.30	0.32	0.33	0.34	0.37	0.39	0.65	0.61	0.42	0.66	0.47	0.45	0.34	0.31	0.27
0.31	0.46	0.35	0.34	0.38	0.40	0.47	0.37	0.45	0.59	0.42	0.32	0.32	0.26	0.29
0.30	0.32	0.43	0.51	0.55	0.54	0.35	0.44	0.38	0.39	0.36	0.33	0.42	0.29	0.29
0.39	0.45	0.31	0.51	0.42	0.37	0.44	0.40	0.62	0.44	0.47	0.33	0.29	0.30	0.31
0.37	0.33	0.31	0.47	0.36	0.46	0.65	0.37	0.44	0.50	0.42	0.33	0.30	0.30	0.30
0.37	0.41	0.41	0.34	0.41	0.60	0.43	0.49	0.45	0.55	0.34	0.44	0.34	0.30	0.26
0.39	0.34	0.34	0.46	0.38	0.48	0.43	0.34	0.44	0.34	0.38	0.33	0.30	0.29	0.30
0.35	0.45	0.43	0.57	0.38	0.52	0.59	0.38	0.48	0.46	0.49	0.35	0.30	0.29	0.26
0.34	0.28	0.35	0.34	0.39	0.34	0.41	0.51	0.50	0.43	0.40	0.39	0.34	0.30	0.31
0.33	0.31	0.41	0.35	0.39	0.38	0.39	0.31	0.36	0.32	0.32	0.38	0.32	0.31	0.25
0.28	0.33	0.34	0.28	0.31	0.26	0.30	0.32	0.33	0.31	0.29	0.30	0.27	0.28	0.26
0.27	0.27	0.27	0.30	0.35	0.30	0.28	0.27	0.31	0.29	0.31	0.26	0.36	0.35	0.25

Freeze-dryer Nr 2

FD04 5% sucrose 25 mg/ml BSA

Sh3

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
0.201	0.23	0.198	0.285	0.221	0.212	0.246	0.225	0.246	0.242	0.189	0.273	0.233	0.205	0.195
0.223	0.299	0.238	0.317	0.267	0.335	0.254	0.243	0.354	0.191	0.312	0.237	0.211	0.185	0.204
0.234	0.244	0.372	0.297	0.402	0.311	0.435	0.512	0.385	0.297	0.255	0.359	0.371	0.243	0.218
0.323	0.272	0.439	0.5	0.373	0.361	0.398	0.407	0.405	0.376	0.458	0.325	0.377	0.295	0.261
0.245	0.259	0.384	0.446	0.379	0.51	0.298	0.323	0.387	0.272	0.21	0.382	0.274	0.185	0.265
0.297	0.271	0.456	0.324	0.331	0.401	0.458	0.469	0.464	0.482	0.323	0.43	0.302	0.279	0.211
0.212	0.313	0.44	0.367	0.428	0.368	0.248	0.266	0.367	0.397	0.377	0.499	0.355	0.274	0.293
0.284	0.252	0.368	0.246	0.408	0.353	0.434	0.347	0.433	0.393	0.388	0.285	0.416	0.291	0.266
0.217	0.316	0.306	0.434	0.363	0.499	0.361	0.32	0.406	0.461	0.303	0.409	0.312	0.429	0.325
0.27	0.383	0.397	0.355	0.422	0.377	0.466	0.551	0.294	0.429	0.32	0.282	0.38	0.278	0.26
0.19	0.32	0.239	0.495	0.531	0.359	0.412	0.108	0.478	0.328	0.358	0.306	0.32	0.273	0.336
0.387	0.305	0.375	0.335	0.455	0.63	0.486	0.381	0.398	0.424	0.418	0.214	0.406	0.369	0.208
	0.346	0.435	0.513	0.371	0.382	0.487	0.484	0.475	0.319	0.337	0.299	0.361	0.284	0.315
0.209	0.258	0.318	0.583	0.503	0.372	0.495	0.341	0.448	0.451	0.387	0.349	0.287	0.384	0.205
0.195	0.328	0.463	0.549	0.377	0.581	0.379	0.415	0.563	0.432	0.449	0.334	0.279	0.314	0.252
0.289	0.279	0.32	0.482	0.476	0.646	0.442	0.317	0.527	0.398	0.404	0.408	0.359	0.301	0.349
0.23	0.336	0.36	0.372	0.361	0.372	0.369	0.482	0.374	0.357	0.344	0.432	0.205	0.285	0.306
0.365	0.306	0.403	0.515	0.36	0.438	0.492	0.396	0.484	0.453	0.355	0.377	0.492	0.385	0.21
0.279	0.339	0.372	0.452	0.319	0.42	0.349	0.763	0.434	0.363	0.421	0.377	0.335	0.295	0.235
0.32	0.26	0.313	0.514	0.296	0.371	0.481	0.443	0.474	0.389	0.329	0.353	0.329	0.3	0.231
0.165	0.206	0.231	0.262	0.324	0.287	0.231	0.233	0.308	0.222	0.319	0.238	0.304	0.22	0.25
0.166	0.18	0.203	0.172	0.17	0.168	0.188	0.172	0.176	0.213	0.225	0.186	0.167	0.199	

• Background

- Substitution of an old freeze dryer into an existing facility during running operations
- Scale-up from 14 m^2 to 28 m^2
- Introduction of improvements such as Point-of-fill filtration
- Determination of intra- and inter-batch variability and systematic QbD approach to comply with recent FDA guidelines

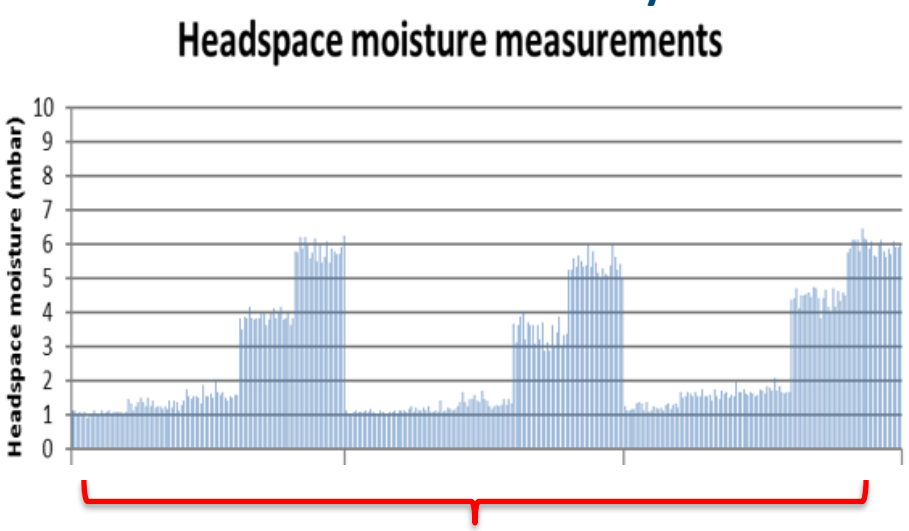
Note: These case study slides were presented at the 2018 PDA Pharmaceutical Freeze Drying Technology conference, Seville, Spain.

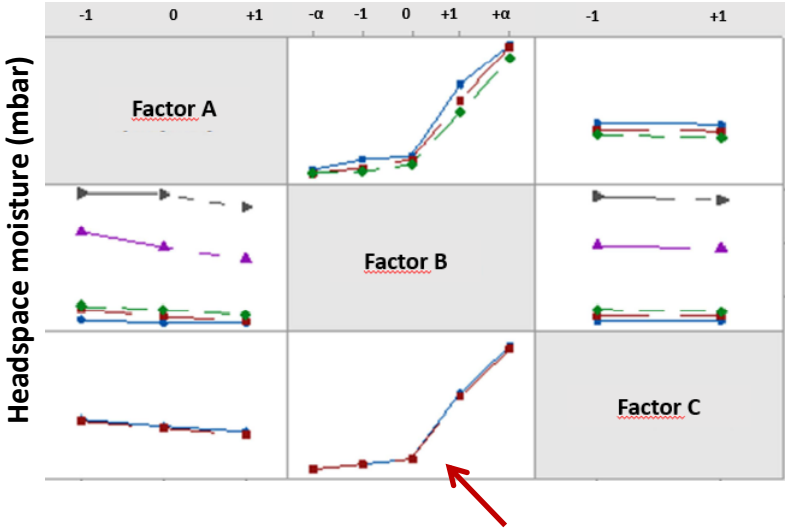
- **Headspace Moisture determination**

- Performance of Design of Experiments in small-scale
- 100% determination of intra-batch variability
- Moisture results were used to analyze the impact and interaction of critical process parameters during freeze drying and process inherent product variability
- Determination of a suitable placebo for full-scale runs based on moisture
- Samples used for moisture analysis were still available for other destructive tests in contrast to Karl-Fischer to allow 1:1 correlation of results

Note: These case study slides were presented at the 2018 PDA Pharmaceutical Freeze Drying Technology conference, Seville, Spain.

Results of DoE small-scale study





- Different lyo cycles to verify design space of the process
- Cycles show comparable moisture pattern and interaction with other parameters

- High dependency of product specific attributes with moisture results
- Results were used to define suitable placebo

Note: These case study slides were presented at the 2018 PDA Pharmaceutical Freeze Drying Technology conference, Seville, Spain.

DoE Study Conclusions

- Proof of concept for full-scale runs to minimize project risk and number of full-scale runs
- Determination of suitable Placebo to mitigate lack of drug substance and minimize costs
- Verification of robust design space
- Process knowledge about interaction of critical parameters and their effect in intra- and inter-batch variability

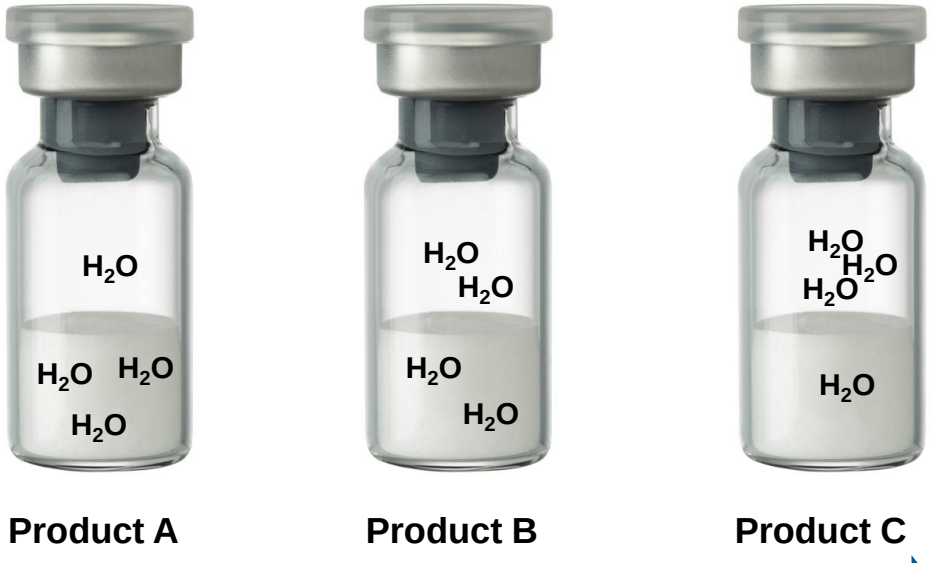
Note: These case study slides were presented at the 2018 PDA Pharmaceutical Freeze Drying Technology conference, Seville, Spain.

USP <922> Headspace moisture as a formal method

- The previous case studies demonstrated that headspace moisture analysis is a very useful analytical tool for gaining statistical insight into process and product quality.

- USP <922> describes headspace moisture (water activity) as a formal moisture determination method that in many cases is more useful than a total moisture content determination.

Moisture content vs. Water activity



Total water content is equal in all product vials.
Ratio of bound to unbound water is different.

Water Activity and Water Content are Different

$Kf \neq a_w$

- Total Water Content measured by Karl Fischer USP<921> is very different than Water Activity USP<922>
- Each ingredient in a formulation has its own unique water activity versus water concentration. This relationship is typically plotted as a sorption isotherm.
- If you change the formulation or the manufacturing process the water activity of the drug product will change.
- Water activity measures the amount of loosely bound water that is available to participate in undesirable chemical, physical, and microbiological reactions.

Industry case study: Water activity method study

- **Motivation:**
  - Replace KF titration with rapid non-destructive method for lyo product moisture determination
  - Assess correlation between headspace water vapor pressure and degradation of a hydrolytic small molecule API
- **Measurements:**
  - Sample sets with range of cake moisture from 0.5-3.0% by weight.
  - Measure initial moisture in headspace (water activity at fixed temperature)
  - Since measurement in non-destructive, the same samples can be put on stability
  - Degradation of the API measured on stability with HPLC
  - Look for correlation between water activity and API degradation

Industry case study: Lyo water activity method study

Correlating headspace moisture directly to product degradation

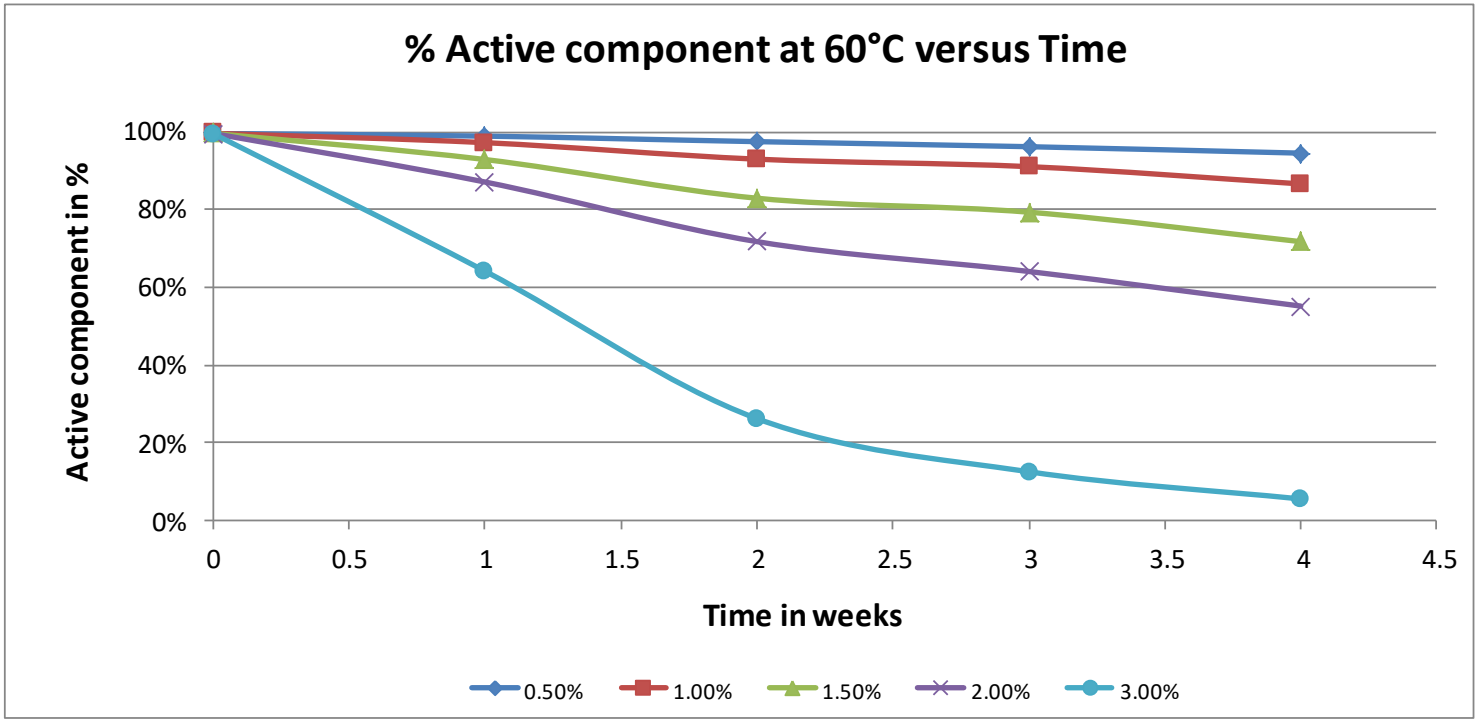
Stability study

Moisture	0.50%	1.00%	1.50%	2.00%	3.00%
25°C	X	X	X	X	X
40°C	X	X	X	X	X
60°C	X	X	X	X	X

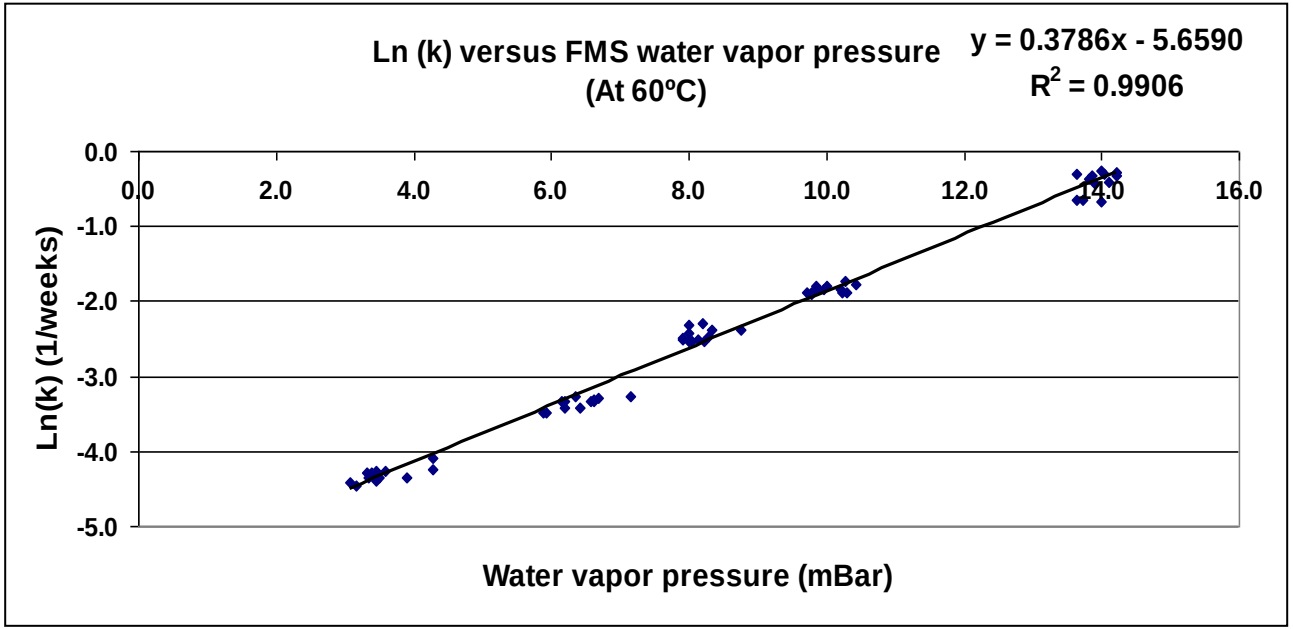
Targeted moisture content groups:	**0.50 %**	**1.00 %**	**1.50 %**	**2.00 %**	**3.00%**
Corresponding water vapor levels:	**4 torr**	**6 torr**	**8 torr**	**10 torr**	**14 torr**

Industry case study: Lyo water activity method study

Product degradation results



Industry case study: Lyo water activity method study



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

- Water vapor (activity) measurement predicts the product stability!
- Potential to replace KF with rapid non-destructive technique for lyo moisture determination

Industry case study: Dynamic Vapor Sorption (DVS) isotherm

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Noninvasive Moisture Detection in Lyophilized Drug Product Using NIR Spectrometer and Headspace Moisture Analyzer

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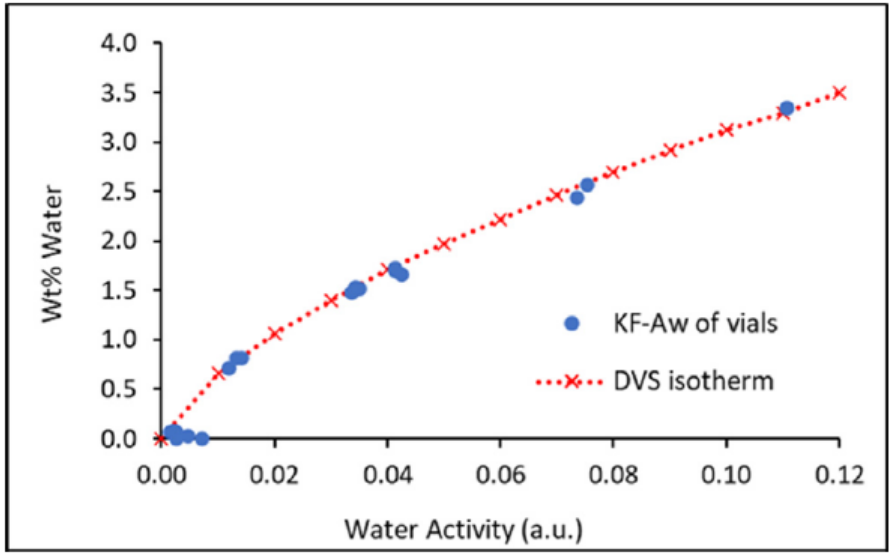
ABSTRACT

Utilization of laser headspace and near-infrared (NIR) methods provides rapid and non-destructive approaches for moisture detection of lyophilized drug products to facilitate lyophilization formulation characterization and process development. In the present study, the NIR method was developed based on a partial least square regression (PLSR) model calibrated and validated with Karl Fisher (KF) data, whereas the laser headspace method was developed with aid of dynamic vapor sorption (DVS) method so that the water vapor pressure measured from the headspace of a lyophilized drug product vial can be converted directly to water content value through the water vapor sorption isotherm of the lyophilized drug product bypassing KF calibration. The water contents of lyophilized samples obtained from both methods agreed well with KF data, with a root mean squared error of prediction (RMSEP) of less than 0.15%. The pros and cons of NIR and laser headspace method were evaluated. The results suggest that traditional off-line KF method can be potentially replaced by at-line laser headspace method combined with water sorption isotherm data from DVS. Further studies may be needed to evaluate the quantitation limit and generality of this method to a variety of lyophilized formulations.

Industry case study: Dynamic Vapor Sorption (DVS) isotherm



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DVS system used to generate a moisture adsorption isotherm for a lyophilized biopharmaceutical formulation

Accurate and precise relationship between residual moisture (Wt % Water) and headspace moisture (water activity or %ERH)

Isotherm can be used to correlate residual moisture to water activity measured using headspace

A rapid non-destructive water activity measurement gives BOTH free water and total water content. Titration not needed anymore.

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Principles and Practices of Lyophilization in Product Development and Manufacturing

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Laser-Based Headspace Moisture Analysis for Rapid Nondestructive Moisture Determination of Lyophilized Products

Derek Duncan, James R. Veale, Ken Victor & Adriaan H. de Goeij

Chapter | First Online: 25 April 2023

215 Accesses

Part of the AAPS Advances in the Pharmaceutical Sciences Series book series (AAPS,volume 59)

Abstract

Residual moisture content is a critical quality parameter for freeze-dried pharmaceutical product and exists in different forms. Only the relatively “free” – in contrast to the more “bound” – water is capable of inducing degradation events within the product. However, traditional moisture analysis techniques employing gravimetric or Karl Fischer (KF) titration methods cannot distinguish between the different water states. Furthermore, these methods

Summary

- Current moisture determination methods for freeze-dried pharmaceutical product (KF titration, LOD methods) give limited insight into process and product quality.
- Headspace moisture analysis is an analytical tool that can be used for formulation development, process optimization, freeze dryer qualification, and as a formal water activity test method to determine product stability.

Appropriate analytical methods needed for a robust science-based understanding of process and product quality – regulators appreciate and encourage such an approach.

Thank you

for your attention!