Headspace Moisture and Water Activity Applications for Lyophilized Product

Rapid non-destructive moisture determination using headspace analysis

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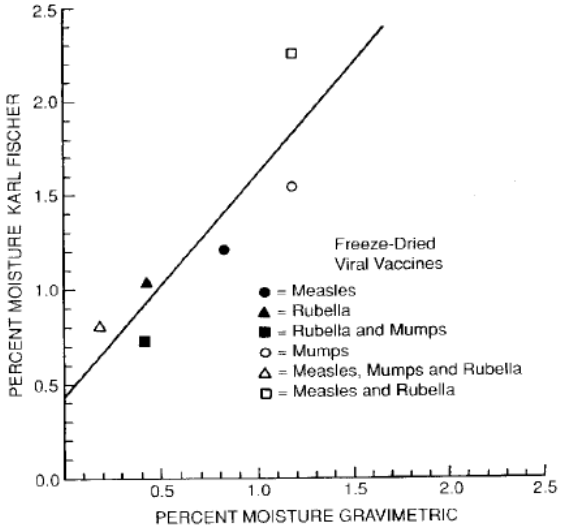
Moisture determination – a short history

- 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

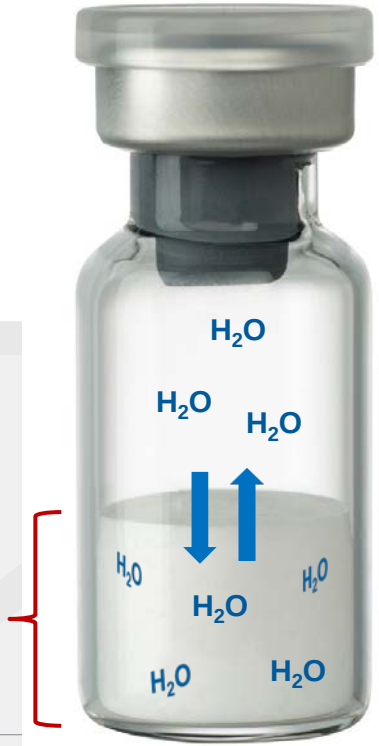
Agenda

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

Freeze dried vial moisture determinations

Where is the water?

Headspace measures free water. Other methods do not distinguish between different forms of water.



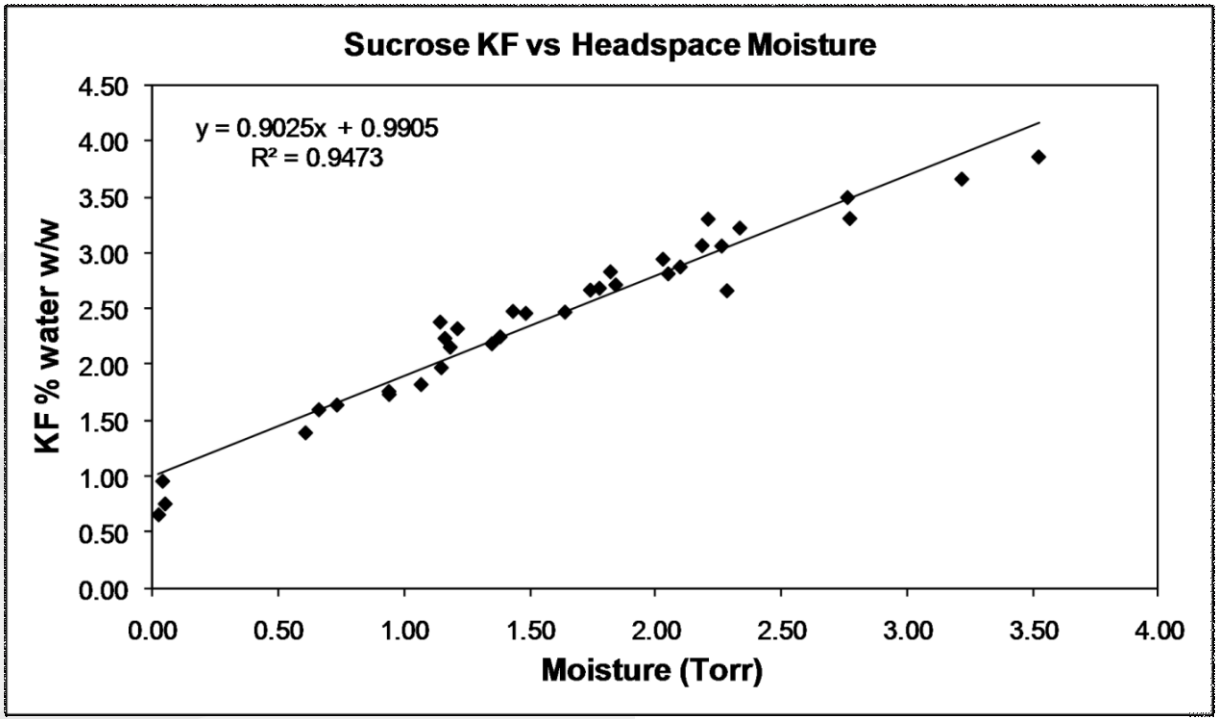
Water activity (a_w) is the **partial vapor pressure of water** at a fixed temperature

Headspace moisture
(laser-based headspace analysis)

Total cake moisture
(Karl-Fischer titration)

Partial 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

Headspace moisture analysis = water activity determination

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

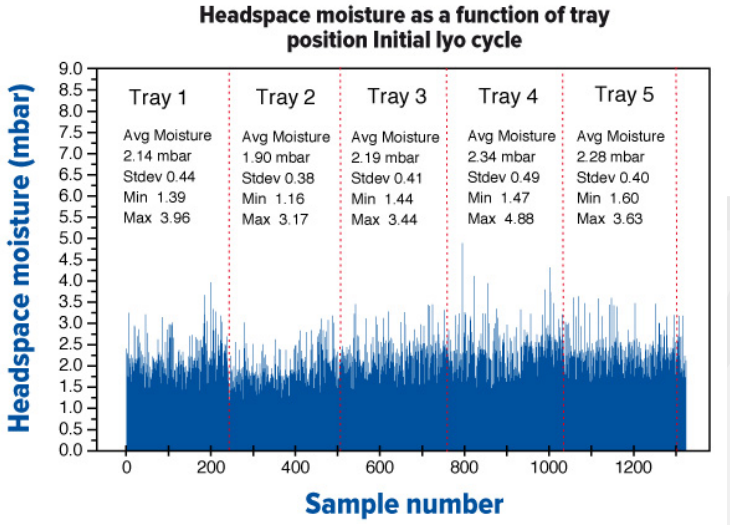
- Measurement of the water vapor pressure in a sealed container at a defined temperature is a water activity determination.
- Measurement concept can be applied to general containers containing dry material.
- **There will be a trend to replace some total moisture measurements with a water activity determination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

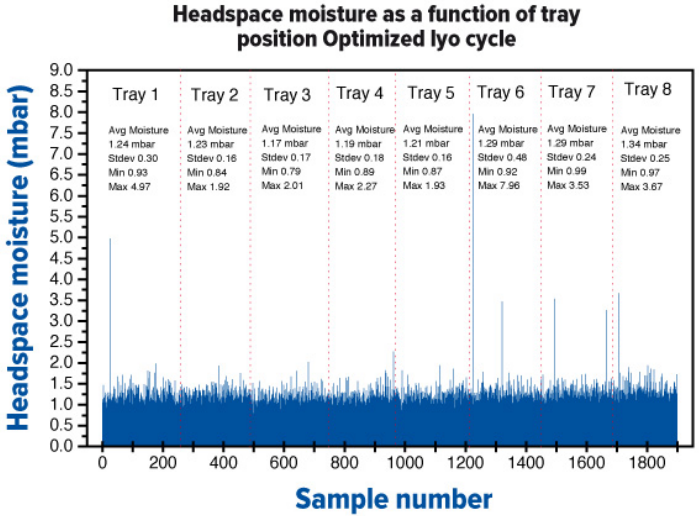
Headspace Platforms for Lyo Moisture Analysis

The same moisture method can be scaled up from manual benchtop platforms, to semi-automated platforms, to automated production scale inspection machines.

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!

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

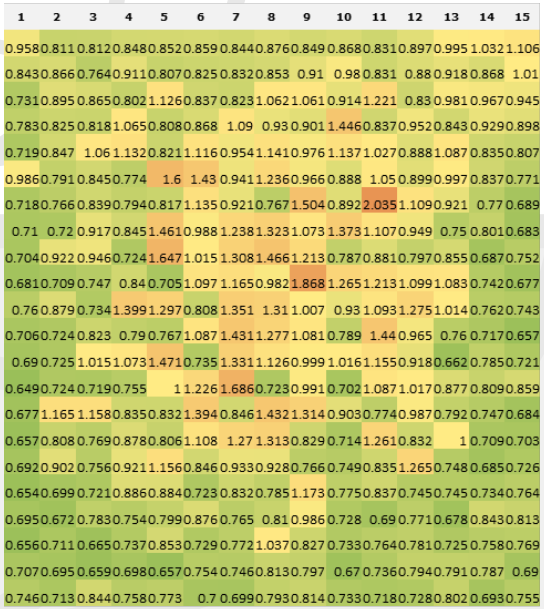
SH2

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

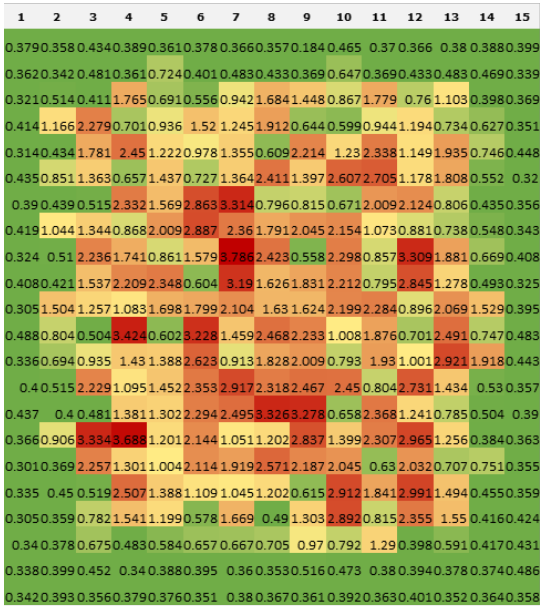
5% sucrose, lyophilized with **non-optimized cycle** on two different freeze-dryers

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	

USP <922> Headspace moisture as a formal method

- The previous case studies demonstrated that headspace moisture analysis gives very accurate and efficient insight into process and product quality during process development and scale-up.

- 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.

What is the optimal water content for a freeze dried formulation?

- **What do you mean by 'water content'?**
  - adsorbed water?
  - chemically bound water?
  - free water?
  - hydration shells (e.g., of proteins)?
  - water of crystallization?

Not just pragmatically, but fundamentally the moisture content paradigm being used by the pharmaceutical industry (total water content) is not the correct one.

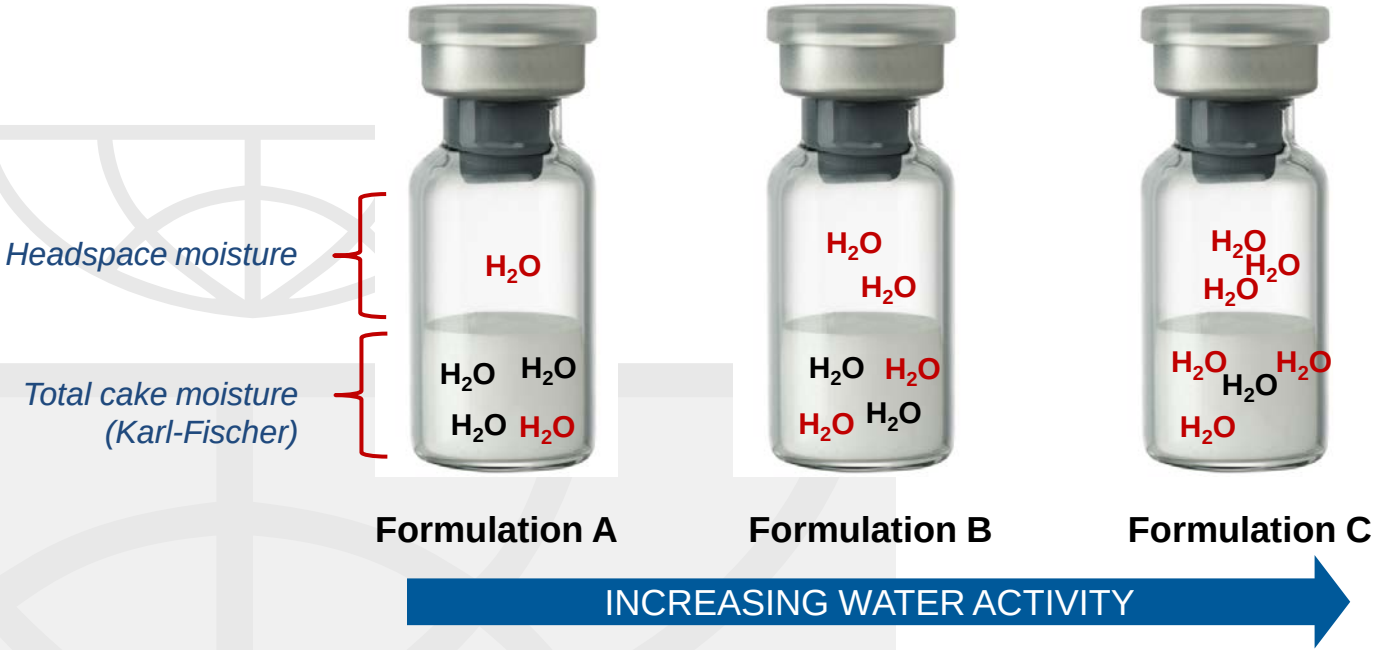
Introduction to USP<922> Water Activity Chapter

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
  - …"

Total water content vs. Water activity



Total water content in the cake is equal in all product vials but the water activity is very different (why? - ratio of bound to unbound water is different).

Industry case study: Correlation of stability to Water Activity (USP <922>)

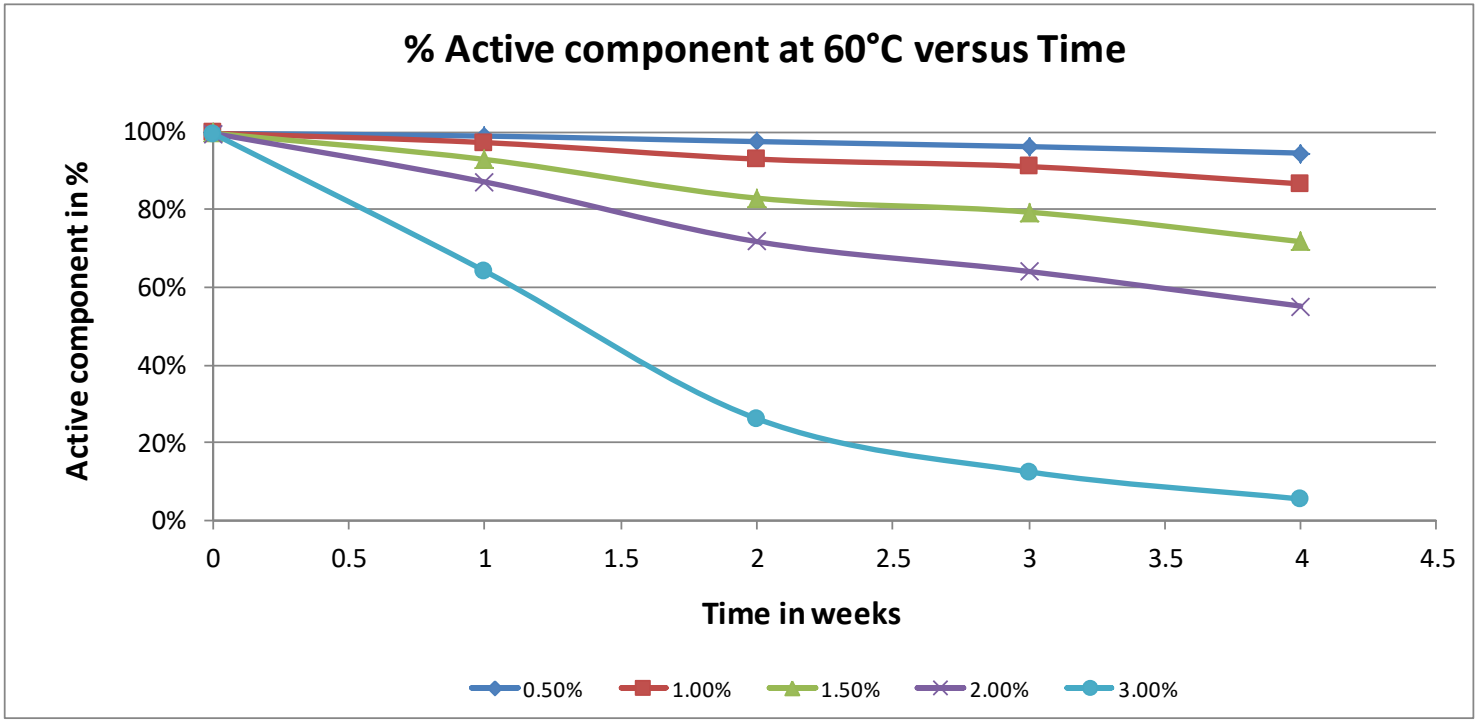
- Assess correlation between headspace water vapor pressure (water activity) and degradation of a hydrolytic small molecule API (mannitol excipient)
- Measure initial headspace moisture of several lyo sample groups
- Since measurement is non-destructive, the same samples can be put on stability
- Degradation of the API measured on stability with HPLC

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

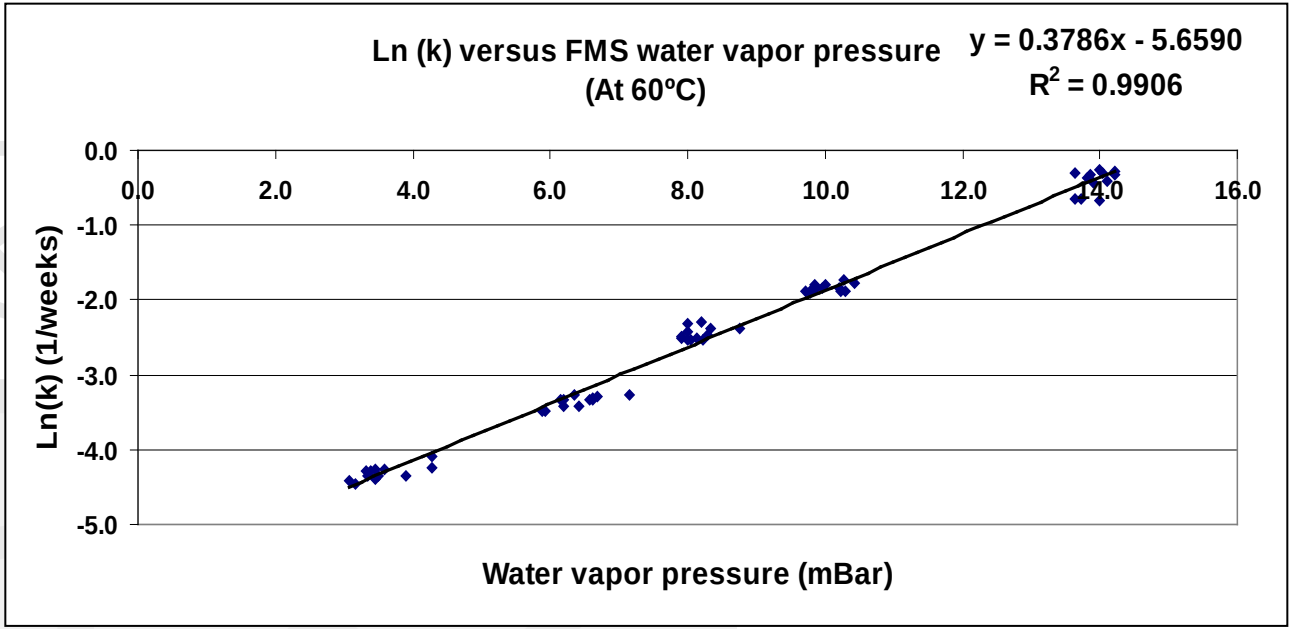
Targeted moisture content groups:	**0.50 %**	**1.00 %**	**1.50 %**	**2.00 %**	**3.00%**
Corresponding water vapor levels:	**4 torr**	**6 torr**	**8 torr**	**10 torr**	**14 torr**

Industry case study: Correlation of stability to Water Activity (USP <922>)

Product degradation results



Industry case study: Correlation of stability to Water Activity (USP <922>)



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

- Correlation of product stability to water activity is exceptional
- **Potential to replace KF with rapid non-destructive technique** for lyo moisture determination

The future of lyo moisture determination?

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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

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

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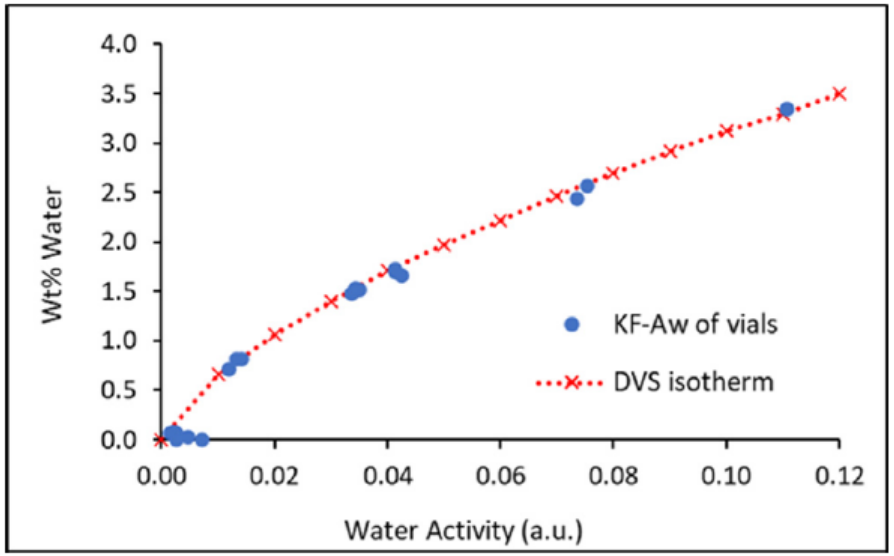
ABSTRACT

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.

The future of lyo moisture determination?



Pu, Yu-Elaine, Ying Li, and Dong Xiang. "Noninvasive Moisture Detection in Lyophilized Drug Product Using NIR Spectrometer and Headspace Moisture Analyzer." *Journal of Pharmaceutical Sciences* (2022). https://doi.org/10.1016/j.xphs.2022.11.009

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

Isotherm correlates water weight gain (Wt % Water) and relative humidity conditions (%ERH water activity) measured in the headspace

After generation of a moisture isotherm, a rapid non-destructive water activity measurement gives both the water activity and water content of a formulation.

KF titration not needed anymore.

New Book Chapter

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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

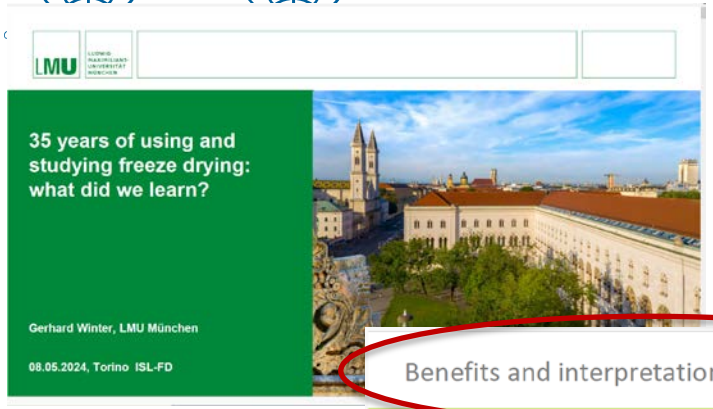
215 Accesses

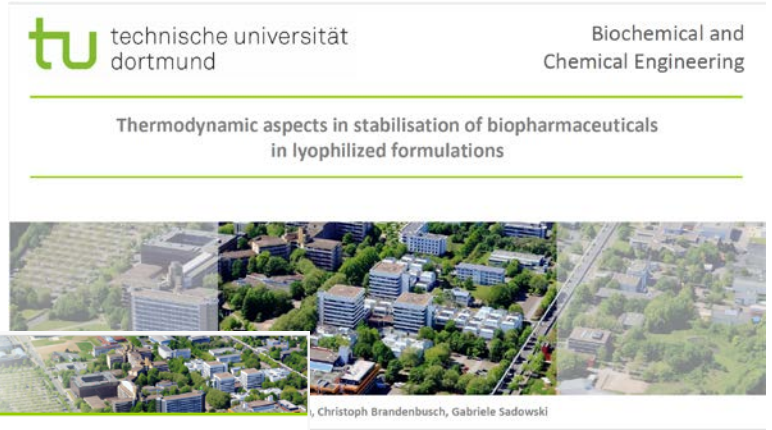
Part of the AAPS Advances in the Pharmaceutical Sciences Series book series (AAPS,volume 59)

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

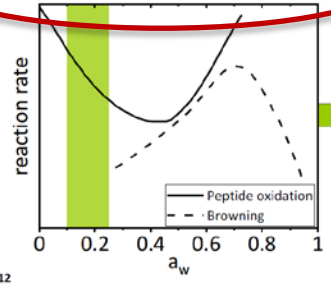
Lyo formulation experts moving towards a_w





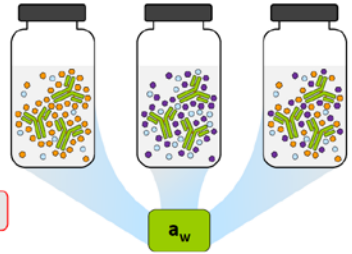
Benefits and interpretation of water activity

- a_w is a **comparable value**
- a_w enables comparison of environments for the antibody
  - ➡ Close to a_w of native antibody in liquid formulation
- Degradation reactions dependent on a_w [1]



$0.10 < a_w < 0.25$

Various excipient (combinations) and residual moistures



Q How is a_w modeled?

[1] Sandulachi, 2012

Summary

- Current moisture determination methods for freeze-dried pharmaceutical product (KF titration, LOD) give limited insight into process and product quality.
- Headspace moisture analysis (water activity) is an analytical tool useful for formulation development, process optimization, freeze dryer qualification, and as a formal water activity test method to determine product stability.
- USP <922> is recommending changing the moisture paradigm from total water content to water activity.

Goal: A robust science-based understanding of process and product quality.

PDA Parenteral Drug Association
Connecting People, Science and Regulation®

Thank you

for your attention!