Time-Dependent Relative Humidity in Nested Packaging

Vanessa M. Breslin, Brooke Tatarian, Maximilian Plajer, Maria J. Krisch, Jon Swanson, and Kenneth C. Waterman

FreeThink Technologies, Inc.

Purpose

- Test and validate a model for predicting the change in relative humidity (RH) as a function of time in nested packaging.
- The ability to model the RH inside a package over time has been coupled with explicit measurement of the RH sensitivity of drugs to determine the appropriate packaging for drug products without package screening using the ASAP*prime*® stability software.
- Being able to use single-layer packaging data to predict nested packaging moisture barrier behavior will enable modeling of a greater range of packaging options.

Two Compartment Modeling Approach

- To model RH change in nested packaging, calculations must account for an intermediate compartment RH (Figure 1 and Equation 1).

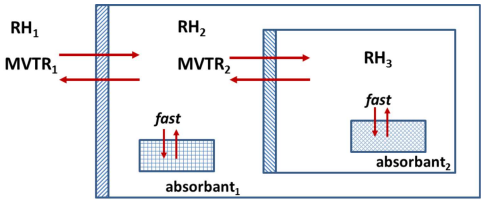


Figure 1. Schematic representation of nested packaging and the relevant moisture vapor transmission rates (MVTR) for the outer ($MVTR_1$) and inner ($MVTR_2$) packages. The RH is indicated for the external/storage condition (RH_1), intermediate container (RH_2), and inner container (RH_3). The inner and intermediate containers may each contain an absorbent (desiccant or excipient), which will have a characteristic moisture sorption capacity as a function of RH.

- Equation 1:

$$dW_2 = p_{1-2}(RH_1 - RH_2)dt + p_{2-3}(RH_2 - RH_3)dt$$

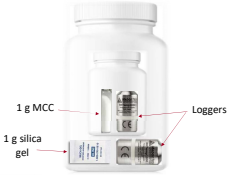
  - dW_2 = change in amount of water in outer container in time step dt
  - p_{1-2} = permeability of outer container (as a function of temperature)
  - p_{2-3} = permeability of inner container (as a function of temperature)
  - RH_1 = external RH
  - RH_2 = RH inside the outer container
  - RH_3 = RH inside the inner container

- Model Inputs:
  - Experimental nested packaging MVTRs
  - Moisture sorption isotherms of excipient or desiccant used
  - Packaging headspace volume
  - Initial packaging headspace moisture content
  - Storage temperature and RH

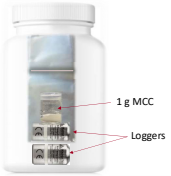
Methods

- Nested packaging configurations (n = 5)
  - Microcrystalline cellulose (MCC; Avicel® PH-102) used as an excipient absorbent with known moisture sorption isotherm was preequilibrated to 33% RH prior to being added to nested packaging
  - Nested packaging configurations exposed to 40°C/75% RH condition over 25 days
  - MadgeTech RHTemp1000 data loggers used to measure RH in each compartment

	Outer Package (250-cc HDPE bottle)	Inner Package (75-cc HDPE bottle)
Contents	Empty	1 g MCC
Initial RH	Ambient	33%



	Outer Package (250-cc HDPE bottle)	Inner Package (75-cc HDPE bottle)
Contents	1 g silica gel	1 g MCC
Initial RH	0%	33%

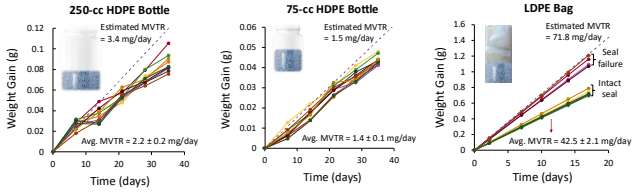


	Outer Package (250-cc HDPE bottle)	Inner Package (LDPE bag)
Contents	Empty	1 g MCC
Initial RH	Ambient	33%

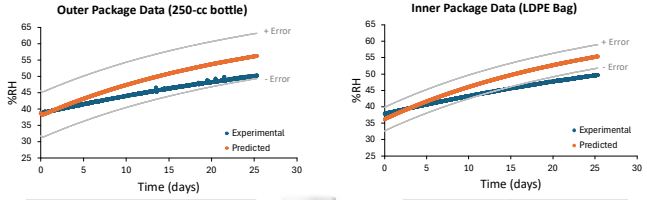
- Measured the MVTR of 250- and 75-cc HDPE bottles and LDPE bags at 40°C/75% RH (n = 10)
- Compared experimental RH data to model predictions (Python code)

Results

MVTR Measurements



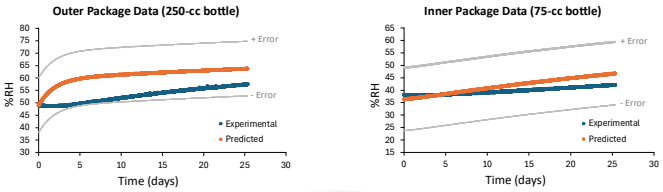
Bag-in-a-Bottle Nested Packaging Comparison



	Outer Package (250-cc HDPE bottle)
Model Prediction (Final %RH)	56.3 ± 6.9%
Experimental Data (Final %RH)	50.2%

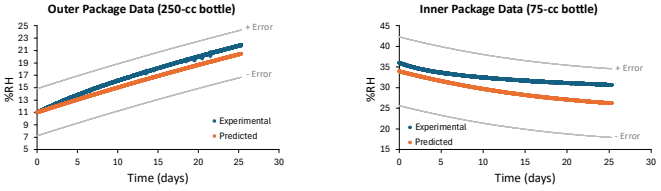
	Inner Package (LDPE Bag)
Model Prediction (Final %RH)	55.4 ± 3.6%
Experimental Data (Final %RH)	49.7%

Bottle-in-a-Bottle Nested Packaging Comparison



	Outer Package (250-cc HDPE bottle)
Model Prediction (Final %RH)	63.8 ± 10.9%
Experimental Data (Final %RH)	57.4%

	Inner Package (75-cc HDPE bottle)
Model Prediction (Final %RH)	46.7 ± 12.7%
Experimental Data (Final %RH)	42.1%



	Outer Package (250-cc HDPE bottle)
Model Prediction (Final %RH)	20.5 ± 3.8%
Experimental Data (Final %RH)	21.9%

	Inner Package (75-cc HDPE bottle)
Model Prediction (Final %RH)	26.3 ± 8.3%
Experimental Data (Final %RH)	30.7%

Conclusions

- Experimental RH data are consistent with the two-compartment model using single-layer packaging permeability to predict the change in RH as a function of time in nested packaging.
- As expected, when there is a large difference in moisture permeability between the two packaging layers, the lower permeability packaging dominates.
- Differences observed in some cases between model predictions and experimental data are likely due to the data logger itself absorbing a significant amount of moisture (being verified).

Contact

vanessa.breslin@freethinktech.com

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