Poster Number: T0930-13-102

Moisture Vapor Transmission Study to Support a Lyophilized Vial Dosage Form

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PURPOSE

Modeling moisture content in a drug product is important, since water could degrade the drug during its shelf life. Biphasic kinetics of water uptake were seen in stability studies for a lyophilized drug product packaged in rubber stoppered glass vials. It was proposed that the rubber stoppers could transfer measurable water to the drug product early in shelf-life. A gravimetric approach was taken to study moisture transmission rate (MVTR) effects for this packaging by determining the uptake of moisture into rubber stoppers and into desiccant sachets placed inside stoppered glass vials as a function of temperature and relative humidity (RH).

OBJECTIVES

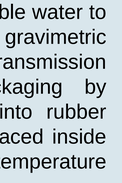
- Determine the actual MVTR through the stoppers.
- Determine moisture uptake by the stoppers.
- Assess transfer of water from the stoppers to the vial contents.

METHODS

The vials, stoppers and aluminum crimp seals were representative of those used to package the drug product (DP). The stoppers were sterilized and dried according to the DP manufacturing process.

Part	Description
Rubber stopper	West Pharma Grey with Flurotec coating on plug, chlorobutyl formulation, 20 mm
Glass vial	Schott, Type I glass, 20-mm, 6R (10 mL)
Crimp cap	West 20-mm Flip-off seal
Desiccant	Impak 0.25 g molecular sieve sachet

1) For the setup, the initial weights of the stopper, vial and crimp seal were recorded for each vial.
2) A desiccant sachet was added to each vial, the stopper was immediately placed on the vial which was then sealed with the crimp cap.



3) The weight of the desiccant was determined by subtracting the weights of the vial, stopper, and crimp seal from the weight of the complete assembly.
4) The assembled vials were placed at three different temperatures (40°C, 50°C, or 60°C) and 75% RH for up to 6 months.
5) At each time point from 4 weeks to 6 months, vials were removed, the vial assembly weighed, then disassembled to determine the weights of the stopper, crimp seal, vial and sachet (by subtraction).

RESULTS

Both stoppers and desiccant sachets gained weight over time. Plots showing the amount of water taken up by the desiccant and stopper as a function of time for each storage condition are shown in Figures 1-3.

At each temperature, the stopper weight increased and plateaued by about 60 days. The amounts of water taken up were 1 mg at 40°C/75% RH, 2.6 mg at 50°C/75% RH, and 3.5 mg at 60°C/75% RH. These results confirm that stoppers inserted into a vial and covered with a crimped cap can absorb significant amounts of water in 2 months.

Figure 1: Water uptake by desiccant and stopper at 40°C/75% RH

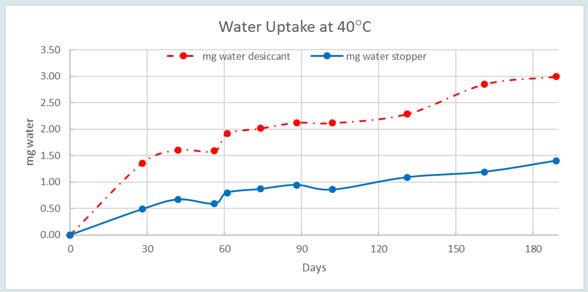


Figure 2: Water uptake by desiccant and stopper at 50°C/75% RH

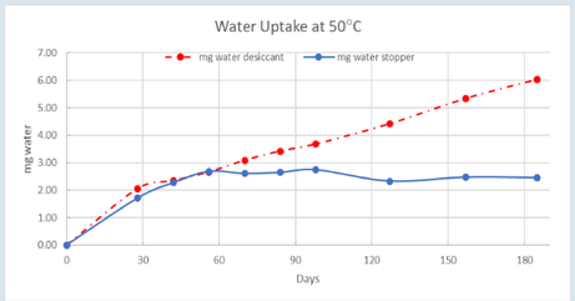
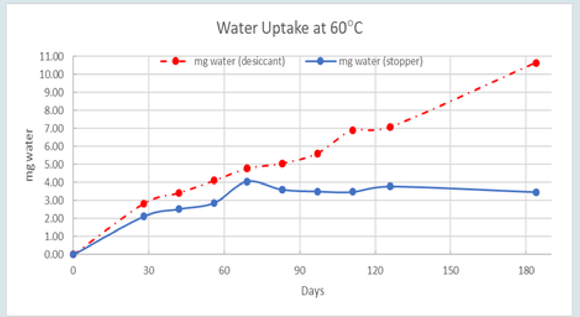
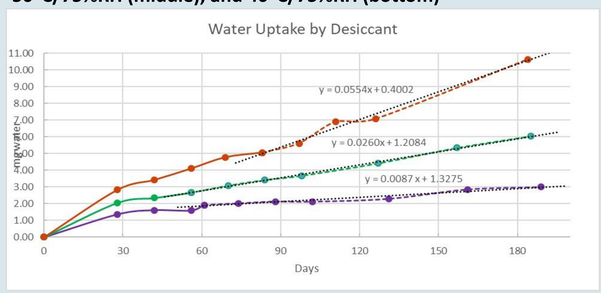


Figure 3: Water uptake by desiccant and stopper at 60°C/75% RH



The desiccant sachet showed rapid initial weight gain, followed by a slower linear increase (Figure 4). The initial water uptake most likely represents transfer of water from the stopper. The slope was determined from the point where water uptake by the stopper had reached a plateau and represents the MVTR through the stopper into the vial at that temperature and RH.

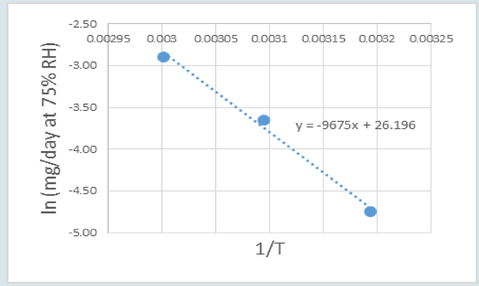
Figure 4: Water uptake by desiccant sachet at 60°C/75%RH (top), 50°C/75%RH (middle), and 40°C/75%RH (bottom)



Temperature/RH Condition	MVTR (mg/day)
40°C/75% RH	0.009
50°C/75% RH	0.026
60°C/75% RH	0.055

The log of the rate of water uptake by the desiccant was plotted vs 1/T (Figure 5), yielding a straight line consistent with Arrhenius (classical diffusion) behavior. From the slope, the activation energy (E_a) was calculated to be 19.2 kcal/mol. Projecting to 25°C leads to an estimated MVTR of 0.002 mg/day or 0.35 mg water increase inside the vial over 6 months. At 5°C, the projected MVTR is 0.0002 mg/day or 0.03 mg water gain over 6 months.

Figure 5: Arrhenius plot of MVTR data



CONCLUSIONS

An experimental approach to study moisture transmission effects for packaging relevant to a lyo drug product has been demonstrated in which uptake of moisture into rubber stoppers and desiccant sachets inside stoppered glass vials as a function of temperature and RH was determined.

At each temperature there was an initial uptake of water by the stopper that reached steady state after 60 days. The amount of water that the stoppers could absorb was significant, reaching 3.5 mg at 60°C/75% RH. These results demonstrate significant water gain by the intact rubber stoppers on the vials.

Water uptake by the desiccant sachet was biphasic and reflected water transfer from the stopper followed by transmission from the external environment through the stopper. Biphasic kinetics of water gain are consistent with that seen in the lyo drug product stability studies, suggesting that rubber stoppers can transfer measurable water to the drug product early in the shelf-life. The amount of moisture released from the stopper and the MVTR values are consistent with the water content data collected in the drug product stability studies.

The data from the present study will be used in the ASAP*prime*® software with the available accelerated stability and drug product moisture sorption isotherm data to predict shelf life for the drug product when stored at 5°C and 25°C/60% RH.

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